

Chapter 9 Adrenergic Transmission and Adrenergic Drugs

ADRENERGIC TRANSMISSION

Adrenergic (more precisely 'Noradrenergic') transmission is restricted to the sympathetic division of the ANS. There are three closely related endogenous catecholamines (CAs) which act as signal molecules.

Noradrenaline (NA) It acts as transmitter at postganglionic sympathetic sites (except at sweat glands, and some vasodilator fibres) and in certain areas of brain. Small quantities are secreted by the adrenal medulla.

Adrenaline (Adr) It is secreted by adrenal medulla as the major hormone. It may also have a transmitter role in the brain, but not at peripheral sympathetic nerve terminals.

Dopamine (DA) It is a major transmitter in basal ganglia, limbic system, CTZ, anterior pituitary, etc. and in a limited manner in the periphery (renal blood vessels, etc.) as well.

1. Synthesis of CAs Catecholamines are synthesized from the amino acid phenylalanine as depicted in Fig. 9.1. Tyrosine hydroxylase is a specific and the rate limiting enzyme. Its inhibition by α -methyl-p-tyrosine (metyrosine) results in depletion of CAs. This inhibitor can be used in pheochromocytoma before surgery and in inoperable cases to block synthesis of CAs. All other enzymes of CA synthesis are rather nonspecific and can act on closely related substrates, e.g. dopa decarboxylase can form 5-HT from 5-hydroxytryptophan and α methyl DA from α methyl dopa. Synthesis of NA occurs in all adrenergic neurones, while that of Adr occurs only in the adrenal medullary cells. It requires

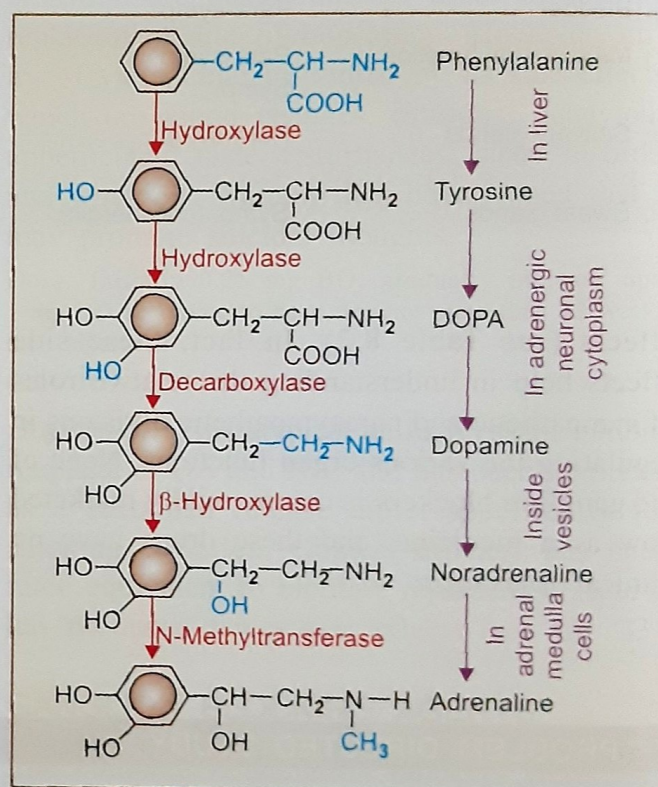


Fig. 9.1: Steps in the synthesis of catecholamines

high concentration of glucocorticoids reaching there through the intraadrenal portal circulation for induction of the methylating enzyme.

2. Storage of CAs NA is stored in synaptic vesicles or 'granules' within the adrenergic nerve terminal (Fig. 9.4). The vesicular membrane actively takes up DA from the cytoplasm and the final step of synthesis of NA takes place inside the vesicle which contains dopamine β -hydroxylase. NA is then stored as a complex with ATP (in a ratio of 4 : 1) which is adsorbed on a protein *chromogranin*. In the adrenal medulla the NA thus formed within the chromaffin granules diffuses out into the cytoplasm, is methylated and

Adr so formed is again taken up by a separate set of granules. The cytoplasmic pool of CAs is kept low by the enzyme monoamine oxidase (MAO) present on the outer surface of mitochondria.

3. Release of CAs The nerve impulse coupled release of CA takes place by *exocytosis* (see p. 106) and all the vesicular contents (NA or Adr, ATP, dopamine β hydroxylase, chromogranin) are poured out. In case of vesicles which in addition contain peptides like enkephalin or neuropeptide Y (NPY), these cotransmitters are simultaneously released. The release is modulated by presynaptic receptors, of which α_2 inhibitory control is dominant.

The autoreceptors of other cotransmitters (Y_2 receptor of NPY and P1 receptor of ATP) also inhibit transmitter release. In addition, numerous heteroreceptors are expressed on the adrenergic neurone which either inhibit (dopaminergic, serotonergic, muscarinic and PGE_2 receptors) or enhance (β_2 adrenergic, angiotensin AT_1 and nicotinic receptors) NA release.

Indirectly acting sympathomimetic amines (tyramine, amphetamine, etc.) also induce release of NA, but they do so by displacing NA from the nerve ending binding sites and by exchange diffusion utilizing norepinephrine transporter (NET) the carrier of uptake-1 (described below) as depicted in Fig. 9.5. This process is not exocytotic and does not require Ca^{2+} .

4. Reuptake of CAs There is a very efficient mechanism by which NA released from the nerve terminal is recaptured. This occurs in 2 steps—

Axonal uptake An active amine pump (NET) is present at the neuronal membrane (see Fig. 9.4) which transports NA by a Na^+ coupled mechanism. It takes up NA at a higher rate than Adr and had been labelled *uptake-1*. The indirectly acting sympathomimetic amines like tyramine/amphetamine but not isoprenaline, also utilize this pump for entering the neurone. This uptake is the most important mechanism for terminating the postjunctional action of NA. From 75% to 90% of released NA is retaken back into the neurone. This pump is inhibited by cocaine, desipramine and few other drugs.

Vesicular uptake The membrane of intracellular vesicles has another amine pump the 'vesicular monoamine transporter' (VMAT-2), which trans-

ports CA from the cytoplasm to the interior of the storage vesicle. The VMAT-2 transports monoamines by exchanging with H^+ ions. The vesicular NA is constantly leaking out into the axoplasm and is recaptured by this mechanism. This carrier also takes up DA formed in the axoplasm for further synthesis to NA. Thus, it is very important in maintaining the NA content of the neurone. This uptake is inhibited by reserpine, resulting in depletion of CAs.

Extraneuronal uptake of CAs (uptake-2) is carried out by extraneuronal amine transporter (ENT or OCT3) and other organic cation transporters OCT1 and OCT2 into cells of other tissues. In contrast to NET this uptake transports Adr at a higher rate than NA, is not Na^+ dependent and is not inhibited by cocaine, but inhibited by corticosterone. It may capture circulating Adr, but is quantitatively minor and not of physiological or pharmacological importance.

5. Metabolism of CAs The pathways of metabolism of CAs are depicted in Fig. 9.2. Part of the NA leaking out from vesicles into cytoplasm as well as that taken up by axonal transport is first attacked by MAO, while that which diffuses into circulation is first acted upon by catechol-o-methyl transferase (COMT) in liver and other tissues. In both cases, the alternative enzyme can subsequently act to produce vanillylmandelic acid (VMA). Other intermediate step enzymes involved are aldehyde reductase (AR), aldehyde dehydrogenase (AD) and alcohol dehydrogenase (ADH). The major metabolites excreted in urine are VMA and 3-methoxy-4-hydroxy phenyl glycol (a reduced product) along with some metanephrene, normetanephrene and 3,4 dihydroxy mandelic acid (DOMA). These metabolites are mostly conjugated with glucuronic acid or sulfate before excretion in urine. Only 25–50 μg of NA and 2–5 μg of Adr are excreted in the free form in 24 hours. However, metabolism does not play an important role in terminating the action of neuronally released CAs.

