THE PHARMACOLOGY OF PRESSOR DRUGS

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The usual definitions of "sympathomimetic" involve either structural resemblance to adrenaline or a pattern of pharmacological effects similar to that of adrenaline. Unfortunately the ranges of both the structure and actions of sympathomimetics (table I) are so wide that definitions based on these properties are bound to admit drugs which are not members of the group. It seems preferable therefore, to use a practical definition, based on the experiments done to determine whether an unknown drug is a sympathomimetic. A sympathomimetic is a drug whose actions are specifically and competitively antagonized by a mixture of phentolamine and propranolol in doses which similarly antagonist the actions of adrenaline. This definition does not require that all actions of a sympathomimetic should be blocked by these antagonists but if an action escapes blockade then the same action of adrenaline will also escape (e.g. hyperglycaemia).

**TABLE I**

*The chemical structure of some sympathomimetics.*

<table>
<thead>
<tr>
<th>SYMPATHOMIMETIC</th>
<th>Ring</th>
<th>β-C</th>
<th>α-C</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>(-)-noradrenaline</td>
<td>3, 4 diOH</td>
<td>OH</td>
<td>-</td>
<td>CH</td>
</tr>
<tr>
<td>(+)-adrenaline</td>
<td>3, 4 diOH</td>
<td>OH</td>
<td>-</td>
<td>CH(2CH₃)</td>
</tr>
<tr>
<td>(+-)-isoprenaline</td>
<td>3, 4 diOH</td>
<td>OH</td>
<td>-</td>
<td>CH</td>
</tr>
<tr>
<td>(-)-phenylephrine</td>
<td>3 OH</td>
<td>-</td>
<td>-</td>
<td>CH</td>
</tr>
<tr>
<td>(+)-methoxamine</td>
<td>3, 6 diOHCH₃</td>
<td>OH</td>
<td>CH₂</td>
<td>-</td>
</tr>
<tr>
<td>(+)-metaraminol</td>
<td>3 OH</td>
<td>OH</td>
<td>CH₂</td>
<td>CH₄</td>
</tr>
<tr>
<td>(-)-ephedrine</td>
<td>-</td>
<td>OH</td>
<td>CH₂</td>
<td>CH₄</td>
</tr>
<tr>
<td>(+)-hydroxy-amphetamine</td>
<td>4 OH</td>
<td>-</td>
<td>CH₄</td>
<td>-</td>
</tr>
<tr>
<td>(+)-methyl-amphetamine</td>
<td>-</td>
<td>-</td>
<td>CH₂</td>
<td>CH₄</td>
</tr>
<tr>
<td>Mephentermine</td>
<td>-</td>
<td>-</td>
<td>diCH₃</td>
<td>CH₄</td>
</tr>
</tbody>
</table>

The effects of local adrenergic nerve stimulation and of noradrenaline in vitro or intra-arterially

The chemical transmitter of most postganglionic sympathetic nerves is noradrenaline; the effect of noradrenaline added to an isolated effector organ is qualitatively that of adrenergic nerve stimulation in vitro (though the time course differs). This is identical with that produced by the intra-arterial injection or infusion of doses causing no systemic effects. The principal non-adrenergic postganglionic sympathetic nerves are those to eccrine sweat glands and those which cause vasodilatation in skeletal muscles on fainting: these are both cholinergic.

Noradrenaline is sympathomimetic in that the actions which it shares with adrenaline are blocked by phentolamine and propranolol as much as are those of adrenaline. It acts directly as shown by the changes in its activity induced by reserpine, cocaine and chronic postganglionic denervation (Eger and Hamilton, 1959; Trendelenburg et al., 1962a, b; Schmidt and Fleming, 1963).

**Blood vessels.**

Cutaneous, mucosal and skeletal muscular blood vessels are all constricted by noradrenaline; the alpha-blocking agents reduce but do not reverse this action (Kolin and Ross, 1965; Johnson, Green and Lanier, 1953; Cohn, 1965; Haddy et al., 1962). Renal vessels are constricted (Aviado, Wnuck and de Beer, 1958b) as are the splanchnic vessels and spleen (Deal and Green, 1956; Texter et al., 1964). Cerebral vessels are slightly constricted but both drug and neurally-induced changes in cerebral vascular resistance are unimportant determinants of cerebral flow in the face of PCO₂ and mean arterial pressure. Pulmonary vessels are also constricted but here the effects of drugs on cardiac output and on capacitance vessels are much more important determinants of pulmonary pressures, flows and resistances than are direct effects on pulmonary vessels. Pressure in small systemic
veins is increased (Texter et al., 1964; Haddy et al., 1962) by venous constriction.

**Heart.**

The actions on the heart may be resolved into direct actions on at least five different components. The heart rate is determined by the slope of diastolic depolarization of the cells of the sinoatrial node; this slope is increased by noradrenaline (Trautwein, 1963), with consequent cardiac acceleration. Intra-arterial injection into the right coronary artery reveals this sinus tachycardia most readily (West, Guzman and Bellet, 1957). On the atria, noradrenaline slightly increases rate of conduction, slightly reduces refractory period and increases force, but atrial actions are relatively unimportant. On ventricular conducting apparatus, the atrioventricular node, bundle of His, and Purkinje fibres, noradrenaline increases the speed of conduction (especially through the a-v node), thus reducing the degree of any pre-existing a-v block and reducing the relative duration of systole. It increases the slope of diastolic depolarization, thus increasing automaticity (Trautwein, 1963) and predisposing to nodal and ventricular ectopic beats, tachycardia and fibrillation; this is best seen after left circumflex arterial injection (West, Guzman and Bellet, 1957). The myocardium shows an increased force per unit fibre length or increased stroke volume at constant filling pressure (Kukotetz et al., 1959; West, Guzman and Bellet, 1957). There is a disproportionate increase in oxygen consumption. Direct actions on the coronary vessels are probably unimportant, for coronary flow is controlled by local accumulation of metabolites so that the system is responsive to changes in cardiac work.

**Other actions.**

Mydriasis is produced by contraction of the dilator pupillae. Salivary glands are mildly stimulated to produce a thick viscid secretion. The propulsive musculature of the gut is inhibited while its sphincters are contracted. The bladder's detrusor is relaxed while its trigone and sphincters are contracted. The vas deferens and seminal vesicle are contracted (ejaculation is a sympathetic reflex). The uterus is relaxed in some species (e.g., rat), contracted in others (e.g., rabbit) and in yet others the effect varies with the stage of the sexual cycle. The skin's pilomotor muscles are contracted. The bronchioles are dilated. Glycogenolysis occurs in liver and muscle, with rise in the blood glucose, lactic acid and potassium. There is also a rise in plasma-free fatty acids.

The central nervous system is stimulated; this is usually seen as anxiety and increased respiratory minute volume.

