CHOLINERGIC & PARASYMPATHOMIMETIC AGENTS

• cholinergic and parasympathomimetic agents can be divided into three groups,

1. Choline esters   - carbachol, methacholine

2. Alkaloids   - pilocarpine, muscarine, arecoline

3. Anticholinesterases   - neostigmine, pyridostigmine

The Parasympathetic Nervous System

• *acetylcholine* (ACh) serves as the synaptic transmitter at,

a. all autonomic ganglia, SNS & PNS

b. postganglionic parasympathetic nerve endings

c. postganglionic SNS endings to eccrine sweat glands

d. neuromuscular junction

e. central nervous system

• ACh also has a direct *vasodilator* action on arterioles, despite the absence of PNS innervation
• *choline acetyl transferase* cataylses the formation of ACh from *choline* and *acetyl-CoA*
• the later is synthesised in the nerve terminal & choline taken up by active transport from the ECF
• within the nerve, ACh is stored in synaptic vesicles, which are released as discrete *"quanta"* in response to depolarisation of the nerve terminal and an increased influx of Ca^{++}
• there are a number of different ACh receptors throughout the body,

a. nicotinic   - autonomic ganglia & adrenal medulla
                 - neuromuscular junction

b. muscarinic - autonomic effector cells

• *muscarinic receptors* have been further subdivided into,

1. M_1-receptors
   • which appear to be localised to the CNS and perhaps the PNS ganglia
   • *pirenzipine*, still under investigation, is selective at M_1 receptors

2. M_2-receptors
   • which are the non-neuronal receptors of smooth muscle, cardiac muscle, and glandular epithelium
   • *bethanecol* appears to be a selective agonist at M_2 receptors

• the cellular events associated with receptor activation remain uncertain, but may involve,

    a.   accumulation of cGMP

    b.   increased permeability to monovalent ions

    c.   hydrolysis of phosphatidylinositol

    d.   mobilization of, or increases in the intracellular $[Ca^{++}]$

    e.   inhibition of adenylate cyclase $\rightarrow$ cAMP

• rapid hydrolysis of ACh at the synaptic cleft by *acetylcholinesterase* (AChE) inactivates the enzyme
• this enzyme is distinct from butyrocholinesterase BChE found in the plasma

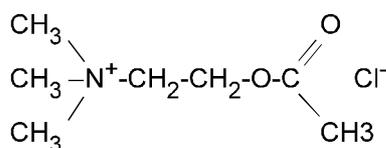| Physiological Responses to Cholinergic Stimulation	
Tissue	**Response**
Eye	
Sphincter muscle (iris)	contraction - miosis
Ciliary muscle	contraction - near vision
Heart	
SA node	decrease in HR
Atria	decrease in contractility
AV node	decrease in conduction ± block
Ventricle	± decrease in contractility
Lung	
Bronchial smooth muscle	constriction
Bronchial glands	increased secretion
Stomach	
Gastric smooth	increased motility & tone
Sphincters	relaxation
Gastric glands	increased secretion
Intestines	
Intestinal smooth	increased motility & tone
Sphincters	relaxation
Intestinal glands	increased secretion
Bladder	
Detrusor	contraction
Trigone & internal sphincter	relaxation
Adrenal Medulla	increased secretion NA & A
Exocrine glands	
Pancreas	increased secretion
Salivary	increased secretion
Lacrimal	increased secretion
Pharyngeal	increased secretion
Sweat Glands	increased secretion
Sexual organs	erection (male)

CHOLINE ESTERS

• ACh has had virtually no clinical application due to its rapid hydrolysis at the synaptic cleft by AChE and in the plasma by BChE
• consequently numerous derivatives have been synthesised in attempts to provide drugs with longer durations of action and more specific effects
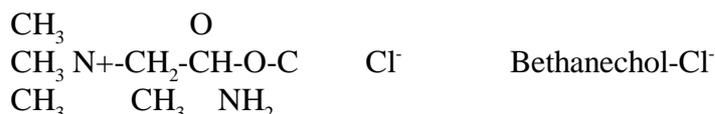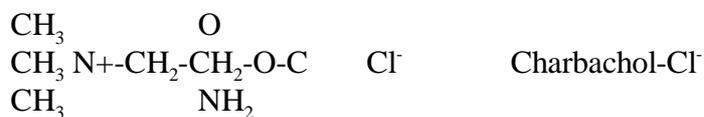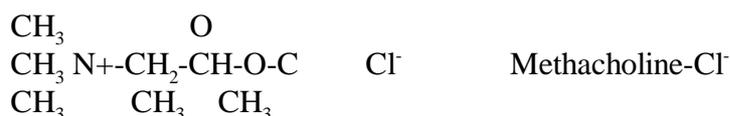
■ *History*

• ACh was first synthesised by Baeyer in 1867; and of the several hundred choline derivatives, only bethanechol, carbachol & methacholine have been of any real use
• *methacholine* is the β-methyl derivative of ACh
• first synthesised in 1911, however it was not until the 1930's it received adequate clinical trial
• *carbachol*, the carbamyl-ester of choline, and *bethanechol*, its β-methyl derivative, were both synthesised in the early 1930's

■ *Structure Activity Relationship*

• ACh is the acetyl ester of choline, and is a quaternary ammonium compound which possesses a cationic (positively charged) head joined by a two carbon chain to an ester grouping
• the chemical structures of the important choline esters are given below,

$$CH_3-N^+-CH_2-CH_2-O-C \overset{O}{\underset{CH3}{=}} \quad Cl^-$$

Acetylcholine Chloride

$$CH_3 \ N^+-CH_2-CH-O-C \quad Cl^- \qquad \text{Methacholine-}Cl^-$$

$$CH_3 \ N^+-CH_2-CH_2-O-C \quad Cl^- \qquad \text{Charbachol-}Cl^-$$

$$CH_3 \ N^+-CH_2-CH-O-C \quad Cl^- \qquad \text{Bethanechol-}Cl^-$$

• these may differ from ACh in any of three ways,

1.   relative muscarinic activity

2.   relative nicotinic activity

3.   resistance to enzymatic hydrolysis

• the degree of muscarinic activity decreases if the acetyl group is replaced; however, some substitutions result in resistance to hydrolysis

• carbachol, where the acetyl group is replaced by a carbamyl, has both muscarinic & nicotinic properties, but is almost entirely resistant to hydrolysis by AChE or BuChE

• bethanechol is similarly resistant to hydrolysis; however, it possesses mainly muscarinic activity, as does methacholine, due to the β-methyl substitution

• although both carbechol & bethanechol possess muscarinic activity, their effects on the heart are minimal and their GIT & GUS effects predominate

• methacholine, conversely, has its effects predominantly on the heart; it is hydrolysed by AChE, but only at ~ 1/3 the rate of ACh and it is resistant to BChE

Pharmacological Properties of the Choline Esters [1]							
	AChE [2]	Muscarinic Effects					Nico-tinic
		CVS	GIT	GUS	Eye [3]	Atropine [4]	
Acetylcholine	+++	++	++	++	+	+++	++
Methacholine	+	+++	++	++	+	+++	+
Carbachol	-	+	+++	+++	++	+	+++
Bethanechol	-	±	+++	+++	++	+++	-

[1]   Goodman & Gilman 7th Ed.

[2]   susceptibility to hydrolysis by cholinesterases

[3]   eye effects are topical

[4]   antagonism by atropine

Cardiovascular System

• ACh has three primary effects upon the heart,

    1.   vasodilation ~ all beds, including pulmonary & coronary

    2.   negative chronotropic effect

    3.   negative inotropic effect

• the later is of lesser significance in ventricular than atrial muscle
• these can be obscured by the ACh mediated release of catecholamines and from dampening by the baroreceptor reflex
• although ACh is rarely given systemically, its cardiac effects are important because of the vagal involvement in the action of the cardiac glycosides and antidysrhythmics
• small doses cause a fall in BP & a reflex tachycardia; considerably larger doses are required to produce bradycardia by a direct action on the heart
• if atropine is given prior to this blocking the muscarinic effects, then a rise in BP is seen due to sympathoadrenal activation and ganglionic stimulation
• the dilation of vascular beds is due to the presence of muscarinic receptors, despite the apparent lack of parasympathetic innervation
• further, these receptors appear to be in the ***endothelium***; which, when stimulated releases some factor, (***endothelium derived relaxing factor***), which diffuses through the smooth muscle in the media and causes relaxation
• ACh has actions on all types of specialised cardiac cells, as does the vagus
• parasympathetic fibres being distributed extensively to the SA & AV nodes and the atria
• with minimal innervation of the ventricles, these fibres ending predominantly on cells of the His-Purkinje system
• in the ***SA node*** ACh decreases spontaneous depolarisation, by reducing the rate of phase 4 depolarisation and hyperpolarising the resting cell membrane
• in ***atrial muscle***, ACh slows conduction, however also reduces the AP duration and the effective refractory period, therefore exacerbating atrial flutter or fibrillation from an ectopic foci
• conversely, in the ***AV node*** and the Purkinje system, ACh slows conduction, but increases the AP duration and the effective refractory period
• the increased vagal tone, as seen with the cardiac glycosides, and the increased refractory period can contribute to the reduction in transmission of aberrant impulses from the atria
• ACh also has a (-)'ve inotropic effect, whether applied directly or by vagal stimulation
• however this effect is smaller than that observed in the atrium and is more pronounced when contractility is enhanced by adrenergic stimulation
• automaticity is decreased and the threshold for VF is increased
• SNS & PNS nerve terminals lie in close proximity and M-receptors are believed to be both post- & pre-synaptic
• ACh's ability to modulate the heart is due both to its ability to modulate the hearts response to NA and, also, its ability to inhibit the release of NA
• the effects produced by ***methacholine*** (MCh) are identical to those produced by ACh, however the effective dose is only ~ 0.5%
• the CVS effects of carbachol & bethanechol are less significant following the usual s.c. or oral doses; these consist of a small fall in diastolic BP and a mild reflex tachycardia

Gastrointestinal System

• all agents in this class are capable of producing increased GIT tone & motility and increasing secretion; however, decrease the tone of sphincters
• this may be accompanied by abdominal cramps, N&V

Urinary Tract

• carbachol & bethanechol, compared to the other two agents, stimulate somewhat selectively the urinary tract; resulting in increased ureteric peristalsis, detrusor contraction, and relaxation of the trigone and internal sphincter

■ *Other Systems*

• in the respiratory tract these agents increase tracheobronchial secretions, bronchial tone and stimulate the carotid sinus and aortic body chemoreceptors
• in the eye they produce miosis, though, the ensuing fall in intraocular pressure may be preceded by a transient rise due to vasodilation & increased permeability of the vessels of the blood-aqueous humor barrier
• the effects at ganglia and the NMJ of skeletal muscle are generally insignificant at therapeutic concentrations

Synergisms & Antagonisms

• ACh & MCh are hydrolysed by cholinesterases, therefore the concurrent administration of anti-AChE agents will significantly enhance the effects of these agents
• when administered prior to carbachol & bethanechol, antiAChE agents produce only additive effects
• the muscarinic effects of these agents are competitively blocked by atropine
• adrenaline and other sympethomimetic amines antagonise many of the muscarinic effects of these agents
• the nicotinic actions at autonomic ganglia are blocked by hexamethonium and their actions at the NMJ are antagonised by dTC and its analogues

Therapeutic Uses

• ACh is used practically exclusively as an intraocular solution
• carbachol, similarly may be used intraocularly, though, it is also used as a topical ophthalmic solution
• MCh is rarely if ever used (not marketed in Aust.)
• bethanechol is used both in tablet and injection form, as a urinary tract & GIT stimulant, where there is no evidence of organic obstruction
• injectable forms are always s.c., not i.m. for obvious reasons
• the major contraindication to the use of these agents are;

a.	asthma	- bronchoconstriction
b.	ischaemic heart disease	- hypotension & lowered CBF
c.	hyperthyroidism	- may produce AF
d.	peptic ulcer	- gastric secretion increased

CHOLINE ALKALOIDS & SYNTHETIC ANALOGUES

• the three naturally occurring cholinomimetic alkaloids are,

1.	arecholine	- muscarinic & nicotinic actions
2.	muscarine	- almost exclusively muscarine receptors
3.	pilocarpine	- dominant muscarinic actions*

• only the later is in widespread clinical use and although the actions are primarily muscarinic it causes anomalous CVS responses
• pilocarpine is the chief constituent of the leaves of the Pilocarpus shrubs of South America
• its use today is limited to topical *miosis* for the treatment of glaucoma and the reversal of mydriasis

THE ANTICHOLINESTERASES

Cholinesterases

• there are two enzymes found in man capable of hydrolysing esters of *choline*
• **AChE** is found in the region of cholinergic nerve fibres and in rbc's; it is *not* found in plasma
• **BuChE** is synthesised in the *liver* and is found in the liver, plasma, kidney, and the intestine
• the physiological action of BuChE is unknown, however it is responsible for the hydrolysis of succinylcholine and the ester local anaesthetics

Acetylcholinesterase

• exists in two classes of molecular forms,

> 1. simple *oligomers* of a 70,000 MW catalytic subunit, and
>
> 2. elongated form of complex molecular structures

• the former contain a hydrophobic surface and are often found in association with the plasma membrane
• the elongated forms consist of *tetramers*, linked by a number of disulphide bonds to a filamentous structure; the MW of these forms $\sim 10^6$
• these forms are localised in the outer basal lamina of the synaptic cleft (basement membrane); and are primarily found in the NMJ
• the active centre of the enzyme consists of an *anionic subsite*, which attracts the quaternary ammonium group, and an *esteratic subsite*, where nucleophillic attack occurs on the acyl-carbon of the substrate
• the catalytic mechanism resembles other *serine esterases* in the body, and the active site probably consists of serine, with its hydroxyl group activated by an adjacent imidazole group, probably from histidine
• the products of hydrolysis are,

> 1. choline
>
> 2. acetic acid, and
>
> 3. regenerated enzyme

• AChE is one of the most efficient enzymes in the body and has the capacity to hydrolyze $\sim 3 \times 10^5$ molecules/enzyme/min

> $\rightarrow$ equivalent to a turnover of 150 μsec

Mechanism of Action of AChE Inhibitors

· (see G&G, fig. 6-1)
· quaternary compounds inhibit the enzyme reversibly by either binding with the ***esteratic site***, or with a site spatially removed, termed the ***peripheral anionic site***
· ***edrophonium*** binds reversibly and selectively to the active centre; this reversible binding and its rapid renal elimination result in its short duration of action

· ***physostigmine*** & ***neostigmine***, possessing a carbamyl-ester linkage are hydrolysed by AChE, but at a much slower rate
· both of these agents exist as cations at physiological pH, thus enhancing their association with the active site
· the quaternary nitrogen of neostigmine, while not essential for anti-AChE activity, confers increased potency
· physostigmine, existing in equilibrium with the nonionic species has access to the CNS
· the alcohol moiety is cleaved, giving rise to the carbamylated enzyme
· this is far more stable than the acetylated enzyme and the dissociation $t_{\frac{1}{2}\beta}$ for the dimethylcarbamyl-enzyme is 15-30 minutes
· the *in vivo* duration of inhibition of the enzyme is 3-4 hours

· ***organophosphates***, such as DFP, serve as true hemisubstrates, the resultant phosphorylated enzyme being extremely stable
· these compounds act at the esteratic site, the tetrahedral geometry of the organophosphates resembling the transition state for the acetyl-ester hydrolysis
· stability of these complexes is enhanced by *"aging"*, in which one of the phosphonate alkyl groups is lost
· with many of these agents, significant regeneration of the enzyme is not observed and synthesis of new enzyme is required
· also termed acid transferring inhibitors, in contrast to the reversible, competitive inhibitors such as edrophonium

> ***NB:*** the mechanism of action of ACh, the carbamyl esters and the organophosphates is essentially identical, only ***regeneration*** of the active enzyme differs

INDIVIDUAL ANTICHOLINESTERASE DRUGS

• the pharmacological effects of the anti-AChE agents are the result of the following actions;

    a.   stimulation of muscarinic receptors at autonomic effector organs

    b.   stimulation, followed by paralysis, of all autonomic ganglia and skeletal muscle (nicotinic actions)

    c.   stimulation, with occasional subsequent depression, of cholinergic receptor sites in the CNS (mainly muscarinic)

• however, with the smaller doses used clinically, there are several modifying factors
• the response of effector organs also depends on;

    a.   whether the organ receives impulses tonically or phasically

    b.   the presence of a quaternary nitrogen group and lipid solubility $\rightarrow$ distribution

Neostigmine

• neostigmine is a ***carbamyl-ester***, acid transferring cholinesterase inhibitor and inhibits both AChE & BuChE
• it contains a quaternary ammonium group, does not significantly cross the BBB and is poorly absorbed from the GIT
• it is rapidly eliminated from the plasma after IV administration, with a $t_{\alpha\frac{1}{2}}$ ~ 1 - 3.5 min
• the elimination half life varies considerably, $t_{\beta\frac{1}{2}}$ ~ 15 - 80 min
• renal function has a marked effect upon elimination; the $t_{\beta\frac{1}{2}}$ is increased to 180 minutes and the clearance decreased from 16 ml/kg/min to 8 ml/kg/min in anephric patients
• this may be advantageous; prolonged NMJ blokckade may occur with dTC and pancuronium in the presence of renal impairment, however, the concurrent delayed excretion of neostigmine may prevent recurarization
• effects are demonstrable 2 mins after IV administration and reach a maximum after 7-15 mins
• the NMJ blocking effects of succinylcholine are significantly prolonged by neostigmine due to inhibition of BuChE

■ ***Cardiovascular System***

• effects depend upon the relative degree of nicotinic & muscarinic stimulation
• peripheral accumulation of ACh may $\rightarrow$ profound bradycardia and, in addition, vasodilation and hypotension may occur
• cardiac dysrhythmias & arrest have been reported following the administration of neostigmine/atropine at the completion of anaesthesia
• occasionally, when muscarinic effects are blocked by atropine, nicotinic stimulation may $\rightarrow$ increased HR & BP

■ ***Respiratory***

• bronchoconstriction, increased oropharyngeal & tracheobronchial secretions may occur

■ *Neuromuscular Junction*

• by inhibiting AChE, allows ACh to accumulate at the NMJ, which, by mass action competes with the competitive blocking agents
• reversal of competitive NMJ blockade is limited as, once the enzyme is fully inhibited, increased doses of neostigmine will not increase the [ACh] at the NMJ any further
• very large doses of neostigmine may, either by a direct effect, or by allowing excessive ACh to accumulate at the NMJ, produce NMJ blockade
• this is rarely seen except,

    a.   following subclinical organophosphorus poisoning

    b.   as a "cholinergic crisis" in patients with myasthenia gravis who have received excessive anti-AChE therapy

