Biochemistry and pharmacology of hypertension

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High blood pressure is an extremely common condition, being present in 15% of the adult population. The vast majority (98%) of these patients have so-called 'essential' hypertension in which there is no single discernible cause. However, there are a vast array of biochemical changes associated with the condition. Similarly, drugs used in the treatment of essential hypertension perturb biochemical systems involved in the control of blood pressure. Rarely, tumours may elaborate excessive hormones and thereby increase blood pressure, but in the present context we are concerned only with the common condition known as essential hypertension.

The ultimate determinants of blood pressure are cardiac output and peripheral resistance. These interact with a third variable, blood volume. Except for the early stages of essential hypertension in young adults, cardiac output is normal and peripheral resistance is raised. According to Laragh and colleagues (Laragh, 1975), increased vasoconstrictor tone or increased blood volume dominates in individual cases of hypertension.

Role of the renin–angiotensin–aldosterone system

The precise role of altered activity of the renin–angiotensin–aldosterone system in essential hypertension is hotly debated and has been for more than a decade. An increase in activity would be expected to raise blood pressure by two mechanisms: vasoconstriction mediated by angiotensin II and an increase in blood volume due to aldosterone induced sodium retention. The most used marker of activity of the renin–angiotensin–aldosterone system is the plasma renin activity. As this in turn is dependent on the amount of sodium taken in the diet (Laragh, 1975) plasma renin activity is usually related to urinary output of sodium. High plasma renin activity is seen predominantly in young hypertensives and in some cases of secondary hypertension, while low levels are more often found in elderly hypertensives. Some investigators such as Laragh favour renin-lowering drugs for those patients with high plasma renin activity, as they claim that the raised blood pressure depends on the presence of high circulating angiotensin II. However, most clinicians use a less structured approach. They find renin profiling impracticable and use drugs irrespective of their effects on plasma renin activity.

Drugs affecting the renin–angiotensin–aldosterone system

Renin. By inhibiting renin release from the kidney, β-adrenoceptor blocking drugs prevent the conversion of angiotensinogen to angiotensin I. These drugs, irrespective of additional properties such as intrinsic sympathomemetic activity or membrane-stabilizing effect, all have the ability to suppress plasma renin activity. In addition to this action there are other putative mechanisms of the antihypertensive effect. Firstly, there is a central nervous system site of action whereby these drugs decrease sympathetic nervous system output (Dollery & Lewis, 1976). Secondly, these drugs decrease cardiac output by β-adrenoceptor blockade in the heart. Finally, inhibition of presynaptic β-receptors may be important as this would lead to a diminished release of noradrenaline from sympathetic nerve endings. While cardiac output is reduced in patients taking β-adrenoceptor blocking drugs, it has proved difficult to correlate changes in cardiac output with changes in blood pressure and it therefore seems likely that additional mechanisms are involved (Tarazi *et al.*, 1976).

Angiotensin II. The conversion of inactive angiotensin I to the extremely potent vasoconstrictor, angiotensin II is catalysed by converting enzyme. Captopril is a competitive inhibitor of converting enzyme with a K_i value of 1.7×10^{-9} M.

$$\text{Angiotensin I} \xrightarrow[\text{(= kinase II)}]{\text{Converting enzyme}} \text{angiotensin II}$$

$$\text{Bradykinin} \longrightarrow \text{inactive fragments}$$

The degradation of the potent vasodilator nonapeptide bradykinin depends on the same enzyme. Both these results favour a decrease in blood vessel tone and a fall in blood pressure. In addition, aldosterone levels are consistently reduced (Atlas *et al.*, 1979), an effect which may contribute to the antihypertensive action. Captopril is an extremely effective blood pressure lowering drug, particularly in patients who are resistant to more conventional antihypertensive drugs.

The interaction of angiotensin II with its receptor in the adrenal cortex (aldosterone release) and resistance blood vessels (constriction) can be antagonized competitively by saralasin, which is [Sar^1, Ala^8]angiotensin II. This analogue has three shortcomings as a clinically useful drug. It has an extremely short duration of action (it must be given by i.v. infusion), it is not active orally and therefore it must be given parenterally, and finally it is a partial agonist which in some patients causes an increase rather than a decrease in blood pressure. Initially it was used diagnostically to discriminate between those in whom raised blood pressure was dependent on excessive circulating angiotensin II and those in whom this mechanism was not important. This initial promise has not been confirmed by subsequent experience.

Aldosterone. Aldosterone action on the distal renal tubule is inhibited by spironolactone, but this drug has not been found to be useful in the management of hypertension. The main value of spironolactone is that it can be used to minimize potassium loss in patients taking thiazide or loop diuretics as these may cause a serious potassium deficiency in some cases.

Drugs used in the management of high blood pressure may alter plasma renin activity as a 'side effect'. For example, the vasodilatory drugs and diuretics increase plasma renin activity while those drugs which attenuate sympathetic nervous system activity have the opposite effect. By combining a drug which elevates plasma renin activity with one that suppresses it the end result is that plasma renin activity changes little (O'Malley *et al.*, 1976). Reduction of plasma renin activity by the second drug may be an important component of its blood pressure lowering effect (Fig. 1).

