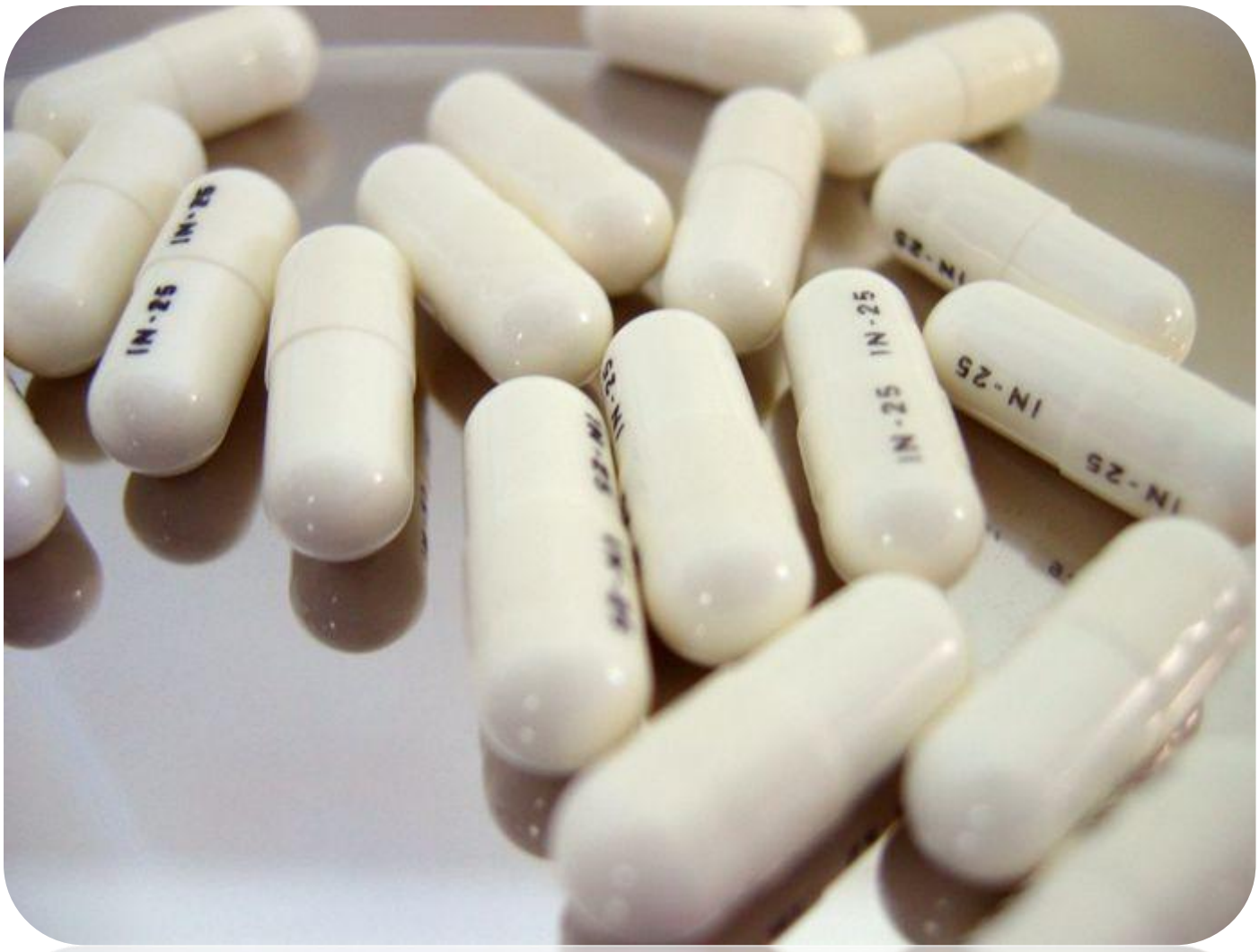
PHARMACOLOGY

2010



1. BASIC PRINCIPLES

Pharmacology; study of substances that interact with living system
Pharmacogenomics; relation of genetics and response to specific substances

General Principles

Nature of Drugs

- Drug molecules interact with ***receptors***
- Chemical ***antagonists*** interact with other drugs
- Osmotic agents interact with H_2O
- Synthesis is either ***Biological*** (eg hormone) vs ***Xenobiotic*** (not endogenous)
- ***Poisons*** almost exclusively harmful effects (all drugs harmful at high dose)
- ***Toxins*** poisons of biological origin

Basic Properties of Drugs	
Physical Nature	• Determines route of transmission
Size	• Most have MW 100-1000 • Best size for selective binding MW > 100 • Best size for diffusion MW < 1000
Reactivity & Bonds	• Covalent (strongest) • Electrostatic (most common, med strength bond) • Hydrophobic (weakest bind = more selective)
Shape & Atomic Composition	• ***Chirality***[1] common in biology • > ½ drugs are chiral with one stronger[2] • ***Racemic mixture*** = combination of both
Transport	
Inactivation or Secretion	

[1] mirrored but unable to superimpose eg hands
[2] vice versa with metabolism

Drug-Body Interactions

Pharmacodynamics: action of drugs on body
Pharmacokinetics: action of body on drug (***absorption***, ***distribution***, ***elimination***)

Pharmacodynamics briefly

1. Drug-receptor interaction
   - ***Agonists*** activate receptors
   - ***Antagonists*** prevent binding of said receptor
2. Pseudo/partial Receptor interaction
   - Mimic agonists by inhibiting termination of endogenous agonists (eg neostigmine inhibits AChE to prevent ACh breakdown)
   - Other drugs have a partial ant/agonist effect
3. Duration of Action
   - Spontaneous dissociation
   - Receptor destruction (usually covalent bonds eg aspirin)
   - Desensitizing (eg receptor upregulation)
4. Receptors & Inert Sites
   - Selectivity avoids constant activation
   - Inert binding sites (important in V_D)

Pharmacokinetics briefly

- ***Prodrug;*** absorbed and distributed then converted to active form via biological processes (eg codeine)

Permeation

a. Aqueous diffusion
- Aquaporins (not in brain, testes) which allow MW up to 20,000
- Driven via passive [gradient]

b. Lipid diffusion
- ***Most important limiting factor***
- Lipid : aqueous partition coefficient of drug determines diffusability
- Weak acids/bases depend on ***pH*** for driving force

c. Special Carriers
- Active or facilitated transport ∴drugs can target and either saturate or inhibit
- MDR transporters are eg of expelling foreign molecules (important in brain, testes) (multi drug resistant transporter, found in brain and testes, ATP transporter)

d. Endo/exocytosis
- Large cells

Fick's Law of Diffusion

$$flux = (C_1 - C_2) \times \frac{Area \times Permeability\ Co efficient}{Thickness}$$

Henderson-Hasselbach Equation

- Ionized molecules are polar (attract H_2O) ∴ H_2O soluble, lipid insoluble

Most drugs are weak acids or bases
- Weak acids reversibly dissociate into anion + proton eg *neutral aspirin* ⇔ *aspirin anion* + H^+
  ∴ Unprotonated form more lipid soluble AND ↓ pH = ↑ solubility & concentration
- Weak base form cation with protons eg *pyrimethamine cation* ⇔ *pyrimethamine* + H^+
  ∴ Protonated form more lipid soluble AND ↑ pH = [↑]

Explained by equ:

$$log\frac{protonated}{unprotonated} = pK_a - pH$$

- Bases contain specific amine groups (with free e^- for binding & specific configurations):
  - Primary 1 Carbon, 2 Hydrogen
  - Secondary 2C, 1H
  - Tertiary 3C, 0H
  - Quaternary 4C

2. PHARMACODYNAMICS

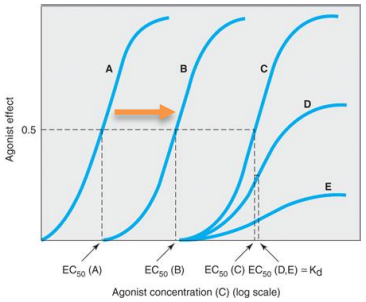
Receptors

- Mediate selective action of both ant/agonists
- Determine quantitative relationship between drug-effect

Nature of Receptors (macromolecular)
- Most are proteins (allow for ***Diversity, Specificity, Charge***)
- *Regulatory proteins* (mediate action of endogenous chemicals)
- *Enzymes* (eg cholinesterase)
- *Transport Protein* (eg Na/K ATPase)
- *Structural Proteins* (eg tubulin)

Quantitative Relationship: Concentration vs Response
- Mostly ***Hyperbolic*** ie response rises quickly at [low] but slows with [higher]
- NB dose-response usually uses Log[Concentration]
  (Expands the lower concentrations ∴ response is greatest per [unit])

Coupling & Spare Receptors
- ***Coupling*** link btwn drug occupancy & response
- ***Coupling co-efficient*** depends on
  1. Conformation receptor Δ (∴ full agonist more efficient)
  2. Biochemical events
     - Some linear (eg ion channel associated)
     - Others complex (eg enzymatic cascade)
- ***Spare receptors*** if drug elicits maximal response without activating all receptors (either temporal or spare in number)



Proof of Spare Receptors

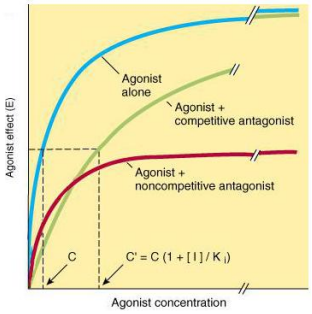
A Agonist response in absence of antagonist

B Agonist with some antagonist (more receptors occupied by ant/agonists)

C Large antagonist load (all receptors occupied by ant/agonist)

D & E gradual ↓ effect due to supersaturated receptors with either ant/agonist

Antagonist Actions
- Competitive antagonists will eventually reach maximal effect due to spare receptors
- Non-competitive antagonists will never reach maximal agonist effect

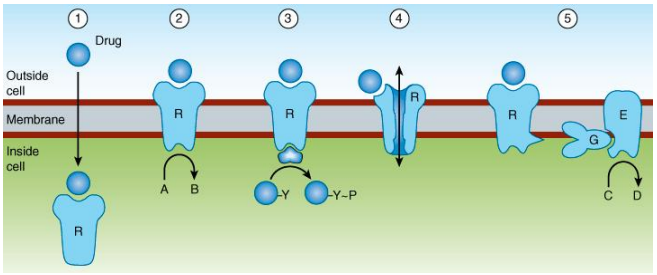


Antagonists: Mechanism, Intensity & Reversibility

Mechanism of Antagonism	
Competitive	• Binds same receptor site as agonist • Effect dependant on receptor affinity & reversibility (see below)
Non-Competitive *Allosteric*	• Binds to another site on the same receptor → conformational Δ • Reduced K_{Max} (and right shift, not as prominent vs competitive)
Un-competitive	• Requires agonist activation before inhibiting via non-competitive mechanisms ∴ more effective with higher doses of agonist
Chemical	• Alters agonist chemistry to inactivate eg protamine (+ve) binds heparin (-ve charge) through ionic attraction to inhibit fcn or Charcoal vs everything
Physiological	• Activation of endogenous regulatory pathways to change activity of another receptor • Less specific eg β-agonist for brady has more SE than atropine

Intensity	
Silent *"True or Full"*	• True "antagonists" in that they have no intrinsic activating activity
Partial Agonist	• Binds receptor with submaximal agonist effect with "competitive antagonist" effect • Curve is similar to silent + agonist curve
Inverse Agonist	• ↓ receptor activity below basal levels (ie antagonist of receptors with basal activity in absence of agonist

Reversibility	
Reversible *propranolol*	• Moves hyperbole **right** ∴ degree inhibition still depends on concentration of drug (related to dose and clearance) & any agonist activity
Irreversible ***organophosphates***	• Hyperbole plateau at lower effect • Usually via covalent bonds • If ***spare receptors*** present; low antagonist dose or higher agonist → *response* • Duration of activity limited by turnover of receptors (not rate of elimination)



Signalling Mechanisms & Drug Action

1. **Lipid soluble** | *steroids, thyroid hormones*
- Acts on intracellular receptors ∴ time to effect 30min to hrs (reflecting protein synth)
- Effects persist for hrs to days (reflects slow turnover of most enzymes and proteins)

2. Allosteric regulation internally from external binding

3. **Transmembranous Enzymes or Cytokines** | *tyrosine kinase, guanylyl cyclase*
- External ligand-binding site activating a transmembranous cascade
- End products include insulin, EGF, PDGF, ANP

Down regulation
- Limits duration and intensity of products when receptor destruction > de novo synthesis
- Receptor endocytosis also accelerated when bound

4. **Ion channel** | *BZDPs*
- Natural ligands include Ach, serotonin, GABA, glutamate
- Regulated by endocytosis & phosphorylation

5. **G Protein coupled and/or 2nd Messengers** | cAMP, Ca
- Receptor is part of the serpentine family
- Spare receptors exist from G-protein amplification[1]: binds & hydrolysis GTP
- Rapid desensitisation occurs since ligand activation of the receptor binds ***β-arrestins***
  (ligand removal inhibits Gs thereby ↓ β arrestin affinity → sensitisation restored (minutes)
- β-arrestin also ↑ endocytosis of receptors

[1]One ligand can activate many different G proteins

Most Common Second Messengers Systems

1. cAMP
- Stimulates cAMP dependant PKA
- Kinases have 2 Regulatory Dimers (R) & 2 Catalytic dimers (C)

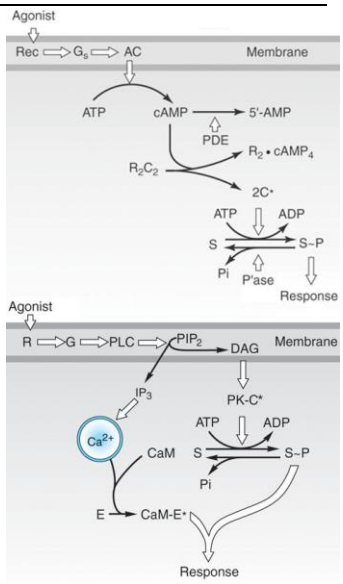
cAMP binds R_2 which activates & releases C chains ⇒ ATP → ADP + protein substrate

2. cGMP

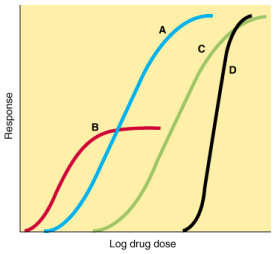
Cytoplasmic cGMP → PKA → dephosphorylation of myosin light chains
- Endogenous ligands incl ANP or NO
- incl intestinal & vascular smooth muscle
- Terminated by enzyme degradation

3. Ca & Phosphoinositide
- Opposes cAMP 2nd messenger in some & synergistic in others
- some enzyme driven, others G-protein driven
- crucial step: ***PLC stimulation***

Agonist ⇒ R ⇒ G ⇒ PLC ⇒ PIP_2 → IP_3 + DAG 2nd messengers
- IP_3 ↑ intracellular Ca (from stores)
- DAG activated PKC



Phosphorylation
- Most 2nd messengers involve *Phosphorylation* ⇒ amplification & flexible regulation
- ***Amplification:*** attachment of phosphryl group acts as 'molecular memory'
- ***Flexible Regulation:*** provides branch points (PKs) in signalling pathway to independently regulate



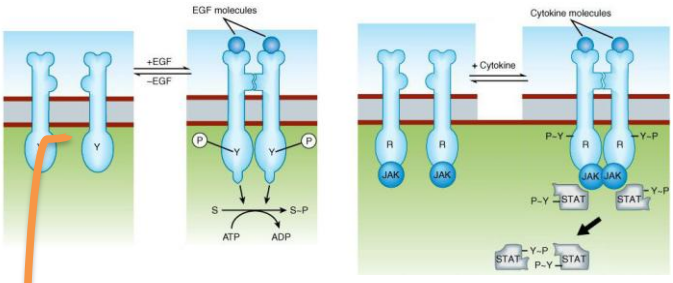
Drug Dose & Clinical Response Curves

Efficacy: Maximal Response
- A, C, D have same efficacy > B

Potency: EC_{50}
- EC_{50} (B) > EC_{50} (A) ∴ B more potent than A
- B > A > C > D

Toxicity
- D steep ∴ careful use if toxic effects

A. Graded Dose-Response Relations (Potency & efficacy)
- ***Potency:*** EC_{50} (concentration) or ED_{50} (dose) required to produce 50% Max Effect
  NB no reflection on max response ∴ useful for *administration dose* not choice of drug)
- ***(Maximal) Efficacy:*** determined by receptor interaction, receptor-effector system
- ***(Practical) Efficacy:*** achieving therapeutic end point limited by propensity for toxic effects

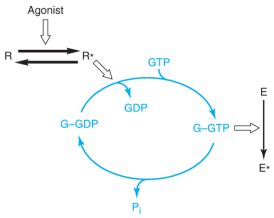


Transmembranous Enzyme Receptor Structure
- Extracellular Ligand binding domain & Cytoplasmic enzyme domain
- Ligand binds receptor → conformational Δ (extra & intracellular binding)
- Intracellular tyrosine domains bind (non-covalent) → phosphorylates → effect

Cytokine receptors
- similar to tyrosine kinase receptors except they activate separate mobile tyrosine kinase (JAK) ⇒ phosphorylation & activation of STAT ⇒ nucleus & regulate transcription

Components Of 2nd Messenger System
- Cell surface receptor
- Cytoplasmic G protein activation (amplifies signal)
- Δ Effecter element (ion or enzyme) activity
- Δ [2nd Messenger]

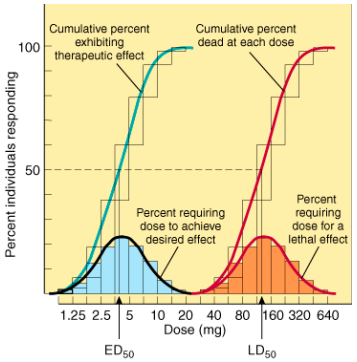
eg Ligand ⇒Gs (g-protein) ⇒ adenyl cyclase (enzyme) ⇒ cAMP (2nd messenger)



G protein
- Located on the cytoplasmic side of membrane
- Δ activity of effector element (enzyme or ion channel)

Ligand Binding ⇒ GDP release/GTP binds ⇒ effect ⇒ GTP hydrolysed ⇒ G protein inactivated

B. Shape
- Not all clinical responses are Log Hyperbole
- Different shaped curves result from summation of separate organ actions



C. Quantal Curves (all or none)
- Relevant if effect is all-or-none eg death
- Quantal curve for one patient is different for others ∴ useful for graphing *variability*
- Expressed as proportion/% of individuals who exhibit effect vs function of log Dose
- Important points on graph; ***ED_{50}*** ***TD_{50}*** ***LD_{50}***

ED50 = effective dose for 50%
TD50 = toxic dose for 50%
LD50 = lethal dose for 50%

Therapeutic Index: ratio of TD_{50}:ED_{50}
- Less for drugs treating lower severity eg headache
- Higher for drugs treating high severity eg HL

Variations in Drug Responsiveness
- Idiosyncratic response; infrequent, cause usually genetic diff in metabolism (incl allergic)
- Hypo/Hyper-reactive/sensitivity
- Tolerance; diminishing drug tolerance
  (NB ***Tachyphylaxis*** = rapid tolerance)

Factors Influencing Variability	
Age	Disease States
Sex	Other Drugs
Race	Diet
Body Habitus	Environment
Genetic Predisposition	

Mechanisms influencing Variation

1. *[Drug] altered reaching receptor site*
   - Rate of absorption/distribution/clearance
   - Active transport esp MDR genes
2. *Variation in endogenous Ligand*
   - Bigger variation with partial agonists eg ***propranolol*** in healthy (no Δ) vs pheo (↓ HR)
3. *Variation in Number/Function of Receptors*
   - Can be from other hormones (eg thyroid to β receptors and thyrotoxicosis)
   - Down regulation/Desensitization
   - Contributes to tachyphylaxis and ***over shoot phenomenon***
   - Antagonists can upregulate receptors by preventing downregulation by binding to endogenous ligand ∴ removal of antagonist reveals > number of receptors
   - Vice versa for agonists (downregulation = less receptors when removed) eg ***clonidine***
4. *Δ Component of Response Distal to Receptor*
   - **Largest class to cause variation**
   - Age/co-morbidities influence

Clinical Selectivity
- Drugs are *selective* but NOT *specific* with use dependant on *therapeutic vs toxic effects*
- 3 areas of effect

a. Same receptor-effector
   - Toxicity due to extreme spectrums of receptor activity

b. Same receptor-different tissue
   - ∴ start at lowest dose or change route to lower dose
   - Adjunctive drugs may allow for lower dose of 1st

c. Different receptor
   - Different classes of receptors found in different areas of the body eg β selective drugs

SECTION I: BASIC PRINCIPLES

3. PHARMACOKINETICS

Pharmacodynamics = concentration : effect | ***Pharmacokinetics*** = dose : concentration

Basic Principles

- *Standard dose: based on trials in healthy volunteers & patients with average ability to absorb, distribute, eliminate drugs*
- Basic parameters of pharmacokinetics
  a. *Clearance* – ability to eliminate the drug
  b. *Volume of Distribution* – apparent space in body able to contain the drug

Volume of Distribution (V_d)

$$V_d = \frac{Amount\ of\ drug\ in\ body}{[drug\ in\ medium]}$$

Medium:
Blood (C_b)
Plasma (C_p)
H_2O (unbound) (C_u)

- V_d is an apparent volume[1] ∴ can exceed physical volume
- V_d = 1 = all drug in *vascular compartment*

Clearance

$$CL = \frac{rate\ of\ elimination}{C} \quad \therefore rate\ of\ elimination = \frac{CL}{C}$$

Medium:
Blood (CL_b)
Plasma (CL_p)
H_2O (CL_u)

- $CL_{total} = CL_{organ\ 1} + CL_{organ\ 2}$ ...etc
- Major sites of CL = kidney & liver
  - CL_{Renal}; clearance of unchanged drug in urine
  - CL_{Liver}; unchanged/biotransformation into bile
- CL is constant regardless of concentration (ie not saturable within these levels)

First order elimination

- occurs when rate of elimination ∝ concentration
- estimated by calculating area ↓ curve of time vs [ ]

1. *Zero Order Elimination (capacity limited)* eg phenytoin, ethanol, aspirin

- At high concentrations, most drugs elimination pathways will become saturated

$$Rate\ of\ elimination = \frac{V_{max} \times C}{K_m + C}$$

V_{MAX} = max elimination capacity
K_M = [drug] where rate of elimination is 50% of V_{Max}

- ∴when [drug] > Km, elimination independent of [drug] & AUC can't describe elimination

2. *Flow Dependant Elimination*

- High extraction drugs undergoing extensive 1st pass metabolism
  ∴ Elimination dependant on delivery sys, blood flow, protein binding, blood cell partitioning

Half Life (T ½)

- Time required to attain 50% of steady state or decay 50% from steady state conditions
- True T ½ depends on multi compartment pharmacokinetics

$$t_{\frac{1}{2}} = \frac{\log 2 \times V_d}{CL}$$

Drug Accumulation

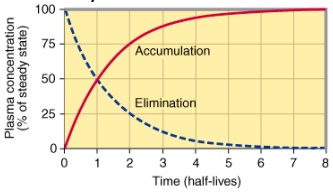
- Practically, dosing *≤ 4 T½* apart accumulation will be detectable

$$accumulation\ factor\ (AF) = \frac{1}{fraction\ lost\ in\ 1\ dosing\ interval} = \frac{1}{1 - fraction\ remaining}$$

∴ Drug given once every T ½ has accumulation factor = 2

- Useful in calculating [peak] after multiple doses; [peak] = [First $Dose_{Peak}$] x AF

Bioavailability



- *Fraction of unchanged drug reaching circulation after administration*
- Area ↓ curve (concentration-time)

Route	Bioavailability	Characteristics
IV	100	Most rapid onset
IM	75 to ≤ 100	Painful; larger v than SC
SC	75 to ≤ 100	Painful; smaller v than IM
PO	5 to < 100	Convenient; 1st pass metabolism, incomplete absorption
PR*	30 to < 100	Less 1st pass effect then PO
IN	30 to < 100	Less 1st pass effect then PO
SL*	30 to < 100	Less 1st pass effect then PO
Inh	5 to < 100	Rapid onset
TD*	80 to ≤ 100	Slow absorption/prolonged duration of action limited 1st pass effect

**Avoids 1st pass metabolism, NB suppositories can move up the rectum ∴ 50% avoids 1st pass*

PO Bioavailability

1. *Absorption via*

- Gut absorption (eg *digoxin*) | Hydrophilic (eg *atenolol*) | Lipophilic (eg *acyclovir*)
- P-glycoprotein is a gut membrane active drug transporter (grapefruit juice inhibits)

2. *1st Pass Metabolism*

- Oral ⇒ Gut Wall ⇒ Portal System ⇒ Liver ⇒ Systemic Circulation
- Sites of potential metabolism include: *gut wall (CYP3A4), Portal Blood, Liver*

$$ER = \frac{CL_{Liver}}{Q}$$

ER = extraction ratio
Q =hepatic flow 990L/hr

eg *morphine* is almost completely absorbed (f=1) but ER = 0.67

$$F = f(1 - ER)$$

F = systemic bioavailability
f = extent of absorption

∴ F = 0.33 ie bioavailability is 33%

3. *Rate of Absorption*

- Rate vs extent of absorption (rate depends on route & formulation)
- *Zero order* drug; rate of absorption independent of amount in gut eg determined by gastric emptying or controlled release formulation

Extraction Ratio & 1st Pass Effect

- Although systemic Cl doesn't affect BioAv directly, Cl can determine ER
- Some drugs not given orally because metabolites are toxic
- *Higher ER = more variable interpatient variability*

TIME COURSE OF DRUG EFFECT

Immediate Effects

- Effect vs concentration not linear
- Drugs like *Enalapril* are given once daily but consider
  - T ½ = 3 hrs ∴ after 24 hrs = [0] ie 7 T ½ but despite this, still 30% ACE inhibition
  - Due to high initial [ ] in relation to EC_{50}
  - Common for drugs that target ***enzymes or compete at receptors***

Delayed Effects

- *Minute* effects due to distribution from plasma to site of action
- *Hourly* effect due to physiological turnover of substance
  eg *warfarin* acts immediately on vitamin K epoxidase (which inhibits PT formation) but has a T ½ = 14 hrs ∴ effects not immediate

Cumulative Effects

- Accumulation of *aminoglycosides* good example of cumulative effect
- Infusion vs intermittent dosing at same steady state
  - Infusion will create toxic changes to renal cortex
  - Intermittent dosing produces higher peaks ∴ saturating uptake mechanisms & limiting renal cortex accumulation

TARGET CONCENTRATION

- Rational dosing regimen aims at reaching a target concentration (with best effect : toxic)

Maintenance dose

- Maintenance dose aims at replacing dose = eliminated dose

$$dosing\ rate = rate\ of\ elimination = CL \times TC$$

$$maintanence\ dose = dosing\ rate \times dosing\ interval$$

TC = target concentration = known value from clinical trials

If BioAv is not 100% then need to factor into TC (ie ÷F)

Loading dose

$$loading\ dose = V_d \times TC$$

Applies in single compartment pharmacokinetics
Used for drugs with long T ½

NB if $Rate_{Absorbtion}$ > $Rate_{Distribution}$ (eg IV) transient toxic effects inevitable (eg *lignocaine*)

	Summary of Variables	
Pharmacokinetics	Absorption	Compliance | Rate/extent of transfer from administration to blood
	Clearance	Impairment of Kidney, Liver, Heart NB although CL_{Crea} reflects renal fcn, CL_{Drug} can be better indicator Hepatic disease doesn't always affect intrinsic $CL_{Hepatic}$
	V_D	Binding tissues vs Binding plasma proteins ↓ apparent V_D ↑ apparent V_D eg V_D overestimated in obese if drug does not distribute well in fat
	T ½	Determined by V_D ∴ ↑ age = ↑ T ½ diazepam but ↓ CL
Dyn	Maximum Effect	E_{MAX} | Important in calculating to avoid unnecessary toxic doses
	Sensitivity	EC_{50} reflects this: If EC_{50} ↑ = less sensitive Factors are usually physiological

Interpretation of Drug Concentrations

Clearance

- *Single most important factor in determining [drug]*
- Influenced by *dose, organ blood flow, liver/kidney function*
- Use Creatinine in plasma to estimate (85% in women as < muscle)
- Can be misled by [drug] eg Δ protein binding

Factors effecting protein binding;		
Albumin	*Phenytoin, salicylates, Disopyramide*	all extensively bound to albumin
α1-acid glycoprotein	*Quinine, Lidocaine, propranolol*	↑ during acute inflammation | NB Drug elimination unchanged
Capacity limited protein binding	Most drugs have this	At high concentrations as when capacity met [plasma] will rise quickly

- Dosing history
- Timing of sampling
- Body habitus; V_D needs to calculated according to ideal body weight (in obese) or effective body weight (ascites etc) depending on distribution pattern of drug to these areas

$$ideal\ body\ weight\ (man) = 52 + 1.9\ kg/inch$$
$$ideal\ body\ weight\ (woman) = 49 + 1.7 kg/inch$$

[1] Necessary to contain the amount of drug homogenously at [ ] found in blood, plasma or H_2O

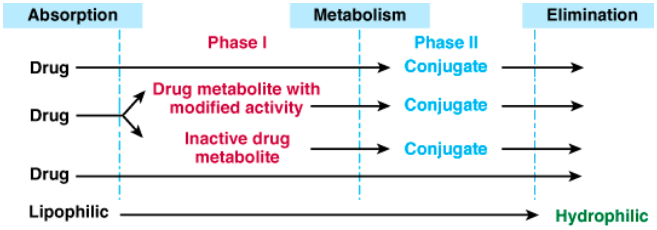
4. BIOTRANSFORMATION

Xenobiotic *pharmacological, endocrinal, toxicological substance foreign to an organism*

Biotransformation Necessity

- Metabolism (eg most Lipophilic xenobiotics are metabolised to ionized form for clearance)
  - Renal excretion common pathway for most drugs with barriers including:
    Larger molecules | Less ionized | Strongly bound to plasma protein | Lipophilic
- ↑ Xenobiotic effect (also potentially toxic)
- Active inactive drugs

Role of Biotransformation in Drug Disposition



Phase 1 *Oxidation, Reduction, Hydrolysis*

- Convert parent drug to ***polar metabolite*** by unmasking a functional group (-OH, -NH_2, -SH)
- Metabolites usually inactive & rarely enhanced
- If parent drug already has a functional group then bypass phase 1 reaction

Phase 2

- Convert phase 1 metabolite to ***highly polar metabolite*** by reaction with endogenous substrate[2] (found in diet) to ***modify, activate*** metabolite
- Occurs if phase 1 metabolites aren't excreted (rapidly)

Biotransformation Locations

- Liver principle organ of drug metabolism *(although all tissues are capable to some extent)*
- Other secondary organs incl GIT, Lungs, Skin, Kidneys
  GIT > Liver; clonazepam, chlorpromazine, cyclosporine
- Lower Gut has ***microorganisms*** capable of biotransformation
- Other phase 1 catalysts: Gastric Acid, Digestive Enzymes, Enzymes in GI Wall

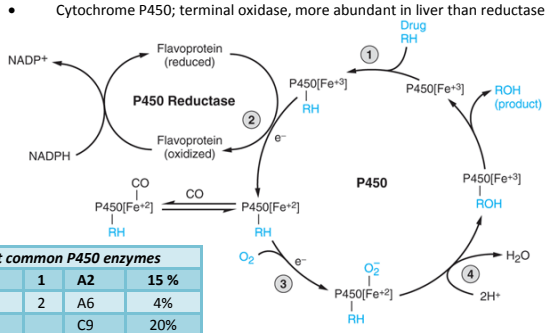
Microsomal Mixed Function Oxidase (MFO) System & Phase 1 Reactions

- ER membranes contain most drug metabolizing enzymes

Microsomes

- Small vesicles that form following cell homogenization or fractionation
- Contain most morphological & functional characteristics of original cell including sER or rER
- rER microsomes dedicated to protein synthesis
- sER microsomes rich in enzymes req in oxidative drug metabolism
  - ***MFO*** is a specialized class of sER microsomes that catalyse oxidation-reduction

  2 important MFOs;
  - NADPH-cytochrome P450 reductase
  - Cytochrome P450; terminal oxidase, more abundant in liver than reductase



Most common P450 enzymes			
CYP	1	A2	15 %
	2	A6	4%
		C9	20%
		D6	5%
		E1	10%
	3	A4*	30%

**responsible for > 50% of clinically prescribed drugs*

Enzyme Induction

- Some P450 substrate drugs can induce P450 synthesis/reduce degradation
  ∴ ↓ in pharmacological effect of inducer & co administered drugs can occur
- Pollutants can also induce P450 enzymes eg tobacco smoke

Enzyme Inhibition

- Some metabolites bind tightly to P450 enzyme ∴ rendering it inactive eg ***erythromycin***
- ***Suicide inhibitors*** attack heme or protein moiety eg steroids

METABOLISM OF DRUGS TO TOXIC PRODUCTS

- Most commonly seen when resources exhausted
- Eg paracetamol (95% metabolised via phase 1, 5% phase 2)
  - Overdose = more dependent on P450 ie phase 1 metabolites accumulate
  - Fulminant hepatotoxicity occurs

Clinical Relevance of Drug Metabolism

- Individual Differences
- Diet & environment; smokers, pesticides metabolise faster
- Age & Sex; very young/old most susceptible
- Drug-Drug/Endogenous ; induce enzyme synthesis, inhibit metabolism
- Co morbid States
- Genetic; eg ***succinylcholine*** metabolised ½ as fast in those with genetic pseudocholinesterase defects (***Sux apnoea***)

3 most common genetic varieties of drug metabolism polymorphism	
Debrisoquinsparteine oxidase	CYP2D6 impaired → Ultra-fast metabolism (∴ higher dosing)
Aromatic (4)-hydroxylation	CYP2C19 → Poor metaboliser of ***mephenytoin***
CYP2C*2 or CYP2C*3	Impaired functional interaction with P450 Lowered affinity for substrates (eg lower tolerance for warfarin, clearance = 10%)

5. DEVELOPMENT & REGULATION OF DRUGS

Drug Discovery

- Identify drug target
- Rational drug design (based on biological mechanisms, receptors, structure)
- Chemical modification
- Screening for biological activity in natural products, peptide libraries
- Biotechnology & cloning genes to produce new peptides & proteins
- Combination drugs

Drug Screening

- Used to define activity & selectivity with demonstration of un/suspected toxic effects
- Good drugs lacking in poorly understood disease states eg Alzheimer's
- Forms ***pharmacological profile:*** *molecular, cellular, system, organism effects*

Preclinical Safety & Toxicity Testing

- All drugs toxic at some dose
- Goal: identify, design tests to identify, predict & monitor during trials
- Main quantitative measurements;
  - No effect dose; max dose without toxic effect
  - ***Minimum Lethal Dose*** & ***Medial Lethal Dose*** (LD_{50})
- Limitations
  - Time consuming/expensive
  - Large numbers of animal studies required
  - Extrapolation is not always transferable from animal to human models
  - Rare adverse effects unlikely to be detected

Evaluation in humans

Confounding factors

- Variable nature of and other un/known compounding diseases
- Subject/Observer Bias

Orphan Drugs & Treatment of Rare Disease: For rare disease affecting < 200,00

Adverse Drug Reactions: Harmful, unintentional response | 4th leading cause of death

Clinical testing

Phase 1

- Small number
- Healthy volunteers (skip to phase 2 if targeting specific group with lenient toxic allowance)
- Drug function & dose assessed
- Determines animal-human correlation
- Establishes probable limits for safe dosage
- Open study

Phase 2

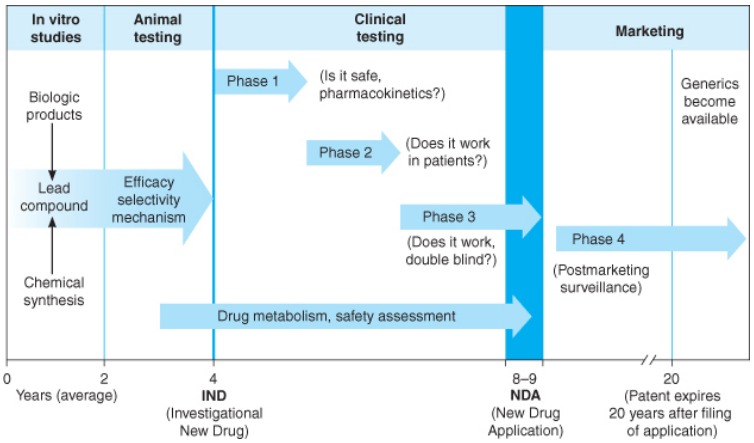
- Patients with targeted disease
- Efficacy
- Modest number
- Single blind

Phase 3

- Larger number with targeted disease
- Further establish efficacy & safety
- Double blind & cross over studies
- Minimize errors caused by placebo effect

Phase 4

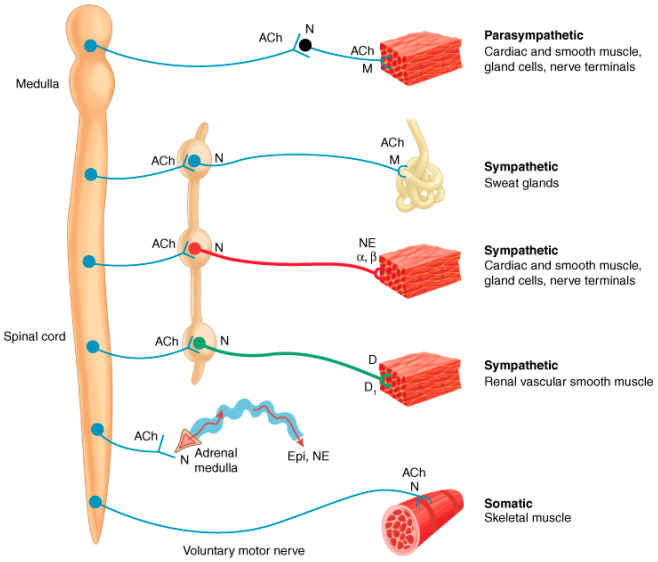
- Safety monitoring in public
- Rare incidence toxicities picked up eg COX 2 inhibitors

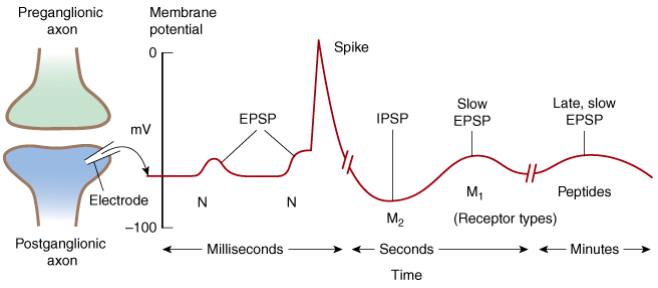


[2] Glucuronic acid, sulphuric acid, acetic acid, amino acid

SECTION II: AUTONOMIC DRUGS

1. BASIC PRINCIPLES





Nonadrenergic, Non Cholinergic Neurons (NANC)

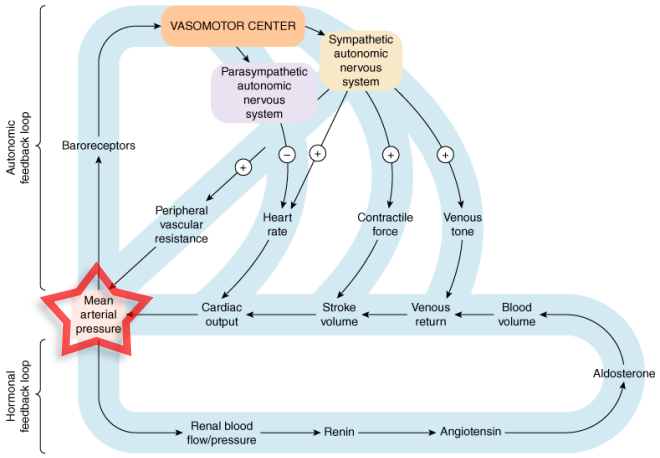
- Most extensively studied in the gut
- Some neurons have up to 5 different transmitters
- Act as "sensory local-effector"

Functional Organization of Autonomic Activity

- Fundamentally fight or flight:
  - Parasympathetic = energy conservation; fast gut, slow heart
  - Sympathetic = energy expended = slow gut, fast heart

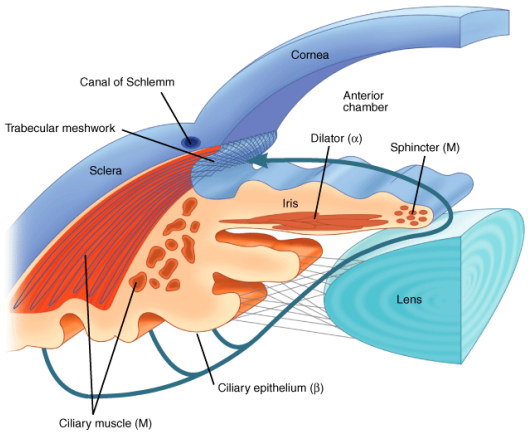
Integration of Cardiovascular Function

- Primary control variable = ***MAP***
- Eg: Noradrenaline; both peripheral vasoconstrictive & Chronotropic
  - ↑ Peripheral R ⇒ Baroreceptor activation ⇒ ↑ Parasympathetic & Sympathetic
  - Chronotropic effect appears paradoxically



- Presynaptic Regulation
  - ***Autoreceptors:*** usually inhibitory
  - Some cholinergics (esp somatic motor) are excitatory
  - ***Heteroreceptors:*** eg vagal endings have sympathetic input
- Postsynaptic Regulation
  - Receptor up or down regulation eg Denervation supersensitivity
  - Modulation by transmitters on different postsynaptic receptors eg ganglionic transmission

Pharmacology of the Eye



Multiple autonomic functions

Location	Receptor	Action
Pupillary Dilator	α1	Mydriasis (dilation)
Pupillary Constrictor	M3	Miosis (constriction)
Ciliary Muscles Contraction	M3	Accommodation of focus (*cyclospasm*) & facilitates outflow of aq humor into canal of Schlemm (↓ IOP)
Ciliary epithelium	β	aq humor secretion

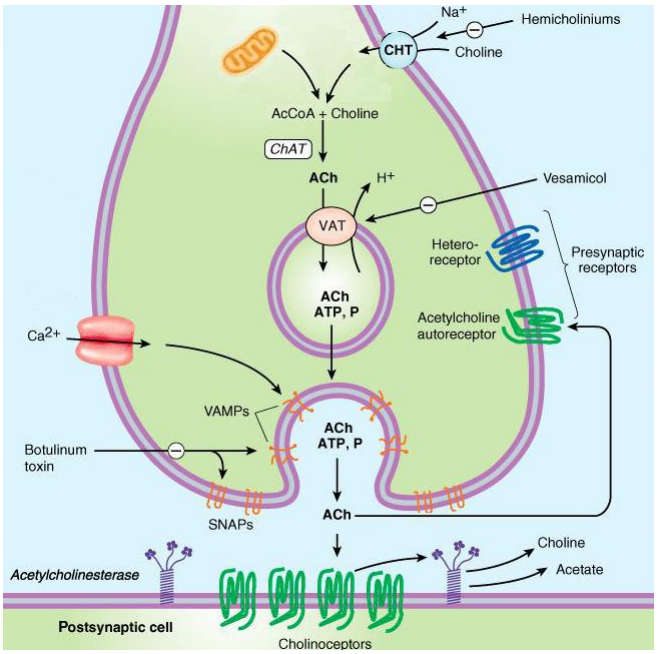
CHOLINERGIC | Nicotinic or Muscarinic | ACh

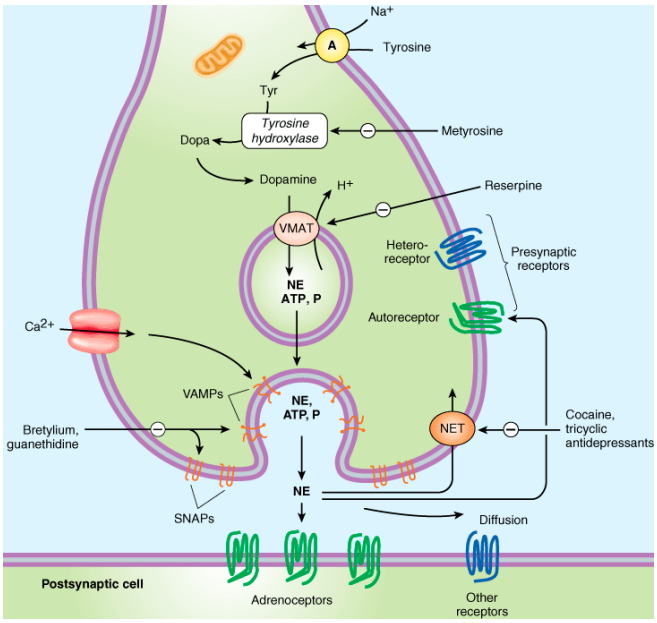
ADRENERGIC | α or β | Epinephrine, Norepinephrine, Dopamine

	Cholinergic	Adrenergic
Fibre Types	1. All preganglionic efferents 2. All somatic motor fibres 3. All pre & postganglionic parasympathetics 4. Postganglionic sympathetic sweat glands & Renovascular smooth muscle	1. Postganglionic sympathetic (not sweat or renal vascular smooth muscle)
Synthesis	Terminals have 1. **Small** membrane bound vesicles containing Ach 2. **Larger** dense core vesicles containing co transmitters • Either synthesised from neuronal stroma or recycles from previous transmission $Acetyl\text{-}CoA + Choline \xrightarrow{choline\ transferase} ACh \xrightarrow{VAT} vesicles \xrightarrow{Ca\ influx} exocytosis$ • Acetyl-CoA synthesised in mitochondria • Choline transported from ECF via Choline transporter • VAT driven by H^+ efflux • VAMPs align vesicles with SNAPs to trigger release of Ach • Ca influx interacts with **VAMP synaptotagmin** to trigger fusion and exocytosis	$Tyrosine \xrightarrow{tyrosine\ hydroxylase} dopa \rightarrow dopamine \xrightarrow{VMAT} vesicle \xrightarrow{Ca\ influx} exocytosis$ • Tyrosine transported from ECF via Na dep Symporter • VMAT driven by H^+ efflux • Ca influx main trigger, also mixed sympathomimetic • Tyramine, amphetamines, ephedrine • Poor agonists at receptor level • Excellent substrates for monoamine transport • NET; Transmembrane channel re-uptakes NE • DAT & SERT; reuptake of dopamine or serotonin
Termination	$ACh \xrightarrow{acetylcholinesterase} Aceytl\text{-}CoA + Choline$ • T ½ seconds • AChE also found in RBCs	• Diffusion & eventual metabolism in plasma or liver • Reuptake via NET

	COMT	MAO
Epinephrine	Metanephrine	VMA
Norepinephrine	Normetanephrine	
Dopamine	3-methoxytyramine	Homovanillic acid

	MOA	COMT
Epinephrine	Dihydroxymandelic acid	VMA
Norepinephrine		
Dopamine		Homovanillic Acid





Receptor	Location	Mechanism	Fcn
M_1	CNS Neurons Sympth Postganglionic Some presynaptic sites	Gq coupled	↑ IP_3 | DAG Cascade ↑ Intracellular Ca
M_2	CNS Neurons Myocardium Smooth Muscle Some presynaptic sites	Gi coupled	↓ cAMP Activates K^+ ch
M_3	CNS Neurons Exocrine Glands Vessel: muscle/endoth	Gq coupled	↑ IP_3 | DAG Cascade ↑ Intracellular Ca Release NO from intact endothelium
M_4	CNS Neurons Maybe presynaptic vagal nerves	G coupled	↓ cAMP Activates K^+ ch
M_5	CNS Neurons Vascular Endothelium (esp cerebral)	G coupled	↑ IP_3 | DAG Cascade ↑ Intracellular Ca
N_N	ANS Ganglia	α2β2 or α3β3 Ion Ch	Open K & Na = depolarization
N_M	Skeletal Muscle	Pentamer Ion Ch (α2βγδ)	Open K & Na = depolarization

	Location		Fcn	Effect
α_1	Post synaptic Effector Cells Esp smooth muscle	Gq	↑ IP_3 | DAG Cascade ↑ Intracellular Ca	Contraction Secretion
α_2	Presynaptic Adrenergic Plt, Lipocytes, Smooth Muscle	Gi	↓ cAMP Inhibit adenyl cyclase	Contraction
β_1	Postsynaptic Effector Cells Esp cardiac muscle, JGA, lipocytes	Gs	↑ cAMP Stim adenyl cyclase	Inotropic/Chronotropic Renin secretion
β_2	Postsynaptic Effector Cells Esp Smooth & Cardiac	Gs	↑ cAMP Stim adenyl cyclase	Relax smooth muscle ↑ glycogenolysis Inotropic/Chronotropic
β_3	Postsynaptic Effector Cells Esp Lipocytes & heart	Gs	↑ cAMP Stim adenyl cyclase	↑ Lipolysis

Dopamine
- D & DA
- Part of adrenergic receptors
- Renal & Splanchnic vessels
- D1 &2 most important

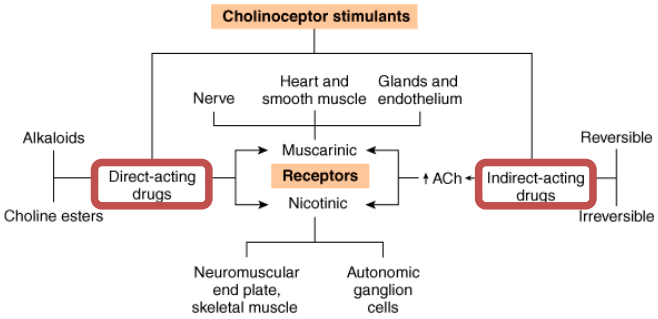
Muscurinic
- DAG: opens smooth muscle Ca channels
- IP_3: releases Ca from ER & SR
- NO activates guanylyl cyclase = ↑cGMP = smooth muscle relaxation
- Direct on K Channels in myocardium
- ↓ cAMP

Nicotinic
- Ion Channels

Cotransmitters in Cholinergic & Adrenergic Nerves
- Role not fully understood
- Can act as noncholinergic/Nonadrenergic transmitters
- Can potentiate or slow Ach/epinephrine effect
- Feedback inhibition
- Examples:
  1. CCK: some excitatory neuromuscular ENS neurons
  2. NO: inhibitory NMJ (esp sphincters)
  3. 5HT: co/transmitter neuron=neuron jcn in ENS

SECTION II: AUTONOMIC DRUGS

2. CHOLINOMIMETICS



Mode of Action: ***Cholinomimetic***

1. *Direct:* bind & activate receptors
2. *Indirect:* inhibit AChE ⇒ ↑ Ach

DIRECT

	Esters of Choline ***Ach, Methacholine, Carbamic Acid, Carbachol, Bethanechol***	Alkaloids ***Muscurine, Nicotine, Pilocarpine, Lobeline***
Structure	Quaternary NH_3 Group (permanently charged ∴ lipid insoluble) M receptors strongly stereo selective: Eg S-Bethanechol 1000x R-Bethanechol	Tertiary: all others Quaternary: muscurine = less GIT absorption
Absorption, Distribution, Metabolism	Poorly absorbed, Distributes in CNS (lipid soluble) Hydrolysed in GIT Differing hydrolysis susceptibility Ach, Met, Carb, Beth (easiest to hardest)	Well absorbed (quart less so) Nicotine absorbs across skin (lipid sol)

****prolonged agonist occupancy = cessation of effect & "depolarizing blockade"***

Pharmacodynamics: organs

Eyes

- Contraction of: 1. Iris sphincter ⇒ contraction ⇒ *miosis*
  2. Ciliary muscle ⇒ *accommodation*
- Facilitates aq flow (draining ant chamber)

CVS

- M2: ↓ Peripheral Resistance (+ reflex tachy)
- M3: Large doses ***↓SA/AV conduction*** by:
  ↑ $I_{K(Ach)}$ in atrial muscles, SA, AV nodes | ↓ I_{ca} | ↓ I_f (diastolic depolarization)
- Ventricular effect > during sympth stim
- Choline esters have longer duration of action (more resistance to AChE)
- Alkaloids have similar effect to Ach

  NB ***Pilocarpine*** ⇒ HTN due Sympth stim ⇒ preganglionic M1 activation ⇒ ↓ $I_{K(Ach)}$

Resp

- Bronchial smooth muscle ***contraction***, Tracheobronchial mucosal ***secretion***

GIT

- ↑Glandular secretion (Salivary & Gastric > pancreatic & SI) & ↑ Peristaltic activity
- Sphincter relaxation
- M2 ↓ cAMP & relaxation caused by sympathomimetics
- M3 directly activates smooth muscle

GUT

- Detrusor contraction | Trigone/Sphincter relaxation
- Uterus not sensitive to M receptors
- M2 & 3 have same function as GIT

Misc Secretory Glands

- Thermoregulatory sweat, Lacrimal, Nasopharyngeal

INDIRECT

- Most indirect cholinomimetics ***inhibit AChE*** (some are nicotinic agonists)

Structure

1. Simple alcohols (***edrophonium***)
2. Carbamic acid esters of alcohol with quat or tert NH_3 (***neostigmine***)
3. Organic Derivatives of phosphoric acid (***organophosphates***)

Absorption

- Quaternary carbamates is poor (permanent +ve charge), negligible CNS distribution
- Stable in aq solution, broken down by other esterases as well
- Duration of effect depends on inhibitory=enzyme complex
- ***Physostigmine*** well absorbed

Organophosphates Absorption

- Well absorbed from skin/lung/conjunctiva
- More unstable than carbamates ∴ shorter T ½
- Thiophosphates (***parathion, malathion***) req activation in body (fast - 150 μs)
- Some organophosphate insecticides (***malathion***) metabolise fast in mammals and birds but not insects ∴ safe (***parathion*** does not metabolise fast in mammals)

Mechanisms of Action

- AChE main target, ***butyrlcholinesterase*** also inhibited
- 2 step process: 1. ACh binds AChE active site & hydrolysed ⇒ Acetyl + Choline
  2. AChE covalent bond split ⇒ H_2O + AChE

1. *Quaternary Alcohols*
   - Reversibly bind & electrostatically by hydrogen bonds on active sites
   - Since no covalent bonding = short lived (2-10 min)
2. *Carbamic Esters*
   - Binds AChE & undergoes 2 step metabolism like ACh
   - Esters covalently bound ∴ step 2 (hydrolysis) prolonged ∴ action is 30 min - 6 hrs
3. *Organophosphates*
   - Binds AChE & also undergoes 2 step metabolism like ACh & Carbamic Esters
   - Hydrolysis leads to phosphorylation of active site (slow process – hundreds of hours)
   - After 1st binding-hydrolysis step, may undergo ***ageing*** (strengthening of phosphors-enzyme bond = longer duration of action)

Pharmacodynamics: organs

CNS

- Alerting in low concentrations
- Convulsions in large +/- coma +/- resp arrest

Eyes, Respiratory, GI, GUT

- Same as direct acting cholinomimetics

CVS

- ↑ Para/sympathetic ganglia
- Parasympathetics > Sympathetic
  ∴ -ve inotropic & chronotropic & dromotropic ⇒ ↓ CO
- Lesser effects on vascular smooth muscle vs direct acting muscurinic
- Net effect: *Modest brady, ↓CO, no change/slight fall in BP*
  Larger doses = marked brady & hypotension

NMJ

- ↑ strength of contraction | Fibrillation at high concentrations
- Depolarizing neuromuscular blockade at highest doses followed by non-depolarising phase
  eg ***suxamethonium***
- Some carbamates eg ***neostigmine*** also are nicotinic agonists (good for myasthenia)

Clinical Use

Overview

- Eye: ***glaucoma***, accommodative esotropia
- GI & GUT: post op atony, ***neurogenic bladder***, congenital megacolon
- NMJ: ***Myasthenia***, curare induced muscular paralysis
- Heart (rarely): Atrial arrhythmias
- Overdose: ***Atropine***

Eye

- ↓ IOP by contraction of ciliary body NB ***β-blockers*** or ***PG derivatives*** now used for chronic
- Acute angle glaucoma = combination therapy eg ***Pilocarpine*** + ***Physostigmine***

GI & GUT

- ***Bethanechol*** most common drug used (10-25mg TDS) or
- ***Neostigmine*** (0.5-1mg s/c or 15mg oral)
- ***Pilocarpine***: ↑ salivary secretions (eg ***Sjogren's***)

NMJ

- ***Myasthenia*** = autoimmune block of nicotinic receptors
  ∴ Cholinesterase inhibitors (not direct acting cholinomimetics) help
- ***Edrophonium*** used for diagnosis (2mg IV, test muscle strength, 8mg IV after 45s & retest, +ve = muscle strength for 5 minutes)
- Side effects; muscurinic (abdo cramps, diarrhoea, salivation, bronchial secretions, miosis, bradycardia) Tx with ***atropine*** as tolerated

Heart

- Paradoxical SVT (***adenosine*** now used)

Antimuscarinic Drug Intoxication

- ***Atropine*** & ***TCA*** offer competitive blocking of M receptors ∴ AChE inhibitors can reverse
- ***Physostigmine*** used but can accentuate arrhythmia/CNS effects

CNS

- ***Tacrine*** has both anticholinesterase and other Cholinomimetic actions
- Used in Alzheimer's but hepatic toxicity significant

TOXICITY

Direct acting muscarinic stimulants

- Nausea, vomiting, diarrhoea, urinary urgency, salivation, sweating, cutaneous vasodilation, bronchial constriction (mushroom toxicity mimics)
- ***Atropine*** reverses

Direct acting nicotinic stimulants

- Fatal dose = 40mg (2 cigarettes)
- CNS stimulation, end plate depolarization, HTN, arrhythmias, addiction, vasc path, ulcers
- Tx with ***atropine*** for peripheral and ***diazepam*** for central targets
- End plate not responsive to pharmacology
- Nicotine metabolised & excreted quickly therefore if > 4 hrs better outcome

Cholinesterase Inhibitors

- Major source: pesticides
- Muscarinic excess:

  "SLUDGEM"

  salivation/sweating/seizures, lacrimation, urination, defecation (sphincter relaxation), GI upset (including diarrhoea), Emesis, Meiosis & Muscle Spasm
- Tx: decontaminate, atropine

3. ANTICHOLINERGICS

- ***Muscarinic*** (1-5) vs ***Nicotinic*** (N_1 = ganglionic, N_2 = NMJ)

Source & Chemistry
- ***Atropine*** & ***Scopolamine*** both presented as racemic (L-isomers 100x potent as D-)

Absorption
- Natural alkaloids: Well absorbed from *gut, conjunctiva* & *dermal*
- Quaternary Antimuscarinic: 10-30% absorption

Distribution
- Tertiary agents (incl ***atropine***) widely distributed incl ***Sig CNS levels after 30min – 1hr***
- ***Scopolamine*** has greater effects in CNS
- Quaternary derivatives poorly taken by CNS

Metabolism & Excretion
- ***Atropine***: 60% unchanged in urine, T ½ 2 hrs, *iris effects persist > 72 hrs*

Pharmacodynamics

A. Mechanism of Action
- ***Atropine***: reversible blockade ⇒ ↓ IP_3 & ↓ adenyl cyclase
- Tissues most sensitive: *salivary, bronchial, sweat glands*
  least sensitive: *gastric acid secretion*
- Block exogenous Ach better then endogenous
- Highly selective for M vs N but not selective within M1,2,3 (synth more selective)

B. Organ System Effects

1. CNS
- ***Atropine*** has *minimal effects*: slower longer lasting sedation
- ***Scopolamine:*** Drowsiness, amnesia at normal/mod doses, excitation, agitation, Hallucination, coma at toxic levels
- Parkinson's tremor due to relative ↑ Ach (due to ↓ dopaminergic activity in basal ganglia-striatum) ∴ combining antimuscarinic with dopamine agonist effective
- Corrects ***vestibular disturbance***

2. Eye
- ***Mydriasis*** (due to unopposed sympathetic stimulation)
- ***Cycloplegia*** = loss of ability to accommodate (mainly near vision)
- ↓ Lacrimal secretions
- Can ***induce acute angle glaucoma***

3. CVS
- SA & AV node sensitive to M2 blockade ⇒ unopposed symp drive ⇒ ↑ HR & ↓ ecg P-R seg
- At low doses ***atropine*** has an initial ↓ HR 2ry to prejunctional M1 on vagal post Ganglionics
- Atrial contraction ↓ (only useful in ***AF, flutter***) with little muscarinic input in ventricles
- Blocks parasympathetic coronary dilation & sympth cholinergic skeletal muscle bed dilation

4. Respiratory
- Bronchodilation, ↓ secretions
- Antimuscurinics not as useful as ***β-agonists***

5. GIT
- Better with exogenous muscurinic stimulants (local hormonal control, feedback)
- ↓ salivation, gastric secretions (pan & intestinal mostly hormonal ∴ minimal effect), gastric emptying, motility
- ***Pirenzepine*** most useful since M3 selective

6. GUT
- Relaxes uterus (minimal) & bladder, slows voiding to the point of ***urinary retention in BPH***

7. Sweat Glands
- "***Atropine Fever***": ↓ thermoregulatory sweating ⇒ ↑ body temp

Clinical Pharmacology

A. CNS

1. Parkinson's
- Antimuscurinics only as an adjunct to ***dopamine agonists***

2. Motion Sickness
- ***Scopolamine*** | IM IV, PO, TOP | Sedation & dry mouth at therapeutic doses

B. Ophthalmic Disorders
- Long acting potential benefit in children (short acting used in adults)
- ***Glycopyrrolate*** (quart agent) just as good as ***atropine***
- Ointment better as less lost through Lacrimal duct

C. Respiratory Disorders
- Previously used when ***ether*** was anaesthetic (produced lots of secretions)
- ***Asthma*** caused by vagal firing on muscurinic bronchial smooth muscle
- ***Ipratropium*** (atropine analog) inhaled, ***tiotropium*** is once a day preparation

D. CVS
- MI can sometimes ⇒ ↓ SA or AV node function (via reflex vagal discharge)
- Hypersensitive carotid sinus reflex can also benefit from antimuscurinics

E. GIT
- Rarely used for ***PUD*** | Travellers' diarrhoea: ***Lomotil*** = atropine & ***diphenoxylate*** (slows intestinal motility via opioid receptors)

F. GUT
- Urinary urgency | M3 (directly) & M2 (via nor/epinephrine inhibition)
- M2 acts indirectly by inhibiting relaxation by nor/epinephrine
- ***Oxybutynin*** (M3 selective) used in urology to prevent spasm post op
  Darifenacin & ***Solifenacin*** are more selective & ***Trospium*** (unselective)

G. Cholinergic Poisoning in…

1. Antimuscurinic Therapy
- No effective method of blocking cholinesterase inhibitors (esp on N receptors)
- Tertiary amine required to reverse effects of cholinomimetics incl ***organophosphates***
- ***Atropine*** is 1st choice 1-2mg q5-15min (up to 1g/day up to 1 month)

2. Cholinesterase Regenerator Compounds
- ***Pralidoxime***, ***Diacetylmonoxime***
- High affinity for phosphorus atom ⇒ hydrolyse phosphorylated enzyme (if not aged)
- ***Pralidoxime*** doesn't cross BBB ∴ effects seen in NMJ not in CNS, 1-2g over 15min
  **not useful if AChE inhibited by carbamates inhibitors*
- ***Diacetylmonoxime*** crosses BBB

3. Pre-treatment with Reversible Enzyme Inhibitors
- ***Pyridostigmine*** or ***Physostigmine*** | Simultaneous atropine used
- Used prophylactically eg in chemical warfare to "reserve" AChE

4. Tx Mushroom Poisoning
- Rapid vs delayed (6-12 hrs) onset
- ***A Muscaria***: antimuscarinic effects > muscurine
- ***Inocybe***: muscurine effects predominate, rapid
- ***Atropine*** used for muscurine dominant effects
- Major toxicity: hepatic & renal cell injury by ***amatoxins*** inhibiting RNA polymerase

H. Other applications
- ***Hyperhidrosis*** (excess sweating)

Adverse Effects
- ***Atropine*** relatively safe drug in adults (not in kids) | Side effect profile from systemic effects

"Dry as a Bone, Mad as a Hatter, Hot as a Hare, Red as a Beet, Blind as a Bat"

Dry mouth, Hallucinations/Agitation/Delirium, peripheral thermoregulatory inhibition/hot flushed skin, Mydriasis/Cycloplegia

Contraindications
- Obvious muscurine excess treated with atropine
- Antimuscurinics contraindicated in ***glaucoma***
- Avoided in ***prostate hyperplasia***
- ***PUD***

Ganglion-Blocking Drugs
- Block ACh on N receptors in para/sympth ganglia (some also block ion channel)
- Limited clinical use due to ***lack of specificity***

