The pharmacological basis for the use of α_1 -adrenoceptor antagonists in the treatment of essential hypertension

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1 Effective preventive antihypertensive therapy is more likely to be achieved with drugs whose mechanisms and sites of action are congruent with the underlying aetiology and pathophysiology than by drugs that lower blood pressure by means unrelated to the process of hypertension.

2 A vast amount of experimental and clinical data exist in favour of the neurogenic hypothesis. Thus hyperactivity of the sympathetic nervous system plays a major role in the pathogenesis and maintenance of essential hypertension and a generalized increase in peripheral vascular resistance is the fundamental haemodynamic abnormality.

3 Reduction in increased sympathetic activity by α -adrenoceptor blockade was one of the earliest pharmacological attempts to treat hypertension. However the discovery of postjunctional α_1 -adrenoceptor antagonists represented the crucially important step in the development of agents to combat specifically adrenergic predominance in essential hypertension. This has yielded antihypertensive drugs of high specificity which preserve feedback control of transmitter noradrenaline release and consequently cause minimal reflex activation of the sympathetic nervous system.

4 These properties have important clinical implications with respect to the therapeutic application of α_1 -adrenoceptor antagonists in the treatment of hypertension, and in addition explain why the clinical expectations of the early α -adrenoceptor antagonists remained unfulfilled.

5 α_1 -Adrenoceptor antagonists represent an attractive alternative choice for initial therapy in all grades of hypertension.

Keywords α_1 -adrenoceptor antagonists hypertension pathophysiology peripheral resistance prazosin

Introduction

Whereas it has been long established that lowering arterial pressure increases survival in the most severe forms of hypertension it is now becoming increasingly apparent that the treatment of mild hypertension also improves prognosis. Consequently, antihypertensive drugs are being used in an increasing proportion of hypertensive patients in whom the risk from hypertension is less than in patients with more severe forms of hypertension, and in whom it is appropriate to consider the possibility of additional risk arising from the therapy employed.

For example, although hypertension is a well established coronary risk factor, controlled randomized clinical trials with untreated and

placebo-treated control groups have failed to show a definite preventive effect on the incidence of coronary heart disease. This fact has aroused interest over the possible adverse effects of some commonly used antihypertensive drugs. Presently, there is concern over (1) diuretic-induced hypokalaemia since hypokalaemia may lead to potentially lethal arrhythmias particularly after myocardial infarction; (2) the increase in plasma cholesterol that occurs during diuretic therapy; and (3) the possibility that β -adrenoceptor antagonists may pose a long-term atherogenic risk because of their adverse effects on lipid and carbohydrate metabolism (Kaplan, 1983).

The treatment of mild-moderate asymptomatic hypertension should be regarded as preventive medicine, the overall goal of which should be to

favourably affect morbidity and mortality. It is reasonable to assume that effective preventive antihypertensive therapy is more likely to be achieved with drugs whose mechanisms and sites of action are congruent with the underlying aetiology and pathophysiology than by drugs that lower blood pressure by means unrelated to the hypertensive process.

Thus the site of action of an antihypertensive drug should ideally be focused on the specific aberration responsible for the hypertensive state. Whereas first-step treatment is now a matter of several choices (β -adrenoceptor antagonist, α_1 -adrenoceptor antagonist, calcium entry blocker, converting enzyme inhibitor, or diuretic) a corresponding growth in the understanding of the pathogenesis of essential hypertension has not occurred. Additionally it is not yet feasible to analyse the mechanisms giving rise to hypertension in individual patients before the start of therapy.

Whatever the underlying cause however, it is widely accepted that a generalized increase in peripheral vascular resistance is the fundamental haemodynamic abnormality in essential hypertension. Consequently, it is rational to treat hypertension with drugs that lower blood pressure as a consequence of a dilator action on vascular smooth muscle, provided the vasodilation produced by these agents has the same geography as the vasoconstriction by which hypertension is produced.

Pharmacological action of α_1 -adrenoceptor antagonists

There is overwhelming evidence of the importance of the sympathetic nervous system in the maintenance of arteriolar tone and that it is an important factor in the pathogenesis and maintenance of essential hypertension (De Quatro & Miura, 1973). Admittedly, whilst this does not prove the neurogenic hypothesis of essential hypertension from the standpoint of adrenergic mechanisms unequivocally playing an initiating role in its aetiology, it more than adequately justifies the search for compounds that inhibit sympathetic vasoconstrictor tone.

