# CHAPTER-I

# ANTIHYPERTENSIVE AGENTS

Antihypertensive agents

In the first half of this century, there were no adequate drugs available for the treatment of hypertension. Physicians had to resort to the use of blood letting, saline purges, potassium iodide, nitrites, xanthines and occasionally the veratrum alkaloids. Sedatives and hypnotic drugs such as chloral hydrate and phenobarbital were available but also proved to be ineffective. A major breakthrough which provided a new approach in the search for antihypertensive agents occurred in the mid-1940s when Louis Goodman demonstrated that N,N-dibenzyl-beta-chloroethylamine blocked the constrictor action of adrenaline (ADR) and noradrenaline (NA) in arterial muscle, and it was discovered that tetraethylammonium acting as a ganglionic blocking agent, resulted in a decrease in transmission of sympathetic impulses to arterial muscle. These studies gave great impetus to the search for other compounds which might affect the autonomic nervous system and led to the development of the first potent agents in the treatment of hypertension, i.e. the ganglionic blocking drugs. In the early 1950, Rauwolfia alkaloids such as reserpine, became available and were used in the treatment of mild labile hypertension. Another significant breakthrough in this field was the introduction of chlorothiazide in 1958, the first in now long series of relatively non-toxic

effective oral diuretics. It was soon realized that these agents also produced an antihypertensive effect. Subsequently, these drugs not only have proved extremely effective in the treatment of hypertensive diseases but have directed attention to the study of vascular smooth muscle and its relation to the etiology of hypertension.

The search for a selective sympathetic blocking agent led to the introduction of bretylium and guanethidine in 1959. These agents appeared to exert their effects by specific blockade at the sympathetic nerve endings. In the past few years, considerable interest has centered around the hypotensive effects of compounds which interfere with enzymes involved in the degradation and synthesis of catecholamines for example, monoamine oxidase (MAO) and dopa-decarboxylase inhibitors. The use of MAO inhibitors as therapeutic agents is limited because of serious side effects. However, the dopa-carboxylase inhibitor, alpha-methyldopa has been shown to be an effective antihypertensive drug. Certain indole derivatives have been found to be long acting (90 to 190 days) hypotensive agents in animals (Briggs and Holland, 1971).

Many new drugs with a variety of proposed actions have been introduced in the past years for the treatment of hypertension. These actions include effects on the higher nervous centres, the sympathetic nervous system and

vascular smooth muscle with its extracellular fluid surroundings. The precise role of the inter-relationship of these systems in the regulation of peripheral vascular resistance and the etiology of hypertension is unknown. It appears, however, that the various antihypertensive agents available exert their effects by interfering with the interaction of these three systems to effect a reduction in peripheral vascular resistance and/or cardiac output. There is no evidence to suggest that any of these drugs works by a direct attack on the cause of hypertension. The search for specific pharmacologic agents has been and still is severely limited by the lack of information on the disease itself, and until we know more about the basic mechanisms of its causation one shall have to direct treatment toward the relief of the generalized increased vascular resistance. Ideally, a therapeutic agent should produce this effect without any significant reduction in cardiac output or cerebral, renal or coronary blood flow.(Briggs and Holland, 1971).

Although many antihypertensive compounds were available during the past 20 years which could lower blood pressure, they were all limited by serious side effects, short duration of action, or the development of tolerance. The main advantage of some of the newer agents is that the control of hypertension can be obtained with fewer of

the side effects usually associated with the use of the older compounds. Thus, with the variety of drugs available, it is now possible to obtain blood pressure control in a majority of patients with a minimum of untoward side effects. In addition to the therapeutic importance of these compounds, the study of their anti-hypertensive actions had led to a greater knowledge of the mechanism of normal blood pressure control.

1. Drugs that alter central sympathetic nervous system activity

(a) Methyldopa

Alpha-methyldopa was originally conceived as an inhibitor of the enzyme dopa decarboxylase (Sourkes, 1954) and it has been suggested that it produces sympathetic blockade by interfering with the biosynthesis of NA (Oates et al., 1960). However, subsequent studies have failed to establish a relationship between inhibition of dopa decarboxylase and the reduction of arterial pressure which occurs (Levine and Sjoerdsma, 1964; Day et al., 1973). It has also been proposed that a metabolic product of alpha-methyldopa, alpha-methylnoradrenaline, displaces NA within the post-ganglionic sympathetic nerve endings and acts as a weak or false neurotransmitter substance (Day and Rand, 1964; Cohen, 1966). However, experimental evidence

indicates that the antihypertensive effect of methyldopa is not dependent upon blockade of the peripheral sympathetic nervous system (Haefely et al., 1966; Mohammed et al., 1968; Ayitey-Smith and Varma, 1970) and that the vasopressor potency of alpha-methylnoradrenaline is almost as great as NA (Conradi et al., 1965; Trinker, 1971; Altura, 1975).

Although the pharmacological mechanism by which methyldopa lowers arterial pressure is not completely understood, there is a growing body of evidence to suggest that the major site of action is within the central nervous system, presumably at the level of the brain stem (Henning, 1969, 1975; Finch and Haeusler, 1973; Van Zwieten, 1973, 1976). Methyldopa readily crosses the blood-brain barrier and is enzymatically converted to alpha-methylnoradrenaline by dopamine decarboxylase and beta-hydroxydopamine within the adrenergic neurones of the central nervous system (Carlsson and Lindqvist, 1962; Conradi et al., 1965; Finch and Haeusler, 1973). Alpha-methylnoradrenaline is released with NA in response to nerve stimulation (Muscholl and Maitre, 1964) and apparently lowers arterial pressure by stimulating central alpha-adrenoceptors which reduce the sympathetic outflow from the central nervous system (Baum et al., 1972; Heise and

Kronenberg, 1972). Although the mechanism appears complex current evidence suggests that peripheral adrenergic blockade is probably of secondary importance in regard to the antihypertensive effect of methyldopa (Nickerson and Ruedy, 1975).