Chemistry & Pharmacokinetics
- All are synthetic amines

Pharmacodynamics

A. Mechanism
- Depolarizing or non-depolarizing blockade
- Depolarizing: ***nicotine***, ***carbamoylcholine***, ***ACh***
- ***Hexamethonium*** inhibits via ion channel | ***Trimethaphan*** blocks N receptor

B. Organ Effects

1. CNS
- ***Mecamylamine*** crosses BBB ⇒ Sedation, tremor, choreiform movements, mental change

2. Eye
- ***Cycloplegia*** (loss of ciliary action ie accommodation)
- Moderate ***Mydriasis*** (parasympathetics usually dominate)

3. CVS
- ↓ vascular resistance, chronotropy, +ve inotropy, Orthostatic hypotension

4. GIT
- ↓ secretions, motility (***profound***)

5. Other
- Hesitancy in urination +/- retention
- Sexual dysfunction
- ↓ thermoregulation

6. Response to Autonomic Drugs
- Exaggerated response or reversed (eg norepinephrine causes a tachycardia)
- Due to lack of normal reflexes

SECTION II: AUTONOMIC DRUGS

4. SYMPATHOMIMETICS

Modes of Action

- Direct
- Indirect: 1. Displacement of stored Catecholmines (*amphetamines*, *tyramine*)
  2. Inhibiting reuptake of Catecholmines (*Cocaine* & *TCAs*)
  *Some drugs have both effects

Pharmacology

> *α | Epinephrine ≥ norepinephrine >> isoproterenol (isoprenaline)*
> *β | Isoproterenol > epinephrine ≥ norepinephrine*

A. Alpha Adrenoceptors

- *α1A, B, D* (unknown inter-variable difference) | *α2A, B, C*

B. Beta Adrenoreceptors

- All ↑ cAMP
- β-non selective | Agonist: *Isoproterenol*
- β1 | epinephrine = norepinephrine | Agonists: *dobutamine*
- β2| epinephrine > norepinephrine | Agonist: *Albuterol*

C. Dopamine Receptors

- Important in brain, Splanchnic, renal vascular
- D1-5: D1-like: *D1, 5* | D2-like: *D2-4* *subtypes important in antipsychotic drugs

Receptor Selectivity

- Selectivity not usually absolute eg norepinephrine preferentially activates β1 vs β2

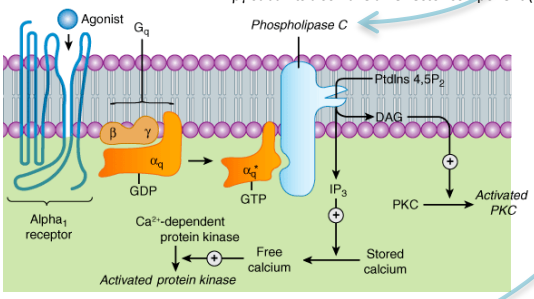
Overview of Molecular Mechanisms of Sympathomimetics

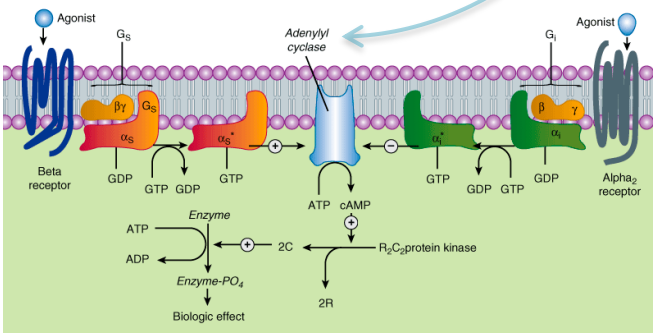
- Adrenoceptors are G protein coupled receptors
- G proteins have α, β & γ subunits *(α subunit determines G protein types)*
- G proteins on Adrenoreceptors;

> Gs | adenylcyclase stimulation
> Gi | adenylcyclase inhibition
> Gq | couples α receptor to PLC

- Mechanism:
  1. Receptor activation ⇒ GDP dissociation from α subunit
  2. GTP binds to α subunit
  3. α≡GTP complex dissociated from G-protein
  4. α≡GTP ⇒ effectors including: a. adenyl cyclase
     b. cGMP phosphodiesterases
     c. PLC
     d. ion channels
  5. α *inactivation* by GTP → GDP + phosphate & α reintegration to βγ

  NB βγ subunits also have an effector component (mostly ion ch)





Specific Receptor Mechanisms

A. Alpha Receptors

- α1; Couples Gq to PLC —+→ DAG & IP_3
  IP3 → release of stored Ca → ↑ [intracellular] —+→ PKC → effect
  DAG —+→ PKC
- α2; inhibit adenyl cyclase →↓ intracellular cAMP via Gi Protein
  Also utilises other signalling pathways (incl ion ch & enzymes)

B. Beta Receptors

- Same receptor mechanism as α2 but *stimulate* Adenyl cyclase production via G_S
  ∴ ATP → cAMP ⇒ activation of protein kinases (different effect in different tissues)

C. Dopamine Receptors

- D1 associated with adenyl cyclase (effect also via ion channels or enzymes)

Receptor Regulation

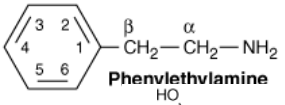
- Multiple factors regulating receptor expression on membranes incl *concentration of catecholamines, hormones, other drugs, age, diseases*

  Multiple mechanisms in process:
  - Transcription, translation, critical covalent modification
  - *Phosphorylation* of receptor enhances their affinity for *β-arrestins* ⇒ endocytosis

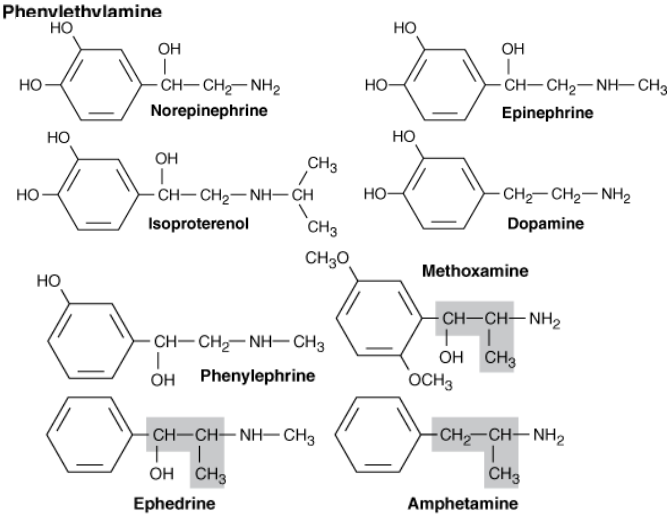
  Desensitization; ↓ response with chronic exposure to Catecholamines/Sympathomimetics

  2 types:
  1. *Homologous:* Loss of responsiveness to receptors exposed to original catecholamine
  2. *Heterologous:*
     - Loss of responsiveness of other cell surface receptors not directly activated
     - 2nd messenger; cAMP —+→ PKA ⇒ phosphorylation of any structurally similar receptor

Chemistry & Pharmacokinetics of Sympathomimetics



- *Phenylethylamine* is parent drug:
  Benzene ring +Ethylamine side chain



Substitutions at:

1. *Terminal amino group*
   - ↑ amino group side = ↑ β affinity
   - Very large amino side chains = β2 selective
   - Eg *epinephrine* has higher affinity than norepi
2. *Benzene ring with Catecholmines*
   - Potency dramatically reduced if one –OH removed (esp C3 position)
   - Catecholmines subjected to inactivation by COMT (found in gut & liver)
     ∴ Absence of –OH ↑ bioavailability & access to CNS
   - Eg *amphetamines* have higher bioavailability and CNS activity vs catecholamines
3. *α carbons*
   - Substitution at α blocks MAO oxidation ∴ prolongs action
   - Some also have enhanced ability to displace catecholamines from storage site in noradrenergic nerves (ie indirectly acting sympathomimetics)
4. *β Carbon*
   - Direct acting agonists have a β hydroxyl group
   - Important for storage of sympathomimetics amines in neural vesicles

Organ System Effects of Sympathomimetic Drugs

Type	Tissue	Actions
α1	Vascular Smooth Muscle incl cutaneous, upper airway, splanchnic	Constriction
	Pupillary Dilator	Mydriasis (↓ IOP)
	Pilomotor	Erect hair
	Bladders (base)	Contraction
	Prostate	Contraction/Ejaculation
	Heart	+ve chronotropy
α2	Post synaptic CNS	Central mediated hypotension
	Platelets	Aggregation
	Adrenergic/cholinergic nerves	Inhibit release
	Lipids	Inhibit lipolysis
	Metabolic	Inhibit insulin & renin secretion
β1	Heart	+ve chronotropy[1] & inotropy
β2	Lungs, Uterus, Gut, Vascular, Skel[2]	Relaxation
	Bladder & Gut (wall)	Relaxation
	Skeletal Muscle	K uptake
	Liver	Glycogenolysis
	Eye	Aqu production, Slight ciliary relaxation
	Metabolic	Promote insulin & renin secretion
β3	Lipids	Lipolysis
D1	Renal, Cerebral, Splanchnic, Coronary	Dilation
D2	Nerve endings	Modulate transmitter release

[1]HR dominated by BP reflexes if pathway preserved

[2]Endogenous β2 activation responsible for skeletal muscle bed dilation during exercise

Specific Sympathomimetic Drugs

Mixed α & β agonists

Epinephrine

$\beta_1 = \beta_2$	potent vasoconstrictor/cardiac stimulator
$\alpha_1 = \alpha_2$	+ve inotropic, chronotropic
	Skeletal muscle bed vasodilation (eg in exercise)
	Peripheral vasoconstriction
	Overall = TPR maintained or fall

Norepinephrine

$\beta_1 >> \beta_2$	potent vasoconstrictor/cardiac stimulator
$\alpha_1 = \alpha_2$	+ve inotropic, chronotropic
	Peripheral vasoconstriction
No β_2 agonism	No overall rise in BP
	Vagal reflexes > direct chronotropic effect but +ve inotropy persists

β agonists

Isoproterenol

$\beta_1 = \beta_2 >>>> \alpha$	+ve chronotropic & inotropic
	potent peripheral vasodilator
Minor α effect	Overall: ↑ CO ↓ diastolic p ↓ MAP, slight ↓ systolic p

Dobutamine

$\beta_1 > \beta_2 >>>> \alpha$	+ve chronotropic & inotropic
	Minimal peripheral dilation (no β_2 effects)
Minor α effects	*+ isomer β1 agonist but α1 antagonist*
	– ve isomer potent α1 agonist

Metaraminol

$\beta_2 > \beta_1 >>>> \alpha$	Potent vasopressor activity

Ephidrine

β agonist	High bioavailability, long duration of action (hours)
	Sig amount excreted in urine unchanged (accelerated by acidic urine)
	Nasal Decongestant but restricted due to manufacturing abuse

α agonists

Phenylephrine, Methoxamine

	Not catecholamine ∴ no COMT breakdown = longer duration of action
$\alpha_1 > \alpha_2 >>>>> \beta$	Uses: mydriasis, decongestant, HTN

Clonidine

$\alpha_2 > \alpha_1 >>>>> \beta$	HTN, Diarrhoea in diabetic autonomic neuropathy

Midodrine

α_1 predominantly	Prodrug broken down to *desglymidodrine*
	Peak concentration 1hr
	Clinical use: postural hypotension

Xylometazoline
Oxymetazolinea

α agonists	Topical nasal decongestant

Dopamine Antagonists

Dopamine

$D_1 = D_2 >> \beta >> \alpha$	Vasodilation of renal, brain, coronary, splanchnic vasculature
	D_2 contributes somewhat to D_1 effect but not known how much

Fenoldopam

$D_1 >> D_2$	Peripheral vasodilation

Other Sympathomimetics

Cocaine	LA with peripheral sympathomimetic actions (inhibit ACh reuptake)
	Readily enters CNS (inhibit dopamine reuptake)
	Shorter, more intense then amphetamines
Amphetamine	Promotes release of catecholamines
	CNS stimulant
	Metamphetamines (ephidrine derived) has a higher CNS:PNS
Tyramine	Normal by-product of tyrosine metabolism
	High 1st pass metabolism via MAO metabolism in liver
	Parenteral administration ⇒ release of stored catecholamines

Clinical Pharmacology

CVS

A. Enhanced Flow or BP (by central redistribution)

- Used to preserve tissue perfusion
- Direct α agonists (norepinephrine, Phenylephrine, Methoxamine) for short term in shock
- Chronic orthostatic hypotension; oral Ephidrine, Midodrine

B. Reduce Flow or BP (directly)

- Used for haemostasis in surgery, epistaxis, decongestion
- α receptors main target
- Epinephrine in epistaxis (or cocaine)

C. Cardiac

- Isoproterenol or epinephrine in complete HB or cardiac arrest
- Redistributes flow to heart and brain
- Heart failure (tolerance prevents long term use)

Pulmonary

- Bronchial asthma
- β2-selective via inhaler to prevent systemic effects

Anaphylaxis

- IgE mediated reactions cause: bronchospasm, mucous congestion, angioedema, severe hypotension
- Responds to ephidrine (0.3-0.5mg) since it agonises; α, β1, β2
- Glucocorticoids and antihistamines also used as adjuvant

Ophthalmic

- Phenylephrine = mydriatic
- Localise Horner's (pre or post ganglionic)
  - Localised lesion in nerve degenerates distal portion (distal neuron remains intact)
  - Indirectly acting sympathomimetics will work for preganglionic lesions
  - Eg cocaine or hydroxyamphetamines
- Glaucoma

GUT

- Ritodrine & Terbutaline inhibit uterine contraction
- β2 selective

CNS

- Amphetamines are mood elevating, alerting, insomniac
- Modafinil in narcolepsy
- ADHD

Other

- Clonidine (α2 agonist) in HTN, diarrhoea in diabetics with autonomic neuropathy
- Diminish cravings from alcohol & nicotine, menopausal flushing

Toxicity

- Extension of pharmacological effects; Elevated BP, tachycardia, cardiac work ⇒ failure
- CNS: convulsions, coma

SECTION II: AUTONOMIC DRUGS

5. ADRENOCEPTOR ANTAGONIST DRUGS

- α non-selective blockade in ***Pheochromocytoma***
- α_1 blockade in ***HTN, BPH***
- β blockade in ***HTN, IHD, Arrhythmias, Glaucoma*** etc

Alpha Receptor Antagonists

Pharmacology of Alpha Receptor Antagonists

Mechanism

Reversible (***phentolamine, prazosin***)
- Sufficiently high agonist can reverse

Irreversible (***phenoxybenzamine***)
- Effects can outlast the drug since receptor regeneration required to regain fcn (days)

Pharmacological Effects

A. CVS
- α receptor antagonists ***prevent peripheral vasoconstriction***
- "***epinephrine reversal***" turning a pressor into depressor since it has both α & β effects
  ∴ Overall response = β mediated skeletal bed vasodilation ⇒ ↓ BP

B. Other
- Miosis, Nasal stuffiness
- α1 blockade decreases resistance to urine flow at base of bladder & prostate

Specific Agents

Phentolamine
$\alpha_1 = \alpha_2$
5HT, M, H1 &2 (minor)
↓ PVR + Reflexive tachycardia
Enhanced release of norepi from sympathetic nerves (α_2 blockade)
Limited oral absorption | T ½ 5-7 hrs | Peak concentration 1 hr
Used in ***intra operative Pheochromocytoma***

Phenoxybenzamine
$\alpha_1 > \alpha_2$
5HT, H1
Covalent bonding = long duration of action (14-48 hrs)
Inhibits norepinephrine re uptake
↓ BP with high sympathetic tone (no Δin normal patient)
Oral (< 100mg/d) low bioavailability
Used in ***Tx Pheochromocytoma***
Adverse; postural hypotension, reflex tachycardia, nonspecific CNS effects

Prazosin
$\alpha_1 >>>>> \alpha_2$
↓ BP without tachycardia (miniscule α2 effects)
Relaxation of venous/arterial/prostate smooth muscle
50% bioavailability | T ½ 3 hrs

Terasozin, Doxazosin
$\alpha_1 >>>>> \alpha_2$
Tamsulosin
$\alpha_{1A} >>>>> \alpha_2$
Used in ***BPH*** with urinary symptoms or ***HTN***
High bioavailability | Liver Metabolism | T ½ 9-12 hrs (Ter) 22 hrs (Dox)

Prostate specific (vs vascular smooth muscle) via ***α1A***
Less effect in postural changes | T ½ 9-12 hrs

Other Agents

Alfuzosin
α1 antagonist
Indoramin
BPH | 60% bioavailability T ½ 5 hrs

HTN

Urapidil
α_1 antagonist
HTN & BPH

Labetalol
α1 & β
See *"Beta Blockers"*

Clinical Pharmacology of Alpha Receptor Antagonists

Pheochromocytoma
- ***Phenoxybenzamine*** & ***Phentolamine***
- Nor/epinephrine secreting tumour ⇒ ***HTN, headaches, Palpitations, Sweating***
- Intraopertively can cause catecholamine excess ∴ use ***phentolamine*** or ***nitroprusside***
- Sometimes use ***phenoxybenzamine*** to control ***BP 1-3 weeks pre op***
- Persistent symptoms with α blockade benefit from β blockade or Ca ch inhibitors
- ***Metyrosine*** is a competitive inhibitor of tyrosine hydroxylase ⇒ ↓ synth of dopamine, nor/epinephrine. Particularly useful in ***non-operable pheo***

Hypertensive Emergencies
- Limited value

Chronic HTN
- ***Prazosin*** (α_1-antagonist) good in treating ***mild/moderate HTN***
- Questionable value in HF on own (***ALLHAT study***)
- Major adverse effect; postural hypotension

Peripheral Vascular Disease
- May be used in severe ***Reynaud's*** (no clinical data)

Local vasoconstrictor Excess
- ***Phentolamine*** reverses accidental adrenergic eg LA + adrenaline or tissued cannula running adrenaline

Urinary Obstruction
- ***Prazosin***, ***Doxazosin***, ***Terasozin***
- α_1 blocker; outflow relaxation (probably 1A subtype)
- Adverse effects; postural hypotension

Erectile Dysfunction
- ***Phentolamine*** + ***Papaverine*** (non-specific smooth muscle relaxant)
- Adverse effects; fibrotic reactions, orthostatic hypotension, priapism
- Other Tx better; ***PG inhibitors, cGMP inhibitors***

α2 Antagonists
- Little clinical use
- Theoretical benefit in ***Reynaud's, T2DM*** (inhibit insulin secretion), depression

Beta Receptor Antagonists

Clinical Pharmacology of Beta Receptor Antagonists
- ***Pure β blockers***
- ***Partial β blockers*** (antagonist effect with low levels of catecholamines and vice-versa)
  - Limited clinical value (perhaps if too bradycardic or bronconcosntrictive with pure)
- ***Inverse agonists***; reduce β receptor activity

Pharmacokinetics of β receptor antagonists

A. Absorption
- Good | Peak concentration 1-3 hrs | SR formula exist for ***propranolol*** and ***metoprolol***

B. Bioavailability
- ***Propranolol*** & ***Metoprolol*** undergoes extensive 1st pass metabolism (P450) ∴ low BioAv
- Higher doses ⇒ hepatic saturation ⇒ ↑ plasma concentration

C. Distribution & Clearance
- Rapidly distributed
- ***Propanolol*** & ***penbutalol*** are lipophilic ∴ ***cross BBB***
- T ½ 3-10 hrs (esmolol T ½ 10 min) ***Nadolol*** longest T ½
- ***Atenalol***, ***celiprolol***, ***pindolol*** less extensively metabolised

Pharmacodynamics of β receptor antagonists

A. CVS
- Used in Angina & HF
- Suppression of renin-angiotensin system via β1
- -ve Inotropic & chronotropic effects without hypotension in normal reflexive people
- AV nodal slowing & PR elongation
- Skeletal muscle vessel constriction ⇒ ↑ PVR (↓with chronic use unknown why)

B. Respiratory
- ↑ Airway resistance via β_2 on smooth muscle
- β_1 selective antagonists (***Metoprolol, Atenalol***) better if asthma/copd etc

C. Effects on the Eye
- ↓ IOP (via ↓ production)

D. Metabolic/Endocrine
- Inhibit sympathetic stimulation of ***lipolysis***
- Partial inhibition of liver glycogenolysis (via β_2 receptors) ∴ use cautiously in IDDM
- Unfavourable chol profile (↑VLDL ↓HDL)

Specific Agents

Non-Selective Blockers

Propranolol β1,2 blocker	Dose dependant BioAv
Nadolol β1,2 blocker	Long duration of action
Timolol β1,2 blocker	For glaucoma
Labetalol SR isomer ***α1 block*** RR isomer β1,2 blocker	Potent (less so then phentolamine or propranolol)
Carvedilol β1,2 blocker + α1 blocker β > α	T ½ 6-8 hrs, extensively metabolised in liver Inhibit smooth muscle mitogenesis, attenuate lipid peroxidation

Selective Blockers

Metoprolol, Atenolol β1 blocker	Safer in those with ***bronchoconstrictive*** effects to ***propranolol*** Caution in asthmatics, benefits > Risks in COPD Also better in IDDM, PVD
Levobunonol, Betaxolol β1 blocker	Ocular preparation for ↓ IOP
Esmolol β_1 blocker	***Ultra short acting*** (esterases in blood metabolise quickly) T ½ 10 min For; SVT, Thyrotoxic arrhythmias, perioperative hypertension, MI

Partial Antagonists

Pindolol, Acebutolol, Carteolol, Bopindolol, Oxprenolol, Celiprolol, Penbutolol	Partial β agonists HTN, Angina, less ***likely to cause bradycardia*** Or other beta antagonist adverse effects

Clinical Pharmacology of β Blockers

HTN

- Often used with ***adjuvant diuretics or vasodilator***
- Despite short T ½ can be OD or BD and have effect

IHD

- ↓ Fq angina ↑ exercise tolerance due to ↓ cardiac work (∴ O_2 demand)
- ***Propranolol*** or ***Metoprolol*** prolongs survival (partly due to arrhythmia suppression)
- Useful in acute setting
- Contraindications; LV failure, airway disease, hypotension, shock, heart block

Arrhythmias

- SVT & some ventricular arrhythmias
- Arrhythmia suppression may contribute to prolonged survival post MI
- Survival by ***↑AV nodal refractory period*** (esp in AF & Fibrillation)
- ↓ ventricular ectopics precipitated by catecholamines
- ***Sotalol*** also has ***ion channel blockade***

Heart Failure

- ***Metoprolol***, ***Bisoprolol***, ***Carvedilol***
- Worsens acute CHF but prolongs survival
- Theoretical benefit in ***myocardial remodelling***

Other CV

- ↑ SV in ***obstructive cardiomyopathy*** by slowing ventricular ejection & ↓ outflow resistance
- Used in ***dissecting aortic aneurysms*** (↓ systolic pressure)

Glaucoma

- Prevent ciliary body production of aq humour via activated cAMP
- ***Timolol*** doesn't have local anaesthetic effects ∴ useful as topical
- β-blockers have same efficacy as ***Epinephrine*** & ***Pilocarpine*** but better tolerated
- ***NB max ocular dose is 1mg, can interact with systemic verapamil ⇒ HB***
- ***Betaxolol*** is β_1 selective

Hyperthyroidism

- Causes excess catecholamine action
- β blockade acts on Adrenoreceptors as well as ***Thyroxine to Triiodothyronine***
- ***Propanolol*** used in ***thyroid storm*** to control tachycardia

Neurological Diseases

- Migraine and headaches
- Stop ***peripheral tremors*** | Somatic manifestations of anxiety
- ***Propanolol*** in alcohol withdrawal (symptomatic tx)

Misc

- ↓ Portal vein pressure in cirrhosis
- ↓ first incidence of ***oesophageal varices bleed***
- ***Nadolol*** + ***Isosorbide mononitrate*** more efficacious than sclerotherapy in preventing re-bleed
- Variceal banding + β-blocker even more efficacious

Toxicity of Beta Blockers

- Minor; rash, fever, drug allergy
- CNS; sedation, sleep disturbance, depression
  Use high lipid soluble drugs (***Nadolol, atenolol***)
- Major; airways, severe PVD, severe LV dysfunction, hypoglycaemia in IDDM

Drugs for Glaucoma

Cholinomimetics*	Ciliary muscle contraction
Pilocarpine, Carbachol, Physostigmine, Echothiophate, demecarium	Opening trabeculae network Increased outflow
PG	
Latanoprost, Bimatoprost, travoprost, unoprostone	Increased outflow
Alpha Agonists (unselective)	
Epinephrine, dipivefrin	Increased outflow
Alpha Agonists (alpha 2)	
Apraclonidine, Brimonidine	Decreased aq secretion
Beta Blockers	
Timolol, Betaxolol, carteolol, levobunolol, metipranolol	Decreased aq secretion
Diuretics*	
Dorzolamide, brinzolamide	Decreased aq secretion through lack of HCO_3
Acetazolamide*, dichlorphenamide, Methazolamide	

*used in acute angle glaucoma due to rate of onset

SECTION III: CARDIOVASCULAR-RENAL

1. ANTIHYPERTENSIVES

Aetiology

- 85% essential (↑ resistance with normal CO) with 30% heritability
- Other: ***renal artery constriction, coarctation, Pheo, Cushing's, 1ry Aldosteronism***
- Hypertensive patients have *normal reflexes* but an ***inherently higher set baroreceptor & renal blood volume-pressure control system***

Type	Baroreflex	Renin-Angiotensin
Onset	Rapid	Long Term Adjustment
Target	Vascular Smooth Muscle	Circulating Volume
Mech	1. Baroreceptors lose stretch 2. Central Inhibition (NTS & Vasomotor centres) 3. Peripheral Vasoconstriction	1. ↓ Perfusion (or β stimulation) 2. ↑ renin secretion ⇒⇒⇒ ↑ ATII 3. Resistant vessel constriction or Aldosterone synth (↑ Na retention) NB vasopressin release also

Basic Pharmacology of Antihypertensive Agents

Target		Examples
Sympathoplegics	Central (Vasomotor)	***Methyldopa, Clonidine***
	β blockade in heart or JGA	***Propranolol***
	α blockade on vessels	***Prazosin***
Direct Vasodilators	Vascular Smooth Muscle	***Hydralazine, Minoxidil, Nitroprusside, Diazoxide Verapamil, Fenoldopam***
Diuretics	Kidney Tubules	***Thiazides***
Angiotensin Blockers	↓ Intravascular volume	***Losartan***

1. Drugs That Alter Na & H_2O Balance

Mechanism

- Na ↑ PVR by ↑ vessel stiffness & neural reactivity by ***↑Na-Ca exchange*** ⇒ ↑ intracellular Ca
- Diuretics ↓ circulating Na
  - Acutely ↓ circulating volume & ↓ CO
  - After 6-8 wks CO normalises & ***↓PVR*** = ↓ BP 10-15 mmHg
- Good ***monotherapy in mild hypertension***
- Severe hypertension requires polypharmacy (sympathoplegics or vasodilators)
- Other non Na effects;
  - ***Indapamide*** has direct vasodilating effects
  - ***Amiloride*** inhibits smooth muscle response to contractile stimulation

Use of Diuretics

- ***Thiazides*** appropriate for ***mild/moderate HTN*** (with normal renal & cardiac fcn)
- ***Loops*** more potent ∴ used in ***severe HT***, GFR < 30, Disease states with ***Na retention*** (Cardiac failure, cirrhosis)
- ***K Sparing*** used when digitalis is used, or to enhance natriuretic effect of diuretics
- Dosing: Thiazides more natriuretic at higher does without change to BP
  Loops continue to ↑ BP response at higher doses

Toxicity

- Hypokalaemia (∴ contraindicated in digitalis patients, arrhythmias, AMI, LV dysfunction)
- Since K secretion coupled to Na, ↓ Na intake = ↓ hypokalemic effect
- Other effects: Mg depletion, impaired glc tolerance, hyperlipidaemia, precipitate gout, RCC, hyperkalemia (in K sparing)

Drugs That Alter Sympathetic Nervous System Function

1. CNS

- ***↓sympathetic*** outflow but ***retain or accentuate baroreflex***

Methyldopa

- Methyldopa → α-methyldopamine → α-methylnorepinephrine → stored in presynaptic adrenergic vesicles ∴ ***acts as a "false" transmitter*** for nor/adrenaline
- ***Stimulating α-receptors (α_2 >>> α_1) in medulla*** ⇒ *↓HR ↓BP ↓renal vascular resistance*

Pharmacokinetics & Dosage

- T ½ 2hrs | BioAv25% | Initial 1g/day Maintenance 1-2g/day | Dose-response limited
- Onset of action 4-6 hrs | sustained for 24 hrs
- Enters brain via aromatic amino acid transporter

Additional Toxicities

- ***+ve coombs test*** (10-20% > 12 month use), haemolytic anaemia, hepatitis, drug fever

Clonidine

- Central & Peripheral actions
  - Peripheral: brief ↑ BP from direct α1 stimulation
  - ***Stimulating α-receptors (α_2 >>> α_1) in medulla*** ⇒ *↓HR ↓BP ↓renal resistance*
    (More potent vs Methyldopa probably by targeting different α2 receptor)

Pharmacokinetics

- T ½ 8-12 hrs | Bioavailability 95% | 0.2mg/day 0.2-1.2mg/day | Lipid soluble
- Dose-response exponential

Toxicity

- Dry mouth, no antihypertensive effect with ***TCA***, ***hypertensive crisis*** with ceased quickly

2. Ganglion Blocking Agents

- ***No longer used*** due to adverse effects; sympathoplegia, parasympathoplegia
- First agent for HTN Tx | Competitively block nicotinic receptors on para/sympth ganglia

3. Adrenergic Antagonists: Blocking Norepinephrine Synthesis/Release

Guanethidine

- Rarely used due to toxic effects: marked postural hypotension, diarrhoea, impaired ejaculation
- Too polar to enter CNS

Mechanism

- Transported into nerve ending via ***NET***
- Concentrated into vesicles, ***displacing norepinephrine*** ⇒ depletion of norepinephrine ∴ ***NET inhibitors block effect*** (***cocaine, amphetamines, TCAs***)
- Early effects: ↓ CO (bradycardia & relaxation of capacitance vessels)
- Late effects: ↓ PVR

Pharmacokinetics & Dosage

- T ½ 5 days Bioavailability 3-50% | 10mg/day 25-50mg/day
- Onset of action days, maximal at 1-2 weeks | Persistent effects long after withdrawal

Toxicity

- ↓ flow to heart & brain | Hypertensive crisis in Pheochromocytoma | No effect with TCAs

Respirine

Mechanism & Site

- ***Inhibits VMAT*** ∴ ACh cant form vesicles for exocytosis
- nonspecific inhibition ∴***nor/epinephrine, dopamine,*** 5HT inhibited CNS & PNS (Peripheral component known to ↓ BP but central component might as well)
- also inhibits adrenal medulla chromaffin granules ⇒ ***depleted catecholamines***
- irreversible effect on adrenergic vesicles, ***bound for days***
- can deplete catecholamine number to zero in high doses

Pharmacokinetics

- T ½ 24-48hr Bioavailability 50% | 0.25mg/day

Toxicity

- Readily enters brain: sedation, depression, parkinsonian
- GIT: diarrhoea, cramps, ↑ gastric secretions
- Effects may be delayed by months

4. Adrenergic Antagonists: Receptor Blockers

Propranolol

- Non-selective β antagonist ∴ prevents reflex tachycardia from vasodilating agents

Mechanism & Site

- ***↓CO*** ⇒ ↓ BP | β1 blockade on adrenals ***prevents renin release***

Pharmacokinetics

- T ½ 3-5hrs BioAv 25% | 80mg/day 80-480mg/day

Toxicity

- Premorbid asthma, bradycardia, arrhythmia, PVD, DM
- Acute withdrawal ⇒ rebound β agonism (supersensitive receptors)

Other β-blockers

1. ***Metoprolol***
   - Equipotent to propranolol at β_1, little β_2 activity ∴ theoretical value in ***asthmatics***
   - T ½ 3-7hrs BioAv 40% | 50-100mg/day 200-400mg/day
2. ***Nadolol, Carteolol, Atenolol, Betaxolol, Bisoprolol***
   - ***Nadolol, Carteolol*** non selective β-blocker
   - ***Atenolol*** β_1 selective blocker, less CNS effects
   - ***Betaxolol, Bisoprolol*** longer T ½
3. ***Pindolol, Acebutolol, Penbutolol***
   - Partial agonists
   - ↓ BP via ↓ vascular resistance (CO, HR less so than others) ∴benefit in ***bradycardic*** patients
4. ***Labetalol & Carvedilol***
   - Overall: ***↓PVR without Δ HR/CO***
   - Particularly useful in ***HTN of pheo or emergency*** (20-80mg bolus)
   - Carvedilol has S(-) & R(+) isomers, both α blockers (equal potency)
5. ***Esmolol***
   - β_1 blocker
   - Quickly metabolised by blood esterases (∴useful in intra-operative HTN, emergency (esp when tachycardia)
   - T ½ 10 min

Prazosin **& Other α1-blockers**

Mechanism

- α_1 blockade on arteries and veins (reflex tachycardia not as marked as nonselective)
- Allows unopposed α_2 stimulation vs nonselective block ⇒ run off β stimulation

Pharmacokinetics

- T ½ 3-4 hrs BioAv 70% | 3mg/day 10-30mg/day

Toxicity

- Initial postural drop (not seen in long term use)
- Other effects minor; dizziness, palpitations, headache, +ve ANA (without clinical sx)
- No change to chol profile

Other Adrenoceptor Blocking Agents

- ***Phentolamine, Phenoxybenzamine*** helpful in Dx/Tx Pheochromocytoma

Toxicity

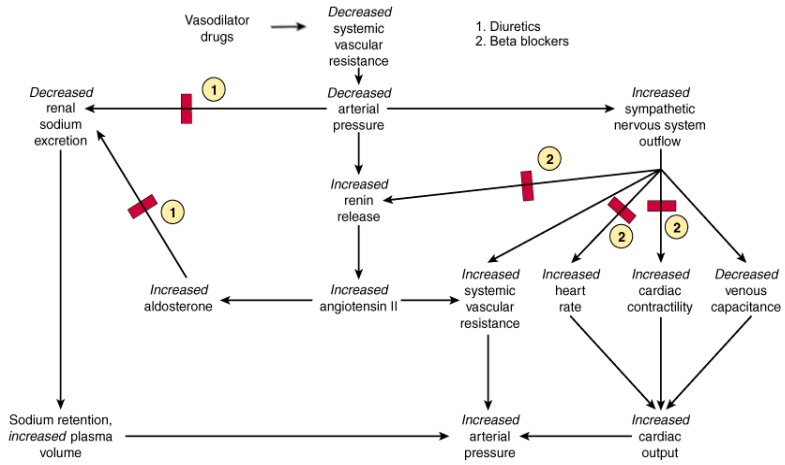
1. CNS: sedation, depression, sleep disturbance, extrapyramidal
2. Autonomic Ganglia: para/sympathetic inhibition
3. Norepinephrine release: postural hypotension, inhibition of ejaculation
4. Postsynaptic block: depends on site

Vasodilators

Mechanism

1. Oral/IV: ***Hydralazine, Minoxidil***
2. IV: ***Nitroprusside, Diazoxide, Fenoldopam***
3. Ca Ch blockers

- Relax smooth muscles of arterioles (***nitroprusside*** also relaxes venules)
- Does not inhibit sympathetic reflex ∴ no orthostatic hypotension/sexual dysfunction
- Best used with other agents to oppose cardiovascular reflex



Hydralazine

- Not normally used in monotherapy due to ***tachyphylaxis***

Pharmacokinetics

- T ½ 1.5-3 hrs BioAv 25%
- Effects last longer than drug concentration (***avid binding of vascular tissue***)

Toxicity

- Reflex tachycardia/sympathetic stimulation ⇒ ***IHD*** in prone patients
- SLE-like syndrome with doses > 400mg (reversible)

Minoxidil

- ↑ K membrane permeability = more stable = less likely to contract
- Dilates arteries (not veins) | Used when high doses of hydralazine show little effect

Pharmacokinetics: T ½ 4hr BioAv 90%

Toxicity

- More pronounced sympathetic and cardiac ***reflexive effects***
- Common: headache, sweating, Hirsutism | Used topically (***Rogaine***) for hair growth

Na Nitroprusside

- Arteriole & venule dilation via guanylyl cyclase activation ⇒ NO release
- Overall: ↓ BP without Δ CO (unless in HF)

Pharmacokinetics

- T ½ Ultra short | Fast onset/offset (1-10min) | Start at 0.5 mcg/kg/min (max 10)
- Rapidly metabolised in plasma cells (cyanide liberated & metabolised by mitochondria)
- Sensitive to light ∴ cover in opaque film

Toxicity

- ***CN accumulation***; metabolic acidosis, arrhythmias, excessive hypotension, death
- ***Na thiphosulfate*** facilitates cyanide metabolism

Diazoxide

- Long acting ***arteriolar dilator***
- ↑ K membrane permeability = more stable = less likely to contract
- Pronounced reflex tachycardia

Pharmacokinetics

- T ½ 24 hrs | Onset 5 minutes, duration 4-12 hrs
- Chemically similar to thiazides (but no diuretic effect)
- 50-150mg boluses q5min (most crisis respond to 3-4 doses) | IV infusion 15-30mg/min
- Smaller doses in renal patients given extensive protein binding

Toxicity

- Excess hypotension (sometimes at 300mg) ⇒ ***Stroke & MI***
- Sympathetic response ⇒ angina, ecg Δ's, failure
- Inhibits insulin release (∴ ***used to treat hypoglycaemia of insulinoma***)

Fenoldopam

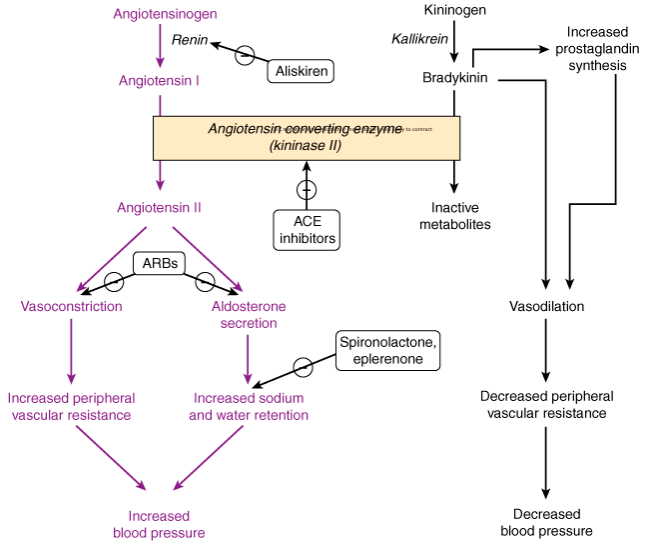
- ***D_1 agonists*** ⇒ peripheral arteriole dilation & natriuresis
- T ½ 10 min (used in ***hypertensive emergencies***, post op)
  - IV infusion at 0.1 mcg/kg/min titrated every 16 min max 1.6
  - Toxicity; headache, palpitations, flushing, ↑ IOP

Calcium Channel Blockers

- Inhibits Ca influx in arterial smooth muscle ⇒ ↓ PVR also antiarrhythmic, anti-anginal
- Common drugs: ***verapamil, diltiazem, dihydropyridines (amlodipine, felodipine, isradipine, nicardipine, nifdeipine, nisoldipine)*** | Equally efficacious for HTN
- ***Dihydropyridines*** have less cardiac depressant effects
- ***Verapamil*** has greatest depressant effect
- Doses similar to Tx angina
- Short acting Ca ch blockers not suggested in MI risk (precipitate arrhythmias)

Inhibition of Angiotensin

- 20% of essential HTN have high plasma renin (respond well to β-blockers)
- 20% of essential HTN have low plasma renin



Mechanism

- Renin release stimulated by; ↓ renal arterial pressure/ Sympathetic activity
  ↓ Na delivery or ↑ in DCT
- AT II vasocosntricts & Na retains
- AT contributes to ↑ PVR in renal stenosis, malignant HTN, intrinsic renal disease
  NB still benefit found from Tx

1. ACE Inhibitors

- Inhibit ATII conversion ∴ ↓ PVR without Δ to CO/HR
- No reflex sympathetic activation (due to downward resetting of baroreceptors)
- Although beneficial in HTN with high renin circulation, also useful if low
- Used in CKD to improve plasma throughput or MI & HF

Pharmacokinetics

- ***Captopril*** T ½ 2.2 BioAv 65%, 50-75mg/day 75-150mg/day | Renally excreted

Toxicity

- ARF (esp in renal stenosis) | Hyperkaelmia
- Angioedema, Dry cough +/- wheeze (due to bradykinin & Substance P activation)
- Interacts with K sparing diuretics and not as effective with NSAIDs (inhibits bradykinin driven vasodilation)

Captopril

- Inhibit hydrolysis of ATI → II & also inhibits bradykinin (vasodilates via NO & PG release)

Enalapril

- Prodrug, hydrolysed to enalaprilat | Similar function to captopril | ***Only for IV use***

2. Angiotensin Receptor Blocking Agents

- ***Losartan, Valsartan*** are AT1 blockers
- ***Candesartan, Eprosartan, Irbesartan, Telmisartan***
- No effect on bradykinin system
- Theoretically more complete block of ATII (as other enzymes are capable of converting ATI)
- Adverse effects same as ACE inhibitors (but ***cough, angioedema less so***)

Clinical Pharmacology of Antihypertensive Agents

Outpatient

- Non pharmacological: Limit Na intake to 70-100 mEq/day & weight reduction

Variation	Preferred 1st Line Rx	
African American	diuretics, Ca ch blockers	2nd Line: Diuretics
Asian	β blockers	3rd line sympathoplegic or vasodilator
CKD	ACE I	
Angina	β or Ca ch blockers	
BPH	α1 blockers	Fixed combination drugs available
Hyperlipdemia or Diabetes	No thiazides	

- Failure of control due to noncompliance, ineffective diuretic use, drug interactions

Hypertensive Emergencies

- Rare but Seen in abrupt termination of antihypertensives or already poorly controlled
- Clinical presentation:
- ***Malignant;*** due to progressive arteriopathy & ***inflammation/necrosis of arterioles***
  - Can present with ***hypertensive encephalopathy*** (headache, confusion)
  - Can proceed to coma/convulsion in 12-48hrs without treatment
- ***Haemodynamic;*** HF, stroke, dissecting aneurysm
- Treatment
  - Monitored environment
  - Fluid balance
  - IV antihypertensive (aim correct within hours)
  - Correct 25% (keeping diastolic > 100mmHg) to *prevent* ***cerebral hypoperfusion*** from when autoregulated to higher chronic BP
  - Change to oral once controlled
  - ***Nitroprusside*** normally used (***esmolol*** intra-op)

2. VASODILATORS & ANGINA

- Chest pain caused by ***accumulation of metabolites from ischemia***
- ***Classical angina*** = atheromatous obstruction of larger coronary arteries, effort induced
- ***Variant angina*** (Prinzmetal's) = transient spasm of local arteries with underlying atheroma
- ***Unstable Angina*** = ↑ epicardial tone or small plt clots around plaque

> Underlying Tx aimed at either ↓ O_2 demand (↓ cardiac work)
> ↑ O_2 delivery (nitrates or Ca ch blockers)
> Prophylaxis with statins

Pathophysiology

Determinant of Myocardial O_2 Demand

- Major: Wall Stress | Heart Rate | Contractility
- 75% O_2 consumption at rest
- Fuel: Favours fatty acids over CHO
  Since fatty acids req more O_2 then CHO for same energy yield, ***fatty acid oxidase inhibitors can*** redirect without compromising haemodynamics

Determinants of Flow & O_2 Supply

- Coronary flow negligible in systole
- Coronary flow ∝ perfusion (aortic diastolic) pressure
- Coronary flow 1/∝ coronary resistance (↑ in damaged vessels)

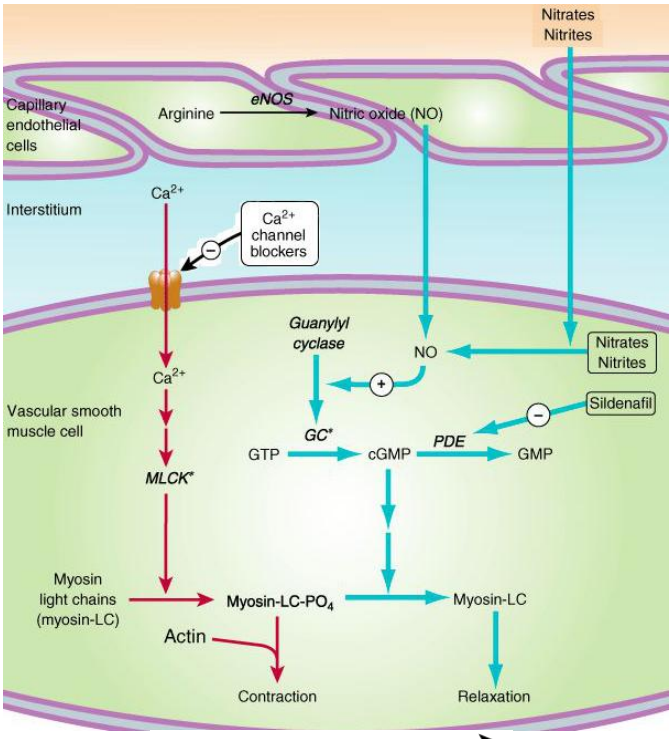
∴ Prime determinant is ***diastolic time***

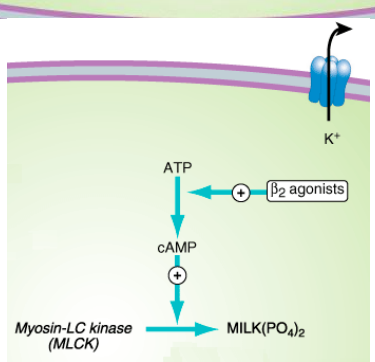
Determinants of Vascular Tone

- ***Arterial*** pressure determines ***systolic wall stress***
- ***Venous*** tone determines ***diastolic wall stress***

Pharmacological Targets

Target	Mechanism	Drugs
↑ cGMP	cGMP facilitates dephosphorylation of MLC	NO main source for cGMP (nitrates & nitroprusside)
↓ Ca^{2+} entry	inhibits intracellular Ca from activating MLCK	Ca channel blockers & β-blockers ↓ Ca influx
↑ cAMP	β2 ↑ cAMP to ↑ MLCK inactivation	Not used in angina
Membrane Stabiliser	↑ K permeability stabilises membrane (probably via ATP dependant channels)	Nicorandil has some stabilising effects





Basic Pharmacology of Drugs Used To Treat Angina

- ↓ O_2 demand: Nitrates, Ca Channel blockers, β-blockers
- Reverse vasospasm (to a certain degree): Nitrates, Ca Channel blockers

Nitrates & Nitrites

Pharmacokinetics

- Liver contains high capacity organic ***nitrate reductase*** ∴ bioavailability low (<10%)
  ∴ S/L given (to avoid 1st pass)
- Onset in minutes, duration 15-30 minutes, T ½ 2-8 min
- ***Amyl nitrite***; volatile, avoids 1st pass metabolism, short duration of action
  Obsolete these days
- Nitroglycerin → 2 Dinitroglycerins + 2 Mononitroglycerins (Dinitro- has sig vasodilation)
- Renally excreted

Pharmacodynamics

A. Mechanism on Smooth Muscle

- NO from Nitroglycerin 2 ways:
  1. Denitration by glutathione S-transferase, then converted to NO
  2. Unknown enzyme releases NO from Nitroglycerin directly
- NO activates guanylyl cyclase ⇒ cGMP ⇒ MLCK clearance
- ***Nicorandil*** also opens K channels

B. Organ System Effects

1. *Vascular Smooth Muscle*
   - Veins respond first | Arterioles & Precapillary sphincters last
   - Overall effect: ***↑venous capacitance ↓diastolic pressure***
     ∴ Orthostatic hypotension can be a problem & benefit in HF (high preload)
   - Reflex responses are intact ⇒ ***tachycardia, chronotropy***
   - Intermediate & long acting nitrates ***retain Na & H_2O***
     NB total flow in patients with CAD is unchanged, ***symptomatic relief is from redistribution***
2. *Other Smooth Muscle*
   - Although airways, GIT, GUT have smooth muscle, brief duration of action prevents any real clinical problems but some use in erectile dysfunction

> ***Erectile Dysfunction***
> - Parasympathetic discharge ⇒ non-adrenergic, non-cholinergic neurons release NO ⇒ relaxation of nonvascular smooth muscle of corpora cavernosa ⇒ ↑ pressure into cavernosa (at arterial pressures) ⇒ erection
> - ***Sildenafil*** inhibits cGMP breakdown by inhibiting PDE
> - Contraindicated with nitrates (potentiates effects, allow 6 hrs between)
> - Blue-green discrimination
> - ***Alprostadil*** (PGE1 analog) can be injected into cavernosa if sildenafil doesn't work
> - NB ***Sildenafil*** will not work in transected cord, denervated or loss of libido

3. *Platelets*
   - ↑ cGMP ⇒ ***↓plt aggregation*** (despite this no reported benefit in AMI)
4. *Other Effects*
   - Pseudocyanosis; NO + Hb → ***Met-Hb*** (low affinity for O_2)
   - Met-Hb excess treated with methylene blue
   - Met-Hb excess can be useful in Cyanide poisoning

Toxicity

A. Acute Effects

- Vasodilation ⇒ orthostatic hypotension, tachycardia, headache
- Raises ICP (but not IOP)

B. Tolerance

- Occurs after 1-2 days &requires few hrs between doses

C. Carcinogenesis

- Nitrosamines (nitrites & nitrates + amines) have theoretical carcinogenic potential
- Cultures with high nitrogen dietary intake have higher rates of ***oesophageal and gastric Ca***

Mechanisms of Clinical Effects

A. Nitrate Effects in Angina

- ↓ Venous return ⇒ ↓ preload ⇒ ↓ O_2 demand
- ↑ calibre of large epicardial coronary arteries (if given IV, intracardiac or S/L)
- Overall ↓ coronary flow (***↑collateral flow***) if given systemically

B. Nitrate Effects in Variant Angina

- Relaxes smooth muscle of epicardial coronary arteries & stops spasm

C. Nitrate Effects in Unstable Angina

- Useful in AMI for ↓ work, vasodilation/spasm reversal, plt aggregation inhibition

Clinical Use of Nitrates

- Fast onset/offset
- Slow release formulations require ***8 hr 'rest' period*** to prevent 'tolerance'
- Transdermal administration only effective in first 6-8hrs
- ***Nitroglycerin*** given as 0.15-1.2mg duration of action 10-30 min
- ***Isosorbide dinitrate*** given as 2.5-5mg duration of action 10-60minutes
- ***Isosorbide mononitrate*** 20mg BD lasts 6-10hrs

Other Nitro-Vasodilators

- ***Nicorandil*** ↓ pre AND afterload
- Activates cardiac K channels (ATP dep)

Calcium Channel Blockers

Chemistry & Pharmacokinetics

- Orally active, high 1st pass metabolism, high plasma binding, extensive metabolism
- Classes as ***Verapamil, Diltiazem, Dihydropyridines (Nifedipine)***
- Since ***Verapamil & Diltiazem*** bind the same receptor site and different to ***Dihydropyridines***

Pharmacodynamics

A. Mechanism

Calcium Channel Types		
L	Muscles, Neurons	Long large high threshold
T	Heart, Neurons	Short small low threshold
N	Neurons	Short high threshold
P/Q	Cerebellar Purkinje Neurons	Long high threshold
R	Neurons	pace making

dominant in cardiac & smooth muscle & main target

- Acts from inner membrane to block Ca influx

B. Organ System Effects

1. Smooth Muscle

- Vascular smooth muscle most sensitive: arterial > venous
- ***Dihydropyridines*** more vascular selective with differing vascular bed distribution eg ***nimodipine*** selective for cerebral vessels

2. Cardiac Muscle

- ***Verapamil*** & ***Diltiazem*** have higher affinity ∴ block tachycardia (via SA/AV nodal block)
- Also effect Na channels (***Verapamil*** > ***Diltiazem***)

3. Skeletal Muscle

- Not affected since Ca utilisation is from intracellular stores vs Ca influx

4. Cerebral Vasospasm & Infarct Following SAH

- ***Nimodipine*** has theoretical benefit in SAH given cerebral vascular selectivity

5. Other Effects

- Minimal interference with glands & nerve endings (selectivity) but known to inhibit insulin release (high doses)
- Prevent platelet aggregation
- Blocks P-glycoprotein (transporter in cancer to remove drugs) ∴ ***chemotherapy more efficient***

Toxicity

- Cardiac depression: arrest, arrhythmia, bradycardia, AV block, HF
- ***Nifedipine*** ↑ risk of MI in hypertensive patients
- β-blocked patients more sensitive to Ca ch blockers
- Minor: flushing, dizziness, nausea, constipation

Mechanisms in Clinical Effects

- ↓ O_2 demand, PVR, Rate of SA & AV ∴ clinical benefit in ***SVT, AF, A Flutter***

Clinical Use

- HTN, SVT
- Theoretical benefit in ***HOCM, Raynaud's, Migraine***
- Most Ca channel blockers unsuitable for HF given ***–ve inotropic effects*** (***Amlodipine*** ok)
- Contraindicated in unstable angina but beneficial in non-Q-wave MI (***Diltiazem***)

β-Adrenoreceptors Blocking Agents

- ↓ Chronotropy ↓ Inotropy ↓ BP ⇒ ↓ O_2 demand
- ↓ Chronotropy = ↑ diastolic volume = ↑ O_2 demand (may be offset with nitrate)

Newer Anti Anginal Drugs

- Metabolic modulators (***Ranolazine***); inhibit fatty acid oxidase ⇒ shift to CHO energy source ⇒ more efficient utilisation of ATP

Clinical Pharmacology of Drugs To Treat Angina

- Modify risk factors
- Conjunctive pharmacological interventions: ***antiplatelet & lipid lowering***

Angina of Effort

- Hypertensive patients; Ca channel blocker or β blocker
- Normotensive patient; nitrate
- Dual therapy with Ca channel and β blocker or 2 different Ca channel blockers have utility

Vasospasmic Angina

- Nitrates + Ca channel blockers improve outcome (70% nil recurrence of angina)

Unstable & ACS

- Antiplatelet therapy in non-acute or IV heparin
- ***Abciximab***
- ***Nitroglycerin*** & β blocker considered if requires stenting
- Ca channel blockers after procedure & modify risk factors

	Nitrate	β or Ca Blocker	Combined
HR	↓*	↓	↓
Arterial P	↓	↓	↓
EDV	↓	↑	-/↓
Contractility	↑*	↓	-
Ejection Time	↓*	↑	-

*baroreflex

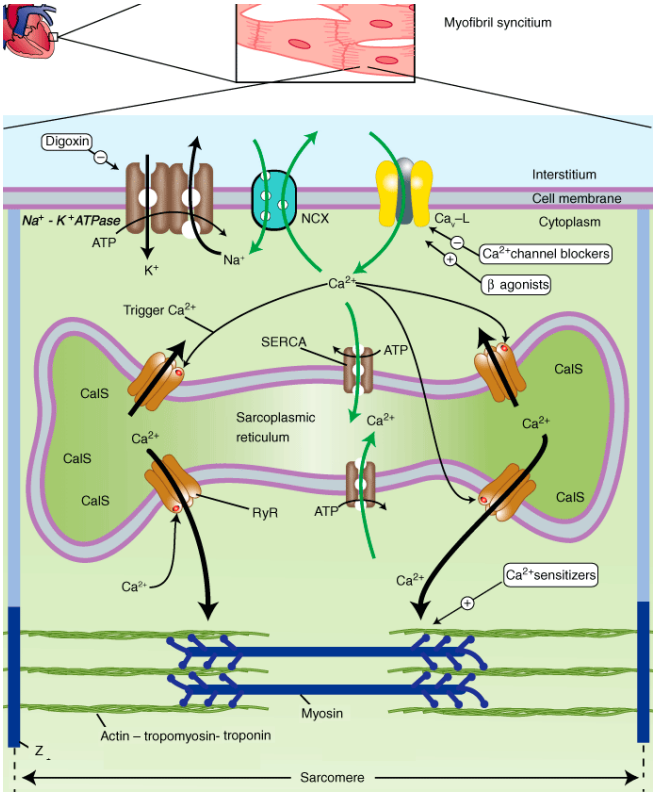
SECTION III: CARDIOVASCULAR-RENAL

3. HEART FAILURE

- Systolic failure vs diastolic failure
- Primary defect; excitation=contraction coupling

Control of Normal Cardiac Function

- Contraction results from activator calcium interacting with actin=myosin
- Amount of Ca released depends on ***amount stored in SR*** and ***strength of Trigger Ca***



Cardiac Property	Drugs & Mechanisms
Troponin sensitivity to Ca	***Levosimendin***, unknown mechanism
Ca Release From SR	***RyR2*** channels in SR
Ca Storage	SERCA channels (ATP driven) & [Ca] setup by Na-Ca
Na-Ca exchange (NCX)	Determined in part by Na-K ATPase & Ca-L
Ca influx	Via L-type Ca channels controlled by β receptors

Pathophysiology of Heart Failure

- Systolic failure; ↓ EF
- Diastolic dysfunction; hypertrophy/stiffness, no Δ EF usually, ***unresponsive to inotropes***
- High output failure; demands > CO eg hyperthyroidism, beriberi, anaemia, AV shunts
- Sx: tachycardia, palpitations, SOB, muscle fatigue, oedema (pulmonary & peripheral)

1. *Neurohumoral compensation via renin & baroreflex*
   - Baroreflex reset in HF

   Sympathetic Response
   - ↑ HR ↑ Force ↑ Preload ↑ Afterload
   - Initial ↑ CO (through ↑ HR ↑ Force ↑ Preload)
   - Eventually ↑ Afterload ⇒ ↓ CO ↓ EF ↓ Renal perfusion
   - β1 receptors down regulated but β2 and β3 not effected
   - Excess β activation ⇒ ↑ SR Ca leak through RyR2 ⇒ stiffening of myocardium
2. *Intrinsic Compensation*
   - Myocardial hypertrophy
   - Compensation in early stage but eventually ⇒ impaired diastole, wall motion abnormality, ischemia
3. *Remodelling*
   - Dilation & slow structural changes in myocardium
   - Proliferation of CT & abnormal myocytes ⇒ ↑ apoptosis
   - Stimulated by ↑ ATII
   - Cause of ↓ contractility ∴ inotropes not effective

New York Heart Association Classification	
Class I	Symptomatic with greater than usual exercise
Class II	Slight limitation of ordinary activity
Class III	Symptoms with less than ordinary activity
Class IV	Symptoms at rest

Basic Pharmacology of Drugs Used in heart Failure

Digitalis

Kinetics

- Widely V_D (incl CNS) | Not extensively metabolised (2/3 renally excreted unchanged)

Pharmacodynamics

- ***Inhibit Na-K ATPase*** in ALL tissues

A. Cardiac Effects

1. Mechanical

Inhibit Na-K ATPase ⇒ ↑intracellular Na ⇒ ↓Na-Ca exchange ⇒ ↑Intracellular Ca ⇒ ↑intra SR Ca (via SERCA) ⇒ ↑contractility

2. Electrical

- ↑ intracellular Ca = ↑ K^+ conductance
  ⇒ Early/brief prolongation of AP then shortening of AP (esp plateau phase)
- Higher concentrations; ↑ intracellular Na ⇒ ↓ K ⇒ ↓ membrane potential threshold
  ⇒ Oscillatory depolarization after AP (due to overloading of intracellular Ca stores)
- Bigeminy ensues ⇒ self-sustaining tachycardia ⇒ ***fibrillation***
- Also effect para/sympathetic systems
  - Para predominate at lower doses; sensitise baroreflex, central vagal stimulation, facilitation of muscarinic transmission in myocytes
- ***Most common cardiac manifestations***;
  - AV junctional rhythm, Bigeminy, premature ventricular ectopics, 2nd degree block

B. Effects on other Organs

- GIT most common extra cardiac site: anorexia, nausea, vomiting, diarrhoea
- CNS; vagal & CTZ stimulation, disorientation, hallucination (rare)
- Gynocomastia

C. Interactions with K, Ca, Mg

- K & Glycosides compete for Na-K ATPase binding site
  ∴↑ [K] ⇒ ↑ effect & vice versa
- Ca accentuates toxicity of digitalis

Other Positive Inotropic Drugs Used in Heart Failure

Bipyridines

- ***Inamrinone*** & ***Milrinone***
- Phosphodiesterases inhibitors (PDE-3)
- T ½ 3-6 hrs (10-40% renal)
- ↑ inward Ca flux during AP
- Inhibition ⇒ ↑ cAMP ⇒ ↑ contractility & peripheral dilation

β-Agonists

- ***Dobutamine*** most widely used in HF; ↑ CO ↓ Ventricular filling pressure
- Adverse effects include tachyphylaxis ie ↑O_2 consumption

Drugs WITHOUT Positive Inotropic Effects Used in HF

- First line: diuretics, ACE I, β blockers, Angiotensin Receptor Antagonists

Diuretics

- Aim to ↓ venous pressure & ↓ preload
- ***Spironolactone*** improves survival if already on ACE I
  (Theoretical evidence that aldosterone ⇒ myocardial fibrosis)

ACE I, Angiotensin Receptor Blockers

- ***Captopril***
- ↓ volume ⇒ ↓ afterload, also ↓ Na, H_2O retention (ie ↓ preload)
- ↓ remodelling

Vasodilators

- ***Hydralazine, Isosorbide mononitrate***
- ↓ preload and afterload +/- ↓ remodelling

β blockers

- Unknown mechanism
- ***Bisoprolol***, ***Metoprolol***, ***Carvedilol*** works (***bucindolol*** doesn't)

Clinical Pharmacology of Drugs Used in Heart Failure

Management of Chronic Heart Failure

1. ↓ Workload; limit activity, ↓ weight, control HTN
2. ↓ Na intake & ↓ H_2O intake + Diuretics to aid removal
3. ACE Inhibitors or AT receptor blockers
4. Digitalis if ***systolic dysfunction or AF***
5. β blocker if ***class II-IV and stable***
6. Vasodilator
7. Cardiac Resynchronize

ACE Inhibition & Angiotensin Receptor Blockers

- Should be used as 1st line therapy esp in ***LV dysfunction without oedema***
- Slows dilation by ↓ pre and after load
- ***ATII receptor blockers*** have similar effects to ACE Inhibitors but ***not as efficient*** ∴ use limited to patients intolerant to ACE-I

Vasodilators

- Preload symptoms; SOB = give venous dilator (***nitrate***)
- Afterload symptoms; fatigue = give arterial dilators (***hydralazine***)
- Severe chronic failure usually has both

β & Ca Channel Blockers

- Can worsen failure initially
- Improvement after several months; ↑ EF, ↓ HR ↓ Symptoms
- ***Ca channel blockers have no role***

Digitalis

- Initiated in AF or after ACE-I and Diuretics not working (only 50% with NSR have relief)
- Slight persistent +ve inotropic effect ∴↓ HF morbidity but ↑ chance of sudden death

Other Clinical Uses for Digitalis

- Atrial arrhythmias (although Ca ch blockers and ***adenosine*** preferred)
- Contraindicated in WPW

Toxicity (digitalis)

- Common: visual, GIT
- Arrhythmias
- Severe toxicity = hyperkalaemia, suppressed automacity ∴ antiarrhythmic ⇒ arrest
  Pacemaker and digitalis antibodies are best treatment
  Cardioversion also worsens ∴ only use in VF

Cardiac Resychnronization Therapy

- NSR & widened QRS = desynchronised ⇒ ↓ CO
- Tx with pacing shows good effect

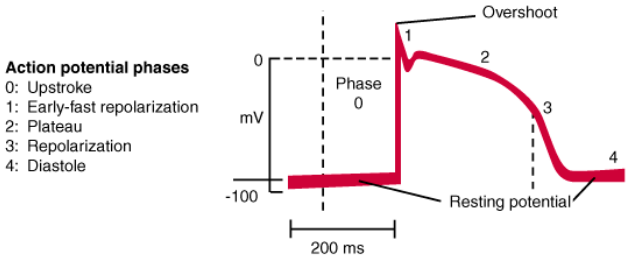
Management of Acute Failure

- AMI (either acute or acute on chronic)
- Precipitant of chronic HF include non-compliance, fevers/infection, exercise, emotion, stress, salt
- Tx angioplasty or lysis
- main measurements:
  1. Atrial pressure
  2. LV filling pressure
  3. Cardiac index

4. ANTIARRYTHMICS

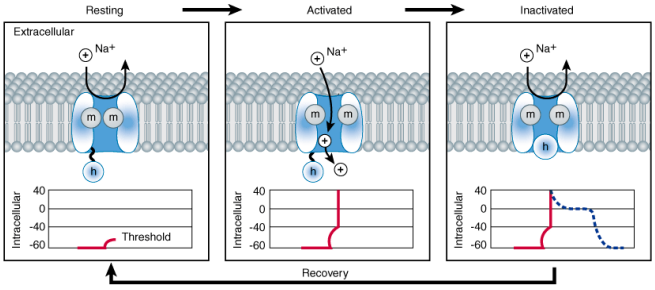
- 25% with digitalis | 50% of anaesthetised patients | 80% of AMI
- If asymptomatic or minimally symptomatic don't treat