• in general, at clinical doses, neostigmine intensifies the block produced by succinylcholine (SCh), but antagonises a competitive blocker
• however, when repeated doses of SCh are given such that phase II block is attained, neostigmine antagonises the blockade

■ *Gastrointestinal System*

• increases gastric contractility & secretions
• increases intestinal tone & peristalsis

Dosage & Administration

• available as 15 mg tablets & solutions of 0.25, 0.5 and 1.0 mg/ml
• atropine or another muscarinic antagonist should always be given in conjunction with neostigmine to prevent adverse CVS effects
• usual adult dose for the reversal of neuromuscular blockade at the end of anaesthesia ~ 2.5 - 3.0 mg neostigmine / 1.2 mg atropine

    NB: recommended doses: adult ~ 0.04 - 0.045   mg/kg
                                        child ~ 0.05 - 0.07   mg/kg

• adult doses ≥ 5.0 mg are unlikely to be beneficial and may be harmful
• usual response to administration of combined reversal is a *biphasic response*
    →   an initial tachycardia produced by the atropine, followed by bradycardia
• the vagolytic effects of atropine generally precede the muscarinic effects of neostigmine by 1-2 mins; and the peak muscarinic effects are not usually seen until 7-11 mins
• the duration of action of neostigmine is ~ 40-60 mins

■ *Toxicity & Precautions*

• atropine must always be given when the drug is administered parenterally
• should be used cautiously in patients with IHD or asthma

Pyridostigmine

• is a pyridine analogue of neostigmine, which is also used for the reversal of NMJ blockade and may posses a number of advantages over neostigmine,

    a.   less bradycardia

    b.   less hypersecretion

    c.   a longer duration of action

    d.   a lower incidence of dysrhythmias   (Katz & Katz)

• the initial tachycardia, when given with atropine, is higher than with neostigmine, possibly due to the slower onset of action of pyridostigmine
• peak antagonist effects are seen at ~ 12-17 mins, and the duration of action is ~ 60-80 mins
• the volume of distribution, V_{dSS} **~ 0.35 ml/kg**
• the distribution half life is rapid, $t_{\frac{1}{2}b}$ **~ 6-8 mins**
• studies have suggested that the combination of pyridostigmine plus *glycopyrrolate*, a synthetic quaternary ammonium anticholinergic agent, may possess advantages over the use with atropine, producing a closer "mirror image" of the cholinergic effects due to its slower onset of action

■ *Dosage & Administration*

• may be given orally (also SR preparations), IM, or IV
• is a standard anti-AChE drug in the R_X of myasthenia gravis
• standard NMJ blockade reversal dose being 10-15 mg in the adult; as for neostigmine, atropine or glycopyrrolate should always be administered concurrently when given IV
• when rapid reversal is required with this agent, edrophonium may be added for rapid, short duration reversal

Edrophonium

• as stated above, this agent is an anti-AChE agent with a rapid onset but short duration of action due to freely *reversible* binding with AChE
• glycopyrrolate displays weak muscarinic effects and has been used in the investigation of *myasthenia gravis*, the differentiation of cholinergic & myasthenic crises, and to assess the residual NMJ blockade at the end of anaesthesia
• use in the evaluation of myasthenia gravis is aided by a direct agonist action at the NMJ; this is seen with neostigmine and other quaternary ammonium compounds, in addition to their anti-AChE actions

■ *Dosage & Administration*

• may be used to detect the type of NMJ blockade in patients with prolonged apnoea following the use of NMJ blocking agents; 10-20 mg administered IV, preceded by atropine,

      a.   competitive blockade →   improvement of muscle function

      b.   depolarising blockade →   no change or worsening

• in the diagnosis of **myasthenia gravis**, 2 mg is given IV, followed by 8 mg in 1 min if there is no improvement in muscular function
• this is also used to distinguish,

      1.   myasthenic crisis   →   improvement

      2.   anti-AChE overdosage, "cholinergic crisis" →   no change

      NB: however the dosage is only 1mg & 1mg

PHYSOSTIGMINE

• physostigmine, a **tertiary amine**, is an alkaloid obtained from the calabar bean of West Africa
• the drug is well absorbed from the GIT & mucous membranes, and it exists in equilibrium at physiological pH, the nonionic species diffusing across the BBB
• it has a prominent muscarinic activity and has greater effects on the CVS and CNS than neostigmine or pyridostigmine
• it is hydrolysed in the plasma at the ester linkage by BuChE, and usually eliminted within 2 hours of administration
• it is used in the R_X of glaucoma, atropine intoxication and overdosage with the tricyclic antidepressants
• the concomitant use of a quaternary anticholinergic agent to prevent the peripheral muscarinic effects of the drug is recommended

Echothiopate

• is a long acting anti-AChE drug that is used in the R_X of glaucoma
• SucCh should be avoided in patient receiving this agent as they have impaired hydrolysis and prolonged apnoea may result

4-Aminopyridine

• this is **not** an AChE inhibitor, however has been suggested for the reversal of NMJ blockade
• increases both spontaneous and evoked release of ACh from the presynaptic terminal, thereby increasing the force of muscle contraction
• also, it has been shown to antagonise the neuromuscular blocking action of many of the antibiotics and to be relatively free of muscarinic actions
• 4-aminopyridine potentiates the the antagonistic actions of neostigmine and pyridostigmine

      NB: major side effects are restlessness and agitation due to actions in the CNS
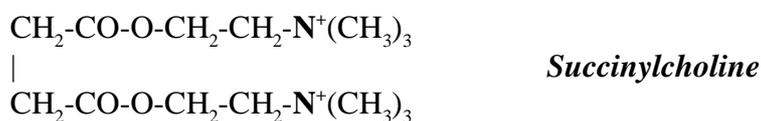
ORGANOPHOSPHORUS INHIBITORS

• organic esters of phosphoric acid were first shown to inhibit AChE in 1937 and were subsequently used as insecticides in agriculture, and as "nerve gases" during WW2
• more important from a toxicological sense
• form relatively *irreversible* complexes with the enzyme and regeneration is in terms of weeks to months
• accidental or suicidal intoxication may lead to,

  a. central nervous system effects

  b. neuromuscular and respiratory paralysis

  c. bronchorrhoea, bronchospasm & pulmonary oedema

  d. bradycardia, circulatory collapse, and depressed cardiac function

• the usual cause of death is respiratory depression and secondary circulatory failure
• immediate treatment is with atropine and RS/CVS support
• the stability of the phosphorylated enzyme increases with "aging"
• the administration of *pyridine-2-aldoxime methyl chloride* 2-PAM, prior to aging can result in regeneration of the enzyme and is the treatment of choice
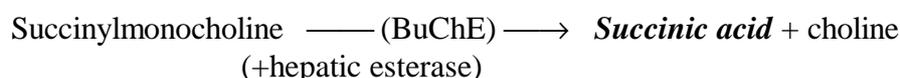
  NB: oximes are ineffective, and are in fact contraindicated in overdosage with neostigmine, physostigmine, or the *carbamyl-esters*

Butyrylcholinesterase

• synthesised in the *liver* and found in the plasma but not the RBCs
• present in many other tissues, including brain, kidney, intestine and pancreas
• the physiological function of the enzyme is unknown, however it is pharmacologically important as it hydrolyses succinylcholine and a number of the ester local anaesthetics
• succinylcholine is the dicholine ester of succinic acid, and is essentially 2 ACh molecules joined through their acetate groups, viz.

$$CH_3\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_2\text{-}N^+(CH_3)_3 \qquad \textit{Acetylcholine}$$

$$CH_2\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_2\text{-}N^+(CH_3)_3$$
$$|\qquad\qquad\qquad\qquad\qquad\qquad \textit{Succinylcholine}$$
$$CH_2\text{-}CO\text{-}O\text{-}CH_2\text{-}CH_2\text{-}N^+(CH_3)_3$$

• the short duration of action of SCh is due to rapid hydrolysis by BuChE
• hydrolysis occurs in 2 steps, the second being less rapid and the intermediate* possessing only weak NMJ blocking activity

  SCh ——— (BuChE) ⟶ *Succinylmonocholine** + choline

  Succinylmonocholine ——— (BuChE) ⟶ *Succinic acid* + choline
                 (+hepatic esterase)

• plasma BuChE activity may be abnormal due to an,

    a.   acquired enzyme defect

    b.   inherited enzyme defect

■ ***Acquired Enzyme Deficiency***

• plasma BuChE levels are ***reduced*** in the following conditions,

    a.   the newborn, reaching adult levels by 2-6 months

    b.   patients with acute or chronic liver diseases

    c.   pregnancy

    d.   collagen diseases

    e.   chronic anaemia

    f.   uraemia

    g.   malnutrition

    h.   myxedema

    i.   other chronic debilitating diseases

    j.   severe burns

    k.   chronic pesticide exposure & accidental poisoning

    l.   echothiopate eyedrops

    m.   drugs

        i.   MAO inhibitors

        ii.   trimethaphan

        iii.   cytotoxic drugs   - azathioprine

        iv.   echothiopate eye drops

        v.   hexafluorenium bromide

        vi.   tetrahydroaminocrine

        vii.   quinidine

        viii.   propanidid

        ix.   OCP

        x.   chlorpromazine

        xi.   pancuronium, neostigmine

• ***increased*** levels are associated with ***obesity*** & ***toxic goitre***

    NB: a large study by Viby-Mogensen confirmed that blockade from the usual dose of succinylcholine is only ***modestly increased*** by low plasma cholinesterase activity

■ *Inherited Enzyme Defect*

• plasma cholinesterase is coded for by two allelomorphic genes on an *autosomal* chromosome
• four variants are described,

    1.   normal gene   **N**

    2.   dibucaine resistant gene   **D**

    3.   fluoride resistant gene   **F**

    4.   silent gene   **S**

• the most frequent atypical form, the dibucaine resistant gene, has a far lower affinity for succinylcholine at normal serum concentrations
• the population *prevalence* for the D-gene is *~ 1:53*   (? reference, doesn't support below)
• the usual laboratory estimates of plasma cholinesterase do not differentiate between the varieties

• Kalow & Genest found that the local anaesthetic *dibucaine* inhibits normal plasma cholinesterase to a far greater extent than the atypical enzyme

    Def'n: dibucaine number, the *percentage inhibition* of plasma cholinesterase
            produced by a standard titre of dibucaine $= 10^{-5}$ mmol/l

• if abnormalities are found, the entire family should be tested
• another cholinesterase variant has been found, the electrophoretic **C_5-*band*** enzyme, which shows *increased* plasma cholinesterase activity
• patients possessing the *silent gene* are extremely sensitive to succinylcholine

Genoptype	SCh Sensitivity	DN[1]	FN[2]	Incidence (%)
NN	normal	~ 80	~ 60	94 (96.2)[3]
ND	mildly increased	~ 50	~ 40	4 (3.8)
DD	greatly increased	~ 20	~ 20	0.036
NF	mildly increased	~ 80	~ 40	0.5
NS	normal	~ 80	~ 60	0.5
DF	greatly increased	~ 50	~ 40	0.02
DS	greatly increased	~ 20	~ 20	0.02
FF	greatly increased	~ 60	~ 20	0.0025
FS	greatly increased	~ 60	~ 20	0.0025
SS	greatly increased	~ 0	~ 0	0.0025

[1]   DN = % inhibition of plasma cholinesterase by dibucaine 10^5 mmol/l

[2]   FN = % inhibition of plasma cholinesterase by fluoride 5 x 10^{-5} mmol/l

[3]   frequencies from Wood & Wood

ANTIMUSCARINIC AGENTS
& ANAESTHETIC PREMEDICATION

• acetylcholine (ACh) serves as the synaptic transmitter at,

    a.   all autonomic ganglia, SNS & PNS

    b.   postganglionic parasympathetic nerve endings

    c.   postganglionic SNS endings to eccrine sweat glands

    d.   neuromuscular junction

    e.   central nervous system

• ACh also has a direct vasodilator action on arterioles, despite the absence of PNS innervation
• there are a number of different ACh receptors throughout the body,

    a.   nicotinic   - autonomic ganglia & adrenal medulla

    b.   muscarinic   - autonomic effector cells

        i. M_1 - receptors
            • which appear to be localised to the CNS and perhaps the PNS ganglia

        ii. M_2 - receptors
            • which are the non-neuronal receptors of smooth muscle, cardiac muscle, and glandular epithelium

• muscarinic receptors may exist in the absence of cholinergic innervation; e.g., blood vessels, the placenta and ventricular myocardium

Anticholinergic Drugs

• may therefore be divided into three groups,

    1.   Antimuscarinic drugs   - atropine, scopolamine

    2.   Ganglionic blocking drugs

    3.   Neuromuscular blocking drugs

• atropine and other antimuscarinic agents have little effect at nicotinic receptors, autonomic ganglia and the NMJ
• within the CNS, cholinergic neurons have predominantly either nicotinic (spinal cord), or muscarinic (thalamus & cortex) receptors

Physiological Responses to Muscarinic Blockade	
Tissue	**Response**
Eye	
Sphincter muscle (iris)	dilation - mydriasis[1]
Ciliary muscle	relaxation - distant vision
Heart	
SA node	increase in HR
Atria	increase in contractility
AV node	increase in conduction $\pm$ block
Ventricle	$\pm$ increase in contractility
Lung	
Bronchial smooth muscle	dilation
Bronchial glands	decreased secretion
Stomach	
Gastric smooth	decreased motility & tone
Sphincters	contraction
Gastric glands	decreased secretion
Intestines	
Intestinal smooth	decreased motility & tone
Sphincters	contraction
Intestinal glands	decreased secretion
Bladder	
Detrusor	relaxation
Trigone & internal sphincter	contraction
Adrenal Medulla	decreased secretion NA & A
Exocrine glands	
Pancreas	decreased secretion
Salivary	decreased secretion
Lacrimal	decreased secretion
Pharyngeal	decreased secretion
Sweat Glands	decreased secretion

[1] mydriasis is associated with elevated intraocular pressure

Structure Activity Relationship

• the belladonna alkaloids are widely distributed in nature, especially in the *Solanaceae* plants
• the deadly nightshade, *Atropa belladonna*, yields mainly **atropine**, which is also found in *Datura stramonium*, or the Jamestown weed
• the alkaloid **scapolamine** is found mainly in *Hyoscyamus niger*, henbane and *Scopolia carniolica*

• these alkaloids are organic esters, formed by the combination of an aromatic acid, **tropic acid**, and complex organic bases, either tropine, or scopine
• the synthetic alkaloids contain **mandelic acid**, rather than tropic acid
• scopine differs from tropine by having an oxygen bridging C_6 & C_7 of the organic ring
• each of these tertiary amines can be modified to the quaternary form by the addition of a second methyl group to the basic nitrogen

• the intact ester of tropic acid & tropine is essential for the action of atropine, as neither the free acid, nor the base exhibits significant antimuscarinic activity
• the presence of a free -OH group in the acid portion of the ester is also important
• substitution of other aromatic acids for tropic acid modifies but does not necessarily abolish antimuscarinic activity

• when given parenterally, the quaternary ammonium derivatives of atropine & scopolamine are, in general, more potent in both muscarinic and nicotinic actions; but are less potent in the CNS due to exclusion by the BBB
• given orally they are poorly and unreliably absorbed

• the presence of an asymmetrical carbon atom in the acid portion of the ester conveys optical activity to these compounds
• scopolamine is l-hyoscine and is far more potent than the d-isomer
• atropine is a racaemic mixture of d & l-hyoscyamine but the antimuscarinic activity is almost entirely due to the l-isomer

• antimuscarinic agents are competitive antagonists of ACh and other muscarinic agonists; most data supports binding for identical sites on the M-receptor
• antagonism can therefore be overcome by sufficiently high concentrations of agonist agents
• the effects of cholinergic neural activity are less readily blocked than parenteral administration of agonist agents; probably due to the local high [ACh] at the synaptic cleft and possibly some limitation to diffusion into the synaptic region
• studies (1978) of the effects of vagal stimulation, atropine, and a number of different muscarinic agonists on the tone of the lower oesophageal sphincter led to the classification of M_1 & M_2 receptors
• at the same time, studies on cortical membranes showed two sub-populations of binding sites, with different affinities for muscarinic agonists
• relative large numbers of binding sites, with high affinity for **pirenzipine** (M_1-receptors), are present in the cerebral cortex, corpus striatum, hippocampus and probably autonomic ganglia
• the low pirenzipine affinity, (M_2-receptor), predominates in the heart, cerebellum, and GIT smooth muscle
• it is hypothesised that the M_2-receptor is linked to adenylate cyclase; activation inhibiting the activity of this enzyme

• the M_2-receptor may also exist on adrenergic and cholinergic nerve terminals; activation inhibiting the release of neurotransmitter

• as for other receptors linked to adenylate cyclase, its action appears to be mediated by a membrane bound G-protein, inferred by the pronounced effect of GTP on the binding of agonists

• the M_1-receptor appears to be involved in the regulation of Ca^{++} fluxes and the generation of phosphorylated derivatives if inositol

Atropine

· is the ester of the organic base ***tropine*** and ***tropic acid***
· it is a nonselective competitive antagonist of M_1 & M_2 receptors, with negligible effects, in clinical doses, at nicotinic receptors

■ ***Central Nervous System***

· atropine is a tertiary amine and, therefore, freely enters the CNS
· high doses of atropine stimulate and then depress the medulla and higher cerebral centres
· the rate and occasionally the depth of respiration are increased; however this may represent a response to bronchodilation and the increase in physiological dead space
· even moderate doses may depress the motor tone coordinating centres, as is seen with the effects in the R_X of the tremor and rigidity of Parkinson's disease
· usual clinical doses cause only transient central vagal stimulation, with subsequent bradycardia, however this is generally counteracted by the peripheral action on the heart
· toxic doses lead to excitement with restlessness, tremor, irritability, delirium, hallucinations and hyperthermia → ***central anticholinergic syndrome***

■ ***Cardiovascular System***

· small doses of atropine (0.2-0.3 mg) → a transient fall in HR due the central effect, however this is soon overcome by peripheral blockade
· larger doses cause a tachycardia due to vagal blockade at the SA & AV nodes; though, these effects are less in the elderly, in whom vagal tone is low
· often causes dysrhythmias, however these are seldom serious; atrial arrhythmias (mainly children) & A-V dissociation (mainly adults) may occur
· usual therapeutic doses have little effect upon blood pressure; larger doses (> 2 mg) may lead to a reduction in BP due to a reduced CO, secondary to a reduction in diastolic filling
· atropine is capable of blocking the peripheral vasodilation cause by ACh or the other choline esters; however, administered alone at usual doses it has little effect