6. Adrenergic receptors Adrenergic receptors are membrane bound G-protein coupled receptors which function primarily by increasing or decreasing the intracellular production

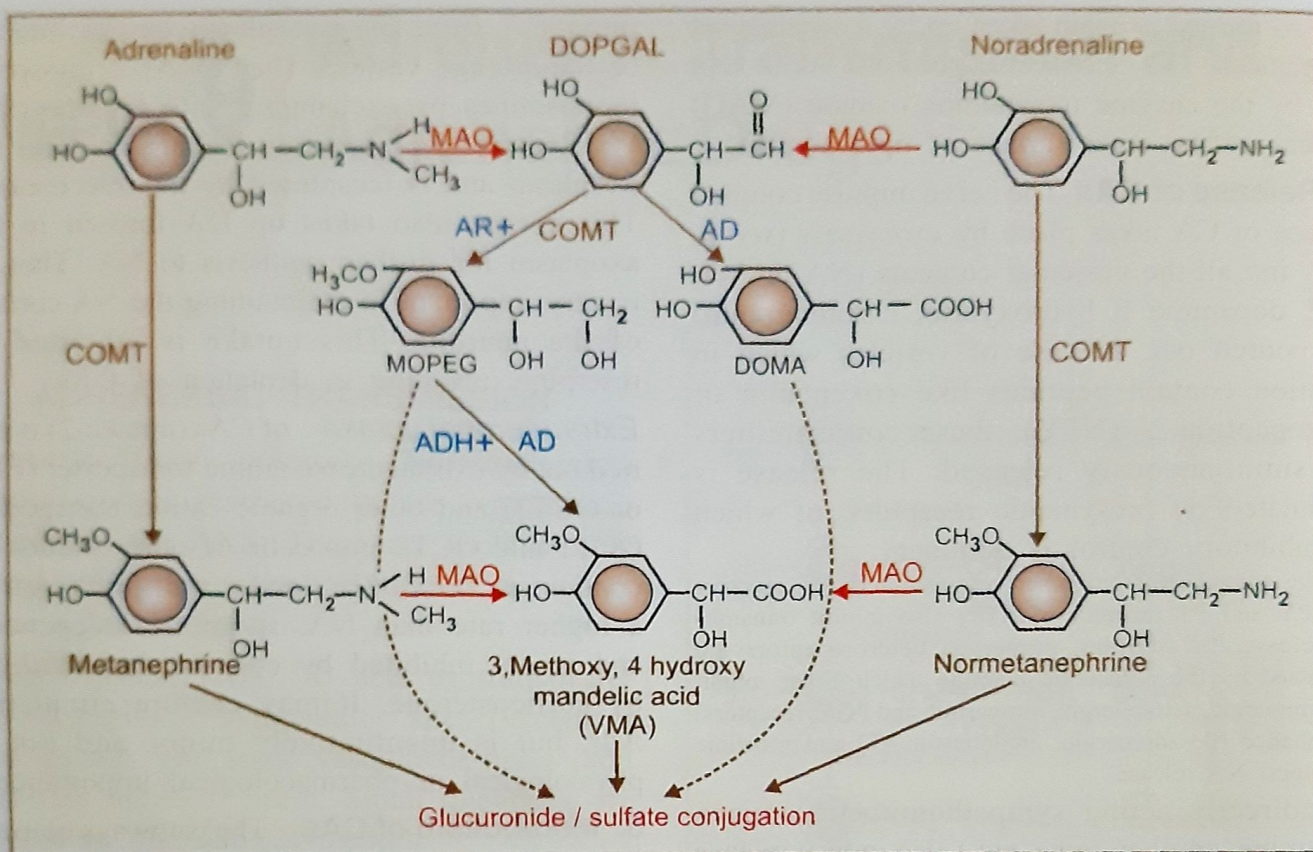


Fig. 9.2: Metabolism of catecholamines

MAO—Monoamine oxidase; COMT—Catechol-O-methyl transferase; AR—Aldehyde reductase; AD—Aldehyde dehydrogenase; ADH—Alcohol dehydrogenase; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-methoxy, 4-hydroxy phenyl glycol; VMA—vanillyl mandelic acid

of second messengers cAMP or IP_3 /DAG. In some cases the activated G-protein itself operates K^+ channels or Ca^{2+} channels, or increases prostaglandin production.

Ahlquist (1948), on the basis of two distinct rank order of potencies of adrenergic agonists

(Fig. 9.3), classified adrenergic receptors into two types α and β . This classification was confirmed later by the discovery of selective α and β adrenergic antagonists. Important features of α and β receptors are given in Table 9.1.

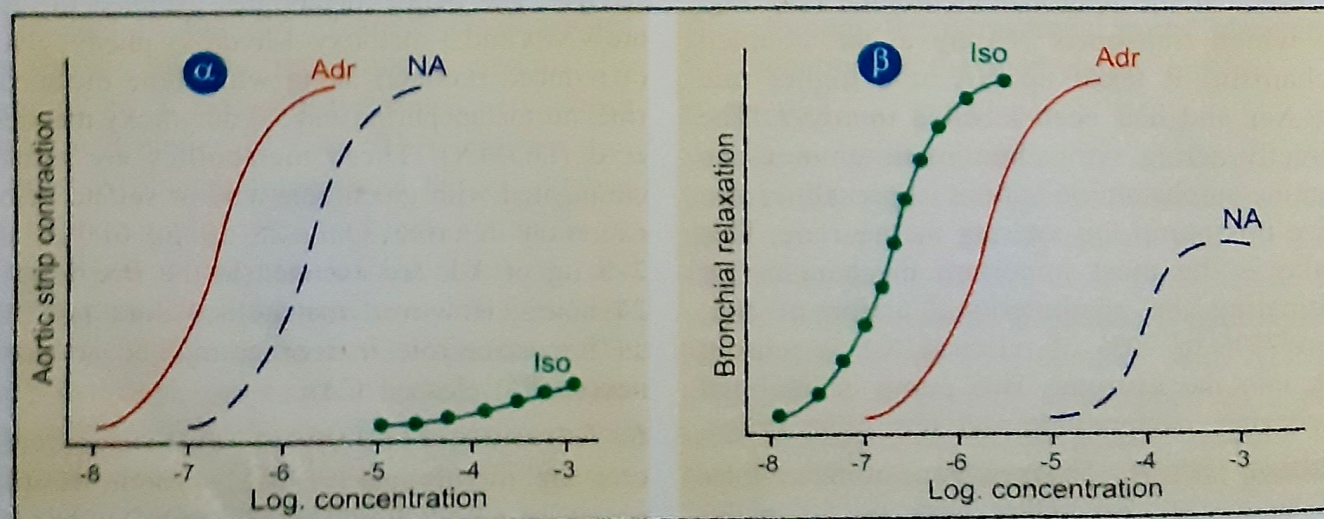


Fig. 9.3: Dose-response curves of 3 catecholamines adrenaline (Adr), noradrenaline (NA) and isoprenaline (Iso) on isolated aortic strip and isolated bronchial smooth muscle illustrating two distinct rank orders of potencies respectively for α and β adrenergic receptors

Table 9.1: Differences between α and β adrenergic receptors

	α	β
1. Rank order of potency of agonists	*Adr > NA > Iso	Iso > Adr > NA
2. Antagonist	Phentolamine	Propranolol
3. Coupling protein	Gq/Gi/Go	Gs
4. Effector pathway	IP ₃ /DAG $\uparrow$, cAMP $\downarrow$, K ⁺ channel $\uparrow$	cAMP $\uparrow$, Ca ²⁺ channel $\uparrow$

* Though inherently NA is equipotent to Adr on α receptors, in test systems with intact neuronal reuptake, it appears less potent due to faster reuptake.

On the basis of relative organ specificity of selective agonists and antagonists, the β receptors were further subdivided into β_1 and β_2 subtypes. Later, β_3 (atypical β) receptors were described which are more sensitive to NA than to Adr, and have very low affinity for the classical β blockers. The β_3 receptors are located on adipocytes, mediate lipolysis and

induce thermogenesis. Selective β_3 agonists have been investigated as antiobesity drugs. Another location of β_3 receptors is on detrusor muscle of urinary bladder; activation causing relaxation. A relatively β_3 selective agonist *mirabegron* has been recently found useful in the symptomatic treatment of overactive bladder by relaxing the detrusor muscle.

Table 9.2: Differences between β_1 , β_2 and β_3 receptors

	β_1	β_2	β_3
1. Location	Heart, JG cells in kidney	Bronchi, blood vessels, uterus, liver, g.i.t., urinary tract, eye	Adipose tissue, Detrusor muscle of bladder
2. Selective agonist	Dobutamine	Salbutamol, terbutalin	Mirabegron
3. Selective antagonist	Metoprolol, Atenolol	ICI 118551 α -methyl propranolol	CGP 20712A (also β_1) ICI 118551 (also β_2)
4 Relative potency of NA and Adr	Adr $\geq$ NA	Adr $\gg$ NA	NA > Adr

In the mid 1970s the α receptors were demonstrated to be present prejunctionally as well. To differentiate these release inhibitory prejunctional α receptors, a subdivision into α_1 and α_2 was suggested. However, the present classification into α_1 and α_2 is based on pharmacological criteria (selectivity of agonists and antagonists) and not on anatomical location. Thus, α_2 receptors are located prejunctionally as well as postjunctionally in certain tissues. The vascular smooth muscle cells express both α_1 and α_2 receptors, and NA causes vasoconstriction by activating both subtypes. Molecular

cloning has further identified 3 subtypes of α_1 (α_{1A} , α_{1B} , α_{1D}) and 3 subtypes of α_2 (α_{2A} , α_{2B} , α_{2C}) receptors.