Electrophysiology of Normal Cardiac Rhythm



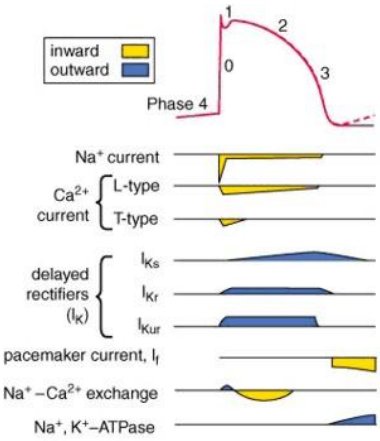
- Pacemaker cells: spontaneous depolarization occurs in diastole (K dependant)

Active Cell membrane



- Fast Na channels exists in 3 states; ***resting, active, inactivated***
  (Reflect different states represent different protein conformations of H & M gates)
- Ca channels act in a similar manner but slower
- K channels are either I_{Kr} (rapid)or I_{Ks} (slow) another IK may exist in SA node given that some IK inhibiting drugs don't effect SA nodal depolarization

Phases



Phase 0
Opening of M gates of Na channels

Phase 1 & 2
Na channel closure & waxing/waning Ca current & slowly opening K channels

Phase 3
Complete Na & Ca channel closure, progressive opening of K channels

Phase 4
Equilibrium, all channels closed

Effects of resting Potential on Action Potential

- Na channels are inactivated at potential -75 to -55 mV
  ∴ Resting potential of-60 mV will have more than at -80mV
- ↓ permeability ⇒ ↓ amplitude ↓ excitability ↓ conduction velocity, prolonged recovery time
- ***Refractory period:*** between phase 0 to 3 (when H gates occupy channel)
- Slow depolarisation occurs in AV & SA node;
  - Ca influx dependant to reach AP
  - Resting potential = -50 to -70 mV
- Other causes of ***slow depolarisation***; Hyperkaelmia, Na pump blockade, ischemia

Mechanism of Arrhythmias

- Underlying cause due to defects in *impulse formation, conduction or both*

A. Impulse Formation

- Slow rate: ↓ phase 4 slope (vagal stimulation, β blocking)
- Fast rate: ↑ phase 4 slope (hypokalemia, β stimulation, chronotropic drugs, stretch, acidosis)
- ***After-depolarisation*** responsible for some arrhythmias
  1. ***Early after depolarisation*** (EAD); occurs in phase 3 = long QT
     Contribute to long QT arrhythmias
  2. ***Delayed After Depolarisation*** (DAD); occurs in phase 4 (↑ intracellular Ca)

B. Impulse Conduction

- Common disturbances; ***block*** (sometimes relieved with ***atropine*** since AV node has sig parasympathetic innervation) and ***re-entry*** (incl WPW, AF, VF)
- To stop re-entrant: further ***slow depressed conduction*** to create bidirectional block (theoretically speeding up would do the same, but not practiced clinically)
- ***Lengthening refractory*** period will also revert re-entrant circuit

Molecular Basis of Arrhythmias

- ↑ inward current (Na, Ca) or ↓ outward current (K)
- ***Torsades*** (congenital or acquired) is due to ***defect in IK channel***
- ***Mexiletine***, Na Ch blocker may treat Long QT
- Short QT reflects gain of function of IK
- ***Brugada:*** VF, persistent ST elevation, ***loss of function mutation in Na channel***

Basic Pharmacology of Antiarrhythmic Agents

Class	Mechanism	Drugs
I	**Na Channel** Blockade	
	IA Intermediate dissociation | Prolonged AP duration	***Procainamide*** ***Quinidine*** ***Disopyramide***
	IB Rapid dissociation | Shorten AP duration	***Lidocaine*** ***Mexiletine***
	IC Slow dissociation | No effect on AP duration	***Flecanide*** ***Propafenone*** ***Moricizine***
II	Sympatholytic (ie ↓ β adrenergic activity on heart)	***Esmolol*** ***Sotalol***
III	**IKr** block to prolong action potential duration	***Amiodarone*** ***Bretylium*** ***Sotalol*** ***Dofetilide*** ***Ibutilide***
IV	**Ca channel** blockers (esp useful in SA & AV nodes)	***Verapamil*** ***Diltiazem***

*NB drugs can have more than one class effect eg **amiodarone** has class I-IV effects but most drugs are discussed through their predominate effect*

CLASS IA

Procainamide

Cardiac Effects

- Slows upstroke of AP, conduction, prolongs QRS } Depresses SA
- Has 2ry nonspecific K blockade to prolong AP too } & AV nodes

Extracardiac Effects

- Ganglion blocker ⇒ ↓ PVR (less prominent in therapeutic levels)

Toxicity

- Prolonged AP, QT ⇒ Torsades
- 1/3 SLE-like; arthralgia, arthritis | All have raised ANA
- Renal lupus rare but ***pleuritis, pericarditis,*** parenchymal pulmonary disease not uncommon
- Other; nausea, vomiting, diarrhoea, rash, fever, hepatitis, agranulocytosis

Kinetics

- PO, IM, IV | T ½ 3-4 hrs (T ½ NAPA slower ∴ need to monitor levels of both)
- Hepatic metabolism to NAPA (has class III actions with accumulation⇒ torsades)
- Renally excreted
- Dose for rapid onset: 12mg/kg @ 0.3mg/kg/min then 2-5mg/min guided by levels
- 2-5g/day required to control ventricular arrhythmias

Therapeutic Use

- Effective in most atrial & ventricular arrhythmias
- ***Usually second line to Lidocaine*** given need to dose & lupus effects
- ***Sustained ventricular arrhythmias*** in MI

Quinidine

Cardiac Effects

- Similar to ***procainamide*** with more pronounced cardiac muscarinic effects

Toxicity

- ***Cinchonism:*** tinnitus, headache, dizziness, deafness, anaphylaxis

Kinetics

- PO | Bound to albumin & α1-acid glycoprotein | Hepatic metabolism

Therapeutic Use

- Restricted to ***normal hearts with arrhythmia*** (due to cardiac/systemic effects)
- Studies show x2 rate of maintained NSR but also death
- Used in ***severe malaria*** (optical isomer of ***quinine***)

Disopyramide

Cardiac effects

- Similar channel profile to ***procainamide*** & ***quinidine*** but *GREATEST* Antimuscurinic effect
  ∴ Give co-therapy with drug that slows AV conduction

Toxicity

- Arrhythmias | Precipitates HF given –ve inotropic effect
- Antimuscurinic ***effects; urinary retention, dry mouth, blurred vision, worsening IOP***

Kinetics & Dose

- 150mg TDS PO

Therapeutic Use

- Mainly ***ventricular arrhythmias*** (though shown to work in supraventricular arrhythmias

CLASS IB

Lidocaine

- Low toxicity / high effectiveness in arrhythmias from AMI

Cardiac Effects

- Blocks A & I Na channels
- Rapid Kinetics

Toxicity

- ***Safest class I***
- Uncommon: SA nodal arrest, impaired conduction, precipitation ventricular arrhythmias
- Common Extracardiac manifestations; paraesthesia, deafness, slurred speech, convulsion

Kinetics & Dose

- Extensive 1st past metabolism | T ½ 24-36 hrs | VD & total body clearance reduced in failure
- Load with 150-200mg maintain 2-4mg/min aiming for 2-6mcg/ml
- Acute settings req higher concentration (***α1-acid glycoprotein*** is ↑ in AMI & binds Lidocaine)

Therapeutic Use

- Termination of VT | Prevent VF after shock (not routinely used as prophylaxis)

Mexiletine

- Orally active congener of Lidocaine ∴ similar dynamics
- Indicated in ventricular arrhythmias | Chronic pain (esp neuropathic diabetic)
- T ½ 8-20 hrs | Dose 600-1200 mg/day
- Adverse effects seen at therapeutic doses; tremor, blurred vision, lethargy

CLASS IC

Flecanide

- Indicated in SVT with ***normal hearts***
- Good at supressing PVBs but also causes fatal arrhythmias not infrequently (***CAST study***)
- Well absorbed | T ½ 20 hrs | Metabolised by liver & kidneys | Dose 100-200mg BD

Propafenone

- Structurally similar to ***propranolol*** (∴ weak β effect)
- Electrophysiological effects similar to ***quinine*** (Na blockade similar to ***Flecanide***)
- T ½ 5-7 hrs | Dose 450-900mg in 3 doses
- Used for SVT
- Common adverse effects; metallic taste, constipation

Moricizine

- Used in ventricular arrhythmias
- Common adverse effects; dizziness, nausea
- Dose 200-300mg TDS PO | Multiple active metabolites that outlive primary

CLASS II

- Lower efficacy (vs Na channel blockers) for supressing ventricular ectopic depolarisations
- Good evidence for prevention of recurring MI
- ***Esmolol***; short acting, used intraoperatively for rhythm control
- ***Sotalol:*** non selective blocker, prolongs AP

CLASS III

- Some have ***Reverse use dependence*** for drug: prolongation ***weakest at fast rates*** (where its required most) & ***strongest at slow rates*** (where it isn't really required)

Amiodarone

- Used to treat ventricular arrhythmias but also very effective in supraventricular arrhythmias

Cardiac Effects

- IKs blocked in chronic use | ***No real evidence of reverse use dependence***
- Also blocks inactivated Na channels (as shown by prolonged AP) and weak adrenergic/Ca channel blocking effect ⇒ ***↓HR ↓conduction*** (multiple targets may explain high efficacy & low adverse effect profile)

Toxicity

A. Cardiac: bradycardia , HB, VF

B. Extracardiac

- Accumulates in many tissues
- Lung; most common (1%) fibrosis | Liver; hepatitis | Skin: photo dermatitis, blue-grey disc
- Eyes; asymptomatic corneal micro deposits
- Thyroid: blocks $T_4 \rightarrow T_3$

Kinetics

- BioAv 35-65% | Hepatic metabolism (major metabolite desethylamiodarone is active)
- T ½ occurs in 2 steps: 1. Rapid: 3-10 days, 50% drug | 2.Slower; weeks
  On discontinuation, effects maintained 1-3 months
- Loading dose 0.8-1.2g, maintenance 200-400mg
- IV: modest prolongation of QT , marked bradycardia & AV block
- Many drug interactions, in particular, those that supress CYP3A4 (histamine & cimetidine)

Therapeutic Use

- Low doses to ***maintain SR in AF or prevent tachycardia***

Bretylium

- Direct antiarrhythmic properties, initial wave of catecholamine release

Cardiac Effects

- Prolongs ventricular AP, ***targeting ischemic cells*** (to prolonged pathologically shortened AP)
- Catecholamine release ⇒ ***brief, slight initial inotropic effect & proarrythmic*** (esp vent)
- Sympathoplegic ⇒ postural hypotension (relieved if given concurrent TCA)

Kinetics

- IV bolus 5mg/kg rpt after 30 min then every 4-6 hrs (or infuse at 0.5-2mg/kg)

Therapeutic Use

- Rarely used
- 3rd line drug; after VF arrest and ***Lidocaine*** & ***Cardioversion*** fail (but ***Amiodarone*** preferred)

Sotalol

- Both β blocking & AP prolonging effect
- β blocking non-specific and maximal at doses required for AP prolongation
- BioAv 100% | Not bound to plasma proteins | Excreted unchanged in kidneys | T ½ 12 hrs
- Risk of ***torsades 6%*** at maximal therapeutic range, depresses LV function furthering HF
- Used in life threatening vent arrhythmias, ***maintain NSR in AF***, ***paediatrics*** arrhythmias
- ↓ threshold for cardiac defibrillation

Dofetilide

- Dose dependant blockade of **IKr** (↑ block in hypokalemia) – no other channels
- Reverse dependence due to other channels not being effected
- BioAv 100% (***verapamil*** ↑potency by ↑ intestinal absorption)
- 80% renally excreted unchanged
- Contraindicated in QTc > 450, HR < 50, hypokalaemia
- Used in ***AF to maintain NSR*** (or restoring)

Ibutilide

- Blocks IKr (may also activate slow inward Na current)
- Rapid hepatic metabolism | Renal excretion | T ½ 6 hrs
- Therapeutic use; ***conversion of atrial flutter/fibrillation*** (better at flutter)
- Reversion in 20 minutes
- Adverse: torsades, QT prolongation

CLASS IV

Verapamil

- Block both ***in/activated L channels*** ∴ more potent in tachycardia, less completely polarised at rest and cells rely exclusively on Ca current (SA & AV node)
- AV & SA node slow (but some offset by reflex of hypotension)
- Can supress both early & delayed after depolarisations
- Can ***antagonise slow response from damaged*** (depolarised) tissue

Extracardiac Effects

- Peripheral vasodilation | Smooth muscle effects

Toxicity

A. Cardiac

- VF if already in VT | -ve inotropy | AV block (give atropine or β agonist)
- Sinus arrest with premorbid sinus node disease

B. Other

- Constipation, lassitude, nervousness, peripheral oedema

Kinetics & Dosage

- T ½ 7 hrs | BioAv 20% (extensive liver metabolism)
- Given orally to ***terminate SVT*** (***adenosine*** first line): 5mg bolus, 5-10mg QID

Therapeutic Use

- Termination of SVT | ↓ ventricular rate in AF (rarely converts)

Diltiazem

- Same profile as ***Verapamil***

Miscellaneous Antiarrhythmic Agents

Adenosine

- Nucleoside that occurs naturally in body | T ½ 10 seconds
- Activates ***inward rectifier K current*** & ***inhibits Ca current***
  ⇒ Marked hyperpolarization & inhibited Ca-dependant AP
  Ie ***directly inhibits AV conduction*** by ***↑AV refraction*** (less effect on SA)
- Used to convert SVT | Dose: 6mg then 12mg PRN
- Less sensitive in presence of adenosine receptor blockers (***theophylline, caffeine***)

Toxicity

- 20% flushed | 10% SOB (?bronchospasm) | Can precipitate AF
- Headache, hypotension, nausea, paraesthesia

Magnesium

- Unknown mechanism of action; ***'influences' Na-K ATPase, Na, Ca, K channels***
- Effective in digitalis arrhythmias with low Mg | Used in torsades with normal Mg

Potassium

- Low K ⇒ ↑ risk of DAD & EAD, ectopic activity
- High K ⇒ depressed ectopic activity, slowed conduction

Principles in clinical use of antiarrhythmic

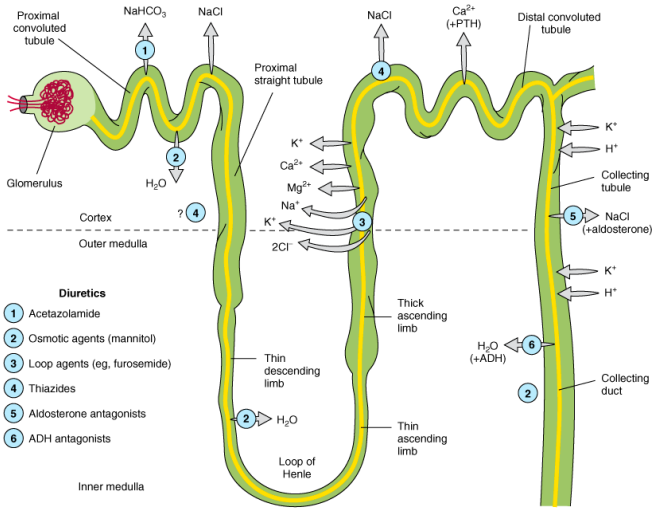
Pre-treatment Evaluation

1. Eliminate cause: Hypoxia, electrolyte imbalance, drugs, disease
2. Firm diagnosis: eg ***verapamil*** in ventricular vt can be fatal
3. Determine baseline condition: to quantify efficacy
4. Question need for therapy: conservative usually best if not symptomatic (CAST study)

Benefits & Risks

- Reduce symptoms
- Reduce mortality in asymptomatic patients (β blockers only one shown to do this)
- Many serious adverse effects

5. DIURETICS



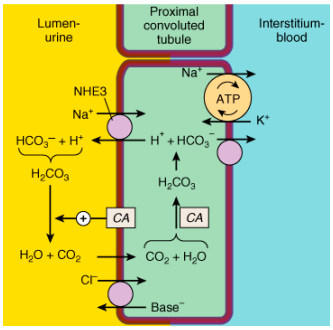
Segment	Fcn	H_2O	1ry Porter	Diuretics
Glomerulus	Formation of filtrate	↑↑↑	None	
PCT	Reabsorbs ***65% of Na***, K, Ca, Mg 85% of $NaHCO_3$ 100% Glc & aa Isosmotic reabsorption of H_2O	↑↑	Na-H CA	CA inhibitors (*acetazolamide*)
Prox Straight	Secretion/Absorption of Organic acids & bases (incl uric acid & diuretics)	↑↑	Acid & Base Transporters	None
Thin Desc	Passive resorption H_2O	↑	Aquaporins	None
Thick Asc	Active reabsorption of ***15-25% filtered Na***, K, Cl 2ry reabsorption of Ca & Mg	↓↓	Na=K=2Cl	*Loops*
DCT	Active reabsorption of ***4-8% filtered Na*** & Cl Parathyroid control	↓↓	Na=Cl	*Thiazides*
CCT	***2-5% Na*** reabsorption (coupled to K & H secretion)	V	ENaC K channels H porters Aquaporins	*K sparing diuretics*
MDT	H_2O reabsorption Vasopressin control	V	Aquaporins	*Vasopressin antagonist*

V = variable CA = Carbonic Anhydrase

Proximal Tubule

- Na-K ATPase sets up low intracellular Na
- Na-H works via gradient setup above
- H combines with $HCO_3 \rightarrow H_2CO_3$
- H_2CO_3 dissociates (catalysed by CA)
- CO_2 enters cell
- CO_2 combines with H_2O —CA→ H_2CO_3
- Dissociates to HCO_3 + H+
- HCO_3 diffuses into interstitium while H+ recycled in Na-H transporter
- Cl exchanged for base to maintain neutrality

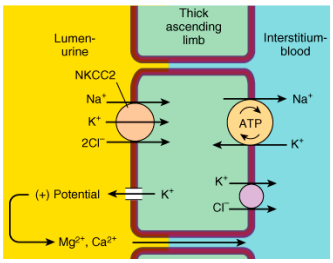
Net: Na, HCO_3 & Cl reabsorption



Loop of Henle

- Descending limb permeable to H_2O
- Thick ascending limb impermeable to H_2O
- Na-K ATPase sets up low intracellular Na
- Na=K=2Cl (NKCC2) moves down gradient
- K-Cl cotransport into interstitium K recycled in Na-K ATPase
- Passive K efflux into lumen
- Passive paracellular influx of Mg & Ca

Net: Na & Cl reabsorption
(some Mg & Ca also)



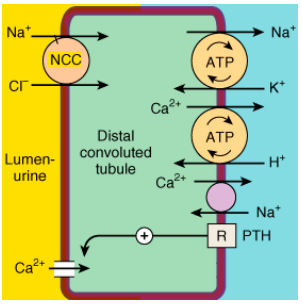
Distal Convoluted Tubule

- H_2O impermeable
- Na-K ATPase & Ca-H ATPase sets up gradient
  - Na-Cl (NCC) moves down gradient
  - Ca-Na moves down gradient

Net: Na & Ca reabsorption

Extrarenal Influences

- Thiazides inhibit NCC channels
- PTH inhibit passive Ca resorption

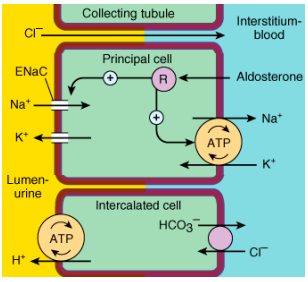


Collecting Tubule

- Despite 2-5% NaCl reabsorption
  Plays important role in *fine tuning*
- Mineralocorticoids also play a role
- *Balance occurs here (for all diuretics)*
- NA-K ATPase sets up gradient
- Na influx down gradient via ENaC
- K efflux down gradient
- Paracellular Cl diffuse into interstitium

Upstream Influences

- K efflux by gradient formed by Na influx
  ∴ Upstream luminal retention of Na = ↑ K excretion



Extrarenal Influences

- Aldosterone released during volume depletion enhances ENaC & Na-K ATPase

Diuretic	NaCl	$NaHCO_3$	K	pH
CA Inhibitors	+	+++	+	-
Loops	++++		+	+
Thiazides	++	+	+	+
Loop + thiazide	++++++	+	++	+
K-sparing	+	(+)	-	-

*urine electrolytes, body pH

Carbonic Anhydrase Inhibitors

- Net result of inhibition = blocked Na & HCO_3 absorption in PCT | Rarely used as diuretic

Kinetics

- Well absorbed | Onset 30 min peak 2 hrs duration 12 hrs | Excreted in PCT (S2)

Renal Effects

- Effect only lasts days since ↑ HCO_3^- excretion ⇒ ↑ NaCl reabsorption distally

Non renal effects

- *Ciliary body secretes HCO_3^- from blood into aq humour*
- *CSF production requires HCO_3 secretion*

} Both inhibited by CA inhibition

Clinical Indications & Dosage

A. Glaucoma

- ↓ IOP | Topical and oral routes available

B. Urinary Alkalinisation

- To ↑ renal excretion of uric acid, cysteine and other weak acids
- Effects lasts 2-3 days (need *concurrent administration of HCO_3^-* for ongoing benefit)

C. Metabolic Alkalosis

- Clinically used in HF with excessive use of other diuretics ⇒ Hypovolaemia
- Also used to rapidly *correct respiratory acidosis*

D. Acute Mountain Sickness

- Can cause pulmonary and cerebral oedema if ascend > 3000m fast
- Acetazolamide *↓CSF production & pH* ⇒ ↑ cerebral ventilation

E. Other

- Adjuvant to epilepsy, hypokalemic paralysis, ↑ urinary PO_4 excretion

Toxicity

A. Hyperchloremic Metabolic Acidosis

- Due to lack of luminal Cl exchange to correct urinary acidosis ∴ use limited to 2-3 days

B. Renal Stones

- ↑ [HCO_3] ⇒ ↑ luminal PO_4 & Ca ⇒ stone formation

C. Renal K Wasting

- ↑ [Na] in DCT ⇒ ↑ K exchange ∴ usually give K supplement

D. Other

- Drowsiness & paraesthesia more common
- Hypersensitivity (fever, rash, bone marrow suppression)

Contraindications

- Acetazolamide ↑ urinary pH ∴ ↓ NH_4 excretion ∴ will ↓ excretion in *hyperammonemia and hepatic encephalopathy*

Loop Diuretics

- ***Furosemide***
- Efficiency not compromised by acidosis (unlike CA inhibitors)

Kinetics

- Rapidly absorbed 2-3 hrs | Renal (filtrate & tubular secretion) excretion
- Reduced secretion with competing weak acids (***NSAIDs*** or ***Probenecid***)

Dynamics

- Also inhibits Mg & Ca paracellular reabsorption
- Although hypomagnesaemia can occur, hypocalcemia absorbed in DCT or diet
- Also induce PG synthesis to cause diuresis (NSAIDs inhibit this)
- Vascular bed: ↑ renal flow, ↓ pulmonary & LV fill

Clinical Indications

- APO, Acute hypercalcaemia, other oedematous states
- Other: hyperkalaemia, ARF, anion overdose

A. Hyperkaelmia

- Enhanced by simultaneous NaCl & H_2O administration

B. ARF

- ↑ urine flow & K excretion | Does not shorten duration
- If ***large pigment loads*** cause ARF, loops can help 'flush' out faster/reverse obstruction
- But can ***worsen cast formation in myeloma & light chain nephropathy***

C. Anion Overdose

- Bromide, fluoride, Iodide (reabsorbed in TAL) | Need to run NaCl concurrently

Toxicity

A. Hypokalemic Metabolic Alkalosis

- ↑ [Na] in DCT ⇒ ↑ K exchange ∴ usually give K supplement

B. Ototoxicity

- Dose related hearing loss
- More common in diminished renal function with cotherapy (***aminoglycosides*** etc.)

C. Hyperuricemia

- Hypovolumia associated enhanced uric acid resorbtion in prox tubule ⇒ ***gout***

D. Hypomagnesemia

- Reversed with oral magnesium

E. Allergic & Other

- Sulphonamides
- Skin rash, eosinophilia, interstitial nephritis
- Severe dehydration (Hyponatremia less common vs ***thiazides***)

Contraindications

- Cross reactivity with other ***sulphonamides***
- Hepatic toxicity

Thiazides

- Emerged while looking for more potent CA inhibitor ∴ some have minor CA inhibiting properties

Kinetics

- ***Chlorothiazide*** not very lipid soluble, only IV type (all others oral only), need large doses
- Excreted primarily through ***biliary system*** but enough gets to DCT
- Secreted via organic acid system ∴ ***competes with uric acid*** for excretion (implications on high plasma uric acid levels)

Pharmacodynamics

- Inhibit Na=Cl cotransporter on luminal surface of DCT ∴ enhance Ca resorption due to
  - Low intracellular Na ↑action of basal Na-Ca transport thus creating a gradient for luminal Ca passive transport
- Do not cause overall hypercalcaemia but can unmask hypercalcaemia of other cause
- ***Thiazides*** also induce PG synthesis for end effect ∴ ***NSAIDs*** can inhibit

Clinical Indications & Dose

- HTN
- HF
- Nephrolithiasis (hypercalcuric)
- Nephrogenic DI

Chlorothiazide 0.5-2g 2 divided doses
Hydrochlorothiazide 25-100mg OD
Indapamide 2.5-10mg OD

Toxicity

A. ***Hypokalemic*** Metabolic Alkalosis & Hyperuricemia: similar to ***loops***
B. Impaired CHO tolerance: impaired pancreatic release of insulin & diminished tissue utilisation of glc ⇒ Hyperglycaemia in diabetics/resistant
C. Hyperlipidaemia: 5-15% increase in total & LDL (reversible)
D. Hyponatremia: Hypovolaemia ⇒ ↑ ADH, ↓ diluting capacity, ↑ thirst
E. Allergic: share cross reactivity, photosensitivity, generalised dermatitis, rare: haemolytic Anaemia, thrombocytopenia, acute necrotizing pancreatitis
F. other toxicities: weakness, fatigue, paraesthesia

Contraindications

- Hepatitic cirrhosis, borderline renal failure, heart failure

K Sparing Diuretics

- ***Spironolactone*** & ***Eplerenone***: mineralocorticoid receptor antagonist
- ***Amiloride*** & ***Triamterene***: Inhibit ENaC on CT

Kinetics

- ***Spironolactone*** & ***Eplerenone***:
  - inactivated in liver | slow onset (days)
  - ***Eplerenone*** is a spironolactone derivative with ***greater selectivity***
- ***Amiloride*** & ***Triamterene***:
  - ***Triamterene*** shorter T ½, metabolised in liver, renal excretion
  - ***Amiloride*** not metabolised

Dynamics

- ***Spironolactone*** & ***Eplerenone***
  - steroid, competitive antagonists to ***aldosterone***
  - To ↓ ENaC on luminal surface, ↓Na-K ATPase on basal surface
  - Also ↓ intracellular formation of active metabolites of aldosterone
  - Also synth PG for effect
- ***Amiloride*** & ***Triamterene***
  - Inhibit Na entry through ENaC

Since K secretion is coupled (via gradient) to Na reabsorption, ↓reabsorption ⇒ ↓K secretion

Clinical Indication & Dosage

- Mineralocorticoid excess or hyperaldosteronism

Toxicity

A. Hyperkalaemia: ↑ risk in renal disease or renin reducing drugs (βblockers and NSAIDs) or AT II activity (ACE inhibitors, AT receptor blockers)

To avoid, fixed ***combination K sparing & Thiazide diuretics used***

B. Hyperchloremic Metabolic Alkalosis: inhibited H secretion
C. Gynocomastia: synthetic steroids, impotence, BPH
D. ARF: only seen with triamterene + indomethacin
E. Stones: Triamterene is slightly soluble in urine ∴ can precipitate to form stones

Contraindications

- Hyperkalaemia (endogenous or iatrogenic)
- Chronic renal insufficiency
- Blunting of Renin-Angiotensin system
- Liver disease in ***triamterene*** & ***spironolactone***

Agents that Alter Water Excretion

1. Osmotic Diuretics

- Proximal and desc limb freely permeable to H_2O
- Agents filtered but not reabsorbed will retain H_2O in the lumen
- Useful in ***↓intracranial pressure***, promptly removing toxins
- ***Mannitol*** most commonly used drug

Kinetics

- Poorly absorbed (for good reason) | Not metabolised | Excreted within 30-60min

Dynamics

- Most effect seen in prox & desc tubules
- ***Oppose action of aldosterone in CT***
- ↓ H_2O resorption ⇒ ↑ luminal volume ⇒ ↓ contact time with epithelium ⇒ ↓ Na resorption

Clinical Indications

A. ↑ Urine Volume
- Avid retention of Na refractory to other means
- Prevention of anuria in presence of large pigment load (***haemodialysis, rhabdo***)
- Test dose of *12.5mg should yield > 50ml/hr over 3 hrs* (ineffective in patients who don't pass) ⇒ *12.5 – 25mg q1-2hr aiming UO 100ml/hr*

B. ↓ ICP or IOP
- By way of ↓ intracellular volume (↑ osmotic gradient)
- 1-2g/kg bolus effects within 60-90 min | Monitor ICP

Toxicity

A. Extracellular Volume Expansion
- Rapidly distributed in extracellular compartments ∴ extracts water into compartments ⇒ ***exacerbation of HF, pulmonary oedema***
- Other symptoms: headache, nausea, vomiting

B. Dehydration, Hyperkaelmia, Hypernatremia
- Without appropriate fluid balance, ↑ H_2O loss ⇒ ↑ K & Na

2. ADH Agonists

- ***Vasopressin*** & ***Desmopressin*** for central DI
- Acts on V2 receptors

3. ADH antagonists

- SIADH or CHF = ↑ ADH ⇒ ↑ H_2O retention ⇒ ↓ Na
- ADH receptor antagonists prevent this
- ***Conivaptan*** & ***Demeclocycline*** (***lithium*** never used)

Kinetics

- T ½ 5-10 hrs | Orally active

Dynamics

- Both work at collecting tubules
- ***Conivaptan*** antagonist at V1A & V2 whereas ***Demeclocycline*** inhibits cAMP formation

Clinical Indications

A. SIADH

- First line is water restriction
- ***Demeclocycline*** 600-1200mg/day PO or ***Conivaptan*** IV

B. Other Causes of Raised ADH

- ADH released in response to ↓ circulating blood volume eg congestive HF

Toxicity

A. Nephrogenic DI: severe hypernatremia & DI from excess

B. RF: ***lithium*** & ***Demeclocycline*** ?Mechanism, ***lithium*** also causes nephritis

Diuretic Combinations

Loop + Thiazide

- Synergistic
- Na & H_2O resorption in TAL or DCT ↑ when the other is blocked
- Thiazides block Na in PT but make up for it in TAL, Loops prevent TAL uptake
- ***K wasting common*** in these scenarios

K Sparing + Loop or thiazide

- 1st line of K wasting in ***loop + thiazide*** is NaCl restriction/K supplementation
- 2nd line is adding a K sparing diuretic
- Avoid in renal insufficiency & concurrent ACE I use (hyperkalaemia)

Clinical Pharmacology of Diuretic Agents

Oedematous States

- States that ↓ renal perfusion ⇒ NaCl & H_2O retention
- Diuretics mobilise this excess interstitial retention since excess usage ↓ vital organ perfusion

Heart Failure

- HF ⇒ ↓ CO ⇒ sensed in kidneys as hypovolaemia ⇒ salt & water retention
- Underlying disease worsens ⇒ ↓↓↓ CO ⇒ ++ salt & water retention ⇒ ***interstitial oedema***
- Diuretics (esp ***loop***) ↓ volume ⇒ ↓ preload ⇒ more efficient contractions
- Severe NaCl retention requires combination therapy
- NB HF pts require a higher filling pressure ∴ aggressive Tx can impair CO (esp RV failure)
- Metabolic alkalosis can occur ⇒ replace K & Volume as able (if can't replace v, give acetazolamide)

Kidney Disease

- Most renal disease = salt & water retention
- Severe failure is refractory to diuretics (insufficient glomerular filtrate)
- Glomerular diseases eg diabetic nephropathy, SLE benefit (esp to ↓ K)
- ***Nephrotic syndrome***: complex, fluid retention with ↓ plasma volume (owing to ↓ oncotic pressure)…diuretics can further ↓ plasma volume
- Loops 1st choice; ***acetazolamide*** exacerbates acidosis, K sparing ↑ K, thiazides ineffective at GFR < 30 ml/min

Hepatic Cirrhosis

- ↓ renal perfusion │↓ plasma volume (from ascites) │↓ oncotic pressure (hypoalbuminemia)
- ↑ aldosterone ⇒ Na retention
- ***Loops*** aren't useful due to high circulating aldosterone ∴ ***spironolactone*** good
- Aggressive use ⇒ depleted intravascular volume, hypokalemia, metabolic alkalosis ⇒ ***hepatorenal syndrome*** & ***hepatic encephalopathy***

Idiopathic Oedema

- Salt restriction

Non Oedematous States

Hypertension

- ***Thiazides*** for most
- Loops for HF or renal insufficiency
- Restricted Na intake (60-100 mEq/day)

Nephrolithiasis

- 2/3 Ca stones (usually caused by defect in Ca reabsorption)
- ***Thiazide*** diuretics enhance Ca reabsorption
- Reduce NaCl intake will allow thiazides to potentiate effect on Ca
- Other causes of high Ca include absorption & idiopathic

Hypercalcaemia

- Loop diuretics useful in Ca diuresis
- Too much loop ⇒ volume depletion ⇒ ↑ Ca reabsorption ∴ usually run NS with ***furosemide*** then match UO

DI

- Deficient production or inadequate response
- ADH supplementation only useful in central DI
- ***Thiazides*** ↓ polyuria & polydipsia in both (due to ↓ plasma volume ⇒ ↓ GFR ⇒ enhanced NaCl & H_2O resorption & ↓ delivery downstream (where ADH works)

SECTION IV: SMOOTH MUSCLE

1. HISTAMINE, 5-HT & ERGOT

- ***Histamine*** & ***Serotonin*** are neurotransmitters found in non-neural tissue
- Broad and undesirable effects ∴ not useful as a drug (selective agonists or antagonists are)

Histamine

Functions
- Allergic and inflammatory response (minor role in anaphylaxis)
- Gastric secretion
- Neurotransmitter/Neuromodulator
- Chemotaxis of WBC

Locations
- Mast cells | CNS | Enterochromaffin-like Cells
- Mast cell locations in nose/mouth/feet, blood vessels (esp bifurcation, pressure points)
- ECF cells located in fundus

Basic Pharmacology

Chemistry & Kinetics

$$l-histidine \xrightarrow{histidine\ decarboxylase} Histamine \rightarrow stored\ or\ inactivated\ quickly$$

- Most tissue histamine sequestered & ***bound in vesicles in mast cells or basophils*** (inactive)
- Histamine content ∝ mast cell numbers
- NT fcn; neuroendocrine control, cardiovascular regulation, thermal, body weight, arousal
- ECL cells; activates H^+ secreting ***parietal cells***

Storage & Release

A. Immunological Release
- Most important release mechanism
- Cells sensitised to IgE antibodies degranulate explosively when in contact with antigen aka ***Type I reaction*** (IgG & IgM reactions also release histamine)
- Along with histamine, ATP & other mediators released from same granule
- **-ve feedback:** displayed by basophils & some mast cells (in skin & blood, not in lungs)
- Injury ⇒ histamine release ⇒ local vasodilation ⇒ leakage of acute inflammatory mediators & chemotaxis
- Most of these actions via ***H_1 or H_4 receptors***

B. Chemical & Mechanical Release
- ***Morphine*** & ***tubocuraine*** can displace histamine from heparin-protein complex
- No mast cell injury or degranulation
- Loss of granules extracellularly ⇒ Na displacing histamine ⇒ release
- Mast cell injury

Dynamics

A. Mechanisms
- Via amine transporter receptors coupled to G proteins (H1-4)
- H_1 similar to muscarinic receptor | H_2 similar to 5-HT_1 receptor
- H_3 & H_4 have 40% homology (and no relation to H1 & 2)
- Some drugs are agonists at one receptors and inverse agonists at others

	Distribution	G protein	Agonist*	Antagonist*
H1	Respiratory smooth muscle Endothelial Dilation via NO Gastric smooth muscle Brain: insp/exp modulation Sensory Endings esp pain/itch	Gq ↑ IP3 DAG	***Histaprodifen***	***Mepyramine*** ***Triprolidine*** ***Promethazine*** ***Loratidine*** ***Cetirizine***
H2	Gastric Mucosa[1] Cardiac Muscle: chronotropic Mast Cells Endothelial dilation, directly Brain: Postsynaptic	Gs ↑ cAMP Gq ⇒ IP_3+DAG[2]	***Amthamine***	***Ranitidine*** ***Tiotidine***
H3	Brain: Presynaptic Myenteric Plexus Gastric Mucosa: inhibit H^+ ↓ NT release Sensory Endings incl pain	Gi ↓ cAMP[3]	***R-α-Methylhistamine*** ***Imetit*** ***Immepip***	***Thioperamide*** ***Iodophenpropit*** ***Clobenpropit***
H4	Eosinophils	Neutrophils CD4 T cells Central Nociception	Gi ↓ cAMP[4]	***Clobenpropit*** ***Imetit*** ***Clozapine***	***Thioperamide***

**Partially Selective*
[1] *Acid, Pepsin & IF*
[2] *under certain circumstances*
[3] *leads to ↓ Ca influx (through N-type channels) ⇒ ↓ transmitter release*
[4] *Chemotaxis*

Only Clinically Relevant Targets

B. Tissue & Organ Specific Effects

1. CVS
- Tachycardia by direct (H_2) and indirect; H_1 (NO mediated) & H_2 (direct)
- Low doses activate H_1, higher doses H_2

2. Other Smooth Muscle Organs
- Insignificant effects on eye & GUT
- Pregnancy anaphylaxis ⇒ uterine contraction ⇒ abortion

3. Metabolic
- Knockout of H3 ⇒ ↑ appetite, obesity, ↓ energy expenditure, insulin resistance

Triple Response (seen in intradermal injection of histamine)
1. Red spot; smooth muscle dilation
2. Oedema; endothelial contraction ⇒ ↑ pore size
3. Flare; axon reflex + itch

Clinical Pharmacology

Clinical Use: Provocative test for bronchial hyper reactivity

Toxicity/Contraindications
- Flushing, hypotension, tachycardia, headache, wheals, bronchoconstriction, GI upset
  ∴ Contraindicated in asthma, GI ulcers

Histamine Antagonists

- Physiological antagonists (eg ***epinephrine***) act on different receptors
- Release inhibitors ***reduce mast cell degranulation***
  - ***Cromolyn*** & ***Nedocromil***
  - β2 Adrenoreceptors to a smaller degree
- Histamine receptor antagonists
  - H3 &4 not in clinical use

H1 Receptor Antagonists

Basic Pharmacology

Chemistry & Kinetics
- Rapid oral absorption | Peak action 1-2 hrs, duration 4-6 hrs | High VD
- Liver metabolism (2nd gen via CYP3A4)

First Generation				
Ethanolamines				Marked Sedation
Diphenhydramine (Benadryl)	25-50mg	+++	Anti-motion sickness	
Phenothiazine Derivatives				
Promethazine (Phenergan)	10-25mg	+++	Antiemetic α-blocker	
Second Generation				Non-sedating
Loratidine (Claritin)	10mg	-	Longer acting	
Cetirizine (zyrtec)	5-10mg	-		

Dynamics

A. Hisamine Receptor Blockers
- Reversible competitive antagonism (negligible action on H_2 & H_3 ∴ heart/lungs unaffected)

B. Actions not caused by blockade
- Due to ***similar structure to muscarinic***, α-Adrenoceptors, 5HT, LA receptor sites

1. ***Sedation***; similar to centrally acting Antimuscurinic, excitation/coma in high doses
2. ***Antiemetic***; ***prophylaxis in motion sickness*** (1st gen), not so good in established
3. ***Antiparkinsons***; including ***Diphenhydramine***, inhibit extrapyramidal effects or acute dystonic reactions to antipsychotics
4. ***Anticholinoceptor***; ***Ethanolamines*** & ***Ethylenediamines*** have ***atropine*** like effects ∴ used in non allergic rhinorrhoea (but also urinary retention & blurred vision)
5. ***Adrenoceptor blocking***; α not β blocking, esp from phenothiazine group, most pronounced effect is postural hypotension
6. ***5-HT blocking***; some 1st gen esp ***Cyproheptadine***, similar structure to ***phenothiazine***
7. ***LA***; block Na ch locally, ***diphenhydramine*** & ***Promethazine*** more potent than ***procaine***, also weak K blocking effects
8. ***Other***; inhibit mast cell degranulation through alternative means (unknown)

Clinical Pharmacology

A. Allergic Reactions
- Histamine primary mediator in allergic rhinitis/urticarial ∴ H_1 antagonists 1st line
- Not effective in bronchial asthma (other mediators also involved)
- ***Angioedema*** is precipitated by histamine but maintained by peptide Kinins
  ∴ Histamines ***unable to reverse***
- Therapeutic efficacy varies between drugs & people and diminish over time

B. Motion Sickness
- ***Scopolamine***
- ***Diphenhydramine***; same dose as for allergy, used exclusively for motion sickness
- ***Promethazine***
- Better prevention in combination with ***ephidrine*** or ***amphetamine***
- May have some use in ***Meniere's syndrome***

C. N&V in pregnancy
- No longer used
- ***Piperazine*** has teratogenic effects
- ***Doxylamine*** does not (but public perception thinks so)

Toxicity
- Major; Sedation, Anti muscurinic effects
- Less common; kids (convulsions, excitation), postural hypotension, allergy
- Overdose in old people ***resembles atropine overdose***

Interactions
- Early 2nd gen H_1 antagonists + ***ketoconazole***, ***itraconozole*** or ***macrolide*** ⇒ ***vent arrhythmia***
- Due to inhibition of CP450 and accumulation of H_1 antagonist (grapefruit juice also inhibits)
- Accumulation ⇒ ***IKr blockade*** ⇒ arrythmias

H2 Receptor Antagonists

- Reduce gastric acid secretion | Low toxicity (no H_1 effects)

H3 & 4 receptor Antagonists

- None for clinical use
- Theoretical benefit in obesity, cognition & psychiatric disorders
- H4 blockers have potential in chronic asthmatics

Serotonin (5HT)

- Neurotransmitter
- Local gut hormone (smooth muscle stimulant)
- Component of platelet clotting and vessel wall constriction
- Mediates *carcinoid syndrome* (from carcinoid tumour – ECF cells tumour)

Pharmacology

Chemistry & Kinetics

- Synth by tryptophan | deconstructed by MAO
- Packed into vesicles by VAT (in either ECF cells or platelets) blocked by *Respirine*
- Brain serotonergic neurons involved in; *mood, sleep, appetite, perception of pain, temp regulation, BP regulation, vomiting*

Dynamics

A. Mechanism

- Large number of membrane receptors | 7 families (6 g-protein linked, 1 ligand gated)

	Distrbtion	G protein	Agonist	Antagonist
5-HT $1_{D/B/P}$	Brain Enteric	Gi, ↓ cAMP	*Sumatriptan*	
5-HT 2	Vascular Smooth Muscle	G something		*Chlorpromazine*
5-HT 3	Area Postrema Sensory & Enteric Nerves Vomiting Reflex	Na=K ion ch		*Granisetron, Ondansetron, Tropisetron*
5-HT 4	CNS & Myenteric nerves Smooth Muscle	Gs, ↑ cAMP	*Maxalon*	
5-HT 6,7	Brain	Gs, ↑ cAMP		*Clozapine*

B. Tissue & organ Specific

1. NS

- Neurotransmitter | Vomiting | Enteric
- Serotonin is a potent stimulant at pain and itch sites (esp insects/plants)
- Main receptor in *chemoreceptor reflex* of coronary vascular bed ⇒ vagal ⇒ ↓HR ↓BP

Melatonin

- 5HT precursor released from pineal at night ?sleep-wake cycle
- MT1 & 2 receptors in brain (Suprachiasmic) are Gi coupled ↓ Adenyl cyclase
- MT1 activation ⇒ sleepy | MT2 activation ⇒ light-dark synchrony
- *Ramelteon* selective MT1 & 2 agonist T ½ 1-3hrs, T ½ (metabolites 5 hrs)

2. Respiratory

- Small direct stimulation of bronchiolar smooth muscle
- Facilitated ACh release from bronchial vagal efferents

3. CVS

- Vascular smooth muscle contraction (esp pulmonary & renal) ($5HT_2$)
- Dilates skeletal and coronary vessels
- Small direct +ve chronotropic & inotropic effect on heart
- Venocosntriction ⇒ "flushed" feeling
- Injection shows triphasic response to BP;
  1. ↓ HR, CO, BP (due to reflex)
  2. ↑ BP (vasoconstriction)
  3. ↓ BP (vasodilation)

4. Skeletal

- $5HT_2$ receptor mediated (unknown role)

Serotonin syndrome

- MAOI's or SSRI's ⇒ ↑ circulating 5-HT
- Skeletal contraction (2ry hyperthermia), CNS effects
- Tx; BZDP sedation, 5-HT_2 blocker (*Chlorpromazine* or *Cyproheptadine*)

Syndrome	Drug Interactions	Sx	Tx
Serotonin Syndrome	*SSRIs* 2nd gen antidepressant *MAOI* *Linezolid* *Tramadol* *Fentanyl* *Ondansetron* *Sumatriptan* MDMA, LSD St Johns Wart Ginseng	HTN Hyperthermia Clonus Tremor Hyper reflexia Hyperactive Bowel Diarrhoea Mydriasis Agitation Coma Onset: hrs	BZDP sedation ABC 5HT2 blocker (*chlorpromazine*)
Neuroleptic Malignant Syndrome	D2 blocking antipsychotics	Acute severe parkinsonism HTN Hyperthermia Normal/Low bowel activity Onset: 1-3 days	*Diphenhydramine* Cooling BZDP
Malignant Hyperthermia	Volatile anaesthetics *Succinylcholine*	Hyperthermia Muscle Rigidity HTN Tachycardia Onset: minutes	*Dantrolene* Cooling

Clinical Pharmacology

Serotonin Agonists

- *Buspirone* 5-HT_{1A} agonist anxiolytic | *Sumatriptan (imigran)* migraines

5HT1D/1B agonists & Migraines

- Pathology; trigeminal nerve distribution of intra/extracranial arteries ⇒ *calcitonin gene-related peptide release* ⇒ powerful vasodilation ⇒ extravasation of plasma & plasma proteins ⇒ perivascular oedema ⇒ activation of pain nerve endings in dura +/- temporal pulsation
- *Triptans*, *Ergot Alkaloids*, Antidepressants inhibit 1D/1B receptors ⇒ inhibition of CGRP release & cause vasoconstriction at same time
- Antiseizure agents supress excessive firing
- *Propanolol*, *Ca Channel blockers*, *amitriptyline*; prophylaxis

Sumatriptan (Imigran)

- Oral, nasal, s/c | Onset 1.5 hrs (0.2 s/c) | Dose 25-100mg PO max 200mg | T ½ 2 hrs
- Adverse: alt sensation, dizziness, muscle weakness, chest pain, coronary vasospasm

Naratriptan (Naramig)

- Oral, onset 2 hrs, 1-2.5mg max 5mg, T ½ 5 hrs
- Contraindicated in severe hepatic, renal impairment, PVD

Zolmitriptan (Zomig)

- Oral, Nasal, onset 1.5-3hrs, 1.25-2.5mg max 10mg, T ½ 2.8hrs
- Contraindicated in WPW

Other Clinical Uses

- *Fluoxetine* & SSRIs used for depression

Serotonin Antagonists

- Production; limited use due to widespread functions
- Storage; as above
- Receptor; main method of antagonism

Serotonin Receptor Antagonist

- Variety of drugs with other primary functions
- *Phenoxybenzamine*; long lasting $5HT_2$ receptor block
- *Ergot Alkaloids* are partial agonists
- *Cyproheptadine* (similar to phenothiazine) has 5HT1 & 2 blocking actions (∴ effects smooth muscles but not gastric secretion), along with Antimuscurinic effects (sedation), used as Sx Tx in *carcinoid and cold induced urticaria*, 12-16mg in 4 divided doses
- *Ondansetron*; 5-HT_3 receptor antagonist, useful in N&V

Ergot Alkaloids

- Grown from fungus in damp places | Agonist effect on *D, 5HT & α Adrenoreceptors*
- Main effects of overdose; dementia, florid hallucinations, prolonged vasospasm +/- gangrene, uterine contraction in pregnancy

Pharmacology

Chemistry & Kinetics

- Variable absorption in gut
- *Ergotamine* has 10x absorption oral vs IM (both improved with concurrent caffeine)
- Amine alkaloids absorbed from rectum, buccal, inhalation
- *Bromocriptine* & *Cabergoline* well absorbed orally

Dynamics

A. Mechanism

Ergot Alk	α	D	$5HT_2$	Uterine
Bromocriptine	-	+++	-	0
Ergonovine	+	+	- PA	+++
Ergotamine	- - PA	0	+ PA	+++
LSD	0	+++	-- (++ in CNS)	+
Methysergide	+/0	+/0	--- PA	+/0

B. Organ Specific

1. CNS: Hallucinogenic

2. Vascular Smooth Muscle

- Drug/species/vessel dependant
- Venoconstriction mainly due to α & 5-HT_2 agonism by *ergotamine*, *Ergonovine*
- *Ergotamine*; prolonged generalised vascular constriction, epinephrine reversal, blocked by α blocking agents
- Overdose ⇒ severe prolonged vasospasm not easily reversed by α antagonist

3. Uterine Smooth Muscle

- α & 5-HT agonism (α receptors upregulated in pregnancy ∴ small dose = contractions)
- *Ergonovine* is most selective for uterus

4. Other Smooth Muscle

- Minimal effect on bronchiolar & urinary smooth muscle
- GIT: diarrhoea, nausea & vomiting due to central and gastric 5-HT receptor agonism

Clinical Pharmacology

A. Migraines

- *Ergotamine* given during *prodrome* of attack
  - Oral, S/L, PR | Combined with *caffeine* combination
  - Max dose 6mg per attack (long T ½) max 10mg/week

B. Hyperprolactinaemia

- Due to secreting pit tumours or centrally acting D antagonists (esp D_2 antipsychotics)
- Sequelae; amenorrhea, infertility, galactorea
- *Bromocriptine*; effective, tumour regression in some cases, 2.4mg BD or TDS
  - Also used to supress physiological lactation (post partum cardiovascular toxicity)
- *Cabergoline*; more potent

C. Postpartum Haemorrhage

- Oxytocin preferred but 0.2mg *ergotamine* IM if not, onset 1-5 min | NEVER before delivery

D. Diagnosis of variant Angina

- Ergonovine during angio to locate variant angina

Toxicity & Contraindications

- Mainly GI upset
- Prolonged vasospasm (can lead to gangrene, ischemic bowel)
  - Some reversal with nitroprusside or Nitroglycerin
- Chronic 5-HT agonists use can cause fibrotic Δ ⇒ mass effect in ureters & heart
- Not contraindicated in pregnancy but warned

2. VASOACTIVE PEPTIDES

- Cell to cell communication
- Some have direct effects on vascular/other smooth muscle

Vasoconstrictors	Vasodilators
• AT II • Vasopressin • Endothelin • Neuropeptide Y • Urotensin	• Bradykinin & related Kinins • Natriuretic Peptide • Vasoactive Intestinal Peptide • Substance P • Neurotensin • Calcitonin Gene-related Peptide • Adrenomedullin

Angiotensin

Biosynthesis

$$angiotensinogen \xrightarrow{Renin} ATI \xrightarrow{ACE} ATII \xrightarrow{Aminopeptidase} ATIII \xrightarrow{Angiotensinases} Peptide\ Fragments$$

Renin & Factors Controlling Secretion

- Synth & stored in JGA | Innervated by noradrenergic neurons

A. Renal Vascular Receptors

- ***Stretch*** receptor on afferent arteriole; ↓ ⇒ renin release (via Δ Ca)

B. Macula Densa

- Chemoreceptor sensing ***flow*** of Na or Cl through DCT | ↓ flow ⇒ renin release
- Drugs that interfere; ***adenosine, PG, NO***

C. Sympathetic NS

- Norepinephrine ⇒ β_1 receptors ⇒ renin secretion

D. Angiotensin

- ATII inhibits renin secretion (***negative feedback***)

E. Pharmacological Alteration of Renin Release

- Stimulating renin

Group	Drugs
Vasodilators	***Hydralazine*** ***Minoxidil*** ***Nitroprusside***
β Adrenoceptors agonists	***Isoproterenol***
α Adrenoceptors antagonists	
Phosphodiesterases Inhibitors	***Theophylline*** ***Milrinone*** ***Rolipram***
Most Diuretics & Anaesthetics	

Angiotensinogen

- Factors ↑ production; corticosteroids, oestrogen, thyroid hormones, ATII, pregnancy
  (May contribute to hypertensive states that commonly manifest)

Converting Enzymes: ACE, Peptidyl, Dipeptidase, Kininase II

- Most important substrates; ***Bradykinin & AT I***
- ACE widely distributed in body, on luminal surface of vascular endothelium
- ACE2 highly expressed in vascular endothelium of kidney, heart, testes
  - Converts ATI or II ⇒ AT 1-9 (no known function) & AT 1-7 (vasodilator)
  - AT 1-7 may counteract effects of AT II
  - Does not hydrolyse bradykinin

Angiotensinase

- AT II T ½ 15-60 seconds
- Metabolised by Angiotensinase in most vascular beds (except lungs)
- Metabolites are largely inactive (apart from initial ATIII)

Actions of AT II

- Vascular smooth muscle, adrenal cortex, kidney, heart, brain
- Regulates fluid/electrolyte balance & arterial blood pressure

Blood Pressure

- 40x more potent ***pressor*** than norepinephrine | Onset 10-15 seconds
- Direct action on vascular smooth muscle (esp arteriolar) but also on brain & ANS
- No bradycardic reflex due to ***"resetting" of baroreflex*** through CNS
- ANS; stimulates ↑ release of nor/epinephrine & facilitates sympathetic transmission at nerve endings (through ↑ release / ↓ reuptake of nor/epi)
- ***Inotropic*** on the heart (to a small degree)

Adrenal Cortex

- ATII acts directly on Zona Glomerulosa ⇒ aldosterone synthesis ⇒ glucocorticoid synthesis

Kidney: Renal vasoconstriction | ↑ prox tubule Na reabsorption | Inhibit renin secretion

CNS: Stimulate drinking | ↑ ADH & ACTH

Cell Growth

- Mitogenic for vascular & cardiac muscle (?contribution to hypertrophy)
- ACE I & ATII receptor antagonists ***limit remodelling*** in disease states

Angiotensin Receptors & Mechanism of Action

- AT_1 & AT_2 receptors | AT II binds equally to both but most actions mediated through AT_1

	Actions
AT_1R	• Most of AT II actions occur on these Gq coupled receptors (PLC → IP3 & DAG) • Overall effect = ***smooth muscle contraction***
AT_2R	• Similar structure to AT 1	Stimulation ⇒ vasodilation (NO dependant) • In foetus: high density in all tissues • In adult: high density in adrenal medulla, reproductive tissues, vas endothelium • Upregulated in pathological states (incl HF & AMI) • Functions: foetal growth, inhibition of growth/proliferation/cell differentiation, apoptosis, vasodilation

Inhibition of Renin-Angiotensin System

Drugs that Block Renin Secretion

- ***Clonidine*** ↓ renal sympathetic nerve activity ⇒ ↓ renin secretion (+- direct Intrarenal effect)
- ***Propranolol*** blocks intra/extra renal β-linked neural control of renin secretion

Renin Inhibitors

- ***Aliskiren*** (dose dependant reduction in renin activity)

ACE Inhibitors

- ***Captopril*** & ***Enalapril*** | Block conversion of ATI ⇒ AT II
- ↓ systemic vascular resistance without ↑HR, also promote natriuresis
- Also inhibit degradation of bradykinin, substance p, enkephalins
  (Inhibition of bradykinin degradation ⇒ hypotension, cough, angioedema)

Angiotensin Receptor Antagonists

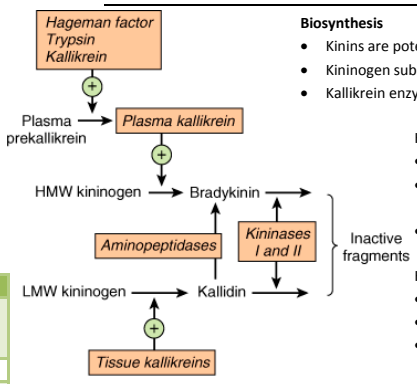
Peptide agonists

- ***Saralasin***; partial agonist, only peptide agonist available
- Has pressor response when AT II low | Used to investigate renin-dependant HTN

Non peptide Agonists

- ***Losartan, Valsartan, Eprosartan, Irbesartan, Candesartan, Olmesartan, Telmesartan***
- Orally active, potent, AT_1 antagonist
- Similar efficacy to ACE inhibitors (***lower incidence cough***)
- Prolonged treatment ⇒ high circulating AT II ⇒ AT2 activation (theoretical benefit)

Kinins



Biosynthesis

- Kinins are potent vasodilators
- Kininogen substrate
- Kallikrein enzymes

Kallikreins

- Kallikreins exist in plasma and other tissues
- Plasma prekallikrein activated by trypsin, Hageman factor, Kallikrein
- Tissue Kallikreins have different properties

Kininogens

- Kinin precursor
- Found in plasma, lymph, interstitial fluid
- LMW Kininogens can cross capillaries ∴ substrate for tissue Kallikreins
- HMW Kininogens confined to blood stream

Formation of Kinin in plasma & Tissue

- 3 Kinins known
  1. ***Bradykinin***; other 2 contain this structure, predominant in plasma, formed from plasma Kininogens
  2. ***Kallidin*** (lysylbradykinin); from tissue Kininogens, predominant in urine
  3. ***Methionyllysylbradykinin***; from pepsin & pepsin-like enzymes

Actions of Kinins

CVS

- Marked arteriolar ***dilation*** on heart, kidney, intestines, skeletal muscle, liver
- x10 potency of histamine
- Both in/direct effects (release NO, PGE_2, PGI_2) | ***Venoconstriction*** (in/direct PGF2α)
- Contraction of most ***visceral smooth muscle***
- Following IV administration; unsustained ↓ BP due to ***reflex tachycardia***/chronotropy/↑CO
- Net result; extravascular movement ⇒ oedema

Endocrine & Exocrine

- Pre/Kallikreins present in pancreas, kidney, intestines, salivary glands, sweat glands
- Local ***modulator of blood flow***
- Modulate ***duct tone*** in pancreas & salivary glands
- Regulate intestinal motility
- Activate prohormones (incl proinsulin & prorenin)

Inflammation

- ↑ production of Kinins in inflammation to cause redness, local heat, swelling & pain directly

Sensory Nerves

- Potent pain producing substance | Aggravate nociceptive afferents

Kinin Receptors & Mechanism of Action

- 2 types: B1 & B2
- B1 limited distribution, may be involved in Kinin part of inflammatory response
- ***B2 widespread***, include B2A &2B, bradykinin has highest affinity (except venous smooth muscle – lysylbradykinin more potent)
- G protein coupled

Metabolism

- T ½ < 15 seconds | Kininase I; synth in liver | Kininase II; in plasma and vascular endo
- Bradykinin completely hydrolysed during ***single passage through pulmonary vascular bed***

Drugs Affecting Kallikrein-Kinin System

- **Only research** | Theoretical benefit in anti-inflammatory and nociceptive blunting

Vasopressin

- Long term BP control | Water retention through ***aquaporin upregulation***
- ↑ TPR but Maintained BP due to down regulation of CO

Vasopressin Receptors & Antagonists

- V1A | vasoconstriction (via PLC & ↑ intracellular Ca)
- V1B | potentiates ACTH release
- V2 | mediate antidiuretic effect (via adenyl cyclase activation)
- ***Desmopressin*** (dDAVP) V2 antidiuretic analog

Natriuretic Peptides

NP	Synth & Structure
ANP	• Synth in atrial cells (some in ventricular) also in CNS & PNS, lungs • Factors ↑release; ***stretch (main),*** volume expansion, head out of water immersion, standing to supine, exercise, α 1A agonism • Pathological states; HF, 1ry Aldosteronism, CRF, SIADH • ANP ***natriuresis***: ↑ Na excretion/urine flow, ↑ GFR but no Δ renal blood flow • Inhibits secretion of renin, aldosterone, vasopressin • ↓ ABP by ↓ sympathetic tone/antagonise AT II
BNP	• Synthesised in heart; ***volume related release*** • Similar natriuretic, diuretic, hypotensive effects as ANP • Low levels of circulation
CNP	• Found mainly in CNS • Less naturetic & diuretic effect but ***potent dilator*** • Not seen in circulation (unknown function)

Receptors & Kinetics

- ANP_A | ANP & BNP ligand, coupled to guanylyl cyclase
- ANP_B | CNP ligand, coupled to guanylyl cyclase
- ANP_C | remove A,B,CNP from circulation (equal affinity)
- Short T ½ | Metabolised by kidney, liver, lung by NEP 24.11

Vasopeptidase Inhibitors

- Inhibit NEP 24.11 & ACE ⇒ ↑ circulating naturetic peptides (↓ AT II formation)
- **None for clinical use**

Endothelins

Biosynth, Structure, Clearance

- Matured by ***Endothelin Converting Enzyme*** | Cleared by enzymes eg NEP 24.11

Widely distributed

Isoform	Location
ET-1	*vascular endothelium*, neurons/astrocytes, endometrium, Mesangial, Sertoli, breast)
ET-2	kidneys, intestines
ET-3	brain, lung, kidneys, GIT

- ET low concentration in blood
- Upregulated by AT II & Vasopressin | Down regulated by NO, Prostacyclins, ANP

Receptor	Affinity	Action	Type
ET-A	ET-1 > ET-3	Smooth Muscle Contraction	G-protein
ET-B	ET-1 = ET-3	PG & NO release	G-protein

Actions

- Dose dependant ***vasoconstriction***; initial drop due to PG & NO release
- Cardiac; Inotropic & chronotropic
- Respiratory; tracheal/bronchial smooth muscle contraction
- Renal; vasoconstriction, ↓ GFR
- Endocrine; ↑ renin, aldosterone, vasopressin, ANP
- Smooth muscle; Mitogenic

Inhibitors of Endothelins Synth & Action

- ***Bosentan***; non-selective receptor antagonist via IV or oral route, used in ***pulmonary HTN***

Physiological & Pathological Roles of Endothelin: Effects on Endothelin Antagonists

- Cause vasodilation & ↓ ABP
- Since Endothelins are implicated in multiple disease states, inhibition may reverse
- ***Sitaxentan***; ET-A selective receptor antagonist | HF, Pulmonary & Essential HTN
- Toxicology; teratogenic, hepatotoxic

Vasoactive Intestinal Peptides (VIP)

- In CNS & PNS as a NT/modulator | Also in blood, GIT, CVS, Lungs, Kidneys (not hormonal)
- CVS: dilator (more so than ACh), chrono/inotropic
- Receptors; VPAC1,2 (g-protein linked)

Substance P

- Hormonal; GIT | Neurotransmitter; CNS
- Actions: arteriolar vasodilator (via NO release), anxiety, depression ,nausea, emesis, contraction of venous, intestinal, bronchial smooth muscle, diuresis/natriuresis
- Receptors; NK1,2,3; g-protein linked (most effects through NK1)
- ***Aprepitant***: NK1 receptor antagonist used in ***anti-emesis in chemotherapy***

Neurotensin

- Brian & GIT as Neurotransmitter/modulator & local hormone
- Brain: Neurotensin & neuromedin N released together at nerve endings
- GIT: mainly Neurotensin, both released into circulation after ingestion of food
- Central actions: close relation to dopamine
- Peripheral actions:
  - Vasodilation (hypotension) ↑ vascular permeability
  - ↑ secretion of ant pit hormones, Hyperglycaemia,
  - Inhibition of gastric acids, motility
- Receptors; NT1,2,3 (1,2 G protein linked, 3 sorting protein)
- Clinical use may include PD

Calcitonin Gene-Related Peptide

- Calcitonin, Adrenomedullin, Amyline | Large quantities with calcitonin in thyroid gland
- Also found with substance P or Ach
- Central: HTN, ↓ appetite | Peripheral; hypotension, tachycardia
- May play a role in ***migraines*** | Receptors: CGRP1,2

Adrenomedullin

- Calcitonin family
- Dilates resistance vessels, reflex tachycardia, Naturesis, ↑ sympth outflow
- Receptors: AM1,2 (cAMP)
- High levels in intense exercise & pathological states (HTN, cardiac/renal failure, septic shock)