The reduction of supine blood pressure with both acute and chronic administration of methyldopa is associated with a fall in systemic vascular resistance and the cardiac output is variably affected but often slightly reduced (Dollery et al.,1963; Weil et al.,1963; Chamberlain and Howard, 1964; Onesti et al., 1964). In the upright position an orthostatic fall in pressure occurs which corresponds to a reduction in cardiac output and little or no change in peripheral resistance (Onesti et al., 1964; Onesti, 1976). Renal blood flow and glomerular filtration rate are maintained (Weil et al.,1963; Onesti, 1976) and myocardial (Cohen et al., 1967) and cerebral blood flow (Meyer et al., 1968) are reported to be increased in many patients.

(b) Clonidine

This imidazoline derivative is a potent antihypertensive drug. The clinical use of the drug is almost entirely on a chronic basis, though the available data on effects in both laboratory animals and man are from acute

experiments. After intravenous injection of a few micrograms per kilogram, clonidine produces a brief rise and a subsequent more persistent fall in blood pressure, both of which are prolonged by anaesthesia. The initial pressor response to clonidine is due to direct stimulation of peripheral alpha-adrenergic receptors; this action has also been demonstrated on the nictitating membrane and other structures. Clonidine also produces significant peripheral alpha-adrenergic blockade. Thus, it is a partial agonist. The pressor response is accentuated and prolonged by drugs and procedures that interfere with reflex adjustments of blood pressure (e.g. ganglionic blockade) (Terrence and Kenneth, 1980).

The hypotensive action of clonidine is a result of the direct action of the unchanged drug. The current hypothesis about central regulation of blood pressure stems from the observations that stimulation of alpha-adrenergic receptors in the vasomotor centres results in inhibition of peripheral sympathetic activity; when these receptors are blocked, there is increased peripheral sympathetic outflow (Van Zweiten, 1973; Haeusler, 1975). Clonidine presumably stimulates alpha-adrenergic receptors in the central nervous system. Indeed the central effect of clonidine in animals is antagonized by alpha-adrenergic blocking drugs administered either intravenously or

directly into the cerebral ventricles (Schmitt and Schmitt, 1970). There is a limited amount of evidence that clonidine is a more potent agonist at presynaptic alpha$_2$-adrenergic receptors than at post-synaptic alpha$_1$-receptors (Titeler et al., 1978), but the relevance of this difference to the therapeutic effect of the drug is uncertain. Study of animals with lesions at various levels of the central nervous system indicates that a major site of action for clonidine is the medulla oblongata. The hypotension produced after acute administration of clonidine is associated with a clear reduction of the discharge rate of preganglionic adrenergic nerves, as well as by bradycardia. The latter is due to both a decrease in sympathetic and an increase in vagal tone, as would be expected from the known central interactions of these two mechanisms. The increase in vagal discharge involves an increased sensitivity of baroreceptor reflexes (Nayler and Stone, 1970). Whether adrenergic neurons in the central nervous system are necessary for the baroreceptor reflex arc and for the action of clonidine are unknown (Dollery and Reid, 1973; Reid et al., 1973; Haeusler, 1974, 1975). Clonidine may also depress sympathetic transmission by peripheral actions, but this effect seems unimportant relative to its effects on the central nervous system.

## 2. Vasodilators

### (a) Hydrallazine

Hydrallazine was first synthesized and tested for antihistaminic activity. However, subsequent investigations demonstrated its hypotensive action instead of antihistaminic activity. Early studies on hydrallazine attributed its antihypertensive effect successively to specific renal vasodilatation and to an action on the central nervous system. However, present evidence indicates that the major action of hydrallazine is direct relaxation of vascular smooth muscle; the effect on arterioles is greater than on veins (Ablad, 1963). Hydrallazine inhibits pressor reactions after stimulation of afferent nerves without interfering to the same extent with the pressor response produced by stimulation of the afferent sympathetic nerve. The drug is not very active in experimental animals when the vasomotor centre is severed from the spinal cord. Hence, it was believed to act centrally. However, recent human experiments have shown that it can induce peripheral vasodilatation and can block the peripheral vasoconstrictor action of NA. It also enhances the vasodilator action of ADR on peripheral blood vessels and coronaries.

Mclean et al.(1978) investigated the mechanism and relative potency of hydrallazine and two hydrazone derivatives i.e. hydrallazine acetone hydrazone and hydrallazine butanone hydrazone on vascular smooth muscle. Hydrallazine and hydrazone derivatives relaxed established $K^+$ and NA contracture and inhibited development of contracture to these two agents on pre-incubation. It was concluded that hydrallazine and hydrazone derivatives produce effects on vascular smooth muscle both by interaction with the fluxes of $Ca^{+2}$ from extracellular space and effects on release from cell stores. However, the other possibilities need to be assessed experimentally.

Worcel (1978) reported that hydrallazine reversibly inhibited the contractions induced by either phenylephrine (PE) or 5-hydroxy tryptamine (5-HT) in the distal segments of the caudal artery of normotensive Wistar male rats.

Stan (1980) suggested that antihypertensive action of minoxidil and hydrallazine may not be related to direct depressant action of drugs on vascular smooth muscle function as maximal contractile tension development of mesenteric arteries to NA, angiotensin (ANG), $CaCl_2$ and KCl were not affected by chronic treatment of spontaneously hypertensive rats with minoxidil but by hydrallazine treatment. Hydrallazine has been shown to inhibit contractile and relaxant responses of blood vessels to both vasoconstrictor and vasodilator substances (Ablad et al., 1962).

It has been suggested that hydrallazine may act as vasodilator by chelation of metal ions such as $Ca^{2+}$, $Mn^{+}$ and $Cu^{2+}$ which may be essential in enzymatic process related to initiation or support of contractile process (Schroeder, 1959).

Suzanne and Robert (1981) studied the inhibitory action of hydrallazine on the contractility of human blood vessels by using in vitro human digital artery and metacarpel vein preparation obtained postmortem. Cumulative contractile concentration response curves were performed to NA, 5-HT, histamine, ANG, KCl and $BaCl_2$ in both arteries and veins. With the exception of $BaCl_2$, hydrallazine shifted the concentration effect curves to the right and reduced the maximal responses to these agonists. This effect was markedly greater in arteries than in veins in which hydrallazine had no effect. It was concluded that human arteries are much more sensitive to effects of hydrallazine than are human veins and that mechanism of action of hydrallazine is probably due to inhibition of release of tightly bound calcium ions.