Though tissue distribution of subtypes of α_1 and α_2 receptors has been mapped, there is lot of overlap. Sufficiently subtype selective agonists or antagonists have also not yet been developed to pharmacologically exploit the molecular heterogeneity of subtypes of α_1 and α_2 receptors.

The adrenergic neuronal mechanisms and action of drugs which modify them are depicted in Fig. 9.4. A summary of drugs acting through adrenergic neuronal mechanisms is presented in Table 9.4

Table 9.3: Differences between α_1 and α_2 receptors

	α_1	α_2
Location	Postjunctional on effector organs	Prejunctional on nerve ending (α_{2A}), also postjunctional in brain, pancreatic β cells and extrajunctional in certain blood vessels, platelets
Function subserved	GU Smooth muscle—contraction Vasoconstriction Gland—secretion Gut—relaxation	Inhibition of transmitter release Vasoconstriction Decreased central sympathetic flow Decreased insulin release Platelet aggregation
Selective agonist	Phenylephrine	Clonidine
Selective antagonist	Prazosin	Yohimbine, Rauwolscine
Coupling protein	Gq	Gi/Go
Effector pathway	IP ₃ /DAG $\uparrow$ Phospholipase A ₂ $\uparrow$ —PG release	cAMP $\downarrow$ K ⁺ channel $\uparrow$ Ca ²⁺ channel $\downarrow$ or $\uparrow$ IP ₃ /DAG $\uparrow$

GU: Genitourinary

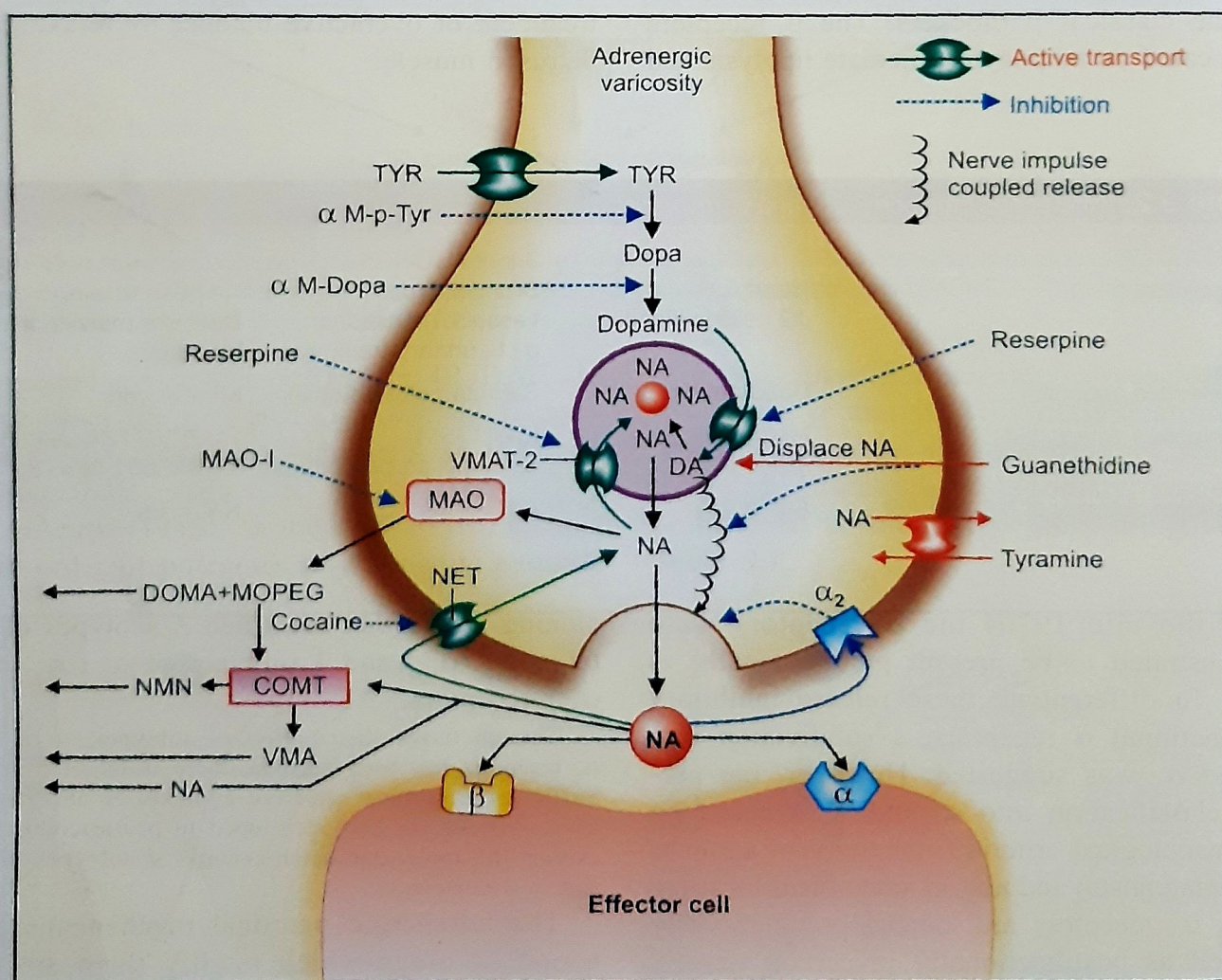


Fig. 9.4: Schematic representation of adrenergic neurotransmission and its modification by drugs
 TYR—tyrosine; α M-p-Tyr— α methyl-p-tyrosine; α M-Dopa— α methyl dopa; MAO—monoamine oxidase; MAOI—monoamine oxidase inhibitor; COMT—catechol-o-methyl transferase; NMN—nor-metanephrine; VMA—vanillyl mandelic acid; NET—Norepinephrine transporter; VMAT-2—Vesicular monoamine transporter; DOMA—3,4 dihydroxy mandelic acid; MOPEG—3-Methoxy,4-hydroxy phenyl glycol.

Table 9.4: Summary of drug action through modification of adrenergic transmission

Step/site	Action	Drug	Response
1. Synthesis of NA	Inhibition Utilisation of same synthetic pathway	α -methyl-p-tyrosine α -methyl dopa	Depletion of NA Replacement of NA by α -methyl NA (false transmitter)
2. Axonal reuptake	Blockade	Cocaine, desipramine, guanethidine	Potentialiation of NA (endo- and exogenous), inhibition of tyramine action
3. Vesicular reuptake	Blockade	Reserpine	Depletion of NA (degraded by MAO)
4. Nerve impulse coupled release of NA	Inhibition	Guanethidine, bretylium	Loss of adrenergic transmission
5. Neuronal NA pool	Exchange diffusion	Tyramine, amphetamine	Indirect sympathomimetic
6. Metabolism	MAO-inhibition	Nialamide, tranlycypromine	Potentialiation of NA (slight), —of tyramine (marked)
	MAO-A inhibition	Moclobemide	Potentialiation (slight) of NA and tyramine
	MAO-B inhibition COMT inhibition	Selegiline Tolcapone, entacapone	Potentialiation of DA in brain Potentialiation of NA and DA (slight)
7. Receptors	Mimicking	Phenylephrine Clonidine Isoprenaline Dobutamine Salbutamol	α_1 sympathomimetic α_2 —inhibition of NA release, ↓ sympathetic outflow $\beta_1 + \beta_2$ —sympathomimetic β_1 —sympathomimetic: cardiac stimulation β_2 —sympathomimetic: bronchodilatation
	Blockade	Phentolamine Prazosin Yohimbine Propranolol Metoprolol	$\alpha_1 + \alpha_2$ —blockade α_1 —blockade α_2 —blockade $\beta_1 + \beta_2$ —blockade β_1 —blockade

ADRENERGIC DRUGS (Sympathomimetics)

These are drugs with actions similar to that of Adr or that of sympathetic stimulation. They can be divided into:

Direct sympathomimetics These are drugs which act directly as agonists on α or β or both α and β adrenoceptors, e.g. Adr, NA, isoprenaline (Iso), phenylephrine, methoxamine, xylometazoline, salbutamol and many others.

Indirect sympathomimetics These drugs act on adrenergic neurone to release NA, which then acts on the adrenoceptors, e.g. tyramine, amphetamine.

Mixed action sympathomimetics These drugs act directly as well as indirectly—ephedrine, mephentermine.