Neuropeptide Y

- *Most abundant* neuropeptide in CNS & PNS
- Sympth NS: noradrenergic ⇒ vasoconstriction and co-transmission with norepinephrine
- Central effects; hypotension, hypothermia, resp depression
- Receptors Y1-6 (g protein – except Y3)
- Y1,2 | cardiovascular, peripheral Y4 | pancreatic polypeptide
- Y5 | CNS, food intake Y6 | unknown sig

Urotensin

- Expressed in brain, spinal cord, kidney
- Potent constrictor at arterioles (more than Endothelin 1)
- UT receptor; g-protein

3. EICOSANOIDS: PG, LK, TX...

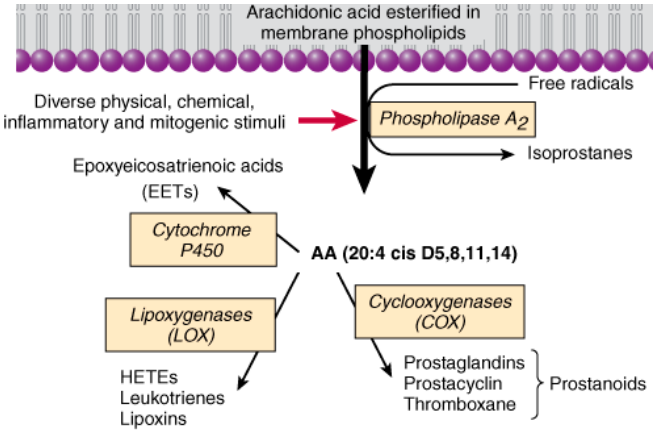
- Oxygenation products of polyunsaturated long chain FA
- Wide spectrum of biological activity

Arachidonic Acid & Other Polyunsaturated Precursor

- Arachidonate released from membrane by lipase (usually PLA$_2$)

4 ways to oxygenation of arachidonic acid
1. COX
2. P450
3. LOX
4. Isoprostane Pathway

Factors determining types of Eicosanoids Synth
- Species
- Type of cell
- Phenotype
- Manner of stimulation
- Nature of precursor FA



Synthesis of Eicosanoids

Production of PG Endoperoxide Synthase (COX)
- COX 1 & 2 convert arachidonic acid ⇒ PG endoperoxidases

$$Arachadonic\ acid \xrightarrow{COX\ 1\ or\ 2} PGG_2 \xrightarrow{COX\ 1\ or\ 2} PGH_2 \rightarrow Prostanoids\ (PG, TX, Prostacyclin)$$

COX 1 |
- Expressed in most cells
- Prostanoids for *housekeeping* eg gastric epithelial cytoprotection

COX 2 |
- Inducible in early response
- Upregulated by *shear stress, GF, tumour promoters, cytokines*
- Prostanoids for inflammation, cancer
- Epithelial COX 2 *1ry source for vascular PG* but *renal COX2 for housekeeping*

COX Inhibiting Drugs

Specificity	Drugs
Non-specific	*Ibuprofen, Aspirin**
COX-1	*Indomethacin, Sulindac*
COX-2	*Celecoxib, Diclofenac, Rofecoxib*

**Aspirin inhibits both covalently; Low dose (<100mg) = COX-1 preferential, High dose inhibit both*

Prostanoid	Drug	Action
PGE$_1$	*Alprostadil*	Relaxes muscle to maintain PDA, Tx Impotence
PGE$_1$	*Misoprostol*	PUD prophylaxis, TOP (with *mifepristone*)
PGF$_{2\alpha}$	*Latanoprost*	Open Angle Glaucoma
PGI$_2$	*Prostacyclin*	Tx pulmonary HTN through vasodilation, inhibit plts
TX	*Thromboxane*	Vasoconstriction & ptt aggregation

- All have rapid metabolism (hydration or oxidation)

Products of Lipoxygenase

$$Arachidonic\ Acid \xrightarrow{5-LOX\ \&\ FLAP} HPETEs \xrightarrow{5-LOX} HETE + Leukotrienes$$

- LTA4 $\xrightarrow{LTA4\ hydrolase}$ LTB4 or LTA4 $\xrightarrow{LTC4\ syntahse}$ LTC4 ⇒ LTD4 ⇒ LTE4
- LTC4 & D4 are potent bronchoconstriction
- Associated with *asthma, anaphylaxis (slow component), CVD*
- Stimulation ⇒ ↑ intracellular Ca, release of Arachidonate
- Main targets for drugs (still in research)
  5-LOX inhibition | Leukotriene Receptor | FLAP inhibition | PLA2 inhibition

Epoxygenase Products (via P450)

- Synth in endothelial cells | Unstable | Can be incorporated in phospholipid for storage
- Cause vasodilation

Isoprostanes

- Stored as part of membrane | Vasoconstrictor locally

Pharmacology of Eicosanoids

Mechanism & Effects

Receptor
- Autocrine & Paracrine (due to short T 1/2)
- G protein: Contractile effects; release of Ca | Relaxing effects; cAMP generation

Effects of PG & TX

A. Smooth Muscle

1. Vascular
- TXA$_2$ potent *vasoconstrictor* & *smooth muscle mitogen*
- Mitogenic effect potentiated by testosterone (↑ TP receptor population)
- PGF$_{2\alpha}$ vasoconstrictor only (PGI2 & PGE2 also)

2. GIT
- PGE$_2$ & PGF$_{2\alpha}$ constrict longitudinal fibres
- PGF$_{2\alpha}$ & PGI$_2$ constrict circular fibres (PGE$_2$relaxes)
- Leukotrienes have powerful constricting effects

3. Airways
- Relax: PGE$_2$, PGI$_2$
- Contract: PGD$_2$, TXA$_2$, PGF$_{2\alpha}$ *bronchospasm in 10% of NSAIDs due to shift* in arachidonic metabolism from COX-1 metabolism to leukotriene formation

B. Platelets
- PGE$_2$; low levels enhance aggregation, high levels inhibit
- PGD$_2$, PGI$_2$; inhibit aggregation
- *TXA$_2$; platelet aggregator & amplifies more potent plt agonists (eg thrombin)*
- Plt release TXA$_2$ during activation & aggregation
- *Aspirin* inhibits (inverse dose-response, high doses may inhibit PHI$_2$ synthesis)

C. Kidneys
- Medulla synth more than cortex
- Eicosanoids regulate renal function (COX inhibitors ↓ fcn in marginal functioning kidneys)
- Cortex; PGE$_2$ & PGI$_2$ ⇒ ↑ renin release, Na/H$_2$O excretion, ↑ GFR
- Loop diuretics produce part of effect through COX stimulation
  ∴ COX inhibitors ↓ loop potency
- TXA$_2$; Intrarenal vasoconstriction ⇒ ↓ renal function

D. Reproductive Organs

1. Female
- TXA$_2$ & PGF$_{2\alpha}$ & PGE$_2$ (low) ⇒ uterine contraction(Parturition involves PGF2α & oxytocin)
- PGI$_2$ & PGE$_2$ (high) ⇒ relaxation

2. Male
- Seminal vesicles | Testosterone promotes production | Low seminal vesicle PG are infertile
- PGE$_1$ relaxes smooth muscle ⇒ enhanced erection

E. CNS & PNS

1. Fever;
- PGI$_2$, PGF$_{2\alpha}$ all ↑ T but *not involved in natural pyretic response*
- Pyrogens release IL-1 ⇒ PGE$_2$ synth⇒ pyretic response
- *Aspirin* inhibits PGE$_2$ synth

2. Sleep
- PGD$_2$ intracerebral induces sleep

3. Neurotransmission
- PGE inhibits norepinephrine release from sympth nerve endings
- *NSAIDs ↑norepinephrine release*
- Peripheral: PGE$_2$ & PGI$_2$ sensitize peripheral nerve endings to painful stimuli
- Central: PGE$_2$ ↑ excitability in neuronal pain transmission

F. Neuroendocrine Organs
- PGE$_2$ promotes secretion of all ant pit hormones (not physiology significant amount)

G. Bone Metabolism
- PG from osteoblasts | PGE$_2$ *↑bone turnover* (part of cause of Osteoporosis in menopause)
- COX inhibitors can slow skeletal bone healing

H. Eye PGE & PGF's *↓IOP*

Effects of Lipoxygenase & Cytochrome P450 derivative metabolites

A. Blood Cells & Inflammation
- Leukotrienes are heavily implicated in inflammation
- LTB4 is a chemoattractant for PMNs, eosinophils, monocytes
- LTC4 & LTD4 are chemoattractant for eosinophils
- At higher doses; adherence, degranulation, O$_2$ free radical formation
- PG inhibit lymphocyte function/proliferation
- PGD$_2$ & TXA$_2$regulate T lymphocyte proliferation (and apoptosis)
- PGE$_2$ inhibits B cell differentiation & T cell proliferation
- Lipoxins A & B inhibit NK cells

B. Heart & Smooth Muscle

1. CVS
- 12(S) HETE promotes myointimal proliferation (esp after angioplasty)
- 12(R)HETE inhibits Na/K ATPase in cornea
- LTC4 & LTD4 ↓ chronotropy & flow
- Lipoxin A & B are vasoconstrictive on coronary vessels

2. GIT:Colonic epithelium synthesizes LTB4 ⇒neutrophil Chemotaxis | IBD has ↑ LTB4

3. Airways
- LTC4 & D4 ↑ Microvascular permeability, plasma exudation, mucus secretion, bronchoconstriction

C. Renal: 5,6 epoxide is a powerful vasodilator (mainly speculative roles)

D. Cancer
- Angiogenesis is required for multistage carcinogenesis
- Angiogenesis promoted by COX2 derived TXA$_2$ & PGE$_2$ & I$_2$
- COX inhibitors ↓ colon tumour formation
- NSAIDs ass with 40-50% reduction in colon Ca formation

E. Misc
- Unknown effects on reproductive & nervous system

Inhibition of Eicosanoid System

- Corticosteroids stimulate synthesis of annexins & lipocortins ⇒ ***block eicosanoid synthesis***
  - Also inhibit PLA2 activity by interfering with binding
- ***NSAIDs block PG & TX formation by reverse inhibition COX activity***
  - Don't inhibit LOX at maximal COX inhibition dose (make more substrate for LOX pathway)
- ***Aspirin irreversibly inhibits COX***
- Since platelets are anuclear, COX inhibition cannot be restored = extended inhibition of TXA_2 biosynthesis

Clinical Pharmacology

Main prostaglandins in clinical use;

- ***Alprostadil*** | PGE1 |
- ***Misoprostol*** |PGE1 analog |
- ***Dinoprostone*** (***Cervidil***) |PGE2 |
- ***Epoprostenol*** |PGI2 |

Female Reproduction

A. Abortion

- PGE_2 & $PGF_{2\alpha}$ are potent oxytocic agents & terminate pregnancy by uterine contraction
- Primes & Ripens cervix for abortion or labour

Dinoprostone (Cervidil)

- PGE_2; ***Stimulates contraction, Softens cervix***
- Metabolised in local tissue, lungs (95%), Excreted in urine | T ½ 2-5min
- Induction: Gel 0.5 mg or 10mg SR (0.3mg/hr) = less GI side effects
- Cervical Ripening: Gel 0.5 mg q6h
- Abortion: 20mg vag sup, rpt 3-5hrs (mean time to abortion 17 hrs, 25% incomplete)

Mifepristone (***RU486***) & ***Misoprostol***

- Antiprogestin combined with oxytocic PG
- Oral & vaginal same potency (vaginal more likely to get sepsis)
- Toxicity; diarrhoea, cramping

B. Facilitation of Labour

- $PGF_{2\alpha}$ can induce labour but ***PGE_2 x10 potency*** (equal efficacy)
- Comparable "time-to-delivery" as oxytocin but more adverse effects; N&V, diarrhoea
- Oral PGE2 same efficacy as IV oxytocin
- No cardiovascular change (1/20 dose required)
- PGF2α cautioned in asthma |Foetal toxicity uncommon

C. Dysmenorrhea

- Due to ↑ endometrial synthesis of PGE2 & PGF2α during menstruation
- NSAIDs inhibit PG
- Aspirin not useful since it has a short T ½ and irreversibly binds COX ⇒ ↑ bleeding

Male Reproduction

Alprostadil

- intracavernous or urethral suppository | 2nd line therapy | 2.5-25 mcg
- Toxicity: penile pain, priapism

Renal

- ↑ PG synth ⇒ ***Bartter's syndrome*** (unknown cause)
- Low/normal BP | ↓ angiotensin sensitivity | Hyper-reninemia & aldosteronism
- Excess K loss | ↑ PG urinary excretion (esp PGE)
- ***Cox inhibitors return most functions to normal*** (not K wasting)

Cardiovascular

A. Pulmonary HTN

- PG ↓ peripheral, pulmonary, coronary resistance

Epoprostenol

- 1ry pulmonary HTN | Short T ½ ∴ only used as infusion

B. PVD

- Raynaud's | Peripheral atherosclerosis (theoretical benefit in infusion to allow remodelling)

C. PDA

- ***Patency relies on PGE_2 (COX_2 derived) acting on EP4 receptors***
- At birth ↑ PGE_2 consumption ⇒ ↓ levels ⇒ closure
- Congenital diseases where patency is essential; ***transposition of great vessels, pulmonary atresia, pulmonary artery stenosis***

Alprostadil

- PGE1; vasodilator, inhibits platelet aggregation
- Toxicity; apnoea, bradycardia, hypotension, hyperpyrexia
- Rapid pulmonary clearance ∴ cont infusion
- Long term therapy ⇒ ductal fragility & rupture

- Delayed closure can use COX inhibitors

Blood

- TXA_2promotes plt aggregation | PGI_2 inhibits | ***Aspirin*** inhibits COX1

Respiratory

- PGE_2 ***powerful bronchodilator*** (inh) + cough
- $PGF_{2\alpha}$ & TXA_2 are both strong bronchoncstrictors
- ***LTC_4, D_4, E_4 dominate asthmatic constriction***
  ∴ Leukotriene receptor antagonists are effective (***Montelukast***)
- ***Corticosteroids*** inhibit eicosanoid synthesis
- ***Cromolyn*** inhibits eicosanoid release

GIT

- ***Misoprostol*** used to prevent NSAID induced peptic ulcer | 200mcg QID
- Inhibit gastric secretion at high doses (cytoprotective at low)
- Toxicity: abdo discomfort, diarrhoea, bone pan (all dose dependant)

Immune System

- T & B lymphocytes supply arachidonic acid to monocytes for eicosanoid synthesis
- PGE_2 & PGI_2 limit T cell proliferation

A. Cell mediated Organ transplant Rejection

- Acute rejection cell mediated immune response: PGI_2 reverses rejection
- ***Corticosteroids*** are first line (lymphocytic effect)

B. Inflammation

- COX-2 more specific for inflammatory reactions
- Leukotrienes & HETEs are Chemotactic

C. RA

- Eicosanoids amplify effect of immune complex deposition in joints

D. Infection

- Not well defined | ***NSAIDs*** don't seem to alter response

Glaucoma

- ***Latanoprost***, ***Bimatoprost***
- PGF2α | Once or twice daily in conjunctiva
- Toxicity; irreversible brown pigmentation of iris, eyelashes, dry eyes, conjunctivitis

Dietary manipulation

- Highly saturated fat diets have ↑ platelet aggregation

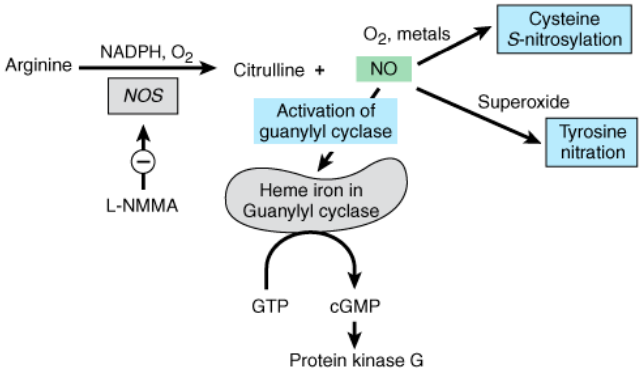
4. NITROUS OXIDE

- Signalling molecule that readily diffuses across cell membranes

Endogenous NO

- Generated in most ells in almost all tissues with vasodilatory effect

NO Synthase, Signalling Mechanism & Inactivation



Isoformso f Nitrous Oxide Synthase			
Isoform Name	**NOS-1**	**NOS-2**	**NOS-3**
Other name	nNOS	iNOS	eNOS
Tissue	***N***euronal Epithelial	Macrophages Smooth Muscle	***E***ndothelial
Expression	Constitutive	Transcription	Constitutive
Ca regulation	Y	N	Y
Chromosome	12	17	7

- nNOS = neuronal, I = inducible, e = endothelial
- eNOS & nNOS activated by ↑ cytosolic Ca (forming Ca-Calmodulin complexes)
- iNOS inducible by inflammatory mediators from macrophages etc – cause of septic shock

Signalling Mechanism

1. Metalloproteins
   - NO interacts with many metals esp Fe in heme
   - Guanylyl cyclase contains heme & readily binds NO ⇒ GC activation ⇒ ↑ cGMP ⇒ Protein Kinase G activation ⇒ ***vasodilation***
   - NO inhibits mitochondrial respiration (inhibits cytochrome oxidase)
   - Major component in ***inflammatory liver disease***
2. Thiols

   $$NO + thiols \xrightarrow{O2\ or\ metal} Nitrosothiols$$

   - Reaction occurs on NO exposure to some tissues, nitrosothiols activate or inhibit these proteins
   - Glutathione also interacts with NO, ↓ in DM & atherosclerosis
3. Tyrosine Nitration
   - NO + superoxide → Peroxynitrite ⇒ DNA damage, irreversible nitration of tyrosine, oxidation of cysteine
   - Several disease, cellular degeneration ⇒ ↑ superoxide production

Inactivation

- Rapid reaction with metals & O_2
- NO + heme → ***partial S-nitrosylation*** (carry NO throughout tissues)
- Also inactivated by superoxides

Inhibition of NO Synthesis

- NOS inhibitors bind to NOS arginine binding site & are non-selective
- Ideal: iNOS for inflammation/sepsis | nNOS for neurodegenerative conditions
- Reality: eNOS inhibition ⇒ constriction ⇒ ischemia as well

NO Upregulation: "*Donors*"

- Underlying mechanism; release NO ⇒ smooth muscle relaxation

1. Organic Nitrates

   Nitroglycerin —aldehyde reductase→ NO
   - ***Aldehyde reductase*** in mitochondria of ***venous*** smooth muscle
   - ***Isosorbide dinitrate*** has unknown enzyme to release NO
   - Less significant plt aggregation than inorganics
   - Nitrate tolerance due to –ve feedback; NO on mitochondrial aldehyde reductase
2. Organic Nitrites
   - ***Isoamylnitrite*** metabolised to NO by unknown enzyme → Arterial vasodilation
   - Tolerance not seen
3. Na ***Nitroprusside***
   - NO release through reaction with light, enzyme, chemicals → Rapid ↓ BP
4. Hybrid NO donors
   - In testing | NO donors on cardiac drugs eg aspirin, captopril
5. NO gas inhalation
   - ↓ pulmonary artery pressure & ↑ perfusion | Used in ARDS, acute hypoxemia, CPR
6. Alternate Strategies
   - Enhance downstream NO signalling pathway
   - ***Sildenafil*** (PDE_5 inhibitor) ⇒ prolonged NO induced cGMP elevation

NO in Disease

Vascular Effects

- ACh & Bradykinin (and others) ⇒ ↑ Ca ⇒ NO synthesis
- Protects against ***thrombosis*** & ***atherogenesis***
  - Inhibit proliferation/migration of vascular smooth muscle
  - Seen with NO donors, NOS gene transfer, NO inhalation post angioplasty
  - Inhibit plt aggregation | NO on plasminogen ⇒ enhanced fibrinolysis
  - ↓ adhesiveness of monocytes, leukocytes (inhibits expression of adhesion molecules)
  - Acts as antioxidant, block oxidation of LDLs preventing foam cell formation

Septic Shock

- Gram –ve bacteria ⇒ ↑ nitrate urinary excretion
- Lipopolysaccharides on bacterial cell wall ⇒ iNOS synthesis ⇒ hypotension, shock, death
- Methylene blue also inhibits NOS ⇒ reverse hypotensive effect
- NO scavengers also ↓ NO in circulation ⇒ reverse hypotensive effect

Inflammation

- Host response includes leukocyte recruitment & release of inflammatory mediators
- Cytokines, TNF, IL induce iNOS transcription ⇒ ↑ NO
- NO is a microbicide but also vasodilator and alters protein/lipid/nucleotides
- NO also stimulates PG synth from COX 2
- But TH_1 also synth NO to protect

CNS

- Neurotransmitter & modulator
- NMDA receptor activation ⇒ ↑ Ca ⇒ NO synth & release, nNOS activation
- May have roles in co-transmission, synaptic plasticity

PNS

- NANC synapses widespread - NO may be one of these; penile erection

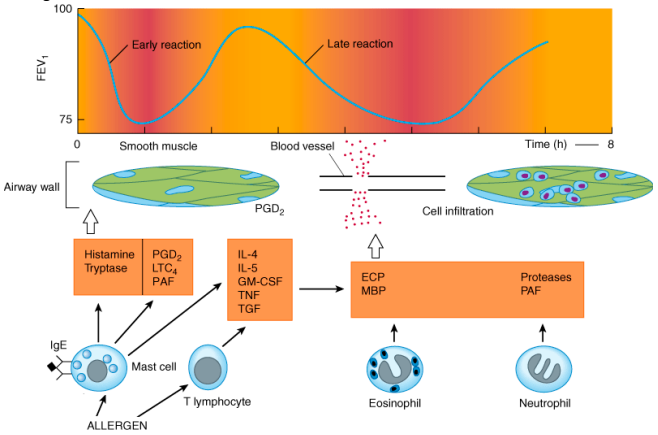
Respiratory

- NO useful in pulmonary HTN
- Useful in pulmonary resistance eg ARDS
- Bronchodilator as well as vascular effects

5. ASTHMA

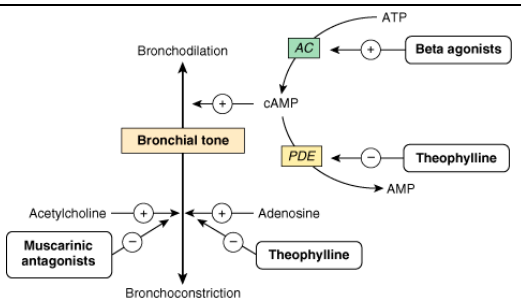
- Physiologically; ***widespread reversible airway narrowing & bronchial hyper responsiveness***
  Airway Narrowing includes
  - Bronchoconstriction (most easily reversible - β agonist)
  - Viscous mucous
  - Bronchial mucosal thickening (gland hyperplasia, infiltration, oedema)
- Pathologically; lymphocytic, eosinophilic inflammation, bronchial mucosal remodelling
- Long term Tx targets inflam process: ***inhaled corticosteroids or leukotriene antagonist***

Pathogenesis



- Allergens provoke IgE production ⇒ binds mast cells
  - Not always allergenic, usually just hypersensitive (eg response also from H_2O)
- Re-exposure ⇒ mast cells release mediators ⇒ airway contraction & vascular leakage
- ***Early response;*** contraction/vascular leakage triggered by mediators diffusing through
- ***Late response;*** influx of inflammatory cells into bronchial mucosa, ↑ airway responsiveness

Basic Pharmacology



Sympathomimetic Agents ***epinephrine, Ephidrine, isoproterenol, Albuterol***

- Pulmonary mechanisms: ***relax airway smooth muscle, inhibit release of mediators from mast cells, ↑ciliary activity, ↓leakage***
- Extrapulmonary effects; tachycardia, skeletal tremor
- Delivery; inhaled
  - factors determining efficacy incl particle size, pattern of breathing, airway geometry
  - < 1-2 μm exhaled | 90% deposited in upper airways/oropharynx

Epinephrine

- Rapidly acting even s/c (0.4 ml 1:1000) or aerosol | Peak 15 min, duration 60-90 min
- Extrapulmonary effects can be severe (makes it useful in shock but little else)

Ephidrine

- Longer duration, orally active, pronounced CNS effects (vs epinephrine)
- Lower potency | ***No longer used due to more reliable β2 selective agonists***

Isoproterenol

- Inhaled (80-120 mcg) | Peak 5 min duration 60-90min
- Rarely used due to high risk of arrhythmia

β_2 selective Drugs ***salbutamol, Terbutaline, Salmeterol, Metaproterenol, Isoetharine***

- Delivery: Inhale or oral (longer duration of action) | MDI same efficacy as isoproterenol (Nebulised doses are higher due to larger particle size)
- Peak effect 15-30 min duration 3-4 hrs
- Interact with corticosteroids to improve function

Terbutaline

- MDI, S/C, Oral (no advantage over inhaler) | Peak 15-30 min duration 3-4 hrs

Salbutamol & ***Salmeterol***

- Potent β_2 agonist | Duration 12 hrs (high lipid solubility)

Toxicity

- Arrhythmias, tachyphylaxis, tolerance (all theoretical)
- Chronic treatment can have effects on genetic variants

Methylxanthine Drugs ***Theophylline, Theobromine, Caffeine***

- Major sources; Tea, Cocoa, Coffee (respectively)
- ***Theophylline*** previously used before β_2 selective & anti-inflammatory aerosols came to market, most selective of the three

Mechanism

- Inhibit PDE (PDE$_4$ has least toxicity) at high doses ⇒ ↑ cAMP ⇒ dilation

Dynamics

1. CNS; mild arousal, alertness, deferred fatigue
2. CVS: chronotropic, inotropic
   - Low doses due to enhanced catecholamine release
   - Med doses due to PDE inhibition, ↑ cAMP ⇒ ↑ Ca influx
   - High dose due to impaired sequestration of Ca by SR
   - ↓ blood viscosity; ***Pentoxifylline*** used in intermittent claudication
3. GIT; stimulate gastric acid and enzyme secretion
4. Renal; weak diuretic by ↑ GFR ↓ Na reabsorption
5. Smooth Muscle; inhibit antigen induced histamine release
6. Skeletal Muscle; reverse fatigue on diaphragm (may contribute more than suspect)

Clinical Use

- ***Theophylline most effective dilator***
- Well absorbed orally | Duration 12 hrs in SR forms | Dose 3-4mg/kg q6h
- Narrow therapeutic window; 5-20mg/L | > 40 mg/L = seizures, arrhythmias
- Need to check levels

Antimuscurinics ***Atropine, Ipratropium bromide, Tiotropium***

Mechanism

- Inhibit Ach at muscarinic receptors: vagal stimulation ⇒ bronchoconstriction & ↑ secretions

Clinical Use

- ***Ipratropium Bromide*** (quaternary NH_4 derivative of atropine) is ***more selective***
  - Poorly absorbed into circ or CNS | variable response | 2nd line (after β agonists)
- ***Atropine*** given at a low dose (so as not to effect HR) causes Bronchodilation
- ***Tiotropium*** – longer acting, 18mcg/24hrs

Corticosteroids ***Beclomethasone, Budenoside, Flunisolide, Fluticasone, Mometasone***

Mechanism

- Inhibit lymphocytic, eosinophilic mucosal inflammation | ↓ airway reactivity (long term use)
- Potentiate β effect by contracting engorged vessels in bronchial mucosa

Clinical Use

- Adverse effects with chronic use ∴ used only in ***acute settings***
- Acute Tx; 30-60mg/day with weening dose | Best dosed early in morning (after peak ACTH)
- ***Beclomethasone*** 400mcg/day = 15mg/day prednisone
- Adverse effect; oral candida, hoarseness, osteoporosis, cataracts, stunt growth

Cromolyn **&** ***Nedocromil***

- ***Prophylactic*** only in antigen or exercise induced asthma to ↓ airway reactivity only

Mechanism

- Alter delayed Cl channel ⇒ inhibited cell activation | Also inhibits cough this way
- Inhibitory effect on mast cell degranulation

Clinical Use

- Useful before exercise or known allergen exposure | Allergic rhinoconjunctivitis
- Poorly absorbed ∴ low adverse profile: throat irritation, cough, mouth dryness

Leukotriene Pathway Inhibitors ***Zafirlukst, Montelukast***

- Inhibition of 5-LOX or inhibiting binding of LTD$_4$ (***Zafirlukst***, ***Montelukast***) to receptor
- Less efficacious than corticosteroids but similar in reducing frequency of attacks
- Leukotriene inhibitors particularly useful in aspirin induced asthma
- Underlying cause probably COX inhibition, ↑ leukotriene substrate

Other

Anti IgE Monoclonal Antibodies

- ***Omalizumab*** inhibits IgE binding to mast cells without provoking already formed IgE=mast
- Inhibits IgE synth by B cells | ↓ magnitude of early & late response & corticosteroid need

Future

- Monoclonal antibodies against cytokines, Antagonists of cell adhesion molecules, Protease inhibitors, Immunomodulators

Clinical Pharmacology

Bronchodilators

- For occ symptoms: ***> 2/wk, nocturnal Sx, FEV$_1$ < 80% predicted*** then additional Tx req
- Usually add ***corticosteroid*** (but leukotrienes or ***Cromolyn*** can be useful) ***Theophylline*** 3rd line

Muscarinic Antagonists

- Limited value | Used on conjunction with sympathomimetics to relieve ***severe airflow***
- Better in COPD | Used if adverse effects of β2 agonists

Corticosteroids

- Used in ***severe asthma attacks*** | Combination therapy with long actin β_2 agonist useful

Cromolyn & ***Nedocromil***, Leukotriene Antagonists

- Alternatives to corticosteroids if >2 exac/wk, nocturnal Sx | Higher compliance vs 'roids
- ***Cromolyn*** & ***Nedocromil*** good in ***seasonal or exercise induced asthma*** (as prophylaxis)
- ***Montelukast*** low side effect profile

ANTI-IgE Antibodies

- Chronic severe asthma NOT responsive to steroids | s/c injection twice weekly

Acute Asthma

- β_2 agonists as effective as epinephrine
- O_2
- Steroids

SECTION V: CENTRAL NERVOUS SYSTEM

1. INTRODUCTION

- Most act on specific receptors that ***modulate synaptic transmission*** (general anaesthetics & alcohols may have nonspecific action on membranes but still modulate synaptic transmission)
- Used to define cellular physiology and pathology (eg dopaminergics work on schizophrenics ∴ underlying mechanism of schizophrenia involves dopamine)

RECEPTOR TYPES

Voltage
- Δ membrane potential ⇒ fast transmission from neuronal body ⇒ axon terminal
- Found on initial segments of axons

Ligand (ionotropic)
- Made of subunits
- Can be insensitive or weakly sensitive to Δ membrane potential
- Channels open/close quickly
- Found in fast synaptic transmission in ***CNS hierarchical pathways***

Metabotropic (voltage & ligand)
- Ligand gated receptors activating G protein to modulate ion channel function either directly or via diffusible 2nd messenger systems
- Action lasts seconds to minutes (vs voltage or ligand)
- Predominates in ***diffuse CNS***

Membrane Delimited
- Ca & K are main ion channels targeted: Presynaptic inhibition of Ca ch; Postsynaptic activation of K ch

Diffusible 2nd messenger
- Instead of G protein modulating ion channel,
- Occurs over considerable distances (membrane delimited occurs in micro domains)
- eg β Adrenoreceptors; generates cAMP via activation of adenylyl cyclase

Synapse & Potential

Sequence of events
1. AP arrives in presynaptic terminal
2. Ca channels open
3. Ca influx ↑ intraterminal concentration
4. Synaptic vesicles fuse with membrane
5. Exocytosis of neurotransmitters
6. Cross synaptic cleft
7. Bind to postsynaptic receptor
8. Altered ion permeability on postsynaptic cell

Most neurons are joined by chemical synapses (electrical coupling occurs but not yet understood/effected by drugs)

Time delay: 0.5ms (mostly opening of Ca channels)

EPSP
- Excitation Potential ⇒ opening of Na^+ & K^+ channels
- When sufficient number of fibres activated to threshold ⇒ Action Potential (all or none)

IPSP
- Inhibition Potential ⇒ opening of Cl^- channels
- Since equilibrium potential of Cl^- (-65 mV) is only a little more than resting potential, inhibition is minor (but enough that an EPSP that would normally evoke an AP doesn't)

Presynaptic Inhibition
- Exist on most CNS cells (axoaxonic inhibition limited to cord)

Site of Drug Action

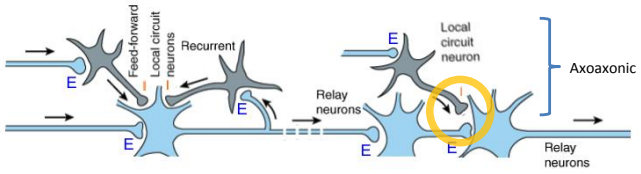
Presynaptic	AP Propagation Synthesis Storage Metabolism Release	• *Respirine* inhibits intracellular packaging • Blockade of catabolism ↑ [NT] release • *Amphetamines* induce release of catecholamines • *Capsaicin* peptide substance P release • *Tetanus toxin* blocks transmitter release
Postsynaptic: Cleft	Uptake Degradation	• *Cocaine* inhibits reuptake • ACh broken down by AChE
Postsynaptic: receptor	Agonist Antagonist Direct Inhibitor 2nd Messenger inhibition	• Agonist eg *opioids* • Antagonists • Direct ion ch inhibitor eg *barbiturates* • *Methylxanthines* block cAMP metabolism ⇒ prolonged effect

Cellular Organization of the Brain
- Hierarchical vs Nonspecific/Diffuse

Hierarchical
- Sensory & motor
- Contain large myelinated fibres conducting 50m/s, phasic
- 2 types of cells

Projection Neurons	Local Circuit Neurons
• Large cell body	• Small cell body
• Axons arborize extensively	• Arborize on cell body only
• Excitatory	• Inhibitory
• Short lived influence	• Transmitter GABA or Glycine
• Glutamate NT	• Usually synapse on cell body of projection[1]
	• Synapse of projection neuron cell bodies

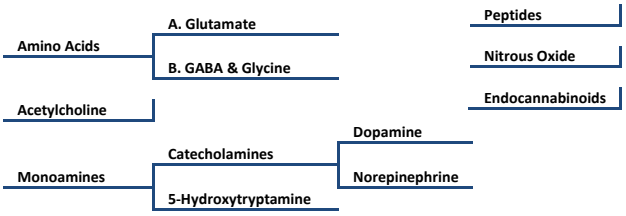
[1]Can also synapse on dendrites



Pathways: Feed forward, Recurrent feedback, Axoaxonic

Nonspecific or Diffuse Neuronal Systems
- Include monoamines (norepinephrine, dopamine, 5HT)
- Noradrenergic bodies found in ceruleus
- Axons are fine/unmylinated ∴ move 0.5m/s
- Repetitive branching ∴ monosynaptically can influence large area
- Varicosities along axons contain vesicles (not always in line with synapse)
- Most receptors are metabotropic ∴ long lasting effects
- Functions include wake, sleep, appetite, emotion

Central Neurotransmitters



Amino Acids

A. Glutamate
- Excitatory
- Release via Ca dependant exocytosis | Cleared by glutamate transporters
- Converted to Glutamine in glial cells (back to glutamate in presynaptic end)
- VGLUT packages glutamate
- Receptor types include ionotropic & metabotropic

Ionotropic Receptors of Glutamate

	AMPA	KA	NMDA
Location	All (most contain GluR2 subunit)	Hippocampus, Cerebellum, Cord	All (contain at least NR1 subunit)
Ion	Na, K[1]	Na, K[2]	Na, K, Ca[3]
Activation	Glutamate binding only to activate Ch opening at RMP		Glycine binding req for activation Ch opening only during depol[4]

[1]Some located on inhibitory neurons, are permeable to Ca and don't contain GluR2
[2]Some Ca permeability too depending on subunit combinations
[3]Ca enhances synaptic strength ie ***Long Term Potentiation*** (LTP), as with learning & memory
[4]Extracellular Mg block at RMP, during depolarisation Mg expelled and ch opens

Metabotropic Receptors
- G protein linked ion channels include ***mGluR1-8*** split into 3 groups:

Group	1	2	3
Location	Postsynaptic	Presynaptic	
Action	Excitatory	Inhibitory	
Mechanism	Activate phospholipase C ⇒ IP3 ⇒ Ca influx	Inhibit adenylyl cyclase ⇒ ↓ cAMP ⇒ block Ca influx ⇒ ↓ transmitter release	
Activation	Stimulation	Repetitive stimulation	

Excitatory Synapses
- Have a postsynaptic density with specific receptor arrangement
- NMDA in centre, AMPA towards periphery, KA sometime integrated but unknown location
- Group I adjacent to PSD

B. GABA & Glycine
- Inhibitory
- Local interneuron transmission

	Glycine	GABA
Location	Cord & Stem Only	All incl Cord
Receptors	Cl^- [1]	$GABA_A$ & $GABA_B$
	$GABA_A$	**$GABA_B$**
	Inotropic receptor ∴ fast IPSPs Selective permeability for Cl^- Inhibited by ***Picrotoxin*** & ***bicuculline***	Metabotropic Receptors ∴ slow IPSPs G protein ⇒ Ca inhibition[2] or K activation[3] Also inhibit adenylyl cyclase/cAMP Located on periphery of postsynaptic membrane[4] Activated by ***baclofen***

[1]Strychnine inhibits ⇒ cord convulsions
[2]Leading to inhibition of transmitter release
[3]Responsible for slow IPSP, same K Ch as 5-$HT1_A$
[4]Activation occurs from GABA spill over from synapse

Ach
- Most CNS responses to Ach mediated by G-protein linked muscurinic receptors
- M1; slow excitation by ↓ K permeability (opp to all others), more common M receptor
- M2; slow inhibition, opens K ch
- Both slower than nicotinic response
- Clinically important in cognition (Alzheimer's has profound loss of cholinergic neurons

Monoamines

- Small quantities but well investigated
- ***Cocaine*** & ***amphetamines*** work on catecholamine synapses
- ***Cocaine*** inhibits reuptake of norepinephrine & dopamine
- ***Amphetamines*** cause transmitter release

A. Dopamine

- Projection links between neostriatum & ventral tegmentum to limbic structures
- 5 receptor types D1-5 (grouped into D1 like or D2 like)
- Metabotropic; G protein linked: slow inhibition via opening of K channels
- ***Levodopa*** associated with neostriatum
- ***Antipsychotics*** associated with limbic structures

B. Norepinephrine

- Most neurons lie in reticular formation (locus ceruleus)
- Most regions of CNS receive input
- Metabotropic; $\alpha_2 \Rightarrow \uparrow$ K conductance
- Enhances excitatory inputs mediated by α_1 or β
    1. Indirect: Inhibiting local inhibitory circuit neurons
    2. Direct: Blocking K conductance that slow neuronal discharge

C. 5-HT

- Originate from raphe or midline pons/upper brain stem
- Carried in unmylinated fibres and inputs to most of CNS
- Acts on more than 12 receptors
- All but 5-HT_3 are metabotropic 5-HT_3 ionotropic & occur at limited sites
- Mostly ***inhibitory*** signalling by ***$\uparrow$K conductance*** (5-$HT1_A$ & $GABA_B$ share same K channel)
- 5-$HT_{2\ \&\ 4}$ have some excitation & neurons can have both ex & inhibitory 5-HT receptors

Peptides

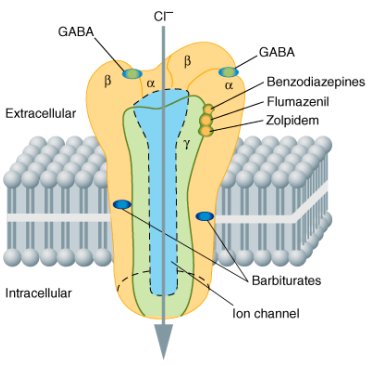
- Opiod, nuerotensin, substance P, somatostatin, CCK, CIP, Neuropeptide Y, TrH
- Often coexist with conventional non-peptide transmitter (eg Substance P with Glutamate)

NO

- NMDA $\Rightarrow \uparrow$ intracellular Ca $\Rightarrow$ Ca=Calmodulin activation $\Rightarrow$ NOS activation $\Rightarrow$ NO
- Unknown role (but found substantially in CNS)

Endocannabinoids

- CB1 main cannabinoid receptor expressed in all parts of CNS
- Depolarization $\Rightarrow$ Ca influx $\Rightarrow$ CB1 ligand synthesis & release
  ie cannabinoid transmitters are synthesised when receptors bind and then released
- Endogenous cannabinoids can also function as ***retrograde messengers*** (ie released from postsynaptic membrane & act on presynaptic receptors) to prevent transmitter release



SECTION V: CENTRAL NERVOUS SYSTEM

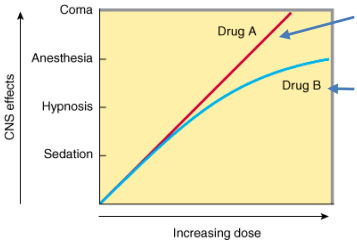
2. SEDATIVE-HYPNOTICS

Basic Pharmacology of Sedative-Hypnotics

Sedatives are anxiolytics (minimal CNS depression)

Hypnotics produces drowsiness (greater CNS depression)

many drugs are sedatives at low doses & hypnotics at high



Drug A

- Typical of most older drugs
- Barbiturates & Alcohols

Drug B

- Requires greater dosage at higher efficacy range
- BZDP

Chemical Classification

- BZDP; ***Diazepam, Oxazepam, Lorazepam, Alprazolam, Nitrazapam, Triazolam***
- Barbiturates; ***Pentobarbital, Phenobarbital***
- Other drugs with sedative/hypnotic properties;
    - ***Zoldipem*** (imidazopyridine)
    - ***Zaleplon*** (pyrazolopyrimidine)
    - ***Eszopiclone*** (cyclopyrrolone)
    - ***Ramelteon*** (melatonin receptor agonist)
    - ***Antipsychotics***
    - ***Antidepressants***
    - ***Antihistaminics***

Kinetics

A. Absorption & Distribution

- ***Triazolam*** & ***Diazepam*** have extremely/rapid absorption vs other BZDP
- Barbiturates & newer agents also rapidly absorbed orally
- ***Triazolam*** is highly lipid soluble ∴ rapid CNS absorption
- All cross placental barrier & detectable in breast milk

B. Biotransformation

- Most need to be metabolised to H_2O soluble in order to clear body (usually done in liver)

1. ***Benzodiazepines***
    - Hepatic metabolism
    - Phase 1; microsomal oxidation (some form active metabolites & have long T ½)
    - Phase 2; conjugated to glucuronides and excreted in urine

	Peak	T ½	Notes
Alprazolam	1-2	12-15	Rapid oral absorption
Diazepam[1,3]	1-2	20-80	Active metabolite, IM erratic BioAv
Lorazepam[2]	1-6	10-20	No active metabolite
Oxazepam[2]	2-4	10-20	No active metabolite
Temazepam	2-3	10-40	Slow oral absorption
Triazolam[3]	1	2-3	Rapid onset, short duration
Zolpidem	1-3	1.5-3.5	No active metabolite

[1]Phase 1 metabolite: desmethyldiazepam (also active)
[2]Phase 1 metabolite inactive
[3]Effected by drugs that alter P450

2. ***Barbiturates***
    - Mostly hepatic metabolised to alcohol, ketones, acids in urine (***Phenobarbital*** excreted unchanged)
    - Overall hepatic metabolism of all is slow: phenobarbital 4-5 days

3. Newer Hypnotics

Zolpidem (Stilnox)

- Onset 1.6 hrs T ½ 1.5-3hrs
- P450 metabolism

C. Excretion

- Renal (failure doesn't impede parent drug elimination)
- ***Phenobarbital*** excreted unΔ 30%, improved with alkalization of urine (it's a weak acid)

D. Factors Affecting Biodisposition

- Δ hepatic function or microsomal enzyme activity
- ***Phenobarbital*** induces enzymes to biotransform other agents

Pharmacodynamics of BZDP, Barbiturates, Newer Hypnotics

A. Molecular Pharmacology of GABA Receptors

- $GABA_A$ is target for ***BZDP, Barbiturates & Zolpidem*** ∴causes Cl^- shift
- Requires binding of both GABA & drug ligand for activation
- $GABA_A$ is a pentamer with multiple different isoforms & forms basis of neuron selectivity
- ***BZDP & Zolpidem*** have high affinity for α_1 subunit on $GABA_A$ receptors (none for $GABA_B$)
- ***Barbiturates*** bind to different subunits

$GABA_A$ α_1; sedation, amnesia, anti-seizure
$GABA_A$ α_2; anxiolytic, muscle relaxation

B. Neuropharmacology

- ***GABA is the major inhibitory transmitter in CNS***
- BZDP & Barbiturates potentiate GABAergic inhibition by "catalysing" GABA action
- *BZDP* ↑ ***fq*** of ch opening (never GABA-mimetic)
- *Barbiturates* ↑ ***duration*** (also GABA-mimetic at high concentrations)
  - Also depress excitatory action of other transmitters eg glutamic acid
    ∴ Less selective/More wider-spread action than *BZDP* ∴ useful in full surgical anaesthesia (but also more pronounced/less safe central depression)

C. BZDP Binding Site Interactions

1. Agonist
   - Multiple BZ receptor sites on α_1 subunits
   - Non-BZDP drugs also bind here (Zolpidem)
2. Antagonist
   - *Flumazenil* blocks binding to BZ receptor site
   - Doesn't affect barbiturates, ethanol
3. Inverse Agonist
   - Block effects of *BZDP* but mainly modulates $GABA_A$ receptor fcn
   - Produce anxiety and seizures

D. Organ Level Effects

1. Sedation
   - Calming effect at low doses (with associated elements of behavioural disinihibition & cognitive depression)
   - *BZDP* have dose dependant anterograde amnesia
2. Hypnosis
   - *BZDP*: ↓ time to sleep ↑ stage 2 NREM ↓ REM ↓ stage 4 NREM
   - *Zolpidem*: ↓ REM
   - REM rebound at end of sleep cycle seen with older hypnotics (*Zolpidem* doesn't have rebound REM but do have rebound insomnia if previously on high doses)
   - Some tolerance to all after 2 weeks
3. Anaesthesia
   - *Barbiturates* (*Thiopental*) are very lipid soluble (∴ rapid onset) & distribute rapidly (∴ fast offset/duration)
   - *BZDP* are slower in onset
4. Anticonvulsant
   - BZDP & Phenobarbital useful
   - Newer hypnotics not (too specific for $GABA_A$)
5. Muscle Relaxation
   - BZDP & Carbamates inhibit polysynaptic reflexes & NMJ
   - Newer drugs do not
6. Respiratory & CVS
   - Same respiratory Δ as sleep at hypnotic levels via dose related depression of medullary respiratory centre (more so in premorbid lung disease)
   - Cardiovascular depression only seen in hypovolumic states

Tolerance; Psychological & Physiological Dependence

- Poorly understood but common
- ↑ rate of metabolism & ↓ regulation of BZDP receptors
- Withdrawal states include anxiety, excitability, convulsions

BZDP Antagonists: *Flumazenil*

- High affinity for BZ receptor on α_1 subunit of $GABA_A$
- Doesn't antagonise other sedative hypnotics (namely *ethanol, opioids, GA*)
- Despite reversing most effects of *BZDP*, respiratory reversal is less predictable
- Rapid hepatic clearance T ½ 0.7-1.3 hrs

Clinical Pharmacology of Sedative-Hypnotics

- Anxiety
- Insomnia
- Anaesthesia; pre-operative sedation/amnesia, intra-operative balanced anaesthesia
- Epilepsy & Seizure disorders
- Withdrawal states (from ethanol or other sedative-hypnotics)
- Muscle Relaxation
- Diagnostic aid/Treatment in psychiatry

Treatment of Anxiety States

- Anxiety states incl situational (eg surgery), generalised anxiety disorder, panic disorder etc
- *Alprazolam* selective for panic disorders & acrophobia
- Disadvantages of *BZDP*: dependence, depression of CNS, amnesia, additive effect with EtOH
- *SSRIs* probably 1st line for generalised anxiety disorder & phobias
- Use for < 2 months and reassess
- Combination treatment is dangerous

Treatment of Sleep Problems

- Primary insomnia rare ∴ tx underlying condition
- Trial non-pharmacological means first, if necessary use for limited period
- *BZDP* have longer T ½ ∴ hangover effect may exist next morning, anterograde amnesia & tolerance (newer sedative-hypnotics don't have this effect)

Drug	Sedative Dose	Hypnotic Dose
Alprazolam	0.25-0.5 mg 2-3x daily	
Diazepam	5mg BD	
Lorazepam	1-2mg 1-2x daily	2-4mg
Oxazepam	15-30mg 3-4x daily	
Phenobarbital	15-30mg 2-3x daily	
Temazepam		7.5-30mg nocte
Zaleplon		5-20mg
Zolpidem		5-10mg

Clinical Toxicology

Direct toxic actions

- Low doses; drowsy, impaired motor skills
- Higher doses: CNS depression
- Anterograde amnesia
- ↑ sensitivity in cardiovascular, liver, respiratory disease, geriatrics
- Disinihibition
- Hypersensitivity reactions
- Deliberate overdose requires; ABC, *dialysis*, *flumazenil*
  Remember flumazenil is shorter acting, less predictable respiratory reversal, can lead to withdrawal effects of BZDPs
- *Barbiturates* enhance porphyrin synth ∴ absolutely contraindicated in acute intermittent porphyria

Alterations in drug dosing

- Tolerance rare < 4 weeks
- Long term use contraindicated
- Withdrawal symptoms potent ∴ ween
- *Cross dependence* exists (ability of one drug to supress abstinence symptoms from discontinuation of another)

Drug interactions

- Most common; other CNS depressants (∴ useful in anaesthesia)
- *Alcohol*, *opioids*, *anticonvulsants*, *phenothiazine's* are most common
- Antihypertensive, antihistamine, antidepressants also

SECTION V: CENTRAL NERVOUS SYSTEM

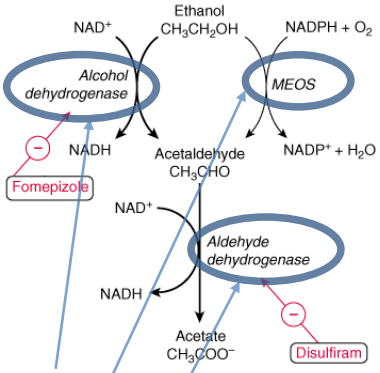
3. THE ALCOHOLS

Basic Pharmacology of Ethanol

Kinetics

- H_2O soluble
- Rapidly oral absorption, Distribution (Vd = 0.5-0.7 L/Kg)
- Peak action 30 min
- Crosses BBB
- 90% oxidized in liver (remainder excreted lungs, urine)
- Zero order kinetics (7-10g/hr)

Pathways to Metabolism



A. Alcohol Dehydrogenase

- 1ry pathway
- Cytosolic enzyme catalysing ethanol → acetaldehyde (by NAD reduction – NADH formed contributes to metabolic disorders of chronic alcoholism)
- Located in liver (brain & stomach to a smaller degree, stomach metabolism > men)
- Asian polymorphism have ↓ form of Alcohol Dehydrogenase

B. Microsomal Ethanol Oxidizing System

- NADPH cofactor for metabolism
- Little contribution < 100mg/dL ethanol (pathway shifts to MEOS with high levels when NAD depleted)
- High Km for EtOH
- Chronic alcoholism ⇒ MEOS upregulated ⇒ ↑ metabolism & clearance & toxic by-products

C. Acetaldehyde Metabolism

- Acetaldehyde from EtOH metabolism
- Metabolised by ***Acetaldehyde Dehydrogenase*** (NAD dependant) → Acetate → $CO_2 + H_2O$
- ***Disulfiram*** prolongs acetaldehyde circulation (***metronidazole***, ***trimethoprim*** also inhibit)
- Asian polymorphism for def in ALDH (also in chronic abuse due to liver toxicity)

Dynamics of Acute EtOH consumption

A. CNS

- Low doses: anxiolytic, sedation, flushing
- Higher doses: slurred speech, ataxia, impaired judgement, disinihibition
- CNS depressant ∴ doses > 500mg/dL ⇒ coma/resp depression, death
- GABA-mimetic (esp on $GABA_A$ receptors) &inhibits glutamate via NMDA (since NMDA is related to cognition/memory, memory loss likely related to NMDA antagonism)

B. Heart

- Impaired contractility > 100mg/dL

C. Smooth Muscle

- Central & Peripheral dilator; ***Acetaldehyde*** directly relaxes smooth muscle (incl uterus)
- Hypothermia in cold

BAL[1]	Effect
50-100	Sedation, slowed reaction
100-200	Impaired motor fcn, slurred speech, ataxia, ↓ contractility
200-300	Emesis, Stupor
300-400	Coma
400-500	Resp Depression, Death

[1] mg/dL

Consequences of Chronic Consumption

- Low potency ∴ large dose required
- Caused by direct & metabolite injury: ↑ oxidative stress, glutathione depletion, mitochondrial damage, growth factor dysregulation, cytokine-induced injury

A. Liver & GIT

- Most common (15-30% of chronic alcohol abusers)
- Worse in women, Hep B & C
- Depends on daily consumption & duration of abuse
- ***Liver Cirrhosis***: ethanol oxidation, dysregulation of FA oxidation/synthesis, activation of innate immune system, ↑ TNFα pivotal in progression of liver disease (unknown mechanism)
- ***Chronic Pancreatitis*** by altering pancreatic epithelial permeability & promoting protein plug formation & Ca Carbonate stones
- ***Gastritis*** ⇒ Anaemia, malnutrition (protein, vitamin)

B. NS

1. Tolerance/Dependence

- Complex, poorly understood
- Withdrawal symptoms include; hyper excitability, seizures, toxic psychosis, ***delirium tremens***
- Seizures likely due to upregulation of NMDA subtype of glutamate receptors (mainly Ca ch)
- Naltrexone (non-selective opioid antagonist) helps withdrawal ∴ a neurotransmitter reward system likely in play

2. Neurotoxicity

- Most common: generalised symmetrical peripheral nerve injury starting with distal paraesthesia
- Gait disturbance & ataxia later (centrally mediated)

Wernicke-Korsakoff Syndrome

- Paralysis of external eye muscles, ataxia, confusion
- Impaired vision over weeks ⇒ optic nerve degeneration
- Associated thiamine deficiency (**Thiamine** reverses Sx quickly)
- Chronic disabling memory disorder remains (***Korsakoff's psychosis***)

C. CVS

1. Cardiomyopathy & HF

- Dilated cardiomyopathy (ventricular hypertrophy, fibrosis)
- Due to membrane distribution, impaired mitochondrial & SR, intracellular accumulation of phospholipids, FA, upregulation of voltage dependant Ca channels
- Poor outcomes vs idiopathic (less responsive to ***β blockers*** & ***ACE inhibitors***)

2. Arrhythmias

- Both atrial & ventricular
- Due to abnormal K & Mg metabolism

3. HTN

- 5% of all HTN
- Unknown mechanism but reversible

4. CAD

- J shaped curve by inhibiting inflammatory processes underling atherosclerosis
- ↑ HDL in low doses
- Anti-oxidants

D. Blood

- Supresses bone marrow indirectly via metabolic and nutritional deficits
- Most common; anaemia from folate def

E. Endocrine/electrolyte

- Deranged steroid balance ⇒ gynocomastia, testicular atrophy
- Ascites, oedema, effusion
- Hypoglycaemia 2ry to impaired GNG
- Electrolyte disturbance from emesis

F. Foetal Alcohol Syndrome

- Teratogenic; ***foetus has no alcohol dehydrogenase*** ⇒ ↑ circulating EtOH ⇒ apoptotic neurodegeneration, abnormal neuromigration
- IUGR, microcephaly, poor co-ord, flattened face (undeveloped), minor jt abnormalities
- CHD, Mental Retardation

G. Immune System

- Hypofunction in some areas incl lung vs hyperfunction in liver
- Supress alveolar macrophage function, Inhibit chemotaxis of granulocytes, ↓T cell population ∴ ↑ risk of pneumonia
- ↑ liver innate contribution, cytokine production ⇒ cirrhosis

H. Cancer

- Mouth, pharynx, larynx, oesophagus, liver
- Acetaldehyde damages DNA

Alcohol-Drug Interaction

- Activated P450
- Most important is paracetamol (↑conversion to toxic metabolite)
- Acute consumption inhibits metabolism of drugs (↓ liver flow)

Clinical Pharmacology

- Environmental & Genetic links to dependence/abuse
- Polymorphisms protect from abuse

Management of Acute Intoxication

- Prevent respiratory depression, aspiration
- Tx hypoglycaemia, ketosis & thiamine if chronic
- Electrolyte replacement

Management of Withdrawal

- Motor agitation, anxiety, insomnia, ↓ seizure threshold
- Mild; Tx symptoms
- Severe; Tx electrolytes, thiamine, seizures
- 2 principles to detoxifying;
  1. Replace with alternative sedative then
  2. Ween

Alcoholism

Naltrexone

- μ opioid receptor antagonist
- Long acting, reduce cravings, 50mg OD
- If given to opioid dependant people ⇒ withdrawal
- Hepatotoxic

Acamprostate

- Weak NMDA receptor antagonist / $GABA_A$ activator
- 333-666mg TDS
- Poorly absorbed, renal elimination
- Adverse; nausea, vomiting, diarrhoea

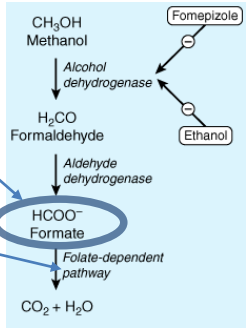
Disulfiram

- Inhibits aldehyde dehydrogenase ⇒ extreme discomfort with drinking
- No effect on non-drinkers & Relies on compliance
- Rapidly absorbed, Peak onset 12 hrs, Slow elimination (days)
- Interaction: inhibits breakdown of ***phenytoin,*** oral anticoagulants, ***isoniazid***

Pharmacology of Other Alcohols

Methanol

- Metabolism
- ***Methanol*** toxicity from formate
- Sx; snowstorm visual disturbance, metabolic acidosis
  Other: bradycardia, coma, seizure
- > 50mg/dL = haemodialysis & ***ethanol***
- 3 types of Tx
  1. Inhibit alcohol dehydrogenase
  2. Haemodialysis
  3. Alkalinize (Bicarbonate) & folate



Ethylene Glycol

- Antifreeze
- Eliminated in kidneys
- Converted to toxic aldehydes & oxalates
- Toxic threshold; 20mg/dL
- 3 stages to toxicity
  1. CNS Excitation/Depression
  2. Metabolic Acidosis (accumulation of acidic metabolites)
  3. Renal insufficiency (oxalate deposition)
- Dx; anion gap, osmolar gap, oxylate crystals, no visual disturbance
- Tx same as ***methanol; ethanol*** infusion, haemodialysis
- ***Fomepizole*** can be used (expensive)

SECTION V: CENTRAL NERVOUS SYSTEM

4. Antiseizure

Basic Pharmacology of Antiseizure Drugs

Kinetics

- Absorption 80-100%
- Not highly bound to protein (except phenytoin)
- Cleared by liver (many metabolites are active)
- T ½ med-long (> 12 hrs)
- Target: Glutamate or GABA

GLUTAMATE TARGET

↓glutamate release

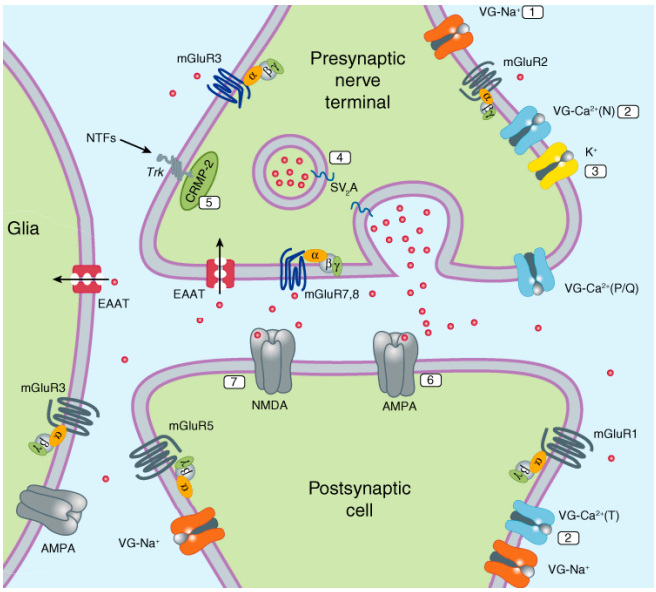
- 1. Voltage Gated Na Channels
  - Phenytoin
  - Carbamazepine
  - Lamotrigine
  - Lacosamide
  - *Valproate*
- 2. Voltage Gated Ca Channels
  - Ethosuximide
  - Lamotrigine
  - Gabapentin
  - Pregabalin
- 3. K Channels — Retigabine

Synaptic Vesicle

- 4. SV_2A — *Levetiracetam*
- 5. CRMP-2 — *Lacosamide*

Post synaptic Targets

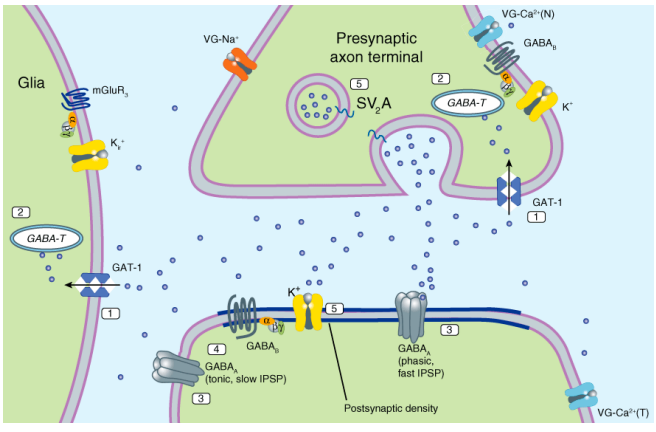
- 6. AMPA
  - *Phenobarbital*
  - *Topiramate*
  - *Lamotrigine*
- 7. NMDA
  - *Felbamate*
  - *Valproate*



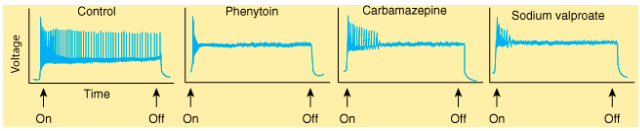
GABA TARGETS

- Presynaptic
  - GABA Transporters[1] — *Tiagabine*
  - GABA Transaminase — *Vigabatrin*
  - SV_2A — *Levetiracetam*
- Receptors
  - $GABA_A$ Receptor — *BZDP*
  - $GABA_B$ Receptors
- Non Specific
  - Voltage Gated
  - Synaptic proteins

[1] esp GAT-1



Drugs Used in Partial & Generalised Tonic-Clonic Seizures



Phenytoin (Dilantin)

Mechanism
- *Binds Na channel in inactive state* to prolong inactivation
- ↓ presynaptic release of glutamate/enhances GABA release
- ↓ Ca influx

Use
- Partial & generalised tonic-clonic

Kinetics
- Complete oral absorption (IM erratic) | Peak 3-12 hrs T ½ 12-36 hrs
- Highly bound to plasma (90%)
- CSF ∝ plasma
- Accumulates in brain, liver, muscle, fat
- Elimination dose dependant: 1st order kinetics up to a threshold (variable)
- 5-7 days to reach steady state

Therapeutic Levels & Dosing
- 10-20mcg/ml
- Start 300mcg/day ↑ 25mcg increments (due to zero order kinetics above threshold)
- Compliance an issue

Drug Interactions & Interference with lab Tests
- Mainly due to protein bindings and metabolism
- Bindings; ***phenylbutazone*** & ***sulphonamides*** displace phenytoin
- Binds thyroid-binding globulin
- ***Phenobarbital*** & ***CBZP*** ↓ phenytoin steady state by ↑ hepatic metabolism

Toxicity
- Low levels; nystagmus, gingival hyperplasia, Hirsutism
- Mod Levels; diplopia, ataxia
- High; sedation
- Long term use; mild peripheral neuropathy, diminished tendon reflexes in LL, abnormal Vit D metabolism ⇒ Osteomalacia

Carbamazepine

Mechanism
- *Na ch blocker* & ↓ presynaptic transmission

Clinical Use
- Originally for bipolar, trigeminal neuralgia
- Not commonly used nowadays for generalised tonic-clonic seizures, partial seizures

Kinetics
- Almost complete oral absorption
- Peak 6-8 hrs
- V_D 1L/kg, 70% Protein bound (without other drugs displacing)
- Low clearance (1L/kg/day), T ½ 36 hr
- Completely metabolised (derivatives also have anticonvulsant properties)

Therapeutic Levels & Dosage
- Oral only, 1-2g OD, children 15-25 mg/kg/day
- Trough levels 4-8 mcg/ml (diplopia if > 7 mcg/ml but some can tolerate > 10)