Central nervous system

The central nervous system control of blood pressure has been the subject of much recent work (Antonaccio, 1977). Biochemical systems with receptor sites for various peptides are present. In the case of angiotensin II all the requirements for its formation are present in the brain. Also angiotensin II has a central pressor action mediated by increased sympathetic vasomotor discharge. Pertubation of this system causes blood pressure change, but its precise physiological role in the control of blood pressure is not clear at present. Similarly its importance in the pathophysiology of high blood pressure is unknown. Other peptides possibly involved in blood pressure control include opioids and substance P.

It is now known that the sites of action of several important antihypertensive drugs are in the central nervous system. The most important of these drugs are clonidine and methyldopa. The latter was initially thought to act as a 'false' neurotransmitter but recent evidence shows it to be a potent α_2-agonist acting on neurones controlling sympathetic nervous system

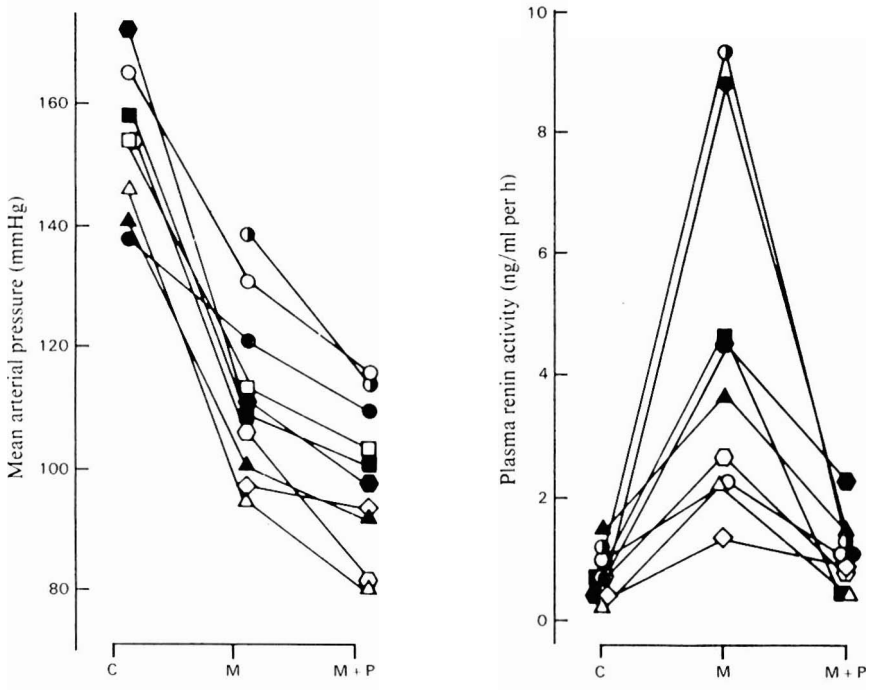

Fig. 1. *Effect of drugs on plasma renin activity*

C, control; M, minoxidil; M + P, minoxidil plus propranolol. Minoxidil, a vasodilator, increased plasma renin activity in all patients while addition of the β-adrenoceptor blocking drug propranolol markedly reduced plasma renin activity towards control values. Minoxidil lowered blood pressure and the addition of propranolol produced a further decrement (O'Malley *et al.*, 1976).

discharge from the medulla (Scriabine, 1980). Clonidine has a similar mechanism of action. Both drugs cause a marked decrease in sympathetic nervous system outflow.

Membranes and ions

Changes in the transport of ions, particularly sodium and potassium, have been reported by many investigators (for review see Tosteson *et al.*, 1981). Changes in sodium homeostasis are of interest because they may be involved in the pathophysiology of high blood pressure, act as genetic markers for essential hypertension or be important pointers to future prophylactic and therapeutic approaches. However, the field is full of confusion, mainly because the methods and systems studied vary enormously. Most work has been carried out on formed elements in the blood: red blood cells, lymphocytes and polymorphonuclear leucocytes. Defects in sodium transport have been suggested for extrusion of sodium by the sodium/potassium co-transport system (Garay & Meyer, 1979) and by the ouabain-sensitive sodium/potassium ATPase system (Edmondson *et al.*, 1975). McGregor *et al.* (1981) suggest that there is a circulating inhibitor of sodium/potassium ATPase in essential hypertension. Though this inhibitor may encourage sodium loss by its action in the kidney, by virtue of its inhibitory effect on sodium transport on other cells, specifically the smooth muscle cells of arterioles, it would tend to increase intracellular sodium and water and thereby increase cellular volume. Such an effect would lead to an increase in resistance and hence an increase in blood pressure. In fact intracellular sodium concentrations have been found to be elevated in essential hypertension by some investigators (Edmondson *et al.*, 1975). Changes in the lithium/sodium countertransport system have also been reported in essential hypertension (Canessa *et al.*, 1980).

It is not at all clear what significance these various findings have. However, it does seem likely that sodium transport is abnormal in essential hypertension. Interestingly, defects in sodium transport have been linked with the hereditary background of essential hypertension and the interesting question arises as to whether this is a causative link or 'if two sets of genes, coding respectively for products involved in ion transport and vascular resistance, segregate together and lead to an indirect association between abnormal transport and hypertension' (Tosteson *et al.*, 1981). Ultimately it seems likely that it will be found that hypertension develops in those people who are genetically predisposed to it but who in addition are subjected to environmental factors such as excess salt or alcohol intake. Thus genetic susceptibility would be unmasked by such environmental factors.

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