**THE EFFECTS OF NORADRENALINE INTRAVENOUSLY IN VIVO**

Mean arterial pressure is increased because of a rise in both systolic and diastolic pressures. This is caused by an increase in total peripheral resistance due to a patterned vasoconstriction most prominent in skin and mucosae, renal (Aviado, Wnuck and de Beer, 1958b; Mills and Moyer, 1957) and superior mesenteric (Corday and Williams, 1960) beds. Flow through skeletal muscle is reduced in man (Churchill-Davidson and Swan, 1952) but rises in the cat (Kolin and Ross, 1965); hepatic arterial flow increases (Corday and Williams, 1960). The resistance to flow is due primarily to arteriolar constriction but veins are also contracted, as shown by a fall in their volume and distensibility (Cohn, 1965; Eckstein and Hamilton, 1957). The constriction of small veins can lead to a sufficient increase in resistance to flow to raise capillary pressure in spite of the concurrent arteriolar constriction (Haddy et al., 1962); this increases interstitial volume at the expense of plasma volume. Loss of circulating blood volume seems to be the major factor both in the development of so-called tolerance or dependence on an increasing noradrenaline infusion rate to maintain a steady blood pressure effect, and in postinfusion hypotension (Rosenthal and Di Palma, 1959). Central venous pressure (filling pressure, right ventricular end-diastolic pressure, in the literature widely miscalled "venous return") is raised though left atrial pressure may fall (Rose et al., 1962).

The heart rate is reduced reflexly. The raised mean arterial pressure increases stretch of baroreceptor afferent nerve endings raising the frequency of action potentials ascending from the carotid sinus, common carotid artery, aortic arch and root of the right subclavian artery to the vagal cardio-inhibitory centre (which is stimulated)
and vasomotor centre (which is inhibited) in the medulla. This reduction in vasoconstrictor tone, which is part of the baroreceptor reflex, explains why the resistance of a vascular bed in vivo may be reduced by a drug demonstrated to constrict it in vitro or when infused intra-arterially. Since the reflex is elicited by raised arterial pressure, it will dilate maximally the beds least strongly constricted by a drug whose pressor action depends on vasoconstriction; for a drug whose pressor action depends on increased cardiac output it will dilate most the beds having highest vasoconstrictor tone.

The cardiac output falls less than the heart rate and the stroke volume rises with an increase in systolic ejection velocity. After vagotomy, heart rate, stroke volume and cardiac output all rise (Aldinger, 1964). In the face of a raised arterial pressure this must signify increased cardiac work (Goldberg et al., 1953, 1960). The vagal cardio-inhibition suppresses the noradrenaline-induced tachycardia but fails to suppress its increase in force because vagal innervation of the ventricular muscle is very sparse. There is a marked tendency for ventricular arrhythmias to emerge (Orth et al., 1939); this is less after atropine or vagotomy (Trautwein, 1963).

Hyperglycaemia and increased respiratory minute volume are the only other effects commonly observed on intravenous administration of noradrenaline. The pharmacodynamics of an intravenous injection are well known to anaesthetists—a drug’s effects are determined by its concentration in a tissue and this is dependent on the tissue’s blood flow. The high flows to liver and central nervous system explain why effects here rather than on, say, the dilator pupillae are obvious.

**PHYSIOLOGY OF THE ADRENERGIC NEUROEFFCTOR JUNCTION**

The action potentials travelling down a sympathetic adrenergic axon enter the ground plexus (Malmfors, 1965) and follow each subdivision of the axon throughout this ramifying network to the nerve terminal. Noradrenaline is present (Dahlström, Fuxe and Hillarp, 1965) in the whole neurone (dendrites, cell body, axon, ground plexus and terminals) because the enzymic apparatus for synthesizing it is present and active throughout the neurone. At the nerve terminals the noradrenaline is present in its highest concentration and in at least two forms; the larger amount is bound within granules while the smaller exists in the cytoplasm—this may or may not be bound. Each arriving action potential causes a complete (but transient) collapse of the normal membrane’s impermeability to the outward diffusion of noradrenaline. It may, at the same time, free some bound noradrenaline. An amount of noradrenaline which is determined by the recent history of the nerve ending leaves the nerve ending and crosses the synaptic space to reach the membrane of an effector cell. For noradrenaline to exert a measurable effect on an effector cell, the cell and drug must interact in some way. It is considered that the component of the effector cell with which an agonist drug first interacts in order to bring about a measurable change in the effector cell has a special place in any discussion of the mechanism of drug action. It is this first component which is labelled “the receptor”. It is thus unreasonable to regard receptors as hypothetical—they are defined into existence. The contribution of receptors to drug action is twofold; the receptor will only allow certain drugs to interact with it (stereospecific) and the interaction with effective drug triggers a series of changes in the cell’s function which lead to the measured change. The interaction is dynamic in that each molecule of noradrenaline is in constant motion and is able to closely approach one receptor, trigger with it a quantum of change in cell function and disengage itself by its own kinetic energy without the molecule of noradrenaline being chemically changed. Drugs which are accepted by the receptor but whose interaction with the receptor produces no effective trigger are antagonists.

When the train of action potentials is finished, noradrenaline’s concentration in equilibrium with the receptor population declines. What factors determine the cessation of the response being recorded from the effector cell? Noradrenaline is present in relatively high concentration in the synaptic space. There is a concentration gradient for it to follow by diffusion leading through interstitial fluid to nearby capillaries and thus into the general circulation; this would result in only slow termination of the effects of adrenergic nerve stimulation. There is no enzyme comparable in location, amount and activity with cholinesterase.
at cholinergic neuro-effector junctions, though some catechol-O-methyl transferase is present. There is, however, another mechanism capable of removing noradrenaline from the synaptic space sufficiently quickly to be regarded as the physiological mechanism for terminating the effects of adrenergic nerve stimulation. This is the uptake mechanism, located in the adrenergic neurones; driven by metabolic energy, it is capable of accumulating noradrenaline into not only the terminals but the whole neurone (Dahlström, Fuxe and Hillarp, 1965) against a considerable concentration gradient.

This uptake mechanism accumulates noradrenaline faster than any other drug, but uptake is by no means restricted to L-noradrenaline. Other drugs which have been shown to be taken up by this mechanism are adrenaline (Iversen, 1965a, c), isoprenaline (Callingham, 1965), metaraminol (Shore, Busfield and Alpers, 1964; Carlsson and Waldeck, 1965a, b) and guanethidine (Brodie, Chang and Costa, 1965), and we infer that many others are taken up (e.g., all sympathomimetics). The fact that this uptake mechanism is largely responsible for limiting and terminating the activity of noradrenaline released from adrenergic nerves means that any drug capable of inhibiting uptake will potentiate noradrenaline. A very large number of drugs is known to inhibit the uptake mechanism. Some of these are:

α-blocking agents; phenoxybenzamine and phenotamine.