ACTIONS

The peripheral actions of Adr in most tissues have been clearly differentiated into those

Table 9.5: Adrenergic responses mediated through α and β receptors

α actions	β actions
1. Constriction of arterioles and veins $\rightarrow$ rise in BP ($\alpha_1 + \alpha_2$)	Dilatation of arterioles and veins $\rightarrow$ fall in BP (β_2)
2. Heart—little action	Cardiac stimulation (β_1), $\uparrow$ rate, force and conduction velocity
3. —	Bronchodilatation (β_2)
4. Contraction of radial muscles of iris $\rightarrow$ mydriasis (α_1), decreased aqueous secretion	No effect on iris, slight relaxation of ciliary muscle, Enhanced aqueous secretion
5. Intestinal relaxation, contraction of sphincters	Intestinal relaxation (β_2)
6. Bladder trigone, prostate—contraction (α_1)	Detrusor—relaxation (β_2, β_3)
7. Uterus—contraction (α_1)	Relaxation (β_2)
8. Splenic capsule—contraction (α_1)	Relaxation (β_2) (slight)
9. Neuromuscular transmission facilitated, $\uparrow$ ACh release	Active state—prolonged in fast contracting muscle, abbreviated in slow contracting muscle; tremors (β_2)
10. Insulin secretion inhibited (α_2) (dominant)	Augmented insulin (mild) and glucagon secretion (β_2)
11. —	Liver—glycogenolysis (β_2) $\rightarrow$ hyperglycaemia Muscle—glycogenolysis (β_2) $\rightarrow$ hyperlactacidaemia Fat—lipolysis ($\beta_1 + \beta_2 + \beta_3$) $\rightarrow$ increased blood FFA, calorogenesis
12. —	Renin release from kidney (β_1)
13. Male sex organs—ejaculation (α_1)	—
14. Salivary gland— K^+ and water secretion (α_1)	Ptylin secretion
15. —	ADH secretion from posterior pituitary (β_1)
16. Adrenergic nerve—inhibits NA release terminals	Facilitates NA release (mild action)

mediated by α or β receptors depending on the predominant receptor type present in a given tissue. These are tabulated in Table 9.5. The receptor subtype, wherever defined, has been mentioned in parenthesis. The actions of a particular sympathomimetic amine depend on its relative activity at different types of adrenergic receptors.

Adr : $\alpha_1 + \alpha_2 + \beta_1 + \beta_2$ and weak β_3 action
 NA : $\alpha_1 + \alpha_2 + \beta_1 + \beta_3$ but no β_2 action
 Iso : $\beta_1 + \beta_2 + \beta_3$ but no α action

Important actions of Adr, NA and isoprenaline are compared in Table 9.6.

The overall actions are—

1. Heart Adr increases heart rate by enhancing the pacemaker activity of SA node. The slope of slow diastolic depolarization

of cells in the SA node is increased. Adr also activates latent pacemakers in A-V node and Purkinje fibres. As a result arrhythmias can occur with high doses that raise BP markedly. Raised BP reflexly depresses the SA node and unmasks the latent pacemakers. Certain anaesthetics (chloroform, halothane) sensitize the heart to arrhythmic action of Adr. Idioventricular rate is increased in patients with complete heart block.

Force of cardiac contraction is increased. Development of tension as well as rate of relaxation is accelerated. Thus, systole is shortened more than diastole. Cardiac output and oxygen consumption of the heart are markedly enhanced.

Conduction velocity through A-V node, bundle of His, atrial and ventricular fibres is increased; partial A-V block may be overcome. Refractory period (RP) of all types of cardiac

Table 9.6: Comparative effects of intravenous infusion of adrenaline, noradrenaline and isoprenaline

	Adr	NA	Iso
1. Heart rate	↑	↓	↑↑
2. Cardiac output	↑↑	—	↑↑
3. BP—Systolic	↑↑	↑↑	↑
Diastolic	↓↑	↑↑	↓↓
Mean	↑	↑↑	↓
4. Blood flow			
Skin and mm	↓	↓	—
Sk. muscle	↑↑	—, ↓	↑
Kidney	↓	↓	—
Liver	↑↑	—	↑
Coronary	↑	↑	↑
5. Bronchial muscle	↓↓	—	↓↓
6. Intestinal muscle	↓↓	↓	↓
7. Blood sugar	↑↑	—, ↑	↑

cells is abbreviated. All cardiac actions are predominantly β_1 receptor mediated.

When BP rises markedly, reflex bradycardia occurs due to stimulation of vagus. Noradrenaline injected i.v. usually elicits bradycardia by this mechanism.

2. Blood vessels Both vasoconstriction (α) and vasodilatation (β_2) can occur depending on the drug, its dose and the vascular bed. Constriction predominates in cutaneous, mucous membrane and renal beds. Vasoconstriction occurs through both α_1 and α_2 receptors. However, location of α_2 (extrajunctional) receptors is such that they are activated only by circulating CAs, whereas α_1 (junctional) receptors primarily mediate responses to neuronally released NA. Vasodilatation predominates in skeletal muscles, liver and coronaries. The direct effect on cerebral vessels is not prominent—blood flow through this bed parallels change in BP.

The action of adrenergic drugs is most marked on arterioles and precapillary sphincters; larger arteries and veins are affected at higher doses.

3. BP The effect depends on the amine, its dose and rate of administration.

- NA causes rise in systolic, diastolic and mean BP; it does not cause vasodilatation

(no β_2 action), peripheral resistance increases consistently due to α action.

- Isoprenaline causes rise in systolic but marked fall in diastolic BP (β_1 —cardiac stimulation, β_2 —vasodilatation). The mean BP generally falls.
- Adr given by slow i.v. infusion or s.c. injection causes rise in systolic but fall in diastolic BP; peripheral resistance decreases because vascular β_2 receptors are more sensitive than α receptors. Mean BP generally rises. Pulse pressure is increased.
- Rapid i.v. injection of Adr (in animals) produces a marked increase in both systolic as well as diastolic BP (at high concentration α response predominates and vasoconstriction occurs even in skeletal muscles). The BP returns to normal within a few minutes and a secondary fall in mean BP follows. The mechanism is—rapid uptake and dissipation of Adr → concentration around the receptor is reduced → low concentrations are not able to act on α receptors but continue to act on β_2 receptors.

When an α blocker has been given, only fall in BP is seen which was first described by Dale, and is called *vasomotor reversal of Dale*.

4. Respiration Adr and isoprenaline, but not NA are potent bronchodilators (β_2). This

action is more marked when the bronchi are constricted. Adr given by aerosol additionally decongests bronchial mucosa by α action. Adr can directly stimulate respiratory centre (RC) but this action is seldom manifest at clinically used doses. Rapid i.v. injection (in animals) causes transient apnoea due to reflex inhibition of RC. Toxic doses of Adr cause pulmonary edema by shifting blood from systemic to pulmonary circuit.

5. Eye Mydriasis occurs due to contraction of radial muscles of iris (α_1), but this is minimal after topical application, because Adr penetrates cornea poorly. The intraocular tension tends to fall, especially in wide angle glaucoma.

Adr has complex effects on aqueous humor dynamics (see p. 168).

Action of adrenaline on aqueous humor dynamics

Receptor	Agonist action
α_1	: Vasoconstriction of ciliary vessels → reduced aqueous formation
α_2	: Reduced secretory activity of ciliary epithelium
$\gamma\alpha$	: Augmentation of uveo-scleral outflow
β_2	: Enhanced secretory activity of ciliary epithelium Facilitation of trabecular outflow

Overall, aqueous formation is reduced and outflow is facilitated.

6. GIT In isolated preparations of gut, activation of both α and β receptors produces relaxation. In intact animals and man peristalsis is reduced and sphincters are constricted, but the effects are brief and of no clinical import.

7. Bladder, prostate, vas deferens Detrusor is relaxed (β_2 , β_3) and trigone is constricted (α_1); both actions tend to oppose bladder voiding. The tone of prostatic muscle is increased by activation of α_1 receptors. Rhythmic contractions of vas deferens and seminal vesicles which participate in ejaculation are also mediated through α_1 receptors.

8. Uterus Adr can both contract and relax uterine muscle, respectively through α and β receptors. The overall effect varies with species, hormonal and gestational status. Human uterus

is relaxed by Adr at term of pregnancy, but at other times, its concentrations are enhanced.

9. Splenic capsule Contracts (α) and more RBCs are poured in circulation. This action is not evident in man.

10. Skeletal muscle Neuromuscular transmission is facilitated. In contrast to action on autonomic nerve endings, α receptor activation on motor nerve endings augments ACh release probably because it is of the α_1 subtype. The direct effect on muscle fibres is exerted through β_2 receptors and differs according to the type of fibre. The active state is abbreviated and less tension is developed in the slow contracting red fibres. There is incomplete fusion of individual responses. This along with enhanced firing of muscle spindles is responsible for the tremors produced by β_2 agonists. The action on rapidly contracting white fibres is to prolong the active state and increase the tension developed.