Interactions
- Due to hepatic enzyme inducing properties

Toxicity
- Common; diplopia, ataxia (diplopia may be fixed by rearranging divided doses)
- Mild gastro upset
- Idiosyncratic blood dyscrasias
- Leukopenia
- Erythematous skin reaction

Oxcarbazepine
- Similar to CBZP with improved toxic profile
- T ½ 1-2 hrs but active metabolite T ½ 8-12 hrs
- Less potent (1/2)
- Less enzymatic activation, hypersensitivity reaction

Phenobarbital
- Mainly used in infants
- Other less sedating drugs are used for convulsant control

Mechanism
- Unknown mechanism; probably enhances inhibitory mechanism/inhibits excitatory mechanisms
- May selectively block abnormal neurons
- Supresses high frequency firing by *blocking Na conductance*
- *Block L & N type Ca channels* at high doses
- *Enhances $GABA_A$ activation by opening Cl channels*
- *Inhibits Glutamate action on AMPA receptor*

Clinical Use
- Partial seizures & general tonic-clonic seizures (not for generalised seizures)
- Useful in febrile seizures

Therapeutic Level & Dose
- 10-40 mcg/mL (< 15 ineffective)

Primidone
- Metabolised to ***Phenobarbital*** & PEMA
- All 3 are anticonvulsants

Mechanism
- Similar to ***phenytoin*** (despite being broken down to phenobarbital)

Clinical Use
- Partial seizures
- Generalised tonic clonic seizures
- More effective than ***phenobarbital*** but not as good as ***CBZP*** or ***phenytoin***
- Younger patients metabolise slower, older patients metabolise faster but both show seizure control before ***phenobarbital*** levels significant

Kinetics
- Completely absorbed, Peak 3 hrs
- VD 0.6 L/kg, 30% bound o plasma proteins
- Clearance larger T ½ 6-8 hrs
- PEMA clearance ½ ***Primidone***, ***Phenobarbital***
- Chronic therapy ***phenobarbital*** x2-3 ***Primidone***
- Time to reach steady states;
  Primidone 30-40 hrs | ***Phenobarbital*** 20 days | PEMA 3-4 days

Dosage
- Therapeutic level = 8-12 (corresponds with ***phenobarbital*** level 15-30)
- 10-20mg/kg/day

Toxicity
- More sedating, otherwise same as ***phenobarbital***

Vigabatrin
- GABA aminotransferase (GABA-T) inhibitor = ↑ levels GABA
- Irreversible
- Racemic S(+) active R(-) inactive

Clinical Use
- Partial seizures, West's syndrome
- T ½ 6-8 hrs
- Dose; 500mg TDS max 2-3g/day
- Toxicity; drowsiness, dizziness, weight gain, agitation, confusion, psychosis
- Visual field defects 33% (reversible)

Lamotrigine
- Suppresses sustained rapid AP conduction by *blocking Na channels*
- *Ca channel blockade* may contribute to efficacy in childhood generalised seizures
- Also ↓ synaptic release of glutamate

Clinical Use
- Widely used as ***add on therapy***
- Can be used as monotherapy for partial seizures
- Toxicity; dizziness, headaches, diplopia, nausea, somnolence, skin rash

Kinetics
- Completely absorbed
- VD 1-1.4 L/kg
- 55% bound to plasma protein
- Linear kinetics, excreted in urine
- T ½ 24 hrs
- Dose 100-300mg/day (therapeutic level = 3mcg/ml)
- Valproate doubles T ½

Gabapentin & Pregabalin
- GABA analog (but don't act on GABA receptors)
- Partial seizure use

Mechanism
- *Bind Ca channels to ↑brain GABA concentration (through an L amino transporter)*
- *↓glutamate release by inhibiting Ca entry*

Clinical Use/Dosage
- Partial seizures or generalized tonic-clonic seizures
- Usually adjuvant therapy
- Max 2400 mg/day (high doses required in monotherapy)
- ***Pregabalin*** 150-600mg/day
- Also used for neuropathic pain
- Adverse effects; dizziness, ataxia, headache, tremor

Kinetics
- Not metabolised, doesn't induce hepatic enzymes
- Absorption nonlinear, Elimination linear (renal), T ½ 5-8 hrs
- No drug drug interactions, Not bound to plasma proteins

Levetiracetam (Keppra)
- Ineffective to maximum electric shock, used in *partial seizures*
- Binds to SV_2A (synaptic vesicular protein) ⇒ modified release of glutamate & GABA
- Complete absorption unaffected by food, Peak effect 1.3 hrs
- Linear kinetics
- Protein bindings < 10%
- T ½ 6=8 hrs
- 2/3 excreted unchanged
- Dose: 500mg BD max 3g
- Adverse effects; somnolence, asthenia, dizziness

Tiagabine

- GABA uptake inhibitor (neurons & glia)
- Preferential inhibition of GAT-1 (vs 2, 3)
- Use: adjuvant therapy, 16-56mg/day
- Adverse: nervousness, dizziness, tremor, difficulty concentrating, depression
- Kinetics: 90-100% BioAv, T ½ 5-8 hrs, linear kinetics, highly protein bound

Topiramate

- Substituted monosaccharide
- Used in partial and generalised tonic-clonic seizures, migraines
- Dose: 200-600mg/day
- Adverse effects occur in 1st 4 weeks, somnolence, fatigue, dizziness, cognitive slowing
- Acute myopia & glaucoma require prompt withdrawal
- Teratogenic
- BioAv 80%
- Rapidly absorbed (2hrs), 15% protein bound, 20-50% metabolised (none active)

Drugs Used in Generalised Seizures

Ethosuximide

- Little activity against maximal electroshock
- 1st line in absence seizures due to safety/efficacy

Mechanism

- ↓*T-type Ca channel current in thalamus* (pacemakers, initiating absence seizures)

Kinetics

- Completely absorbed, Peak 3-7 hrs, Not protein bound
- Completely metabolised (inactive) but slow to clear T ½ 19-72 hrs

Levels & doses

- 750-1500mg/day aiming for 60-100mcg/mL
- Interacts with ***Valproate*** to ↓ clearance

Toxicity

- Gastric distress most common
- Lethargy, fatigue transient
- Less common; dizziness, headache, hiccup, euphoria
- SLE with combined therapy rarely

Valproic Acid & Sodium Valproate (Epilim)

- Fully ionized at body pH ∴ therapy poorly correlates with blood/tissue levels

Mechanism

- Similar action to ***Phenytoin*** & ***CBZP*** (*presynaptic Na current inhibition*)
- Also *blocks NMDA receptors*
- ↑ GABA (probably enhancing GAD (enzyme for GABA synth) & GAT-1 inhibition)
  At high levels blocks GABA transaminase ⇒ ↓ GABA breakdown

Use

- Absence (second line due to idiosyncratic hepatotoxicity)
- Absence + generalised tonic-clonic
- Myoclonic seizures

Kinetics

- Well absorbed BioAv > 80%, VD 0.15 L/kg
- Peak levels 2 hrs, 90% protein bound
- Clearance low T ½ 9-18 hrs
- Dose 25-30 mg/kg/day aiming for 50-100mcg/ml

Drug Interactions

- Displaces ***phenytoin***
- Inhibits metabolism of some drugs; ***phenobarbital, phenytoin, CBZP***

Toxicity

- Common: nausea, vomiting, GI upset
- Sedation uncommon (unless with phenobarbital)
- Idiosyncratic hepatotoxicity (rare but fatal), Idiosyncratic thrombocytopenia (more rare)
- ↑ rate of spina bifida in pregnant women

Other Drugs in Epilepsy

BZDP

- ***Diazepam*** better for electroshock, ***Clonazepam*** for pentylenetetrazols

1. ***Diazepam***
   - Stopping continuous generalized tonic-clonic status
   - IV or PR
   - Not used reg due to tolerance
2. ***Lorazepam***
   - Longer acting than diazepam
3. ***Clonazepam***
   - Used in absence, myoclonic, infantile spasm
   - Long acting, Most potent
   - Sedation common
   - Dose 0.1-0.2 mg/kg
4. ***Nitrazepam***
   - Infantile spams & myoclonic seizures
5. ***Clobazam***
   - 1,5 BZDP
   - Less sedating

Kinetics

- Well absorbed, Widely distributed
- Extensively metabolised (active metabolites)
- Very rapid onset, VD 1-3 L/kg, T ½ 20-40hrs

Limitation

- Sedation & Tolerance

Acetazolamide

- Diuretic: CAD inhibitor ⇒ mild acidosis ⇒ reversion of severe or inhibition of HCO_3 efflux via GABA receptors
- Rapid development of tolerance

Clinical Pharmacology of Anticonvulsants

Seizure Classification

- Partial vs generalised
- Partial seizure drugs are similar
- Generalised seizure drugs vary depending on type

Partial (localised onset)

1. Simple partial
   - Minimal spread of abnormal discharge
   - Remains conscious
2. Complex partial
   - More widespread, usually involving limbic system, bilateral
   - Brief warning common
   - Automatism; lip smacking, swallowing, fumbling, scratching, walking about
3. Secondarily generalised attack
   - Partial seizure followed by generalised tonic-clonic

Generalised (no evidence of localised onset)

1. Generalised Tonic-clonic
   - No localised onset
   - Same Tx as partial
2. Absence
   - Sudden onset/offset, Duration 10-45 seconds
   - ALOC +/- clonic eyelid movements
   - Begins in childhood, up to 100x per day
3. Myoclonic Jerking
   - Normally found in a wide variety of seizures, only sometimes the chief complaint
   - Tx for other seizure type
4. Atonic Seizures
   - Sudden loss of posture, more common in children
5. Infantile Spasms
   - Not a seizure type
   - Bilateral recurrent myoclonic jerks before age 1
   - Most are mentally retarded
   - Cause unknown

Management of Epilepsy

Partial Seizures & Generalised Toni-Clonic Seizures

- Older drugs are more established due to extensive research ie ***Phenytoin*** & ***CBZP***
- Lesser used are ***BZDP*** & ***barbiturates***

Generalised Seizures

- Same as for partial + ***valproate***
- Absence: ***Ethosuximide*** & ***Valproate*** (non-sedating), ***clonazepam*** (tolerance)
- Myoclonic syndromes; ***valproate***
- Juvenile myoclonic epilepsy aggravated by ***phenytoin*** & ***CBZP*** (use ***valproate***)
- Atonic seizures; difficult to control, ***valproate*** & ***Lamotrigine*** used

Infantile Spasm

- ***Prednisolone*** or intramuscular ***corticotrophins***
- ***Clonazepam*** & ***Nitrazapam*** just as good

Status Epilepticus

- ***Diazepam*** max 20-30mg with resp depression
- ***Lorazepam*** longer lasting
- If not in active seizure than BZDP not required, and start on phenytoin
- Loading dose 13-18 mcg/kg as a push (or rate 50mg/min)
- Precipitates in glc
- Unresponsive to ***phenytoin*** ⇒ ***phenobarbital*** 100-200mg max 400-800mg
  Severe resp depression common
- ***GA*** in seizures refractory to all else

Special Aspects

Teratogenicity

- x2 ↑ risk of malformation
- ***Phenytoin***; foetal hydantoin syndrome
- ***Valproate***; spina bifida

Withdrawal

- ↓ seizure threshold
- Withdrawal of anti-absence drugs easier
- ***Barbiturates*** & ***BZDP*** more difficult

Overdose

- Resp depression
- Other Tx options ineffective eg alkalinisation of urine

SECTION V: CENTRAL NERVOUS SYSTEM

5. GENERAL ANAESTHETICS

- Analgesia
- Amnesia
- LOC
- Inhibition of sensory & autonomic reflexes
- Skeletal Relaxation

Types

Intravenous

- Either alone or combination
- Barbiturates (***Thiopental, Methohexital***)
- BZDP (***Midazolam, Diazepam***)
- ***Propofol***
- ***Ketamine***
- Opioid Analgesic (***Morphine, Fentanyl, Alfentanil, Remifentanil***)
- Misc Sedative-Hypnotics (***Dexmedetomidine***)

Inhaled

- ***Isoflurane, Desflurane, Sevoflurane***
- Volatile liquids
- ***NO*** adjuvant

Balanced Anaesthesia

- Combination therapy
- IV for induction | Inhaled for maintenance
- Surgical Stimulation/Intubation: Muscle relaxants | Opioids |LA
- Cardiovascular drugs to counter adverse effects of above

Guedel's Signs

1. *Stage of Analgesia*
   - Initially amnesia without analgesia ⇒ Late: amnesia + anaesthesia
   - Corresponds with interruption of ***transmission through substantia gelatinosa*** (*ie nociceptive stimuli*)
2. *Stage of Excitement*
   - Delirious, amnestic, respiration irregular in volume & rate
   - +/- retching/vomiting with stimulation (∴ aim to limit this stage)
   - Corresponds with progressive ***depression in ascending pathways Golgi type II***
3. *Stage of Surgical Anaesthesia*
   - Spectrum of recurrence of regular respiration ⟶ apnoea
   - Four planes of Δ ; ocular movements, eye reflexes, pupil size
   - Best way to assess is trapezius squeeze + spont resp
   - Corresponds with progressive depression in RAS, spinal reflexes also supressed ⇒ muscle relaxation
4. *Stage of Medullary Depression*
   - Severe depression of vasomotor & respiratory centres
   - Death rapidly ensures without cardioresp support
   - Corresponds with progressive depression in respiratory and cardiovascular centres of medulla

- 4 stages are obscured in due to rapid onset of action and obscurity with cotherapy eg
  - Atropine & Glycopyrrolate (for secretion control, bradycardia) dilate pupils
  - Muscle relaxants inhibit purposeful movement
  - Opioids depress respiration
- Intraoperative assessment of depth; haemodynamic, EEG, BIS (bispectral index), PSI (physical state index), CSI (cerebral state index)

Inhaled

Kinetics

Uptake & Distribution of Inhaled Anaesthetics

- Concentration in mixture ∝ partial pressure

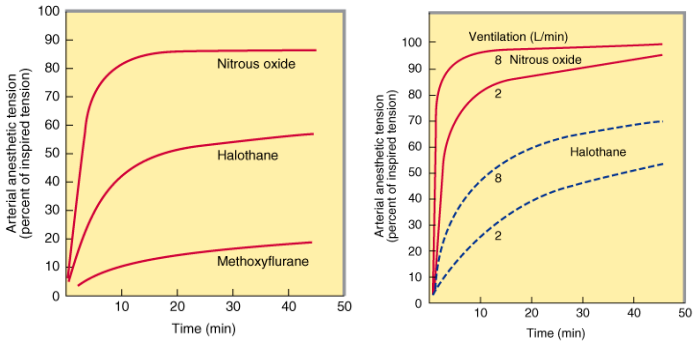
A. Solubility
- Blood:Gas partition co-efficient is an index of solubility
- ***Desflurane*** & ***NO*** are relatively ***insoluble*** in blood
  ∴ Low coefficient
  ∴ Δ Partial pressure requires less gas exchange or "Perfusion Limited"
  ∴ Equilibrates with brain faster
- ***Halothane*** & ***Isoflurane*** are relatively ***soluble*** in blood
  ∴ Med-high coefficient
  ∴ Δ Partial pressure requires more gas exchange (initially diffuses in blood)

B. Anaesthetic Concentration in Inspired Air
- ↑ concentration ⇒ ↑ rate of induction (useful in mod blood soluble anaesthetics eg ***enflurane, Isoflurane, halothane***)
- For these drugs, induction can be at a higher concentration than maintenance

C. Pulmonary Ventilation
- Potentiates effect on mod-high coefficient drugs

D. Pulmonary Blood Flow
- ↑ blood flow (ie CO) ⇒ ↑ arterial tension, more useful in mod-high coefficient drugs

E. Arteriovenous concentration Gradient
- Depends on tissue uptake
- > uptake = > difference = longer time required to reach CNS equilibrium
- Tissues with greatest influence = highest perfused; *brain, hear, kidney, liver, splanchnic bed*
- Anaesthetics accumulates more slowly in skin, muscle, adipose due to limited perfusion (usually through redistribution)
- Steady state usually not reached in operation



Elimination

- Similarities: *Blood:Gas partition co efficient, pulmonary flow, ventilation, tissue solubility, duration of exposure*
- Differences: concentration to lungs, variable tissue anaesthetic tension
- Lower coefficient uptake faster and eliminate faster
- Lungs are main route of elimination – some drugs have hepatic metabolism
  - ***Halothane*** (more sol than ***Enflurane***) has more rapid recovery due to 40% hepatic metabolism (vs 10%)
- Metabolism of ***Enflurane*** & ***Sevoflurane*** ⇒ fluoride ion (doesn't reach toxic levels)
- ***Methoxyflurane*** is metabolised by liver (70%) and fluoride released here can be nephrotoxic

Gas	B:G	B:B	MAC	Metabolism	Comments
NO	0.47	1.1	> 100	None	Incomplete Anaesthetic
Desflurane	0.42	1.3	6-7	<0.05%	Low volatility, Poor Induction
Isoflurane	1.40	2.6	1.40	< 2%	Med on/off
Sevoflurane	0.69	1.7	2.0	2-5%*	Rapid on/off
Enflurane	1.80	1.4	1.70	8%	Med on/off
Halothane	2.30	2.9	0.75	> 40%	Med on/off
Methoxyflurane	12.0	2.0	0.16	> 70%*	Slow on/off

B:B = Blood:Gas Coefficient B:B = Brain:Blood Coefficient MAC = minimal alveolar concentration
**Fluoride production*

Dynamics

Mechanism

$GABA_A$ receptor
- Inh & IV anaesthetics act directly (low doses amplify GABA action vs ***BZD*** – no direct action)
- Don't bind directly onto $GABA_A$ site but on α or β subunit

NMDA
- ***Ketamine*** doesn't bind $GABA_A$ but antagonises NMDA receptors (excitatory receptor)
- ***NO*** targets as well

K Channel ⇒ Hyperpolarisation (ie inhibition)
- Some linked to neurotransmitters
- ↓ open duration of ***nicotinic*** receptor activating ion channels (ie ↓ Ach action)

Glycine receptor
- Also ion ch Complexes

Dose Related Characteristics: MAC
- For gaseous drugs; concentration & flow rates easy to measure/control
- Dose-response more difficult
- Anaesthetic **potency** can be measured using Quantal dose-response

  MAC; median concentration that results in immobility in 50% of patients when exposed to a noxious stimulus ie ED50 on Quantal dose-response curve
- ∴ since NO MAC > 100% = least potent | MAC = 1 = 50% don't respond to stimulus
- Doesn't show dose-response relationship
  (Likely steep ∴ 95% may fail to respond at MAC 1.1
- MAC ↓ elderly, hypothermia, concomitant IV anaesthetic, other volatile agents
- No Δto mac with gender, height, weight

Organ System Effects of Inhaled Anaesthetics

A. CVS

Parameter	Action	Volatile Agent
MAP	↓	***H, E, D, S, I***
CO	↓[1]	***H, E***
PVR	↓[2]	***D, S, I***
HR	↑	***D***[3]***, I***
	No Δ	***E, S***
	↓	***H***[4]
Inotropy	↓	***NO*** > ***H*** & ***E*** > newer/less sol
O_2 consumption	↓[5]	***All***

[1]No Δ net PVR though marked Δ to individual beds eg brain
[2]No Δ CO
[3]Transient sympathetic activity, catecholamine release
[4]Via direct vagal stimulation
[5]Via alterations to MAP, contractility

- Other factors effecting inhaled anaesthetic-response
  - Surgical stimulation
  - Intravascular volume status
  - Ventilator status (hypercapnia ⇒ catecholamine release ⇒ ↓ BP)
  - Duration of anaesthesia
- Newer, less soluble volatiles less arrythmogenic

B. Respiratory

Function	
• **Tidal Volume**	All ↓
• **Respiratory Rate**	All ↑ (but not to a compensatory degree)
• **Minute Volume**	∴ ↓
• **Respiratory depression**	***Isoflurane*** & ***Enflurane*** depress most
• **Apnoeic Threshold/ Ventilatory Response to hypoxia**	All ↑, implications on post op persistent sedation
• **Mucociliary Function**	All ↓
• **Bronchodilation**	variable, ***Halothane*** & ***Sevoflurane*** best
• **Airway Irritation**	Desflurane only

C. Brain

- All ↓ metabolic rate of brain
- Soluble volatile agents ↑ cerebral perfusion by ***↓cerebral vascular resistance*** (Contraindicated in raised ICP)
- Hyperventilation prior to volatile may help

D. Kidney

- ↓ GFR, blood flow, ↑ filtration fraction (due to impaired regulation)

E. Liver

- 15-45% ↓ hepatic flow with intraoperative deranged LFTs but no long term sequela

F. Uterine Smooth Muscle

- Potent relaxant (except ***NO***)

Toxicity

A. Hepatotoxicity (***Halothane***)

- 1 in 20,000
- Obese patients more prone
- Probably due to active metabolite causing direct hepatocellular insult
- No treatment apart from transplant

B. Nephrotoxicity

- ***Methoxyflurane, Enflurane, Sevoflurane*** cause through fluoride production
- ***Methoxyflurane*** & ***Enflurane*** metabolised in kidneys ∴ > insult
- ***Sevoflurane*** reacts with CO_2 absorbents to form compound A ⇒ rebreathed ⇒ proximal tubular necrosis
- ***Methoxyflurane*** ***no longer used in clinical practice because of nephrotoxic effect***

C. Malignant Hyperthermia

- Autosomal dominant
- Reaction to volatiles & muscle relaxants
- Symptoms: rapid onset tachycardia, HTN, muscle rigidity, hyperthermia, hyperkalaemia, acid-base imbalance with acidosis
- Mechanism ↑ free Ca in skeletal muscle
- Tx: ***Dantrolene*** (***↓SR release of Ca***), body temp, electrolyte correction

D. Chronic Toxicity

1. Mutagenicity/Carcinogenicity: None
3. Reproduction: Unknown data
4. Hemotoxicity: Nitrous oxide ⇒ ↓ methionine synthase ⇒ megaloblastic anaemia (seen in poorly ventilated dental suites)

Clinical Use

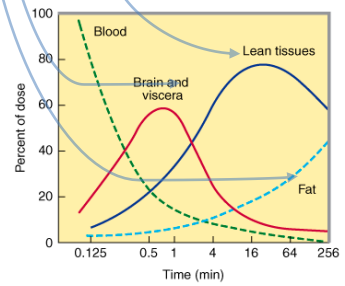
- Rarely used as monotherapy
- Common: ***Sevoflurane, Desflurane, Isoflurane***
- ***Halothane*** still used in paediatrics but gradually being replaced by ***Sevoflurane***

Intravenous

- Rapid onset
- No specialised delivery equipment required
- Recovery faster
- Adjuvant opioid ↓ cardiovascular effects

Barbiturates

- ***Thiopental***
- Rapidly crosses BBB
- LOC in 1 circulatory time
- B:B ***equilibrium*** reached in < 1 min due to High lipid solubility
- Also rapidly ***redistributed*** to muscle & fat ∴ Sedation brief
- Metabolism: 12-16% per hour, 99% metabolised
- Large doses ⇒ ↓ contractility & ↑ venous capacitance ⇒ ↓ SV ↓ BP ↓ CO
- Respiratory depressant similar to volatiles
- ICP & blood volume not effected ∴ useful with raised ICP
- ↓ hepatic flow & GFR without effecting function
- Contraindicated in porphyria producing disease



BZDP

- ***Diazepam, Lorazepam, midazolam***
- ***Diazepam*** & ***Lorazepam*** are water insoluble ∴ IV administration can be painful
- Slower onset
- Plateau effect inadequate for Stage III
- ***Midazolam*** more rapid onset, shorter T ½ (2-4 hrs), steeper dose-response curve
- ***Flumazenil*** can be used to reverse/shorten recovery (resp depression not reversed)

Opioid Analgesics

- Useful with adjuvant ***BZDP*** when cardiovascular reserve limited eg CTS
- ***Morphine*** 1-3mg/kg
- ***Fentanyl*** 100-150 mcg/kg (more common given potency)
- ***Sufentanil*** 0.25-0.5 mcg/kg
- ***Remifentanil*** used to minimise resp depression
- No amnestic properties even at high doses ∴ ***BZDP*** also given
- High doses also ⇒ chest wall & laryngeal rigidity ⇒ impaired ventilatory ability
- Higher post op requirements also
- ***Remifentanil*** metabolised by plasma esterases ∴ fast offset
- Used in epidural & subarachnoid
- Neuroleptanesthesia = ***fentanyl*** & ***droperidol*** to produce analgesic/amnestic state

Propofol

- Onset similar to ***barbiturates***, offset faster, ↓ PONV
- Cumulative effects ⇒ delayed arousal
- Distribution T ½ = 2-8 min, redistribution T ½ = 30-60 min
- Metabolised by liver (x10 faster thiopental) 99%, urinary excretion
- Respiratory effect similar to thiopental
- Marked ↓ BP (↓ PVR), -ve inotropic effect
- May sting on administration
- Transient rise in plasma lipid profile

Etomidate

- Carboxylated imidazole
- Used in limited cardiac reserve (minimal cardiorespiratory depression)
- No analgesic effect
- Offset > prop (10 min)
- Rapid distribution, biphasic concentration curves @ 3 & 29 min
- 98% metabolised
- Adverse; pain at injection site, myoclonic activity, PONV

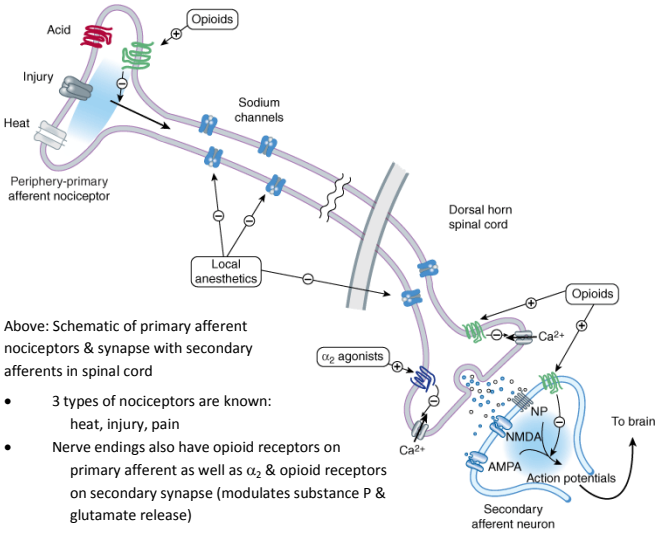
Ketamine

- ***NMDA receptor antagonist***
- Dissociative anaesthetic state, Analgesia
- Lipophilic
- Cardiovascular stimulation (peak 2-4 min off 10-20 min) via central sympathetic stimulation (Also inhibits norepinephrine reuptake) ∴ No cardiovascular effects if catecholamine depleted
- ↑ Cerebral blood flow, O_2 consumption, ICP
- Depressed respiration but maintained reflex and tone
- Adverse effects; ***emergence phenomenon*** (post op disorientation, sensory/perceptual illusions) diazepam or midazolam prior to may help

SECTION V: CENTRAL NERVOUS SYSTEM

6. LOCAL ANAESTHETICS

- Blocks impulse conduction through Na channels
- ***Cocaine*** 1st drug used | ***Procaine*** developed after | ***Lidocaine*** commonly used now



Above: Schematic of primary afferent nociceptors & synapse with secondary afferents in spinal cord

- 3 types of nociceptors are known: heat, injury, pain
- Nerve endings also have opioid receptors on primary afferent as well as α_2 & opioid receptors on secondary synapse (modulates substance P & glutamate release)

Basic Pharmacology

Chemistry

- Exists in body in 2 forms: *unchanged base* or *cation* & $log\frac{cationic\ form}{unchanged\ form} = pK_a - pH$
- pKa (LA) = 8.0 to 9.0 ∴ at physiological pH most is in cationic form (more active)
- Base form important for diffusion across cell membrane ∴ since infective tissue is acidic, harder to anesthetise

Amides	Potency*	Duration	
Lidocaine (Xylocaine)	4	M	Metabolised in liver
Mepivacaine	2	M	
Bupivacaine (Marcaine), Levobupivicaine	16	L	
Prilocaine	3	M	
Ropivacaine	16	L	
Esters			
Cocaine	2	M	Metabolised in plasma by pseudocholinesterase
Procaine	1	S	
Tetracaine	16	L	
Benzocaine	Surface only		

*Procaine = 1

Kinetics

Drug	T ½ α	T ½ β	VD	CL
Bupivacaine	28	3.5	72	0.47
Lidocaine	10	1.6	91	0.95
Mepivacaine	7	1.9	84	0.78
Prilocaine	5	1.5	261	2.84
Ropivacaine	23	4.2	47	0.44

A. Absorption

- Depends on dosage | site | drug-tissue binding | blood flow | drug properties
- Flow ∝ absorption

  For nerve blocks, order of flow:

  Intercostal (highest) > Caudal > Epidural > Brachial plexus > Sciatic (lowest)

> ***Epinephrine***
> - Prolongs LA action by 50%
> - 2 targets of action:
>
> 1. Vasoconstriction ⇒ ↑ local concentration
> 2. Directly on α_2 Adrenoreceptors ⇒ inhibits substance P release (∴ ***Clonidine*** & ***Dexmedetomidine*** may be useful as adjunct in subarachnoid & peripheral nerves)
>
> - Less effective on lipid-soluble LA

Cocaine is unique - sympathomimetic

B. Distribution

- Widely distributed | Some evidence of lipophilic sequestration

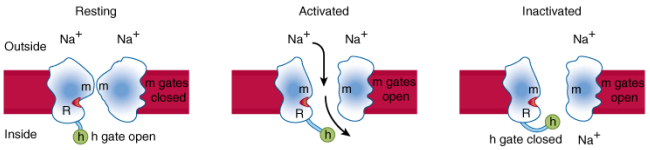
C. Metabolism & Excretion

- Metabolised in liver (amine) or plasma (ester) to H_2O soluble form for urinary excretion
- No excretion of unchanged form (highly lipophilic)
- Urinary ***acidification*** helps speed up clearance

Dynamics

A. Mechanism

- Resting potential -90mV to -60mV
- Excitation ⇒ opening fast Na channels ⇒ +40mV ⇒ Na close | K open ⇒ -95mV ⇒ Na 'rest'



Local Anaesthetics

- Bind/Blocks receptors near ***intracellular*** end
- LA ⇒ ↑ threshold to AP ⇒ ↓ impulse conduction ⇒ ↑ rate of rise of AP ⇒ ↓ AP amplitude ⇒ No AP generated (progressive effects from binding of more and more Na channels)
- ***Critical length*** to stop propagation = 2-3 nodes of Ranvier
- High doses of LA interferes with intra-axonal transport & Ca homeostasis ⇒ ***spinal toxicity***
- Duration/Selectivity of block depends on voltage & time properties of neurons

Voltage

- Channels in resting state (closed m, open h gates) have a more –ve potential ∴ ↓ affinity for LA
- Rapidly firing neurons have a higher proportion of In/Activated (open M gates) channels ∴ ↑ affinity for LA
- Ca antagonises effect vs K agonises effect

Time

- LA Block slows recovery of block by 10-1000x ∴ in refractory period longer

> Biological Toxins
> - Include batrachotoxin, aconitine, vertridine, scorpion venom
> - Binds to receptor ***within ch*** ⇒ ***prevents inactivation*** ⇒ prolonged influx of Na
>
> Marine Toxin
> - Tetrodotoxin (TTX), Saxitoxin
> - Bind receptors ***close to extracellular surface***
> - Similar effects to LA (block conduction, not resting potential)
> - Spinal neurons are either TTX-sensitive or TTX-resistance (pain transmission)

B. Structure Activity Characteristics

- Smaller, more lipophilic LA's interacts faster with Na Channels
- Long lasting effect from > protein binding (***Tetracaine, Bupivacaine, Ropivacaine***)
- For optically active isomers: S(+) is more active than R(-)

C. Other Actions on Nerves

- Spinal anaesthesia; motor paralysis (incl resp, ANS block ⇒ hypotension)
- Susceptibility to bock depends on nerve size & myelination

Fibre	Fcn	Diameter µm	Myelination	Conduction m/s	Sensitivity
Type A					
α	Proprioception, motor	12-20	Heavy	70-120	+
β	Touch Pressure	5-12	Heavy	30-70	++
γ	Muscle Spindle	3-6	Heavy	15-30	++
λ	Pain Temperature	2-5	Heavy	12-30	+++
Type B	Preganglionic ANS	< 3	Light	3-15	++++
Type C					
Dorsal Root	Pain	0.4-1.2	None	0.5-2.3	++++
Sympathetic	Postganglionic ANS	0.3-1.3	None	0.7-2.3	++++

1. Effect of Fibre Diameter
   - Smaller more susceptible vs Larger fibres (longer distance between nodes)
   - Myelinated block before unmylinated
2. Effect of Firing Frequency
   - ***Pain fibres have a high firing rate & long AP ∴ most susceptible to LA***
   - Type Aλ & C participate in high frequency firing ∴ preferentially blocked
3. Effect of Fibre Position in Nerve bundle
   - Larger nerve trunks have ***motor fibres on periphery***
   - In extremities; prox sensory fibres peripheral, distal fibres central

D. Activity on Other Excitable Membranes

- Cardiac membrane
- Slight neuromuscular blockade

Clinical Pharmacology

- Topical; eyes, ENT
- Local injection
- Nerve block
- Epidural
- Spinal (subarachnoid)
- IV regional (Bier's)

- Onset accelerated by HCO_3 (more drug in lipid soluble state)
- Repeated doses ⇒ tachyphylaxis (extracellular acidosis)
- Pregnancy ↑ susceptibility to toxicity ⇒ cardiac arrest (esp ***bupivacaine***) (unknown mech)
- Neuropathic Pain Syndrome; ***IV/oral LA*** + ***TCA*** + ***Anticonvulsant***

Toxicity

- Systemic effects vs Local neurotoxic effects

A. CNS

1. All LA
   - Depress cortical inhibitory pathways
   - Low doses: sleepiness, dizziness, visual/auditory hallucinations
   - Early signs of toxicity; circumoral & tongue numbness, metallic taste
   - Later signs; nystagmus, muscular twitching ⇒ tonic-clonic seizures
   - Very late: generalised CNS depression

     Tx
     - ABC
     - Hyperventilation ⇒ ↑ blood pH ⇒ ↓ extracellular K ⇒ membrane hyperpolarization ⇒ Na favours resting state (less LA affinity)

2. Cocaine
   - Same as all LA but also severe cardiac toxicity ⇒ HTN, arrhythmias, MI

B. Neurotoxicity

- All LA at high concentrations
- ***Lidocaine*** & ***chloroprocaine*** more common (esp in spinal anaesthetic)
- Transient radicular irritation due to pooling in cauda equina
- Spinal toxicity not due to Na blockade but to axonal transport & Ca homeostasis

C. CVS

- Direct effects on membrane & indirect effects on ANS
- Initial toxic effect: Na blockade ⇒ depressed pacemaker activity/excitability/conduction
- Higher doses: Ca block
- ***Cocaine*** is different; blocks ***norepinephrine*** reuptake ⇒ HTN, arrhythmias, + inotropy ⇒ ischemia
- ***Bupivacaine*** is more cardiotoxic since its actions of cardiac Na channels is longer lasting (than fibres) ***Ropivacaine*** may be slightly safer

D. Haematological

- ***Prilocaine*** > 10mg/kg during regional block ⇒ metabolite ***o-toluidine*** accumulation

$$Hb \xrightarrow{\text{o-toluidine}} MetHb$$

- Tx with IV ***methylene blue*** or ***ascorbic acid***

E. Allergic

- Esters are metabolised to p-aminobenzoic acid derivatives
- Amide based allergies very rare

SECTION V: CENTRAL NERVOUS SYSTEM

6. SKELETAL MUSCLE RELAXATION

Intravenous

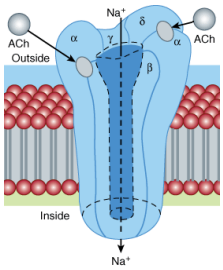
- 2 therapeutic groups: 1.Neuromuscular blockade (acts peripherally only)
  2. Neurological conditions (acts centrally)

Neuromuscular Blocking Drugs

Normal Neuromuscular Function

- Ca influx ⇒ Ach Release ⇒ Activation of N_M receptor
- NM receptor made of 5 subunits; 2α, 1β, 1γ, 1δ
- 3 Locations for AChR:

1. Neuromuscular End Plate
   - Activation by binding to α≡β & δ≡α subunits
   - Activation is graded (∝ ACh concentration)
   - AChE breaks down Ach
2. Presynaptic Axon
   - Mobilises additional vesicle to synaptic membrane
3. Perijunctional Cells
   - Not normally involved in neuromuscular transmission
   - Upregulated in prolonged immobilisation, thermal burns



2 mechanisms for block:
1. AChR antagonist (aka ***non-depolarizing***)
2. ***Depolarizing*** agonist; paradoxical saturation of AChR

Basic Pharmacology of Neuromuscular Blocking Drugs

Drug	Elimination	Duration[a]	Potency[1]
Non-depolarising			
Isoquinolines			
Atracurium	Spontaneous[2]	20-35	1.5
Cisatracurium	Mostly Spont	25-44	1.5
Mivacurium	Plasma ChE[3]	10-20	4
Tubocuraine	Kidney (40%)	>35	1
Steroids			
Pancuronium	Kidney (80%)	>35	6
Rocuronium	Liver (75%) Kidney	>35	6
Vecuronium	Liver (75%) Kidney	20-35	6
Depolarizing			
Succinylcholine	Plasma ChE[3]	<8	0.4

[1]Versus Tubocuraine, lesser potent have faster onset & shorter duration
[2]nonenzymatic & enzymatic hydrolysis of ester bonds ("Hoffmann Elimination")
[3]Pseudocholinesterase
[a]Minutes

Kinetics

- All are highly polar & ***inactive orally***

A. Non-depolarizing

- 2 main families; isoquinolines & steroids
- *Rapid* initial distribution (VD = 80-140 ml/kg) but *slower* elimination
- Highly ionized ∴ not readily cross cell membrane
- Steroids metabolised by liver ∴ shorter T ½ (intermediate steroids rely on biliary excretion)
  - Metabolised to 3-hydroxy, 17-hydroxy or 3,17-dihydroxy products
  - Only 3-hydroxy has blocking effects (only sig after 3-4 days therapy)

Atracurium

- Intermediate acting
- Partly metabolised by hepatic | Partly ***Hoffmann Elimination*** (spont)
- No active metabolites
- *Laudanosine* is one of the metabolites, crosses BBB ⇒ seizures in high doses & ↑ need for volatile anaesthetics
- ***Cisatracurium*** is a stereoisomer of ***Atracurium*** (less Laudanosine production, less liver metabolism, less histamine release)

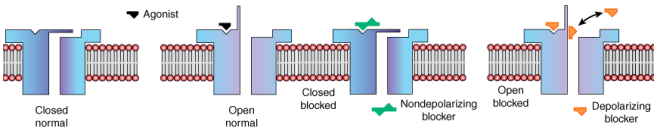
Mivacurium

- Fast offset (cleared by plasma cholinesterase), slow onset
- Profound histamine release

B. Depolarizing Relaxant Drugs

- ***Succinylcholine***
- Duration of action 5-10 minutes
- Metabolised by liver and plasma cholinesterase's (more so plasma)
- Primary metabolite; *Succinylmonocholine* rapidly metabolised to *succinic acid* & *choline*
- Given fast metabolism, not much succinylcholine reaches NMJ
- Genetic variants of plasma cholinesterase prolong effect of ***Mivacurium*** & ***succinylcholine*** "Sux Apnoea"

Mechanism



A. Non-depolarizing Relaxant Drugs

- *Tubocuraine* is prototype
- Small doses *competitively antagonise* N_M receptors
- High doses enter pore to physically block (diminishes ability of AChE inhibitors to reverse)
  - Can also interfere with ***presynaptic Na channels*** ⇒ inhibits Ach vesicle movt

B. Depolarizing Relaxant Drugs

1. Phase I (depolarizing)

- Similar action to ACh but longer effect; activates N_M receptors to open Na channels & depolarise motor end plate
- High doses cause Succinylcholine to enter pore and 'flicker'
- Not metabolised ∴ membrane remains in depolarized state & unresponsive "Flaccid paralysis"
- ∴ AChE inhibitors augment action

2. Phase II (desensitizing)

- Following repolarisation, receptors are 'desensitised" (unknown mechanism)
- Later on become like non depolarizing block ; non sustained twitch response to tetanic stimulus (∴ AChE inhibitors can reverse)

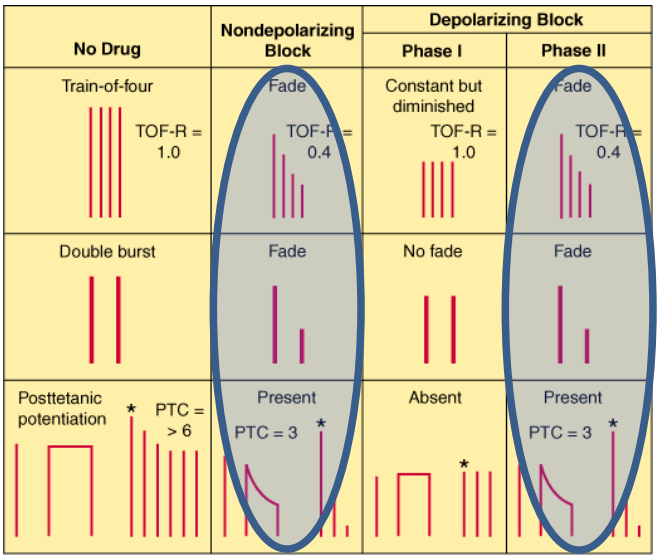
Action	*Rocuronium*	*Succinylcholine*	
		Phase I	Phase II
+ *Tubocuraine*	Additive	Antagonist	Augmented
+ *Succinylcholine*	Antagonist	Additive	Augmented
+ *Neostigmine*	Antagonist	Augmented	Antagonist
Skeletal Muscle	None	Fasciculation	None
Tetanic Stimulus	Unsustained	Sustained	Unsustained
Post tetanic fasciculation	Yes	No	Yes
Rate of Recovery	30-60min	4-8min	> 20 min

Clinical Pharmacology

Skeletal Muscle Paralysis

- Previously done using deep anaesthesia WITH adverse cardiorespiratory effects

Assessment of Neuromuscular Transmission



Above: nerve response to different patterns of transdermal stimulation

PTC = post tetanic count

** = 1st post tetanic contraction*

1. TOF: 4 stimuli applied @ 2 Hz

- **TOF-R = strength of 4th ÷ 1st**
- Depolarising blocks ↓ all four in dose-related fashion until phase II
- Non-depolarising blocks ↓ TOF-R (fades) 1/∝ degree of blockade

2. Double Burst

- 3 stimuli applied @ 50Hz then 700ms rest
- Newer, easier to detect fade
- Absence of fade = blockade not existent

3. Post tetanic Potentiation

- Tetanic stimulation: Non depolarizing & Phase II show fade & at high doses, "post tetanic twitch response" is supressed
- Post tetanic potentiation = 50Hz for several seconds then rest then single stimuli @ 0.5 Hz, due to Partial non depolarization block ↓ intensity

A. Non Depolarizing Relaxant Drugs

- Administration of *Tubocuraine* = motor weakness initially ⇒ flaccid & unexcitable
- Larger muscles more resistant/recover quicker (diaphragm last)
- *Tubocuraine* 0.3mg/kg lasts 45-60 min (subtle weakness may last for hours)
- *Rocuronium* most rapid onset (60-120 seconds)

B. Depolarizing Relaxant Drugs

- *Succinylcholine* 0.75-1.5 mg/kg
- Transient fasciculation within 30 seconds | Paralysis within 90 seconds | Duration 10 min

Adverse Effects of Depolarizing Blockade

A. Cardiovascular Effects

- Non-depolarizing: *M-,A-,P-* have effects via ANS or Histamine (*M-,A-,T--* ⇒ histamine release ⇒ hypotension)
- *Pancuronium* ↑ HR and small ↑ CO (no Δ to vascular resistance)
- *Succinylcholine*: arrhythmias, activation of autonomic cholinoceptors incl N_M in heart
  - *Atropine or Glycopyrrolate* used to counter
  - Large doses has a +ve chrono/inotropic effect

B. Hyperkaelmia

- Occurs with succinylcholine in patients with comorbidities (*burns, nerve injury, neuromuscular disease, closed head injury*)

C. Raised IOP

- *Succinylcholine*: rapid rise within 60 sec peak 2-3 min, declining after 5 min
- Mechanism: transient tonic contraction of myofibrils, dilation of ocular choroid vessels
- Only contraindication is open ant chamber

D. Raised Intragastric Pressure

- Occurs in heavily muscled patients during fasciculation
- Sequela: regurgitation/aspiration (rarely perforation)
- More common in delayed gastric emptying (diabetes, traumatic injury, oesophageal dysfunction, morbid obesity)

E. Muscle Pain

- Common post op complaint particularly in ambulant patients
- Due to ***unsynchronised contractions*** of adjacent muscles prior to paralysis

Interactions with Other Drugs

A. Anaesthetics

- Potentiates in dose-dependent fashion
- In order of most potentiating; *Iso-, Sevo-, Des-, Enf-, Halothane, NO*
- Mechanism: NS depression proximal to NMJ & ↑ muscle blood flow
- *Succinylcholine* may interact ⇒ ***malignant hyperthermia*** (abnormal release of SR Ca)

B. Antibiotics

- Some antibiotics (eg *aminoglycosides*) block P-type Ca channels ⇒ ↓ normal Ach response at NMJ ∴ enhance blocker effect

C. LA & Antiarrhythmic

- Small doses: depress post tetanic potentiation (through prejunctional neural effect)
- High doses: block transmission
- Higher doses: Block Nicotinic ion channels ⇒ block Ach induced contraction
- Similar chain with Na channel blocking antiarrhythmic (not at normal doses)

D. Other NM Blocking agents

- "***Pre-curization***" used to be common practice to ↓ fasciculation & post op myalgia
- Requires 50-90% higher dose of succinylcholine
- Patients feel weak post op

Effects of Disease & Ageing on N_M Receptors

- Augment: Myasthenia Gravis, Old Age (due to clearance)
- Diminish: severe burns & UMN disease (proliferation of extra-junctional receptors)

Reversal of Nondepolarizing NM Blockade

- *Neostigmine* & *Pyridostigmine* antagonise non depolarising blocks by ↑ [Ach] in synapse through inhibition of AChE & slight ↑ in presynaptic release

Use of NM Blocking Drugs

A. Surgical Relaxation: most important use esp intrabdo/intrathoracic

B. Tracheal Intubation: relaxes laryngeal/pharyngeal airways

C. Control of Ventilation: ↓ chest wall resistance ⇒ ↑ compliance

D. Treatment of Convulsions: Effective at Tx muscular manifestations but not central cause

Spasmolytic Drugs

- Spasticity; ↑ tonic stretch reflex & flexor muscle spasm (seen in MS, CP, Stroke)
- Cause: UMN cause with damage to descending pathway ⇒ hyper-excited α receptors
- Mechanism of drugs: ↓ reflex arc by 2 methods
  1. ↓ Ia fibre activity
  2. Enhance inhibitory feedback neurons

Diazepam

- Clinical experience with other BZDP limited
- $GABA_A$ receptor agonist (with some spinal cord mediation)
- Clinically useful doses cause sedation; 4mg/day max 60mg/day

Baclofen

- $GABA_B$ agonist ⇒ hyperpolarizing membrane through ↑ K conductance
  AND ⇒ presynaptic inhibition of Ca influx
- As effective as *diazepam* but less sedating
- No Δ in overall muscle strength (vs *Dantrolene*)
- Rapidly absorbed T ½ 3-4 hrs | 15mg BD max 100mg
- Adverse effects; drowsiness (tolerance ∴ ween when withdrawing)
- Intrathecal administration when all else fails, has poor egress from cord ∴ low peripheral sx

Other Centrally Acting Spasmolytic Drugs

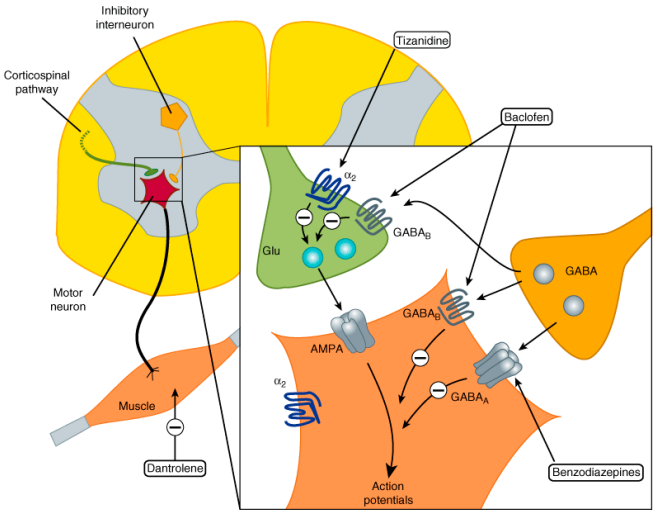
- ***Gabapentin*** & ***Glycine*** are undergoing trials

Dantrolene

- Related to phenytoin
- Interferes with muscle fibre (ie not central)
- ***Binds RyR channel ⇒ inhibit activator Ca release***
- Cardiac & Smooth muscle not effected (different RyR channel)
- 25mg max 100mg | 1/3 absorbed | T ½ 8 hrs
- Adverse effects; generalised muscle weakness, sedation, hepatitis
- Also used in ***malignant hyperthermia***; 1mg/kg max 10mg/kg

Botulin Toxin

- Uses: Ophthalmic | Local muscle spasm | CP | Lasts weeks-months



SECTION V: CENTRAL NERVOUS SYSTEM

7. PARKINSONISM & OTHER MOVEMENT DISORDERS

Tremor

- Rhythmic oscillation around a joint
- Classified by relation to movement:
  - Rest: Parkinsonism
  - Sustained Posture: Postural (eg benign or familial tremor)
  - Movement: Intention (eg alcohol, cerebellum, brainstem lesion)

Chorea

- Irregular, unpredictable, involuntary jerking movt inhibiting voluntary movt

Other Abnormal Movements

- **Athetosis**: slow, writhing
- **Dystonia**: sustained abnormal movements
- Both can occur with perinatal brain damage, focal/generalised cerebral lesion, inherited (idiopathic torsion dystonia or dystonia musculorum deformans)
- **Tics**: sudden co-ordinated abnormal movements that are repetitive and voluntarily supressed

PARKINSONISM

- Sx: rigidity, bradykinesia, resting tremor, postural instability
- Idiopathic (?neurotoxic exposure ?genetic ?free radicals)
- Pathology: ↓ Dopamine in basal ganglia (usually high concentration) ∴ ↑ GABA output (presynaptic dopaminergic neurons usually inhibit)

Mechanism of Treatment

- Restore dopamine via dopamine agonist (***Levodopa***)
- Antimuscurinic to restore dopamine ⇔ cholinergic balance

Levodopa

- Immediate metabolic precursor to dopamine
- Dopamine doesn't cross BBB but Levodopa does, then is decarboxylated to dopamine
- Main target are D_2 receptors (and D2 antagonists can induce parkinsonism)

Pharmacokinetics

- Rapidly absorbed (depending on gastric emptying, pH)
- Peak plasma concentration 1-2 hrs | T ½ 1-3 hrs
- 1-3% crosses BBB (10% with co-administration with dopa decarboxylase inhibitor eg ***Carbidpoa***)

Clinical Use

- Best result in first 3-4 years (due to adverse effects or tolerance thereafter)
- Lowers mortality rate
- Most effective in relieving bradykinesia
- Response: 1/3 well | 1/3 less well | 1/3 unable to tolerate SE
- ***Sinemet*** (25/100 or 25-/250) TDS/QID

Adverse Effects

A. GI

- Without peripheral decarboxylase inhibitor, 80% have anorexia, N&V (tolerance forms), 20% with decarboxylase inhibitor
- Vomiting due to CTZ stimulation (outside of BBB)

B. CVS

- Postural hypotension (asymptomatic, diminishes with prolonged treatment)
- Tachycardia/Arrhythmias (uncommon, due to catecholamine release, less effect with decarboxylase inhibitors)

C. Dyskinesia

- 80% occurrence with prolonged duration of therapy
- Dose-related with large patient variability

D. Behavioural

- Wide spectrum, more common in combination with decarboxylase inhibitor
- Precipitated in illness
- Treated with atypical antipsychotics

E. Fluctuations

- Time dependant: end of dose akinesia
- Time independent: ***on-off phenomenon***
  - Off periods show marked akinesia (apomorphine can provide temp relief)
  - On periods show improved mobility with marked dyskinesia

F. Misc

- Mydriasis ⇒ glaucoma
- Blood dyscrasias including +ve coombs
- Gout
- Brownish discolouration of secretions
- Transient elevation of BUN, Transaminases, ALP, Bilirubin

Drug Holidays

- Ceasing for 3 to 21 days
- Can improve responsiveness/alleviate adverse effects
- Does not effect on-off phenomenon
- Indirect adverse effects incl aspiration pneumonia, DVT/PE, Depression (from immobility)

Interactions

- Vitamin B6; enhances peripheral decarboxylation of ***levodopa***
- ***MAOIs*** (within 2 weeks); hypertensive crisis

Contraindications

- Psychotic patients
- Angle closure glaucoma
- Cardiac disease (slight risk)
- Active PUD
- Malignant Melanoma/Undiagnosed skin lesions

DOPAMINE RECEPTOR AGONISTS

- Do not require enzymatic conversion, freely pass BBB
- Limited adverse effect profile
- Older agonists (ergot derivatives): ***Bromocriptine*** & ***Pergolide***
- Newer agonists: ***Ropinirole***, ***Apomorphine***
- All have same efficacy (except ***apomorphine***…potent), older agonists have > adverse profile
- Individual response to any/all
- Can be used as 1st line, or 2nd line after ***Levodopa/Carbidopa*** combination
- Also used in end-of-dose akinesia or on-off phenomenon
- Not beneficial if not responsive to Levodopa

Bromocriptine

- D_2 agonist
- Variably-good absorption, 1-2 hr peak plasma, excreted in bile/faeces
- Also used in hyperprolactinemia (lower dose)

Pergolide

- D1 & D2 receptor agonist
- More effective than Bromocriptine but 1/3 have valvular ♥ disease
- Increases "on-time" during fluctuations ∴ allows ↓ levodopa

Ropinirole

- Pure D2 agonist, non-ergot
- Used as monotherapy in mild disease prior to transition to levodopa
- Metabolised by CYP1A2

Adverse Effects

- GI: anorexia, N&V (minimised by taking with meals), Reflux
- CV: postural hypotension (initially), painless digital vasospasm (***ergot's***), arrhythmias, valvulopathy (***Pergolide***)
- Dyskinesia: similar to ***levodopa***
- Mental: more common than with ***levodopa***
- Other: headache, nasal congestion, arousal, pulmonary infiltrates, erythromelalgia, narcolepsy

Contraindications

- Psychotic illness, recent MI, active PUD, PVD

APOMORPHINE

- Subcutaneous
- Temporary relief of off-periods
- Potent nausea (treat 3 days prior and weeks after)
- Onset 10 minutes, Duration 2hrs (dose dependant, individual variability)

MONAMINE OXIDASE INHIBITORS

- MAO A: metabolises norepinephrine & 5-HT
- MAO B: metabolises Dopamine

Selegiline

- Low doses: MAO-B inhibitor | High doses: Both
- Used as adjunct to ***Levodopa*** (minimal effects as monotherapy)
  - Reduced mild on-off & wearing-off
  - Also ↑ adverse effects of ***Levodopa***
- Some evidence that it may slow progression
- Contraindicated in ***TCA's***, ***SSRI*** ⇒ Serotonin Syndrome

COMT (Catechol-O-Methyltransferase Inhibitors)

- Peripheral Dopa Decarboxylase inhibition ⇒ upregulation of COMT ⇒ Peripheral ***Levodopa*** metabolism ∴ COMT inhibitors act like Dopa Decarboxylase inhibitors

Entacapone

- Useful for response fluctuations & ↑ "on-time"
- Less hepatotoxicity than others
- Rapidly absorbed, protein bound, metabolised prior to excretion
- Acts peripherally only
- T ½ 2 hrs
- Adverse effects relate to ↑ ***Levodopa*** exposure
- ***Stalevo***: ***Entacapone*** & ***Levodopa*** & ***Carbidopa***

Amantadine

- Antiviral agent with chance anti-parkinsonian properties
- Unknown mechanism: ?effects dopamine synth/release/reuptake
- Kinetics: peak plasma 1-4 hrs | T ½ 2-4 hrs | Not metabolised/excreted in urine
- Clinical Use: less potent vs Levodopa, short lived effects (weeks only)
- Adverse: restless, depression, irritability, insomnia, agitation, convulsions (in high doses)

ACETYLCHOLINE-BLOCKING DRUGS

- Improve tremor, rigidity | No effect on bradykinesia
- Includes ***Benztropine Mesylate, Biperiden, Orphendrine***
- Adverse Effects: usual Antimuscurinic effects, dyskinesia, suppuratives parotiditis

SURGICAL PROCEDURES

- Thalamotomy
- Posteroventral pallidotomy
- Ablative
- High frequency deep brain stimulation (lowest mortality)
  - Thalamic stimulation: relief of tremors
  - Subthalamic nucleus or Globus Pallidus: fluctuations
- Contraindicated in secondary or atypical parkinsonism
- Transplantation of dopaminergic tissue (experimental)

Overview of treatment Methodology

Stage	Treatment
Early	Dopaminergic[1]
Necessary Tx	Amantadine or Antimuscurinic (or both)
Disease Progression	Dopaminergic +/- Sinemet
	Physical Therapy
Levodopa Complications	COMT Inhibitor
	Regulation of Dietary Protein Intake
Failed Response	Deep Brain Stimulation

[1]Symptomatic treatment in mild Parkinson's should be delayed

- Young patients with mild symptoms may benefit from ***Selegiline*** (MAOI)

DRUG-INDUCED PARKINSONISM

- Dopamine depletion: ***Reserpine***
- Dopamine Antagonist: ***Haloperidol, phenothiazine's***
- Onset: 3 months (clears over weeks/months)
- Treat with Antimuscurinic (***Levodopa*** can aggravate mental effects)

OTHER MOVEMENT DISORDERS

TREMOR

- Treat with ***propranolol*** (β_2 effects probably relate to tremor)
- ***Metoprolol*** if concomitant pulmonary disease
- ***Topiramate*** or ***Primidone*** (antiepileptics) also useful
- Small doses of ***alcohol, botulin toxin***, thalamic stimulation also used
- Exaggerated effects with ***bronchodilators, TCAs, Valproate, Lithium***

HUNTINGTONS DISEASE

- Autosomal dominant on chromosome 4
- Due to imbalance of dopamine ⇔ ACh ⇔ GABA in basal ganglia
- Chorea due to overactive dopaminergic activity
- Dopamine depleting agents (***tetrabenazine***) or dopamine antagonists (***phenothiazine's, butyrophenones)*** used to treat chorea

OTHER FORMS OF CHOREA

- Thyrotoxicosis, Polycythemia Rubra Vera, SLE, Hypocalcemia, hepatic cirrhosis
- Drug-induced
- **Sydenham's Chorea** (short lived post strep ⇒ rhematic fever)

BALLISMUS

- Unknown mechanism but same treatment as chorea

ATHETOSIS & DYSTONIA

- Unknown mechanism
- Dystonia's can trail a variety of drugs (***diazepam, amantadine, antimuscurinics, levodopa, CBZP, Baclofen, Haloperidol, Phenothiazine's***
- Focal dystonia's can have ***botulinum toxin*** injections

TICS

- Unknown mechanism
- Haloperidol or ***clonazepam, clonidine, CBZP***
- Sedation most common adverse effect

DRUG-INDUCED DYSKINESIAS

- Caused by ***Phenothiazine***
- Relieved with ***benztropine*** or ***diazepam***

Tardive Dyskinesia

- Complication of long term neuroleptic drug use
- Unclear mechanism but irreversible
- Increase in dose usually relieves
- Symptomatic relief comes with interfering with dopamine
- Combination therapy with antimuscurinics increases likelihood

RESTLESS LEGS SYNDROME

- Unknown cause
- May be seen in pregnancy, neuropathy (diabetes, uraemia) but mostly idiopathic
- Tx: ***diazepam***, ***clonazepam***, ***opiates, levodopa***, ***Ropinirole*** (dopamine receptor agonist)

WILSONS DISEASE

- Cu metabolism disorder
- ***Penicillamine*** used to chelate Cu
- ***Trientine*** also chelates
- ***Zinc Acetate*** increases faecal excretion of Cu

SECTION V: CENTRAL NERVOUS SYSTEM

8. ANTIPSYCHOTICS & LITHIUM

- Schizophrenia: clear sensorium, marked thinking disturbance
- Dopamine Hypothesis
  - Effective antipsychotic drugs act on D2 receptors
  - Drugs that ↑ dopaminergic activity aggravate/induce psychosis
  - Post mortem studies show ↑ Dopamine receptors
  - PET shows ↑ Dopamine receptor density in un/treated patients
- 5-HT may exert synergistic effect

Basic Pharmacology of Antipsychotic Agents

Types
- Phenothiazines: Chlorpromazine, Thioridazine
- Butyrophenones: Haloperidol
- Misc: Clozapine, Olanzapine, Quetiapine, Risperidone

Pharmacokinetics
- Absorption: readily/incompletely absorbed (chlorpromazine & Thioridazine 25-35% vs haloperidol 65%)
- Large VD (sequesters in lipid compartments ∴ effects outlive plasma T ½)
- Mostly inactive metabolites (except mesoridazine – from Thioridazine, more potent)
- 100% metabolism prior to excretion

Effects

A. Dopaminergic
- 5 dopaminergic pathways
- Antipsychotic actions target Mesolimbic-Mesocortical pathway

Pathway	Proposed Action
Mesolimbic-Mesocortical	Psychosis
Nigrostriational	Co-ordination of movement[1]
Tuberoinfundibular	Inhibits prolactin secretion
Medullary-periventricular	Eating behaviour
Incertohypothalamic	Anticipatory motivational phase of copulation

[1]Parkinsonism when inhibited

B. Dopamine Receptors & Effects
- D_1-D_5: Grouped into "D_1-like" and "D_2-like"

D_1-like	D_1, D_5	Gs coupled activation of adenylyl cyclase ⇒ ↑ cAMP ⇒ Ca ch activation
D_2-like*	D_2, D_3, D_4	Gi coupled inhibition of adenylyl cyclase ⇒ ↓ cAMP ⇒ Ca ch inhibition/K activation

*Most antipsychotics target D_2 inhibition

C. Differences Among Antipsychotics
- Newer antipsychotics have ↓ potency for D_2 but ↑ potency for 5-HT_2 ∴ ↓ adverse effects

D. Psychological Effects
- Most have unpleasant subjective effects (but show improvement from psychosis)

E. Electroencephalographic Effects
- Antipsychotics **slow** electrical activity
- Some lower seizure threshold

F. Endocrine
- Problem with older antipsychotics
- Mainly adverse effects on reproduction

G. Cardiovascular
- Orthostatic hypotension, ↑resting HR, ↓ MAP/TPR/SV
- ***Arrhythmias: QT prolongation & ST/T abnormalities (reversible)***

Drug	Receptor Blocked					
	D_2	D_4	α_1	$5HT_2$	M	H_1
Haloperidol	+++	0	+	0	0	0
Clozapine	0	++	++	++	++	+
Olanzapine	+	0	+	++	+	+
Quetiapine	+	0	+	++	+	+
Risperidone	++	0	+	++	+	+

Clinical Pharmacology

Indications

A. Psychiatric Conditions
- Many show little response, none show complete response
- Schizophrenia, Schizoaffective disorder, Mania (in Bipolar), Atypical Psychosis
- To a lesser extent: Tourette's, Alzheimer's, PTSD (anxiolytics safer)
- Not used in withdrawal syndromes

B. Nonpsychiatric Conditions
- Antiemetic effect
- *Prochlorperizine* (stemetil)
- *Droperidol*

Drug Choice
- Depends on adverse effect profile, cost & routes of admission
- Newer antipsychotics better for negative symptoms
- Florid psychosis has equal response to new/old
- *Clozapine* reserved as 2nd line due to agranulocytosis & seizures

Parenteral Preparations
- Older antipsychotics for rapid and non-compliant maintenance

Adverse Effects
- ***Behavioural:*** pseudodepression
- ***Neurological***
  - Extrapyramidal: occurs early in Tx with older agents
  - Parkinson's (self limiting), akathisia, acute dystonic reaction
  - Seizures (2-5% with *clozapine*)