β-blocking agents; propranolol, pronethanol and dichloroisoprenaline.

Adrenergic neurone blocking agents; bretylium, guanethidine, bethanidine.

Sympathomimetics; metaraminol, ephedrine, methylenephtamine, etc.

Dibenzazepines; imipramine, amitriptyline and their derivatives.

Phenothiazines; chlorpromazine, etc.


(Burgen and Iversen, 1965; Iversen, 1965a, b; Koelle, 1965; Carlsson and Waldeck, 1965a, b).

With the majority of these drugs it is simple to demonstrate considerable potentiation of noradrenaline if an appropriate in vitro system is chosen. With all these drugs, and probably many more, the possibility of dangerous potentiation of noradrenaline and adrenaline in clinical practice exists. Maxwell, Wastila and Eckhardt (1966) dispute the generally accepted cause-and-effect relationship between inhibition of uptake and potentiation. It should be realized that the evidence relating to drug uptake mechanisms has arrived suddenly and recently and so a complete picture does not emerge. There is certainly more than one uptake mechanism—and possibly more than two (Iversen, 1965c; Koelle, 1965; Malmfors, 1965; Giachetti and Shore, 1966; Carlsson and Waldeck, 1965a, b), with different patterns of drug uptake and different sensitivities to inhibitors. In the foregoing paragraphs I have grouped them together.

**ADRENERGIC RECEPTORS**

Attention has been drawn to the two functions of a drug receptor; it is the trigger of the drug’s effects and its stereospecificity determines which drugs can press the trigger (and which can prevent others doing so). There is only a very small range of closely related compounds which is accepted by and trigger effects with adrenergic receptors—they must be β-phenylethylamines with either an m- or both m- and p-hydroxy groups. Let us consider (as did Ahlquist, 1948) the activity of two closely-related directly-acting sympathomimetics—noradrenaline and isoprenaline. Examination of the relative potencies of these two drugs on the effector systems discussed on pages 690–691 reveals that noradrenaline is very much more potent than isoprenaline in causing constriction of the dilator pupillae, the spleen, the vas deferens and seminal vesicle and the uterus (in those species whose uterus is contracted by noradrenaline), the pilomotor muscles, the sphincters of the intestine and urinary bladder, in stimulating salivary secretion and in constricting blood vessels throughout the body. In contrast, isoprenaline is very much more potent than noradrenaline in stimulating the heart, dilating the bronchioles, relaxing the uterus (in those species whose uterus is relaxed by noradrenaline), the pilomotor muscles, the sphincters of the intestine and urinary bladder, stimulating salivary secretion and constricting blood vessels through the body. In contrast, isoprenaline is very much more potent than noradrenaline in stimulating the heart, dilating the bronchioles, relaxing the uterus (in those species whose uterus is relaxed by noradrenaline) and dilating certain vascular beds, in particular that of skeletal muscle but also renal and splanchnic, and in causing an elevation of plasma-free fatty acid concentration (Pilkington et al., 1966). These differences are quantitatively so striking that a subdivision of
adrenergic receptors is postulated; some (labelled \( \alpha \)) have a much higher affinity for noradrenaline than for isoprenaline, while in others (\( \beta \)) this affinity pattern is reversed. The tissues found experimentally to be more sensitive to noradrenaline than to isoprenaline are therefore regarded as being equipped with \( \alpha \)-receptors while those which are more sensitive to isoprenaline are equipped with \( \beta \)-receptors. Notice that discussion of receptor types is unrelated to the response (stimulation or inhibition) elicited. Both the type and the presence or absence of receptors in a tissue are unrelated to innervation; for example, the developing chick amnion reacts to noradrenaline before nerves have grown into it, and placental vessels have adrenergic receptors but are not innervated—receptors are part of the effector cell and are nothing to do with the autonomic nervous system. Certain tissues have both \( \alpha \)- and \( \beta \)-receptors; these may mediate opposite actions as in blood vessels of skeletal muscle which are constricted by noradrenaline and dilated by isoprenaline; or they may both mediate the same action as in the propulsive muscle of the intestine where noradrenaline and isoprenaline have similar inhibitory potency. Another independent stream of evidence which proves the existence of two adrenergic receptors differing in their stereospecificity is found in a consideration of blocking agents. The classical adrenergic blocking agents, such as ergot, piperoxane, phentolamine and phenoxybenzamine, only block the actions of catecholamines on those tissues described as being more sensitive to noradrenaline. With the advent of dichloroisoprenaline, followed by pronethalol and propranolol, it became possible to antagonize the actions of catecholamines on those tissues described as being more sensitive to isoprenaline. With the advent of dichloroisoprenaline, followed by pronethalol and propranolol, it became possible to antagonize the actions of catecholamines on those tissues described as being more sensitive to isoprenaline. Skeletal muscle vessels constricted by a large infusion of adrenaline dilate if an \( \alpha \)-blocking agent is injected; this reversal can be eliminated by propranolol. The relaxation of the gut induced by adrenaline can only be partially blocked by even massive doses of phentolamine or propranolol singly; combined \( \alpha \)- and \( \beta \)-blockade is necessary to eliminate adrenaline’s action. Thus each of these two independent lines of evidence, strong in its own right, entirely substantiates the other and allows us to speak of the theory of \( \alpha \)- and \( \beta \)-receptors rather than the hypothesis.

INDIRECTLY-ACTING SYMPATHOMIMETICS

Although this concept developed long before reserpin became available, it is most clear cut in relation to the action of this drug. Reserpine causes a virtually complete loss of the noradrenaline from adrenergic nerves. The precise mode of action of reserpin in releasing noradrenaline from its granular-bound form is unclear but the noradrenaline diffuses freely from the granules into the cytoplasm where some leaks out of the cell while most of it is broken down by monoamine oxidase. The initial displacement of noradrenaline by reserpin is almost instantaneous but it takes some time for the tissue content of noradrenaline to fall to levels which no longer allow adrenergic neuroeffector transmission. This rate of depletion can be increased by sympathetic nervous activity. The role of intracellular monoamine oxidase in the catecholamine-depleting action of reserpin is clearly shown by the greatly delayed depletion which occurs in tissues whose noradrenaline has been replaced by \( \alpha \)-methyl noradrenaline (by treatment with \( \alpha \)-methyl dopa) or by metaraminol (by treatment with \( \alpha \)-methyl-\( m \)-tyrosine).