11. CNS Adr, in clinically used doses, does not produce any marked CNS effects because of poor penetration in brain, but restlessness, apprehension and tremor may occur. Activation of α_2 receptors in the brainstem (by selective α_2 agonists like clonidine) results in decreased sympathetic outflow → fall in BP and bradycardia.

12. Metabolic Adr causes glycogenolysis → hyperglycaemia, hyperlactacidaemia (β_2), as well as lipolysis → rise in plasma free fatty acid (FFA) and calorogenesis ($\beta_2 + \beta_3$). These are due to direct action on liver, muscle and adipose tissue cells. In addition metabolic effects result from reduction of insulin (α_2) and augmentation of glucagon (β_2) secretion.

Transient hyperkalaemia followed by hypokalaemia occurs due to initial release of K^+ from liver, and later its enhanced uptake into skeletal muscles as well as in liver.

Biochemical pathways of adrenergic responses

β actions The β actions are mediated through cAMP (see Fig. 4.6). Adr activates membrane bound enzyme *adenylyl cyclase* through a regulatory protein Gs → ATP is broken down to cAMP at the inner face. This in turn phosphorylates a number of intracellular

cAMP-dependent protein kinases and initiates a series of reactions:

(i) In *liver* and *muscle*, glycogen phosphorylase is activated causing glycogenolysis while glycogen synthase is inhibited. Both actions result in hyperglycaemia and hyperlactacidemia. Neoglucogenesis in liver adds to the hyperglycaemic response.

K⁺ is first released from liver causing short-lasting hyperkalaemia. This is followed by more prolonged hypokalaemia due to K⁺ uptake in muscle and later in liver as well.

(ii) In *adipose tissue*, triglyceride lipase is activated → increased plasma free fatty acids. Increased O₂ consumption and heat production result primarily by action on brown adipose tissue, which has predominant β₃ receptors.

(iii) In *heart*, proteins like troponin and phospholamban are phosphorylated. The former results in increased interaction with Ca²⁺ at the myofilaments → increased force of contraction; the latter causes sequestration of Ca²⁺ by sarcoplasmic reticulum → more rapid relaxation. The activated protein Gs, in addition, interacts directly with the Ca²⁺ channels in the membrane promoting influx of Ca²⁺ which reinforces the positive inotropic action exerted through cAMP.

(iv) In the *gut* and *bronchial muscle*, relaxation (accompanied with hyperpolarization) is induced, but the intermediate steps have not been clearly delineated.

(v) In *pancreatic islets* activation of β₂ receptors on α cells increases glucagon secretion, and that on β cells increases insulin secretion, both by raising intracellular cAMP. However, augmentation of insulin secretion is weak. **G-protein independent β receptor signaling and biased β receptor agonists**

Continuous high rate activation causes desensitization of the β adrenergic receptors. An important mechanism of this desensitization is their interaction with an intracellular protein β-arrestin (β-arr) which prevents binding to Gs (see p.62). It has now been realized that the β-arr-β receptor complex, though incapable of generating G-protein mediated actions, can transduce qualitatively different responses through G-protein independent pathways. For example, normally excessive cardiac β₁ receptor activation produces cardiotoxic effects by increasing cardiac work load which play a role in the progression of CHF. However, activation of G-protein independent β₁ signaling has cardioprotective effect.

Attempts are now being made to produce β₁ agonists which will trigger only the β-arr mediated G-protein independent cardioprotective effects, and not the usual G-protein mediated cardiotoxic effects. Such agonists are being labeled 'Biased β receptor agonists'.

α actions The pathways of α actions are varied and less well defined.

(i) In *smooth muscles* (including vascular) that are contracted through α₁ receptors, the activated Gq-protein increases IP₃/DAG produc-

tion → mobilization of Ca²⁺ from intracellular organelle → activation of calmodulin dependent myosin light chain kinase → phosphorylation of myosin → contraction. The vasoconstrictor α₂ receptors probably enhance Ca²⁺ influx without utilizing IP₃.

(ii) The *prejunctional* α₂ receptor activates Gi-protein which then inhibits neuronal Ca²⁺ channels and also limits the intracellular availability of Ca²⁺ by decreasing cAMP production. Transmitter (NA) release is consequently diminished. Hyperpolarization through activation of G-protein gated K⁺ channels may also occur.

(iii) In the *gut*, α₂ receptor activation hyperpolarizes the cholinergic neurone → decreased release of ACh → reduced tone; whereas α₁ receptors located directly on the smooth muscle cell increase K⁺ efflux (by activating Ca²⁺ dependent K⁺ channels) leading to hyperpolarization → relaxation.

(iv) In *pancreatic β cells*, stimulation of α₂ receptors reduces the formation of cAMP → decreased insulin release.

Administration and preparations

CAs are absorbed from the intestine but are rapidly degraded by MAO and COMT present in the intestinal wall and liver. They are thus orally inactive.

1. **Adrenaline (Epinephrine)** For systemic action, 0.2–0.5 mg s.c., i.m., action lasts ½ to 2 hrs. ADRENALINE 1 mg/ml inj; ADRENA 4 mg (of Adr. bitartrate=2mg Adr. base)/2 ml inj.

As local vasoconstrictor, 1 in 200,000 to 1 in 80,000 added to lidocaine;

in XYLOCAINE with ADRENALINE: lidocaine 21.3 mg + adrenaline 0.005 mg/ml inj; 30 ml vial. Lidocaine 2% with adrenaline 1:80,000 in 1.5 ml cartridge for dental anaesthesia.

2. **Noradrenaline (Norepinephrine, levarterenol)** It is administered only by slow i.v. infusion (2–4 µg/min). Local tissue necrosis occurs if the solution extravasates. Do not mix with NaHCO₃ in the same bottle, because rapid oxidation occurs at alkaline pH. The action of NA starts declining within 5 min of discontinuing infusion. Currently, NA is used as a pressor agent (along with volume replacement) only when strong vasoconstriction is required.

ADRENOR, NORAD, VASCUE, NORDRIN 2 mg (base)/2 ml amp.

3. *Isoprenaline (Isoproterenol)* 20 mg sublingual, 1–2 mg i.m., 5–10 µg/min i.v. infusion; action lasts 1–3 hrs. It is occasionally used to maintain idioventricular rate till pacemaker is implanted. For bronchial asthma, it has been superseded by selective β_2 agonists.

ISOPRIN, ISOSOL 4 mg/2 ml inj, NEOEPININE 20 mg sublingual tablets.

Adverse effects and contraindications

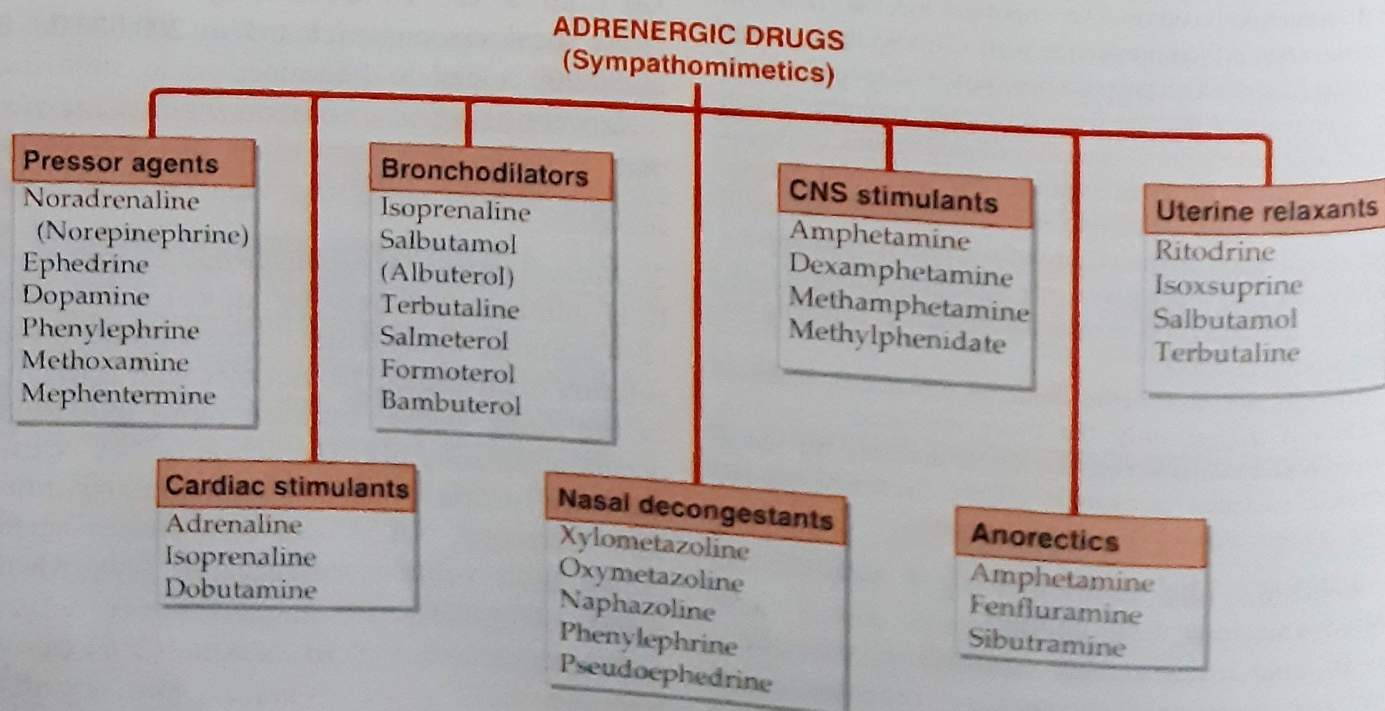
- Transient restlessness, headache, palpitation, anxiety, tremor and pallor may occur after s.c./i.m. injection of Adr.
- Marked rise in BP leading to cerebral haemorrhage, ventricular tachycardia/fibrillation, angina, myocardial infarction are the hazards of large doses or inadvertent i.v. injection of Adr.
- Adr is contraindicated in hypertensive, hyperthyroid and angina patients.
- Adr should not be given during anaesthesia with halothane (risk of arrhythmias) and to patients receiving β blockers (marked rise in BP can occur due to unopposed α action).