Although the antihypertensive actions of hydrallazine are still not clearly understood, it has been suggested that the major effect of this drug is exerted post-

synaptically on the vascular smooth muscle of resistance vessels (Uchida and Bohr, 1969). However, the results of recent in vitro studies have suggested that hydrallazine also exerts a significant additional inhibitory effect at sympathetic nerve terminals by preventing the release of NA (Worcel, 1978; Chevillard et al., 1980). Hicks et al. (1981) reported that hydrallazine is similarly effective in antagonizing the vasoconstrictor responses to exogenous NA and ANG II in pithed rats and those following sympathetic nerve stimulation. No evidence was obtained to support the idea of preferential pre-synaptic inhibitory action of hydrallazine. It is therefore suggested that the antagonism of vasoconstrictor responses by hydrallazine can be explained on the basis of an inhibitory action at a post-synaptic site.

Cardiac stimulation by hydrallazine probably involves a reflex response to the fall in blood pressure, but it is somewhat more marked than would be expected on this basis alone and is not well correlated with changes in blood pressure. Tachycardia can be induced by very small doses injected into the cerebral ventricles (Gupta and Bhargava, 1965) and hydrallazine tachycardia can be prevented by ganglionic or beta-adrenergic blocking agents.

Pharmacological properties: All major effects of hydrallazine are on the cardiovascular system. In both

laboratory animals and man, adequate doses decrease arterial blood pressure, diastolic often more than systolic and peripheral vascular resistance. The drug increases heart rate, stroke volume and cardiac output. The preferential dilatation of arterioles, as compared to veins minimizes postural hypotension and promotes the increase in cardiac output. When hydrallazine is given alone, the latter may limit the reduction in mean blood pressure produced by the drug. The effect of hydrallazine develops gradually over 15 to 20 minutes even after intravenous administration. The peripheral vasodilatation is widespread but not uniform; splanchnic, coronary, cerebral and renal blood flows increase unless the fall in blood pressure is very marked. Glomerular filtration, renal tubular function, and urine volume are not consistently affected; however, in common with many other antihypertensive agents, hydrallazine can cause retention of sodium and water and decreased urine volume. Hydrallazine usually increases renin activity in plasma, presumably as a result of increased secretion of renin by renal juxtaglomerular cells in response to reflex sympathetic discharge (Freis et al., 1953; Ablad, 1963).

(b) Diazoxide

Diazoxide is a benzothiadiazine derivative closely related chemically to the thiazide diuretics. However, it is a potent vasodilating agent which is devoid of

natriuretic activity and in fact causes sodium and fluid retention. Intravenous administration of diazoxide to a hypertensive subject causes a prompt fall in both systolic and diastolic pressures associated with a considerable increase in cardiac output and some tachycardia. When the drug is used appropriately, the pressure rarely falls below the normal range and postural hypotension does not develop. Diazoxide directly dilates arterioles but has very little effect on large veins (Gaskell and Diosy,1959; Thirwell and Zsoter, 1972), although it can affect small post-capillary resistance vessels (Ogilvie and Mikulic,1972).

(c) Minoxidil

It is a powerful vasodilator which is being investigated. It is a piperidinopyrimidine derivative and is unrelated chemically to the other vasodilating agents. Its pharmacological action is similar to that of hydrallazine and diazoxide in that it exerts a direct relaxant effect on arteriolar smooth muscle (Chidsey et al., 1973).

Minoxidil has little or no effect on the venous capacitance vessels. The decrease in arterial pressure is associated with a fall in peripheral resistance and a reflex increase in cardiac output (O'Malley et al., 1976). Minoxidil produces hyperreninaemia (O'Malley et al., 1975) and is associated with marked sodium and fluid retention which,

if uncontrolled, can lead to massive oedema and congestive heart failure.

(d) Nitroprusside

Sodium nitroprusside is a powerful directly acting vasodilator that has been used sporadically as a hypotensive agent in man for over 5 decades but marketed recently as drug. An important difference between this vasodilator and others is that nitroprusside relaxes both arteriolar and venous smooth muscle; furthermore, it has little effect on the gastrointestinal tract or uterus. Venodilatation results in a decreased cardiac preload. In the absence of heart failure, the cardiac output falls or does not change (Schlant et al., 1962; Bhatia and Frohlich, 1973). However, if cardiac output is decreased because of myocardial disease, nitroprusside usually increases output. The drug lowers blood pressure in patients who are either in the supine or upright positions. However, because nitroprusside causes venous dilatation, more venous pooling occurs when the patient is upright. The heart rate of such patients often increases unless heart failure or tachycardia are already present; under these circumstances the heart rate may fall as the drug is given (Guiha et al., 1974). Renal blood flow and the glomerular filtration rate are maintained, and secretion of renin is increased during the use of nitroprusside. Angina often improves when

this agent is given. This effect is in contrast to that of arteriolar vasodilators that do not affect veins.

(e) Prazosin

Prazosin is a relatively new peripheral vasodilator antihypertensive agent. Pharmacologically, it is a quinazoline derivative and an inhibitor of the enzyme phosphodiesterase which hydrolyses cyclic-AMP and cyclic-GMP (Hess, 1974). Its mechanism of action is not yet fully understood. It was originally thought to have a direct relaxant effect on arteriolar smooth muscle, presumably by increasing intracellular cyclic-AMP (Hess, 1974), but it has now been shown to have alpha-adrenoceptor blocking properties (Graham et al., 1977). Experimental evidence suggests that its mode of action probably resides in selective interference with post-synaptic alpha-adrenoceptors (Bolli et al., 1975; Wood et al., 1975). Unlike conventional alpha-adrenoceptor blocking drugs, it has little or no affinity for pre-synaptic alpha-receptors (Cambridge et al., 1977).