■ ***Respiratory System***

· inhibits secretions in the mouth, pharynx, trachea, & bronchi
· relaxes bronchial smooth muscle,

> → increased anatomical & physiological dead space
> decrease airways resistance

· this bronchodilation is most evident with ACh/cholinomimetic induced bronchoconstriction
· however, it is also moderately effective in histamine-induced asthma
· also, atropine is a more potent bronchodilator than scopolamine
· both atropine & scopolamine reduce the incidence of laryngospasm due to their effect on secretions

■ *Gastrointestinal System*

• atropine can completely abolish the effects ACh on the gut, but inhibits only partially the effects of vagal stimulation; this is particularly evident for motility
• the cause for this is unknown but suggests the involvement of GIT hormone or neurotransmitters other than ACh
• atropine almost completely abolishes salivary secretion and talking and swallowing become difficult
• gastric secretion is reduced in volume but may, or may not be reduced in acid content
• both are reduce in animals, and this effect is only seen in man at doses (> 1 mg) which cause significant effects in other systems
• full doses of atropine diminish and may completely abolish the fasting secretion of acid, though, this is less prominent in ulcer patients
• histamine, caffeine, and alcohol induced acid secretion is reduced but not abolished in man
• atropine also reduces the secretion of mucin & enzymes from the gastric cells which are also under vagal control

• regarding motility; CNS derived vagal influences only modify the effects of intrinsic reflexes in the gut wall
• the terminal neurons of the intramural plexuses are cholinergic and are blocked by atropine; however, atropine independent movements of the gut are observed
• therapeutic doses inhibit GIT tone and the amplitude & frequency of peristalsic contractions
• in moderate doses, stimulation by histamine & vassopressin, are unaltered; these do not act at ACh receptors
• in contrast, stimulants such as nicotine & 5HT, acting through the myenteric plexus are inhibited
• atropine & hyoscine possess antiemetic action, hyoscine being more potent
• atropine, however, reduces the tone of the lower oesophageal sphincter, thereby increasing the risk of passive regurgitation

■ *The Eye*

• the *constrictor pupillae* muscle, supplied by PNS fibres from the 3rd cranial nerve is blocked by atropine → *mydriasis*, due to the unopposed influence of SNS dilator tone
• the oculomotor nerve also supplies the *ciliary muscle* of the lens, atropine leading to paralysis of accommodation, *cycloplegia* → loss of *near vision*
• the usual premedicant dose of atropine has little occular effect, c.f. hyoscine which causes marked mydriasis and loss of accommodation
• this leads, through narrowing of the irido-corneal angle, to an elevation of *intraocular pressure*; therefore these agents are contraindicated in narrow angle *glaucoma*
• locally applied atropine or scopolamine cause marked loss of ocular reflexes, which may not fully recover for 7-12 days

■ *Other Effects*

• small doses inhibit *sweating* and the skin becomes hot and dry; larger doses may result in a rise in body temperature
• dilates the ureters and bladder, decreases tone and may result in urinary retention

  NB: administration to during parturition may lead to loss of variability of the foetal HR

Pharmacokinetics

• absorbed from the GIT and other mucosal surfaces; the duodenum & jejunum are the major sites of absorption after oral administration
• total absorption ~ 10-25% of administered dose
• plasma protein binding ~ 50%
• the elimination half life, $t_{1/2\beta}$ **~ 2.5 hrs**
• up to 80% of the administered dose is excreted in the urine in the first 8 hours, and ~ 95% in 24 hours
• metabolised by enzymatic hydrolysis to tropine & tropic acid
• only a small fraction being excreted unchanged by the kidney
• readily crosses the placenta

■ *Dosage & Administration*

• the usual adult premedicant dose is 0.4-0.6 mg
• the usual child dosage is 0.02 mg/kg to a maximum of 0.6 mg
• often used in conjunction with anti-AChE agent for reversal of NMJ blockade; the usual adult dose being 0.6-1.2 mg

■ *Toxicity, Precautions & Contraindications*

• should be avoided where there is a marked tendency to tachycardia, as for hyperthyroidism or CVS disease, when scopolamine may be a better choice
• atropine overdosage presents with,

  a.   dry mouth

  b.   blurred vision, mydriasis

  c.   hot dry skin, hyperpyrexia

  d.   restlessness, anxiety, delerium, mania, hallucinations

  NB: →   all of which eventually lead to CNS depression and coma

• many H_1-antagonists, such as the phenothiazines and tricyclic antidepressants have significant antimuscarinic activity; poisoning with these agents may lead to clinical features similar to atropine toxicity
• treatment consists of valium & physostigmine

Scopolamine

• is the ester of the organic base *scopine* and *tropic acid*
• its principal actions resemble those of atropine, however the two agents differ quantitatively in their antimuscarinic actions
• scopolamine has a more prominent action on the iris, ciliary body, and exocrine secretory glands (salivary, bronchial & sweat)
• like atropine, being a tertiary amine, scopolamine crosses the placenta
• its duration of action is shorter

■ *Central Nervous System*

• *scopolamine* (10 µg/kg) cf. *atropine* (20 µg/kg) has,

a.	vagolytic properties	~ equal	
b.	antisialogogue	~ 2-3x	(NB: MCQ)
c.	CNS depressant	~ 5-15x	
NB:	doses being slightly > adult	~ 5-7 µg/kg	

• as for atropine, scopolamine is a tertiary amine; the only difference being an oxygen bridge across the C_{6-7} atoms of the base ring
• in therapeutic doses causes drowsiness, euphoria, amnesia, fatigue and dreamless sleep with a decreased REM component; all of which may last longer than with atropine
• these effects are obviously useful for premedication
• however, occasional patients experience excitement, restlessness, hallucinations and delirium, especially in the presence of severe pain and in the elderly
• these effects appear regularly after toxic doses
• produces a more marked EEG decrease in ARAS activation by sensory stimulation or sympathomimetic amines

■ *The Eye*

• as for atropine produces cycloplegia & mydriasis, with photophobia and fixed distant vision
• however, at conventional systemic doses the effect is far greater than for atropine

■ *Cardiovascular System*

• with low doses of scopolamine (0.1-0.2 mg), the initial cardiac slowing is more marked than with atropine (central vagal stimulation)
• with higher doses, cardioacceleration occurs initially but is short lived and is followed within 30 mins by a normal rate or bradycardia
• therefore, after an initial short period, doses of scopolamine producing ocular effects have little effect on heart rate
• conversely, doses of atropine producing ocular effects are accompanied by tachycardia

■ *Dosage & Administration*

• generally used as a premedicant, where its CNS depressant effects and smaller rise in HR are desirable
• usual dose is 0.2 to 0.6 mg, however due to the occasional excitatory phenomena it is usually given with an opioid

Glycopyrrolate

• originally used in the treatment of *peptic ulcer* disease, then used as an anaesthetic premedicant
• compared with the belladonna alkaloids, glycopyrrolate possesses a marked antisialogogue action which is of *long duration* → potency relative to atropine ~ 2:1
• it is a quaternary amine, therefore crosses the BBB and placenta to a minimal degree and is relatively devoid of adverse CNS effects
• the morbidity & mortality following gastric aspiration is less serious if the pH of contents is > 2.5 (Nunn states Mendelson's syndrome doesn't occur until pH is less than this)
• anticholinergic drugs reduce the volume of acid secretion and may reduce the secretion of acid

> *NB:* reports are conflicting: G&G states acid secretion *does not* decrease in man unless high doses are given, however the fasting secretion of acid may be abolished and this is most likely to apply to anaesthetic induction

• some evidence to suggest glycopyrrolate may be more effective in this regard than atropine, therefore may be of benefit in *obstetric anaesthesia*
• when used with neostigmine or pyridostigmine → protects against tachycardia with less bradycardia
• the duration of action is longer **~ 6-8 hrs**
• when used as premedicants, atropine & scopolamine have a high incidence of dysrhythmias
• this incidence being lower for glycopyrrolate
• usual adult doses ~ 0.1 - 0.2 mg
• for children 0.004 - 0.008 mg/kg

ANAESTHETIC PREMEDICATION

• the aims of anaesthetic premedication are,

      1.   to allay anxiety and sedate the patient

      2.   to aid the induction of anaesthesia

      3.   reduce the overall dose of anaesthetic required

• in addition, there may be special requirements such as aiding hypotension or hypothermia
• the sedative drugs most commonly used include,

      a.   morphine

      b.   pethidine

      c.   the benzodiazepines

• phenothiazines are also used for their sedative and antiemetic actions
• premedication with 10-15 mg of morphine decreases the MAC for halothane by 7%; diazepam similarly reduces the MAC
• major problem with the use of the opioids is the occurrence of postop. nausea & vomiting; therefore, these are frequently administered with an antiemetic
• the main uses of anticholinergics in premedication are;

      a.   protection against vagal reflexes

      b.   decreased salivation

• they may also,

      a.   decrease gastric acidity

      b.   reduce the incidence of laryngospasm, cough & hiccough associated with the barbiturates

• arguments against their use include,

      a.   reduction of the tone of the lower oesophageal sphincter

      b.   increased incidence of dysrhythmias, especially on laryngoscopy & intubation

• with the older, irritating inhalational agents, the antisialogogue effects were essential; however, this is not so for the modern inhalational agents
• neonates still require these agents, both to reduce secretions in small airways and the block the cholinergic influence on the heart
• where sedation is a major consideration, such as for hyperthyroid patients, scopolamine is the logical choice of agent (also produces less tachycardia)
• atropine induced tachycardia will antagonise deliberate hypotension and should be avoided in these circumstances
• patients receiving *MAO inhibitors* should not receive opioids, however, adverse reactions do not always occur
• patients with Parkinson's disease should not receive butyrophenones; these are CNS dopamine antagonists and may precipitate rigidity

• patients having recently received steroids may be HPA suppressed; this is less likely if therapy is ceased > 2 months before surgery and routine prophylaxis need only be considered for this group
• patients suffering from sever shock, hypovolaemia, or severe pulmonary disease should rarely be premedicated in the ward

Premedication in Children

• although the anti-ACh agents may be criticised in adults, their use in paediatrics is clearly justified (? G&G)
• the presence of secretion in the smaller airways of the infant significantly increases airway resistance, causes respiratory obstruction and laryngeal spasm
• vagal reflexes being more readily elicited in the paediatric group

Paediatric Drug Doses		
Drug	Dose (mg/kg)	Maximum (mg)
Atropine	0.02	0.6
Scopolamine	0.01	
Glycopyrrolate	0.004 - 0.008	
Pethidine	1.0 - 1.5	
Diazepam	0.2 - 0.4	10
Promethazine	0.5	

CATECHOLAMINE SYMPATHOMIMETIC AGENTS

History

• the pressor effects of suprarenal extracts was first demonstrated in 1895 by Oliver and Schäfer
• the active principle was named epinephrine, or *adrenaline* (AD) by Abel in 1899 and was first synthesised by Stolz & Dakin
• Dale & Berger (1910) studied a wide range of synthetic amines related to adrenaline and termed their action *sympathomimetic*
• later discovered that cocaine, or chronic denervation, reduced the response to ephedrine & tyramine but not to adrenaline
• thus it became evident that the differences between amines were not solely quantitative
• Ahlquist (1948) described α & β adrenergic receptors
• Bertler et al. (1956) showed that *reserpine* depleted tissues of noradrenaline NA
• Burn & Rand (1958) showed that *tyramine* and certain other amines did not have a direct effect, but acted by the release of NA from nerve terminals

Sites and Mechanisms of Action

• most of the actions of such agents can be categorised into six groups,

1. a peripheral excitatory action on certain types of smooth muscle
   i. blood vessels supplying the skin & mucous membranes; and
   ii. gland cells, including the salivary & sweat

2. a peripheral inhibitory action on certain types of smooth muscle
   i. including the wall of the gut & bronchial tree; and
   ii. the blood vessels supplying skeletal muscle

3. a cardiac excitatory effect, increasing the rate & force of contraction

4. metabolic actions, including,
   i. increasing the the rate of glycolysis in muscle & liver, and
   ii. the liberation of free fatty acids from adipose tissue

5. endocrine actions, including modulation of the secretion of renin, insulin & pituitary hormones

6. CNS actions, including stimulation of respiration, and with some agents, increased psychomotor activity & wakefulness, and decreased appetite

NB: all agents do not show all of the above effects, or various effects to the same degree; however, many of the differences in their effects are only quantitive

α & β Adrenergic Receptors

• in 1948, Ahlquist studied the effects of adrenaline (AD), noradrenaline (NA) and isoproterenol (ISO) on a variety of target tissues and concluded that the actions of these agents could only be described by the presence of two distinct types of receptor, denoted α and β
• Lands and coworkers (1967) described the subdivision of β_1 & β_2 receptors,

    a. β_1 receptors predominating in cardiac tissues

    b. β_2 receptors predominating in smooth muscle and gland tissue

• however, individual tissues may contain both receptors in varying concentrations
• α receptors are also heterogeneous,

    a. α_1 receptors predominating at postsynaptic receptor sites on smooth muscle and gland cells

    b. α_2 receptors are located on presynaptic nerve terminals and are believed modulate the release of NA and possibly ACh $\rightarrow$ (-)'ve feedback

• α_2 receptors are also located at a number of postsynaptic sites, including the brain, uterus, parotid gland and certain regions of vascular smooth muscle

Receptor Sensitivities to Sympathomimetic Amines[1]			
α_1 adrenergic	AD ~ NA > DA > ISO		
α_2 adrenergic	AD <> NA[2]		
β_1 adrenergic	ISO > AD ~ NA ~ DA		
β_2 adrenergic	ISO ~ AD >> NA > DA		
	Adrenaline	Noradrenaline	Isoproterenol
α_1 adrenergic	+++(+)	+++	+
α_2 adrenergic	++(++)	++(++)	-
β_1 adrenergic	+++	+++	++++
β_2 adrenergic	++(+)	±	+++

[1]   see Goodman & Gilman table 4-1

[2]   the effects of AD may be either < or > NA depending upon the tissue

• in general, the effects of activation of α_1 receptors in smooth muscle are excitatory, whereas those of β_2 receptors are inhibitory
• in other tissues β receptors may mediate excitatory effects, eg. heart, pancreas etc.

• the catecholamines (catecholamine's) inhibit the propulsive activity & reduce the tone of most GIT smooth muscle
• this appears to be mediated by both α & β receptors, the former by a presynaptic action, inhibiting the release of ACh
• an important factor in the response of an organ to these agents is the relative proportion, and densities, of α & β receptors
• NA, therefore, has little effect upon bronchial airflow because the receptors are almost entirely β_2
• in contrast to NA, AD & ISO are potent bronchodilators
• cutaneous blood vessels possess almost exclusively α receptors, therefore NA & AD produce marked vasoconstriction, while ISO has little effect
• the vessels of skeletal muscle possess both α & β_2 receptors; small doses of AD producing vasodilation via the later

> *NB:* thus, the tissue threshold for β stimulation is lower, however at higher concentrations where both are stimulated, α receptors are ***prepotent***

• dopaminergic receptors have been identified in the CNS, renal and mesenteric vasculature

■ *Release of Stored Noradrenaline*

• many of the sympathomimetic agents, such as ***ephedrine*** & ***amphetamine***, exert a large fraction of their effects by the release of NA from storage sites within the nerve terminals
• thus, such agents are termed ***indirectly acting*** sympathomimetic amines
• the responses these agents elicit are therefore similar to NA, however are slower in onset and generally longer lasting than those of an equipressor dose of NA
• further, these agents exhibit ***tachyphylaxis***, supposedly due to depletion of the "releasable stores" of NA
• however, the nerve terminals still contain NA and respond to depolarisation
• many agents owe only a part of their activity to NA release and are termed ***mixed-acting sympathomimetic*** agents

■ *Role of Sympathomimetic Amines In Modulating The Release of Noradrenaline*

• α adrenergic agonists are able to profoundly inhibit the release of NA from nerve terminals
• conversely, when neural depolarisation occurs in the presence of an α adrenergic antagonist there is a marked increase in the release of NA from the terminal
• these effects appear to be mediated by presynaptic α_2 receptors
• some agents, such as ***nordefrin*** (α-methyl-noradrenaline) and ***clonidine***, are relatively selective agonists at these receptors, and a large degree of their antihypertensive action is the inhibition of NA release, mainly by a central action
• β adrenergic agonists appear to enhance the release of NA, however this effect is insignificant under normal conditions

> *NB:* proposed by Rand (Melbourne) that presynaptic β_2 receptors form a (+)'ve feedback circuit, enhancing NA release

• this may be responsible for a part of the antihypertensive effect of the nonselective β blockers

- ■ *Reflex Effects*

· the ultimate response of any target organ to these agents is determined not only by the direct effects, but also by reflex homeostatic adjustments of the organism
· stimulation of α receptors → elevation of BP → reflex increase PNS:SNS tone via the carotid and aortic baroreceptors → negative dromotropic & chronotropic effects
· this type of effect is important for agents with little β activity
· thus, *phenylephrine* may be used to treat junctional or nodal tachycardias, the reflex alterations in SNS & PNS tone possibly terminating the arrhythmia

- ■ *Mechanism of the Direct Action On Sympathetic Effectors*

· catecholamine's act by direct binding to membrane bound receptors,

a.	β_1 & β_2	→	largely activation of *adenylate cyclase* & cAMP
b.	α	→	mobilization of Ca^{++}
±	α_1	→	formation of *inositol triphosphate*
	α_2	→	inhibition of adenylate cyclase

· the relationship between electrical events, ion fluxes and contraction of smooth muscle is complex and varies between tissues
· visceral smooth muscle contractions are generally associated with *slow waves* of partial depolarisation and in some muscles superimposed AP's
· in muscles inhibited by β receptors, the membrane becomes hyperpolarised and AP's become less frequent, or may disappear; apparently due to a reduction in cytosolic free Ca^{++}, and both enhanced efflux & sequestration may be involved
· relaxation of some smooth m. due to α activation may be due to hyperpolarisation due to increased gK^+ & gCl^-, in addition to the presynaptic inhibition of ACh release
· contraction of the intestinal sphincter smooth m. by α agonists appears to result from a generalised increase in ion permeability (Na^+, K^+, Cl^- and possibly Ca^{++})
· adrenergic receptors are well localised to the vicinity of the nerve terminals in peripheral target organs, though, there are other receptors located distant to these sites, possibly preferentially stimulated by circulating catecholamine's
· chronic exposure of catecholamine sensitive tissues to the catecholamine's results in a diminution of their response

→ *tachyphylaxis*, down-regulation, refractoriness, or desensitization

· there is evidence for multiple points for this phenomenon,

a.	β receptors become phosphorylated and inactive
b.	receptor & adenylate cyclase become uncoupled (G-protein)
c.	the number of receptors declines

• sympathomimetic effects can also be obtained by elevation of the concentration of cAMP by inhibition of the enzyme ***phosphodiesterase***
• the methylxanthines, such as caffeine & aminophylline act via this mechanism, and their effects are synergistic to the catecholamine's
• further, the bronchodilation and uterine hypotonia seen with halothane, enflurane & isoflurane may be due to an increased rate of generation of cAMP
• this would also explain the sensitisation of the myocardium to catecholamine's by halothane (but then why not other agents!!)