Salient features of important adrenergic drugs are described below.

Dopamine (DA) It is a dopaminergic (D1 and D2) as well as weaker adrenergic β_1 (but not β_2) + very weak α receptor agonist. The D1 receptors in renal and mesenteric blood vessels are the most sensitive; i.v. infusion of low dose of DA dilates these vessels (by raising intracellular cAMP). This increases g.f.r. In addition DA exerts natriuretic effect by D1 receptors on proximal tubular cells. Moderately higher doses produce a positive inotropic (direct β_1 and D1 action + that due to NA release), but little chronotropic effect on heart. Vasoconstriction (α_1 action) occurs only when large doses are infused. At doses normally employed, it raises cardiac output and systolic BP with little effect on diastolic BP. Effect on nonvascular α and β receptors is practically absent. Dopamine does not penetrate blood-brain barrier—no CNS effects.

Dopamine is used in patients of cardiogenic or septic shock and acute heart failure wherein it increases BP and urine outflow. It is administered by i.v. infusion (0.2–1 mg/min) which is regulated by monitoring BP and rate of urine formation.

DOPAMINE, INTROPIN, DOPACARD 200 mg in 5 ml amp; to be diluted and infused i.v.



Dobutamine A derivative of DA, but not a D1 or D2 receptor agonist. Dobutamine acts mainly on β adrenergic receptors, and is a weak α agonist. The only prominent action of clinically employed doses (2–8 $\mu\text{g/kg/min}$ i.v. infusion) is increased force of cardiac contraction and output, without significant change in peripheral resistance and BP. Compared to isoprenaline, increase in heart rate is less marked. As such, it is considered to be a relatively selective β_1 agonist. Dobutamine is used as an inotropic agent in pump failure accompanying myocardial infarction, cardiac surgery, and for short term management of severe congestive heart failure. It is less arrhythmogenic than Adr.

CRDIJECT 50 mg/4 ml and 250 mg per 20 ml amp, DOBUTREX, DOBUSTAT 250 mg vial.

Ephedrine It is a sympathomimetic alkaloid obtained from *Ephedra vulgaris* which mainly acts indirectly, but has some direct action as well on α and β receptors. Repeated injections produce tachyphylaxis, primarily because the neuronal pool of NA available for displacement is small. It is resistant to MAO, therefore, effective orally, but is about 100 times less potent than Adr, and longer acting (4–6 hours). Ephedrine crosses to brain and causes stimulation, but central: peripheral activity ratio is lower than that of amphetamine.

Ephedrine can be used for a variety of conditions, but lacks selectivity, and efficacy is low. Use is now restricted to that in mild chronic bronchial asthma and for hypotension during spinal anaesthesia, or occasionally for postural hypotension; 15–60 mg TDS.

EPHEDRINE HCl 15, 30 mg tab; SULFIDRIN 50 mg in 1 ml inj, in ENDRINE 0.75% nasal drops.

Amphetamines These are synthetic compounds having a pharmacological profile similar to ephedrine; orally active with relatively long duration (4–6 hours). They exert potent CNS stimulant and weaker peripheral cardiovascular actions. Maximal selectivity is exhibited by dextroamphetamine and methamphetamine, which in the usual doses produce few peripheral effects.

The central actions of amphetamines are largely mediated by release of NA from adrenergic

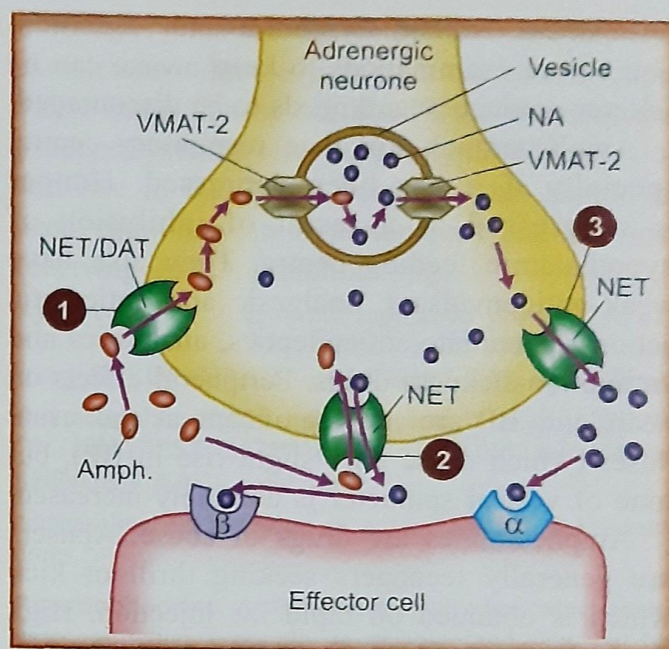


Fig. 9.5: Illustration of the mechanisms of noradrenaline release by amphetamine

Amphetamine (Amph) enters the adrenergic neurone by utilizing the neuronal norepinephrine transporter (NET) or dopamine transporter (DAT)-(1), and then the storage vesicles through vesicular monoamine transporter (VMAT2). It then displaces the stored noradrenaline (NA) into the neuronal cytoplasm, most of which is released into the synaptic cleft by exchange diffusion-(2) with extracellular Amph., or by reverse transport-(3), both utilizing NET. Note that this release is not exocytotic and does not require Ca^{2+} .

neurones in the brain. This occurs mainly by *exchange diffusion* and *reverse transport* involving transporters like NET, DAT and VMAT2 as depicted in Fig. 9.5. However, the effects on locomotor activity, perception and the psychotic phenomena seen at high doses are probably due to DA and 5-HT release by processes similar to that for NA release. In addition, amphetamine inhibits neuronal reuptake of DA.

The central effects include alertness, increased concentration and attention span, postponement of sleep, euphoria, talkativeness, increased work capacity. Fatigue is allayed. Athletic performance is improved temporarily followed by deterioration. It is one of the drugs included in the 'dope test' for athletes. The reticular activating system is stimulated resulting in wakefulness and postponement of sleep deprivation induced physical disability. But this is short-lived and may be accompanied by anxiety,

restlessness, tremor, dysphoria and agitation. Use before examinations to keep awake can be counter-productive and needs to be discouraged.

Amphetamines stimulate respiratory centre, specially if it has been depressed. Hunger is suppressed as a result of inhibition of hypothalamic feeding centre. They also have weak anticonvulsant, analgesic and antiemetic actions: potentiate antiepileptics, analgesics and antimotion-sickness drugs. Peripheral effects on heart and BP are not significant at the usual doses (which cause only slight rise in BP), but tone of vesical sphincter is definitely increased.

Amphetamines are drugs of abuse. Abusers are generally teenagers seeking thrill or kick which is obtained on rapid i.v. injection. High doses produce euphoria, restlessness, insomnia, aggression, panic, marked excitement which may progress to mental confusion, delirium, hallucinations and an acute psychotic state. Peripheral component of toxicity includes rise in BP, palpitation, arrhythmias, vomiting, abdominal cramps and vascular collapse. Death is usually preceded by convulsions and coma.