  Tardive Dyskinesia:
  - relative cholinergic def to extra-sensitive dopamine R
  - 20-40% of chronically treated old antipsychotics
  - Advanced cases difficult to reverse ∴ recognise early
  - Discontinue drug then eliminate all centrally anticholinergic drugs
  - *Diazepam* if above fails
- ***Autonomic (Antimuscurinic):*** urinary retention, orthostatic ↓BP, impaired ejaculation
- ***Metabolic/Endocrine:*** weight gain common, hyperprolactinemia ⇒ infertility
- ***Toxic/Allergic:*** agranulocytosis (1-2%) esp 6th & 18th wk of therapy, reversible
- ***Ocular:*** cornea & lens deposition, Thioridazine causes retinal deposits
- ***Cardiac:*** *Thioridazine* causes T wave abnormalities/conduction block/sudden death
- ***Pregnancy:*** possible small ↑ teratogenicity

Neuroleptic Malignant Syndrome
- Life threatening
- Extreme sensitivity to extrapyramidal effects
- Starts with muscle rigidity ⇒ high fevers (impaired temp control)
- Stress leucocytosis
- Autonomic instability
- Treat with antiparkinson drugs, muscle relaxants (*diazepam*), physical cooling

Overdose
- *Thioridazine* has fatal arrhythmic effects ∴ Tx as for TCA overdose
- All others rarely fatal: drowsy ⇒ agitation ⇒ coma/convulsion

LITHIUM & OTHER MOOD STABALIZING DRUGS
- Lithium is true mood stabiliser
- Others are used as antimanic: CBZP, Valproate, Olanzapine

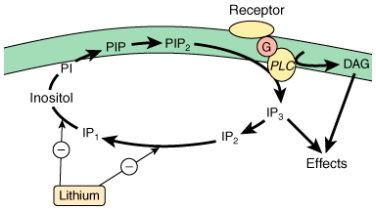
Kinetics
- Rapid/complete absorption
- Renal clearance (not metabolised) | T ½ 20 hrs
- Steady state after 5 days ∴ levels after 5 days
- Clearance effected by changes in body water
  - Dehydration, *thiazides*, *NSAIDs, ACE I*, *loop diuretics* can result in *lithium* toxicity
  - *Caffeine* & *theophylline* increase renal clearance of lithium

Mechanism
- Not well defined

A. Ion Transport
- Li similar to Na; substitutes in AP generation or Na-Na exchanges
- Li-Na exchange inhibits further exchange
- Does not affect Na/Ca exchange or Na/K ATPase pump

B. Neurotransmitters
- Enhance 5-HT
- ↓ Norepinephrine & Dopamine turnover
- Block dopamine receptor super sensitivity
- Augment Ach synthesis

C. 2nd Messenger
- Inhibits IP_2 ⇒ IP_1 & IP_1 ⇒ Inositol ⇒ ↓ DAG & IP_3 2nd messengers
- Selective depression of overactive circuits
- IP_3 & DAG messengers found on α-adrenergic & muscarinic transmission
- Also uncouples G-proteins from receptors



Clinical Use
- Bipolar disorder (benefit also seen in prophylaxis)

Mania
- Acute phase Tx use *Olanzapine* or *Valproic acid*
- *Lithium* slow onset
- After mania controlled, stop antipsychotic/cont *Li* & *BZDP*

Depressive
- Concurrent antidepressant
- *TCAs* ↑ manic relapse
- *SSRIs* less likely, but less efficacious
- *Lamotrigine* may be effective

Other applications
- Recurrent endogenous depression
- Li or Imipramine both work
- Schizoaffective disorders use Li as adjunct to antipsychotic
- Adjunct to TCA or SSRI in unipolar depression

Toxicity
- Tremor, sedation, ataxia, aphasia
- Thyroid enlargement, usually no effect on hormonal balance
- Nephrogenic DI (reversible)
- Oedema common
- Acne common
- Leucocytosis always present
- Contraindicated in sick sinus (due to bradyarrythmia)
- Peripartum: post-delivery clearance ↓ ∴ can go into toxicity

SECTION V: CENTRAL NERVOUS SYSTEM

9. ANTIDEPRESSANTS

The Amine Hypothesis of Mood

- Brain amines (esp NE & 5-HT) have functional components to express mood
- ↓ levels ⇒ ↓ mood
- This was accidently shown with Respirine (induced depression)
- Most antidepressant act on either the metabolism, reuptake or selective receptor antagonism of 5-HT and/or NE (except Bupropion)

Chemistry & Kinetics

Antidepressants
- MAOI
- TCA
- SSRI
- Heterocyclics

A. TCA
- *Amitriptyline, Doxepin, Imipramine*
- Initially used as sedating antihistamine
- Mixed NE & 5-HT inhibiting properties
- Well absorbed orally | Highly protein bound & lipid soluble ∴High V_D
- Metabolised to active metabolites | T ½ 8-36 hrs

B. HETEROCYCLICS
- 2nd (*Bupropion*)& 3rd (*Venlafaxine, Mirtazapine, Duloxetine*) Generation antidepressants
- Kinetics same as TCAs, overall have shorter T ½

C. SSRIs
- *Fluoxetine, Citalopram, Fluvoxamine, Sertraline, Paroxetine*
- Hepatic metabolism | T ½ 18-24 hrs
- *Fluoxetine* forms an active metabolite (T ½ 7 days)

D. MAOI
- Hydrazides (*Phenelzine*) bind irreversibly with enzyme
- Nonhydrazides (*Trancyclopromine*) doesn't bind irreversibly but still has prolonged action
- MAO-A metabolises NE, 5-HT, Tyramine
- MAO-B metabolises dopamine
- *Tranylcypromine* fastest onset: 1 week duration (others 2-3 weeks)
- MAO inhibition continues even when plasma levels are undetectable

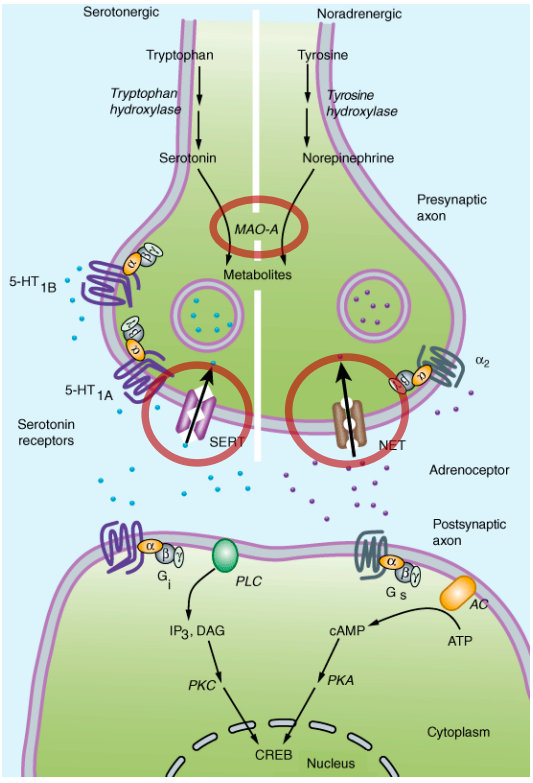
Pharmacodynamics

A. TCAs
- Block NET & SERT ⇒ ↑ [NE] & [5HT] in synapse

B. HETEROCYCLICs
- Variable
- 2nd generations; some inhibit NET or SERT
- 3rd generations; potent inhibition of both NET & SERT
- *Mirtazapine* antagonises α_2 receptor on presynaptic neurons (∴ downregulate NT synth)
- *Bupropion* has an unknown mechanism (not NE or 5HT) but occupies 25% of dopamine reuptake transporters

C. SSRIs
- SERT inhibition

D. MAOIs
- Inhibit metabolism of reuptaken NE & 5HT



PHYSIOLOGICAL EFFECTS

A. Amine Uptake Blockade
- NET blockers also block NET in ANS ∴ peripheral sympathomimetic effects
- *MAOIs* also ↑ NE in ANS synapse
- Long term *MAOIs* = hypotension

B. SEDATION
- Common for TCAs esp *Mirtazapine*
- MAOIs, SSRIs, Bupropion = CNS stimulant

C. M Receptor Blockade
- TCAs esp *amitriptyline* & *doxepin*
- Less common with *Heterocyclics, SSRIs, bupropion*

D. CV Effects
- TCAs ⇒ α block ⇒ ↓ BP & conduction
- Venlafaxine acts like an SSRI at low doses, NET inhibition at high doses ⇒ ↑ HR & BP

E. Seizures
- *TCAs* & *MAOIs* reduce seizure threshold
- More common in OD

CLINICAL USE

- Individual response to different agents
- Newer drugs (SSRIs, some Heterocyclics) are safer in overdose
- *SSRIs* OCD, GAD, Panic Attacks, Social phobias, bulimia, alcohol dependence, ↓ appetite
- *TCAs* have same efficacy, used in psychomotor retardation, sleep disturbance, poor appetite, weight loss , Other uses of TCAs: Bipolar, Panic Attacks, Phobias, Enuresis, ADHD, Chronic Pain
- *MAOIs* used in severe anxiety, phobia, hypochondriasis
- *Venlafaxine*; neuropathic pain, anxiety disorders
- *Duloxetine*: diabetic peripheral neuropathy, anxiety disorders

TOXICITY

A. *TCAs*
- CNS: Sedation, Fatigue, Confusion, Seizures, Orthostatic hypotension, prolonged QTc, tremor, paraesthesia , weight gain
- Sympathomimetics: tachycardia, agitation, sweating, insomnia
- *Atropine*-like effects

Symptoms: 3 C's Coma, Convulsion, Cardiotoxicity
- Agitation, delirium, NM irritability, convulsions, coma
- Respiratory depression, circulatory collapse
- Hyperpyrexia
- Cardiac conduction defects

B. Heterocyclics
- *Mirtazapine*: weight gain, sedation, autonomic effects
- *Bupropion*: anxiety, agitation, dizziness, dry mouth, psychosis, seizures
- *Venlafaxine*: dose dependant increase in BP, CNS stimulant
- Cytochrome P450 inhibition

C. *SSRIs*
- Nausea, headache, anxiety, insomnia, agitation, sexual dysfunction
- Akathisia, dyskinesia, dystonic reactions
- Seizures in OD
- *Citalopram;* QT prolongation
- Inhibit P450
- ***Serotonin Syndrome***: severe muscle rigidity, myoclonus, hyperthermia, cardiovascular instability, marked CNS stimulation (incl seizures)
- Due to interaction with *MAOIs, TCAs, Dextromethorphan, Meperidine, St Johns Wart, Illicit drugs*

D. *MAOIs*
- HTN (sympathomimetic response)
- CNS stimulation, agitation, seizures
- OD: shock, hyperthermia, seizures

⇑ Net effect of all antidepressants = inhibition of NT (NE or 5HT)
All (but MAOI) inhibit transport reuptake via Serotonin transporter (SERT) or Norepinephrine Transporter (NERT). MAOI inhibitors ↑ vesicular storage by ↓ metabolism

SECTION V: CENTRAL NERVOUS SYSTEM

10. OPIOD ANALGESICS & ANTAGONISTS

BASIC PHARMACOLOGY

Chemistry

- Full/partial agonist or antagonist (***morphine*** full, ***Codeine*** partial, ***Naloxone*** Antagonist)

Function	μ[1]	δ	κ
Supra/spinal Analgesia	✓	✓	✓
Hormone & NT modulation	✓	✓	×
Slowed GI transit	✓	×	✓
Sedation	✓	×	×
Respiration inhibition	✓	×	×
Psychotomimetic effect	×	×	✓
Endorphins	+++	+	+
Enkephalins	++	+++	+
Dynorphins	+	+	++++
Presynaptic Ca Ch	✓	✓	✓
Postsynaptic K Ch	✓	×	×

All are G protein coupled receptors

[1]Main opioid receptor

Endogenous Opioid Peptides

- Intrinsic opioid alkaloids (eg morphine), peptides incl *Endorphins, Enkephalins, Dynorphins*

Enkephalins	• Leu- & met- • Analgesia through δ
Endorphins	• Analgesia through μ
Dynorphins	• A, B & α or β neonorphin • A[1] is analgesic on dorsal horn via NMDA (not opioid)

[1]Also known as the "sensitizing" peptide (hyperalgesia in inflammation/tissue injury)

Kinetics

A. Absorption

- Well absorbed oral, s/c, i/m, nasal, dermal, mucosal
- High 1st pass metabolism (∴ nasal/mucosal may be useful, ***codeine*** & ***endone*** have < effect)

B. Distribution

- Binds plasma proteins but disassociated into tissue quickly (preferentially to higher perfused organs; brain, lungs, liver, kidney, spleen)
- Although fat is lowly perfused, highly lipophilic opioids (***fentanyl***) may accumulate here

C. Metabolism

- Converted to polar metabolites & readily excreted by kidneys

Morphine

- Metabolites include M3G (neuroexcitatory) & M6G (x4-6 as potent as morphine)
- Both are polar ∴ limited penetration across BBB (***Probenecid*** or other P-glycoprotein inhibiting drug can ↑ transfer)
- In renal disease/other accumulation ⇒ ***seizures or prolonged analgesic state***

Hydromorphone

- Metabolites include H3G (neuroexcitatory) but not significantly produced

Esters (***Heroin, Remifentanil***)

- Rapidly hydrolysed by tissue esterases
- ***Heroin*** ⇒ monoacetylmorphine ⇒ ***morphine*** ⇒ renal excretion

Phenylpiperidine Opioids (***Meperidine, Fentanyl, Alfentanil, Sufentanil***)

- Hepatic metabolism
- Meperidine ⇒ Normeperidine (in high doses can cause seizures)
- No active metabolite for others

Codeine, Oxycodone

- Manufactured from ***morphine***
- Metabolised by CYP3A4
- ***Codeine*** metabolite (***morphine***) exerts analgesic effect vs ***oxycodone,*** direct effect on μ

Dynamics

A. Mechanism

1. Metabotropic Receptors

A. Presynaptic: close Ca ch ⇒ inhibit NT release (all receptors)

B. Postsynaptic: open K ch ⇒ hyperpolarize membrane (μ receptors only)

2. Relation of Physiologic Effects to Receptor Type

- μ is main target for opioid alkaloids ⇒ analgesia, resp depression, dependence
- δ & κ also activated to a lesser degree (some analgesic properties, less adverse profile)
- Endogenous opioid peptides differ to opioid alkaloids for receptor affinity

3. Receptor Distribution & Neural Mechanisms of Analgesia

- 1ry afferent neurons
  - Inhibit AP propagation from stimulus
  - Inhibit transmitter (glutamate & neuropeptide) release at terminal via Ca inhibition (α_2 agonism also acts here)
  - ***Both endo-/exogenous opioids distribute highly to inflammatory areas***
- 2ry afferent: Opens K channels to hyperpolarise membrane
- Dorsal Horn (ascending tract)
  - All 3 in high concentration in dorsal horn (directly inhibit neuron) ∴ "Spinal anaesthetics" provide less systemic effects
- Descending Tracts
  - Activate Inhibitory neurons (primarily $GABA_A$)
  - Midbrain (periaqueductal grey matter), Rostral Ventral medulla, Dorsal Column

4. Tolerance & Physical Dependence

- Upregulation of cAMP (small component)
- Down regulation of μ receptors (require reactivation by endocytosis to maintain sensitivity)
- Receptor uncoupling; dysfunction of receptor=G-protein communication
- NMDA probably has a role (since ketamine can block tolerance)
- δ receptors may play a role (experimentally)

Degrees of Tolerance		
High	**Moderate**	**Low**
Analgesia	Bradycardia	Meiosis
Euphoria, dysphoria		Constipation
Mental Clouding		Convulsions
Sedation		
Respiratory Depression		
Antidiuresis		
Nausea & Vomiting		
Cough Suppression		

B. Organ System Effects

1. CNS

- Principle effector organ: *analgesia, euphoria, sedation, resp/cough depression*
- ***Analgesia***; ↓ both sensory & affective components of pain
- ***Sedation***; common, no amnesia, less so with synthetic opioids (***fentanyl***)
- ***Resp depression***; through brainstem inhibition, ↓ CO_2 response, responds to stimulus
- ***Cough suppression***; ***codeine linctus***
- ***Meiosis***; constricted pupils (also seen if tolerant)
- ***N&V***; trough brainstem CTZ & vestibular
- ***Temperature***; μ = hyperthermia, κ = hypothermia
- ***Truncal Rigidity***; more common in lipophilic drugs, supraspinal action, ↓ thoracic compliance

2. Peripheral Effects

Cardiovascular; no significant effects

- ***Meperidine*** has Antimuscurinic effects ∴ tachycardia possible
- BP stable unless stressed (hypotension to central & histamine release)
- Minimal effect on cerebral circulation (CO_2 retention from resp depression)

GIT

- High density population in GIT ⇒ Constipation (↓ motility, secretions ↑ tone)
- Effect via CNS & enteric NS
- **Tolerance not acquired**
- Biliary: gallbladder contraction, sphincter constriction ⇒ reflux ⇒ ↑ transaminases/lipase/pain

Uterus

- Prolong labour

Renal

- Function depressed (2ry to ↓ flow)
- μ receptors have antidiuretic effects & enhance renal Na tubular resorption
- ↑ Ureteral & bladder tone ⇒ retention & worsening of colic

Neuroendocrine

- Promote: ADH, prolactin, somatostatin release | Inhibit: LH
- Endogenous opioid peptides may regulate these
- Pruritus
- Flushing/warming of skin +/- sweat/itch (due to histamine release &probably CNS)
- Worse when given parenterally

Misc

- Immune system; (inhibitory) lymphocyte proliferation, antibody production, Chemotaxis

C. Effects of Opioid with both Ant/agonist actions

Buprenorphine

- High binding affinity ∴ antagonise effects of more potent opioids, low intrinsic activity, slow dissociation (prolongs action, maybe better than ***methadone***)
- Weak μ agonist, κ & δ antagonist

CLINICAL PHARMACOLOGY

Clinical Use of Opioid Analgesics

A. Analgesia

- Severe constant pain relieved with high intrinsic active agents (Sharp intermittent pain not as well)
- Chronic pain; fixed-interval better then on demand or SR (***MSContin & OxyContin, Fentanyl patch)***
- Stimulants (eg ***amphetamines***) enhance opioid effect
- May have paradoxical effect in biliary & renal colic (due to smooth muscle spasm)

B. APO

- Effect from anxiety, ↓ preload (venous dilation) ↓ afterload (PVR) ↓ pain (in MI)

C. Cough

- Lower doses than for pain
- Not common nowadays with new synthetic suppressants without adverse effects

D. Diarrhoea

- Again no longer commonly used
- ***Diphenoxylate*** is synthetics, more specific for the gut (low CNS uptake)

E. Shivering

- All have some anti-shivering effect
- ***Meperidine*** is the most pronounced (action on α_2 Adrenoceptors)

F. Application of Anaesthesia

- Either as premed, adjunct or primary component of anaesthesia
- Better for minimal cardiovascular depression (eg CTS)
- Regional analgesia; resp depression & hypotension can occur, pruritus, nausea, vomiting more common, epidural safer

G. Alternative Routes

- Rectal, transdermal, intranasal, buccal
- PCA

Toxicity/Undesired Effects

A. Tolerance/Dependence

A. Tolerance

- Usually seen after ***2-3 weeks*** (but variable with drugs eg ***methadone*** takes longer)
- More commonly seen with ***large doses with short intervals***
- Duration of tolerance: resp/sedation 2-3 days, emesis months
- Cross tolerance exists between different opioids (usually partial or incomplete)
  ∴ "Opioid rotate" useful
- Recouple; resynchronised opioid receptors by using non-opioid drugs
  - NMDA receptor antagonists (**ketamine**)

Physiological Dependence

- Signs/Sx; rhinorrhoea, lacrimation, yawning, chills, piloerection, hyperventilation, hyperthermia, mydriasis, muscular aches, vomiting, diarrhoea, anxiety, obesity
- ***Morphine/heroin***; onset 6-10 hrs of last dose peak 36-48 hrs, 5 day offset
- ***Meperidine***; offset 24 hrs
- ***Methadone***; onset days, offset weeks (less intense Sx)
- Tolerance also disappears
- ***Antagonist-precipitated withdrawal*** occurs with ***naloxone***
  (Onset 3 min peak 10-20 min offset 1 hr)

Psychological Dependence

- Euphoria, indifference to stimuli, sedation, abdominal arousal

B. Overdose

- ***Naloxone*** only for opioid induced sedation

C. Contraindications

- Pure agonist + partial agonist ⇒ diminished analgesia or withdrawal Sx
- Head injury (resp depression ⇒ ↑ CO_2 ⇒ vasodilation ⇒ ↑ ICP)
- Pregnancy; 6mg ***Heroin*** = mild withdrawal Sx, 12mg = severe
- Impaired pulmonary function, hepatic & renal function
- Endocrine disease; prolonged effect in Addison's & hypothyroidism

SPECIFIC AGENTS

	Strong	Mild/Mod	Mixed[1]	Misc
Phenathrenes	***Morphine*** ***Hydromorphone*** ***Oxymorphone*** ***Heroine***	***Codeine*** ***oxycodone*** ***dihydrocodeine*** ***hydrocodone***	***Nalbuphine*** ***Buprenorphine***	*nil*
Phenylheptylamines	***Methadone***	***Propoxyphene***	*nil*	*nil*
Phenylpiperidines	***Fentanyl*** ***Sufentanil*** ***Alfentanil*** ***Remifentanil*** ***Meperidine***	***Diphenoxylate*** ***Difenoxin*** ***Loperamide***	*nil*	*nil*
Morphinans	***Levorphanol***	*nil*	***Butorphanol***	*nil*
Benzomorphans	*nil*	*nil*	***Pentazocine***	*nil*
$5HT_1$	*nil*	*nil*	*nil*	***Tramadol***

[1]Mixed receptor

Strong Agonists

1. Phenathrenes

- ***Morphine, Hydromorphone, Oxymorphone, Heroine***

2. Phenylheptylamines

Methadone

- PO (Oral BioAv > morphine), PR, IV, SC, Spinal, Rectal
- Racemic D & L isomers; block μ, NMDA & Monoamine Reuptake transport
- T ½ 25-52 hrs

Use

- Opioid Rotation
- Opioid Abuse; longer time to tolerance & dependence, milder withdrawal Sx
- ***Heroine detoxification***; 5-10mg BD-TDS for 2-3 days, mild tolerable withdrawal Sx
- Maintenance programs also exist; 50-100mg/day, blocks reinforcement from abuse, requires aggressive non-pharmacological management

3. Phenylpiperidines

Fentanyl & subgroups; ***Sufentanil, Alfentanil, Remifentanil***

- ***Sufentanil*** 5-7x potent
- ***Alfentanil*** less potent, shorter acting
- ***Remifentanil*** shortest acting (blood esterases breakdown)

Meperidine

- Older, less used
- Antimuscurinic effects, negative inotropic effect
- Seizures if accumulated (renal failure)

4. Morphinans

- ***Levorphanol*** is synthetic opioid resembling morphine

Mild to Moderate Agonists

1. Phenathrenes

- ***Codeine, oxycodone, dihydrocodeine, hydrocodone***
- More adverse effects/less efficacious (vs ***morphine***)
- Usually used in combination

2. Phenylheptylamines

Propoxyphene

- Chemically related to ***methadone*** with low analgesic effects
- Analgesic effect poor (1/2 potency codeine)
- Low potential for abuse
- Usually potentiates action of aspirin as an analgesic

3. Phenylpiperidines

Diphenoxylate, Difenoxin (mixed with ***atropine*** to ↓ abuse)

- Used in Mx of diarrhoea
- Poor solubility ∴ IV formulation stings

Loperamide

- Limited access to brain ∴ low potential for abuse
- Dose of all; 2 tablets then 1 after each stool
- Main area of action is large bowel

Opioid with Mixed Receptor Actions

1. Phenathrenes

Nalbuphine;

- Strong κ agonist, μ antagonist, IV
- Definite ceiling to resp depression (resistant to ***naloxone***)

Buprenorphine

- Long acting partial μ agonist (slow dissociation) ∴ naloxone ineffective
- As effective as ***methadone*** for detoxification
- High doses act as μ antagonist ∴ limited resp depression, analgesic effect

2. Morphinans

Butorphanol

- Similar analgesia to ***Nalbuphine*** but less potent, more resp effects
- κ agonist, minor μ ant/agonist

3. Benzomorphans

Pentazocine

- κ agonist, weak μ antagonist
- Oldest of the mixed, PO or IV

Misc

Tramadol

- Blocks $5HT_1$ reuptake
- Weak μ agonist (ltd response to naloxone), also inhibits norepinephrine transport
- 50-100mg QID
- Adverse effects; seizures (contraindicated in epilepsy), N&V – tolerant after 3 days
- No cardiorespiratory effects

ANTITUSSIVES

- Diff receptors to analgesia (isomers with no analgesic, not addictive still supress cough)
- Central & peripheral mechanism (unknown)
- Contraindicated in MAOI
- ***Dextromethorphan***; less constipation, less addictive than ***codeine***, 15-30mg QID, enhances analgesic effect of ***morphine***
- ***Codeine***; 15mg ample
- ***Levopropoxyphene***; devoid of opioid effects, some sedation, 50-100mg q4h

OPIOD ANTAGONISTS

- ***Naloxone, Naltrexone***
- High affinity for μ and less so for δ & κ receptors

Kinetics

- Well absorbed orally (rapid 1st pass)
- Duration of action 1-2 hrs (ie less than most opioids)
- T ½ 10 hrs
- Liver metabolism like morphine
- Dose 100mg

Dynamics

- Inert in non-opioid persons
- Onset 1-3 minutes
- Normalises respiration, LOC, pupil size, bowel activity, awareness of pain
- No tolerance to it

Clinical Use

- Treat acute opioid overdose
- Watch for withdrawal symptoms
- Can relapse back into coma since duration of naloxone < opioids
- Dose 0.1-0.4mg IV, maintenance 0.4-0.8mg PRN
- Also used in IV/epidural opioids to eliminate itching, nausea, vomiting, ileus
- Decreases cravings in alcoholics

SECTION V: CENTRAL NERVOUS SYSTEM

11. DRUGS OF ABUSE

BASIC NEUROBIOLOGY OF ABUSE

Dependence vs Addiction

Physical = dependence
- Tolerance & withdrawal define ∴ not always caused by drugs of abuse

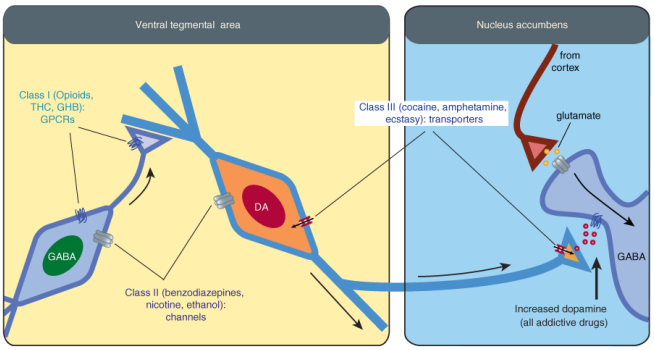
Psychological = addiction
- Compulsive relapsing use ***despite –ve consequences***, with cravings/contextual cues
- Addiction not common but relapse is

- All induce strong feelings of euphoria & reward

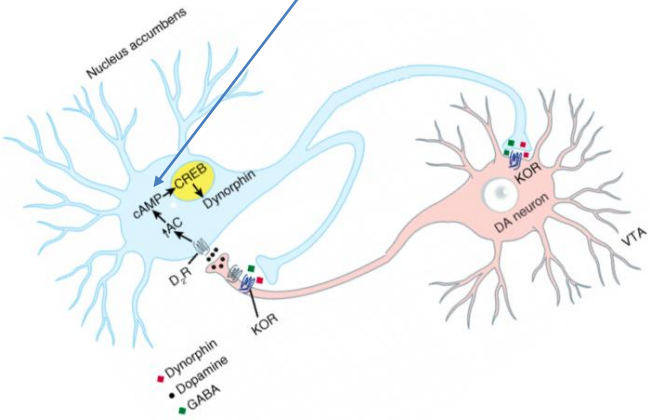
Reinforcement: Addictive Drugs ↑ levels of dopamine
- ***Mesolimbic dopamine*** system main target of addictive drugs
- Located in Ventral Tegmental Area (VTA) projecting to
  Nucleus Accumbens (NA), amygdala & prefrontal cortex
- Most projections ***produce dopamine*** (its release appears to act as a reward)

3 classes to activate the mesolimbic dopamine system

1. *Class I: G_i-coupled receptor*
   - Inhibit (mainly GABA in VTA) via post synaptic hyperpolarisation & presynaptic regulation of transmitter release
   - Includes ***Opioids***, ***THC***, ***GHB***, ***Cannabinoids***, ***LSD***
2. *Class II: Ionoreceptor*
   - Target dopamine & GABA presynaptically in VTA ⇒ enhance dopamine release
   - Includes ***Benzodiazepines***, ***Nicotine***, ***Ethanol***, ***Phencyclidine***, ***Ketamine***
3. *Class III: Monoamine Transport*
   - Block reuptake or stimulate non-vesicular release of dopamine in VTA & NA
   - Also affect other transporters not involved in addiction axis
   - Includes ***Cocaine***, ***Amphetamines***, ***Ecstasy***



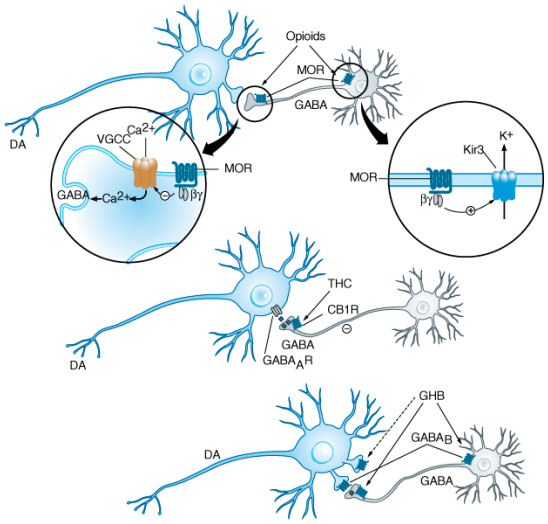
Dependence: Tolerance & Withdrawal
- Adaptation following use, becomes a problem if adverse effects do not show same tolerance
- *Pharmacokinetic tolerance* (↓ concentration or ↓ duration of action)
- *Pharmacodynamics tolerance* (↓ receptor expression)
  - Many μ receptor agonists trigger β-arrestin recruitment ⇒ uncoupling of G-protein from μ receptor ⇒ internalising receptor (probably a protecting mechanism since morphine does not recruit β-arrestin)
- Withdrawal shows adaptation that has taken place
  - Initially μ activation ⇒ inhibition of adenylyl cyclase
  - After days μ activation ⇒ ↓ inhibition ⇒ ↑ cAMP
    ∴ Withdrawal ⇒ overproduction of cAMP ⇒ CREB activation (transcription factor) ⇒ gene upregulation including Dynorphins ⇒ released with GABA ⇒ VTA & back on NA ⇒ inhibition of dopamine release at pre & post synaptic neurons



Addiction: Maladaptive Learning
- Triggers; drug, stress, contextual memory
- Most who are dependant never go on to become addicted
- Addiction may have some genetic link, mechanisms in brain plasticity and ability to learn

Non-addictive Drugs of Abuse
- Hallucinogenic & NMDA antagonists are not "addictive" since they have limited stimulation on ***mesolimbic dopamine axis***
- Chronic use still harmful; ***PCP*** ⇒ psychosis (like schizophrenia)

BASIC PHARMACOLOGY



G_{io}-coupled receptor Target

Opioids

Pharmacology/Clinical Aspects
- Different areas of the brain have different receptor expression
- μ on GABA neurons (as direct & inhibitory on GABAergic inhibitory interneurons), κ Antagonise dopamine neurons (may explain euphoria vs dysphoria)
- Reward effect lacking if μ receptor knocked out

Treatment
- Naloxone for acute overdose, precipitates withdrawal
- Long acting opioid (eg methadone) helpful for weening (less adverse withdrawal effects)
- Some countries use heroin-for-heroin under supervised conditions with good effect

Cannabinoids
- Endogenous cannabinoids; 2-AG & anandamide
- Bind to CB1 receptors on somatic dendritic membranes ⇒ inhibit GABA or glutamate (aka retrograde messaging)
- Exogenous cannabinoids (***marijuana***) contains THC
- THC disinhibits dopamine neurons (via presynaptic inhibition of GABA neurons in VTA)
- T ½ 4 hrs, Onset; minutes, duration 1-2 hrs

  Sx
  - Low doses: euphoria, relaxation
  - High doses: well-being, grandiosity, altered perception
  - Higher doses: drowsy, diminished co-ordination, impaired memory
  - Highest doses; hallucinations, depersonalization, psychosis
- Adverse Effects; appetite, ↓ nausea, ↓ IOP, chronic pain relief
- Mild withdrawal symptoms

Gamma-Hydroxybuteric Acid (GHB)
- Endogenously from GABA metabolism, unknown function

  Target receptors
  - 1μM | high affinity, unknown function
  - **$GABA_B$** | low affinity, *main source of pharmacological effect*
- Rapidly absorbed, max concentration 20-30min @ 10-20mg/kg, T ½ 30 min
- $GABA_B$ on all VTA cells but GHB has affinity for $GABA_B$ on GABA cells (at recreational dose)
- All neurons inhibited at high doses

LSD, Mescaline, Psilocybin
- Hallucinogenic, Psychosis, Somatic symptoms (dizzy, nausea, blurred vision, paraesthesia)
- Flashbacks years later
- No dependence or addiction but fast tolerance
- Mechanism: ↑ glutamate release in cortex by enhancing afferent inputs from thalamus
- Target 5-HT_{2A} (g-protein activating IP3 cascade)

Ionotropic Receptors Targets

Nicotine

Pharmacology
- Target nAChR (important role in cognitive process)
- nAChR on dopamine neurons in VTA ⇒ dopamine release in NA & prefrontal cortex
- Withdrawal symptoms mild

Treatment
- Substituting for other forms and weening
- ***Bupropion*** + behavioural therapy help

BZDP

- ***BZDP*** dependence common, ***withdrawal Sx start within days*** (depression ,insomnia, phono/photophobia, muscle cramps, seizures), ***offset 1-2 weeks***
- +ve moderators of $GABA_A$ receptors (both conductance and open channel)
- $GABA_A$ receptors expressed much higher on interneurons
- ***Barbiturates*** have similar profile but no longer used

ALCOHOL

Pharmacology

- Main receptor targets; $GABA_A$, Kir3/GIRK, Glycine, Adenosine reuptake, NMDA, $5\text{-}HT_1$
- Withdrawal Sx incl tremor, nausea, vomiting, sweating, agitation, anxiety

Time course of Sx

- 6-12 hrs Dependence
- 12-24 hrs Hallucination
- 24-48 hrs Seizures
- 48-72 hrs DT

} (5-15% mortality)

Treatment

- Supportive and less hepatotoxic BZDP (***Oxazepam*** & ***Lorazepam***)
- ***Disulfiram*** for drink aversion
- ***Naltrexone*** & CBT

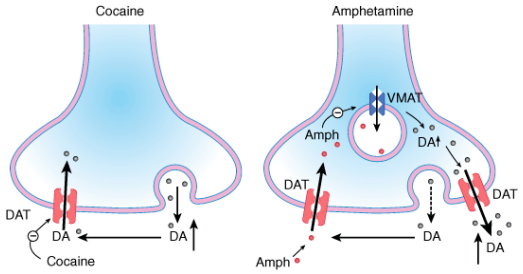
Ketamine & Phencyclidine (PCP)

- Non-competitive antagonism for NMDA
- Psychedelic effects last 1 hr and include HTN, impaired memory, visual alterations, out-of-body experience
- Do not cause dependence or addiction but chronic use of ***PCP*** leads to long lasting psychosis

Inhalants

- Recreational exposure to chemical vapours (***nitrates, ketones, aliphatic & aromatic hydrocarbons)***
- ***NO*** & Fuel additives bind NMDA*R*
- Fuel additives enhance $GABA_A$ receptor function
- ***Amyl Nitrate*** relax smooth muscle and enhance erection but not addictive
- Long term use = white matter lesions
- Mx supportive

Drugs That Bind to Transporters of Biogenic Amines



Cocaine

- Highly addictive
- Previously used for LA & dilating pupils
- Well absorbed in any mucous membrane (also inhaled)
- PNS; inhibits Na channels – no effect on addiction
- CNS: blocks reuptake of dopamine, norepinephrine, 5-HT
  - DAT (dopamine transporter) $\Rightarrow \uparrow$ synaptic concentration $\Rightarrow$ *rewarding effect*
  - Sympathetic activation through NET (norepinephrine transporter)
    $\Rightarrow$ HTN, tachycardia +/- arrhythmias
- Withdrawal less than opioids, reverse tolerance seen

Amphetamines

- Synthetic indirect acting sympathomimetic drug
- Inhibit VMAT packaging $\Rightarrow \uparrow$ cytoplasmic dopamine $\Rightarrow \uparrow$ transfer into cleft via DAT
  ∴ Vesicular release of dopamine ↓& non-vesicular ↑
- Within hrs of oral ingestion, increase alertness, euphoria, agitation, confusion
- Only neurotoxic drug of abuse
- High doses = hypertensive crisis, vasoconstriction, stroke, HIV, hepatitis
- Tolerance in chronic use with withdrawal

Ecstasy (MDMA)

- Amphetamine related compound
- Fosters intimacy & empathy without impaired intellectual capacity
- Similar mechanism to ***amphetamines*** (reverse amine transport) mainly ***SERT***
- Profound mechanism $\Rightarrow$ depletion of $5\text{-}HT_1$ for 24 hrs after
- Adverse effects; *hyperthermia, dehydrations, serotonin syndrome, seizures*
- Withdrawal = depression (up to weeks), aggression

CLINICAL PHARMACOLOGY

- Acute Mx of massive overdose is reversal drugs
- For addiction; taper or substitution methods with CBT

SECTION VI: BLOOD INFLAMMATION GOUT

1. ANAEMIA

Agents Used in Anaemia

Iron (Fe)

Basic Pharmacology

- Fe is nucleus of Heme
- Most common cause of chronic anaemia (microcytic hypochromatic)
- Sx reflect low circulating Hb
- CV adaptions

Fe Body Distribution		
	Men	Women
Hb	3050	1700
MetHb	430	300
Enzymes	10	8
Transferrin	8	6
Storage	750	300
Total	4248	2314

Kinetics

A. Absorption

- Daily intake 10-15mg, 5-10% absorbed (ie 0.5-1mg) in duodenum & jejunum
- Requirements ↑ with menses (1-2mg) & pregnancy (2-4mg)
- Source: ***Meat***: heme & MetHb can be absorbed without breakdown
  Vegetables/Other: reduced to Fe2+ then absorbed

Crossing Luminal membrane

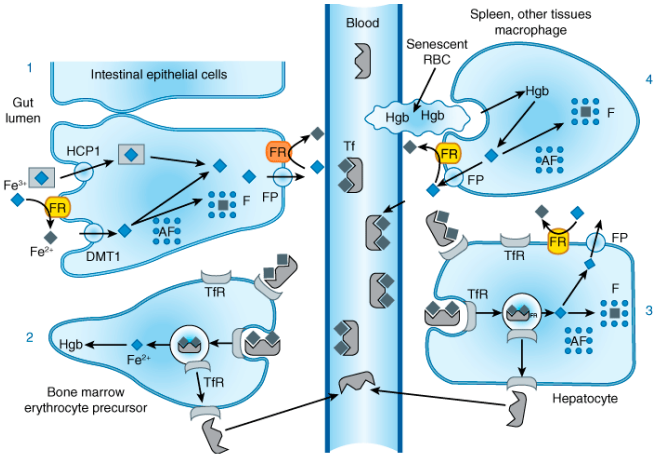
1. Active Transport of Fe^{2+} via DMT1
2. Active Transport of Fe≡Heme via HCP1

Intracellular Mechanisms

- Some transported to blood, some stored
- Storage in the form of Ferritin; ferric hydroxide core + apoferritin shell

Crossing Basolateral Membrane

- Active transport via IREG1 (Ferroportin 1)



B. Transport

- Fe binds to Transferrin (TF) in plasma
- Proliferating erythrocytes express many transferrin receptors
  ⇒ Bind ⇒ endocytosis of Fe≡TF ⇒ complex breaks
  ⇒ Fe to Heme integration, TF & receptor recycled
- TF receptors upregulated by ↑ erythropoiesis

C. Storage

- ***Stored as Ferritin*** in spleen and macrophages in liver, spleen, bone
- Regulated by free Fe | Ferritin ***plasma levels reflect total body storage***

D. Elimination

- Minimal (< 1mg/day)
- From exfoliated intestinal mucosa, sweat, urine, bile, menses (up to 30mg/day)

Clinical Pharmacology

A. Indications

- Treat or prevent ***Fe def***
- Prevent in infants (esp premature), rapid growth, lactation/pregnancy
- Treat in CKD, malabsorbtive states, blood loss

B. Treatment

1. Oral Fe therapy

- Same timeframe to correcting deficit if normal bowel absorption
- Ferrous form of Fe more readily absorbed
- Preparations include ***Ferrous Sulfate, Ferrous Gluconate, Ferrous Fumarate***
- 25% absorbed, Max incorporation into heme is 50-100mg/day ∴ dose to 200-400mg/day
- Treatment duration 3-6 months
- Adverse effects; nausea, epigastric discomfort, abdominal cramps, constipation, diarrhoea (dose related), ***black stools***

2. Parenteral Fe therapy

- Reserve for intolerable oral intake or extensive chronic loss | Fe Dextran via IV or IM
- Less Adverse effects mainly from dextran component ⇒ ***hypersensitivity reaction***
  (Can be delayed up to 48-72 hrs)
- Fe sucrose complex or Fe Na Gluconate
- Oral preparations are regulated by mucosa, no regulation for IV ∴needs continual checks

Clinical Toxicity

A. Acute Fe Toxicity

- Children with 10 tablets (adults are refractory to large doses)
- Develop ***necrotizing gastroenteritis***; vomiting, abdominal pain, bloody diarrhoea
- Shock, lethargy, dyspnoea follow
- Transient improvement metabolic acidosis, coma, death
- Tx; bowel irrigation, ***Deferoxamine*** (Fe chelating compound), activated charcoal ineffective

B. Chronic Fe Toxicity

- Hemochromatosis (usually inherited)
- Deposits of Fe in heart, lung, liver, pancreas
- Tx phlebotomy | Fe chelating agents not useful (except for thalassemia major)

Vit B12

Chemistry

- Microbial synthesis source | Cobalamin centre, porphyrin ring | Liver, Egg, Dairy
- ***Megaloblastic anaemia*** from malabsorbtion

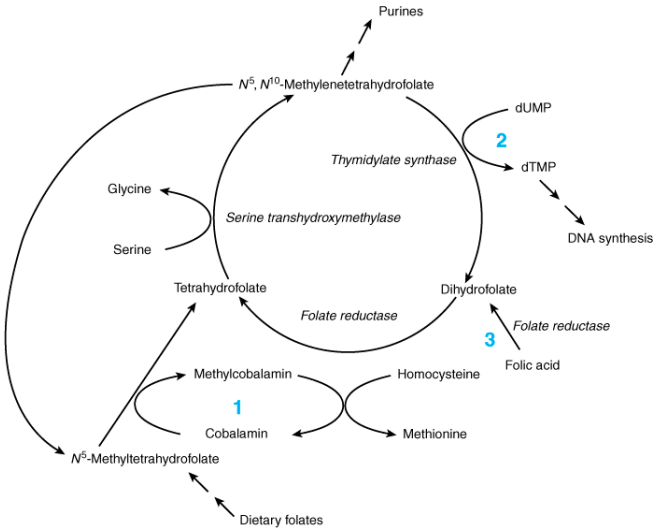
Kinetics

- 5-30mcg in diet, 1-5mcg absorbed
- Stored in liver (3000-5000mcg): daily req is 2mcg ∴ 5 years before def develops
- Trace amounts lost in urine/stool
- Absorption: complexes with IF (from gastric parietal cells) ⇒ absorbed in distal ileum ⇒ bound to transcobalamin for plasma transport ⇒ excess to liver

Dynamics

- Essential in 2 enzymatic reactions
  1. Forms methylcobalamin to catalyse folate conversion & storage (1)
     Downstream ↓ dTMP & DNA synthesis (2)
     Can be corrected with folic acid (3)
  2. L-Methylmalonyl-CoA —(Methylmalonyl-CoA mutase; Deoxyadenosylcobalamin)→ Succinyl-CoA

     Leads somehow to neurological manifestations (not corrected with folic acid)



Clinical Pharmacology

- No evidence for IM B12 in those not deficient
- Manifestations: ***megaloblastic anaemia*** (macrocytic, ass mild leukopenia/thrombocytopenia), hypercellular bone marrow
- Neurology: ***paraesthesia & weakness in peripheral nerves*** progressing to spasticity & ataxia
  B12 may arrest progression but not reverse

Causes

- Common: pernicious anaemia (defective IF release) or distal ileal disease
- Rare: bacterial overgrowth, chronic pancreatitis, thyroid disease

Tx

- ***Cyanocobalamin*** or ***Hydroxocobalamin*** (more protein binding, remains in system longer)
- 100-1000mcg OD for 1-2 weeks then monthly (if neurol Sx daily for 6 months then weekly)
- Oral formula 1000mcg daily for pernicious anaemia not wanting injections

Folic Acid

Kinetics

- Dietary 500-700mcg, 50-200mcg (300-400mcg in pregnancy) absorbed
- Source: ***yeast, liver, kidney, green vegetables***
- Storage 5-20mg in liver
- Elimination via urine, stool & catabolism
- Def onset 1-6 months
- ***Absorbed in prox jej*** (hydrolysed in brush border) via active & passive transport

Dynamics

- Tetrahydrofolate is recycled in most of its reactions except dTMP formation
- Highly proliferating tissues requiring DNA synth consumes much Tetrahydrofolate
  ∴ demand greater (anti Ca drugs are starting to target this)

Clinical Pharmacology

- ***Megaloblastic anaemia*** similar to B12 deficiency without neurology
- Assessment of def by red cell folate (plasma folate levels labile)

- Causes usually dietary; alcoholism, pregnancy & higher demand, drugs (methotrexate, chronic phenytoin, trimethoprim)
- Oral 1mg/day

Haematopoietic Growth Factors

- Glycoprotein hormones
- Clinically used GF include EPO, G-CSF, GM-CSF, IL-11

EPO

Kinetics

- IV, T ½ 4-13 hrs in CRF (Darbepoetin has longer T ½)
- Not cleared by dialysis
- Endogenous EPO from kidneys; tissue hypoxia ⇒ ↑ EPO transcription ⇒ upregulation of red cell progenitors & reticulocyte
- Blocked by red cell malnutrition (esp Fe), 1ry marrow disorder, suppression

Dynamics

Hb 1/∝ plasma EPO (except chronic renal failure)

- Normal EPO < 20 IU/L, mod anaemia 100-500 IU/L
- ∴ anaemia from CRF responds well to EPO

Anaemia of CRF

- 50-150 IU/kg 2-3x wk
- ↑ reticulocyte count within 10 days, ↑ Hb 2-3 weeks
- If no response may have Fe or folate def
- Can also be used in primary marrow disorders or secondary anaemia with low EPO levels (<100IU/L)

Toxicity

- HTN, thrombosis, rarely allergic (mild)

Myeloid GF

Chem/Kinetics

- G-CSF & GM-CSF T ½ 2-7 hrs
- Pegfilgrastim has longer T ½ than G-CSF

Dynamics

- Stim proliferation/differentiation of myeloid progenitor cells

G-CSF

- Stimulates proliferation/differentiation of commited neutrophils
- Activates phagocytosis of mature neutrophils (prolongs their survival too)
- Mobilises haematopoietic stem cells (therefor able to transplant instead of bone marrow stem cells)

GM-CSF

- Broader spectrum of activity
- Targets granulocytes & erythrocyte progenitors
- Also activates mature neutrophils
- Combines with IL-2 to activate T cell proliferation
- Less mobilisation efficacy of stem cells vs G-CSF

Clinical Pharmacology

A. Ca Chemo-induced Neutropenia

- Nadir count = lowest neutrophil level post chemo
- G-CSF improves time to recovery, nadir count
- All theoretical, no evidence

B. Other Applications

- Neutropenia associated with congenital neutropenia, cyclic neutropenia, myelodysplasia, aplastic anaemia
- Sometimes combined with other GF (since they done proliferate ertyhrocytes or paltelets)
- Aid in autologous transplantation (↓ time to engrafment, recovery from neutropenia)
- Peripheral blood stem cell transplant (less rejection, faster platelet recovery)

Toxicity

- G-CSF better tolerated
- Bone pain, fever, malaise, arthralgias, myalgias, capillary leak syndrome
- Allergic reactions uncommon

Megakaryocyte GF

Kinetics

- IL-11 T ½ 7-8 hrs
- Thrompoeitin

Dynamics

- IL-11 stimualtes multiple lym[phoid & myeloid cells
- Syngeristic with other GF for primitice megakaryocyte differentiation
- Stimulates platelet & neutrophils
- Thrombopoietin also stimulates primitive MKC, stimulates mature MKC, activates mature plt

Pharmacology

- Used in thrombocytopenia
- Reduced number of plt transfusions
- S/C 50mcg/kg/day for 14-21 days

Toxicity

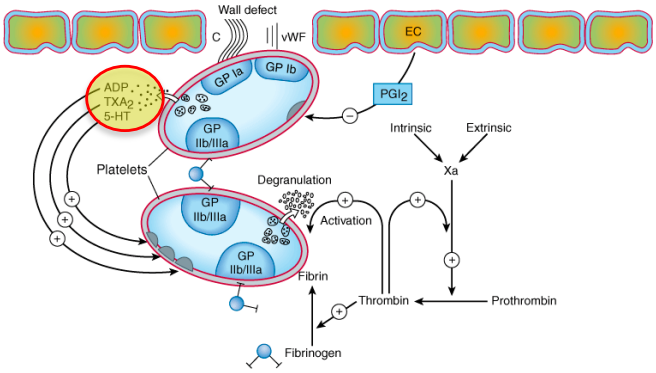
- Common: fatigue, dizziness, CV (anaemia, dyspnoea, atrial arrythmias – transient)
- Reversible

SECTION VI: BLOOD INFLAMMATION GOUT

2. COAGULATION DISORDERS

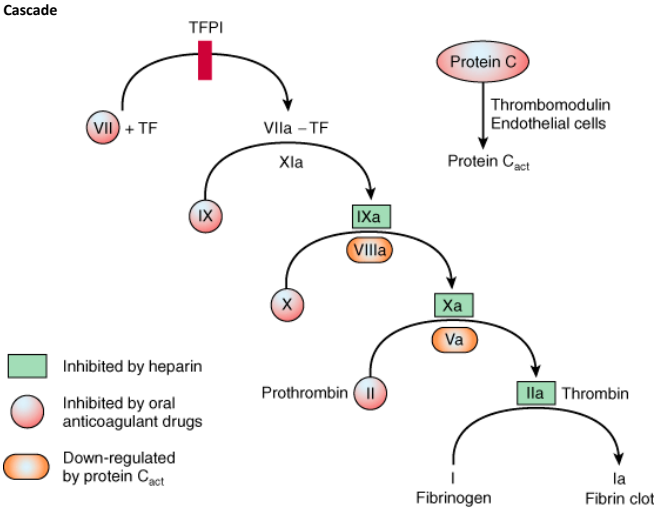
Mechanism of Clotting

- White clots = arterial clots, high in platelets
- Red clot = venous clot, high in fibrin



⇑ Thrombus at site of damaged wall
Platelet binding proteins include: GP Ia, Ib, IIb/IIIa, vWF
PGI2 (antiplatelet prostaglandins) released from endothelium to inhibit
Platelet degranulation; ADP, TXA2, 5HT

Cascade



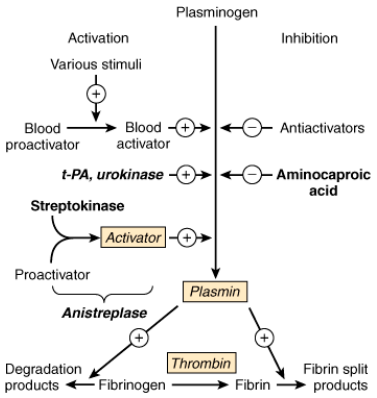
Factor	Aka	Drug action
I	Fibrinogen	
II	Prothrombin	Heparin (IIa); Warfarin (synthesis)
III	Tissue Thromboplastin	
IV	Calcium	
V	Proaccelerin	
VII	Proconvertin	Warfarin (synthesis)
IX	Antihemophilic Factor	
X	Stuart-Prower Factor	Heparin (Xa); Warfarin (synthesis)
XI	Plasma Thromboplastin Antecedent (PTA)	
XII	Hageman factor	
XIII	Fibrin-stabilizing factor	
Protein C & S		warfarin (synthesis)
Plasminogen		Thrombolytic enzymes, aminocaproic acid

Inactivation of Clotting: **Tissue Factor VIIa complex**

- TF expressed outside of vasculature, comes in contact with Factor VII when endothelium exposed ⇒ TF≡VIIa complex initiating cascade
  (Tissue factor Pathway Inhibitor regulates - TFPI)
- Thrombin (IIa) also activates V, VIII, XI (upstream) ⇒ amplification
- Clotting occurs on cell surface through Ca bridging
- Protein C & S are endogenous anticoagulants
  (Factor V def = resistance to inactivation by protein C &S)

Fibrinolysis

- Starts with tissue plasminogen activator (t-PA) plasminogen → plasmin → thrombus remodelling
- Negative regulators; Plasminogen activator inhibitor (PAI), α2 antiplasmin (inactivates unbound plasmin)
- ↑ fibrinolysis by ***tPA, Urokinase, Streptokinase***
- ↓ fibrinolysis by ***Aminocaproic Acid*** (***heparin*** and anticoagulants don't inhibit fibrinolysis)



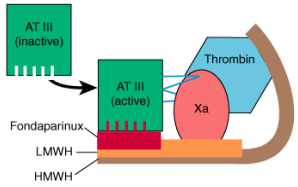
Basic Pharmacology of Anticoagulant Drugs

Indirect Thrombin Inhibitors

Heparin

Chem/Mechanism

- Interacts with Antithrombin III in order to inhibit thrombin (Antithrombin inactivates IIa, IXa, Xa slowly (heparin ↑ 1000x)
- *Heparin* binds Antithrombin ⇒ conformational Δ (↑ binding affinity) ⇒ complexes with activated factors ⇒ *heparin* released (intact)
- Also enhances inactivation of Xa & thrombin (*UFH* > *LMWH*)
- *LMWH* has same efficacy as *UFH* (despite its effect on thrombin not as great)
- *LMWH* includes *Enoxaparin* & *Dalteparin*, bother better BioAv s/c



Monitoring *Heparin* Effect

- Activated partial thromboplastin time (aPTT) for *UFH*
- *LMW* has predictable kinetics & plasma level ∴ only measured in renal insufficiency, obesity, pregnancy

Toxicity

A. Bleeding

- Bleeding major adverse effect ∴ choose patient population
- *Heparin* is of animal origin ∴ allergy possible
- Reverse alopecia, osteoporosis with chronic use

B. *HITS*

- Systemic hypercoagulable state (check plt often) mediated by HIT IgG bindings plts
- 1-4% of *UFH* after 7 days of Tx (less likely in LMWH) (sooner if last given within 3/12)
- Tx with direct thrombin inhibitor

Contraindications

- HIT, Hypersensitivity, Bleeding, infective endocarditis, active TB, advanced liver/renal disease

Administration & Dosage

- *UFH*: bolus 80-100u/kg, infuse @ 15-22u/kg/hr
  - Initial req higher due to binding to acute phase proteins (VIII, vWF)
  - Prophylaxis 5000u BD (NOT IM)
- *LMWH* prophylaxis 40mg OD Tx 1.5mg/kg/day or 1mg/kg BD
- *Dalteparin* 5000u OD Tx 200u/kg OD for venous or 120u/12hr ACS
- *Fondaparinux*; specific Xa inhibitor

Reversal

- *UFH*: *Protamine* binds with heparin to inactive,100u heparin = 1mg *protamine* (max 50mg in 10 min)
- *LMWH*: 1mg per unit but incomplete
- *Dalteparin*: plasmapheresis
- *Fondaparinux*: not reversed by *protamine*

Direct Thrombin Inhibitors

- Binds directly to thrombin to inactivate

Bivalirudin

- Binds to active site & substrate site
- Rapid on/offset & T ½
- 20% renal excretion, remainder metabolised to inactive
- Also inhibits plt activation
- Used for PCA

Lepirudin (contains *hirudin* from leech saliva),

- Can reach bound thrombin ⇒ binds to active site & substrate site
- aPTT used to measure effect
- 40% renally cleared
- used clinically in thrombosis with HITS
- 40% develop antibody formation, complexes that can form may not be cleared (↑ effect) or cause anaphylaxis

Chem/Kinetics

- 100% BioAv | 99% of racemic bound to plasma albumin = small V_D | T ½ 36 hrs
- S isomer x4 potent as R-isomer

Mechanism

- Blocks γ-carboxylation of II, VII, IX, X, Protein C & S (Vit K dependant)
- Forms incomplete (precursor) coagulation factors that are still biologically active
- γ-carboxylation coupled to Vit K oxidation (need to be reduced in order to cont to work)
- *Warfarin* **inhibits reduction of Vit K**
- Genetic variant of Vit K epoxide reductase ⇒ *Warfarin* resistance
- Onset; 8-12 hrs (net of all factor T ½; ***VII = 6 hrs***, IX = 24 hrs, X = 40 hrs, II = 60 hrs)

Toxicity

- Bleeding
- Pregnancy; crosses placenta ⇒frank haemorrhage, also depresses γ-carboxylation found in foetal bone & blood ⇒ *birth defects*
- ↓ Protein C synthesis ⇒ cutaneous necrosis, acute venous thrombosis

Admin/Dosage

- 5-10mg aiming for 25% PT (<20% = ↓ dose warfarin)
- INR = PT ratio against standardised set, reflect PT to mean normal ratio
- *Warfarin* resistance most common in GI Ca (*LMWH* superior in preventing VTE recurrence)

Interactions

- Dynamics vs kinetic effects
- Kinetics: enzyme induction/inhibition, ↓ plasma protein binding
- Dynamics: synergism, competitive antagonism, alter physiological control loop
- *Metronidazole*, *fluconazole*, *trimethoprim*; inhibit metabolism of S-isomer
- *Amiodarone*, *Disulfiram*, *cimetidine* inhibit metabolism of both isomers
- *Aspirin*, hepatic disease, hyperthyroidism augment (inhibit plt fcn, ↑ factor turnover)
- *Cephalosporin* eliminate vit K producing gut bacteria & directly inhibit vit K epoxidase reductase
- *Barbiturates* & *Rifampicin* ↓ effect markedly by inducing metabolic enzymes
- No significant effect*; ethanol, BZDP, paracetamol, opioids, indomethicin*, most other antibiotics

Reversal

- Withhold drug | *Vit K*
- For rapid reversal; *prothrombin complex* or *rFVIIa* + *vit K*

Basic Pharmacology of Fibrinolytics

Pharmacology

- *Streptokinase* combines with protein activator plasminogen to catalyse formation of plasmin
- *Urokinase* is a human enzyme formed in kidney, directly catalyses plasmin formation
- Plasma antiplasmins in circulation prevent the use of plasmin directly but *streptokinase* & *Urokinase* diffuse to the centre of thrombus to activate plasmin
- *Alteplase* (tPA); preferentially activate plasmin bound to fibrin
- *Reteplase* (tPA); less fibrin specific
- *Tenectaplase*; mutant form of tPA, longer T 1/2 , more fibrin specific than tPA

Indication & Dosage

- PE with haemodynamic instability, Severe DVT with SVC syndrome, Ascending thrombophlebitis of iliofemoral vein with oedema, ischemic stroke within 3 hrs, AMI
- *Streptokinase* load 20,000 units then 100,000 units/hr for 24-72 hrs
  - Can develop fever, allergy, resistance
- *Urokinase* load 300,000 units then 300,000 units/hr for 12 hrs
- *Tissue Plasminogen Activator (tPA)* 60mg 1st hr then 40mg over next 2 hrs
- *Reteplase* 10units x2 20 min apart
- *Tenecteplase* IV bolus 0.5mg/kg only

Basic Pharmacology of Antiplatelet

Aspirin

- TXA2 ⇒ plt degranulation/aggregation
- *Aspirin i*rreversibly acetylates COX on TXA2
- Other *NSAIDs* also inhibit COX but shorter duration as they can't acetylate COX

Clopidegral & *Ticlopidine*

- Irreversibly block ADP receptor on platelets with no effect on PG metabolism

Ticlopidine

- Adverse effects; N&V, diarrhoea, haemorrhage, leukopenia, thrombotic thrombocytopenic purpura
- Dose 250mg BD

Clopidegral

- Fewer side effects
- Dose 300mg initially (inhibit 80% plt activity within 5 hrs) maintain 75mg/day
- Inhibits plt for 7 days

Blockade of Plt Glycoprotein IIB/IIIA Receptor

- Used in ACS, targets IIB/III receptor (expressed mainly on fibrinogen, vitronectin, vWF)
- Activation of IIB/IIIA is final common pathway for plt aggregation
- *Abciximab*; monoclonal antibody against IIB/IIIA complex (incl vibronectin)
- *Eptifibatide*; mediates binding of fibrinogen to receptor
- *Tirofiban*; smaller molecule than *Eptifibatide* with similar properties, inhibit ligand binding IIb/IIa receptor without blocking vibronectin receptor

Additional Antiplatelet Directed Drugs

- *Dipyridamole* vasodilator that inhibits adenosine uptake & cGMP phosphodiesterase activity
- Used with *aspirin* (isch stroke) or *warfarin* (thromboemboli with prosthetic valve) for effect (no monotherapeutic effect)

Clinical Pharmacology of Drugs Used to Prevent Clotting

VTE

Risk factors

A. Inherited

- Thrombophilia
- Loss of function mutation; antithrombin, protein C & S (less common, greater risk)
- Gain of function mutation; Factor V, PT20210, hyperhomocysteinemia

B. Acquired

- AF, prosthetic valve, cancer, prolonged immobilisation, aniphospholipic antibody syndrome, drugs (OCP)

Antithrombotic Mx

A. Prevention

- ***Heparin*** or ***warfarin***

B. Tx

- Initially with ***heparin*** and overlap with warfarin, 3-6 months

Arterial Thrombosis

- Platelet activation is underlying factor ∴ antiplatelet best
- Seen in TIA, stroke, unstable angina, AMI

Drugs Used in Bleeding Disorders

Vitamin K

- Activates II, VII, IX, X (and protein C & S)
- Found in green leafy vegetables (K1) and synth in gut bacteria (K2)
- Require bile salts for absorption
- Oral K1 onset 6 hrs, complete 24 hrs

Plasma Fractions

Sources/Preparations

- Haemophilia A (VIII def) & B (IX def) mainly
- Concentrated plasma fractions standard of treatment

Clinical Use

- Jt haematoma aim for 30-50% factor level for 24 hrs
- Soft tissue haematoma 100% for 7 days
- Haematuria 10% for 3 days
- Surgery/trauma 100% 10 days
- Factor VIII; 50units/kg to achieve 100% activity BD
- IX = x2 dose of VIII but OD
- ***Desmopressin Acetate***; ↑ VIII activity in haemophilia A or vWD
  - Used pre-op if response known
  - Intranasal high dose also available
- ***NovoSeven***; recombinant VIIa used for liver disease, major blood loss in trauma
- ***Cryoprecipitate***; plasma protein from whole blood used to treat qualitative abnormalities of fibrinogen (eg in DIC), contains 300mg fibrinogen, also used for VIII def or vWD

Fibrinolytic Inhibitors: ***Aminocaproic Acid***

- Synthetic inhibitor of fibrinolysis
- Competitively inhibits plasminogen activation
- Rapid oral absorption, renal clearance,
- 6g QID, if IV 5g load to stop hypotension
- ***TXA*** has same properties 15mg/kg load with 30mg/kg every 6 hrs
- Clinical use; adjunct in haemophilia, treat bleeding from fibrinolytic therapy, prophylaxis for re-bleeding intracranial aneurysm, also used in post prostatectomy bleeding
- Adverse: IV thrombus, hypotension, myopathy, ado discomfort, diarrhoea, nasal stuffiness

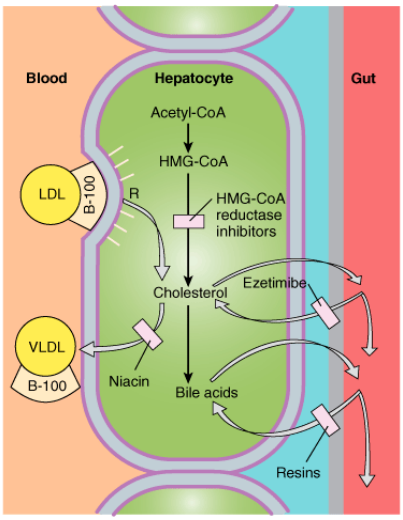
Serine Protease Inhibitors: ***Aprotinin***

- Inhibits fibrinolysis by free plasmin
- Also inhibits plasmin-streptokinase complex
- Used in CABG with high risk bleeding