The antihypertensive action of prazosin is usually not associated with a reflex increase in heart rate or cardiac output and it does not stimulate renin secretion (Graham et al., 1976; Hayes et al., 1976; Koshy et al., 1977). Its pharmacological effect occurs at the level of

the resistance vessels as well as the venous capacitance vessels (Awan et al., 1977). Following acute and chronic administration, prazosin lowers arterial pressure by decreasing peripheral vascular resistance and cardiac output is usually unchanged or slightly increased (Lund-Johansen, 1975). Because of the relaxant effect on venous capacitance vessels, prazosin may cause a reduction in venous return to the heart. Therefore, prazosin may reduce cardiac preload and afterload and has been reported to improve left ventricular performance in patients with refractory heart failure, even when hypertension is minimal or absent (Miller et al., 1977; Awan et al., 1978). Renal blood flow and glomerular filtration rate are maintained with prazosin (Koshy et al., 1977). Fluid retention may occur in some patients and reduce its antihypertensive potency (Koshy et al., 1977).

(f) Thiazides and phthalimidines (diuretics)

Although the exact means by which diuretics lower blood pressure is not completely understood, the immediate effect is a reduction in plasma and extracellular fluid volume which is accompanied by a fall in cardiac output. The total peripheral resistance is increased in the early stage of therapy and initially, the reduction in arterial pressure is brought about by decrease in cardiac output (Frohlich et al., 1968; Dustan et al., 1974). After a period of several weeks, long term haemodynamic

adjustments occur; the cardiac output returns to pre-treatment levels as total peripheral resistance falls. The exact nature of these systemic readjustments is not well understood.

It has been shown that diuretics reduce vascular resistance (Conway and Palmero, 1963; Ogilvie and Schlieper, 1970) and the pressor responses to infusions of NA (Freis et al., 1960; Mendlowitz et al., 1960; Feisal et al., 1961; Frohlich et al., 1972) and ANG II (Heistad et al., 1971; Abboud, 1974). Possibly diuretic induced sodium depletion interferes with the ability of the sympathetic nervous system to adapt to changes in intravascular volume, or it may be a response of the peripheral vasculature to the reduction in cardiac output (so-called autoregulation).

In the final analysis, the reduction in blood pressure with long term therapy is maintained by a diminished total peripheral resistance (Conway and Lauwers, 1960; Lund-Johansen, 1970; Tarazi, 1973a) associated with a persistent reduction in plasma and extracellular fluid volume (Leth, 1970; Tarazi et al., 1976; Tarazi and Dustan, 1977). The extracellular fluid contraction may not be as marked as in the initial stages, possibly because of increased proximal reabsorption of sodium and secondary

aldosteronism. Thus, throughout diuretic therapy, arterial pressure is reduced through the interplay of two mechanisms a contraction of the extracellular fluid and plasma volume and an inadequate cardiovascular compensation for the degree of hypovolaemia.

(g) Calcium antagonists (CAts)

CAts depress the myogenic activity and the responsiveness to vasoconstrictor stimuli of the smooth muscle cells of the precapillary vessels. Thus, they can reduce the afterload of the heart and have antihypertensive properties. Their inhibitory effect on the contractile responses of the vascular smooth muscle cells of large arteries also results in the reduction of the abolition of vasospastic episodes. By inhibiting the constrictor responses of the splanchnic capacitance vessels to the sympathetic nervous outflow, they reduce the preload of the heart. However, different CAts differ in their ability to affect different cardiovascular variables and in the onset and duration of their effect; they also have different degrees of tissue selectivity. This variability must reflect differences in pharmacodynamic and pharmacokinetic properties (Vanhoutte, 1982).

CAts relax the vascular smooth muscle in systemic as well as pulmonary arterial circulations. They thus

decrease the vascular resistance and the blood pressure in both these territories. They have been used with beneficial effect in the treatment of systemic and idiopathic pulmonary hypertension. Further, reduction in the afterload contributes to their efficacy in angina of effort. Nifedipine is a more potent vasodilator than verapamil. The reduction in blood pressure is accompanied by reflex tachycardia in the case of nifedipine but not in the case of verapamil which suppresses the S.A.node.

A general property of organic CAts is that they are able to block stimulated $Ca^{45}$ uptake but do not significantly affect resting $Ca^{+2}$ influx (Rosenterger et al., 1979). In this respect, CAts differ sharply from $La^{3+}$, which blocks all $Ca^{+2}$ entry into the cells including that entering through the passive membrane leak pathway. Also $La^{3+}$ inhibits ionophore-mediated $Ca^{+2}$ flux whereas CAts will not. The actions of trivalent cation $La^{3+}$ can be explained by its competition with $Ca^{2+}$ for negatively charged binding sites. Such sites are probably involved in all $Ca^{2+}$ transport process across the cell membrane. In contrast, CAts are generally organic non-charged lipophilic molecules of widely varying structure which bear little resemblance to calcium ions in either structure or charge density. For this reason, it was somewhat surprising that reversible competition

was described between CAts and $Ca^{2+}$. However, recent report shows that at somewhat higher CAts concentration $[Ca]_e$ is no longer able to overcome inhibition completely (Van Breemen et al., 1982).

Cynthia et al.(1983) reviewing the mechanisms of CAts induced vasodilatation reported that CAts do not reversibly compete with $Ca^{2+}$ for binding to Ca transport sites but that CAts specifically bind to various components of excitable $Ca^{2+}$ channels causing their inactivation. At concentrations that generally exceed therapeutic levels CAts do exert additional effects as discussed below.

(i) Inhibition of intracellular $Ca^{2+}$ release: Van Breemen and Siegel (1980) reported that verapamil and other vasodilators in higher concentration were effective in reducing the NA induced contractions which account well for an interference of the drugs with intracellular $Ca^{2+}$ translocation in this concentration.

(ii) Stimulation of $Ca^{2+}$ extrusion: Some CAts exert relaxing effect due to stimulation of $Ca^{2+}$ efflux while others do not. Nifedipine is reported to stimulate $Ca^{45}$ efflux while flunarizine, verapamil D-600 or diltiazem did not affect $Ca^{45}$ efflux during rest and NA stimulation.

Evidence at this time does not favour a role for $Ca^{+2}$ extrusion pumps in CAts induced vasodilatation.

(iii) Effects on calmodulin: Verapamil, prenylamine and diltiazem inhibited calmodulin activation of myosin light chain kinase, although the concentrations of verapamil and diltiazem needed for this effect were a thousand fold higher than those necessary for vasodilatation. So the ubiquitious calmodulin would also be inconsistent with specificity of CAts action.