Repeated use is more likely to produce long lasting behavioural abnormalities; psychosis may be precipitated. Though drug seeking behaviour is induced, withdrawal symptoms and dependence are not prominent.

Tolerance to central actions and toxic effects of amphetamine develops, and is both pharmacokinetic as well as pharmacodynamic. Starvation due to suppression of appetite produces acidic urine; amphetamine is ionized more at acidic pH and is excreted more rapidly.

Treatment of amphetamine toxicity includes administration of chlorpromazine which controls both central as well as peripheral α adrenergic effects.

Amphetamine: 5–15 mg oral; Dexamphetamine: 5–10 mg (children 2.5–5 mg) oral.

Methamphetamine: 5–10 mg oral.

Phenylephrine It is a selective α_1 agonist, with negligible β action. It raises BP by causing vasoconstriction. Because it has little cardiac action, reflex bradycardia is prominent. Topically it is used as a nasal decongestant and in the

eye for producing mydriasis when cycloplegia is not required. Phenylephrine tends to reduce intraocular tension by constricting ciliary body blood vessels. Because it is orally active with longer duration of action (4–6 hours), it is also a constituent of orally administered nasal decongestant preparations. However, its FDCs with paracetamol and caffeine or with chlorpheniramine, paracetamol and dextromethorphan are banned in India. Central effects are not seen with usual clinical doses.

Dose: 2–5 mg i.m., 0.1–0.5 mg slow i.v. inj, 30–60 μ g/min i.v. infusion; 5–10 mg oral; 0.25–0.5% nasal instillation; 5–10% topically in eye;

FRENIN 10 mg in 1 ml inj; DECOLD PLUS 5 mg with paracetamol 400 mg + chlorpheniramine 2 mg + caffeine 15 mg tab., SINAREST 10 mg with chlorpheniramine 2 mg, paracetamol 500 mg, caffeine 30 mg tab, FENOX 0.25% with naphazoline 0.025% nasal drops, DROSYN 10% eye drops, in DROSYN-T, TROPAC-P 5% with tropicamide 0.8% eye drops, in PHENIL eye drop 0.12% with chlorpheniramine 0.2% eye drops.

Methoxamine Another selective α_1 agonist with no β actions (has weak β blocking action). Resembles phenylephrine very closely. Occasionally used as a pressor agent.

Dose: 10–20 mg i.m.; 3–5 mg slow i.v. inj.

VASOXINE 20 mg/ml inj.

Mephentermine It produces both cardiac stimulation and vasoconstriction by directly activating α and β adrenergic receptors as well as by releasing NA. Cardiac output, systolic and diastolic BP are increased. The direct positive chronotropic effect on heart is generally counter balanced by vagal stimulation due to rise in mean BP.

Mephentermine is not a substrate for either MAO or COMT. Therefore it is active orally with longer duration of action (2–6 hr). It crosses blood-brain barrier to some extent—may produce excitatory effects at higher doses. It is used to prevent and treat hypotension due to spinal anaesthesia and surgical procedures, shock in myocardial infarction and other hypotensive states.

Dose: 10–20 mg oral/i.m., also by slow i.v. infusion.

MEPHENTINE 10 mg tab, 15 mg in 1 ml amp, 30 mg/ml in 10 ml vial, TERMIN 30 mg/ml in 10 ml vial.

SELECTIVE β_2 STIMULANTS

These include, salbutamol, terbutaline, salmeterol, formoterol and ritodrine. They cause bronchodilatation, vasodilatation and uterine relaxation, without producing significant cardiac stimulation. However, β_2 selectivity is only relative. Salbutamol has $\beta_2:\beta_1$ action ratio of about 10. They are primarily used in bronchial asthma (for description see Ch. 16). Other uses are:

- As uterine relaxant to delay premature labour. Ritodrine is sometimes used as the preferred drug (see Ch. 23);
- In familial hyperkalaemic periodic paralysis— β_2 agonists benefit by enhancing K^+ uptake into muscles, thereby lowering plasma K^+ levels.

The most important side effect of selective β_2 agonists is muscle tremor, while tachycardia and arrhythmias are less likely.

Isoxsuprine It is an orally effective long-acting β receptor stimulant which has direct smooth muscle relaxant property as well. It has been used as uterine relaxant for threatened abortion and dysmenorrhoea, but efficacy is poor. Though indicated in peripheral vascular diseases, actual benefits are disappointing. Side effects: nausea, tachycardia, flushing, hypotension, dizziness, tremor.

Dose: 5–10 mg oral or i.m. 4–6 hourly,

DUVADILAN 10 mg tab, 40 mg SR cap, 10 mg/2 ml inj.

NASAL DECONGESTANTS

These are α agonists which on topical application as dilute solution (0.05–0.1%) produce vasoconstriction in the nasal mucosa which primarily expresses α receptors. The imidazoline compounds—naphazoline, xylometazoline and oxymetazoline are relatively selective α_2 agonist (like clonidine). They have a longer duration of action (12 hours) than ephedrine. After-congestion in nasal mucosa is claimed to be less than that with ephedrine or phenylephrine. They may cause initial stinging sensation (specially naphazoline). Regular use of these agents for long periods should be avoided because mucosal ciliary

function is impaired: atrophic rhinitis and anosmia can develop due to persistent vasoconstriction. These drugs can be absorbed from the nose and produce systemic effects, mainly CNS depression and rise in BP. Nasal decongestants should be used cautiously in hypertensives and in those receiving MAO inhibitors.

Xylometazoline: 0.05–0.1% topical in nose; **OTRIVIN** 0.05% (pediatric), 0.1% (adult) nasal drops and nasal spray, **OTRINOZ** 0.025%, 0.05% and 0.1% nasal drops.

Oxymetazoline: 0.025–0.05% topical in nose; **NASIVION**, **SINAREST** 0.025% (pediatric), 0.05% nasal drops, **RHINOJET** 0.05% nasal spray.

Naphazoline: 0.1% topical in nose; **PRIVINE** 0.1% nasal drops.

Pseudoephedrine An enantiomer of ephedrine which causes vasoconstriction, especially in mucosae and skin, but has fewer CNS and cardiac effect, and is a poor bronchodilator. Combined with antihistaminics, mucolytics, antitussives and analgesics in FDCs, it is believed to afford symptomatic relief in common cold, allergic rhinitis, blocked eustachian tubes and upper respiratory tract infections. Its FDC with cetirizine and paracetamol has been recently banned in India. Because of diversion of pseudoephedrine to manufacture methamphetamine for illicit trade as a drug of abuse, its marketing has been restricted globally.

ANORECTIC AGENTS

Though amphetamines suppress appetite, their use as anorectic agents is precluded by their adverse central effects. A number of related drugs were developed which inhibit feeding centre (like amphetamine) but have little/no CNS stimulant action or abuse liability. All of them act by releasing (reverse transport) or by inhibiting the reuptake of NA/DA or 5-HT, thus enhancing monoaminergic transmission in the brain. Accordingly they may be grouped into:

Noradrenergic agents: Phentermine, phenylpropanolamine (PPA), diethylpropion, mazindol.

Serotonergic agents: Fenfluramine, dexfenfluramine.

Noradrenergic + serotonergic agent: Sibutramine.

Fenfluramine and dexfenfluramine were extensively used by slimming centres, though tolerance to the anorectic action developed in 2–3 months. In the late 1990s echocardiographic abnormalities, valvular defects, pulmonary hypertension and sudden deaths were related to their use, and these drugs are now banned in most countries.

Sibutramine and R-Sibutramine Introduced subsequently, these drugs caused weight loss in obese people and were routinely used by slimming centres. Several side effects were noted; serious adverse reactions, including cardiovascular events and death were reported to the US-FDA and drug committees in Europe leading to ban on their

use. After its own assessment, India has also banned these drugs from March 2011.

Thus, currently no sympathomimetic anorectic drug is approved for use.

THERAPEUTIC USES

1. Vascular uses

- **Shock/acute hypotension** Shock may be due to haemorrhage, volume depletion (severe diarrhoea, vomiting, burn, etc.), cardiogenic (myocardial infarction, arrhythmias, etc.), anaphylactic, neurogenic (in trauma, drug overdose, etc.) or septic (gram negative bacteraemia, severe infection). It is a medical emergency. Urgent measures are directed to restoring and maintaining blood pressure and perfusion of vital organs. Volume replacement and treatment of the underlying cause are the primary modalities. However, rapid volume replacement may worsen cardiogenic shock and precipitate pulmonary edema. Continuously monitored i.v. infusion of sympathomimetic pressor agents like mephentermine, phenylephrine or noradrenaline is often used as an expedient measure to elevate very low BP and maintain cerebral circulation. The risk in the use of vasoconstrictor is that while raising BP they may also reduce perfusion of kidney and other vital organs.