Chemistry and Structure Activity Relationships

• catecholamine's, by definition, all possess the ***catechol nucleus*** = a benzene ring with adjacent hydroxyl substitutions; ***O-dihydroxybenzene*** known as catechol
• ***b-phenylethylamine*** can be viewed as the parent compound, consisting of a benzene ring and an ethylamine side chain
• thus the sympathomimetic drugs may be divided into catechol- & noncatecholamines
• most directly acting agents have activity at both α & β receptors, in an almost continual spectrum from pure α agonist activity, phenylephrine, to almost pure β agonist activity, ISO
• despite the multiplicity of actions several generalisations can be made

1. separation of the ***aromatic ring*** & the ***amino group*** shows the greatest activity occurs when 2 carbon atoms intervene

2. substitution on the ***amino group***, increasing the sise of the alkyl substituent increases β receptor activity, eg. ISO, or the addition of a methyl group to NA
   • a notable exception to this is phenylehprine, where the N-methyl substitution is associated with almost pure ~ activity
   • in general, the less the N-substitution, the greater the ~ activity, although N-methylation increases the potency of primary amines; thus, the ~ activity of AD > NA > ISO

3. substitution on the ***aromatic nucleus***, specifically OH groups at the 3 & 4 positions of the ring are required for maximal α & β activity
   • when one or both of these groups is absent, without other aromatic substitution, the overall potency is reduced
   • phenylephrine is thus less potent at both receptors than AD, with β activity almost entirely absent

4. OH groups in the 3 & 5 positions, in compounds with large amino substituents, confers β_2 selectivity, eg. metaproterenol, terbutaline

5. the response of non-catecholamine's is largely determined by their ability to release NA, thus their effects are mainly α & β_1

6. phenylethylamines lacking both aromatic OH groups and the β-OH on the ethyl chain produce almost all of their effects by NA release
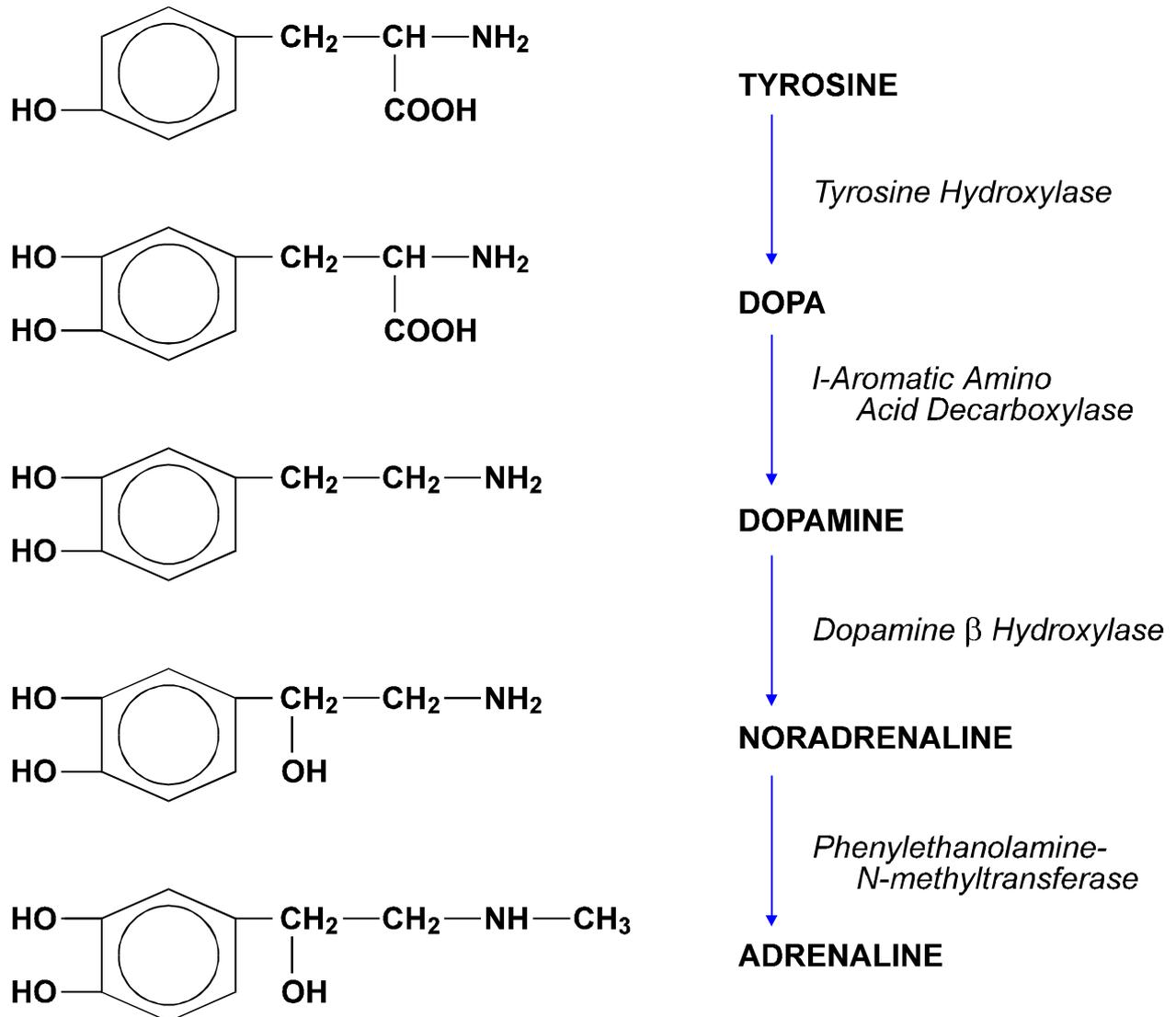
· catecholamine's have only a brief duration of action, and are ineffective orally, due to degradation by COMT
· agents lacking OH substitution, especially the **3-OH**, are resistant to COMT and have a longer duration of action and oral effectiveness
· substitution with groups other than OH, in general, reduces α activity and almost abolishes β activity; actually may produce adrenergic blocker
· albuterol, with a 3-CH_2OH group, is a selective β_2 agonist and an exception to the above

· substitution on the **a-C** *atom* blocks oxidation by MAO, thus greatly prolongs the duration of action of the non-catecholamine's
· the duration of drugs such as amphetamine & ephidrine is in hours rather than minutes
· as intraneuronal MAO is important for degradation of phenylethylamines, compounds with α-substitution are more likely to persist and release NA from intraneuronal storage sites

· substitution on the **b-C** *atom* generally decreases central stimulant action, due to the lower lipid solubility of these agents
· however, this also greatly enhances both α & β potency; thus, ephidrine is less potent than methamphetamine as a CNS stimulant, but is more potent on BP, HR and bronchodilation
· absence of the benzene ring reduces the CNS stimulant action, without reducing peripheral effects, when replaced by a saturated, eg. cyclopentamine
· the proportion of α:β activity varies with the compound, however, the absence of benzene confers greater α activity and many of these agents are used as nasal decongestants

· *optical isomerism* is confered by substitution on either of the ethyl C atoms

   1. *levorotatory* substitution at the β-C atom produces naturally occurring NA & AD, both of which are over 10 times as potent as their isomers

   2. *dextrorotatory* substitution at the α-C atom generally confers greater potency in CNS stimulation, eg. d-amphetamine

Synthesis, Storage & Release of Catecholamines

• the following steps in the synthesis of AD were proposed by **Blaschko** (1939)

HO—⟨benzene⟩—CH$_2$—CH(COOH)—NH$_2$	**TYROSINE**
	↓ *Tyrosine Hydroxylase*
HO,HO—⟨benzene⟩—CH$_2$—CH(COOH)—NH$_2$	**DOPA**
	↓ *l-Aromatic Amino Acid Decarboxylase*
HO,HO—⟨benzene⟩—CH$_2$—CH$_2$—NH$_2$	**DOPAMINE**
	↓ *Dopamine β Hydroxylase*
HO,HO—⟨benzene⟩—CH(OH)—CH$_2$—NH$_2$	**NORADRENALINE**
	↓ *Phenylethanolamine-N-methyltransferase*
HO,HO—⟨benzene⟩—CH(OH)—CH$_2$—NH—CH$_3$	**ADRENALINE**

> **NB:** 1. (-)'ve feedback is via catecholamine competition with the **tetrahydrobiopterin** cofactor of tyrosine hydroxylase
>
> 2. the enzymes tyrosine hydroxylase, dopamine-β-hydroxylase, and phenylethanolamine-N-methyl transferase share AA homology and may be under common genetic control

• none of these enzymes is highly specific, and a variety of endogenous substances and drugs are acted upon at the various steps, eg. the conversion of **methyldopa** to α-methyldopamine then the false transmitter α-methyl-NA

• **tyrosine hydroxylase** is activated following stimulation of adrenergic nerves or the adrenal medulla

• this enzyme is a substrate for **cAMP-dependent protein kinase**, and kinase-catalyzed phosphorylation is associated with increased enzyme activity

• this is also a substrate for **Ca^{++}-*activated protein kinase*** (see G&G, p.83, fig. 4-4 for summary of storage and release)

Metabolism & Distribution of the Catecholamines

• the actions of AD & NA are terminated by three processes,

    1.   ***re-uptake*** into the nerve terminal

    2.   ***dilution*** by diffusion from the junctional cleft and uptake at non-neuronal sites, and

    3.   metabolic ***transformation***

• two enzymes are important in the biotransformation of catecholamine's,

    1.   COMT   →   methylation

    2.   MAO   →   oxidative deamination

• a powerful enzymatic system such as AChE is absent and termination of the action of NA is by presynaptic neuronal uptake
• thus, inhibitors of NA uptake potentiate the effects of SNS activity, whereas, inhibitors of MAO & COMT have little effect
• however, transmitter released within the nerve terminal is metabolised by MAO
• COMT, particularly in the liver, is responsible for the metabolism of circulating endogenous or administered catecholamine's
• both COMT & MAO are distributed widely throughout the body, including the brain
• the highest concentrations of each are found in the liver and kidney
• they differ in their cytosolic locations,

    a.   MAO   →   chiefly the outer surface of mitochondria
                              especially in adrenergic neurons

    b.   COMT   →   mostly in the cytoplasm, plus some in membranes

• the later has no apparent selective association with adrenergic nerves
• there are two different ***MAO isozymes*** of which are found in widely varying proportions in the CNS and peripheral tissues; selective inhibition of either of these two is possible
• refer to G&G fig. 4-5, p.87

• most of the AD & NA entering the circulation, either from the adrenal medulla or administered, is first methylated by **COMT** →   **metanephrine**
                                normetanephrine   respectively

• NA that is released intraneurally by drugs such as reserpine, is initially deaminated by **MAO** to 3,4-dihydroxyphenylglycoaldehyde DOPGAL
• the aldehyde group is reduced to glycol by **aldehyde reductase**, yielding 3,4-dihydroxy-phenylethylene glycol (DOPEG), within the neuron
• if deamination takes place at extraneuronal sites, **aldehyde dehydrogenase** acts to give 3,4-dihydroxy-mandelic acid (DOMA)
• circulating catecholamine's are preferentially oxidised to the acid, whereas catecholamine's in the CNS are reduced to the glycol
• in either case, the final common metabolites formed by the action of **COMT**,

    1.   DOPEG   →   3-methoxy-4-hydroxy-phenylethylene glycol   MOPEG

    2.   DOMA   →   3-methoxy-4-hydroxymandelic acid   VMA

• the later is often but incorrectly called "**vanillylmandelic acid**"   VMA
• the corresponding end-product for dopamine is **homovanillic acid**   HVA
• inhibitors of MAO can lead to increased levels of NA, DA & 5HT in the brain and other tissues with a variety of effects
• no striking pharmacological action is afforded by inhibition of COMT

    NB: these pathways are not the major fate of NA released at adrenergic neurons, or of exogenously administered catecholamine's; rather, the principal mechanism for the inactivation of these agents is **uptake** into peripheral nerve terminals

ADRENALINE   EPINEPHRINE

· AD is a potent stimulator of both α & β receptors and, as such, its administration produces effects resembling generalised activation of the SNS
· particularly prominent are the actions on the heart and vascular smooth muscle
· the occurrence of sweating, piloerection and mydriasis depend largely upon the physiological state of the subject

■ ***Blood Pressure***

· AD is one of the most potent vasopressors known
· given rapidly IV, it evokes a characteristic rise in BP, rapidly peaking in direct proportion to the administered dose
· the rise in systolic pressure being greater than diastolic, thus increasing the pulse pressure
· as the response wanes, the mean BP falls below normal before returning to the control level
· repeated doses continue to have the same effect, in sharp contrast to amine which owe a significant part of their action to the neural release of NA
· the mechanism of the rise in BP with AD is three fold,

    1.   direct myocardial stimulation →   +'ve ***inotropic*** effect

    2.   an increased HR   →   +'ve ***chronotropic*** effect

    3.   peripheral vasoconstriction

· vasoconstriction is most noticeable in the skin, mucosa, and kidney, along with marked constriction of the veins
· the HR, initially raised, may be slowed markedly at the height of the pressure rise due to reflex vagal activity; this effect is absent in the presence of atropine
· small doses of AD (0.1 µg/kg) may cause the BP to fall
· this effect, and the ***biphasic*** effect of larger doses, are due to the greater sensitivity to AD of the vasodilatory β_2 receptors

· the response to slower IV administration, or subcutaneous injection are somewhat different
· there is a moderate increase in systolic pressure due to the effects on the heart, however peripheral resistance falls due to the dominant action on β receptors in skeletal muscle, and the diastolic pressure usually falls
· since the mean arterial pressure does not appreciably alter, reflex activity is minimal and the effects on rate & force of contraction are unopposed
· HR, SV, LVEDP, LV work/beat and RA pressure are all increased
· the later being due to the venous effects

■ *Vascular Effects*

• the primary action of AD is on the smaller arterioles and precapillary sphincters, although veins and the larger arteries also respond

Vascular Effects of Adrenaline			
Vascular Bed	Receptor	Constriction	Dilation
Coronary	α, β_2	+	++[1]
Skin & mucosa	α	+++	
Skeletal muscle	α, β_2	++	++[1,2]
Cerebral	α	slight	
Pulmonary	α, β_2	+	+[1]
Abdominal viscera	α, β_2	+++	+[2]
Salivary glands	α	+++	
Renal	$\alpha_1, \beta_{1,2}$	+++	+[2]
Veins	α_1, β_2	++	++
[1] dilation predominates in situ due to autoregulation			
[2] over the usual [AD] range, dilation predominates in skeletal muscle & liver; constriction in other abdominal viscera			

• pulmonary arterial & venous pressures are raised and although vasoconstriction can be demonstrated, *redistribution* of blood from the systemic circulation is the dominant factor
• overdosage of AD may cause death from *pulmonary oedema*

■ *Cardiac Effects*

• NA causes direct stimulation of β_1 receptors of the myocardium & conducting tissues, independent of the alterations in cardiac function secondary to increased venous return and other peripheral effects
• the heart rate is increased, with systole relatively shortened
• contractility and CO are increased; the work of the heart and its O_2 consumption are markedly increased
• the cardiac efficiency, work output/O_2 consumption, is *decreased*
• responses observed in isolated myocardial preparations include,

      i.   increased contractile force

      ii.   increased rate of rise of isometric pressure ($\delta P/\delta t$)

      iii.   enhanced rate of relaxation

      iv.   decreased time to peak tension

      v.   increased O_2 consumption

      vi.   acceleration of spontaneous discharge

      vii. induction of automaticity in quiescent muscle

· AD produces the following effects in the ECG,

     a.   decreases the amplitude of T waves in all leads

     b.   S-T segments may become biphasic ± depressed

· the later changes may resemble exercise induced changes in patients with IHD, therefore are presumed to be a function of relative myocardial ischaemia
· AD speeds the heart by accelerating the rate of *phase 4 depolarisation* in,

     1.   both the SA & AV nodes

     2.   the His purkinje system

· the amplitude of the AP and the $\delta V/\delta t$ of phase 0 are increased and there is activation of latent pacemakers

     NB: these changes *do not* occur in atrial or ventricular muscle,
             where AD has little effect on the stable phase 4 membrane potential

· some of the effects of AD on the myocardium are secondary to the increase in HR and commensurate decrease in the relative refractory period,

     a.   the increased rate of atrial and ventricular repolarisation

     b.   the increased conduction velocity of the His purkinje system

     c.   a decrease in AV block induced by drugs or vagal stimulation

· conduction through the H-P system is dependent upon the level of the membrane potential at the time of excitation
· the decreased conduction associated with AMI and other disease states often results from excessive reduction in the resting membrane potential
· AD increases the membrane potential and reverses these effects
· however VPB's or VF may occur when the heart is sensitised to the effects of the catecholamine's, such as after MI or by halothane
· the mechanism of induction of these dysrhythmias is uncertain
· **a-*blocking*** agents such as phenoxybenzamine partially protect against AD induced cardiac dysrhythmias during anaesthesia
· protection is in part due to the prevention of increased BP which sensitises the myocardium
· the refractory period of the AV node is directly decreased, but may be prolonged with small doses due to reflex vagal tone
· SVT's are apt to occur with the combination of AD & cholinergic stimulation
· the actions of AD in enhancing automaticity & potentiating dysrhythmias are largely blocked by β blockers (there is some minor α action)

■ *Effects On Smooth Muscle*

• the effects of AD depend largely upon the receptor type predominant in the muscle concerned

Smooth Muscle Effects of Adrenaline			
		Responses	
Organ System	Receptor	Contraction	Relaxation
Stomach • tone & motility • sphincters	α_2, β_2 α	 ++	++[1]
Intestinal • tone & motility • sphincters	$\alpha_1, \beta_{1,2}$ α	 ++	++[1]
Uterus	α, β_2	+[2]	++
Urinary Bladder • trigone & sphincter • detrusor	α β_2	++	 ++
Bronchi	β_2		++
Gallbladder & ducts	β_2		++
Pilomotor muscles	α	++	
Splenic capsule	α, β_2	+++	+
[1] $\beta_2 \rightarrow$ direct relaxation & $\alpha \rightarrow$ presynaptic inhibition of PNS [2] α stimulated contraction only in pregnant state			