It is natural that either an animal or tissue depleted of all its endogenous catecholamine should have been used to answer the question: do some drugs have sympathomimetic actions because they release stored noradrenaline? Tyramine, amphetamine, methylamphetamine and mephentermine are found to have very little action on the reserpinized dog and cat arterial pressure, cat heart rate and nictitating membrane, and rabbit ileum (Eger and Hamilton, 1959; Trendelenburg et al., 1962a; Schmidt and Fleming, 1963); raising the dose of drug does not result in any greater action. These drugs appear to depend entirely on stored noradrenaline to show any action at all, and are described as indirectly-acting. In a normal animal they show sympathomimetic effects by several simultaneous mechanisms: they release noradrenaline from adrenergic nerve terminals (to do this they must be taken into the nerves), and they potentiate this same noradrenaline—also that released by nervous activity—by preventing its uptake back into the adrenergic neurone (Muscholl, 1966).

The action of directly-acting sympathomimetics (which do not depend on an intact store of noradrenaline to have effects) in reserpinized pre-
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Preparations may be unchanged (Trendelenburg et al., 1962a) or potentiated (Eger and Hamilton, 1959; Schmidt and Fleming, 1963). They are noradrenaline, adrenaline and phenylephrine. There is another, intermediate, group which might be described as having both types of action in approximately equal degree, comprising methoxamine, metaraminol, ephedrine and p-hydroxyamphetamine. Both Trendelenburg et al. (1962a, b) and Schmidt and Fleming (1963) have drawn attention to the fact that the whole group of sympathomimetics forms a continuous spectrum from fully directly-acting to fully indirect; they regard as artificial the earlier grouping into three classes. Metaraminol’s action typifies this revised view of the mode of action: some of the drug enters into equilibrium with the receptors, while some is taken into the adrenergic nerves by the uptake mechanism where it displaces an equal amount of endogenous noradrenaline out on to the receptors and blocks its re-uptake (Shore, Busfield and Alpers, 1964).

We have noted already that in order to exert an indirect action by liberating noradrenaline, a sympathomimetic has first to penetrate the adrenergic neurone. Another method used to distinguish directly from indirectly-acting sympathomimetics is to examine the change in their effects when this penetration is prevented by, usually, cocaine. Directly-acting drugs are potentiated, indirectly-acting ones strongly antagonized, and again there is an intermediate group which is but weakly antagonized (Trendelenburg et al., 1962b). Still further methods involve eliminating both the store of noradrenaline within, and the access of drugs to, the adrenergic neurone by chronic postganglionic denervation (Fleckenstein and Burn, 1953) or immunosympathectomy. Comparisons between these methods show remarkable agreement (Trendelenburg et al., 1962a, b) when performed by one worker, though the same method often gives different results in different workers’ hands. The difficulties here are use of parameters determined in vivo, differences in doses and timing—especially with reserpine—and the difficulty of assessing response to drugs which are strongly tachyphylactic.

Many other drugs, in addition to phenylethylamines, are indirectly-acting sympathomimetics. Reserpine, as just mentioned, releases noradrenaline. Guanethidine shows some initial sympathomimetic activity, if given intravenously, before the onset of adrenergic neurone blockade. This drug, as noted on page 693, potentiates noradrenaline by blockade of uptake, is taken up itself and this uptake is blocked by amphetamine and other indirectly-acting sympathomimetics (Brodie, Chang and Costa, 1965). Day (1962) has shown that amphetamine and several other indirectly-acting sympathomimetics permanently restore adrenergic neuroeffector transmission which has been completely blocked by guanethidine. By this criterion hydroxyamphetamine, mephentermine and ephedrine were regarded as indirectly-acting. By means of this battery of tests we can say with certainty that noradrenaline, adrenaline and phenylephrine act directly on adrenergic receptors of effector cells and that methylamphetamine and mephentermine act indirectly. Methoxamine, metaraminol, ephedrine and hydroxyamphetamine, in that order, form an intermediate spectrum.

METABOLISM

The different time courses of these drugs partially reflect their differing rates of uptake, oxidative deamination, O-methylation, further metabolic transformation and excretion, but also different time courses of action once inside the adrenergic nerves. Characteristically the directly-acting catecholamines, noradrenaline and adrenaline, are very short-acting if given by intravenous injection because uptake into adrenergic nerves rather than enzymatic metabolism clears them from the extracellular fluid. The catecholamines are metabolized by both catechol-O-methyl-transferase (in tissues and liver) and by monoamine oxidase (in mitochondria of adrenergic nerves and liver); the former is quantitatively more important. The product of degradation by both enzymes is the well-known vanilmandelic acid (VMA); its rate of urinary output provides an indication of the rate of catecholamine synthesis. Only catechols are susceptible to destruction by catechol-O-methyl-transferase (so only noradrenaline and adrenaline of our group are susceptible) and only compounds lacking an α-methyl group are susceptible to inactivation by monoamine oxidase (so only the catechols and phenylephrine are susceptible).
The provocation of hypertensive crises in patients taking monoamine oxidase inhibitors by cheese or Marmite is due more to the preservation of the tyramine absorbed from these foods than to the potentiation of the noradrenaline released by it.

MECHANISM OF ACTION OF DIRECTLY-ACTING SYMPATHOMIMETICS

The discovery of the role of adenyl cyclase and 3', 5'-AMP (adenosine monophosphate) in the glycogenolytic action of adrenaline has led to widespread speculation regarding the possible role of this enzyme in other actions of directly-acting sympathomimetics (see Pharmac. Rev. (1956), 18, 142–213, for a full treatment of this subject).

ADRENALINE

Adrenaline can be released from the adrenal medulla (there are insignificant amounts in adrenergic nerves) either along with or separately from activation of the adrenergic nerves (Celander, 1954). It is a directly-acting sympathomimetic as shown by modification of its actions by reserpine, cocaine and chronic postganglionic denervation (Fleckenstein and Burn, 1953; Eager and Hamilton, 1959; Trendelenburg et al., 1962a, b; Schmidt and Fleming, 1963).

When given intra-arterially, the vessels of the skin (Johnson, Green and Lanier, 1953) and kidney (Aviado, Wnuck and de Beer, 1958b) are constricted. Skeletal muscular and splanchnic blood vessels show evidence of having two receptor populations; Baltzan et al. (1965) demonstrated human skeletal muscular vasodilatation with low intra-arterial infusion rates and vasoconstriction with high rates; Kolin and Ross (1965) showed the cat to behave in the same way; while Johnson, Green and Lanier (1953) found constriction in the dog which was reversed to dilatation by α-blockade. Deal and Green (1956), in examining the dog superior mesenteric vasculature, found adrenaline to constrict before, but dilate after, α-blockade. As with noradrenaline, veins are strongly constricted (Haddy et al., 1962; Texter et al., 1964).

A direct cardiac stimulant action is easily demonstrated in vitro (Kukotetz et al., 1959) and on intracoronary injection; the force of contraction increases (with associated coronary flow increase) and a sinus tachycardia occurs on right coronary injection while left circumflex administration results in nodal tachycardia.