(iv) CAts binding to membranes: Binding sites for CAts are not identical and they may interact allosterically.

(v) Selectivity of CAts: The molecular basis of the selectivity exhibited by CAts resides in the ability of these agents to interact with specific $Ca^{2+}$ channels in the plasmalema. The ability of CAts to block smooth muscle contraction selectivity over neuro-transmission or cardiac function implies that the $Ca^{2+}$ entry pathways in smooth muscle differ qualitatively from those found in other tissues. Selectivity of CAts in different parts of circulatory system appears to be related to differences in the calcium sources and types of $Ca^{2+}$ channels used to mediate $Ca^{2+}$ influx. It is well known that the initial phase of agonist induced large artery contraction is due to intracellular $Ca^{2+}$ release, which is rather resistant to CAts.

The intracellular Ca released during the initial phase, however, does not contribute to the tonic contraction hence selectivity here would depend on differences among vascular tissues in their pathways of stimulated $Ca^{2+}$ entry. The tonic contractions of vascular smooth muscle depend on the opening of at least 2 types of channels, potential-operated (POC) and receptor-operated (ROC).The different identities of these types of channels forms an obvious basis for specificity of CAts action. CAts are relatively selective for the POC over the ROC. Inhibition by D-600, diltiazem, cinnarizine and nifedipine have been shown to be more sensitive to POC than NA-induced contraction. In contrast, several studies indicate that ROC is more sensitive to CAts than POC in some tissues. So often stated generalization that POC are more sensitive than ROC to CAts does not always apply.

(vi) CAts selectivity for particular vascular bed: In most arteries, in the arterioles and in the splanchnic veins, calcium-entry blockers curtail vasoconstrictor responses to sympathetic nerve stimulation and exogenous NA. In cutaneous veins, the calcium-entry blockers have little effect on the contraction of the vascular smooth muscle cells caused by endogenously released or exogenous NA.

(vii) Effect of agonist concentration on the sensitivity of the ROC to CAts: ROC sensitivity to CAts is inversely related to the agonist concentration in at least one blood vessel. In rabbit aorta, $IC_{50}$, for diltiazem and nisoldipine inhibition of NA induced contraction and $Ca^{+2}$ influx increase dramatically as NA is increased. It could be argued that as the NA increases, more intracellular $Ca^{2+}$ is released. The resulting phasic contractions would thereby become more resistant to these two CAts, since they have little effect on intracellular $Ca^{2+}$ release. However, the $Ca^{2+}$ influx that mediates the tonic phase of contraction also becomes more resistant to the CAts with increasing NA . Hence, it appears that the ROCs exhibit multiple activated states characterized by varying susceptibility to CAts blockade. This phenomenon is not observed with varying the degrees of activation of the POC.

Also neither $alpha_1$ nor $alpha_2$ adrenoceptor subtypes are specifically linked to one activation process or the other (i.e. $Ca^{2+}$ influx or intracellular $Ca^{2+}$ release). Differing sensitivities to CAts toward selective alpha-adrenoceptor agonist-induced contraction may merely reflect the inverse relationship between CAts sensitivity the ROC and degree of activation produced by alpha-adrenoceptor agonists.

(viii) Theoretical basis for CAts selectivity: There are three general observations that (1) CAts often show greater selectivity for high $K^+$ induced over agonist-induced contraction (2), CAts potency for inhibiting agonist-induced contraction varies widely among vascular tissues (3) Susceptibility of agonist-induced contraction to CAts inhibition diminish with increasing levels of agonist activation. In addition, there are several other factors which may influence CAts selectivity and provide theoretical basis for these observations.

a) Chemical differences in $Ca^{2+}$ influx pathways: Some of the specificity exhibited by CAts for one type of activation over another or for particular vascular bed may be due to variation in chemical structure of $Ca^{2+}$ influx channels.

b) Differing degrees of agonist-induced depolarization.

c) Agonist-induced release of intracellular $Ca^{2+}$.

d) Sequestration by the agonists releasable $Ca^{2+}$ store (ARC).

e) Multiple activated states of the ROC.

Verapamil

Verapamil is a novel antiarrhythmic and antianginal agent which although introduced in clinical use in 1966, has only recently gained prominence as a significant agent in cardiovascular therapeutics. Verapamil is a drug which selectively inhibits membrane transport of calcium (Singh and Uaughan, 1972), an action which accounts for the drug's - (a) peripheral and coronary vasodilator property, (b) effect on excitation-contraction coupling and hence its negative inotropic propensity and (c) depressant effect on the sinus node and atrioventricular conduction.

Its pharmacological actions/effects are largely independent of the autonomic nervous system. Hence, verapamil, unlike other calcium channel blockers, exerts its effects primarily upon the heart.

Apart from its proven use in treating supraventricular tachyarrhythmias, it has also been used for the treatment of coronary artery spasm, hypertensive crisis and such non-cardiac conditions as relaxation of the uterus in threatened abortion and premature labour.

Electrophysiological studies in different tissues have revealed that verapamil has a unique cellular action

in selectively inhibiting the transmembrane fluxes of calcium (Kohlardt et al., 1972; Fleckenstein, 1977), a mechanism which undoubtedly accounts for its anti-anginal, antiarrhythmic, cardiac protective, coronary and peripheral vasodilator properties. Moreover, its cardio-vascular actions are found to be independent of the beta-adrenoceptor blockade as well as autonomic nervous system.

Effect of verapamil on haemodynamic properties: Verapamil exerts net effects in various types of tissues. In myocardium and in vascular smooth muscle from coronary, pulmonary or cerebral arteries excitation-contraction coupling is preferentially inhibited while the action potentials continue to occur (Fleckenstein, 1977). Verapamil, therefore, can influence cardiovascular haemodynamics by three principal actions - coronary arterial dilatation, peripheral arterial dilatation and a negative inotropic effect. The net haemodynamic effects depend on the relative strength of each individual action and the reflex mechanisms which they evoke may contribute to or may even be the principal determinant of it.