■ *Respiratory Effects*

• AD stimulates respiration but this effect is brief and of no clinical use
• given rapidly IV, AD may cause a brief period of *apnoea* prior to stimulation, due to reflex inhibition from the baroreceptors
• AD is a potent *bronchodilator* (β_2), especially when the airways are constricted in disease states or by drugs
• AD also assists respiration by increasing *vital capacity* and relieving congestion of the bronchial mucosa (α)
• its effects in asthma may in part be due to β_2 mediated inhibition of release of *histamine*
• in large doses AD may result in progressive *pulmonary oedema* & death due to central relocation of blood volume

■ *CNS Effects*

· in conventional doses AD is not a powerful CNS stimulant due to its polar nature and relative exclusion from the CNS
· may cause restlessness, headache, tremor & apprehension
· however these are largely due to the peripheral metabolic and cardiorespiratory effects

■ *Metabolic Effects*

· AD activates *adenylate cyclase* and cAMP-dependent protein kinase, with subsequent phosphorylation of,

  1. phosphorylase   - liver, kidney & skeletal muscle

  2. glycogen synthase   - inhibited by phosphorylation

  3. glucose-6-phosphatase   - liver & kidney only

  NB: $\rightarrow$ increased concentrations of blood *glucose & lactate*

· *insulin* secretion is inhibited (α) and enhanced (β_2)
          $\rightarrow$ the predominant physiological effect being *inhibition*
· *glucagon* secretion is enhanced (β_2) from the A cells of the islets
· AD also has a direct effect decreasing the peripheral uptake of glucose
· AD raises the concentration of free fatty acids by activation of *triglyceride lipase*
          $\rightarrow$ FFA's and glycerol (hormone sensitive lipase)
· this is mediated via cAMP and β_1 receptors

  NB: the general calorigenic action of AD is reflected by an increase in BMR of 20-30% after usual doses

■ *Miscellaneous Effects*

  a. reduced circulating plasma volume
          $\rightarrow$ increased haematocrit & plasma protein concentration

  b. increase in the total leukocyte count & eosinophilia

  c. increased factor V activity and coagulation

  d. facilitates NMJ transmission via α & β effects

  e. transient hyperkalaemia then prolonged hypokalaemia (? pump)

  f. in large & repeated doses may $\rightarrow$ damage to arterial walls and the myocardium, so called "zonal lesions"

Absorption, Fate & Excretion

• due to rapid oxidation and conjugation in the GIT mucosa and liver AD is ineffective after oral administration
• absorption from subcutaneous tissues occurs slowly due to local vasoconstriction; absorption from muscle being faster
• concentrated solutions (1%) when inhaled have predominantly local effects on the respiratory tract, though systemic reactions & arrhythmias may occur with larger doses
• AD is rapidly inactivated in the body, despite its stability in blood
• the liver is rich in both COMT & MAO, however is not essential in the degradation process
• the vast majority of an administered dose is excreted in the urine as metabolites

Dosage & Administration

• adrenaline is the l-isomer of **b-[*3,4-dihydroxyphenyl*]-a-*methylaminoethanol***
• it is only very slightly water soluble but forms soluble salts with acids
• it is unstable in alkaline solutions and on exposure to air or light

■ *Adrenaline Injection*

• available as sterile solutions of 1:1000 & 1:10000 as the HCl
• the usual s.c. dose ~ 0.2 to 1.0 mg
• AD may be given i.v. if rapid action is required, however the solution must be dilute, < 1:10000, and given very slowly
• usual i.v. dose ~ 0.25 to 0.5 mg
• IV infusion may be obtained by adding 6 mg to 100 ml $\rightarrow$ solution of 60 µg/ml
$\rightarrow$ "ml/hr" = "µg/min"

• infusions may be used to enhance myocardial contractility in the range 1.0 - 50 µg/min
• such infusions have a dose/response relationship (adult doses),

a.	< 2 µg/min	$\rightarrow$	predominantly β effects
b.	2-10 µg/min	$\rightarrow$	mixed α & β effects
c.	> 10 µg/min	$\rightarrow$	predominantly α effects

■ *Adrenaline Inhalation*

• available as a non-sterile 1% HCl solution, for oral, not nasal, inhalation
• extreme care must be taken not to confuse this with the 1:1000 solution
• used for the relief of resistant bronchospasm & symptomatic relief of croup
• actually no more effective for this purpose than the 1:1000 sterile solution, and this is more commonly used for inhalational purposes

■ *Toxicity, Side Effects, and Contraindications*

· AD may cause disturbing reactions such as fear, apprehension, anxiety, tremor restlessness, throbbing headache, dizziness, pallor, palpitations and respiratory difficulty
· these effects rapidly subside with rest but may be alarming to the patient
· hyperthyroid and hypertensive individuals are particularly susceptible to the pressor response to AD
· more serious reactions include,

     a.   cerebral haemorrhage

     b.   ventricular dysrhythmias

     c.   pulmonary oedema

· rapidly acting vasodilators such as the nitrites or sodium nitroprusside may be used to counter the pressor effects, as may α blocking agents
· VF is particularly likely in the presence of pre-existing heart disease, or in the presence of the halogenated anaesthetic agents
· the arrhythmogenic threshold for injected AD is 5 times higher for isoflurane and 2 times higher for enflurane, compared with *halothane*
· the effects of the anaesthetic gases which predispose to *dysrhythmias* are,

     a.   decrease in phase 4 depolarisation in the SA node

     b.   increased automaticity of myocardial fibres

     c.   decreased AV nodal conduction

     d.   ? direct action on β receptors

     NB: Halothane >>> Enflurane > Isoflurane

        →   increased conditions for *reentry* in the presence of AD
               ie., unidirectional block & slow retrograde conduction

· these effects sensitise the myocardium, especially in the presence of *hypercapnia* or *hypoxia*
· they are partly reverted by β blockade
· such tachyarrhythmias are less likely to occur if,

     a.   anaesthesia is sufficient   →   decreased SNS stimulation

     b.   ventilation is adequate   →   normal P_{aCO2}

     c.   use of adrenaline for haemostasis is limited
        i.   concentrations   < 1:100,000   = 1 mg / 100 ml
        ii.   total dose   < 0.1 mg in 10 minutes   = 10 ml
                                   < 0.3 mg in 1 hour   = 30 ml

· AD has also been reported to produce serious dysrhythmias in the presence of *aminophylline*

NORADRENALINE

• levarterenol, norepinephrine, or ***l*-b-[*3,4-dihydroxyphenyl*]-a-*aminoethanol*** is the chemical mediator liberated at mammalian post-ganglionic adrenergic nerve terminals
• it differs from AD only by lacking the methyl substitution on the aminoethanol and, as for AD, the ***l-isomer*** is pharmacologically active
• NA constitutes 10-20% of the catecholamine content of the adrenal medulla and as much as 97% in some ***phaeochromocytomas***

Pharmacological Actions

• both AD & NA are approximately equipotent at cardiac β_1 receptors
• NA is a potent agonist at α receptors but has little action at β_2 receptors
• however, NA is somewhat less potent than AD at most α receptors

■ ***Cardiovascular Effects***

• for a comparison of the effects of AD & NA on BP, see G&G fig. 8-1
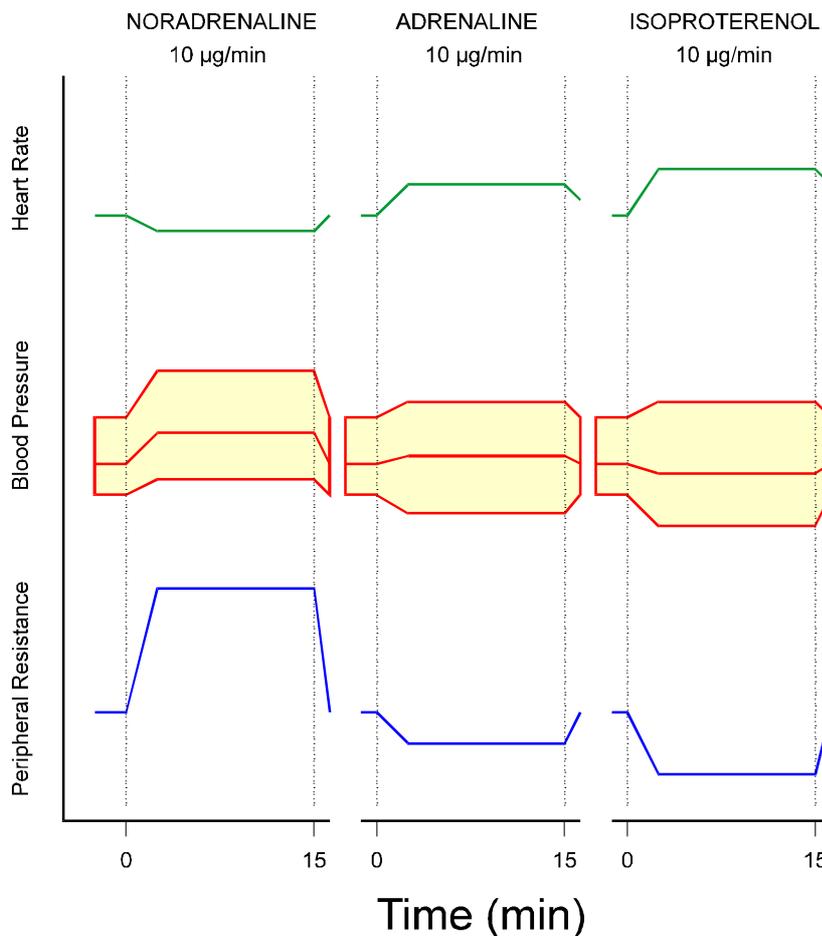
· NA infused at 10 µg/min generally has the following effects,

    a.   elevation of the systolic & diastolic pressures > AD

    b.   a smaller elevation of the pulse pressure

    c.   a marked increase in TPR   → decreased flow to liver, kidney, & skeletal m.
        · marked *venoconstriction* with a central relocation of blood volume

    d.   GFR is maintained unless RBF is markedly reduced

    e.   CO is unchanged, or decreased

    f.   the HR *decreases* due to reflex vagal action

    g.   consequent upon the decrease in HR & inotropic action, the SV increases

    h.   marked increase in coronary blood flow   - indirect

    i.   a decrease in circulating blood volume

    j.   an increased haematocrit & plasma protein concentration

· despite the metabolism induced increase in CBF, patients with Prinzmetal's variant angina are highly sensitive to the α effects of NA, AD and increased SNS tone
· in such patients, endogenous or exogenous catecholamine's may result in a marked decrease in CBF ± AMI, even in the absence of atherosclerotic vessel disease
· unlike AD, small doses of NA *do not* cause vasodilation or lower the BP due to the lack of β_2-agonist activity
· the usual ECG changes are a sinus bradycardia, due to reflex vagal action, with or without prolongation of the PR interval
· nodal rhythm, AV dissociation, bigeminy, VT & VF have all been observed
· Wood & Wood states that cerebral blood flow is reduced
· however, G&G states that the α constrictor effect on the cerebral circulation is minimal and the associated increase in BP *increases* CBF, the increase being limited by *autoregulation*

■ *Other Effects*

· NA has minimal effects on bronchial smooth m., possibly some dilation
· respiratory minute volume is slightly increased
· NA produces *hyperglycaemia* and other metabolic effects similar to AD, however these are observed only when large doses are given
· effects on the CNS are less prominent than with AD
· intradermal injection produces sweating which is not blocked by atropine
· the frequency of contraction of the pregnant *uterus* is increased, however, effects on other smooth muscle are minimal

■ *Absorption, Fate, Excretion*

· like AD, oral absorption is poor due to metabolism in the intestinal mucosa & the liver
· absorption from s.c. sites is slow and unpredictable
· rapidly inactivated in the body by COMT & MAO, negligible amounts appearing in the urine

Dosage & Administration

• **_norepinephrine bitartrate_** is a water soluble, crystalline monohydrate salt, which, like AD, it is readily oxidised
• it is available for injection as 0.2% bitartrate, which is equivalent to noradrenaline 0.1%
• it is usually given as a central i.v. infusion at a concentration of 60 µg/ml

■ *__Toxicity & Precautions__*

• the untoward effects of NA are generally similar to those of AD, however they are less severe and occur less frequently
• NA must not be administered s.c. as this may cause sloughing, as may extravasation at i.v. injection → central venous cannulation is essential
• overdoses, or conventional doses in hypertensive patients may result in a severe headache, photophobia, retrosternal pain, pallor, sweating, N&V
• BP should be monitored continuously
• reduced perfusion to vital organs is a constant danger
• the drug should not be used in pregnancy

ISOPROTERENOL

• isoproterenol, isoprenaline, or ***dl*-b-[*3,4-dihydroxyphenyl*]-a-*isopropylaminoethanol***, is a ***synthetic*** catecholamine acting almost exclusively at β receptors and is the ***most potent*** of the catecholamine's

Pharmacological Actions

• due to the absence of α effects, ISO produces most of its effects in the heart and the smooth muscle of the bronchi, skeletal muscle vasculature, and the GIT
• in addition, ISO produces marked ***metabolic effects*** in adipose tissue, skeletal m., and in the liver in some species

■ ***Cardiovascular System***

• administered i.v., ISO has the following effects,

    a.   decrease in TPR, principally skeletal m., renal and GIT

    b.   diastolic BP consequently falls

    c.   automaticity, HR, contractility, SV, and CO are increased
        $\rightarrow$ (+)'ve chronotropic & inotropic effects

    d.   systolic BP is usually maintained, but mean BP falls

    e.   venodilation and an increased venous capacitance

    f.   RBF is decreased in normotensive subjects,
        but markedly increased in septicaemic or cardiogenic shock

    g.   pulmonary arterial pressure is unchanged

• larger doses may cause a dramatic fall in mean arterial pressure
• ISO may be useful as a (+)'ve inotrope in patients with LV failure, especially those where a reduction in venous filling is desirable & HR is slow, ie. occasionally post cardiopulmonary bypass
• used for its chronotropic action as an interim measure in complete heart block

■ ***Smooth Muscle***

• ISO, relaxes almost all varieties of smooth m. when the resting tone is high
• its action is most pronounced on bronchial and GIT smooth m.
• it is highly effective in reversing the bronchoconstriction associated with drugs or bronchial asthma, however, tolerence to this effect develops with recurrent use
• an additional effect in asthma may be β_2 induced inhibition of release of histamine from mast cells
• ISO decreases the tone & motility of the intestinal tract and the uterus, even when AD causes contraction

■ *Metabolic & CNS*

• ISO causes *less* hyperglycaemia than does AD, in part because insulin secretion is stimulated from the pancreatic islets (β_2), due to the absence of α mediated inhibition
• however, ISO, is equally effective in mobilising FFA's and the *calorigenic* actions of the two agents are approximately equal
• like AD, ISO may cause CNS excitation, though, this is rarely seen in pharmacological doses

■ *Absorption, Fate, Excretion*

• like AD, oral absorption is poor due to metabolism in the intestinal mucosa and the liver
• given parenterally ISO is metabolised primarily in the liver & other tissues by COMT
• ISO is a relatively poor substrate for MAO and is not taken up by adrenergic nerve terminals
• as such, it has a slightly longer duration of action but this is still brief

Dosage & Administration

• available for injection as the water soluble HCl salt, which like the preceding agents is unstable in air or alkali
• concentrations range from 10, 20 to 200 µg/ml
• a solution for infusion may be made by adding 1 mg of ISO to 250 ml of fluid, giving a concentration of 4 µg/ml
• the usual adult dose ~ 0.01 to 0.1 µg/kg/min
• also available as a solution for inhalation, 0.25% to 1%, usually diluted 1:5 with N.saline

■ *Toxicity & Precautions*

• the acute reactions to ISO are generally less than those for AD
• principal problems are excessive tachycardia and hypotension, especially in hypovolaemic subjects, both of which may exacerbate angina
• palpitations, headache and flushing of the skin are common
• anginal pain, nausea, tremor, dizziness, and sweating are less frequent
• cardiac dysrhythmias occur frequently but are not usually serious
• large & repeated doses may lead to myocardial necrosis, c.f. AD, or to cardiac arrest when the heart is subject to an increased work load
• in the past a nebuliser was available with 15 times the present concentration $\rightarrow$ large number of deaths due to ? VF

DOPAMINE

· DA, *3,4-dihydroxyphenylethylamine*, differs from the other naturally occuring catecholamine's, lacking the β-OH group on the ethylamine side chain
· it is the metabolic precursor of NA & AD and is a central *neurotransmitter*
· DA is a substrate for both MAO & COMT and is thus ineffective orally
· it has minimal effects on the CNS, not crossing the BBB

■ *Cardiovascular Effects*

· DA exerts a (+)'ve inotropic effect on the heart, acting at β_1 receptors
· in addition, it has the ability to *release NA* from nerve terminals and this is responsible for a part of its action
· tachycardia is less prominent with infusions of DA than with ISO
· DA usually increases the systolic and pulse pressures, however, either has no effect or reduces the diastolic pressure
· TPR is usually unchanged when low or intermediate infusion rates are used, due to regional dilation in the mesenteric & renal vascular beds (dopaminergic effect)
· however, TPR and BP are increased at higher rates of infusion due to direct α stimulation
· DA receptors also appear in the cerebral and coronary circulations, however vasodilation is minimal due to *autoregulation*
· the vasodilatory effects are antagonised by the butyrophenones, phenothiazines and apomorphine, supporting the existence of a *DA receptor*
· the effects of high doses are antagonised by phentolamine & phenoxybenzamine, supporting the role of α receptors
· the predominant effects for DA are thus *dose dependent*

Dose Dependent Effects of Dopamine[1]		
Infusion Rate	Receptor	Action
1-5 µg/kg/min	DA	· increased RBF, GFR, Na^+ excretion · little or no increase in CO · blocked by haloperidol
5-20 µg/kg/min	DA β	· increased contractility, SV & CO · blocked by propranolol
> 30 µg/kg/min	α + NA	· increased TPR, BP & automaticity · decreased RBF & GFR · reflex bradycardia · blocked by phentolamine
[1] From: Wood & Wood		

Dosage & Administration

• DA-HCl is a water soluble, crystalline, light and alkali sensitive white powder
• marketed in solutions of 40, 80 & 160 mg/ml
• DA is only effective by i.v. infusion, when it is usually diluted to 0.8 to 1.6 mg/ml
• the usual adult dose   ~ 2-5 µg/kg/min initially
                        ~ 20-50   µg/kg/min as indicated clinically