SECTION VI: BLOOD INFLAMMATION GOUT

3. HYPERLIPIDEMIA

- Dietary
- Pharmacological



STATINS: HMG-COA REDUCTASE INHIBITORS

- ***Lovastatin, atorvastatin, fluvsatatin, pravastatin, simvastatin, rosvustatin***
- Reduce LDL
- Also ↓ oxidative stress, vascular inflammation, ↑ atherosclerotic stability

Kinetics

- 40-75% absorption (enhanced by food) | High 1st pass metabolism
- Excretion; bile (5-20% urine)
- T ½ 1-3 hrs (***atorvastatin*** 14 hrs, ***rosvustatin*** 19 hrs)

Mechanism

- HMG CoA Reductase mediates 1st step in sterol biosynthesis
- Upregulates high affinity LDL receptors = ↑ uptake
- Modest ↓ plasma TG & ↑ HDL seen

Dose

- Contraindicated in pregnancy, lactation
- Evening dose since most chol formation occurs at night
- Absorption enhanced by food
- ***Simvastatin*** 5-80mg OD
- ***Atorvastatin*** 10-80mg OD
- ***Rovustatin*** 5-40mg/day (most efficacious)

Toxicity

- Elevation of serum aminotransferase (usually without hepatotoxicity)
- Minor CK rise ⇒ ↑ myoglobinuria ⇒ renal injury
- CYP3A4 metabolism (simvastatin, atorvastatin)
- CYPP2C metabolism (rosvustatin)

NIACIN (NICOTINIC ACID)

- ↓ VLDL & LDL
- ↑ HDL

Mechanism

- Inhibits VLDL secretion = ↓ LDL production
- VLDL cleared through LPL pathway
- No effect on bile acid production

Dose

- Used in combination with either resin or reductase inhibitor
- Normalises LDL
- Useful in combined Hyperlipidemia
- Best agent to ↑ HDL
- 2-6g OD for heterozygous familial hyperlipidaemia
- 1.5-3.5g for all others

Toxicity

- Cutaneous vasodilation (harmless)
- PG mediated therefore aspirin can blunt effect
- Acanthosis nigrans ⇒ insulin resistance warrants ceasing
- Aminotransferase elevation, rarely hepatotoxicity

FIBRATES

- ***Gemfibrozil, Fenofibrate***

Mechanism

- Ligands for PPAR-α (nuclear transcription receptor)
- ↑ lipolysis of lipoprotein TG via LPL
- ↓ intracellular tissue lipolysis
- Modest ↓ LDL & ↑ HDL

Dose

- Used in hyperTG (VLDL predominates dysfunction)
- ***Gemfibrozil*** 600mg OD or BD

Toxicity

- GI irritation
- Slight ↓ WBC, haematocrit
- Potentiate warfarin
- ↑ risk myopathy when used with reductase (less with ***rosvustatin***)
- Risk of chol gallstones

BILE-ACID BINDING RESINS

- *Colestipol, cholestyramine, colesevelam*

Mechanism

- Bile acids normally reabsorbed in jej & ilium for chol resynthesis
- Resins ↑ loss x10
- Enhances conversion of chol to bile acids
- LDL receptor upregulated to compensate = uptake from plasma
- No effect on homozygous familial hyperlipidaemia (no functioning receptors)

Dose

- Used in primary hyperlipidaemia
- 20% ↓ LDL at maximum efficacy
- ↑ VLDL if mixed hyperlipidaemia (need another agent eg niacin)
- Relives pruritus
- Bind digitalis (useful in toxicity)
- Colestipol; start 4-5g/day up to 20g/day

Toxicity

- Constipation, bloating (relieved with fibre in diet)
- Avoid in diverticulitis
- Gallstones
- Drug interactions; *warfarin, digitalis, thyroxine*

COX-2 only	*Celecoxib**
COX-1 > 2	*Aspirin, Indomethicin*
COX-2 = 1	*Ibuprofen*

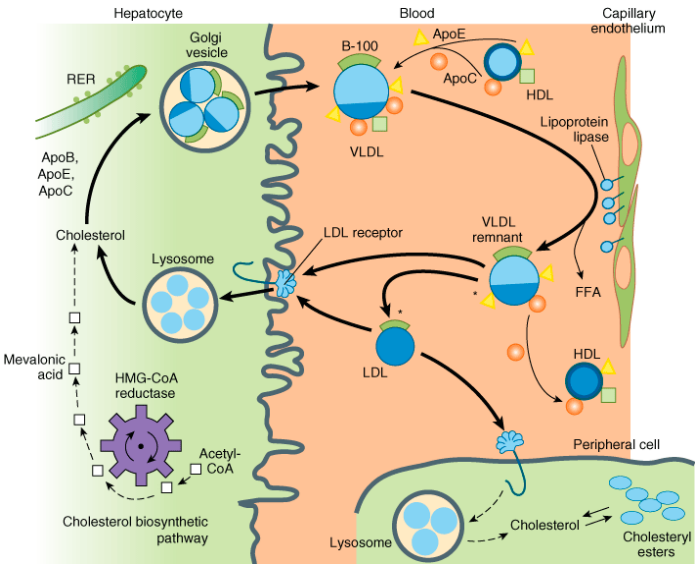
INHIBITORS OF INTESTINAL STEROL ABSORBTION

- Ezetamibe
- Inhibits absorption of phytosterols & cholesterol (targets NPC1L1 receptor)
- Effect = ↓ LDL levels
- 10mg OD
- 18% reduction in LDL, no change to HDL
- Synergetic with reductase inhibitors

INDICATIONS FOR COMBINED THERAPY

1. Resin treatment with ↑ VLDL
2. ↑ VLDL & LDL
3. VLDL or LDL not normalised with monotherapy
4. Co existent ↑ Lp(a) or ↓ HDL

Combination	Situation
Fibric Acid + Resin	Familial combined lipidemia intolerant to niacin or statins Increased risk of Cholelithiasis
Reductase + Resin	Familial lipidemia, does not effect VLDL in combined lipidemia Statins need to be given 1 hr prior or 4 hrs post resin
Niacin + Resin	Controls VLDL levels Can be taken together
Niacin + Reductase	Familial combined lipidemia
Reductase + Ezetamibe	Synergistic Primary or homozygous familial
Reductase + Fibrate	Familial combined Fenofibrate + Rovustatin normally used (P450)



⇑ Metabolism of lipoproteins of hepatic origin: Heavy arrows = primary pathway
VLDL secreted from golgi apparatus in hepatocyte
Gain ApoE & ApoC from HDL
VLDL undergoes lipolysis to VLDL remnant + FFA (catalysed by lipoprotein lipase)
ApoE given back to HDL
IDL converted to LDL through loss of ApoE & TG

LDL degradation via hepatocyte endocytosis (apo B-100 on LDL surface acts as ligand)

SECTION VI: BLOOD INFLAMMATION GOUT

4. NONSTEROIDALS

Kinetics

- Weak organic acids
- Well absorbed (regardless of meal)
- Metabolised by CYP3A or 2C
- Renal excretion (minor biliary role)
- Highly protein bound
- Seen in synovial fluid after a few doses

Dynamics

- Inhibits PG synthesis
- Other actions: inhibit Chemotaxis, down regulate IL-1, ↓ free radical production/superoxides, interfere with intracellular Ca communication
- Analgesic, Antipyretic, anti-inflammatory, inhibit platelet aggregation
- *Aspirin* irreversibly binds COX, most others reversible

*no effect on platelet, ↑ thrombotic events,

Toxicity

- Gastric irritation
- Nephrotoxicity
- Hepatotoxicity
- ↑ thrombotic events in COX2 agents

Non selective COX inhibitors

- *Diclofenac*
- *Ibuprofen*
- *Indomethacin*
- *Ketoprofen*
- *Flurbiprofen*

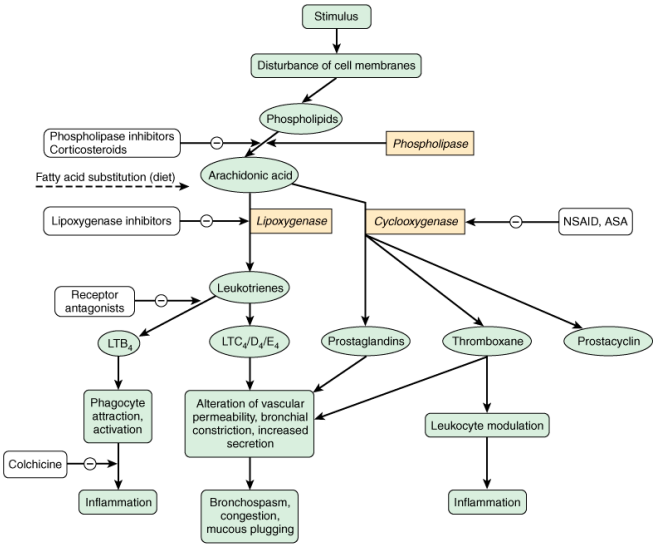
COX 2 Inhibitors

- *Celecoxib*
- *Meloxicam*

ASPIRIN

Kinetics

- Serum T ½ = 15 minutes
- Elimination T ½ = 3-5 hrs (or 12-16 with doses > 3.6g/d)
- Alkalinisation of urine encourages excretion



Mechanism

- COX inhibition (irreversibly binds)
  - ⇒ Anti-inflammatory
  - ⇒ Antipyretic (along with IL-1 inhibition)
  - ⇒ Antiplatelet (irreversibly binds ∴ lasts 8-10 days)
- Inhibits pain on a subcortical level

Aspirin has 3 therapeutic dosing Ranges

- Low < 300mg plt aggregation
- Intermediate 300-2.4g analgesic, antipyretic
- High > 2.4g anti-inflammatory

Adverse Effects

- Gastric upset
- Ulcers
- Transaminitis
- Hepatotoxicity, asthma, blood loss uncommon
- High doses act on medulla to cause hyperpnoea

COX-2 Inhibitors

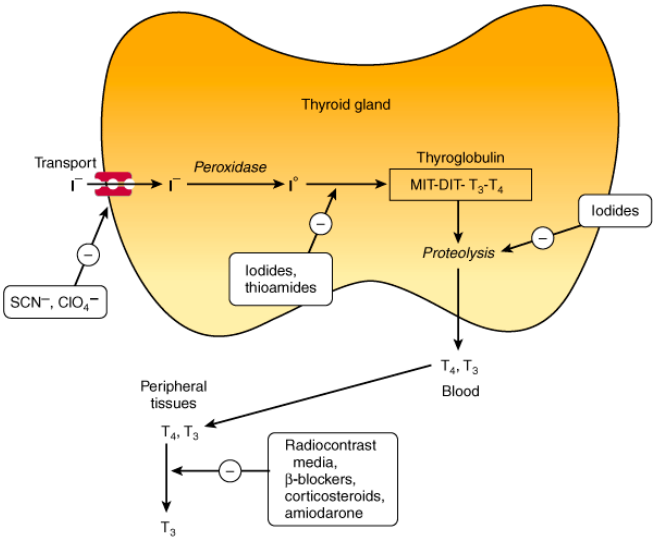
- ↓ risk ulcer formation
- Same risk of renal damage
- ↑ risk thromboembolic events (greater effect on PGI2 formation ie opp to TXA2)

COX Non-specific

Ibuprofen

- *Ibuprofen* T ½ 2 hrs
- *Naproxen* T ½ 12-24 hrs
- *Indomethicin* potent
- *Ketorolac* used as analgesic more than anti inflammatory

1. THYROID & ANTITHYROID



Thyrotoxicosis	Hypothyroidism
Warm, moist skin	Cold, Pale, Puffy skin
Sweating, heat intolerance	Sensation of being cold
↑ HR, SV, CO, Pulse Pressure	↓ HR, SV, CO, P Pressure
Dyspnoea	Pleural effusion, hypoventilation, CO2 retention
↑ appetite	↓ appetite
Nervousness, hyperkinesia, tremor	Lethargy, slow mentation
Weakness, ↑ deep tendon reflex	Stiffness, ↓ deep tendon reflex
Menstrual irregularity, ↓ fertility	Infertility, ↓ libido, impotence, oligospermia
Weight loss	Weight gain
Exopthalmos	

Variable	T4	T3
VD	10L	40L
Extrathyroid Pool	800 mcg	54 mcg
Daily Production	75mcg	25 mcg
Fraction Turnover/day	10%	60%
Metabolic Clearance/day	1.1L	24L
T ½	7 days	1 day
Serum Levels		
Total (mcg/dL)	5-12	70-132
Free (ng/dL)	0.7-1.86	0.23-0.42
Amount Bound	99.96%	99.6%
al absorption	80%	95%

THYROID HORMONES

SYNTHESIS & TRANSPORT

- Iodide is actively taken up and concentrated in thyroid —thyroidal peroxidase⟶ iodine
- Thyroglobulin acts as scaffold for thyroid synthesis
- Tyrosine residues in thyroglobulin iodinated to form Monoiodotyrosine (MIT) or DIT
- Inside thyroglobulin; DIT + DIT → T4 or MIT + DIT → T3
- Proteolysis of thyroglobulin liberates T3 & 4

- Transported in plasma by Thyroxine binding globulin (TBG) (synth in liver)
- Thyroid function controlled by TSH & Iodine (TSH also stimulates thyroid cell hypertrophy)

MECHANISMS of T3 & 4

- T3 10x potency T4
- T4 —target cell⟶ T3
- Bind to intracellular receptors that promote protein synthesis

Effects of Thyroid Hormone

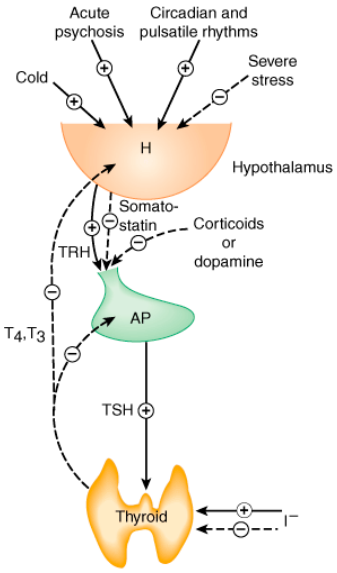
- Normal growth & development (NS, skeletal, reproductive, control of metabolism of fats, CHO, proteins, vitamins)

Clinical Use

- Either T3 or T4
- *Synthetic T4* usually 1st choice since T3 is faster acting and has a shorter T ½ and more expensive

Toxicity

- Hyperthyroidism



ANTITHYROID DRUGS

THIOAMIDES

- *Methimazole, Propylthiouracil*
- Block iodination of tyrosine in thyroglobulin
- Do not inhibit release of preformed thyroid hormone ∴ onset 3-4 weeks
- *Methimazole* OD
- PTU less likely to cross placenta/enter milk
- Toxicity; rash, vasculitis, agranulocytosis, liver dysfunction (all reversible)

Iodide Salts & Iodine

- *Iodide salts* inhibit iodination of tyrosine & TH release
- Reduce size & vascularity of hyperplastic thyroid gland
- Onset 2-7 days
- Resistance after several weeks of treatment
- Clinical use: thyroid storm, pre-op resection of hyperactive thyroid
- Adverse effects: rash, fever, metallic taste

Radioactive Iodine

- Taken up so specifically that large doses rarely cause systemic effects
- Permanent cure for thyrotoxicosis without surgery

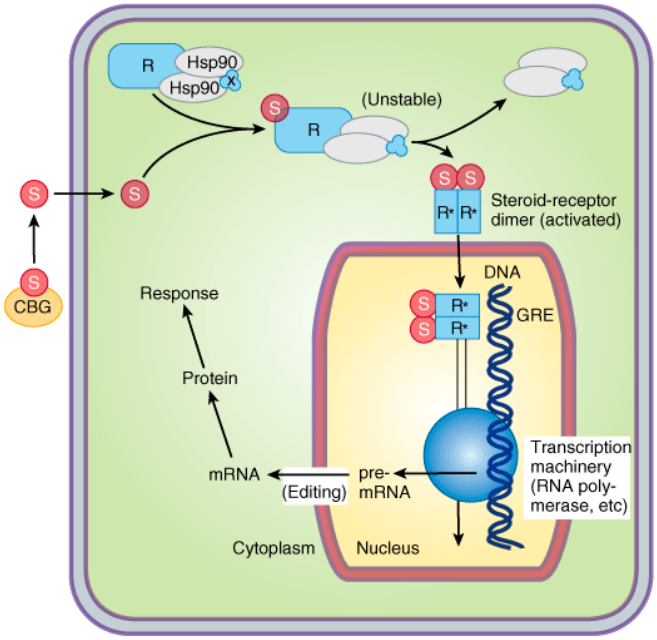
Iodinated Radiocontrast Media

- Rapidly supresses conversion of T4 to T3 in liver, kidney, other peripheral tissues
- Some inhibition on gland release
- Clinical use: rapid reduction of T3 concentrations in thyrotoxicosis

Other Drugs

- β-blockers used to treat effects of hyperthyroidism
- *Propanolol* inhibits peripheral conversion of 4 to 3
- *Amiodarone* contains iodine and can cause hypothyroidism through inhibition of 4 to 3
  Can also cause hyperthyroidism through iodine mediated pathways

2. CORTICOSTEROIDS



GLUCOCORTICOIDS

- Cortisol (*hydrocortisone*)

MECHANISM
- Enter cell & bind to cytosolic receptors that transport steroid to nucleus
- Tissue-specific responses due to different protein regulators that control hormone=receptor complex and response element

ORGAN SPECIFIC EFFECTS
- Metabolic: stimulate gluconeogenesis ⇒ ↑ glc, muscle protein catabolism, insulin secretion
  Lipolysis & lipogenesis stimulated (net ↑ fat deposition)
- Catabolic: muscle protein catabolism, wasting of lymphoid, CT, Fat, skin, bone (osteoporosis)
  ∴ Stunts growth in children
- Immunosupression: inhibit cell mediated response (esp lymphocyte dependant),
  Delay transplant rejection
- Anti-inflammatory: ↑ neutrophils ↓ lymphocytes, eosinophils, basophils, monocytes,
  Chemotaxis due to inhibition of PLA, mRNA for COX2, IL-2 & 3, PAF, cytokines
- Other: normal renal excretion of water loads, behavioural change in CNS, gastric ulcer formation

IMPORTANT GLUCOCORTICOIDS

Cortisol
- Regulated by ACTH & time of day (peak mane, through midnight)
- 95% bound to CBG
- Well absorbed
- Liver metabolism
- Short duration of action (vs synthetics)
- Diffuses poorly across intact skin, well across inflamed skin
- Minor salt retaining (mineralcorticoid) component ⇒ hypertension in cushings

Synthetic Glucocorticoids
- *Prednisone, Prednisolone, Dexamethasone*
- Long T ½, duration of action
- Reduced mineralcorticoid activity
- Better lipid barrier penetration (for topical application)
- Beclomethasone & Budesonide have short T ½ but good mucosal penetration

CLINICAL USE

Adrenal Disorders
- Addison's disease (chronic adrenal cortical insufficiency)
- Congenital adrenal hyperplasia (↓ ACTH stimulation of abnormal glucocorticoids)

Nonadrenal disorders
- Inflammation
- Haemopoetic Cancers
- Vomiting
- Hypercalcemia
- Mountain sickness
- Lung maturation

TOXICITY
- Metabolic: growth inhibition, diabetes, muscle wasting, osteoporosis, psychosis
- Salt retention
- Minimise systemic effects; topical, inhalation, alternate-day therapy, taper doses
- Stress doses required prior to surgery or during illness

MINERALOCORTICOIDS

ALDOSTERONE
- Major natural mineralocorticoid
- Regulated by ACTH & Renin Angiotensin system
- Effect; regulates blood volume & pressure
- Short T ½
- Minor glucocorticoid activity
- Same mechanism of action as glucocorticoids

OTHER
- Deoxycorticosterone (aldosterone precursor)
- Fludrocortisone (sig glucocorticoid activity, long duration of action)

CORTICOSTEROID ANTAGONISTS

RECEPTOR ANTAGONISTS
- *Spironolactone* & *Eplerenone*
- *Aldosterone* receptor antagonist
- *Mifepristone* (RU-486) competitive inhibitor of glucocorticoid receptors (as well as progesterone)

SYNTHESIS INHIBITORS
- Tx of adrenal cancer
- *Ketoconazole* (antifungal)
- Inhibits P450 (necessary for steroid synthesis)

Agent	Activity[1]			Oral Dose	Forms
	Anti-In	Top	Salt-Retain		
Glucocorticoids					
Short-Medium					
Hydrocortisone	1	1	1	20	OIT
Cortisone	0.8	0	0.8	25	O
Prednisone	4	0	0.3	5	O
Prednisolone	5	4	0.3	5	OI
Methylprednisolone	5	5	0	4	OI
Intermediate					
Triamcinolone	5	5	0	4	OIT
Long					
Betamethasone	25-40	10	0	0.6	OIT
Dexamethasone	30	10	0	0.75	OIT
Mineralcorticoid					
Fludrocortisone	10	0	250	2	O

[1]Potency vs hydrocortisone (cortisol)
Forms: O = oral, I = Injection, T = Topical

3. PANCREAS, GLUCAGON, ANTIDIABETICS

Type	Cause
1	Autoimmune destruction of Type B cells
2	Insulin Resistance
3	Raised Glc with normal B cells & insulin receptors
4	Gestational

INSULIN

- Insulin receptors activate transmembranous tyrosine kinase to effect intracellular events

Effects on Liver

Reverse Catabolic
- Inhibit glycogenesis
- Inhibit FA & aa ⇒ Keto Acids
- Inhibits aa ⇒ glc

Anabolic
- ↑ Glc uptake by GLUT2 expression
- ↑ TG synthesis & VLDL formation

Effects on Muscle

↑ Protein synthesis
- ↑ aa transport
- ↑ ribosomal action
- ↑ glycogen synthesis

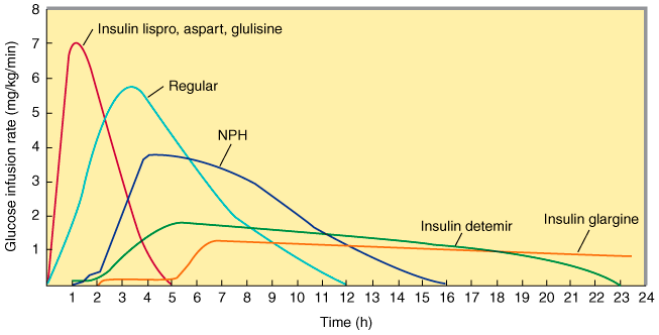
↑ Glc transport into cell
- ↑glycogen synthase activity
- Inhibit phosphorylation

Effects on Adipose Tissue
- ↑ TG storage
- Induce lipoprotein lipase: lipoprotein —hydrolysed→ TG
- ↑ Glc transport into cell

GLUT	Tissues	Glc Km	Fcn
1	All esp red cells & brain	1-2	Basal uptake of glc Transport across BBB
2	B cells in pancreas Liver, Kidney, Gut	15-20	Regulation of insulin release Glc homeostasis
3	Brain, Kidney, Placenta, Other	< 1	Uptake into neurons & other tissues
4	Muscle, Adipose	5	Insulin mediated uptake of glc
5	Kidney, Gut	1-2	Absorption of fructose

Insulin Preparations

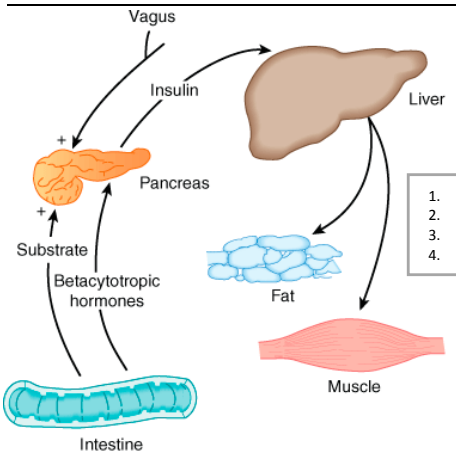
Types	Peak (hr)	Clinical Indications
Rapid Acting		
Lispro *Aspart* *Glulisine*	1 hr	• Control of postprandial glucose(give prior to meal) • Continuous infusion • Emergency treatment
Short Acting		
"Regular"	3 hrs	• Uses now replaced by rapid acting insulins
Intermediate Acting		
Protamine	4 hrs	• Used in combination with either rapid or normal insulin
Long Acting		
Glargine	6 hrs	• Peakless basal insulin dose • 20 hr duration of action



Delivery Systems
- Pen injectors
- Continuous infusion pumps

Hazards
- Hypoglycaemia
- Allergic reactions from protein contaminants
- Lipodystrophy at injection site

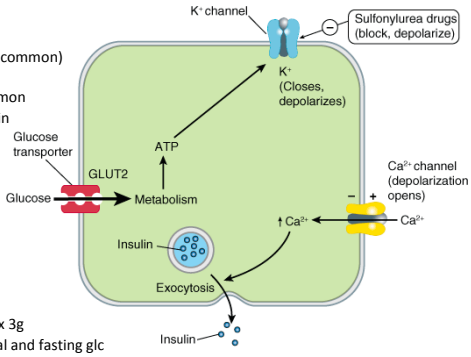
NONINSULIN ANTIDIABETIC DRUGS



1. Insulin Secretagogues
2. Biguanides *Metformin*
3. Thiazolidinedione
4. α-glucosidase inhibitors

A. INSULIN SECRETAGOGUES

- 1st generation sulfonylureas: obsolete
- 2nd generation sulfonylureas: *gliclazide, glipizide, glibenclamide, glimepiride*
  - *Gliclazide* 40mg TDS (MR 30mg OD)
  - *Glipizide* 2.5mg 1-2x daily max 20mg .....high potency
  - *Glibenclamide* 2.5 1-3x daily max 20mg
  - *Glimepiride* 1mg OD
- *Repaglinide*: fast acting ∴ dose before meals, 0.5mg 2-3x daily
- Promote endogenous insulin release by closing K channels



Toxicity
- Hypoglycaemia (not common)
- Protein bound
- Rash/allergy uncommon
- Common: weight gain

B. BIGUANIDES

- *Metformin*
- 0.5-1g 1-2x daily max 3g
- Reduces postprandial and fasting glc
- Inhibit hepatic & renal gluconeogenesis
- Other effects; stimulate glc uptake & glycolysis in peripheral tissue, slow glc absorption in GIT, enhances insulin sensitivity
- *No gain in weight*
- Used in PCOS to restore fertility

Toxicity
- Does not cause hypoglycaemia or weight gain
- Gastric irritation
- Lowers threshold for metabolic acidosis esp in renal failure, EToH, lactic acid production

C. THIAZOLIDINEDIONES

- *Rosglitazone, Pioglitazone*
- Activates PPAR-γ receptor to ↑ insulin sensitivity & glc uptake mainly in adipose & muscle (Peroxisome proliferator activator gamma receptor)
- Regulates transcription of genes encoding lipid & CHO metabolism
- Also inhibit gluconeogenesis
- ↓ Fasting & Postprandial Hyperglycemia
- Mono or co therapy
- Also used for fertility in PCOS

Toxicity
- Fluid retention; mild anaemia & oedema
- *Rosglitazone* ↑ risk MI
- Both ↑ risk bone fractures in women
- Induce P450

D. α-GLUCOSIDASE INHIBITORS

- *Acarbose*
- Inhibits α-glucosidase (converts polysaccharides to monosaccharides for absorption)
- No effect on fasting sugar
- Taken before meals 50-100mg TDS

Toxicity
- Flatulence, diarrhoea, abdo pain (fermentation of bacteria)

E. *EXENATIDE*

- Long acting injectable peptide of GLP-1
- GLP-1 are released from bowel epithelium to augment glc stimulated release of insulin, delay gastric emptying, inhibit glucagon secretion, produce a feeling of satiety
- Used in combination with *metformin* or *sulphonylurea*
- Adverse effects; nausea, hypoglycaemia

F. *SITAGLIPTIN*

- Inhibits DPP-4 (degrades GLP-1)

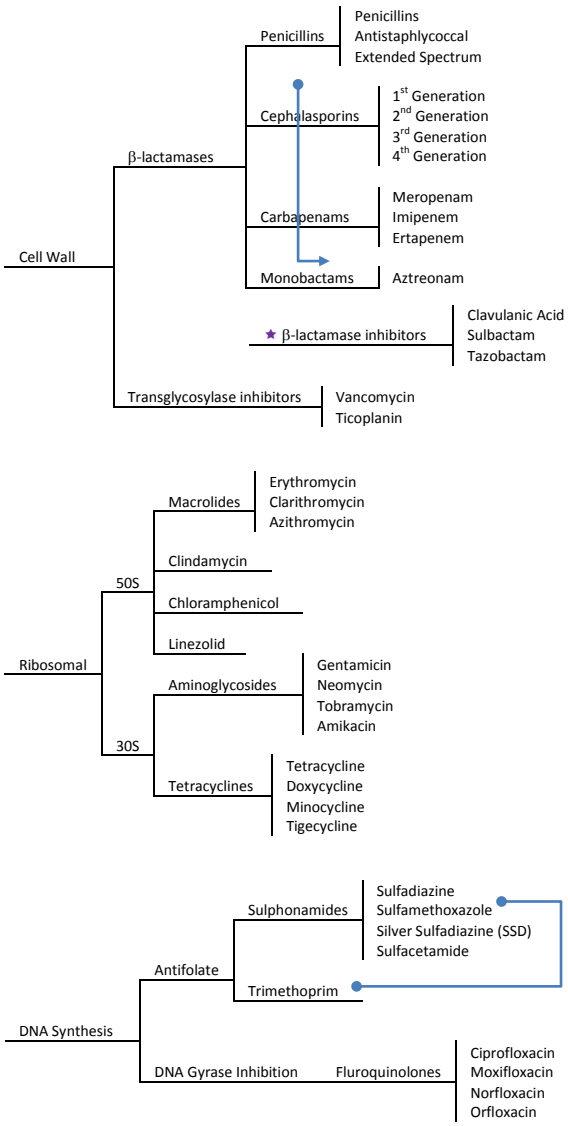
HYPERGLYCEMIC DRUGS

GLUCAGON

- Secreted by A cells in pancreas
- ↑ chronotropy, inotropy, glycogenolysis, gluconeogenesis, relaxes smooth muscle
- Treat severe hypoglycaemia
- Requires intact hepatic glycogen stores
- Also used in severe β blockade

1. OVERVIEW

Classification of Antibiotics Based on Modes of Action



SECTION VIII: CHEMOTHERAPEUTICS

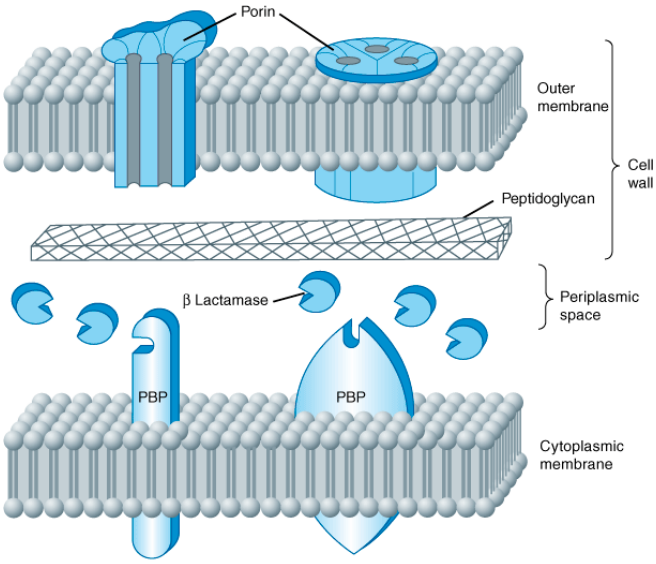
2. β-LACTAM & OTHER CELL WALL/MEMBRANE-ACTIVE ANTIBIOTICS

β LACTAMASES

- Penicillin
- Cephalasporins
- Carbapenams
- Monobactams
- β-lactamase inhibitors

All have same mechanism, pharmacology, immunological characteristics

Bacterial Cell Wall Structure



- Gram –ve's have a "**Cell Wall**" made of outer membrane & Peptidoglycan layer
- Gram-ve's have a thicker Peptidoglycan layer
- **Peptidoglycan layer** unique to bacterial cell membrane
- β-lactamases (when present) reside in **periplasmic space**
- PBP = Penicillin Binding Protein

Mechanism of Action: Penicillin, Cephalosporins, Monobactams, Carbapenams

- PBP required for formation of peptide cross-links ⇨ structure & rigidity
- Penicillin & Cephalosporins bind to PBP to inhibit ***transpeptidation***
  ∴ ***Bactericidal*** & more effective on actively growing bacteria

Mechanism of Action: Vancomycin & Teicoplanin

- Inhibits Transglycosylase by binding to terminal peptide ⇨ Inhibits cell wall synthesis

Types of Bacterial Resistance	
1. β-lactamase	
• Hundreds of types	
• Staph, haemophilus, E. Coli have narrow variety	
• Pseudomonas, Enterobacter have ESBL[1] ∴ hydrolyse many ABx incl ***Pen*** & ***Ceph***	
• ***Carbapenams*** highly resistant to β-lactamase	
2. Target PBP Modification*	
• Prevents binding	
• Basis of resistance in MRSA, pneumococci & enterococci	
3. Outer Membrane Permeability Alteration	Gram –ve only
• Either downregulated[2] or absent porins in outer cell wall	
4. Efflux Channels	
• Efflux channels remove ABx from periplasmic space	

[1]Extended Spectrum β Lactamase

[2]Downregulation alone does not confer resistance, also requires β-lactamase

*Modification in terminal d-ALA-d-ALA peptide confers ***Vancomycin*** resistance (VRE & staph)

Penicillins

Classification	
Penicillins penicillin G	Gram +ve | Gram –ve Cocci | No effect against gram –ve rods Non-β-lactamase producing anaerobes[1]
Antistaphlycoccal Dicloxacillin	Effective against staph & strep[2] Poor against enterococci, anaerobes, gram –ve rods & Cocci
Extended Spectrum Ampicillin, Amoxicillin, Pipercillin, Ticarcillin	Spectrum of cover includes above organisms PLUS Gram –ve organisms[3] ***susceptible to hydrolysis by β-lactamases (like penicillin G)***

[1]Susceptible to hydrolysis by β-lactamases
[2] Resistant to staphylococcal β-lactamases
[3]Able to penetrate outer cell membrane

Clinical Uses		
Penicillins	Penicillin G	Strep/Meningo/Pneumo[1]/Entero-cocci Spirochetes[2], Clostridium, Actinomyces
	Penicillin V	Minor infections only[3]
	Benzathine or Procaine Penicillin	Slow Release Syphilis & Strep Pharyngitis
Antistaphylococcal	Dicloxacillin	Staphylococci + species covered by penicillin
Extended Spectrum	Ampicillin, Amoxycillin	UTI, Sinusitis/Otitis/LRTI Shigellosis[4]
	Ticarcillin	Pseudomonas[5] | Less enterococci cover
	Pipercillin	Klebsiella

[1]No longer used due to resistance
[2]Including syphilis (treponema pallidum)
[3]Replaced by amoxicillin
[4]Ampicillin only
[5]Ampicillin doesn't cover, usually cotherapy with Aminoglycoside or Fluroquinolones if not UTI

Pharmacokinetics

Absorption: depends on acid stability

- Dicloxacillin, Ampicillin & Amoxicillin are acid stable ∴ well absorbed
  - Amoxycillin & ampicillin have same spectrum but amoxicillin has better absorption
  - Amp & Amox are the most active PO β-lactams
- Most are impaired by food (give 1-2 hrs prior to meals) except for Amoxicillin

Distribution

- Polar molecules ∴ high VD (extracellular > intracellular fluid)
- Tissue = Plasma (***poor penetration into CNS***, eye, prostate)

Excretion

- 3-15% sputum & milk
- Penicillin: Kidneys (10% glomerular 90% Tubular) | unchanged
- Dicloxacillin: Renal & Biliary (no dose adjustment required for renal failure)
- Clearance less efficient in newborns
- T ½ Penicillin: 30 min | Extended Spectrum: 1 hr

Adverse Effects

- Mostly non-toxic
- Series effects are hypersensitivity related
  - Antigenic component: degradation products (including penicilloic acid)
  - Anaphylaxis 0.05%
- Other: eosinophilia, haemolytic anaemia, vasculitis, seizures (in presence of renal failure)
- Ampicillin; pseudomembranous colitis
- Candidiasis

BETA LACTAMASE INHIBITORS

Clavulanic acid, Sulbactam, Tazobactam

- Weak antimicrobial properties
- Used in empirical treatment eg PipTaz

Ambler Classes of β-Lactamase	
Class A	Class B
Staph, Gram –ve cocci & rods (not serratia)	Enterobacter,, Serratia, Pseudomonas
β-lactamase inhibitors work well	β-lactamase inhibitors don't work well

Cephalosporins

- Broader spectrum vs penicillins: ***more resistant to β-lactamases***
  NB no *enterococci* cover (penicillin G does), or *listeria*
- Are not effective against ESBL (eg *E coli* & *Klebsiella*)
- All excreted renally

General Rules

- All excreted renally (except ceftriaxone)
- Gram –ve cover increases with each generation
- 1st & 2nd Gen don't cross BBB (except cefuroxime – not effectively)
- 1st & 2nd don't cover *pseudomonas*
- 1st, 2nd, 3rd don't cover *Enterobacter* (2nd is sensitive, but resistance forms quickly)
- All have short T½ (except ceftriaxone) ∴ BD to QID dosing

Generations of Cephalosporins	
First	Cefazolin (IV), Cephalexin (PO), Cephalothin (IV) Good Gram +ve cocci cover (*strep* & *staph*[1]) Some Gram –ve rod cover (*escherichia*, *klebsiella*) • Rarely drug of choice for infection: mild UTI/*Staph/Strep* incl cellulitis • Surgical Prophylaxis (good tissue penetration) • Treatment of *staph* in mild penicillin allergies
Second	Cefaclor (PO), Cefuroxime (PO, IV), Cefoxitin (IV) Extended Gram –ve cover (including Cephalothin resistant *Klebsiella*) Cefuroxime; *haemophilus* but not *b fragilis* Cefoxitin; *b fragilis* but not *haemophilus* • Sinusitis/LRTI (*Haemophilus, Moraxella*) • Peritonitis/Diverticulitis (mixed anaerobes incl *B fragilis*) • CAP (Cefuroxime: *haemophilus, klebsiella, Pneumococ*[2])
Third	Cefotaxime, Ceftazidime, Ceftriaxone (all IV) Extended gram –ve cover (incl *haemophilus* & *Neisseria*) Ceftazidime; *pseudomonas* ***Cephalosporinase***[3] produced by *serratia, providencia, citrobacter* ⇨ Resistance • Ceftriaxone; T½ 7-8 hrs | biliary excretion | 1-4g OD • All others; T ½ 1-1.7 hrs | renally excreted | 2-12g per day • Meningitis due to Gram –ve rods or suspected *pneumococcal*[4] • Sepsis of unknown origin[5]
Fourth	Cefepime (IV) Resistant to hydrolysis by β-lactamases of *Enterobacter* Highly active against *haemophilus* & *Neisseria* • Renal Cleared | T ½ 2 hrs • Covers same as 3rd generation but better *streptococci*[4] cover

[1]Not against MRSA
[2]Penicillin resistant, 3rd generations are the most potent for this
[3]3rd generation only
[4]Penicillin resistant, usually add Vancomycin if suspected
[5]Regardless of immune status, usually with aminoglycoside in immunocompromised

Adverse Effects

- Similar to penicillin (cross reaction 5-10%)
- Local irritation (IM or thrombophlebitis)
- Renal Toxicity (uncommon)
- Disulfiram-like reactions seen in some

Other β-lactamases

MONOBACTAMS

Aztreonam

- Relatively resistant to β-lactamases
- Similar spectrum to ***aminoglycosides***:
  - Covers gram –ve rods (pseudomonas, escherichia, salmonella, klebsiella…)
  - No effect on gram +ve or anaerobes
- Dose: 1-2g q8h | T ½ 1-2 hrs | Renal excretion | No cross reactivity with penicillin

CARBAPENAMS

- Indicated for mixed an/aerobic infections resistant to other ABx eg pseudomonas
  - Pneumococci (highly penicillin resistant strains)
  - Enterobacter (most β-lactamase resistant)
  - Gram –ve that produces ESBL
  - Febrile neutropenia (in combination with ***aminoglycoside***)
- Good tissue, fluid penetration (incl CSF)
- Renal clearance
- Adverse effects: GIT irritation, rash, seizure (in renal failure) | 50% cross-reactivity with penicillin

Imipenem

- Resistant to most β-lactamases (not metallo-β-lactamase)
- Resistant bugs: enterococci , MRSA, clostridium
- Inactivated by ***dehydropepidases*** in renal tubules
  ∴ Co-administered with ***cilastatin*** (a dehydropepidases inhibitor)
- 0.25-0.5g q6-8h | T ½ 1 hr

Meropenam

- Not degraded by dehydropepidases
- Better gram –ve cover (enterobacteriaceae) | less gram +ve cover (strep/staph)
- 1g TDS

Ertapenem

- Least active Carbapenems | No pseudomonal cover
- Not degraded by dehydropepidases
- 1g OD IV or IM | T ½ 4 hrs

Transglycosylase Inhibitors

VANCOMYCIN

- Gram +ve cover only (mostly staph incl MRSA)

Clinical Use

- Sepsis/endocarditis from *MRSA* | ***Penicillin*** better if not resistant since staph killing is slower
- ***Synergistic*** with ***Gentamicin*** against enterococci (not as good as ***penicillin***)
- Highly pen resistant strain of meningitis (pneumococci) when used with 3rd gen Ceph

Kinetics

- Poorly absorbed (oral prep for *c diff* enterocolitis but resistance easily forms
  ∴ ***Metronidazole*** 1st line)
- High V_D | T ½ 6-10 days | CSF 7-30% of plasma during inflammation
- Excretion 90% GFR (not removed by haemodialysis)
- 30mg/kg/day in 2-3 divided doses (usually 1g BD) or 1g per week if anuric

Adverse Reactions

- 10% of cases (mostly minor incl "Red Man" syndrome)
- Rare: ototoxicity, nephrotoxicity

TEICOPLANIN

- Similar spectrum of activity to Vancomycin
- Able to give IM | T ½ 45-70 hrs

BACITRACIN

- Gram +ve cover; kills bacterial flora in skin
- Interferes with dephosphorlation in cycling of lipid carriers that transfer peptidoglycan units
- No cross resistance with any antimicrobials
- Highly nephrotoxic ∴ only used topically (otitis)

CYCLOSERINE

- Used in m tuberculosis (though has both gram +ve & -ve cover)
- Inhibits D-alanine incorporation into peptidoglycan
- Wide VD | Urinary excretion | Serious dose related CNS effects (> 0.75g/day)

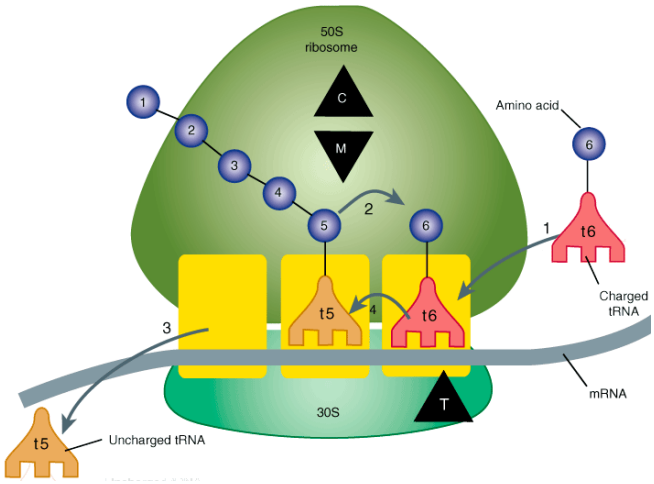
Adverse Effects (tetracyclines)

- Nausea common (1/3)
- Chelates with Ca^{2+} ⇨ binds/damages growing bones/teeth
- Hypersensitivity not common
- GIT irritation incl Δ gut flora ⇨ anal pruritus, vaginal/oral candida, enterocolitis
- Hepatic & Renal Toxicity
- Other: venous thrombosis | photosensitivity | vestibular dysfunction

SECTION VIII: CHEMOTHERAPEUTICS

3. TETRACYCLINES, MACROLIDES, CLINDAMYCIN, CHLORAMPHENICOL & STREPTOGRAMINS

- Human ribosomes have 60S & 40S subunits | Bacterial ribosomes have 50S & 30S
- Most ribosomal targeting antimicrobials are **bacteriostatic**



Normal Protein Synthesis in Bacterial Cells

1. ***Binding:*** tRNA binds a single amino acid to become "charged"
   Charged tRNA binds to acceptor site (yellow box) that traversers both subunits
2. ***Transpeptidation:*** peptidyl tRNA (holding aa chain) binds last aa to aa on charged tRNA
   Peptidyl tRNA becomes uncharged and previously charged tRNA becomes peptidyl tRNA
3. ***Release:*** new uncharged tRNA released
4. ***Translocation:*** new peptidyl tRNA moves into middle position for cycle to restart

50S Subunit

- Chloramphenicol (C), Macrolides (M), Clindamycin & Linezolid
  ∴ Block transpeptidation…reversible
  NB Linezolid has different binding site ∴ no cross-resistance

30S Subunit

- Tetracycline (T) & Aminoglycoside ∴ blocks binding to mRNA …reversible

TETRACYCLINES ***Doxycycline, Minocycline, Tigecycline***

Spectrum of Activity

- Broad spectrum; gram +ve & -ve as well as protozoa (amoebas)
- No proteus or pseudomonal cover
- Enters microorganism via diffusion as well as active transport

Resistance

Impaired Influx/Upregulated Efflux

- Tet(AE) pump found on gram –ve's | Tigecycline (newer tetracycline) unaffected
- Tet(K) pump found on staph | Doxy, Mino, Tige- all unaffected
- Efflux pumps on proteus & pseudomonas ⇨ maximal resistance to all tetracyclines

Binding Site Manipulation

- Tet(M) protein prevents tetracycline binding to 30S (Tigecycline unaffected)

Enzyme Inactivation

Kinetics

- Variable absorption: doxy- & mino- 100% | tetra- 70% | Tiger- poorly absorbed
- Inhibition of absorption: food, divalent cations, dairy, antacids, alkaline pH
- Tetracyclines: 40-80% protein bound | Wide V_D ∴ Good Tissue & Intracellular penetration
- (not CSF) | Cross placenta | excreted in milk
- Excretion: Biliary (+/- intestinal reabsorption) & renal excretion
  Doxy- & Tige- non renal elimination only ∴ no good for UTIs

  T ½: Short acting (6-8 hrs) ***Tetracycline*** | Long acting (16-18 hrs) ***Doxy-***, ***Mino-***
  Longer acting (36 hrs) ***Tigecycline***

Clinical Use

- 1st line for mycoplasma, chlamydia, rickettsia & some spirochetes (also H. Pylori)
- Multidrug resistant nosocomial organisms (MRSA, ESBL gram –ve, acinobacter)
- Vibrio – although resistance mounts quickly
- Cholera – resistance forms during epidemics
- Chlamydia incl STI | Not for gonococcal
- + aminoglycoside to treat plague (yersnia pestis), brucellosis
- Protozoa: entamoeba & plasmodium
- Other uses: acne, bronchitis, Lyme, CAP, leptospirosis, non TB mycoplasma
- Intrinsic resistance in proteus & pseudomonas

MACROLIDES *Erythromycin, clarithromycin, azithromycin*

Spectrum of Activity

- Gram +ve esp pneumococci, strep & staph, cornybacteria
- Some gram –ve cover ("cat scratch" organisms incl Neisseria, bordetella)
- Atypicals: mycoplasma, legionella, chlamydia, helicobacter, listeria

Resistance

- Complete cross-resistance btwn macrolides | also to clindamycin & streptogramin B

Impaired Influx/Upregulated Efflux

Binding Site Manipulation

- Chromosomal mutation on macrolide induced methylase

} Most important mechanisms in gram +ve

Enzyme

- Esterases from enterobacteriaceae hydrolyse macrolides

Kinetics

- Bacteriostatic at low doses, bactericidal at higher doses

	Ery-	Clari-	Azi-	Clindamycin
Absorption	Acid unstable[1]	Better acid stability	Rapidly absorbed	Good
Distribution	Wide V_D incl placenta (but not BBB), good tissue penetration			Incl abscess
Metabolism	Liver	Liver[2]	Liver	Liver
Clearance	Bile	Renal	Renal	Bile & Renal
T ½	1.5 hrs	6 hrs	2-3 days	2.5 hrs

[1] ∴ enteric coating preparations
[2] active metabolite

Adverse Effects

- GI upset (directly stimulates lumen), less with clari-
- Liver toxicity (acute cholestatic hepatitis), does not occur with Azi-
- Hypersensitivity
- C diff overgrowth with clindamycin

Erythromycin

- 1st line for cornybacteria, chlamydia, CAP (esp for atypical cover)
- Staph or Strep with pen allergy (but not group A strep given emergence of resistance)
  Group A strep; pharyngitis, cellulitis, pneumonia

Clarithromycin

- Better acid stability (and absorption)
- Additional coverage: mycoplasma & toxoplasma
- Less SE & dosing regimen vs ery-

Azithromycin

- Same cover as clari- (less active against staph & strep | better against haemophilus)
- Highly active against chlamydia
- Best dosing regimen

Clindamycin

- Not chemically a macrolide but exactly same binding site
- Covers strep & staph (but intrinsically resistant to gram –ve due to poor wall penetration)
- Mixed anaerobic infection including
  - Female genital infection (pelvic abscess, septic abortion)
  - Aspiration pneumonia
  - Penetrating wounds (in combination with aminoglycoside or cephalosporin)
- Immunocompromised: PCP & Toxoplasma

CHLOREMPHENICOL

- Broad spectrum; an/aerobic gram +/- & haemophilus, Neisseria (not chlamydia)
- Resistance: enzymatic breakdown (chloramphenicol acetyltransferase)

Clinical

- Mainly ophthalmic
- Parenteral uses include rickettsia
- Alternative to β-lactams in meningococcal

Kinetics

- Good tissue penetration including BBB
- Hepatic metabolism | urinary excretion (some biliary)

Adverse

- GI upset | Marrow suppression | P450 inhibition | Gray Baby Syndrome

STREPTOGRAMINS A & B

- Bactericidal to most except enterococcus faecium (slow killing)
- Indicated for resistant strains incl MRSA, VRE
- E Faecalis is resistant (efflux mechanism)
- Adverse effects: pain, arthralgia

OXAZOLIDINES *Linezolid*

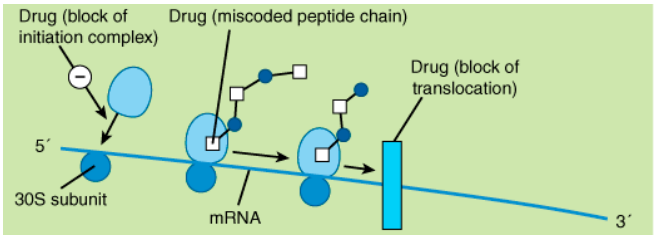
- Bacteriostatic
- Gram +ve cover; reserved for multi-drug resistance
- BioAv 100% | T ½ 4-6 hrs
- Adverse: Haem incl thrombocytopenia or neutropenia (both reversible)

SECTION VIII: CHEMOTHERAPEUTICS

4. AMINOGLYCASIDE

- Bactericidal
- Mostly gram –ve cover

AMINOGLYCASIDES *Neomycin, amikacin, tobramycin, gentamicin*



Mechanism

- Passive diffusion across outer membrane (via porins)
- H^+ ATPase co-transport across inner membrane (ie aerobic)

} Cell wall antimicrobials show synergism

Binds 30S subunit

1. Inhibits charged tRNA binding to mRNA
2. Inappropriate transpeptidation via mRNA misreading
   ⇨ wrong aa sequence ⇨ non-functional or toxic protein
3. Inhibits peptidyl tRNA translocation (thereby forming monosomes)
   Monosomes are mRNA with only 1 ribosome

Resistance

- Enzyme inactivation – most common, Amikacin less cross reactivity (usually sensitive)
- Impaired outer wall entry (strep & enterococci), Amikacin cross reactive
- Receptor site mutation

Kinetics

- 0% oral absorption (unless ulcers present)
- Renal Clearance (∝ crea) | T ½ = 2-3 hrs
- Highly polar ∴ poor penetration into eyes, CSF
- Topical (or oral) only prep for neomycin

- **Concentration dependant killing**
- **Post-antibiotic effect** (hours)
- **Time & Concentration Dependant Toxicity** ie time above concentration determines toxicity
  "Time above concentration" more common in small divided doses

Toxicity

- > 2mcg/ml trough (aim for < 1mcg/ml @ 18-24hrs)
- Since time & concentration dependant, adjust interval or dose
- More commonly seen after 5 days of therapy or renal failure
- High doses can cause resp paralysis via NMJ blockade (reversed with Ca gluconate)

	Gent	Neomycin	Tobramycin	Amikacin
Nephrotoxicity	✓[1]	✓[2]	✓	×
Ototoxicity	Vestibulotoxic[3]	Auditory	?	Auditory

[1] reversible
[2] Slightly less nephrotoxic than gent (clinically irrelevant)
[3] irreversible, 1-5% genetic link

Clinical

- Gram –ve esp resistant strains (broader spectrum with β-lactamase or vanc)
- Combination therapy in enterococci/staph endocarditis, viridians

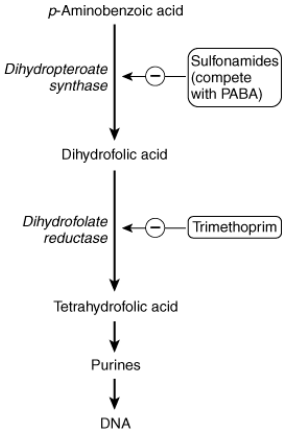
	Cover	Resistance
Gent	Gram -ve & some gram +ve incl Serratia Monotherapy only good in UTI Topical: burns, wounds, ophthalmic Intrathecal: meningitis[2]	Anaerobic Strep & enterococci[1]
Tobramycin	Better pseudomonal cover (vs Gent) Inhalational prep for pseudomonas	E faecium
Amikacin	Multi drug resistant gram –ve Mycobacteria	More resistant to enzymes
Neomycin	Gram -/+ & mycobacteria Infected surfaces incl pleural, jt Bowel prep	Pseudomonas, Strep

[1] wall permeability
[2] 3rd generation cephalosporins much better

SECTION VIII: CHEMOTHERAPEUTICS

5. SULFONAMIDES, TRIMETHOPRIM, QUINOLONES

ANTIFOLATE: Sulphonamides & Trimethoprim



- Some micro-organisms are unable to use exogenous folate
- **Bacteriostatic** sine they Inhibit folate production (necessary for DNA synthesis)

Sulphonamides

- Replaces PABA substrate to prevent folic acid formation

Trimethoprim

- Inhibits ***dihydrofolate reductase*** (preferentially for bacteria vs mammalian x 10,000)

- ***Sulphonamides*** & ***Trimethoprim*** are **synergistic**
  - 1st line in PCP, Toxoplasmosis, Nocardia
  - Ratio 1:20 optimal

Coverage

- Gram +ve/-ve, Nocardia, Chlamydia, some protozoa
- Other: some gram –ve enterobacteriaceae
- Poor anaerobic cover, rickettsiae growth stimulated by ***sulphonamides***

Kinetics

- Well absorbed | Wide V_D incl CSF (***trimethoprim*** lipid sol ∴ wider) | renal excretion (Tx UTI)
- ***Sulphonamides*** PO or TOP vs ***Trimethoprim*** PO or IV
- ***Trimethoprim*** concentrates in prostatic & vaginal fluid (more acidic)

Resistance

Method	Sulphonamides	Trimethoprim
Overproduction	PABA	Dihydrofolate Reductase
Target Dysfunction	Dihydropteroate synthase[1]	Dihydrofolate Reductase
Cell Wall	↓ Permeability	↓ Permeability

[1]Low affinity for sulphonamides

Adverse Effects

- Sulphonamides cross-allergenic with other "sulphur drugs"
- GI: N&V, diarrhoea
- Skin: Steve-Johnson Syndrome, rash, dermatitis, photosensitivity
- Urinary: crystallise in acidic urine
- Anti-folate: anaemia, thrombocytopenia

Sulphonamides: ***Sulfadiazine, Sulfamethoxazole, Silver Sulfadiazine, Sulfacetamide, Sulfasalazine***

- Commonly used in combination therapy

Types
Oral + Absorbable • Short | Intermediate | Long –acting[1] • ***Sulfamethoxazole***; UTIs | ***Sulfadiazine***[2]; toxoplasmosis
Oral + Non-absorbable • ***Sulfasalazine***; UC, Enteritis & other IBD
Topical • ***Sulfacetamide***; ophthalmic conjunctivitis, trachoma (chlamydia) • ***Silver Sulfadiazine***; prophylaxis on burns

[1]***Sulfadiazine*** & ***Sulfamethoxazole*** are intermediate T ½ 10 hrs, slow absorption
[2]Co-therapy with ***pyrimethamine***

Trimethoprim +/- Sulfamethoxazole

Types
Oral Trimethoprim • UTI
Combination • (recurrent) UTI[1], Prostatitis, gram –ve enterics, mycoplasma (non TB) • Pneumonia; haemophilus, strep, resistant staph, PCP
IV Combination • **PCP**[2] • Gram –ve sepsis (incl resistant strains eg Enterobacter, serratia)
Oral Pyrimethamine + Sulphonamide • Leishmaniasis, toxoplasmosis, f. malaria

[1] Up to 30% resistance to escherichia
[2]1st line therapy

FLUROQUINOLONES

- Topoisomerase are enzymes that un/wind DNA to control DNA replication
- Bacteria have 2 unique topoisomerases; DNA Gyrase & Topoisomerase IV (both type II)
- Fluroquinolones inhibit DNA gyrase thereby inhibiting DNA replication depending on target:
  - DNA gyrase – prevents unwinding
  - Topoisomerase IV – prevents double helix separation

Coverage			
Antibiotic	Gram –ve	Gram +ve	Atypicals[4], intracellular pathogens[5], mycobacteria[6]
Norfloxacin	Mod	Poor	
Ciprofloxacin / Ofloxacin	Excellent[1]	Mod/Good[2]	
Moxifloxacin[7]	Mod	Best[3]	

[1]Resistant to MRSA | Staph > Strep cover
[2]***Cipro-*** most potent especially to pseudomonas
[3]Especially Strep and resp staph
[4]mycoplasma, chlamydia
[5]Legionella
[6]M tuberculosis, M avium
[7]Also has good anaerobic cover

Clinical Uses

- UTI with multi drug resistance organisms (renal excretion ∴ moxi- not effective)
- Bacterial diarrhoea; shigella, salmonella, e coli, campylobacter
- ***Cipro*** for gonococcal, chlamydia urethritis, cervicitis or anthrax prophylaxis
- Sometimes used in TB
- Moxi- "respiratory fluroquinolone" given its good gram +ve & atypical cover

Resistance

- Uncommon but mainly to staph, pseudomonas, serratia
- Mutation in binding region of topoisomerase
- Cell wall permeability

Kinetics

- BioAv 80-95% | large VD | renal excretion | concentration-dependant killing

Adverse Effects

- Well tolerated | QTc prolongation | GI upset | Reversible arthropathy

6. ANTIMYCOBACTERIALS

Inherently difficult coverage due to:
- Slow growing / Dormancy
- Lipid rich membrane ∴ ↓ wall penetration
- Intracellular existence

1st Line	Isoniazid Rifampin Ethambutol	Other Line	Amikacin Capreomycin Fluroquinolones Linezolid Cycloserine

TUBERCULOSIS : First Line *Isoniazid, Rifampin, Ethambutol*

- TB treatment relies on combination therapy (to minimise resistance)

Isoniazid + Rifampin + Ethambutol 10% resistance to *Isoniazid* alone
3% resistance to *Isoniazid* & *Rifampin* combination

Property	Isoniazid	Rifampin
Mechanism	Inhibits synthesis of mycolic acid (component of cell wall)[1]	Inhibits RNA synthesis[3] Bactericidal for mycobacteria
Resistance	Enzyme modification	Altered binding site
Absorption	PO/IV	PO/IV
Distribution	Wide	Wide
CSF	20-100%	Only in meningitis
Metabolism	Liver	Liver
Excretion	Renal	Biliary
T ½	1-3 hrs	
Adverse Effects	***Hepatitis*** most common[4] CNS, neuropathy	Orange secretions Flu-like sx Induces P450
Use	Combination[1]	Combination[1]
Monotherapy	Latent TB, Ineffective against atypical mycobacteria	Latent TB resistant to Isoniazid Meningococcal carrier state Haemophilus prophylaxis Serious staph (OM, endocarditis)

[1]For active TB
[2]Req activation by mycobacteria enzyme breakdown
[3]Binds β subunit of RNA polymerase
[4]Worse with old age or EtOH abuse

Ethambutol
- Inhibits arabinosyl transferase (polymerises arabinosyl for cell wall synthesis)
- Resistance forms through overproduction of arabinosyl transferase

Kinetics/Adverse Effects
- PO | Excretion Faeces (20%) Urinary (50%) | Poor CSF dist (4-64%) – used in TB meningitis
- Retrobulbar neuritis, hypersensitivity rare

TB: Others *Capreomycin, Cycloserine, Amikacin, Fluoroquinolones, Linezolid, Rifabutin*

Indicated for
- Resistance to first line drugs
- Failure of clinical response
- Serious adverse effects to first line drugs
- Ability to monitor toxicity of non-first-line drugs

Other-line Antimycobacterials

***Amikacin* (aminoglycoside)**
- Multidrug resistant TB or atypical mycobacteria
- Always used in combination

Fluroquinolones (*Moxi* & *Ciprofloxacin*)
- Multidrug resistant TB or atypical mycobacteria
- Moxi- most active against mycobacteria | *Cipro-* slightly more active against atypical

Capreomycin
- Inhibits protein Synthesis
- Used in *amikacin* resistant mycobacteria (5%)
- Nephrotoxic/ototoxic

Cycloserine
- Inhibits cell wall synthesis by preventing d-alanine incorporation into cell membrane
- Peripheral neuropathy, depression, psychosis (given with *pyridoxine*)

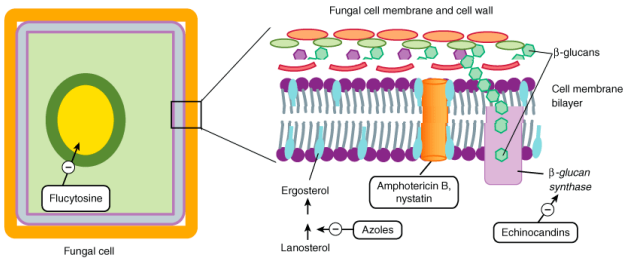
Linezolid
- Binds 50S to inhibit protein synthesis
- Used in multidrug resistant mycobacteria as a "Last Resort"

Rifabutin
- Similar to Rifampin (100% cross-resistance)
- Less P450 effect
- Used in mycoplasma infection in context of HIV (requiring anti-retrovirals) or atypicals in active AIDs (CD4 < 50)

Leprosy
- Mycobacterium leprae
- Use *dapsone* (Antifolate) + *Rifampin* + *clofazimine* (unknown function) together

7. ANTIFUNGAL AGENTS

Systemic	Flucytosine Amphotericin B			
	Echinocandins	Caspofungin		
	Azoles	Imidazoles	Ketoconazole	
		Triazoles	Itraconozole Fluconazole Voriconazole	
Topical	Nystatin Allyllamines			
	Azoles	Imidazole	Miconazole Clotrimazole	



Amphotericin B

Mechanism
- Fungal cell walls have ***ergosterol*** vs human/bacteria (cholesterol)
- Binds to ergosterol ⇨ forms "***amphotericin B associated pores***" ⇨ cell lysis
  NB some binding to human chol (reflected by adverse effects)
  Liposomal amphotericin B aims to minimise (binds preferentially for fungal membrane)

Clinical
- ***BroadEST*** spectrum of fungal cover ∴ ***used as induction in life threatening***
  (Azoles as maintenance)
- Empiric for neutropenia on ABx
- Not 1st line in meningitis due to adverse effects
- Myoctic corneal ulcer/keratitis
- Fungal joint infections
- Bladder irrigation (candiduria)

Kinetics
- Poorly absorbed | > 90% protein bound | T ½ 15 days | Large V_D (CSF 2-3% ∴ Intrathecal route if meningitis)

Adverse Effects
- Infusion related: fevers, headaches, chills (improved by slowing/stopping infusion)
- Cumulative: renal most common (irreversible > 4g/day)

Flucytosine (5-FC)

Mechanism
- Derivative of *5-FU* ∴ causes marrow toxicity
- Multistep conversion by fungal enzymes (cytosine permease):
  5-FC ⇨ *5-FU* ⇨ FdUMP (inhibit DNA) or ⇨ FUTP (inhibit RNA)
  ∴ Resistance forms through alteration of fungal enzymes