With very small intravenous doses of adrenaline the arterial pressure falls, as it does after the pressor action of higher doses. Moderate doses cause little change in mean arterial pressure with a fall in diastolic and a rise in systolic; total peripheral resistance is reduced. High doses can raise systolic, mean and diastolic pressures and peripheral resistance. Blood flow through skin and mucosae and kidney (Aviado, Wnuck and de Beer, 1958b) is reduced by all doses. Flow through skeletal muscle, and the liver in man, is increased by small and moderate doses, and reduced by large doses. Veins are constricted (Eckstein and Hamilton, 1957).

While a reflex bradycardia may be seen during adrenaline’s action it is more usual to observe a rise in heart rate, stroke volume (Goldberg et al., 1953, 1960) and cardiac output (Aldinger, 1964), with increased automaticity (Trautwein, 1963). If adrenaline’s cardiac action is increased by raising the dose or by potentiating it with, for example, cocaine, imipramine, guanethidin, cyclopropane (Orth et al., 1939) chloroform or halothane (Raventós, 1956) ventricular arrhythmias emerge.

The splenic capsule is contracted by adrenaline in animals. The bronchioles are dilated. Skeletal muscular and hepatic glycogenolysis raise blood lactic acid, glucose and potassium; plasma-free fatty acid concentration rises, as does basal metabolic rate. There is central stimulation of respiratory minute volume which may be preceded by a reflex (baroreceptor) apnoea; other expressions of adrenaline’s c.n.s. stimulant action are anxiety, and increased rigidity and tremor in Parkinson’s disease.

The principal differences between adrenaline and noradrenaline are quantitative; adrenaline has about the same affinity as noradrenaline for α-receptors but a much higher one for β-receptors so that for equal effects a much smaller dose of adrenaline is required to produce bronchodilatation, increased plasma-free fatty acid concentration (Pilkington et al., 1966) or increased rate and force of the isolated heart. In certain situations such quantitative differences can lead to qualitative ones which (wrongly) exaggerate the differences between the drugs. The β-receptor-
mediated vasodilatation in skeletal muscle is the principal such difference. The \( \beta \)-receptor population of skeletal muscle vessels is smaller than that of \( \alpha \)-receptors but is more sensitive to adrenaline (and less sensitive to noradrenaline). Skeletal muscle vessels make up a large fraction of the body's vessels, so a qualitative difference in their reaction to equal doses of adrenaline and noradrenaline is reflected by total peripheral resistance changes which secondarily distort the relative cardiac effects of the drugs, reducing that of noradrenaline by reflex cardiac inhibition.

**PHENYLEPHRINE**

Phenylephrine produces a rise in arterial pressure and intestinal relaxation which are blocked by \( \alpha \)-blockade with dibozane but unaffected by \( \beta \)-blockade with dichloroisoprenaline (Levy, 1959). It is a directly-acting sympathomimetic as shown by its interaction with cocaine, and the effects of chronic postganglionic denervation and reserpine (Eger and Hamilton, 1959; Trendelenburg et al., 1962a, b; Schmidt and Fleming, 1963).

When given intra-arterially, Johnson, Green and Lanier (1953), Haddy et al. (1962) and Kolin and Ross (1965) agree that both cutaneous and muscular vessels are constricted in dog fore and hind limbs and cat hind limb. \( \alpha \)-blockade adequate to reverse adrenaline's action did not reveal any dilator component. Aviado, Wnuck and de Beer (1958b) found constriction of renal vessels. Kukotetz et al. (1959) used the Langendorff rat heart and showed phenylephrine to stimulate only in very high doses. West, Guzman and Bellet (1957) showed that intracoronary administration did stimulate the dog heart, increasing its force of contraction and causing a sinus tachycardia when given into the right coronary and a nodal tachycardia into the left circumflex artery.

When given intravenously, a rise in diastolic as well as systolic pressure is seen. The peripheral resistance rises; the renal flow falls (Aviado, Wnuck and de Beer, 1958b) though femoral flow rises in the cat (Kolin and Ross, 1965). The venous pressure increases slightly (Keys and Violante, 1942).

Bradycardia is always seen, the heart enlarges, stroke volume increases considerably, but cardiac output falls; arm-to-tongue circulation time is slightly prolonged. After vagotomy or atropinization, phenylephrine produces a tachycardia and shortens the circulation time, indicating a rise in cardiac output (Keys and Violante, 1942). Goldberg et al. (1953) have shown that phenylephrine causes significantly less cardiac stimulation than several other sympathomimetics. Orth et al. (1939) showed that the combination of cyclopropane and phenylephrine in dogs did not cause arrhythmia.

Pilomotor activity was marked when the drug was injected subcutaneously. There was no feeling of anxiety (Keys and Violante, 1942). The activity of phenylephrine is entirely predictable, if it is regarded as a directly-acting sympathomimetic with an even higher ratio of \( \alpha \)- to \( \beta \)-activity than noradrenaline. The drug is not susceptible to catechol-O-methyl transferase, is taken up less rapidly than noradrenaline by the uptake mechanism, but is susceptible to monoamine oxidase. Its action after intravenous injection is moderately long—about 20 minutes.

**METHOXAMINE**

Levy (1959) found that the pressor and intestinal actions of methoxamine were entirely blocked by \( \alpha \)-blockade, and were unaffected by \( \beta \)-blockade.

Though the original pharmacology described both tachyphylaxis and potentiation of adrenaline with this drug (Hjort, Randall and de Beer, 1948), effects which suggest an indirect mode of action, Eger and Hamilton (1959) decided it acted directly on the dog's arterial pressure while Schmidt and Fleming (1963) found it to have a mixed action on the rabbit ileum; both authors used reserpine in these tests.

Methoxamine constricts cutaneous and muscular blood vessels (Kolin and Ross, 1965; Haddy et al., 1962) and renal vessels (Aviado, Wnuck and de Beer, 1958b) when injected intra-arterially. Kukotetz et al. (1959) found methoxamine to be ineffective in stimulating the isolated rat heart, and West, Guzman and Bellet (1957) saw no increase in the force or rate of the dog heart when they gave the drug into the coronary artery; in large doses it depressed cardiac force.

When given intravenously, methoxamine raises diastolic and systolic pressure entirely by increasing peripheral resistance. Renal flow is reduced in the dog (Aviado, Wnuck and de Beer, 1958b) and in man (Mills and Moyer, 1957). Central venous...
pressure rises (Eckstein and Hamilton, 1957; Aviado and Wnuck, 1957). Limb and splanchnic blood flows are reduced.

There is marked bradycardia, and cardiac output falls. Goldberg et al. (1953) found it to be the least active cardiac stimulant of a series of sympathomimetics examined in vagotomized dogs in which methoxamine caused bradycardia. Goldberg et al. (1960) showed that it caused little increase in right ventricular force in man. It did not lead to arrhythmias when used in dogs during cyclopropane administration (Stutzman, Pettinga and Fruggeri, 1949; Lahti, Brill and McCawley, 1955) but merely gave less bradycardia than before.