■ *Toxicity & Precautions*

• patients to receive DA must have an adequate circulating blood volume; ie. hypovolaemia must be corrected prior to infusion and circulatory status must be constantly monitored during infusion
• untoward effects are generally due to excessive SNS activity, and include nausea, vomiting, tachycardia, dysrhythmias, anginal pain, dyspnoea, headache, and hypertension
• as DA has a very short half-life these effects respond quickly to slowing or cessation of the infusion
• extravasation of DA from the injection site may result in ischaemic nercosis and sloughing of the surrounding tissues, infusion is therefore preferred via a central line
• rarely, gangrene of the fingers & toes has been reported after prolonged administration
• DA should be avoided for patients with,

    1.   hypovolaemia

    2.   cardiac dysrhythmias

    3.   phaechromocytoma

    4.   concurrent MAO administration

DOBUTAMINE

· dobutamine (DB) is a synthetic derivative of *isoprenaline*
· it resembles DA chemically but possesses a bulky aromatic residue on the amino group
     (see G&G table 8-1)
· despite the absence of a β-OH group, DB is a *selective b_1 receptor agonist*
· DB has only slight indirect actions

■ *Cardiovascular Effects*

· DB appears to be slightly more effective in increasing *contractility* than heart rate c.f. ISO

     →   inotropic > chronotropic action

· this is agent specific and not reflex mediated, as neither vagotomy, nor adrenergic blockers affect this response
· while DB enhances the automaticity of the SA node, this is not as evident as with ISO
· DB does not appear to affect atrial conduction velocity, though, it does augment conduction through the *AV node*
· there is little, or no effect on ventricular conduction
· in contrast to DA, DB has no agonist activity at the DA receptors of the renal vasculature, therefore, does not cause renal vasodilation
· overall, its effects on TPR and BP are moderate, making it an effective agent for the management of CCF and post cardiopulmonary bypass
· after administration of β blockers DB produces a slight increase in BP, indicating some direct *a-agonist* activity

Dosage & Administration

· supplied in 20 ml vials containing 250 mg of DB-HCl
· standard solution is either 250 or 500 mg / 100 ml D_5W
· the usual adult dose ~ 2-10 µg/kg/min
· its plasma $t_{\frac{1}{2}\beta}$ ~ 2 mins, therefore, it must be given by constant i.v. infusion
· it is rapidly metabolised in the liver to inactive conjugates with glucuronic acid and to 3-O-methyl-dobutamine

Toxicity & Precautions

· although the electrophysiological effects of DB do not markedly differ from DA or ISO, the incidence of *dysrhythmias* appears to be lower
· nevertheless, DB enhances AV conduction and should be avoided in patients with AF
· other side effects are similar to DA, and like this agent are rapidly treated by alteration of the rate of infusion

Infusion Rates & Concentrations			
	Dosage Range (µg/kg/min)	Adult Dose (µg/min)	Dilution
Adrenaline	0.01-0.7	1-50	6 mg / 100 mls
Noradrenaline	0.01-0.7	1-50	6 mg / 100 mls
Isoproterenol	0.01-0.15	1-10	6 mg / 250 mls
Dopamine	0.5-30	30-2000	400 mg / 100 mls
Dobutamine	0.5-20	30-1400	500 mg / 100 mls

SUMMARY OF EFFECTS				
Effect	AD	NA	ISO	DA
<u>Heart</u>				
• rate	+	-[1]	+	0/+
• contractility	++	0/+	++	++
• cardiac output	+++	0/-	++	++
• arrhythmicity	++++	+++	++++	++
<u>Blood Pressure</u>				
• systolic	++	+++	+	+
• diastolic	-	±	-	0+
• mean arterial	+	++	-	0+
• mean pulmonary	++	++	0	0
<u>Peripheral Circulation</u>				
• total resistance	+	+++	-	0±
• muscle blood flow	+++	0-	++	±
• cutaneous blood flow	--	--	0+	-[4]
• splancnic blood flow	+++	0+	++	++[4]
• renal blood flow	--	--	--[3]	++[4]
• cerebral blood flow	+	0+	0	0+
• coronary blood flow[2]	++	++	++	++
<u>Smooth Muscle</u>				
• bronchial	--	0	--	
• pregnant uterus	--	++	--	
<u>Metabolic Effects</u>				
• O_2 consumption	++	0+		
• blood glucose	+++	0+		
• blood lactate	+++	0+		
• eosinophilia	+	0		

[1] reflex bradycardia due to increased vagal tone

[2] increases in coronary blood flow are secondary to increased myocardial work and autoregulation

[3] RBF decreased in norotensive subjects but markedly increased in septicaemic or cardiogenic shock

[4] DA may either dilate or constrict vascular smooth muscle, depending upon the dose; higher doses release NA from nerve terminals

DOPEXAMINE

• *synthetic* catecholamine, structurally related to dopamine and dobutamine
• produces a combination of DA_1 and β_2-receptor agonist activity
• the relative selectivity for β_2:β_1-receptors ~ 9.8:1
• an inhibitory action in neuronal catecholamine uptake has also been demonstrated
• this most likely accounts for the positive inotropic action of the agent
• continuous infusions at **1-4 µg/kg/min** result in preferential systemic, mesenteric and renal vasodilatation,

    a.   in normal volunteers, this produces,

        i.   a decrease in afterload

        ii.   an increase in CO

        iii.   improved renal perfusion

    b.   in patients with severe CCF,

        i.   a profound decrease in afterload

        ii.   increased renal blood flow

        iii.   mild positive inotropism (~ 5-10%)

        iv.   increased CO   - predominantly a *rate* increase
                                      - there is minimal change in SVI

    NB: substantial increases in *heart rate* and in myocardial MRO_2 at doses
            above 4 µg/kg/min may limit its use in patients with IHD

• in animal models of septic shock, studies have been contradictory in dopexamines ability to preferentially increase splanchnic and renal blood flow
• however, even where splanchnic flow is not increased, gut lactate production was reduced
• this is consistent with other studies which show β_2-receptor agonists redistribute flow within the gut away from the muscularis to the mucosa

NONCATECHOLAMINE SYMPATHOMIMETIC AGENTS

■ ***Background***

• presumed for many years that all sympathomimetic agents produced their effects by action at adrenergic receptors
• this was challenged by the findings that,

    1.   the effects of ***tyramine***, and many other non-catecholamine's, were reduced or abolished following,

        i.   chronic postganglionic adrenergic denervation, or

        ii.   pretreatment with cocaine or reserpine

    2.   under these circumstances the effects of AD & NA were generally ***enhanced***

    NB: these observations led to the concept that these agents acted by ***uptake*** into the adrenergic nerve terminal, with subsequent stoichiometric ***displacement*** of NA from storage sites in synaptic vesicles, or from extravesicular binding sites (Burn & Rand, 1958)

• this concept would explain the inhibition by both,

    a.   ***reserpine*** $\rightarrow$ depletion of tissue stores of NA, and

    b.   ***cocaine*** $\rightarrow$ inhibition of neuronal uptake
                      $\rightarrow$ inhibits the effects of the non-catecholamine's
                      $\rightarrow$ enhancing the effects of the catecholamine's

• the proportions of ***direct***, ***indirect*** & ***mixed*** action of any particular agent are generally assessed by a comparison of the dose-response curve before and after treatment with reserpine (Trendelenburg, 1972)
• agents that release NA have predominantly α actions, however, many of these agents, such as ***ephedrine***, have strong direct β_2 agonist activity
• with few exceptions the actions of the non-catecholamine's fit within the framework of α & β receptors; hence, many of their actions are similar to the catecholamine's
• the additional CNS effects of agents lacking substituents on the ***benzene ring*** have been most extensively studied with ***amphetamine***

False Transmitter Concept

• according to the uptake & displacement hypothesis of Burn & Rand, indirectly acting amines replace NA within the nerve terminal
• phenylethylamines lacking the β-OH substitution are retained poorly
• however, agents with this substitution and those which are acted upon by ***dopamine-b-hydroxylase*** and are retained within the vesicles for a long period of time
• if such agents are considerably different in activity to NA they may therefore act as ***false transmitters***
• this is believed to be the mechanism of action of the hypotensive effect of ***MAO inhibitors***
• these allow dietary ***tyramine*** to be absorbed across the GIT (-MAO)
• subsequently this is taken up into the nerve terminal and its catabolism by MAO again prevented
• tyramine is then β-hydroxylated to ***octopamine*** which is stored in the vesicles and has little α or β activity

> ***NB:*** despite this process, ingestion of foods high in tyramine may precipitate a ***hypertensive crisis*** due to the mass absorption of tyramine and resultant release of large quantities of neurotransmitter (NA & octopamine)

Absorption, Fate & Distribution

• in contrast to the catecholamine's, most of the clinically used non-catecholamine's are effective when given ***orally*** and many act for extended periods
• these properties are due to resistance to metabolism by MAO & COMT
• ***phenylisopropylamines***, the most commonly used non-catecholamine's are widely distributed in tissues and readily cross the BBB, therefore have pronounced effects on the CNS
• substantial fractions of these drugs are eliminated unchanged in the urine
• pathways for metabolism include,

   a.   p-hydroxylation

   b.   N-demethylation

   c.   deamination

   d.   conjugation in the liver

• urinary excretion of ***amphetamine*** (pK_a = 9.9), and many other non-catecholamine's is profoundly influenced by urinary pH
• a large number of the non-catecholamine's have pK_a's between 9.0 - 10.3, therefore their excretion is greatly enhanced by ***acidification*** of the urine
• although these agents are resistant to the actions of the MAO inhibitors, they provoke the release of NA and may cause hypertensive crises if administered concurrently

Amphetamine

· racemic **b-*phenylisopropylamine*** has powerful CNS stimulant actions in addition to the peripheral α & β actions
· unlike AD, it is effective orally and has a duration of action of several hours

- ■ *Cardiovascular Effects*

· increases the systolic & diastolic BP
· reflexly decreases the HR and in large doses may cause cardiac dysrhythmias
· CO is not enhanced by usual doses and cerebral blood flow is little changed
· the *l-isomer* is slightly more potent on the CVS than the d-isomer

- ■ *Smooth Muscle Effects*

· the effects upon other smooth muscles are similar to the catecholamine's, with effects being most marked on the GUS, GIT (unpredictable) and the uterus

- ■ *CNS Effects*

· amphetamine is one of the most potent sympathomimetic CNS stimulants
· effects are thought to be due to stimulation of both the cortex and the ARAS
· in elicitation of these effects, the *d-isomer* is 3-4 times more potent than the l-isomer
· the psychic effects, in man, depend markedly upon the personality and state of the individual, these include,

    a.   increased wakefulness

    b.   elevated mood

    c.   increased initiative, self-confidence & ability to concentrate

    d.   often elation and euphoria

    e.   increased motor and speech activity

    f.   physical performance in athletes is improved

· these effects are not invariable and may be reversed by repeated, or overdosage
· prolonged use, or large doses nearly always is followed by by mental *depression* and fatigue
· many subjects given amphetamine experience headache, palpitations, dizziness, vasomotor disturbances, agitation, confusion, dysphoria, apprehension, delirium or fatigue
· the effects upon *fatigue & sleep* have been extensively studied
· the most marked effect being a decreased frequency of attention lapses after sleep deprivation
· thus the need for sleep can be postponed but not indefinitely avoided
· when the drug is discontinued after prolonged administration, the pattern of normal sleep may take several months to recover
· amphetamine and some of the other sympathomimetic amines have a *mild analgesic* action and potentiate the analgesic action of the opioids
· amphetamine accelerates and desynchronises the *EEG*, causing a shift of the resting pattern to higher frequencies, though, to a smaller degree than occurring during attention

• in children with **behavioral disorders** and an abnormal rhythm (6 Hz rhythm), amphetamine may improve behavior without altering the EEG pattern
• stimulation of the **respiratory centre** increases the rate and depth of respiration
• normal doses only mildly elevate minute volume, however in the presence of central respiratory depression increases may be significant
• this and related agents have been used in the treatment of obesity; weightloss being almost entirely due to decreased food intake, probably due to an action on the lateral hypothalamic **feeding centre**, not the medial satiety centre
• metabolic increases are small, though, some of the weightloss may be attributable to increased physical activity
• the central effects of amphetamine appear to be almost entirely due to the release of NA from storage sites

Dosage & Administration

• amphetamine sulphate is a white, water soluble powder available in 5 and 10 mg tablets
• the d-isomer is available as dextroamphetamine sulphate, in the same dosage and in an elixir

■ *Toxicity & Side Effects*

• the acute toxic effects are generally extensions of the therapeutic action of the drug
• the CNS effects commonly include restlessness, agitation, dizziness, tremor, hyperactive tendon reflexes, irritability, weakness, insomnia, fever and sometimes euphoria
• hallucinations, paranoid delusions, suicidal and homicidal tendencies all occur more frequently in mentally ill patients but can be elicited in any individual with sufficient doses of amphetamine
• CVS effects are common including palpitations, headache, chilliness, dysrhythmias, anginal pain, hypertension or hypotension, and circulatory collapse
• GIT symptoms of N&V, diarrhoea, abdominal cramps and altered taste

• treatment of acute intoxication includes,

1. acidification of the urine with ammonium chloride

2. sedation with chlorpromazine - also has α blocking effect

3. a rapidly acting α blocker if the BP is very high

NB: both tolerance and psycological **dependence** readily develop

Ephedrine

• occurs naturally in many plants, being the principal alkaloid of **Ma Huang** which has been used in China for over 2000 years, prior to its introduction into Western medicine in 1924
• its CNS actions are less pronounced than those of amphetamine and it has agonist activity at both α & β receptors
• the drug owes part of its action to the release of NA but also exhibits substantial effects in reserpine treated animals & man
• **tachyphylaxis** develops to its peripheral actions, and rapidly repeated doses are less effective
• as it contain 2 asymmetrical carbon atoms, 4 compounds are available
• only racemic and l-ephedrine are clinically in use
• ephidrine differs from **adrenaline** mainly by its,

1. effectiveness after oral administration

2. longer duration of action

3. more pronounced central actions

4. much lower potency

   NB: however, its **profile** of action closely mirrors that of adrenaline

■ *Cardiovascular Effects*

• produces a sharp rise in systolic, diastolic and pulse pressures, with a reflex bradycardia, similar to AD but lasting ~ 10 times as long
• the pressor response is mainly due to cardiac stimulation, with some additive vasoconstriction
• contractility and CO are increased providing venous return is adequate
• renal and splancnic blood flows are decreased, whereas cerebral, coronary and skeletal m. blood flows are increased

■ *Respiratory Effects*

• bronchodilation is less prominent but more sustained than with AD
• consequently ephedrine is only of value in the milder cases of asthma

■ *Other Effects*

• mydriasis occurs after local application to the eye
• reflexes to light are not abolished
• accommodation is unaffected and intraocular pressure is unaffected
• however, these drugs are of little use in the presence of inflamation
• other smooth muscles are effected in a similar manner to AD
• however, the activity of the human **uterus** is usually reduced, regardless of the effect of AD
• ephedrine is less effective in raising the blood glucose
• the CNS effects are similar to amphetamine but considerably less

■ *Dosage & Administration*

• ephedrine sulphate is the *l-isomer* and is available in 25 and 50 mg capsules and in syrups
• the average oral administration is 15-50 mg
• for continual medication, small doses are given at 4 hrly intervals
• a sterile solution of 30 mg/ml is available for parenteral administration
• also may be used topically as a nasal decongestant

Phenylephrine

• differs from AD only by lacking the *4-OH group* on the benzene ring and subsequently is resistant to COMT and has predominantly **a**-*agonist* effects
• direct agonist activity accounts for most of its effects, only a small amount being due to the liberation of NA
• central stimulant action is minimal

■ *Cardiovascular Effects*

• the predominant actions are on the peripheral *arterioles*
• i.v., s.c., or oral administration results in a rise in systolic & diastolic pressures
• responses persisting for ~ 20 mins post i.v. and ~ 50 mins post s.c. inj.
• accompanied by a marked *reflex bradycardia* which can be blocked by atropine
• after atropine large doses of the drug produce only a slight increase in HR, consistent with its *minimal* **b**-*agonist activity*
• CO is slightly decreased and the TPR is markedly increased
• the circulation time is prolonged and the CVP increased, though, venoconstriction is not marked
• most vascular beds are constricted → reduced splancnic, renal, cutaneous and limb blood flows
• the pulmonary vasculature is similarly constricted and mean pulmonary arterial pressure is raised
• coronary autoregulation remains intact and CBF is elevated comensurate with the increased work of the heart
• cardiac dysrhythmias are rare and the reflex vagal activity is sufficient to permit the use of the agent in the R_X of atrial tachycardia

■ *Dosage & Administration*

• phenylephrine hydrochloride (NEOSINEPHRINE) is the *l-isomer* and is available as a sterile solution of 10 mg/ml, plus topical nasal and ophthalmic preparations
• absorption after oral administration is unreliable
• for the R_X of hypotension during spinal anaesthesia the usual dose ~ 2-3 mg either s.c. or i.m. (Wood & Wood say 5-10 mg i.m.)
• the drug is also used to raise perfusion pressure during cardio-pulmonary bypass

Methoxamine

· is a potent vasopressor which exerts almost all of its effects by *direct* stimulation of ***a receptors***
· its actions are therefore similar to phenylehprine
· it is resistant to metabolism by MAO & COMT and, therefore, has a long duration of action
· the outstanding effect is an elevation of blood pressure, systolic, diastolic and pulse pressures, due entirely to an increase in TPR which may last 60-90 mins
· a ***reflex bradycardia*** is prominent
· cerebral, renal, splancnic and limb blood flows are reduced
· coronary blood flow is unchanged
· the drug has virtually no stimulant action on the heart and is devoid of β receptor action on smooth muscle
· in the presence of atropine it may decrease the HR slightly due to an α effect on the SA node
· it does not precipitate cardiac dysrhythmias
· it causes little or no CNS stimulation
· as for phenylephrine, it is used to treat hypotension during spinal anaesthesia and C-P bypass; and the reflex effects may be used to treat ***atrial tachycardias***
· methoxamine hydrochloride it is available as a solution of 20 mg/ml for i.m. injection; maximal effects being seen in 20 mins
· slow i.v. injections of 2 to 10 mg may be given, usually in small increments