Cover/Clinical
- Narrow spectrum; *Cryptococcus neoformans,* (some) *candida, dematiaceous molds*
- ***Synergistic*** ∴ only used in combination (also prevents resistance)
  - + *amphotericin* to treat ***Cryptococcus meningitis***
  - + *itraconozole* to treat ***Chromoblastomycosis*** (from *dematiaceous molds*)

Kinetics/Adverse Effects
- Oral only (well) | Penetrates CSF | T ½ 3-4 hrs | Renal excretion
- Marrow suppression | enterocolitis (gut enzymes also breakdown)

AZOLES

Imidazoles; *ketoconazole* | **Triazoles;** *itraconozole, fluconazole, Voriconazole*

Mechanism/Clinical
- Inhibit fungal cytochrome P450 ⇨ inhibition of ergosterol formation
- Broad Spectrum cover including ***amphotericin resistant strains***

	Keto-	Itra-	Flu-	Vori-
Absorption	Variable	Variable	High	High
Presentation	PO	PO/IV	PO/IV	PO/IV
CSF penetration	Poor	Poor	Good	Nil
T ½ (hrs)	7-10	24-42	22-31	6
Elimination	Hepatic	Hepatic	Renal	Hepatic
Fungal P450	Least specific[1]	-	Most specific	Mod specific
Fungal Cover	Broad	*Hisoplasma* *Blastomyces* *Sporothrix*	*Cryptococcus*[2]	*Aspergillosis*

[1]Used mostly as topical as a result
[2]In combination with Flucytosine

Adverse Effects
- Mostly non-toxic | GI upset most common | inconsequential hepatic enzyme derangement
- Vis disturbance in 30% taking *viro-* (incl blurring, photophobia, colour change)

Echinocandins ***Caspofungin***

- Inhibits ***β-glucan synthase*** (β-glucan required for cell wall synthesis)
- Coverage: *candida, aspergillus* (unresponsive to amphotericin) but not *Cryptococcus*
- Clinical: ***disseminated candida, empiric in febrile neutropenia, last line in Aspergillosis***
- Kinetics: IV only | T ½ 11 hrs | Renal & GI excretion
- Adverse effects: well tolerated (GI upset)

Nystatin

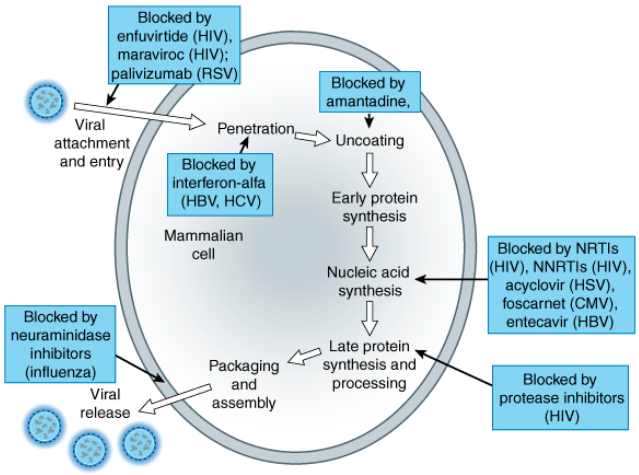
- Too toxic for parenteral administration
- Similar mechanism to amphotericin B
- Cover: candida

Topical Azoles ***Clotrimazole, Miconazole***

- Candida & dermatophytic infections
- Better tasting than Nystatin

SECTION VIII: CHEMOTHERAPEUTICS

8. ANTIVIRAL AGENTS

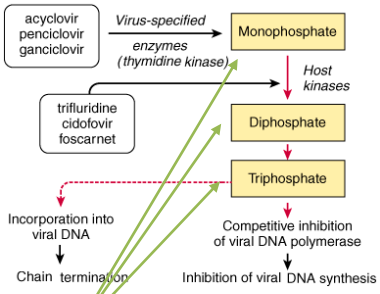


Steps in Viral Replication

1. Viral Attachment/Entry
2. Penetration
3. Uncoating
4. Early Protein synthesis (mainly regulatory proteins eg nucleic acid polymerase)
5. Nucleic Acid Synthesis (ie RNA/DNA)
6. Late Protein Synthesis
7. Packaging & Assembly
8. Release

- **Antiretrovirals**
  - HSV /VZV: Acyclovir, Valacyclovir, Famciclovir, Penciclovir
  - CMV: Gancilovir, Valganciclovir, Foscarnet, Cidofovir
  - NRTI's[1]: Abacavir, Didanosine, Emtricitabine, Lamivudine, Stavudine, Tenofovir, Zidovudine
    - [1]Non/Nucleoside/Nucleotide Reverse Transcriptase Inhibitors
  - NNRTI's[1]: Delavirdine, Efavirenz, Nevirapine
  - Protease Inhibitors: Amprenavir, Atazanavir, Fosamprenavir, Indinavir, Lopinavir +/- Ritonavir, Saquinavir, Tipranavir
  - Fusion Inhibitors: Enfuvirtide
- **Antihepatitis**
  - Interferon α: 2A[2], 2B[1,2], Con-1[2]
  - Adefovir Dipivoxil[1]
  - Lamivudine[1]
  - Entecavir[1]
  - Ribavirin[2]
  - [1] HBV, [2] HCV
- **Anti-Influenza**
  - Amantadine & Rimantidine
  - Neuraminidase inhibitors: Zanamivir, Oseltamivir

HERPES & VARICELLA-ZOSTER *Acyclovir, Valacyclovir, Famciclovir*



Acyclovir

- Covers HSV 1,2 & VZV
- Requires ***3x phosphorylation*** steps to activation (see pic) by virus specific *thymidine kinase*

Mechanism

- Binds irreversibly to DNA template by substituting for deoxyGTP or
- Chain termination: Incorporates into viral DNA

  ∴ Resistance if Δ *thymidine kinase (*more common) or *DNA polymerase*

Scenario	Clinical Use
1st episode genital herpes	↓ Sx by 2/7, Ulcer by 4/7, shredding by 7 days[1]
VZV	↓ lesions if given within 24 hrs (varicella) or 72 hrs (zoster)
Organ transplant	prophylaxis
Parenteral	HSV encephalitis | Neonatal HSV | Serious HSV or VZV
Topical	1st episode only[2]

[1]Doesn't change fq or severity of recurrence
[2]far inferior to oral

Kinetics/Adverse Effects

- BioAv 15% | Good Tissue Penetration (50% CSF) | T ½ 3 hrs | Renal Clearance
- N&V, Headaches, Renal dysfunction

Valacyclovir

- Converted to ***acyclovir*** after 1st pass metabolism (in liver or intestines)
- BioAv 50% otherwise same kinetics
- Clinical use: Genital herpes (both 1st & recurrent), orolabial herpes (single dose)
- Adverse Effects: same as ***acyclovir*** but also CNS, TTP, HUS

Famciclovir

- Metabolised to ***Penciclovir*** (active metabolite, also used as topical agent)
- Lower affinity for DNA polymerase ∴ no chain termination
- Better intracellular penetration and longer effect
- BioAv 70% | T ½ 10 hrs (HSV 1) 20hrs (HSV 2) 7 hrs (VZV) | Renal excretion

CYTOMEGALOVIRUS *Gancilovir, Valganciclovir, Foscarnet, Cidofovir*

- Clinical treatments mainly aimed at ***CMV retinitis*** or ***prophylaxis***
- CMV infections mainly found in immunocompromised patients

- ***Valganciclovir*** hydrolysed to ***Gancilovir*** by intestinal enzymes

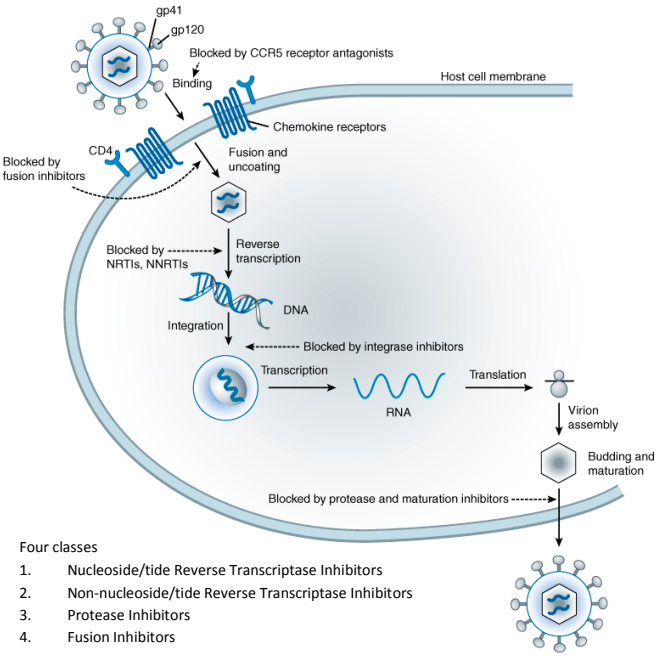
	Gan-	Valgan-	Foscarnet	Cidofovir
Route	PO[1] | IV | PO[2]	PO	IV	IV
BioAv	Poor	60%	Poor	Poor
CSF	-	-	40-60%	Poor
Use	CMV Retinitis CMV Prophylaxis CMV –itis[2]	CMV Retinitis CMV Prophylaxis[3]	CMV Retinitis CMV –itis[2]	CMV Retinitis
Excretion	Renal	Renal	Renal	Renal
Mechanism	Same mechanism as HSV/VZV drugs[4]		Inhibits D/RNA polymerase & HIV reverse transcriptase directly	

[1]intravitreous or slow release ocular implant
[2]Colitis, Oesophagitis, Pneumonitis | ***Foscarnet*** & ***Gan-*** have same efficacy but also synergistic
[3]Transplant
[4]*Phosphotransferase* instead of thymine kinase

Adverse Effects

- Myelosupression (most common) | GI upset | Retinal detachment
- Foscarnet & Cidofovir: nephrotoxicity

ANTIRETROVIRALS



Four classes

1. Nucleoside/tide Reverse Transcriptase Inhibitors
2. Non-nucleoside/tide Reverse Transcriptase Inhibitors
3. Protease Inhibitors
4. Fusion Inhibitors

Life Cycle of HIV

1. Glycoproteins on viral membrane ***bind*** to CD4 & Chemokine receptors on host cell
2. ***Fusion*** & Entry
3. ***Uncoating***
4. ***Reverse Transcription*** (copying of HIV RNA into DNA)
5. DNA ***integration*** into host genome
6. ***Transcription*** of new DNA into mRNA
7. ***Translation*** into protein that make up new virions (immature, non-infectious)
8. ***Proteolytic cleavage***: formation of mature virus

HAART: highly active anti-retroviral therapy (3-4 agents used at once)

Nucleoside/tide Reverse Transcriptase Inhibitors

- Intracellular activation then competitively inhibits HIV-1 reverse transcriptase thereby causing ***chain termination***

Adverse effects

- Inhibits mitochondrial DNA polymerase γ
- Lactic acidosis
- Hepatic steatosis (can be fatal)
- CYP450 metabolism
- All have **renal elimination** and require dose adjustment in failure

Salient Features of NRTIs

Abacavir
- 83% PO | Elimination T ½ 1.5 hrs | Intracellular T ½ 12-26 hrs | CSF 33%
- Resistance requires 2-3 mutations ∴ slow
- Usual adverse effects, 50% skin rashes

Didanosine
- 30% PO | Elimination T ½ 1.5 hrs | Intracellular T ½ 20-24 hrs | CSF 20%
- Cross resistance to ***Abacavir*** & ***Lamivudine***
- Major adverse effect is dose dependant pancreatitis
- Other adverse effects: painful peripheral neuropathy, CNS

Emtricitabine
- Analog of ***lamivudine***
- 93% PO | Elimination T ½ 8-9 hrs | Intracellular T ½ > 39 hrs | CSF poor
- Cross resistance to ***Lamivudine*** only
- Main adverse effects include headache, diarrhoea, hyperpigmentation

Lamivudine
- 80% PO | Elimination T ½ 2.5 hrs | Intracellular T ½ 10-15 hrs | CSF poor
- Synergistic with ***Zidovudine*** (cross-resistance with other antiretroviral)
- Major adverse effects as above

Stavudine
- 86% BioAv | Extracellular T ½ 1.2 hrs | Intracellular 3.5 hrs | CSF 55%
- Main adverse effect is Peripheral Neuropathy

Tenofovir
- BioAv 25% | Extracellular T ½ 17 hrs | Intracellular T ½ 60 hrs
- Main adverse effect is GI upset

Zidovudine
- Good BioAv | Extracellular T ½ 1 hr | Intracellular T ½ 3-7 hrs | CSF 60%
- Liver metabolism
- Main adverse effect is Myelosupression

Non-nucleoside/tide Reverse Transcriptase Inhibitors

- Inhibits ***HIV-1 reverse transcriptase*** thereby causing ***chain termination*** (does not require intracellular activation and does not competitively inhibit)
- Resistance occurs rapidly with monotherapy
- Common adverse effects: GI upset, Rash (incl Stevens-Johnson syndrome)
- All metabolised by CYP450

Salient Features of NNRTI
Delavirdine
• BioAv 85% | Rash in 18%
Efavirenz
• T ½ 40 hrs | Poor CSF | Principle S/E CNS (up to 50% to some degree) • Teratogenic
Nevirapine
• BioAv 95% | CSF 45$ | Elimination T ½ 30 hrs | Rash in 17% • Used as prophylaxis in vertical transmission (started at birth)

Protease Inhibitors

- In order for immature (and non-infective) proteins to mature, they req *protease cleaving*
- ***Resistance much more common*** in this group of antiretrovirals ∴ never monotherapy
- Adverse effects include cushinoid fat distribution, CYP saturation

Salient Features of PI
Amprenavir
• Rapidly absorbed | T ½ 7 hrs | Common S/E GI
Atazanavir
• BioAv 65% | T ½ 7 hrs | Penetrates CSF & Seminal Fluid | Biliary excretion • Common S/E GI
Fosamprenavira
• ***Amprenavir*** prodrug (hydrolysed in intestines)
Indinavir
• BioAv 65% | T ½ 2 hrs | CSF 75% | Faecal excretion • Common S/E due to crystallisation of Indinavir ⇨ hepatocholelithiasis, nephrolithiasis
Lopinavir/Ritonavir
• Combination therapy (***ritonavir*** inhibits CYP breakdown of ***Lopinavir***) | Common S/E GI
Saquinavir
• Poor BioAv | T ½ 12 hrs | Poor CSF | Faecal excretion | Common S/E GI
Tipranavir
• Poor BioAv | Common S/E GI

Fusion-Inhibitors Enfuvirtide

- Binds to viral envelope ⇨ preventing appropriate binding with CD4 on host cell membrane
- Subcut only \| T ½ 3.8 hrs \| CYP metabolism \| Lacks cross-resistance \| Main S/E local reactions (hypersensitivity uncommon)

ANTIHEPATITIS

- Suppressive rather than curative treatment

Interferon α (2a, 2b, con-1)

- ***Endogenous interferons*** regulate immunosuppression & anti-proliferation
- ***IFN-α*** binds to host cell membrane to:
  1. inhibit all viral replication processes
  2. upregulate immunoresponse to virus

	2a	2b	Con-1
T ½	2-5	2-5	6-10
Route	IM or S/C	IM or S/C	S/C only
Clinical Use	Chronic Hep C	Chronic Hep B or Acute/Chronic Hep C	Chronic Hep C

- Metabolism/Excretion renal
- S/E flu-like sx (30%), transient hepatic enzyme derangement, neurotoxicities, abortifacient

HBV Treatment

End points to treatment
- Seroconversion of HBeAg from + ⇨ –
- Undetectable levels of HBV DNA
- Both reflect less risk of necrosis, carcinoma or need for transplant

Lamivudine

- Longer intracellular T ½ in HBV vs HIV (18 hrs vs 12 hrs)
- Inhibits HBV DNA polymerase (vs HIV reverse transcriptase) but both = chain termination
- Seroconversion in 17% \| 70% maintain at 3 years
- Well tolerated at therapeutic doses

Adefovir Dipivoxil

- Competitively inhibits HBV DNA polymerase
- BioAv 59% \| T ½ 7 hrs \| Renal excretion
- Resistance in 3% over 4 years
- S/E nephrotoxicity (dose dependant) \| GI upset

Entecavir

- Competitively inhibits HBV DNA polymerase
- BioAv 100% \| Renal excretion
- Seroconversion rates same as lamivudine but HBV DNA suppression much better
- No resistance
- S/E headache, fatigue, nausea

HCV Treatment

- End point is viral eradication (no detectable virus 6/12 after stopping therapy)
- 5% relapse
- Rate of clearance without therapy = 15-30%
- ***IFα-2a*** shows 95% clearance at 6/12 ∴ if ongoing viral detection at 12 wks, start therapy
- Combination therapy with ***ribavirin*** for ***chronic HCV***

Ribavirin

- Requires intracellular activation by viral enzymes
- Interferes with GTP to inhibit mRNA capping & RNA polymerase
- BioAv 64% \| Renal Excretion \| S/E incl Haemolytic Anaemia, Teratogenic

ANTI-INFLUENZA

- Classified on basis of
  1. Core protein: A, B, C
  2. Species of Origin: Avian, Swine etc
  3. Geography
- Influenza A causes pandemics, infects different species
- Influenza B infects human only

Amantadine & Rimantidine

- Blocks M2 proton ion channel of virus a particles ⇨ inhibits uncoating
- Covers Influenza A only with rapid resistance in 50%
- Amantadine: no metabolism \| Renal elimination
- Rimantidine: extensive liver metabolism \| Renal elimination
- 70-90% successful as prophylaxis \| ↓ Sx by 1-2 days for treatment
- S/E incl GI 7 CNS

Neuraminidase inhibitors

- Prevent release of progeny influenza virus
- Covers A & B
- Replication peaks at 24-72 hrs ∴ need to initiate therapy prior to this
- 70-90% successful prophylaxis

Zanamivir

- Ages > 7 yo \| Inhalation
- 10-20% reaches lungs \| absorbed \| renal excretion

Oseltamivir

- Ages > 1 yo \| PO (prodrug requiring hepatic esterase activation)
- Wide VD \| T ½ 6=10 hrs \| Renal elimination
- S/E incl GI upset
- Resistance rare during therapy

SECTION VIII: CHEMOTHERAPEUTICS

9. MISCELLANEOUS ANTIMICROBIALS

METRONIDAZOLE, MUPIROCIN, POLYMYXINS & URINARY ANTISEPTICS

Metronidazole

- Antiprotozoal (eg trichomonas) & antimicrobial (anaerobes)
- Clinical Use: anaerobic/mixed intra-abdo | vaginitis | clostridium colitis | brain abscess
- BioAv good | CSF 100% | Liver metabolism
- S/E incl GI upset, peripheral neuropathy (prolonged use), ***Disulfiram-like effect***

Mupirocin

- Poor BioAv (inactivated rapidly after absorption) ∴ TOP application only
- Cover: gram +ve cocci incl MRSA
- Mechanism: inhibits tRNA synthetase
- Resistance from mutation of enzyme (95% still susceptible)
- Clinical Use: impetigo etc but not large infected areas (confers resistance)

Urinary Antiseptics

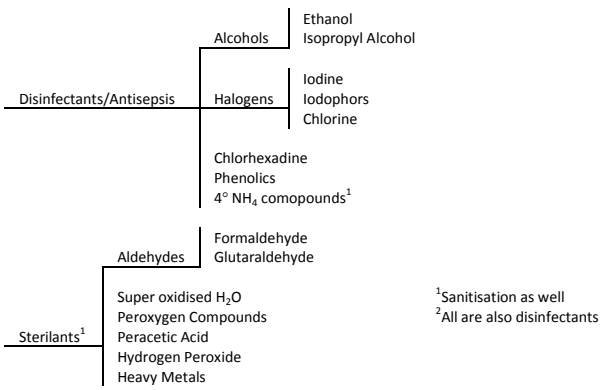
Nitrofurantoin

- Bacteriostatic & -cidal
- Cover: gram +ve & -ve (incl trimethoprim resistant e coli) but not pseudomonas or proteus
- Resistance: slow without crossing to/from other antimicrobials
- BioAv good | Rapid renal metabolism/excretion (minimal S/E) | S/E anorexia, nausea, vomit

Hippurate (Hiprex)

- BioAv good | renal excretion unchanged | releases formaldehyde at pH < 5.5 ⇨ bactericidal
- Cover: gram –ve

DISINFECTANTS, ANTISEPTICS & STERILANTS



Term	Definition
Antisepsis	Application of an agent to ***living tissue*** to ***prevent infection***
Decontamination	***Destruction*** or ***marked reduction in number*** or activity of micro-organisms
Disinfection	Chemical or physical treatment1 that destroys most vegetative microbes or viruses, ***but not spores***, in or on ***inanimate objects***
Sanitization	***Reduction of microbial load*** on an inanimate surface to a level considered ***acceptable for public health purposes***
Sterilization	A process intended to kill or remove all microorganisms, ***including sores*** (usually incl viruses) without an acceptable low probability of survival
Pasteurization	A process that kills ***non-sporulating*** microorganisms by ***hot water or steam*** at 65-100°C

1killing, removing or diluting by chemical or physical means

Evaluation of Agent Effectiveness

- Intrinsic resistance
- Micro-organism population number & type
- Amount of organic material to sustain organism
- Concentration & stability of agent
- Time & temperature of exposure
- Hydration & binding of agent to surface/organism
- Short/Long Term toxicity (inhibits wound healing)

Alcohols *Ethanol, Isopropyl Alcohol*

- Antisepsis/Disinfection | Optimal bactericidal concentration = 60-90%
- Mechanism: denature proteins
- No cover for: spores, protein-containing organic material, hydrophilic viruses
- Disadvantages: Short exposure time (evaporates) | damages exposed tissue incl cornea

Chlorhexadine

- Antiseptic/Disinfection
- Cover: vegetative bacteria (gram +ve cocci > -ve or +ve rods), mycobacteria, fungi, virus, spore germination
- Mechanism: cell membrane destruction
- Bactericidal at 4%
- Disadvantages: middle ear toxicity, slower action vs alcohols but persistent effect

Halogens

Iodine

- Bactericidal in 1 minute | Sporicidal in 15 min
- Most active antiseptic for intact skin | hypersensitivity common

Iodophors

- Iodine + surface active agent (eg povidine)
- Advantages: less irritating than iodine but same onset as Chlorhexadine with broader cover
- Disadvantages: less potent than iodine

Chlorine

- Mechanism: potent oxidization
- Concentration: 5ppm kills vegetative bacteria | 5000ppm kills spores | 1000-10000 TB
- Disadvantages: inactivated by blood, serum, faces, protein-containing material, forms chlorine gas when mixed with acid or urine, corrosive to silver, aluminium, stainless steel

Phenolics

- Disinfectant | Disrupts cell wall
- Cover: bacteria, fungal, not Sporicidal
- Use: hard surfaces only

4° NH_4 compounds

- Mechanism: inactivates energy producing enzymes, denatures proteins, disrupts cell membrane
- Bactericidal (gram +ve > ve), Fungicidal, Not TB or Sporicidal
- Use: **sanitisation** of non-critical surfaces

Sterilising Agents

Aldehydes

- Disinfectant or sterilisation of instruments not able to withstand high heat
- Not corrosive to metals, plastic, rubber
- Mechanism: alkylation
- Pitfalls: dilution, organic material, penetration into small channels in instruments

Formaldehyde

- Sporicidal at 18 hrs | Synergistic with 70% isopropyl alcohol

Glutaraldehyde

- Cover: above + viricidal to both lipophilic and hydrophilic viruses (better Sporicidal, lesser TB vs formaldehyde)

Super oxidised H_2O

- Electrolysis of saline ⇨ *hypochlorus acid* & *chlorine*
- Rapidly bacterio-, fungi-, tuberculo-, Sporicidal (10 min)
- Non-toxic, non-irritating, no special disposal

Peroxygen Compounds

- Decomposition is non-toxic

Hydrogen peroxide

- Good on inanimate objects only (broken down by organic objects)
- 10-25% Sporicidal

Peracetic Acid

- More active at bacteria, spores

SECTION VIII: CHEMOTHERAPEUTICS

10. CLINICAL USE OF ANTIMICROBIAL AGENTS

Considerations prior to starting antimicrobials
- Clinical indications
- Likely agent(s)
- Other measures to prevent spread
- Clinical Evidence

Considerations after identifying cause
- Narrow spectrum utility
- Mono or combined therapy
- Dose | Route | Duration
- Tests to assess response
- Adjuncts to improvement eg drainage of abscess

Choice of Antimicrobials: Host & Pharmacologic factors

Host
- Comorbidities incl ability to eliminate
- Previous drug reactions
- Age
- Pregnancy Status

Pharmacologic
- Kinetics
- Access to site of infection
- Toxicity
- Drug interactions

Lack of confirmatory micro can be due to
- Sample error (incl after initiating therapy or wrong medium delivery)
- Non-cultivable or slow-growing organisms (eg histoplasma, bartonella)
- Non-bacterial infection

EMPERICAL THERAPY

- Because early intervention improves outcome ∴ particularly indicated when there is risk of significant morbidity awaiting microbial evidence
- May be harmful (eg neutropenic patient with multiple aetiologies for pyrexia)
- Response may suggest cause

Bacteriostatic vs Bactericidal

- Bacteriostatic drugs have a lower MIC (minimal inhibitory concentration)
- Bactericidal drugs better for impaired host defence, endovascular disease
  - ***Concentration-dependant killing*** (aminoglycosides & quinolones)
    ∴ once daily dosing appropriate
  - ***Time-dependant killing*** (β-lactams & Vancomycin)

Post antibiotic Effect
- Persistent suppression after limited exposure
- Many gram +ve cocci agents have > 1.5 hr PAE
- Only DNA/Protein synthesis inhibiting agents & Carbapenams have sig gram –ve bacilli PAE
- ***Post Antibiotic Leukocyte Enhancement*** (PALE): reflects longer PAE in vivo vs in vitro

Mechanisms
- Slow recovery after reversible nonlethal damage to cell structure
- Persistence of drug at binding site/periplasmic space
- Need to synth new enzymes before resumption of growth

KINETIC CONSIDERATIONS

Route
- Parenteral for critically ill, endovascular disease, diseases/symptoms showing impaired absorption, antibiotic kinetics
- Com-morbidities can
  ↓ Requirement eg hepatic or renal dysfunction
  ↑ Requirement eg burns, cystic fibrosis
  Elderly, children, pregnancy

Monitoring Serum Levels Required if:
- Direct relationship between concentration and efficacy or toxicity
- Substantial inter-patient variability in dose
- Small therapeutic windows
- Assay available

Combination Therapy

Combination Therapy indicated in
- Broad spectrum empiric cover
- Polymicrobial infection
- Decrease emergence of resistance
- Decrease dose related toxicicty
- To enhance bacteriocidal/static effects

Mechanism of Synergistic Actions
- Blocking sequential metabolic steps eg trimethoprim-sulfamethoxazole
- Inhibiting enzyme inactivation eg Clavulanic acid
- Enhancing antimicrobial uptake eg β-lactam brakind down cell wall

Mechanism of Antagonistic Action
- Inhibition of cidal antimicrobials by static agents (cidal drugs need actively growing membrane to have an effect)
- Induction of enzymatic inactivation (some β-lactams induce β-lactamse)

Prophylaxis

Surgical
- Risk factors for psot operative wound infection (≥ 2 ↑ risk of infection)
  1. Abdominal surgery
  2. Surgery > 2 hrs
  3. Contaminated or dirty wounds
  4. ≥ 3 medical diagnosis
- Indication for Prophylaxis
  - Contaminated operations
  - High risk operations (eg cardiac surgery)
  - Prosthesis placement
  - Immunocompromised

Nonsurgical
- Used to prevent colonisation or for high risk patients (immunocompromised)

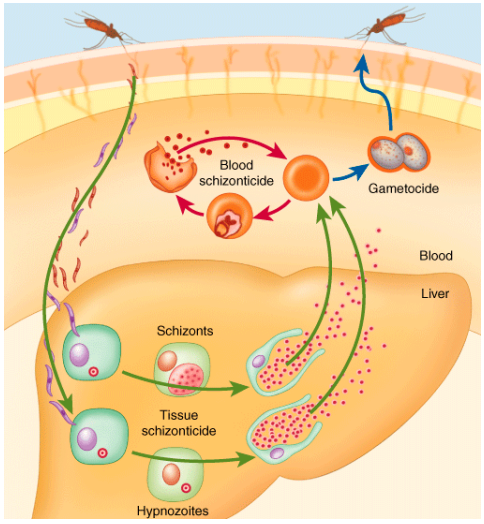
SECTION VIII: CHEMOTHERAPEUTICS

11. ANTIPROTOZOAL DRUGS

Targets for Killing for protozoa & helminths
- Unique *essential enzymes* (cleanest target)
- *Indispensible enzymes* in parasites but found in host (unessential)
- Common *dispensable biochemical functions* with different pharmacological properties

MALARIA

- *Plasmodium falciparum, vivax, malariae, ovale*
- Falciparum responsible for most of the severe effects



Life Cycle
1. Sporozoites carried by mosquito & inoculate human
2. Sporozoites rapidly invade hepatocytes & mature into schizonts & hypnozoites
3. Invade erythrocytes as blood schizonticides
4. Repeated cycles increase population
5. Sexual stage gametocytes also develop in erythrocytes to be taken up by mosquito vector

- Falciparum & Malariae undergo 1 cycle only ∴ spont resolve after 4/52
- Vivax & Ovale form hypnoziotes (dormant sporozoites in hepatocytes – difficult to eradicate)

Chemoprophylaxis & Treatment

Clinical Setting	Therapy	2nd Line
Chloroquine-sensitive Falciparum & Malariae	*Chloroquine*[1]	-
Vivax & Ovale	*Chloroquine*[1] + *Primaquine*[5]	-
Falciparum (Chloroquine resistant)	*Quinine* + *doxy* or *clinda* or *fansidar*[6]	*Malarone*[4] or *Mefloquine*
Severe Falciparum	*Quinidine*	*Artemether*
Prophylaxis	*Chloroquine* or *Mefloquine*[3] or *Malarone*[4]	*Quinine*[2]
Presumptive[7]	*Quinine*[8], *Mefloquine*[8], *Fansidar*[6]	

[1]Blood sporozoites only
[2]Quinidine adverse effects
[3]Covers all malarial species
[4]Made of Atovaquone & proguanil | used for multi-drug resistant strains
[5]**Only therapy for eradication of hypnozoites**
[6]Sulfonamide + Pyrimethamine, 1st line in some developing countries due to cost, not the best presumptive treatment due to resistance
[7]Fever in the travelling patient where medical attention not available
[8]More reliable treatment than Fansidar but more toxic

Primaquine
- Eradication of ***hepatocytic stage*** of *vivax* or *ovale* as well as ***gamateocidal*** against all (also an alternative to treatment of PCP)
- Good BioAv | T ½ 3-8 hrs | Urinary excretion
- Strains in SE Asia may show resistance ∴ requiring repeated therapy (no alternative)
- S/E incl GI upset, myelosupression, cardiac arrhythmias
- Contraindicated in G6PD, myelosupression, intravenous (severe hypotension)

Chloroquine
- High BioAv | High VD | Initial T ½ 3-5 days | terminal T ½ 1-2 months | Renal elimination
- ***Blood schizonticide*** only (not active against liver stage)
- Mechanism controversial; probably due to free heme build up in parasite
- Resistance: probably a transporter mutation
- Other than prophylaxis & treatment, also used as 2nd line in ***amoebic liver abscess***
- S/E incl Common: well tolerated, pruritus
  Less common: GI upset, CNS (confusion, psychosis, seizures)
  High doses: irrev ototoxicity, retinopathy, myopathy, p neuropathy
  Rapid infusion: severe hypotension, cardiorespiratory arrest
- Contraindications: psoriasis, porphyria, liver disease (ok in pregnancy & children)

Quinine
- 1st line for falciparum (given high resistance to Chloroquine) | resistance uncommon
- High BioAv | High VD | PO & IV same
- Other kinetics differ between non/infected:
  Plasma level/protein binding higher in malaria (without ↑ toxicity)
  T ½ 18 hrs (malaria) vs 11 hrs (healthy)
- S/E incl cinchonism (tinnitus, headache, nausea, dizziness, flushing, visual disturbance)
  Prolonged therapy: visual/auditory hallucination, GI upset
  Hypersensitivity incl Blackwater fever (haemolysis & haemaglobinuria of unknown aetiology)
  Parenteral: hypotension
- Contraindications: *Mefloquine* therapy either current or previous

Mefloquine
- Used for Chloroquine resistant (not multi-drug resistant) P. falciparum for prophylaxis or treatment (but not severe or complicated malaria)
- PO (severe irritation IV) | Wide VD | T ½ 20 days | GI excretion
- Schizonticidal only | Sporadic resistance apart from SE Asia
- S/E incl GI upset, CNS, neuropsychiatric, cardiac conduction abnormalities
- Contraindications: psychiatric, epilepsy, arrhythmias, co-administration with quinine
- Safe in children and pregnancy

Atovaquone (part of *Malarone*)
- Used for multi-drug resistant strains & PCP | disrupts mitochondrial electron transport
- Shorter period of treatment vs doxy but also more expensive
- S/E incl GI upset, insomnia | untested in pregnancy

INHIBITORS OF PROTEIN SYNTHESIS: *Pyrimethamine* & *Proguanil*
- Both Slow absorption, moderate BioAv

Pyrimethamine
- *Trimethoprim* derivative | T ½ 3.5 days | extensively metabolised before excretion

Proguanil
- Biguanide derivative | Prodrug (*cycloguanil* is active metabolite)
- Act slowly against blood schizonticides (*proguanil* mildly targets hypnozoites)
- Inhibits plasmodia dihydrofolate (most resistance from mutation here)
- Synergistic with sulphonamides: combination therapies include
  Malarone: *Atovaquone* + *Proguanil*
  Fansidar: sulphonamide + *pyrimethamine*
  Chloroquine + *Proguanil*
- *Fansidar* sometimes 1st line due to cost, toxicity, resistance (not effective against vivax, ovale, malaria), slow acting ∴ not in severe malaria
- Toxoplasmosis: *pyrimethamine* & *sulfadiazine* 1st line (since *sulfadiazine* is main toxic culprit, can replace with *clindamycin*)
- S/E GI upset, uncommon severe cutaneous reactions, safe in pregnancy

ANTIBIOTICS: *Doxycycline* & *Erythromycin*
- Normally used in conjunction with *quinine* to ↓ treatment time & SE
- *Doxycycline* 1st line then *Clindamycin* (children & pregnancy)

Artemether
- Expensive
- Used in combination for treatment of severe falciparum (incl resistant species)
- Better tolerated than most other antimalarials

AMEBIASIS

Amebicide
- Luminal: *Diloxanide Furoate*, *Paromomycin*
- Tissue: *Metronidazole*, *Tinidazole*

Treatment based on clinical presentation
Asymptomatic Infection • Treatment initiated in non-endemic regions only • Uses a luminal amebicide (all other forms of amebiasis require luminal eradication)
Amoebic Colitis • Includes colitis & dysentery • *Metronidazole* + luminal amebicide (2nd line incl tetracycline or erythromycin[1])
Extra intestinal Infections • *Metronidazole* + luminal amebicide (2nd line rpt 1st + Chloroquine) +/- aspiration

[1]No good for severe or extraintestinal infection

Metronidazole & *Tinidazole*
- Kills trophozoites but not cysts
- *Tinidazole* has better toxicity profile
- Good BioAv | Wide V_D | T ½ (M) 7.5 hrs (T) 12 hrs | Liver metabolism | Urinary excretion
- Mechanism: reduction of nitro group by anaerobic bacteria or sensitive protozoa produces toxic products
- Clinical Use: amebiasis, giardiasis, trichomoniasis
- S/E incl nausea, headache, dry mouth, metallic taste, Disulfiram-like effect

12. ANTHELMINTIC DRUGS

- Parasites should be identified before treatment commenced

Albendazole
- Broad spectrum anthelmintic (mostly hydatid but also pin/hookworm)
- Erratic Absorption | rapid 1st pass (liver) | T ½ 8-12 hrs | urinary elimination
  PO (full stomach) targets intraluminal vs PO (fatty meal) targets tissues
- Mechanism: inhibits microtubule synthesis & larvicidal
- S/E incl little for short courses (< 3 days) to abdo distress, headaches, fevers, fatigue…

Doxycycline
- W bancrofti

Ivermectin
- 1st line in strongyloidiasis & onchocerciasis (2nd line in many others)
- PO | Wide VD | T ½ 16 hrs | Faecal excretion
- Mechanism: GABAergic on nematodes & arthropods | Microfiaricidal to onchocerciasis
- S/E incl Mazotti reaction (from filamentous breakdown) or fatigue, nausea etc

Mebendazole
- Broad spectrum anthelmintic with limited S/E profile but teratogenic
- Poorly absorbed (10%) | Rapid 1st pass inactivation | urinary excretion
- Mechanism: inhibits microfilament synthesis

Piperazine
- Ascariasis only; anticholinergic ⇒ paralysis
- Good BioAv | T ½ 6 hrs | urinary excretion
- S/E incl GI upset, not for pregnancy

Praziquantal
- Treat Schistosomes, trematodes, cestodes
- BioAv 80% | CSF 20% | Mostly metabolised after hepatic 1st pass | T ½ 0.8-1.5 hrs
- Mechanism: increases Ca helminths permeability
- S/E are frequent & incl nausea, vomiting, GI upset

Pyrantel Pamoate
- Broad spectrum
- Poorly absorbed (> ½ excreted in faeces unchanged) ∴ used to treat luminal disease
- Mechanism: cholinergic
- S/E infrequent & incl GI upset

SECTION IX: TOXICOLOGY

1. INTRODUCTION

Definitions

- Bioaccumulation; contaminant build up > ability to metabolise
- Biomagnification; ↑ concentration up through food chain
- Hazard; ability to cause injury in a given situation/setting
- Risk; expected frequency of occurrence of an undesirable effect

Routes
- Inhalation
- Transdermal
- Ingestion

Environmental considerations
- Degradability
- Mobility through mediums
- Presence of bioaccumulation & biomagnification

AIR POLLUTANTS

CARBON MONOXIDE

- Colourless, tasteless, odourless, non-irritating gas (CONT)
- By product of incomplete combustion

Mechanism
- Higher affinity for O2 binding sites on Hb (x220)
- CO + Hb ⇒ carboxyhaemoglobin
- Shifts O2 dissociation curve left (ie remaining OxyHb lower affinity for release)

Clinical Effect

Psychomotor impairment
⇓
Headache/temporal tightness
⇓
Confusion/Loss of visual acuity
⇓
Tachycardia/Tachypnoea/Syncope/Coma
⇓
Deep Coma/Convulsions/Shock/Respiratory Failure

%CO	Effect
< 15%	rarely has effect
40%	Collapse
60%	Death

- Prolonged hypoxia = irreversible brain/myocardial ischemia

Treatment
- Remove from source
- High flow O2

Elimination T ½ CO	% O2	atm
320 min	21	1
80 min	100	1
20 min	100	2-3*

*efficacy of hyperbaric O2 yet to be established

SULFUR DIOXIDE

- Colourless, irritant gas
- By product of fossil fuels

Mechanism
- SO2 ⇒ moist membranes ⇒ sulphurous acid = severe irritation
- 90% of inhaled SO2 absorbed in URT (principle site of action)
- Bronchial constriction, parasympathetic reflex, altered smooth muscle tone

Clinical Effects
- Irritation to eyes, nose, throat, bronchoconstriction
- Delayed onset pulmonary oedema
- Treatment mainly for respiratory tract irritation

NITROGEN OXIDES

- Brownish gas
- Deep lung irritant ⇒ pulmonary oedema
- Type I cells target

Clinical Effects
- Irritation of the eyes, nose, cough, mucoid/ frothy sputum production, dyspnoea, chest pain
- APO within 1-2 hrs
- If resolves, will occur over 2 weeks
- Stage 2 occurs after this; recurring APO, bronchiolitis obliterans
- Chronic effects include emphysema like changes to the lung

Treatment
- Same as for non-cardiogenic pulmonary oedema
- Bronchodilators, sedatives, antibiotics

OZONE (O3)

- Bluish irritant gas
- Normal in earth's atmosphere for bouncing UV light
- On surface found around high voltage & air/water purifiers

Clinical Effects
- Mucous membrane irritant
- Mild exposure; URT irritation
- Severe; deep lung irritation, APO
- Shallow rapid breathing, ↓ compliance
- Enhanced sensitivity to bronchoconstrictor
- Chronic Δ: bronchitis, bronchiolitis, fibrosis, emphysema

SOLVENTS

HALOGENATED ALIPHATIC HYDROCARBONS

- Industrial solvents, degreasing agents, cleaning agents
- *Carbon tetrachloride, chloroform, trichloroethylene, tetrachloroethylene*

Mechanism
- CNS depression
- Liver injury
- Kidney injury
- Cardiotoxicity
- Chloroform most potent
- Tetrachloroethylene = impaired memory, peripheral neuropathy
- No specific treatment

AROMATIC HYDROCARBONS

Benzene

- No specific treatment
- Chronic; bone marrow injury

PPM exposure	Effect
7500	Fatal
3000	Euphoria, nausea, locomotor, coma
250-500	vertigo, drowsiness, headache & nausea

Toluene

- No myelotoxic properties

PPM exposure	Effect
800	Severe fatigue, ataxia
10,000	rapid LOC

INSECTICIDES

1. *ORGANOCHLORINE INSECTICIDES*
- Include *DDT, Benzene Hexachlorides, Cyclodienes, Toxaphenes*
- Dermal or inhalational routes
- Bioaccumulation with slow degradation

Mechanism
- Interfere with inactivation of Na channels in excitable membranes = rapid firing
- Ca transport also inhibited
- Net effect; CNS stimulation

2. *ORGANOPHOSPHORUS INSECTICIDES*
- Routes of entry; skin, respiratory, GIT
- Rapid biotransformation

Mechanisms
- Inhibits AChE (phosphorylates esteratic site)
- Some also have direct cholinergic effects
- Also targets **neuropathy target esterase** = delayed neurotoxicity; polyneuropathy, paralysis, axon degeneration

3. *CARBAMATE INSECTICIDES*
- Inhibit AChE
- Shorter duration of effects vs organophosphates
- Non persistent pesticides

4. *BOTANICAL INSECTICIDES*
- *Nicotine, rotenone, pyrethrum*
- Nicotine acts on N receptors
- *Rotenone* is an irritant
- *Pyrethrum* acts on CNS to cause tetanic paralysis

SECTION IX: TOXICOLOGY

2. MANAGEMENT OF THE POISENED PATIENT

TOXICOKINETICS

- V_D: large = haemodialysis ineffective
- Clearance

LAB TESTS

1. ABG
2. Anion Gap = [Na + K] – [HCO3 + Cl]

Type of ↑ Anion Gap	Agents
Organic Acid Metabolites	*Methanol, Ethylene glycol, Diethylene glycol*
Lactic Acidosis	*CN, CO, Ibuprofen, Isoniazid, Metformin, Salicylates, Valproic Acid, seizure, hypoxia, hypotension*

3. Renal Function
4. Osmolar Gap = measured osmolality – calculated osmolality

Substance	Serum Level (mg/dL)	Osmolar Gap (mOsm/kg)
Ethanol	350	75
Methanol	80	25
Ethylene Glycol	200	35
Isopropanol	350	60

5. ECG
6. Imaging

DECONTAMINATION

A. SKIN
- Remove clothing & double bag
- Wash skin with soap & water

B. GIT

1. Emesis
   - *Ipecac*
   - Contraindicated with *corrosives, petroleum distillate*, rapidly acting convulsions
2. Gastric Lavage
   - Awake & protected airways
   - 0.9% NS (body temperature) used
3. Activated Charcoal
   - Large surface area for absorption
   - Optimal ratio 10:1 (charcoal : drug)
   - Contraindicated in *Fe, Lithium, K, alcohol, CN*
   - Not useful in corrosive minerals & alkali
   - Gut dialysis; ↑ gut motility for excretion
4. Cathartics
   - Indicated in *Fe, enteric coated medicines, illicit drug filled packets, FB*

ENHANCING ELIMINATION

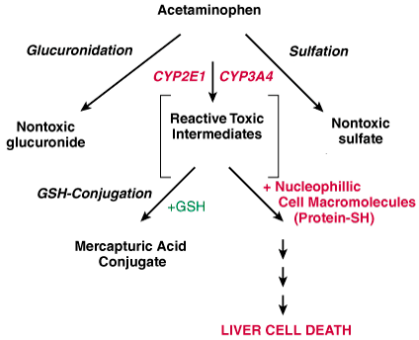
DIALYSIS
- Peritoneal; inefficient for most drugs

Haemodialysis
- maintains fluid/electrolyte balance
- Enhance removal of toxic metabolites
  eg *formate* in *methanol, oxalate* & *glycolate* in *ethylene glycol* poisoning
- Good for *salicylate* intoxication

FORCED DIURESIS & PH MANIPULATION
- Unproved value
- Can cause volume overload/electrolyte disturbance

COMMON TOXIDROMES

ACETAMINOPHEN
- 7g = potentially toxic



Metabolism of *Paracetamol*
GSH = glutathione

Overdose saturates GSH thereby accumulating reactive toxic intermediates

NAC acts as a GSH

Given that toxicity is irreversible, transplant required if unable to salvage

Clinical Correlation
- Asymptomatic to mild GI upset
- 24-36hrs = elevated aminotransferase, hypoprothrombinaemia

AMPHETAMINES & OTHER STIMULANTS
- *Metamphetamines, MNDA (ecstasy), cocaine*

Clinical Correlation
- Low dose: euphoria, wakefulness
- Mod: restless, acute psychosis, agitation, HTN, tachycardia
- Severe: prolonged muscle hyperactivity
  ⇒ Hyperthermia, dehydration, hypotension
  ⇒ Seizures, Rhabdomyolysis, coagulopathy

Treatment
- Symptomatic for temperature
- *BZDP* for seizures
- Neuromuscular paralysis for temperatures if required

ANTICHOLINERGICS

Anticholinergic Syndrome

Red as a beet:	Flushed Skin
Hot as a hare:	Hyperthermia
Dry as a bone:	Dry mucous membranes, no sweating
Blind as a Bat:	Blurred vision, Cycloplegia
Mad as a Hatter:	Confusion, Delirium

Other symptoms
- Urinary retention
- Sinus tachycardia
- CNS: agitated, delirious, coma

Treatment
- Supportive
- Agitation; sedation
- *Physostigmine* 0.5-1.0 mg IV (side effects bradycardia & seizures, contraindicated in TCA)

ANTIDEPRESSANTS

TCA
- Common
- Competitive agonists at muscurinic cholinergic receptors (∴ anticholinergic symptoms)
- Some are also strong α blockers ⇒ vasodilation
- CNS agitation, seizures ⇒ hypotension, depression
- Cardiac: slow conduction, wide QRS, -ve inotropy ⇒ arrythmias

Treatment
- Supportive
- Hypotension; fluids, norepinephrine
- Cardiac: NaHCO3 50-100 mEq/kg to overcome Na blockade
- Physostigmine contraindicated

MAOI
- Severe hypertension
- Serotonin Syndrome with SSRIs

SSRIs & Newer Antidepressants
- Seizures (even in therapeutic doses)
- QT prolongation, Torsades
- Serotonin Syndrome
- Generally safer than TCAs & MAOIs

ANTIPSYCHOTICS
- CNS: depression, seizures, hypotension
- QT prolongation
- D2 blockers cause parkinsonian like movement disorders (dystonic reactions)
- Neuroleptic malignant syndrome

***ASPIRIN* (SALICYLATES)**
- > 200mg/kg = intoxication
- Overdose = uncoupling of oxidative phosphorylation

Clinical Correlation
1. Medullary Stimulation ⇒Hyperventilation/Respiratory Alkalosis
2. Metabolic Acidosis
3. ↑ Anion gap 2ry to lactate accumulation/HCO3 excretion (to compensate for alkalosis)
4. Hyperthermia (from uncoupling of oxidative phosphorylation)
5. Dehydration
6. Coma/Seizure
7. Cardiorespiratory collapse

Treatment
- Aggressive gut decontamination (*lavage, charcoal*, whole bowel irrigation)
- Supportive: fluids
- HCO3 to alkalinise urine
- Haemodialysis in severe cases (> 100 mg/dL)

BETA BLOCKERS
- *Propranolol* most potent since it has Na channel effects at high doses, and is lipophilic so enters CSF easily

Clinical correlation
- Bradycardia/ Arrythmias
- Hypotension
- Partial agonists can cause tachycardia, HTN
- Seizures

Treatment
- Supportive: fluid, beta agonist (atropine) – neither particularly effective
- Glucagon ↑ intracellular cAMP (5-20mg)

CALCIUM CHANNEL BLOCKERS
- Depress SA & slow AV
- ↓ CO & HR

Treatment
- Most CCB are SR so whole bowel irrigation can be helpful, *oral activated charcoal*
- Additional *Ca* 2-10g IV (good for inotropy not for conduction)
- *Glucagon, vasopressin, epinephrine, high dose insulin, glc* supplementation

CHOLINESTERASE INHIBITORS

- *Organophosphates* & *carbamates* cholinesterase inhibitors

Excess muscurinic activity	Excess nicotinic activity
Abdominal cramping	Generalised ganglion activation
Diarrhoea	Hypertension
Excessive salivation	Tachy/Bradycardia
Sweating	
Urinary frequency	
Increased Bronchial Secretions	

AChE Inhibitor Symptoms: DUMBELS

Diarrhoea	Excitation
Urinary Frequency	Lacrimation
Meiosis/muscle weakness	Seizures/Sweating/Salivation
Bronchospasm	

- CNS effects; agitation, confusion, seizures

Treatment

- Supportive
- *Atropine* (M) or *Pralidoxime* (M & N receptors) antidotes

DIGOXIN

- Vomiting
- Hyperkalaemia
- Cardiac arrhythmias (sinus brady, AV block, atrial tachycardia with block, accelerated junctional rhythm), premature beats

Treatment

- *Atropine* for brady or AV block
- *Digoxin* antibodies with improvement in 30-60 minutes

ETHANOL & SEDATIVE-HYPNOTICS

- Euphoric or rowdy to stupor to coma
- Depressed respiratory drive
- *GHB* overdose usually comatose for 3-4 hrs and wake quickly thereafter

Treatment

- Supportive
- Protect airways
- Hypotension; body warming, fluids
- *Flumazenil* for *BZDP* (can precipitate seizures)

METHANOL **&** *ETHYLENE GLYCOL*

- Metabolised to highly toxic organic acids
- CNS: depression, coma, blindness
- *Methanol* ⇒ formic acid ⇒ blindness
- *Ethylene glycol* ⇒ hippuric, oxalic, glycolic acid ⇒renal failure

Treatment

- *Ethanol*: alcohol dehydrogenase competitive inhibitor
- *Fomepizole* also antidote

SECTION X: SPECIAL TOPICS

1. PERINATAL & PAEDIATRIC

DRUG THERAPY IN PREGNANCY

KINETICS

A. Lipid Solubility
- Lipophilic drugs cross placental barrier
- Ionized drugs less so
- Polar crossing is relative (not absolute)
  Eg *salicylates* are highly polar but cross
  Because small amount not ionized is
  Highly lipid soluble

Factors effecting placental delivery
- Chemical structure
- Rate of crossing
- Duration
- Foetal distribution
- Stage of placental development
- Other drug interactions

B. Molecular Size
- MW250-500 cross placenta easily
- MW500-1000 more difficult
- MW>1000 difficult (eg heparin)

C. Placental Transport
- Some placental transporters efflux drug into maternal circulation to prevent toxicity
- Include cancer drugs

D. Protein Binding
- Highly lipid soluble drugs will cross regardless of binding capacity
- Differential protein binding exists with higher affinity for maternal or foetal protein
- Includes *sulphonamides, barbiturates, phenytoin, LA*

E. Placental & Foetal Metabolism
- Placenta has metabolic role in some drugs
- Double edged sword – potentially toxic metabolites can be formed or primary toxic drugs can be inactivated
- Drugs crossing placenta reach foetus through umbilical vein (40-60% enters liver)
- Drugs reaching umbilical artery can be shunted back into circulation

DYNAMICS

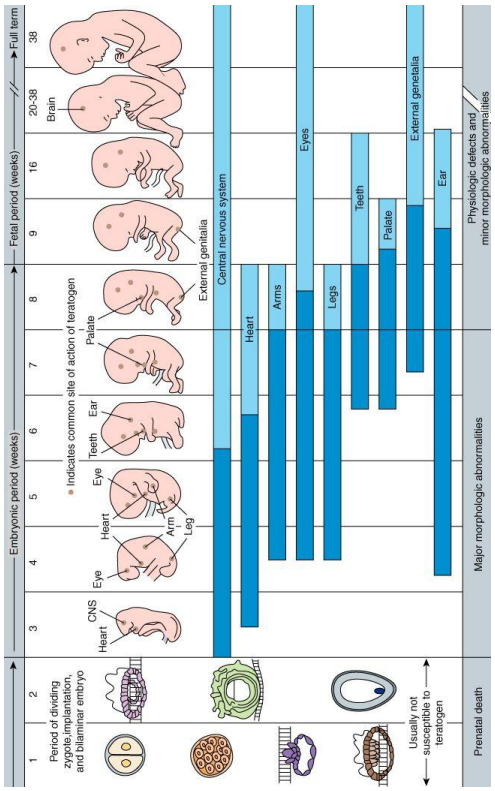
A. Maternal Drug Action
- Altered pregnancy physiology may warrant additional therapeutics eg Pregnancy induced DM or PIH

B. Therapeutic Drug Actions in the Foetus
- Maternal administration with target on foetus
- Includes *steroids* for lung maturation, *phenobarbital* for ↓ jaundice risk

C. Predictable Toxic Drug Actions in the Foetus
- Chronic use of *opioids* ⇒ foetal dependence
- *ACE I* in pregnancy ⇒ irreversible renal failure

D. Teratogenicity

1. Teratogenic Mechanisms
   - Poorly understood, multifactorial
   - Direct effect on tissue
   - Effect on blood, oxygen or nutrient supply
   - Effect on tissue differentiation
   - Deficiency of critical substances eg folate
2. Defining a Teratogen
   - Characteristic malformation (shows selectivity for target organs)
   - Exertion of effect at particular developments
   - Dose dependant incidence
3. Counselling
   - Risk to mother risk to foetus



Australian Categorisation of Pregnancy	
A	Drugs which have been taken by a *large number* of pregnant women and women of childbearing age *without any proven increase in the frequency* of malformations or other direct or indirect harmful effects on the foetus having been observed
C	Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing *harmful effects* on the human foetus or neonate *without causing malformations.* These effects *may be reversible.*
B1	Drugs which have been taken by only a *limited number* of pregnant women and women of childbearing age *without an increase in the frequency* of malformation or other direct or indirect harmful effects on the human foetus having been observed. *Studies in animals* have *not shown evidence* of an increased occurrence of foetal damage
B2	Drugs which have been taken by only a *limited number* of pregnant women and women of childbearing age *without an increase in the frequency* of malformation or other direct or indirect harmful effects on the human foetus having been observed. *Studies in animals* are *inadequate or may be lacking*, but available data show no evidence of an increased occurrence of foetal damage
B3	Drugs which have been taken by only a *limited number* of pregnant women and women of childbearing age *without an increase in the frequency* of malformation or other direct or indirect harmful effects on the human foetus having been observed. *Studies in animals have shown evidence of an increased* occurrence of foetal damage, the significance of which is considered uncertain in humans.
D	Drugs which *have caused are suspected to have caused or may be expected to cause an increased incidence of human foetal malformations or irreversible damage.* These drugs may also have adverse pharmacological effects.
X	Drugs which have such a *high risk of causing permanent damage to the foetus* that they should not be used in pregnancy or when there is a possibility of pregnancy.

DRUG THERAPY IN INFANTS & CHILDREN

DRUG ABSORBTION

A. Blood Flow
- For IM or S/C consideration
- Sick neonates have little muscle mass and are peripherally shut down

B. GI Function
- Gastric acid secretion occurs within hrs of term babies but slower in preterm
- Drugs that are inactivated by low pH may not do so anymore
- Gastric emptying prolonged 1st day after delivery (6-8 hrs)
- Peristalsis irregular and slow
- Gastrointestinal enzymes less potent

Distribution
- Higher % TBW (70-75%)
- ECF (neonate) = 40% vs ECF (adult) = 20%
- Preterm infants have less fat (1% vs 15% in full term)
- Protein binding less

Drug Metabolism
- P450 lower in early life
- Glucuronides formation reaches adult values at 3-4 yrs

Drug Excretion
- GFR lower in newborns (30-40% adults)
- Function improves substantially in first week

Special Dynamics in Neonates
- *Indomethicin* to close DA vs *PGE1* to keep open

Formulation & Compliance
- Elixirs; suspension in alcohol, even throughout, does not require shaking
- Suspension; particles in a a liquid not evenly distributed

DRUG USE IN LACTATION

Avoid Breast Feeding In
- Radioactive Iodine Tx
- Chemotherapy
- Drugs without established data

- Formula feeding has higher mortality & morbidity
- Most drugs excreted into breast milk in minute amounts
- Optimally take 30-60min post feed (3-4hrs prior to next)
- *Tetracyclines*; 70% of plasma concentration, teeth staining
- Isoniazid equilibrates with milk/plasma, can show signs of pyridoxine deficiency
- Sedatives & Hypnotics usually have some effect
- Opioids can prolong dependence
- Minimal *alcohol* consumption not shown to harm
- Nicotine from smoking low (but smoke is a hazard)
- Caffeine is excreted

PAEDIATRIC DRUG DOSE

- Calculating dose based on age or weight (underestimate dose), based on SA more accurate

Age: Young's Rule

$$Dose = adult\ dose \times \frac{Age\ (years)}{Age + 12}$$

Weight (Clark's Rule)

$$Dose = adult\ dose \times \frac{weight\ (kg)}{70}$$

2. GERIATRIC PHARMACOLOGY

PHARMACOLOGICAL CHANGES ASSOCIATED WITH AGEING

- Gradual decline in all major organs

KINETICS

A. Absorption
- No change to absorption across luminal interface
- Slower gastric emptying
- Changes to everyday activity contributes most; nutritional status, use of OTC medications esp laxatives, antacids

B. Distribution
- ↓ Lean body mass | % TBW | serum albumin | kidney weight | hepatic flow
- ↑ Fat

C. Metabolism
- Non consistent decline
- ↓ ability to recover from injury (liver)
- Concurrent disease/comorbidities ↓ ability to metabolise

D. Elimination
- Age related decline in renal function

Cockcroft-Gault formula (age 40-80)

$$Crea\ Clearence\ (mL/min) = \frac{(140 - age)(weight\ in\ kg)}{72 \times serum\ Crea\ in\ mg/dL}$$

- For women x 0.85
- Age related decline in respiratory volume & breathing capacity important in volatile drugs

PHARMACODYNAMIC CHANGES
- More sensitive due to altered kinetics or diminished homeostatic response
- Homeostatic mechanism for exercise good until age 75 (mostly altered SV not HR)
- Temperature regulation also impaired

BEHAVIOURAL & LIFESTYLE CHANGES
- Cognitive; forgetting to take pills
- Economic stress
- Loss of spouse

MAJOR DRUG GROUPS

CNS

Sedative-Hypnotics
- ↑ T ½ by 50-150%
- More variable effect than young people
- Sequelae of supratherapeutic doses; ataxia, accidents

Analgesics
- More sensitive to respiratory effects
- Tend to be underutilised

Antipsychotics & Antidepressants
- No effect on Alzheimer's dementia
- Most effect due to sedation
- Elderly as responsive to antidepressants as young

CARDIOVASCULAR DRUGS

Antihypertensives
- *Thiazides* first line
- *Ca ch blockers* also ok
- *Beta blockers* are less efficacious and higher risk
- *ACE-I* less useful unless HF or DM present
- Orthostatic hypotension can be a problem

+ve Inotropes
- No ↑ in sensitivity
- ↑ T ½ from ↓ clearance/metabolism
- ↑ sensitivity to antiarrhythmic effects

Antiarrhythmic
- Poor reserve, more fq electrical disturbance
- *Lidocaine* better
- Most Sx controlled with ventricular rate than rhythm

ANTIMICROBIALS
- ↓ host defence = ↑ infection
- Lungs: ↓ Mucociliary clearance
- Urinary: retention ↑ fq UTI

ANTI INFLAMMATORIES
- OA common in old age
- *NSAIDs* sometime contraindicated given decline in renal function
- *Corticosteroids* useful in this case

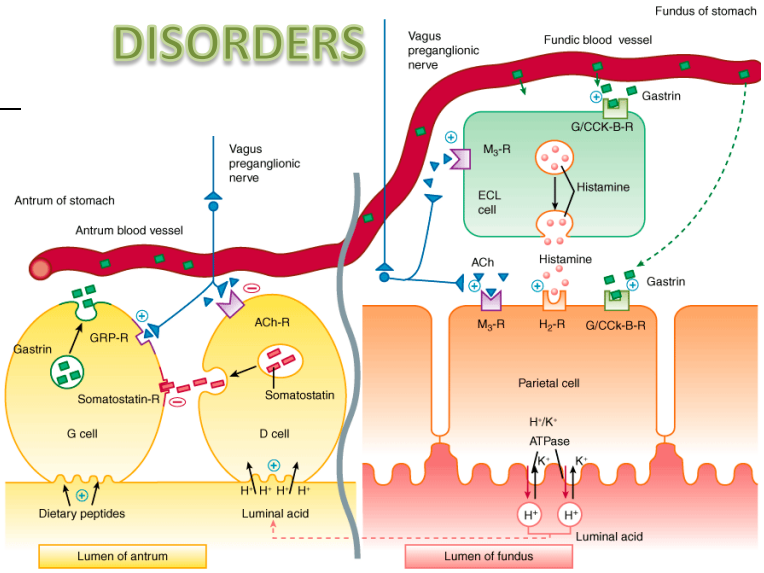
ADVERSE DRUG REACTIONS IN THE ELDERLY

- ↑ age = ↑ number of drugs
- Adverse effects ↑ by 10% per drug
- Drug reactions x2 young population
- Due to practitioner & patient errors (non-compliance, OTC medications)

PRACTICAL ASPECTS

- Physical disability; measuring liquids, opening childproof containers
- Deliberate non-compliance due to previous effect
- Accidental non compliance
- Drug interactions from different prescribers

3. DRUGS USED IN GI DISORDERS



PEPTIC ULCER DISEASE

Final common pathway to acid secretion is H-K ATPase in fundus
Stimulated by: ACh to M3 receptor | Histamine | Gastrin

Antral cells uptake acid from fundus

Antacids
- Weak base = neutralise stomach
- Stimulates mucosa to protect
- Differ in absorption & stool consistency
- *$MgOH_2$* & *$AlOH_3$* most common
- *$MgOH_2$* laxative effect
- *$AlHO_3$* constipating
- *$CaCO_3$* & *$NaCO_3$* also used but absorbed

H2 Receptor Antagonists
- *Cimetidine*
- Still 2 other pathways to H+ secretion

PPI
- *Omeprazole*
- Lipophilic weak bases
- Diffuse into parietal cell canaliculi, concentrate > 1000x
- Irreversibly inactivate H/K ATPase
- Metabolised in liver T ½ 1-2 hrs | Duration of action 24 hrs
- 3-4 days for full effect
- Adverse effects; GI irritation, ↓ B12 BioAv

Sucralfate
- Poorly soluble
- Forms polymers in low pH to protect injured tissues
- Accelerated ulcer healing

Misoprostol
- PGE_1 analog
- Enhances protection and inhibits acid secretion
- Not used because of multiple daily dosing and adverse effects (diarrhoea, GI upset)

Colloidal Bismuth
- Forms protective coating on ulcer
- Stimulates mucosal protection
- Antimicrobial effect
- Sequesters enterotoxins

Antibiotics
- 80% of ulcers have H Pylori in them
- Eradication involves PPI, Bismuth, Tetracycline, Metronidazole or Amoxicillin + Clarithromycin

UPPER GI MOTILITY

- Relevant in gastroparesis or postsurgical delay
- Also useful in GORD
- Dopamine inhibitory in enteric NS (inhibits ACh)
- *Metoclopramide* is a D2 receptor antagonist
- Adverse effects; parkinsonism, extrapyramidal effects, Hyperprolactinemia
- *Erythromycin* and *domperidone* also have hypermobility effects on enteric NS

ANTIEMETICS

- D2 receptor antagonists
- 5HT3 antagonists (*Ondansetron, Granisetron*)
- H1 blockers
- Antimuscurinic (*Scopolamine*)
- Corticosteroids (*dexamethasone*)
- Cannabinoid Receptor agonists

LAXATIVES

- Bulk forming; *psyllium*
- Softening; *docusate, glycerine, mineral oil*
- Osmotic; *MgO, Sorbitol, lactulose, polyethylene glycol*
- Stimulant: *Aloe, senna, cascara, castor oil*
- 5HT4 receptor agonist; *tegaserod*