Aviado and Wnuck (1957) investigated the mechanism of the marked bradycardia in the dog and found section of the aortic and sinus nerves markedly to reduce, but not to eliminate, the bradycardia. Karim (1965), working with the cat, found these procedures only slightly effective in preventing the bradycardia, which therefore could not depend on a baroreceptor-induced reflex increase in vagal inhibition of the heart; the response was completely prevented by reserpine or acute cardiac sympathectomy and must have resulted from reduced sympathetic cardioacceleration.

Other effects of methoxamine include mydriasis, relaxation of the rabbit intestine, contraction of the rabbit and guineapig uteri, pilomotor activity and contraction of the seminal vesicle (Hjort, Randall and de Beer, 1948; Mills and Moyer, 1957). It causes no c.n.s. stimulation.

The actions of methoxamine are those of a directly-acting sympathomimetic with no demonstrable \( \beta \)-activity—all its actions are mediated by \( \alpha \)-receptors. Indeed, the evidence of Karim (1965) indicates that methoxamine is a \( \beta \)-blocking agent. Levy (1964) also demonstrated \( \beta \)-blocking activity with this drug, which was peculiar in that it could be demonstrated in the rat but not the dog. \( \beta \)-blockade, rather than strong reflex vagal activity, may be the reason for its efficacy in paroxysmal supraventricular tachycardia; it has even been shown to antagonize adrenaline-induced ventricular arrhythmias (Lahti, Brill and McCawley, 1955). Neither inactivating enzyme affects it. When given intravenously its pressor effect lasts about 20 minutes.

**METARAMINOL**

This drug's pressor and intestinal relaxing actions are blocked but not reversed by dibozane and unaffected by dichloroisoprenaline (Levy, 1959); it is thus a sympathomimetic.

Trendelenburg et al. (1962a, b) found it to act directly on the cat arterial pressure and nictitating membrane, but indirectly on the heart rate. Schmidt and Fleming (1963) found it to have mixed activity on the rabbit ileum.

Kolin and Ross (1965) have shown constriction of the vessels of both the skin and muscle of the cat hind limb; Aviado, Wnuck and de Beer (1958b) report renal vasoconstriction when the drug is given into the renal artery.

West, Guzman and Bellet (1957) have examined the drug's intracoronary effects in the dog; it increased the force of cardiac contraction; given into the right coronary artery it produced sinus tachycardia, while into the left circumflex it induced nodal tachycardia.

Intravenous administration raises both systolic and diastolic pressure. The peripheral resistance is raised though femoral flow rises (Kolin and Ross, 1965) as does hepatic arterial flow (Corday and Williams, 1960). Renal flow falls (Aviado, Wnuck and de Beer, 1958b) or is unchanged (Mills and Moyer, 1957) and portal flow falls (Corday and Williams, 1960). Central venous pressure is increased because of venous constriction (Braunwald et al., 1957).

There is reflex bradycardia and increased stroke volume; the cardiac output is unchanged but rises after atropine, showing that the drug does stimulate the heart (Goldberg et al., 1960). Arrhythmias result from its potentiation by cyclopropane or halothane (Catenacci et al, 1962).

Metaraminol is susceptible to neither catechol-O-methyl-transferase (it is not a catechol) nor monoamine oxidase (it has an \( \alpha \)-methyl group); it is rapidly taken up by adrenergic nerve endings (Shore, Busfield and Alpers, 1964) by the same mechanisms which take up noradrenaline. Its pressor effect lasts about 20 minutes after intravenous injection and it can be given intramuscularly. It releases an amount of noradrenaline equal to the amount of its own uptake and it can itself be released by such drugs as reserpine, guanethidine and tyramine which also release noradrenaline. As it is being taken up it inhibits the uptake
of noradrenaline (Iverson, 1965c) and therefore potentiates it. These are reflections of the indirect component of its action.

**EPHEDRINE**

Levy (1959) demonstrated the sympathomimetic nature of both the pressor and intestinal inhibitory actions by showing them to be inhibited but not reversed by dibozane and unaffected by dichloroisoprenaline.

Ephedrine usually falls between the clearly defined directly- and indirectly-acting classes as distinguished by cocaine or chronic postganglionic denervation (Fleckenstein and Burn, 1953). The evidence with reserpine is confused, the action of ephedrine being described as indirect (Eger and Hamilton, 1959) or mixed (Trendelenburg et al., 1962a, b; Schmidt and Fleming, 1963; Moore and Moran, 1962). Tachyphylaxis is marked.

Intra-arterially or locally, ephedrine constricts the superior mesenteric, external iliac, carotid and vertebral vessels; in large doses it constricts the renal vessels (Aviado, Wnuck and de Beer, 1958a, b). The forearm vessels in man constrict with small doses—on increasing the dose this effect passes off: phentolamine blocks the constriction without inducing reversal (Cohn, 1965).

Given intravenously ephedrine elevates diastolic as well as systolic pressure; Cohn (1965) reports that the diastolic pressure rises less in relation to the systolic than with noradrenaline. There is little change in calculated peripheral resistance. The nasal mucosa is constricted (Eckfeldt, Abell and Seifter, 1954). Forearm resistance falls slightly (Cohn, 1965) and renal flow can rise or fall (Aviado, Wnuck and de Beer, 1958b). Venous tone rises slightly.

Goldberg et al. (1953) demonstrated cardiac stimulation by intravenously ephedrine in the vagotomized dog. In man, Cohn (1965) found that an intravenous infusion increased heart rate, caused a slight rise in stroke volume and an increase in cardiac output. Orth et al. (1939) found, in dogs given cyclopropane, that ephedrine regularly produced sino-atrial tachycardia, rarely ventricular arrhythmias.

Other readily demonstrable actions are mydriasis, bronchodilatation, hyperglycaemia and c.n.s stimulation.

Ephedrine differs from phenylephrine and methoxamine in having more β-activity; since it is probably indirectly-acting, this is expected. The relative strengths of its in vivo actions need not resemble those of intravenous noradrenaline; they are likely to be dictated by the number of adrenergic nerve fibres per gram of effector organ (richness of adrenergic innervation). The drug is not broken down by either of the two known enzymes; 60 to 75 per cent of an administered dose is excreted in the urine unchanged. Effects last more than 20 minutes.

**p-HYDROXYAMPHETAMINE**

Levy (1959) proved the sympathomimetic nature of its pressor and intestinal actions; dibozane blocked but did not reverse its actions; dichloroisoprenaline had no effect.

Renal vasoconstriction was produced by large doses given by close intra-arterial injection (Aviado, Wnuck and de Beer, 1958b).