Metaraminol   Aramine

· chemical name ***3-hydroxyphenylisopropanolamine***
· possesses both ***direct*** & ***indirect*** actions, the overall effects being similar to noradrenaline
· relative to NA, it is less potent, though, has a longer duration of action,

      a.   IV   ~ 20-30 mins

      b.   IM   ~ 90 mins

· it is effective orally, with a low bioavailability ~ 20%
· CVS effects include,

      a.   increase in diastolic, systolic and mean BP

      b.   ***reflex bradycardia***

      c.   CO $\rightarrow$ little change in normotensive subjects
                        increased in hypotensive/shocked patients
                        marked increase if bradycardia blocked with atropine

      d.   increases venous tone

      e.   decreases renal and cerebral blood flows (even if δBP ~ 40%)

      f.   causes ***coronary vasoconstriction***

      g.   ***pulmonary vasoconstriction*** & increased PA pressures

· available as metaraminol bitartrate, 10 mg / 1 ml solution
· should be diluted prior to IV use in ~ 10-20 ml

Phosphodiesterase III Inhibitors / Inodilators

• non-adrenergic, non-catecholamine agents, classified biochemically,

     a.   bipyridine derivatives   - amrinone & milrinone

     b.   immidazoles   - enoximone & piroximone

• the *inotropic* effects are additive to those of the cardiac glycosides & β-agonists
• the effects are not blocked by α/β antagonists, or reduced by catecholamine depletion
• the effects are due to inhibition of cyclic nucleotide *phophodiesterase* (PDE_3) found predominantly in cardiac muscle
• this results in an increase in **cAMP / cGMP**, which produces,

     1.   in heart muscle
          i.   increased *calcium* influx
          ii.   increase in contractility $\rightarrow$ $\uparrow \delta P/\delta t$, SV, EF
          iii.   increase in HR
          iv.   increase in relaxation   - positive leusotropy

     b.   reduction in PVR
          i.   direct relaxation of bronchial smooth muscle   - "β$_2$-like" involving NO
          ii.   indirect due to increased CO and decreased PCWP

     c.   reduction in SVR

     d.   an increase in DO_2 in septic patients

• amrinone does not affect the transmembrane potentials of the Purkinje fibres but augments the *slow responses*
• these agents are unlikely to cause *afterdepolarisations*, but do potentiate those caused by the cardiac glycosides

• *clinical uses* include,

     1.   management of refractory CCF   - not first line due to cost
     2.   biventricular failure or isolated RV dysfunction
     3.   weaning post cardiopulmonary bypass
     4.   low CO / high SVR phase of septic shock
     5.   pulmonary hypertension where a reversible component exists

• *adverse effects* include,

     1.   gastrointestinal intolerance
     2.   hepatotoxicity
     3.   fever
     4.   reversible *thrombocytopenia*   ~ 20% with amrinone

■ *Milrinone*

· a second generation PDE_3-inhibitor
· similar haemodynamic profile to amrinone, producing positive inotropy & vasodilatation, however the inotropic effects are ~ 12-15 times those of amrinone
· significantly, the increase in CO and decrease in SVR & PCWP are achieved without any significant rise in HR or myocardial MRO_2

> 1. greater inotropic action with less baroreceptor induced increases in rate
>
> 2. greater leusotrophic effect improving myocardial blood flow

· *thrombocytopaenia* appears clinically insignificant with milrinone cf. amrinone
· *arrhythmias* occurred in 14% in the European Milrinone Multicentre Trial Group

> a. prospective study of post-cardiac surgery augmentation of LV function
>
> b. three dosage schedules   - 0.375, 0.5, 0.75 µg/kg/min
>
> c. 90% of arrhythmias were non-serious   - 16/18 patients
>
> d. 2 patients developed rapid AF at the higher dose schedule
>
> *NB:* milrinone was *less effective* cf. digoxin but more arrhythmogenic,
> the combination of digoxin plus milrinone was no more effective than digoxin alone
> (DiBianco *et al.* Milrinone Multicentre Trial Group, 1989)

■ *Enoximone*

· similar cardiac and vascular profile cf. the other agents
· as it is an *immidazole* it has a shorter half-life cf. the bipyridines, $t_{\frac{1}{2}\beta}$ ~ 1.3 hrs
· potential advantages include,

> 1. available as an oral preparation   - Europe only
>
> 2. lower incidence of arrhythmias   - electrophysiological studies

Vesnarinone

■ *Mechanism Of Action*

· weak PDE_{III} inhibitor with other effects,

    1.   prolongs open Na^+-channel conductance

    2.   delays both inward and outward rectifying K^+-currents
        · prolongs the APD duration cf. the Class III antiarrhythmics

    3.   *slows* the HR   - in contrast to other PDE_{III} inhibitors

    4.   modifies cytokine production
        · inhibits lipopolysaccharide induced production of TNFα and γ-interferon

    5.   inhibits granulocyte colony stimulating factor
        · especially seen in those who become neutropaenic (see side effects)

■ *Indications*

· possible symptomatic CCF not responsive to digoxin & ACEI
· reduced mortality at 60 mg/d in NYHA III patients
· however, *increased mortality* at 120 mg/d, ∴ has a *narrow therapeutic margin*

■ *Side Effects*

    1.   neutropaenia   ~ 2.5% of patients
                              - usually within 4-16 weeks of treatment

    2.   hepatic dysfunction

    3.   proarrhythmia

Selective β_2-Adrenergic Stimulants

· because of their *relative selectivity*, these agents relax the smooth muscle of the bronchi, uterus and vascular supply to smooth muscle, but generally have far less action on the heart than ISO and other agents

· increased β_2 agonist activity is conferred by the substitution of increasing bulky lipophillic groups on the amino group of ISO

· changing the benzene OH substitutions on ISO from 3,4 to 3,5 results in metaproterenol, which retains its β_2 actions but has reduced β_1 activity

· further the shift of the OH group produces resistance to MAO and prolongs the duration of action   (see W&W fig. 13.7)

· such agents include,

      a.   salbutamol

      b.   terbutaline

      c.   ritodrine

      d.   metaproterenol

      e.   fenoterol

      f.   isoetharine

■ *Terbutaline*

· is not a catecholamine, therefore is resistant to COMT
· an oral dose of 5 mg produces effective bronchodilation in 1 hr, lasting up to 7 hrs
· can be administered s.c., or by inhalation
· usual s.c. dose ~ 0.25 mg to a maximum of 0.5 mg/4 hrs
· not recommended for children under 12 yrs
· available as,

      a.   injection   1 mg/ml

      b.   tablet   2.5 & 5 mg

      c.   inhalation   0.2 mg per spray

■ *Salbutamol*

· similar to terbutaline, however is a *catecholamine*
· administered by inhalation it produces significant bronchodilation within 15 mins, with effects lasting up to 4 hrs

■ *Ritodrine*

· this agent was produced specifically as a uterine relaxant, though, its actions are essentially the same as above
· it is rapidly but incompletely absorbed after oral padministration and ~ 90% of the drug is excreted in the urine as inactive conjugates
· ~ 50% of the drug is excreted unchanged after i.v. administration

Therapeutic Uses of the Sympathomimetic Drugs

■ *Physiological Considerations*

• prior to i.v. use, hypovolaemia, hypervolaemia, hypoxaemia, and abnormalities of acid base balance should be corrected
• the patient should be monitored haemodynamically with at least IABP and a CVP line
• although increases in TPR increase BP, this also increases myocardial work & oxygen consumption, and limits peripheral perfusion with resultant tissue hypoxia and metabolic acidosis

■ *Clinical Uses*

1. cardiac arrest — any cause
   — especially where a reversible component is present

2. cardiogenic shock / severe CCF
   i. AMI
   ii. acute valvular dysfunction
   iii. cardiomyopathy
   iv. post-cardiopulmonary bypass
   • myocardial MRO_2 is dependent upon ventricular wall tension, HR and contractility
   • any agent which increases these will exacerbate myocardial ischaemia
   • combination with a peripheral vasodilator may result in significant improvement

3. severe acute asthma

4. anaphylaxis

5. hypotension — *per se* is not adequate justification
   • with evidence of inadequate perfusion of vital organs
   • as an emergency measure until definitive treatment is available
   • secondary to spinal, epidural or general anaesthesia
   • overdosage with antihypertensive agents
   • following removal of a phaeochromocytoma

6. other uses
   i. topical haemostasis
   ii. decongestion of mucous membranes
   iii. adjuncts to the local anaesthetics
   iv. topical ophthalmic preparations — mydriatics
   v. narcolepsy — the amphetamines
   vi. Parkinsonism
   vii. obesity & weight reduction
   viii. attention-deficit disorder — hyperkinetic syndrome

ADRENORECEPTOR BLOCKING AGENTS

Background

• these agents competitively antagonise the effects of the catecholamine's at α and/or β receptors
• since the SNS is intimately involved in the modulation of a large number of homeostatic mechanisms, interference with its function impairs the capacity of the organism to generate appropriate physiological responses to provocative or adverse environmental conditions
• thus, many of the side effects of these agents are common to the group as a whole, these include,

      a.   postural hypotension

      b.   sedation or depression

      c.   increased GIT motility & diarrhoea

      d.   impaired ability to ejaculate

      e.   increased blood volume & sodium retention

• the β-blocking agents have received major attention due to their usefulness in the management of cardiovascular disorders, angina pectoris, and arrhythmias
• the first drug shown to produce selective β blockade was ***dichloroisoproterenol*** DCI, in 1958
• however, this agent is a ***partial agonist*** and was therefore not used clinically

• ***propranolol*** was the first agent to come into widespread clinical use
• it is a highly potent, ***non-selective*** β receptor antagonist with no intrinsic sympathomimetic activity (ISA)
• due to its nonselective activity, propranolol also interferes with bronchodilation and with glycogenolysis
• therefore the drug is unsuitable for asthmatics and must be used cautiously in diabetics

• these problems prompted the search for ***cardioselective*** β blocking agents
• ***practolol*** was the first such agent and received widespread use in Europe, however, there were subsequent reports of toxicity involving epithelial structures after long term use of the drug
• there are now large numbers of both non-selective & selective β antagonists available
• recent evidence for the subdivision of α receptors and the relatively selective action of certain agents at these has led to a similar search for selective α receptor blocking agents

β-ADRENERGIC BLOCKING AGENTS

Pharmacodynamic Properties

• all of the available agents *competitively* block the effects of endogenous and exogenous catecholamine's
• this means with a sufficiently high concentration of agonist a full response is still possible
• thus, the dose-response curve is shifted *parallel* to the right and there is no such thing as complete β blockade
• the responsiveness to agonist (ISOproterenol) *decreases* with age
• for a given increase in HR the elderly require 4-5 times the dose of ISO than the young
• receptor theory would predict that following administration of an antagonist, propranolol,

$$DR - 1 \ = \ [P]/K_d \qquad \text{(from Schild)}$$

where,   DR   =   the ratio of the dose of ISO after Propranolol
                 P   =   the unbound propranolol concentration in plasma
                K_d =   the apparent dissociation constant for propranolol

• following the administration of propranolol, it is found that the elderly are 4-5 times more resistant to propranolol than the young
• the receptor has been purified and is a single glycosylated polypeptide

■ *Membrane Stabilizing Activity*

• early studies with propranolol showed that it possessed electrophysiological properties similar to *quinidine*, which were not related to its action at β receptors
• specifically propranolol produces the following effects

      a.   decreases the rate of phase 4 depolarisation

      b.   increases the electrical threshold
               $\rightarrow$ decreases spontaneous & maximal driving frequency

      c.   the resting potential and AP duration (repolarisation) are unchanged

      d.   increase AV conduction time

      e.   decrease the spontaneous rate of ectopic pacemakers in intact hearts

      f.   decreases the inward Na^+ current and $\delta V/\delta t$ of phase 0

• these effects are associated with generalised depression of myocardial function and may result in death in large doses
• a number of other agents also possess this activity, including *alprenolol* and *oxprenolol*
• the magnitude of this effect is such that it is probably of limited clinical value, requiring ~ 100 times the concentration which suppresses arrhythmias and inhibits exercise tachycardia
• β adrenergic blockade is by far the most important factor in precipitation of heart failure in those with poor cardiac reserve and in the efficacy of these agents in the management of arrhythmias

- ■ *Selectivity*

· these drugs are not specific in their actions at β_1 receptors, rather they block these receptors at a lower concentration than is required to block β_2 receptors

> *NB:* thus, conveying some degree of *selectivity* rather than specificity

· in patients with asthma, β_1 selective agents are less likely to precipitate bronchospasm
· however, in some patients at therapeutic doses, and probably in all patients at high doses, these agents will cause **bronchoconstriction**
· in diabetics, nonselective agents may delay the recovery from hypoglycaemia whereas the selective agents are less likely to do so
· in addition, severe bradycardia and elevated diastolic blood pressure have occurred in patients taking propranolol, effects which are less with a selective agent

- ■ *Intrinsic Sympathomimetic Activity*

· some of the β blockers have *agonist* activity, demonstrated in animals pretreated with reserpine (NA depleted)
· this activity is clearly less than the activity of AD or ISO
· thus these agents may act as competitive antagonists of full agonists
· it was initially believed that agents lacking ISA were more effective in the treatment of hyperthyroidism, however this has recently been disputed
· also suggested that agents with ISA were less likely to precipitate CCF in patients with compromised cardiac function
· this is not the case as, the partially failing heart requires a high resting level of SNS tone to maintain an adequate cardiac output, and removal of this by β blockade is likely to precipitate CCF irrespective of the action of the agent on the myocardium *in vitro*

- ■ *Pharmakokinetics*

· the β blockers can be divided into two groups according to their route of elimination
· being either metabolised in the *liver*, or excreted largely unchanged by the *kidneys*

Elimination of β Blockers						
Drug	% Absorb[n]	Bioavail[1] ability	(%) Protein Binding	Half-life (hrs)	Metab-olism	%Urine Unchanged
Alprenolol	>90	15	85	3-6	++++	< 1
Metoprolol	>95	50	12	3-4	++++	< 5
Oxprenolol	70-95	20-60	80	1-1.5	++++	< 5
Propranolol	100	33	90	4-6	++++	< 1
Timolol	>90	75	10	4-5	+++	10-20
Acebutolol		20-60	84	3-6	50-60	> 40
Pindolol	> 90	>90	46	2-5	60	40
Atenolol	45-60	55	<5	6-7	±	85-100
Nadolol	15-25	20	25-30	12-24	+	70
Sotalol		>60	5	5-13	+	60
Esmolol	N/A[2]	N/A	55	10 mins	++++[3]	< 2

[1]   bioavailability dependent upon both absorption and first-pass metabolism

[2]   only available as an IV preparation

[3]   metabolism is by ester hydrolysis in red blood cells

Propranolol, Metoprolol & Timolol

• this group are almost completely absorbed after **oral administration** and peak plasma concentrations are reached quickly
• "first pass metabolism" is high and may be extensive, resulting in a **low bioavailabilit**y
• additionally, hepatic extraction of propranolol appears to be dose dependent
• therefore it is impossible to predict steady state drug concentrations after a single dose, as bioavailability is higher with chronic administration than after the first oral dose
• the factors determining clearance of the drug, and thus SS levels, after oral and i.v. administration are different
• oral clearance is solely dependent upon intrinsic hepatic metabolism, whereas IV clearance is dependent predominantly upon liver blood flow and to a lesser extent metabolising capacity
• hepatic blood flow is far less variable than metabolising capacity, thus the variability following i.v. administration is far less than orally, where 20 fold variations have been found
• although most studies of these effects have been with propranolol, it is likely that these principles also apply to the other highly metabolised drugs

Atenolol, Sotalol & Nadolol

• these agents are mainly excreted unchanged by the **kidneys**, thus their elimination is markedly impaired in renal disease
• also, as they are not subject to significant first pass metabolism, theoretically their SS levels should show less interindividual variation
• however, nadolol especially is poorly absorbed, and variation in absorption will result in variations in SS level
• these variations in absorption are generally **less** than those seen with metabolism

Esmolol   (Breviblock)

• **cardioselective** β_1-blocker with **no** intrinsic sympathomimetic, or membrane stabilising activity
• administered only IV
• the plasma half-life **~ 9-10 mins**
• central and steady-state V_{dSS} ~ 1.9 & 3.3 l/kg respectively
• metabolised by **ester hydrolysis** (rbc's), not by AChE or BuChE
• the principal metabolite is an acid derivative plus **methanol**
• total body clearance ~ 20 l/kg/hr, and clinical effects disappear within 18-30 minutes
• steady state by infusion can be reached in ~ 5 minutes with a,

    a.   loading dose   ~ 0.5-1.0   mg/kg   - over 1 minute

    b.   infusion   ~ 0.05-0.3 mg/kg/min

• onset of clinical effect is within 60 secs, though maximal effects may be delayed ~ 3-5 minutes
• following several hours of infusion, plasma **methanol** levels remain < 10 µg/ml, which is < 2% of levels associated with methanol toxicity and equal to normal endogenous levels
• available as,

    1.   **ampoules**   - 2.5g / 10 ml   (250 mg/ml)
          • **not for injection**, must be diluted prior to use
          • use 2 x 2.5g per 500ml of solution $\rightarrow$ 10 mg/ml
          • stable for 24 hrs

    2.   **vials**   - 100 mg / 10 ml   (10 mg/ml)
          • loading dose for SVT ~ 0.5 mg/kg, or 3.5 ml for 70 kg patient
          • this may be repeated x1 at q5m if no effect

• best suited to situations were short duration, or a therapeutic trial of β-blockade are indicated
• principal adverse effect is **hypotension**, which is worse than that seen with propranolol
• potentially fatal hypotension may occur with the coincident administration of **verapamil**
• occurs in up to 25%, and is severe enough to cause symptoms in ~ 12%
• contraindicated in the presence of CCF, or heart block (other than 1st degree)

■ *Liver Disease*

• this will affect those agents which are highly metabolised; also, the alterations of plasma proteins seen in liver disease may affect those agents which are highly protein bound
• the existence of porta-systemic shunts results in a higher oral bioavailability
• SS concentrations of propranolol are markedly higher in cirrhotic patients due to;

      a.   increased bioavailability (38% vs. 54%)

      b.   decrease in systemic clearance

• increased SS levels and the decrease in protein binding $\rightarrow$ ~ 3 fold increase in the free drug level
• those drugs largely excreted unchanged are little effected by liver disease

■ *Renal Disease*

• those agents excreted largely unchanged in the urine will accumulate in renal disease
• some have suggested that the excretion of the highly metabolised group may also be impaired, however this **has not** been demonstrated with propranolol
• the elimination of nadolol was found to correlate closely with the creatinine clearance, and in those with severe renal failure the $t_{1/2\beta}$ was prolonged from 15-20 to 45 hrs
• the elimination half-life of the acid metabolite of esmolol is significantly prolonged in patients with renal insufficiency

■ *Cardio-Pulmonary Bypass*

• recently demonstrated that propranolol levels rise during such a procedure
• thought to be due to an alteration of the V_{dSS}, however the study in question did not correct for the increase in free fraction caused by the concurrent administration of **heparin**
• this change in free fraction is due to the activation of **lipoprotein lipase** and an increase in circulating **free fatty acids,** occurring even after small doses of heparin

■ *Other Factors*

• SS levels were found to be ~ 2 fold higher in individuals > 35 when compared to those < 35
• further, smokers had significantly lower levels than non-smokers throughout the dosing interval
• the oral intrinsic clearance of propranolol falls significantly with age only in smokers
• this suggests that smoking only increases the ability to eliminate propranolol in the young, the elderly being relatively resistant to this effect
• as creatinine clearance falls with age, so the elimination of the high renal excretion group would be expected to fall in the elderly, with subsequently higher SS levels

Adverse Effects of β-Blockade

· the most dramatic effects are usually seen following the ***first dose***, when blockade quickly demonstrates the subjects dependence on adrenergic stimulation
· further doses produce only relatively modest increases in the degree of blockade, therefore "at risk" patients should be started on small doses

■ ***Bronchospasm***

· blockade of β_2 receptors on bronchial smooth muscle may lead to bronchospasm in patients with asthma or chronic airways obstruction
· this may also occur with the ***selective*** β_1 blockers, however usually only occurs at higher doses
· esmolol may be used with appropriate caution, in asthmatic patients

    a.   infusions ≤ 0.2 mg/kg/min $\rightarrow$ no increase in airways resistance

    b.   infusions $= 0.3$ mg/kg/min
        $\rightarrow$ slight increased sensitivity to dry-air stimulus (not clinically sig.)