The α -adrenoreceptor antagonists were the first substances to receive serious consideration as antihypertensive agents (Werner & Barrett, 1967). It had been anticipated that an agent which inhibited the effect of the sympathetic mediator at the neuro-effector junction would be ideal for inhibiting sympathetic vasoconstrictor tone. It was only at this level that the sympathetic nervous system differed

sufficiently from other divisions of the autonomic nervous system that there was a possibility that sympathetic vasoconstriction could be blocked without complicating cross-reactions. The more active compounds studied belonged to the following chemical groups: β -haloalkylamines, ergot alkaloids, imidazolines, benzodioxanes, phenoxylethylamines, tetrahydroisoquinolines, and dibenzazepine derivatives. They were characterized by their ability to abolish the pressor effect of noradrenaline and to reverse the pressor effect of adrenaline. They did not abolish the effects of adrenaline or sympathetic stimulation on the myocardium or coronary circulation, neither did they reduce their inhibitory actions.

Tissue responses to circulating catecholamines were almost always prevented by lower concentrations of a specific compound than were the effects of stimulation of sympathetic nerves; the ratio between the two effective concentrations varied greatly and was characteristically low for β -haloalkylamines, phenoxylethylamines, dibenzazepines, and the 883F group of benzodioxanes, and high for those of the 933F type (e.g. piperoxan) which abolished the excitatory action of adrenaline but did not alter the effects of sympathetic nerve stimulation.

However, the clinical expectations of these compounds were not fulfilled; although they lowered blood pressure, this effect was accompanied by tachycardia and diarrhoea, and tolerance rapidly developed. The original expectations were based on: (1) the conviction that the prime mover in essential hypertension was an abnormal activity of the sympathetic nervous system; and (2) the demonstration that bilateral excision of the thoracolumbar sympathetic chains lowered blood pressure in essential hypertension by restoring the peripheral resistance toward the normal range (Smithwick, 1940). At this time there was no direct evidence that increased catecholamine production or vasoconstrictor nerve hyperactivity had any aetiological importance in the elevation of peripheral resistance seen in hypertension.

Prazosin, the first selective α_1 -adrenoceptor antagonist

Prazosin was the first α_1 -adrenoceptor antagonist to prove of lasting value in the treatment of hypertension, and since its discovery there has been a renaissance of interest in selective α_1 -adrenoceptor antagonists. The antihypertensive activity of prazosin was closely linked to the peripheral

α_1 -adrenoceptor antagonist activity and yet it differed from the classical α -adrenoceptor antagonists in that it caused little or no tachycardia, increase in plasma renin activity, tolerance or diarrhoea. It was subsequently shown (Cambridge *et al.*, 1977) that prazosin differed from the classical α -adrenoceptor antagonists in possessing a high degree of α_1 -selectivity, estimates for α_1 -adrenoceptor : α_2 -adrenoceptor binding ranging from 10 000 to 100 000:1, thereby enabling the preservation of automodulation of transmitter noradrenaline release.

The effectiveness of prazosin as an antihypertensive agent has provided strong suggestive evidence of the importance of feedback control of transmitter noradrenaline release in man and provided persuasive evidence that the primary pharmacological reason for the failure of the non-selective α -adrenoceptor antagonists in the treatment of hypertension was the loss of this prejunctional α_2 -adrenoceptor mediated inhibitory feedback loop. The high selectivity of prazosin for α_1 -adrenoceptors has made it an invaluable research tool not only for basic pharmacological studies but also for the clinical study of α -adrenoceptor function.

Prazosin was instrumental in demonstrating the presence of a postjunctional α -adrenoceptor which can be activated by selective α_2 -adrenoceptor agonists to produce pressor responses which are blocked by α_2 -adrenoceptor antagonists but not by prazosin (review, Timmermans & van Zwieten, 1981).

The existence of postjunctional α_2 -adrenoceptors may explain why neural influences are preserved in patients treated with prazosin although modulated at lower resting blood pressures, and why prazosin does not significantly modify reflex circulatory responses to cold, to dynamic and isometric exercise, and to altered carotid baroreceptor activity in man (Mancia *et al.*, 1979).