When given intravenously both diastolic and systolic pressures increase; mucosal, cutaneous, splanchnic and renal flows decrease. Heart rate may fall reflexly, but both stroke volume and cardiac output increase. Goldberg et al. (1953) demonstrated the drug's ability to increase the rate and force of the vagotomized dog heart. Orth et al. (1939) gave it to dogs anaesthetized with cyclopropane and produced sino-atrial tachycardia.

It also produces mydriasis and bronchodilatation, but no c.n.s. stimulation.

This compound has been little investigated but seems to resemble ephedrine closely.

**METHYLAMPHETAMINE**

Methyamphetamine certainly acts indirectly; its action is virtually eliminated by reserpine (Eger and Hamilton, 1959).

Kolin and Ross (1965) obtained vasoconstriction of both the cutaneous and muscular beds of the cat hind limb. Aviado, Wnuck and de Beer (1958b) could demonstrate little vascular effect on injection into the renal artery. Aviado (1959) has described vasodilatation in the superior mesenteric bed when the drug is given intra-arterially.

Churchill-Davidson and Swan (1952) found the diastolic pressure to rise less with methylamphetamine than with a dose of noradrenaline.
producing an equal rise in systolic pressure. This indicates a smaller contribution of peripheral vasoconstriction to the pressor effect. Calf resistance was increased, reducing skeletal muscle blood flow slightly. Renal flow rises but the nasal mucosal vessels constrict. Eckstein and Hamilton (1957) observed a rise in venous pressure with a fall in the volume and distensibility of arm veins.

Goldberg et al. (1953) showed that methylamphetamine increased both the force and rate of the vagotomized dog heart. Churchill-Davison and Swan (1952) inferred an increase in cardiac output in man; a small reflex bradycardia was observed. Stutzman, Pettinga and Fruggeri (1949) found that it usually produced sino-atrial tachycardia during cyclopropane anaesthesia in dogs.

Methylamphetamine has the strongest central action of this group of drugs.

It is not metabolized by the two recognized enzymes, and is excreted, largely unchanged, in the urine.

Since it acts entirely by releasing noradrenaline (and potentiating the noradrenaline released) its pattern of action (more increase in cardiac output and less increase in peripheral resistance relative to noradrenaline) presumably correlates with the quantitative distribution of adrenergic nerves. It is difficult to understand the significance of the reported vasodilatation on close arterial injection — see after mephentermine.

Mephentermine

Eckfield, Abell and Seifter (1954) described mephentermine as essentially similar to ephedrine. Dibenamine blocked its pressor action.

Repeated injection revealed tachyphylaxis, and the drug potentiated adrenaline's pressor action. These findings suggest an indirect mode of action; this is amply confirmed by studies using reserpine, cocaine and chronic postganglionic denervation (Trendelenburg et al., 1962a, b; Eger and Hamilton, 1959; Moore and Moran, 1962).

Kolin and Ross (1965) observed both dilatation and constriction of the vessels of the cat hind limb; Haddy et al. (1962) obtained constriction with mephentermine in the dog forelimb. Aviado, Wnuck and de Beer (1958) reported very little effect on the renal vessels, while Aviado (1959) describes dilatation of the superior mesenteric bed on close intra-arterial injection.

West, Guzman and Bellet (1957) demonstrated the cardiac stimulant action of mephentermine on intracoronary injection; increased force, sinus- and nodal-tachycardia could all be produced.

When given intravenously, the rise in arterial pressure is associated with a rise in diastolic pressure and in calculated peripheral resistance (Eckstein and Abboud, 1962). It follows from the observation of blockade of the pressor action by dibenamine that a rise in peripheral resistance must contribute to the pressor effect. The nasal mucosal vessels constrict and flow falls in cutaneous and muscular beds. Renal flow rises with the arterial pressure (Aviado, Wnuck and de Beer, 1958b) and splanchnic flow increases. Venous pressure rises.

Goldberg et al. (1953, 1960) have demonstrated increased heart rate and force in vagotomized dogs, and increased force in man. Horsley and Eckstein (1961) found the pressor action of mephentermine to be associated with a rise in stroke volume and cardiac output; changes in heart rate were small and variable. Eckfield, Abell and Seifter (1954) saw bradycardia in dogs which reversed to tachycardia on cutting the vagi. Raventós (1956) noted no ventricular tachycardia during halothane anaesthesia in animals.

Other sympathomimetic actions which have been noted are mydriasis, pilo-erection and weak intestinal relaxation; c.n.s. stimulation is less than with methylamphetamine.

Again the drug's pattern of activity and known indirect mode of action are in agreement; mephentermine increases both cardiac output and peripheral resistance, the former relatively more than does noradrenaline. It is not broken down by the two enzymes and its effects last about 25 minutes after intravenous administration. The reported (Aviado, 1959) vasodilator action of mephentermine and methylamphetamine given intra-arterially into an artery (the flow through which was being measured) requires further investigation; if confirmed, it might represent a direct action mediated by β-receptors, a non-sympathomimetic effect or an α-receptor blocking action.

Angiotensin amide

Synthetic angiotensin amide has actions identical with the naturally occurring hormone, angiotensin II (Page et al., 1957). This is formed in the renal blood by the action of the enzyme renin on
a plasma \(\alpha\)-globulin. Renin may be released from the juxtaglomerular apparatus by a reduction in the pulsatile mechanical distortion of the apparatus such as is produced by a fall in circulating blood volume, in renal artery pulse or mean pressure or compliance of the kidney. The hormone's first action is downstream constriction of blood vessels—first the efferent arteriole, thus raising the filtration fraction; small stimuli to renin release probably evoke only this local response. The systemic actions of angiotensin, appearing only with more severe stimuli, are stimulation of the zona glomerulosa of the adrenal cortex with subsequent release of aldosterone and a rise in arterial pressure.

The pattern of the actions of angiotensin is different from that of sympathomimetics; reserpine and ganglion blockade (Gross et al., 1965) and adrenergic blocking agents do not affect the pressor response to angiotensin. Therefore this response involves a direct action of angiotensin on cells of the cardiovascular system. That it does not act in the same way as vasopressin is shown by the maintenance of a full response to angiotensin in an animal made tachyphylactic to vasopressin (Page et al., 1957). Tachyphylaxis to angiotensin does not usually occur. While several reports indicate that an interaction does occur between the adrenergic system and angiotensin, the significance of this for its pressor action is small.

Intra-arterial administration into the appropriate vessel has been shown to constrict the vessels of the dog's forelimb (Haddy et al., 1962), the superior mesenteric bed (Texter et al., 1964) and of human skin and skeletal muscle (Bock, Krecke and Kuhn, 1958). It is arteriolar constriction which predominates; the drug has little action on veins, unlike noradrenaline (Texter et al., 1964; Haddy et al., 1962).