Effects on the peripheral circulation: The vasodilating effect of verapamil is not confined to the coronary circulation. Similar to the effects observed in coronary

arteries, tetraethylammonium and $Ca^{2+}$-dependent action potentials in superior mesenteric artery strips from guinea-pigs are inhibited by verapamil (Harder et al., 1979). In the anaesthetized animal, verapamil dilates the pulmonary artery (Haeusler, 1972), hind limb, the hepatic, femoral and renal (Ishikawa et al., 1978), and superior mesenteric vascular beds (Ross and Jorgensen, 1967;,Ishikawa et al., 1978). This widespread vasodilatation reduces systemic vascular resistance both in animals (Hayase, 1971; Rowe et al., 1971; Vater and Schlossman, 1976) and in humans (Vincenzi et al., 1976; Kaltenbach et al., 1979).

According to Galzin and Langer (1983) diltiazem is devoid of $alpha_2$ adrenoceptor blocking property at the level of pre-synaptic release modulating receptors. On the other hand, verapamil enhances noradrenergic transmission by blocking the $alpha_2$ adrenoceptors that modulate transmitter release through a negative feedback mechanism. This was proved in connection with study by Van-Meel et al. (1981) and Cavero et al.(1982) who demonstrated that vascular smooth muscle contains not only $alpha_1$ but also $alpha_2$ adrenoceptors; both mediating contractile responses. The responses to $alpha_2$ adrenoceptor agonists are inhibited by both verapamil and diltiazem whilst responses to $alpha_1$ adrenoceptor agonists are relatively resistant to these calcium channel blockers.

Verapamil in hypertension: Verapamil being a calcium channel blocker is an arteriolar vasodilator and thereby is valuable in treating systemic arterial hypertension. The degree of blood pressure reduction is directly related to the magnitude of the pre-treatment value of arterial pressure (Aoki et al., 1978) or peripheral vascular resistance. For example, in normotensive subjects, there may be little or no reduction in blood pressure after 5 mg intravenous dose of verapamil whereas in patients with severe hypertension the blood pressure reduction with these doses may be quite marked. In patients with normal pulmonary artery pressures intravenous verapamil (10 mg bolus) increased the mean pulmonary artery pressure (Vincenzi et al., 1976). The elevation in mean pulmonary artery pressure from verapamil was considered to be a result of either an increase in pulmonary resistance or a slight reduction in left ventricular function with subsequent increase in left atrial pressure.

By inhibiting the myogenic tone of the precapillary vessels and decreasing their responsiveness to vasoconstrictor substances, calcium-entry blockers reduce the systemic peripheral resistance, which is one of the major dynamic determinants of the circulatory impedance; this then decreases the afterload of the left ventricle

(Shepherd and Vanhoutte, 1979). These effects are most pronounced for substances such as verapamil and nifedipine, which explains their potential use as antihypertensive agents (Godfraind et al.,1968; Van Nueten and Vanhoutte, 1981; Vanhoutte et al.,1981).

3. Adrenergic receptor blocking drugs

(a) Beta-adrenergic blocking drugs

Inspite of considerable differences in their pharmacological properties, all beta-adrenoceptor blocking drugs have antihypertensive activity in man. It is therefore generally accepted that the blockade of beta-adrenoceptors per se, and not any other unrelated pharmacological effect, is responsible for the effectiveness of these drugs in the treatment of hypertension.

Beta-blockers act by competitively inhibiting the effects of catecholamines at beta-adrenoceptor sites, and their pharmacological potencies are determined by their relative abilities to inhibit isoprenaline-induced tachycardia. The various agents are often classified according to their organ sensitivities. Acebutolol, atenolol, metoprolol and practolol are often referred to as 'cardioselective agents' as they are 50 to 100 times more potent in inhibiting cardiac beta-adrenoceptors ($beta_1$-receptors) than the receptors of the peripheral vasculature and bronchial smooth muscle ($beta_2$-receptors) (Waal-Manning,

1976a,b). The other agents are relatively non-selective in regard to their activities against $beta_1$ and $beta_2$-adrenoceptors.

Several of the beta-blocking agents exhibit a small but measurable agonist response when exposed to beta-adrenoceptors in the absence of a primary beta-agonist such as isoprenaline or ADR. This partial agonistic property has been termed 'intrinsic sympathomimetic activity' and is characteristic of acebutolol, alprenolol, oxprenolol, pindolol and practolol. The other beta-blocking agents, propranolol, sotalol, timolol, atenolol, and metoprolol have no measurable agonist effect (Imhof, 1975). Current evidence suggests, however, that relative differences in potency, 'cardioselectivity' intrinsic sympathomimetic activity and membrane stabilizing properties are probably of little significance in determining the antihypertensive effectiveness of the various beta-blocking drugs (Niarchos and Tarazi, 1976; Hansson and Werko, 1977). Inspite of known differences in pharmacological activity, most of the drugs seem to induce similar antihypertensive responses if administered in appropriate doses. Moreover, patients who fail to respond to one beta-blocking agent generally fail to respond to the others (Doyle, 1974; Morgan et al.,1974; Waal-Manning, 1976a, b).

A striking contrast exists between the immediate and long term haemodynamic effects of beta-adrenoceptor blockade with propranolol (Niarchos and Tarazi, 1976). Whereas the cardiac output is depressed to the same extent by acute intravenous or chronic oral administration of propranolol, arterial pressure is reduced only with long term treatment (Frohlich et al., 1968; Tarazi, 1973b). The antihypertensive action of propranolol is therefore apparently related to the adaptability of peripheral resistance to long term reductions in flow. With the chronic oral administration of propranolol, as with other beta-blocking drugs, the arterial pressure response correlates best with changes in peripheral resistance and not at all with variations in cardiac output or heart rate.

The importance of total peripheral resistance in determining the blood pressure response to beta-blockade is underscored by the observations that some beta-blockers may reduce blood pressure without reducing cardiac output (Franciosa et al., 1973; Franciosa and Freis, 1975; Niarchos and Tarazi, 1976).

Some observers have suggested that the blood pressure response to propranolol is closely correlated with both the pre-treatment level of plasma renin activity and the magnitude of renin suppression (Buhler et al., 1972).

There are also major differences among the various beta-blocking agents in regard to suppression of renin release. The evidence therefore suggests that there is probably no significant relationship between the suppression of renin release and the antihypertensive effect of the beta-blocking agents (Michelakis and McAllister, 1972; Bravo et al., 1975).