    NB: not listed as specific C/I, only as a precaution
        if β-blockade absolutely required, then short $t_{\frac{1}{2}\beta}$ makes this agent of choice to determine patient response

■ ***Cardiac Failure***

· these agents may precipitate cardiac failure in patients with limited cardiac reserve
· although the (-)'ve inotropic action of these agents may be responsible in some cases, it is more likely that removal of basal SNS tone is the dominant factor
· this reversal will occur equally with all β blocking agents, irrespective of their ISA or selectivity

■ ***Peripheral Vascular Disease***

· this and Raynaud's phenomenon may be caused by β_2 receptor blockade
· selective agents are therefore preferred, if justified at all

■ ***Diabetes Mellitus***

· β blockers can mask the usual warning signs of hypoglycaemia which are adrenergically mediated
· as ***sweating*** is ACh-SNS mediated this sign may in fact be increased
· the nonselective agents may worsen the effects of ***hypoglycaemia*** by,

    a.   increasing the rise in blood pressure

    b.   inhibiting SNS and adrenaline mediated glycogenolysis and lipolysis, prolonging the period of hypoglycaemia

    c.   increasing the bradycardia

· the selective β_1 agents such as ***metoprolol*** produce less marked changes

- *__Bradycardia__*

• this should only be considered an adverse effect in the presence of signs of an inadequate CO
• bradycardia *per se* is almost never an indication for stopping or reducing the dose of β blocker if CO is maintained

- *__Withdrawal Syndrome__*

• various case reports have described following the cessation of propranolol the development of,

      a.   ventricular arrhythmias

      b.   severe angina

      c.   myocardial infarction

      d.   death

• these effects are postulated to be due to receptor *__supersensitivity__*, due to adaptive increases in receptor numbers
• other theories include an increase in the circulating levels of T_3
• some patients develop premonitory signs, tachycardia, nervousness and sweating
• hypertensives may develop marked *__rebound hypertension__*, well above the pretreatment levels
• the syndrome is claimed to be less severe with agents with ISA, eg. pindolol
• multiple authors now agree there is no case for the cessation of β-blockade prior to surgery
• if treatment is to be stopped this should be done gradually

Pharmacological Effects

· as stated, propranolol is the most widely studied member of this group
· it blocks both β_1 & β_2 receptors *competitively* and shows *no ISA* activity

- **Cardiovascular System**

· these are the most important effects of this group and include,

    a.   decrease in heart rate

    b.   prolongation of mechanical systole

    c.   slight decrease in blood pressure in resting subjects

· the effects on HR and CO are more dramatic during *exercise* and the maximal exercise tolerance is significantly reduced in normal individuals
· however, this may be increased in patients with *angina pectoris*
· peripheral resistance is increased as a result of compensatory SNS reflexes
· blood flow to all tissues, except the brain, is reduced
· the cardiac effects of β blockade are frequently seen in alterations of *sodium excretion*,

    a.   the normal diurnal pattern is reversed, as for patients with moderate myocardial insufficiency

    b.   slow adjustment to an increased ECF volume & total body Na^+

· these effects are most pronounced in patients with some pre-existing myocardial insufficiency
· in severe cases blockade may lead to progressive and severe CCF
· ventricular dimensions and contractility are little affected in normal resting individuals
· however, exercise related reductions in LVED volume and increased contractility are reduced
· in patients with occlusive coronary artery disease, propranolol may result in significant increases in LVED volume and pressure, and an increase in the tension-time index
· also, it may increase ventricular asynergy
· total myocardial O_2 consumption and coronary blood flow are reduced, secondary to the reductions in rate, contractility and pressure

> *NB:* the reductions in blood flow are predominantly *subepicardial*,
>   thus producing a favorable redistribution of blood flow

· while dilation of the ventricle and prolongation of systolic ejection tend to increase O_2 demand, the above reductions predominate

· chronic administration of β blockers results in a slowly developing reduction in arterial blood pressure
· these agents are particularly effective antihypertensive drugs, especially when combined with the peripheral vasodilators, as they block the reflex tachycardia which usually results from the later
· propranolol results in a prompt fall in CO, however this precedes the fall in arterial pressure
· also blocks *presynaptic* β_2 receptors, decreasing the quantity of neurally released NA (Rand)

■ *Cardiovascular System*

• adrenergic agonists (β_1) stimulate the release of *renin* from the juxtaglomerular apparatus and this is blocked by propranolol
• the release of renin induced by Na^+ deprivation is reduced but not abolished
• the effects of modest doses of propranolol are significantly greater in individuals with elevated plasma renin activity, though, hypertensive patients with low PRA do respond to higher doses
• some β blockers lower arterial pressure but have no significant effect upon renin secretion

> *NB:* thus it is likely that some, but not all of the hypotensive effect of the β blockers is due to inhibition of renin secretion

• these drugs augment the pressor response to adrenaline and inhibit the vasodepressor activity of isoproterenol
• they slightly decrease the pressor response to noradrenaline, as its cardiac actions are blocked
• vasodilation due to histamine, ACh and nitroglycerine are unaffected
• they do not affect the renal vasodilation due to dopamine

• propranolol, oxprenolol and alprenolol display *quinidine like* effects

■ *Central Nervous System*

• propranolol readily crosses the BBB but displays few, if any, effects which are clearly attributable to β blockade
• postulated by some that the antihypertensive effects may have a central component

■ *Metabolic Effects*

• these agents considerably modify carbohydrate and fat metabolism,

a. inhibit the rise in FFA's induced by catecholamine's & SNS activity

b. inhibit catecholamine induced lipolysis in isolated adipose tissue

c. reduce the hyperglycaemic response to adrenaline

d. inhibit glycogenolysis in the heart and skeletal muscle

e. possibly inhibit glycogenolysis in the liver

f. do not effect the plasma insulin or glucose levels in normal individuals, or the rate & magnitude of the fall in glucose after administration of insulin

g. they may prolong the subsequent *recovery* from hypoglycaemia and prevent the rebound elevation of plasma glycerol

• these effects are presumably due to inhibition of the glycogenolytic and lipolytic actions of endogenous catecholamine's released in response to hypoglycaemia

■ *Other Effects*

• outside the CVS, the most important effects are on the bronchial smooth muscle
• bronchodilation is mediated by β_2 receptors but the presence of significant intrinsic adrenergic bronchodilation was not demonstrated prior to β blockade
• propranolol consistently increases ***airway resistance***, however this is not functionally significant in normal individuals
• they block the relaxation of the uterus induced by catecholamine's but have no effect when the response is excitatory (α)
• propranolol increases the activity of the uterus more in the nonpregnant state than prior to parturition
• they inhibit the action of adrenaline (β_2 mast cell stabilisation) which prevents the formation of local ***oedema*** in "anaphylactic type" circumstances
• circulating ***eosinophils*** characteristically increase during propranolol therapy and the decrease induced by adrenaline is blocked
• they antagonise the adrenaline induced ***tremor*** in man, but there action in skeletal neuromuscular transmission is unsettled

Therapeutic Uses of the β-Blockers

■ *Hypertension*

• often combined with a diuretic agent, or a vasodilator, but are frequently effective alone
• not associated with postural or exercise induced hypotension and seldom disturbs sexual function (erection = ACh & ejaculation = α)

■ *Coronary Artery Disease*

• β blockers were originally developed for the treatment of ***angina pectoris***
• the dose related reduction of exercise induced tachycardia and hypertension reduces the MRO_2 and prevents ischaemia
• the mainstay of antianginal treatment are the vasodilators, such as nitroglycerine
• β blockade is complementary to their action, preventing the reflex tachycardia and enhanced contractility resulting from reduced afterload

• shown initially with practolol (subsequently withdrawn), then with ***alprenolol***, that the number of deaths following AMI may be reduced by β blockade
• this has subsequently been investigated with several agents, including propranolol, metoprolol, timolol and oxprenolol with confirmation of this finding
• possibly due to their ***antiarrhythmic*** action, preventing VF & "sudden death"
• in those trials in which therapy was started early, a reduction in ***infarct sise*** was also demonstrated
• presumably this is the result of a reduction in myocardial work and O_2 requirements

■ *Arrhythmias*

• the value of these agents relates to their ability to slow the SA node, and to decrease atrial & AV nodal conduction
• the drug also slows conduction in re-entrant pathways
• useful in the treatment of;

      a.   sinus tachycardia   - except when due to incipient failure

      b.   supraventricular tachycardias

      c.   atrial fibrillation, as an adjunct to digitalis

      d.   digitalis induced arrhythmias

      e.   ventricular arrhythmias

■ *Hypertrophic Obstructive Cardiomyopathy*

• clearly demonstrated that the positive inotropic agents worsen the degree of LV outflow obstruction in this condition
• there is also evidence of increased levels of catecholamine's in the myocardium of patients with this disorder
• propranolol is therefore helpful, particularly if the HR is elevated in the absence of fluid retention

■ *Dissecting Aortic Aneurysm*

• the main aim of treatment is to reduce BP and the wall *shear stress*, ie. the maximal velocity of LV ejection
• nitroprusside i.v. effectively lowers the BP but β blockade is required to prevent the reflex SNS changes

■ *Glaucoma*

• these agents lower intraocular pressure in open angle glaucoma
• because of its lack of local anaesthetic (membrane stabilising) effects, timolol, is used topically

■ *Thyroid Disease*

• used for symptomatic relief and in preparation for surgery

α-Adrenergic Blockers

• phenoxybenzamine and its cogner, dibenamine, bind covalently to the α receptor, producing an *irreversible* and insurmountable type of blockade
• phentolamine, tolazoline and prazosin bind reversibly and produce a competitive block similar to the β blocking agents
• these agents differ markedly in their ability to block the two types of α receptors,

    a.   **a$_1$**   - postsynaptic, smooth muscle & glands

    b.   **a$_2$**   - CNS and presynaptic on peripheral nerve terminals

• *prazosin* is far more potent at α$_1$ receptors
• *phenoxybenzamine* is moderately selective for α$_1$ receptors (~ 100:1)
• *phentolamine* is less selective for α$_1$ receptors (~ 3-5:1)
• *yohimbine* is a selective α$_2$ antagonist
• all of these agents by blocking α$_1$ receptors will produce peripheral vasodilation, the fall in BP eliciting reflex increases in SNS tone

    NB: the agents with α$_2$ blocking activity produce a proportional increase in the release of NA from SNS terminals and the reflex tachycardia will be greater

Phenoxybenzamine

• along with dibenamine are haloalkylamines which relatively selectively block α$_1$ receptors and have no agonist activity
• their effects are due to a direct action on α receptors, β receptors being unaffected by conventional doses
• these agents are closely related to the nitrogen mustards, and like the later, the tertiary amine cyclises to form a reactive *ethylenimonium* intermediate
• the molecular configuration responsible for blockade is probably a highly reactive carbonium compound, formed when the ring structure breaks, which binds covalently and *irreversibly* to the receptor
• the formation of these intermediates accounts for the delayed onset of action, even after i.v. administration
• the presence of a catecholamine, or of a competitive α blocking agent can reduce the level of blockade achieved by simple competition
• however, once achieved, phenoxybenzamine blockade is unaffected by exposure to these agents
• this later stage is referred to as *nonequilibrium blockade*
• in addition to the increased release of NA due to α$_2$ blockade, these agents inhibit the *uptake* of NA into nerve terminals and extraneuronal tissues
• thus, they increase the turnover of NA and its precursors and increase tyrosine hydroxylase activity

■ *Pharmacological Actions*

• the onset of action is slow, peak effects not being seen until ~ 1 hr after i.v. administration
• the effects disappear with a half-life of ~ 24 hrs, however demonstrable effects last for 3-4 days
and the effects of daily administration are *cumulative* for nearly a week
• oral absorption is poor, bioavailability ~ 20-30%

> *NB:* many tissues appear to have a "safety factor" for α stimulation, as is the case at the
> neuromuscular junction, and little effect is seen until a critical number of receptors
> are blocked, prior to which maximal responses are still attainable

• by virtue of α blockade phenoxybenzamine results in vasodilation and a decrease in BP
• however, the observed effect depends largely upon the resting SNS tone
• thus, in the supine patient effects are minimal, whereas a profound drop in pressure may be
observed in hypovolaemia from any cause, or in the upright posture
• in addition, impairment of vasoconstriction sensitises the subject to the hypotensive effects of a
variety of agents,

    a.   hypercapnia

    b.   anaesthetic agents

    c.   analgesics, such as morphine & pethidine

• rapid injection of one of these agents can cause a precipitous fall in BP, which probably involves
factors other than α blockade
• these drugs produce a prominent and progressive *increase* in **CO** and decrease in TPR in
recumbent subjects
• the flow to various vascular beds varies, and is largely dependent upon regional SNS tone
• cerebral and coronary blood flows are little affected by α blockade unless the BP is reduced
beyond autoregulatory control
• coronary blood flow normally being *increased* by the reflex stimulation to the heart
• resting skeletal muscle and cutaneous blood flow (in cool environments) is enhanced
• however, SNS vasoconstriction exerts little restraint upon exercising muscle or the skin in warm
environments
• splancnic and renal blood flows are not altered remarkably in the normovolaemic subject at rest,
however, under conditions of enhanced SNS tone flow to these regions is markedly increased
• in the kidney, cortical flow is more dependent upon SNS control, flow to the medulla being under
local control (local prostaglandin effects)
• due to differential effects on precapillary and postcapillary vessels, these agents promote a fluid
shift from the interstitium to the vascular compartment
• the chronotropic and inotropic effects of AD, NA and direct or reflex SNS activity are not
blocked by phenoxybenzamine, or any of the other α antagonists
• the reflex *tachycardia* is usually exaggerated because the pressor response is blocked and reflex
vagal tone is minimised, plus the release of NA is enhanced and its removal inhibited
• cardiac *arrhythmias* generated by catecholamine's are effectively prevented, regardless of
sensitisation of the myocardium by halothane etc.
• arrhythmias following ischaemia/AMI, or those induced by hypothermia are not inhibited
• the precise mechanism for this effect is uncertain, ? myocardial α receptors

• the majority of metabolic regulation occurs via β receptors, however there are some important exceptions
• inhibition of ***insulin*** secretion by adrenaline (α_1) is blocked and the lesser β stimulation becomes evident
• thus, in the presence of phenoxybenzamine,

     a.   the hyperglycaemic effect of adrenaline may be masked by increased peripheral uptake

     b.   glycogenolysis is unaffected

• the ***CNS effects*** may lead to N&V, motor excitability, hyperventilation and convulsions, particularly with large doses injected rapidly i.v.
• these effects begin and terminate far more rapidly than the peripheral blocking effects
• more typically, the usual doses result in mild ***sedation***
• also results in ***miosis***, accomodation being virtually unaffected

Phentolamine & Tolazoline

• both agents are substituted ***imidazolines*** which have a wide range of pharmacological actions, including,

     a.   α adrenergic blockade

     b.   sympathomimetic activity

     c.   cholinomimetic activity

     d.   histamine-like actions

• slight changes in their structure may make one or another of these properties dominant
• both agents produce a moderately effective α blockade which is relatively transient
• phentolamine being more potent in this respect
• responses to ***serotonin*** are also inhibited
• given i.v., these agents result in vasodilation, direct and reflex cardiac stimulation
• the effect on BP depending upon the relative contributions of the two
• the cardiac stimulant effects may result in an alarming ***tachycardia*** and arrhythmias are common
• previously used for the investigation of phaeochromocytoma, though, there is little justification for this use today
• may be used to manage transient hypertensive episodes during the removal of a phaeochromocytoma

Prazosin

• refer to notes on antihypertensives

Therapeutic Uses of the α-Blockers

■ ***Phaeochromocytoma***

• these agents were used in the past as challenge tests but this use is largely obsolete
• main use now is in the pre-operative preparation of patients, and in the long-term management of tumours not amendable to surgery
• also used for the management of transient hypertension during operative manipulation of the tumor
• oral ***phenoxybenzamine*** is the preferred drug in the first two situations, allowing expansion of the blood volume and general improvement in the cardiovascular status of the patient
• a β antagonist is frequently also employed to block the excess stimulation to the heart
• during surgery, i.v. phentolamine may be used for transient elevations of the BP resulting from sudden releases of catecholamine's

■ ***Hypertension***

• with the exception of ***prazosin***, results with this class of drugs have been disappointing
• reflex SNS β mediated effects counter the reductions in BP induced by these drugs

■ ***Other Uses***

• these agents have been used in the treatment of shock in an attempt to reduce afterload and improve tissue perfusion
• obviously CVP must be monitored and they are only indicated if fluid administration has raised the CVP without a commensurate increase in LV output
• however, other vasodilators may be preferable and should probably be combined with a (+)'ve inotrope, especially if there is any evidence of myocardial insufficiency
• also have been used in the treatment of peripheral vascular diseases, though, the results have been less than outstanding
• the most favorable responses are seen when there is a large component of α adrenergic activity, such as in Raynaud's phenomenon, or in acrocyanosis