Use of inotropic sympathomimetic drugs in cardiogenic shock is tricky, because they may increase cardiac workload. Dopamine increases cardiac contractility without causing significant tachycardia. It also improves renal blood flow and may help to raise BP. Dobutamine has relatively more selective inotropic effect. Adrenaline 0.5 mg injected i.m. promptly is the drug of choice in anaphylactic shock (see p. 97). It not only raises BP, but also counteracts bronchospasm and laryngeal edema that may accompany. Because of this profile of action as well as rapidity of onset, Adr is the only life saving measure.

Acute hypotension attending spinal/epidural anaesthesia, drug overdose and neurogenic

shock is due to loss of sympathetic vasoconstrictor tone. It is treated by fluid infusion, elevation of legs, oxygen inhalation and monitored i.v. infusion of a sympathomimetic like mephentermine or ephedrine, which cause vasoconstriction as well as counteract bradycardia.

- **Persistent/postural hypotension** The most important cause of persistent low BP and postural hypotension is autonomic neuropathy which is common in diabetics, elderly people or may be idiopathic. Oral sympathomimetics like ephedrine or mephentermine may be used, but are not entirely satisfactory, because they cannot mimic the reflex vasoconstriction that normally operates to compensate for changes of posture. Adequate hydration, electrolyte balance and use of elastic stockings may be helpful. Oral fludrocortisone may benefit in case of chronic adrenal insufficiency. Hypotension due to medications like α_1 blockers (used for urinary obstruction in prostatic hypertrophy), antihypertensive drugs, tricyclic antidepressants, neuroleptics, etc. should be treated by withholding/changing the drug or adjusting its dose.
- **Along with local anaesthetics** Adr 1 in 200,000 to 1 in 80,000 for infiltration, nerve block and spinal anaesthesia. Duration of anaesthesia is prolonged and systemic toxicity of the local anaesthetic is reduced. Local bleeding is minimised (see Ch. 26).
- **Control of local bleeding** From skin and mucous membranes, e.g. epistaxis, surgery/trauma related bleeding: compresses of Adr 1 in 10,000 or phenylephrine 1% soaked in cotton can control arteriolar and capillary bleeding. Noradrenaline 8 mg in 100–200 ml saline put in stomach through a tube can control bleeding from gastric erosions and stress ulcers.
- **Nasal decongestant** In colds, rhinitis, sinusitis, blocked nose or eustachian tube—one of the α -agonists is used as nasal drops. Shrinkage of mucosa provides relief, but after-congestion when action wears off, and

atrophy of mucosa on prolonged use are still a problem. The imidazolines should be used in lower concentrations in infants and young children, because children are more sensitive to central effects of these drugs. Nasal decongestants should be used very cautiously in hypertensive patients and in elderly males.

Pseudoephedrine and phenylephrine have been used orally as decongestants, but effective doses will constrict other blood vessels as well and cause rise in BP. Many oral FDCs containing these decongestants have been recently banned in India. However, oral vasoconstrictors do not produce after-congestion.

(v) **Peripheral vascular diseases** (like Buerger's disease, Raynaud's phenomena, diabetic vascular insufficiency, gangrene, frost bite, ischaemic ulcers, night leg cramps, cerebral vascular inadequacy) Vasodilators including isoxsuprine have been used, but are far from satisfactory, because in most cases the capacity of the affected vessels to dilate is severely limited, and ischaemia itself is a potent vasodilator.

2. Cardiac uses

- **Cardiac arrest** Adrenaline may be used to stimulate the heart in case of cardiac arrest due to drowning, electrocution, Stokes-Adams syndrome and other causes. Intravenous administration is justified in this setting with external cardiac massage. For i.v. injection, the 1 in 1000 solution of Adr should be diluted 10 times and slowly injected into jugular vein (or another central vein) and flushed with 20 ml saline to reach the heart in the absence of circulation.
- **Partial or complete A-V block** Isoprenaline may be used as temporary measure to maintain sufficient ventricular rate.
- **Congestive heart failure (CHF)** Adrenergic inotropic drugs are not useful in the routine treatment of CHF. However, controlled short term i.v. infusion of DA/dobutamine can tide over acute cardiac decompensation during myocardial infarction, cardiac surgery and in resistant CHF (see Ch. 38).

- **Dobutamine stress test** In patients unable to perform physical exercise (elderly patients or those with osteoarthritis of knee/hip) cardiac stress testing to expose ischaemic areas of the myocardium is accomplished by inducing cardiac stress pharmacologically with dobutamine. Dobutamine is infused i.v. at increasing rate to elicit peak cardiac workload, and ischaemic areas are mapped echocardiographically.

3. Bronchial asthma and COPD Adrenergic β_2 stimulants are the primary drugs for relief of reversible airway obstruction (see Ch. 16).

4. Allergic disorders Adr is a physiological antagonist of histamine which is an important mediator of many acute hypersensitivity reactions. It affords quick relief in urticaria, angioedema and is life saving in laryngeal edema or anaphylaxis (see p. 97). The vasoconstrictor, cardiac stimulant and bronchodilator actions of Adr contribute to its salutary effects. It is ineffective in delayed, retarded and other types of allergies.

5. Ocular uses Phenylephrine (5–10%) dilates the pupil, and is used to facilitate fundus examination, since cycloplegia is not required for this purpose. Lower concentrations (0.1–0.2%) are utilized to decongest conjunctiva in allergic conjunctivitis. Adrenergic drugs also lower intraocular pressure. The ester prodrug of Adr, *dipivefrine* is occasionally used as adjunctive medication in open angle glaucoma. *Apraclonidine* and *brimonidine* are selective α_2 adrenoceptor agonists used as second line add on drugs for glaucoma to supplement ocular PG analogues/ β blockers (see p. 168).

6. Central uses

(i) **Attention deficit hyperkinetic disorder (ADHD):** It is also called minimal brain dysfunction, and is usually detected in childhood. The sufferer is considered a 'hyperkinetic child' (see Ch. 35 also). Amphetamines have an apparently paradoxical effect to calm down hyperkinetic children. This disorder is recognized as a mild grade of mental retardation or a reduction in the ability to concentrate, i.e. the span of time for which attention can be focused on a subject is abbreviated. Amphetamines by increasing attention span

improve behaviour and performance in studies. The child becomes more amenable. However, growth retardation may occur due to reduction in appetite. The risk-benefit ratio of such therapy disfavours use of amphetamine.

Methylphenidate, an amphetamine-like drug which produces milder side effects and less growth retardation, and **atomoxetine** (see Ch. 35) a NA reuptake blocker with better tolerability profile, are now preferred for ADHD. However, only severe cases of ADHD, or those who do not improve with psychological intervention alone should be treated with CNS stimulant drugs. Tricyclic antidepressants are also beneficial.

(ii) **Narcolepsy** Narcolepsy is sleep occurring in fits. It is adequately controlled by amphetamines. Development of tolerance, abuse and behavioural abnormalities are the calculated risks of such therapy. **Modafinil**, a newer psychostimulant with fewer behavioral adverse effects and

lower dependence inducing potential, is being preferred now (see Ch. 35). Imipramine-like drugs are also useful in some patients, and are safer.

7. Uterine relaxant Isoxsuprine has been used in threatened abortion and dysmenorrhoea, but efficacy is doubtful. Selective β_2 stimulants, especially ritodrine, infused i.v. has been successfully used to postpone labour but maternal morbidity and mortality may be increased due to its cardiac and metabolic actions and incidents of pulmonary edema. If at all used, calcium channel blockers are now preferred over sympathomimetics to postpone labour (see Ch. 23).

8. Insulin hypoglycaemia By its hyperglycaemic action, Adr. can rapidly reverse insulin hypoglycaemia, but it should be used only as an expedient measure, while i.v./oral glucose should be given as soon as possible. Glucagon, if available, is a preferable emergency measure, because Adr. has strong cardiovascular effects as well.

PROBLEM DIRECTED STUDY

- 9.1** A lady aged 55 years presented for eye checkup. She has been having visual difficulty over the past few months, and lately she had started noticing 'halos' around the lights. She also has dull chronic ache in the forehead region. Tonometry revealed her intraocular pressure (i.o.p.) to be 22 and 24 mm Hg respectively in the left and right eye.
- (a) Which mydriatic will be suitable for dilating her pupil for fundus examination and why? (see Appendix-1 for solution)