It has also been suggested that beta-blocking agents may lower blood pressure via a central nervous mechanism, possibly similar to that of clonidine and methyldopa. This suggestion is supported by the observation that the injection of propranolol directly into the cerebral ventricles of experimental animals rapidly produces hypotension (Lewis, 1975). Moreover, highly lipid soluble drugs such as propranolol have been found within the brain tissue of patients receiving the drug (Myers et al., 1975; Waal-Manning, 1976a,b). The clinical observation that many of the beta-blockers produce side effects such as sedation, vivid dreams, hallucinations and occasional depression, further strengthens the hypothesis that these agents have definite sites of action within the CNS (Waal, 1967; Simpson, 1974). This concept is far from proven however, because other beta-blockers such as practolol enter the brain poorly, yet have been shown to lower blood pressure.

Weinstock (1976) reviewed the evidence for presynaptic effects of beta-adrenoceptor blocking agents. The concept of peripheral control of adrenergic tone by beta-adrenoceptor blocking agents through an action at presynaptic beta-adrenoceptors is attractive, but conclusive demonstration of its importance in the mechanism of antihypertensive action of beta-adrenoceptor blocking agents is not yet available.

Beta-adrenoceptor blocking drugs by chronic administration to rabbits were shown to reduce tyrosine hydroxylase and dopamine-beta-hydroxylase activities in superior cervical ganglia (Raine and Chubb, 1977). Significant inhibition of both enzymes was also obtained with metoprolol, acebutolol, and practolol. It is therefore likely that reduction in the tyrosine hydroxylase and dopamine-beta-hydroxylase activities in the peripheral sympathetic nervous system contributes to the antihypertensive effectiveness of the beta-adrenoceptor blocking drugs but does not necessarily represent an initial mechanism of action.

Inspite of numerous hypothesis discussed above, the mechanism of antihypertensive action of beta-adrenoceptor blocking drugs should still be considered largely unknwon. The common denominator in most of the discussed hypothesis is the reduction in sympathetic tone induced by beta-adrenoceptor blockade. There is less agreement on the

site of action leading to a decrease in the sympathetic tone. Neither the central effect on catecholaminergic neurone nor the peripheral effect on presynaptic beta-adrenoceptors at sympathetic nerve endings, nor an indirect effect through afferent pathways, can be excluded as possible sites of antihypertensive action of beta-adrenoceptor blocking drugs. It is also conceivable that more than one site of action is involved and the multiplicity of the mechanisms is responsible for a gradual development of an antihypertensive effect free from orthostatic hypotension (Alexander, 1979).

(b) Alpha-adrenergic blocking drugs

(i) Prazosin

(ii) Phentolamine

(iii) Phenoxybenzamine

With the exception of prazosin, results with alpha-adrenergic blocking drugs in the hypertension have been disappointing. An important factor is that beta-receptors are unaffected, and reflex tachycardia and palpitation are added to the other side effects associated with inhibition of sympathetic vasoconstriction. The usefulness of prazosin in hypertension may in part be due to its lack of potency in inhibiting presynaptic alpha-receptors. Small doses of phenoxybenzamine have been found useful in

patients who have developed resistance to adrenergic neurone blocking drugs on the basis of vascular supersensitivity to catecholamines (Sandler et al., 1968). Phenoxybenzamine and phentolamine have been used successfully to control acute hypertensive episodes due to sympathomimetics, and to certain foods and drugs in the presence of MAO inhibition.

4. Drugs that act at postganglionic sympathetic nerve endings

(a) Guanethidine

Guanethidine is a selective inhibitor of the sympathetic nervous system and does not interfere with parasympathetic function (Freis, 1965). It acts at the level of the postganglionic adrenergic neurone by inhibiting the release of NA at the neuro-effector junction, which occurs in response to sympathetic stimulation (Hertting et al., 1962). In order to be effective, guanethidine and other guanidinium compounds such as bethanidine and debrisoquine, must be actively transported into the adrenergic neurone by the 'NA pump' (Mitchell and Oates, 1970). Once it gains access to the neurone, guanethidine accumulates within the intraneuronal storage vesicles and causes depletion of NA stores within the nerve terminal (Chang et al., 1965). Although it is released from storage vesicles with NA

in response to sympathetic nerve stimulation, it does not act as a false transmitter and its sympatholytic action does not depend directly upon the level of NA depletion (Gaffney et al., 1963; Shand et al., 1973). In fact, the exact mode of action has not been completely clarified. There is some evidence to indicate, however, that possibly the major mode of action may reside in the inhibition of nerve pulse transmission at the level of the outer neuronal or vesicular membranes within the sympathetic nerve terminal (Shand et al., 1973).

The intravenous administration of guanethidine produces a transient pressor response with increased cardiac output and peripheral vasoconstriction (Page et al., 1961; Cohn et al., 1963) due in part to the liberation of catecholamines from adrenergic nerve terminals (Harrison et al., 1963). The pressor response generally lasts for less than an hour and is followed by a reduction in arterial pressure as the terminal sympathetic neurones become unresponsive to electrical stimulation (Freis,1965). Tissue catecholamines are not reduced during the early treatment phase; however, with chronic treatment, catecholamine stores are slowly depleted, probably as the result of impaired storage mechanisms (Harrison et al., 1963).

The prolonged oral administration of guanethidine produces a 'denervation sensitivity' of the neuro-effector junction (Abboud et al., 1962). This probably results from the chronic reduction in the amount of NA released from the sympathetic nerve endings. Systemic responses to catecholamines released from the adrenal medulla are not prevented and may even be augmented as a result of this denervation sensitivity (Richardson and Wyso, 1960; Boura and Green, 1965). Thus, a paradoxical hypertensive crisis may occur if guanethidine is administered to patients with phaeochromocytoma, or if NA is given to a patient receiving the drug.

Because of poor lipid solubility guanethidine does not cross the blood-brain barrier and is not associated with central nervous system side effects which are so prominent with other sympatholytic agents such as reserpine, clonidine and methyldopa. In contrast to most neural blocking agents, guanethidine does not appear to suppress plasma renin activity in many patients (Ferguson et al.,1976). In fact, in some patients with 'essential hypertension and suppressed plasma renin activity, guanethidine has been observed to stimulate renin secretion to the range of 'normal renin hypertension' (Lowder and Liddle, 1975). This remains controversial, however.