The effectiveness of prazosin as monotherapy in the treatment of all grades of hypertension has been demonstrated in numerous clinical trials (Stanaszek *et al.*, 1983). Similarly, prazosin has been repeatedly shown to be effective when added to treatment regimens which were not providing adequate blood pressure control (Stanaszek *et al.*, 1983). The long-term use of prazosin for periods of 2–5 years in patients with mild, moderate and severe hypertension has not revealed any loss of efficacy and follow-up studies have shown that satisfactory antihypertensive activity has persisted for periods of several years without the need for upward adjustment of dose (Stanaszek *et al.*, 1983).

The primary haemodynamic effect of prazosin has been shown to be a fall in total peripheral resistance both at rest and during exercise as a direct consequence of α_1 -adrenoceptor antagonism. In contrast to the non-selective α -adrenoceptor antagonists the antihypertensive effect of prazosin is accompanied by little or no increase in heart rate, plasma renin activity or plasma noradrenaline concentration (Colucci, 1982). Prazosin has been shown to cause little or no change in glomerular filtration rate or effective renal plasma flow (Brogden *et al.*, 1977) and has no adverse effect on renal function in patients with renal disease (Bailey, 1977; Heagerty *et al.*, 1982).

Recent studies indicate that α_1 -adrenoceptor antagonists have a favourable effect on blood lipid profile which is in contrast to the adverse effects of diuretics and β -adrenoceptor antagonists on lipid metabolism. Thus treatment of hypertensive patients with prazosin is associated with decreases in serum cholesterol and triglyceride levels and increases in the serum high density lipoprotein (HDL) cholesterol and the cholesterol ratio defined as HDL cholesterol/low density lipoprotein cholesterol + very low density lipoprotein cholesterol (Leren *et al.*, 1980; Kirkendall *et al.*, 1978; Lowenstein & Neusy, 1981; Kokubu *et al.*, 1981; Velasco *et al.*, 1981).

On the other hand therapy with thiazide diuretics results in increases in low density lipoprotein (LDL) cholesterol and triglycerides (Lowenstein & Neusy, 1981), and treatment with β -adrenoceptor antagonists results in increases in triglycerides and a decrease in HDL cholesterol levels (Leren *et al.*, 1980; Lowenstein & Neusy, 1981).

The significance of these findings for patients receiving long-term therapy with those agents with respect to morbidity and mortality due to atherosclerotic events remains to be established. However, at the very least they suggest that it would be preferable to use α_1 -adrenoceptor antagonists, rather than a diuretic or a β -adrenoceptor blocker in hypertensive patients with an unfavourable plasma lipid profile.

The use of prazosin in the treatment of hypertensive patients with diabetes mellitus has not been associated with adverse effects in glucose metabolism (Barbieri *et al.*, 1980a, b; Konigstein, 1978). Diabetic patients who experienced sexual dysfunction when treated with clonidine or methyl dopa, noted significant improvement when prazosin was substituted (Lipson *et al.*, 1981; Moore *et al.*, 1980). Thus prazosin has distinct advantages as an antihypertensive in diabetic patients. Clonidine, propranolol, and thiazide

diuretics all worsen glucose tolerance, β -adrenoceptor blockade can mask insulin-induced hypoglycaemia and decrease peripheral blood flow in the presence of peripheral vascular insufficiency, and methyl dopa and clonidine both impair sexual function (Lipson *et al.*, 1981).

Prazosin, unlike the β -adrenoceptor antagonists, does not aggravate atopic or reactive airways disease (Layton, 1981), is better tolerated by people engaging in vigorous sport or exercise than are β -adrenoceptor antagonists (Stokes & Marwood, 1984), and is particularly indicated in hypertensive patients with cardiac failure.

It can be concluded that the development of selective α_1 -adrenoceptor antagonists represents an important advance in the development of drugs which lower blood pressure via adrenergic mechanisms. They are effective in all grades of hypertension with virtually no contraindications to their use.

α_1 -Adrenoceptor antagonists have a favourable effect on blood lipid profile and no effect on carbohydrate metabolism. This is in contrast to the adverse effects of diuretics and β -adrenoceptor blockers on both lipid and carbohydrate metabolism.

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