In vitro, a definite positive inotropic action of angiotensin can be demonstrated (Fowler and Holmes, 1964). Intracoronary injection produces vasoconstriction (Fowler and Holmes, 1964).

Intravenous administration results in a rise in systolic and diastolic pressure due entirely to an increase in peripheral resistance (Finnerty, 1962). Flow is reduced principally in the cutaneous (Bock, Krecke and Kuhn, 1958), splanchnic and renal beds (Finnerty, 1962; McQueen and Morrison, 1961). The flow through skeletal muscular vessels is increased (Bock, Krecke and Kuhn, 1958). There is no reduction of volume and compliance of veins (McQueen and Morrison, 1961; Rose et al., 1962; Finnerty, 1962) but there is some rise in central venous pressure, which must therefore be a "back pressure" effect (Segel, Harris and Bishop, 1961; Rose et al., 1962; Finnerty, 1962). This is certainly much less than the rise with noradrenaline, and in the rat it is absent (Gross et al., 1965). Again, unlike noradrenaline, there is no fall in plasma volume (Finnerty, 1962) because of the lack of venoconstriction.

A bradycardia is elicited by the pressor response and the cardiac output and venous Po\(_a\) fall (Segel, Harris and Bishop, 1961; Finnerty, 1962); the stroke volume changes little. Atropine prevents the bradycardia and the fall in cardiac output, reduces the rise in venous pressure and increases that of diastolic pressure, thus demonstrating how much restraint the vagal reflex is applying to the heart. Gross et al. (1965) found the normal fall in cardiac output with angiotensin to be reversed by ganglion blockade to a significant rise, which was then reduced by reserpine. No ventricular tachycardia or fibrillation was seen in dogs anaesthetized with halothane or cyclopropane, in marked contrast to noradrenaline (Moraca and Sitprija, 1962).

Angiotensin stimulates many other types of smooth muscle besides vascular, including rat uterus, intestines of several species and bronchioles: all these tissues are relaxed by sympathomimetics. The sensitivity of the adrenal cortex to angiotensin is high, aldosterone secretion occurring with doses having little pressor action. Renal actions are two: vasoconstriction with consequent sodium retention (McQueen and Morrison, 1961) and an action on the distal tubule inhibiting sodium reabsorption. This natriuretic action is most prominent in the rat, rabbit, in certain hypertensive patients, and in those with ascites and portal hypertension.

Angiotensin is a vasoconstrictor drug whose pattern of vasoconstriction is different from that of \(\alpha\)-active sympathomimetics both in terms of relative effects on certain beds (e.g. ratio of muscular to cutaneous constriction) and relative effects within beds (e.g., ratio of arteriolar to venous constriction). Its pressor effects last about 5 minutes after intravenous injection; it is inactivated by peptidase enzymatic attack in the bloodstream.
VASOPRESSIN

Antidiuretic hormone is a nonapeptide manufactured in the supra-optic and paraventricular nuclei of the hypothalamus. The hormone travels down the axons of these cells in the hypothalamic-neurohypophyseal tract and accumulates in their nerve endings in the posterior pituitary. The hormone is liberated by nerve action potentials set up by activation of osmoreceptors by hypertonicity of the blood. The renal action of the hormone is to increase the water permeability of the cells of the collecting ducts, thus allowing the hypertonic interstitial fluid of the renal papilla to extract water osmotically up to the maximum of 44 times plasma-osmolarity in the healthy kidney.

Cardiovascular actions only occur with much greater doses than those which produce renal effects.

Vasopressin has a direct action on the smooth muscle cells; this is not blocked by adrenergic blocking drugs and tachyphylaxis develops.

When given intra-arterially into the appropriate vessel it constricts the vessels of the dog forelimb (Haddy et al., 1962) and superior mesenteric beds (Texter et al., 1964); small blood vessels are especially sensitive, veins much less so.

When given intravenously, systolic and diastolic pressures rise. Peripheral resistance rises and skin, muscle, coronary and portal blood flows fall.

Heart rate, stroke volume and cardiac output are all reduced and the venous pressure rises passively. Part of the bradycardia is not abolished by atropine; it is associated with e.g. changes of myocardial anoxia.

The drug increases peristaltic activity of the large and small intestines.

The plasma half-life of vasopressin is less than 20 minutes.

REFERENCES


THE PHARMACOLOGY OF PRESSOR DRUGS


Johnson, H. D., Green, H. D., and Lanier, J. T. (1953). Comparison of adrenergic blocking action of ilidilar (Ro 2-3248), Regitine (C-7337) and priscoline in the innervated saphenous arterial bed (skin exclusive of muscle) and femoral arterial bed (muscle exclusive of skin) in the anaesthetized dog. J. Pharmacol. exp. Ther., 108, 144.


BOOK REVIEW


This little book is the first one to appear from this country on this subject. Therefore, it can be said to fulfil a very real need. The standard of production and the profusion of illustrations make it a very attractive book to read. The purpose of the book is set out in the first paragraph of the authors' preface, that is "...to provide the reader with a working knowledge of the apparatus and techniques which are used to anaesthetise and resuscitate the newborn infant. In some cases several techniques are described, the choice is left to the reader. The success of any particular technique depends eventually on the skill and experience of the anaesthetists". It must be said the book does achieve it. What one would perhaps criticize a little is that object, for its very nature precludes the possibility of creating a work which has a basic philosophy, and demands the production of something which approximates to a catalogue of techniques. These techniques are described in some detail as to the actual manual process of applying them, rather in the style of the textbook of yesteryear which has now become somewhat rare. As the preface says, the choice is left to the reader, but at what sort of reader is the book directed? Some evidence of this is to be found in the section on open ether, in which the reader is exhorted to hold the stopper on the bottle with his index finger. He who, in this day, reads this sort of advice from a textbook is perhaps in no position to make a choice on a suitable anaesthetic technique for neonates.

The book contains an excellent introductory chapter on neonatal anatomy and physiology, but one would have liked to have seen a little more here on the metabolic responses to cold of the young infant and of the importance of radiation as a means of heat loss by infants in incubators. The chapter on neonatal asphyxia is also excellent and the authors recommend an early resort to intubation and ventilation in cases of neonatal exposure, a practice which will commend itself to all but the most reactionary.

The purpose of a book review is perhaps to indicate which category of reader will profit from the book concerned. In this case one can say, without hesitation, that the anaesthetist who has worked extensively in the paediatric field will find little to interest him. Indeed, the authors intimate that this will be so, but suggest that such a reader might find a few topics which could lead to discussions. The beginner will find much of value in the book but should read it realizing that the practice of anaesthesia can only be learnt in the operating theatre at the hands of an expert and not, as the text might in places lead him to expect, by the following of a recipe after the fashion of a cook. One would commend this book, therefore, to those with little previous experience in this branch of anaesthesia, to whom it will present a picture of what he might expect to see when introduced to its practice.

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