The haemodynamic changes which occur with guanethidine in early phase of treatment are characterised by a fall in cardiac output and little or no change in peripheral vascular resistance (Richardson et al.,1960; Cohn et al., 1963; Onesti et al., 1973). The reduction in arterial pressure is greater in the upright position as a result of a further reduction in cardiac output due to gravitational pooling of blood in the lower extremities and failure of a compensatory rise in peripheral resistance (Richardson and Wyso, 1960; Richardson et al., 1960). With long term therapy, haemodynamic adjustments occur and the cardiac output gradually increases to near pre-treatment levels while the peripheral resistance gradually falls (Chamberlain and Howard, 1964; Villarreal et al., 1964). A significant reduction in both renal blood flow and glomerular filtration rate occurs in the acute treatment phase (Richardson et al.,1960; Onesti et al., 1973). Although there are no studies of the long term effects on renal haemodynamics, chronic therapy is not generally associated with clinically significant changes in renal function (Page et al., 1961; Woosley et al., 1976).

(b) Reserpine

Reserpine,the most widely used derivative of the Rauwolfia alkaloids, is a selective inhibitor of the

sympathetic nervous system. Once widely used in the treatment of hypertension, its popularity has waned with the advent of more effective antihypertensive agents with fewer unpleasant side effects.

Reserpine exerts its sympatholytic effect by depleting the post-ganglionic adrenergic neurones of NA, and the degree of adrenergic blockade appears to be closely related to the level of NA depletion (Gaffney et al., 1963). The exact mechanism by which reserpine acts is not completely understood. It is thought, however, that reserpine inhibits the uptake mechanism by which NA gains entrance into the storage vesicles within the terminal sympathetic nerve endings (Viveros et al., 1969; Weiner, 1970; Haggendal and Dahlstrom, 1972; Shore, 1972) thus exposing it to degradation by cytoplasmic MAO (Harrison et al., 1963; Zarro, 1973). Reserpine may also interfere with synthesis of catecholamines by blocking the uptake of dopamine into the storage vesicles where it is enzymatically converted to NA (Rutledge and Weiner, 1967; Viveros et al., 1969). The NA pump by which catecholamines gain access to the sympathetic nerve terminal is not inhibited by reserpine (Shore, 1972).

Reserpine rapidly crosses the blood-brain barrier and depletes brain tissue of 5-HT and dopamine as

well as NA (Vogt, 1959). This latter action probably accounts for the sedation and depression which is frequently associated with reserpine. However, central sympathetic outflow is not significantly altered by reserpine (Iggo and Vogt, 1960) and the effect on the central nervous system is thought to be less important than its peripheral effect in regard to its antihypertensive potency (Nickerson and Collier, 1975), although this remains controversial.

The reduction in arterial pressure which accompanies the acute administration of reserpine is associated with a reduction in both cardiac output and systemic resistance. With long term therapy, the cardiac output increases to pre-treatment levels while the peripheral vascular resistance remains reduced (Reusch, 1962; Sannerstedt and Conway, 1970). Both renal blood flow and glomerular filtration rate are reduced in the early phase of treatment, but both return to pre-treatment levels with chronic therapy (Reusch, 1962; Sannerstedt and Conway, 1970; Kisin and Yuzhakov, 1976).

(c) MAO inhibitors

Because of their potentially dangerous side effects, the MAO inhibitors are seldom used nowadays with the advent of newer sympatholytic agents with fewer side effects. Pargyline is the only commercially available

MAO inhibitor for the treatment of hypertension. It is a potent antihypertensive agent which, like guanethidine, selectively blocks sympathetic transmission by preventing the release of NA at the neuro-effector junction (Puig et al., 1972). Although the exact relationship of MAO inhibition to its antihypertensive action is unclear, it is hypothesized that there is an accumulation of dopamine and octopamine, which may function as false neurotransmitters (Kopin et al., 1965) or interfere with the biosynthesis of NA (Nickerson and Ruedy, 1975).

5. Drugs that interfere with the renin-angiotensin system

(a) Saralasin and Captopril

Antagonists of ANG II, exemplified by saralasin block responses to ANG II in a competitive manner and with high specificity; thus, they leave uninfluenced responses to biogenic amines and unrelated vasoactive peptides. However, their antagonism extends with varying efficacy to the other ANGs, particularly ANG III (Peach, 1977). They are, however, not themselves devoid of intrinsic activity and thus they are classified as partial agonists. When renin levels are particularly high, as they may be in patients with malignant hypertension or renal arterial stenosis, the hypotensive action of saralasin may be profound and even

dangerous. The hypotensive response involves diminution of both total peripheral resistance and cardiac output (De Carvalho et al., 1977). The other prominent antagonistic effect of saralasin is reduction of the secretion of aldosterone in sodium-depleted subjects. Saralasin competes with circulating ANG II for receptor sites within vascular smooth muscle and the adrenal cortex (Streeten et al., 1977).

Captopril (orally effective inhibitor of peptidyl dipeptidase) seems from the clinical trials to date, well suited to long term therapy of hypertension of various types. When given orally to normal individuals it inhibits PDP within 15 minutes. Profound inhibition is observed shortly thereafter and lasts for hours (Ferguson et al., 1977). In patients with high blood pressure for a variety of causes associated with elevated, normal, or even low activities of renin in plasma, captopril given orally two or four times per day for periods up to 26 weeks causes considerable lowering in blood pressure. This effect is evident in most instances without adjuvant treatment with diuretic drugs. Basal plasma renin activity was not a good predictor of blood pressure responsiveness. The exact mechanism by which arterial pressure is lowered is still not clear;

interference with production of ANG II is undoubtedly important but increase in bradykinin or other yet unspecified drug effects may play a role. The reduction in blood pressure is related to lowering of total peripheral resistance; cardiac output and heart rate are not significantly altered (Cody et al., 1978). Haemodynamic responses to upright posture were not interfered with by the converting enzyme inhibitor even when associated with sodium depletion or diuretic therapy, indicating that baroreceptor reflexes were effectively operative.