Biochemical Pharmacology, Vol 26, pp 171–175 Pergamon Press, 1977. Printed in Great Britain.

COMMENTARY

MECHANISM OF ACTION OF β-BLOCKERS IN HYPERTENSION

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Although the β-adrenoceptor blocking drugs are now recognized as effective antihypertensive agents, none of the hypotheses advanced to explain the mechanism by which they lower arterial pressure is entirely satisfactory. On strict pharmacological grounds, these agents could be expected to raise, rather than lower, arterial pressure by blockade of the vasodilation-mediating vascular β-adrenoceptors. In many animal models of hypertension, β-adrenoceptor blockers are devoid of antihypertensive activity [1–4] and were shown in fact to be hypertensive both in animals [5,6] and in certain groups of hypertensive patients [7]. The excellent antihypertensive profile of these agents in the majority of hypertensives, however, continues to stimulate the search for mechanisms that could adequately explain their antihypertensive effects. These mechanisms include the following four.

Inhibition of renin secretion. Most investigators agree that inhibition of renin secretion is probably a primary mechanism via which β-adrenoceptor blocking agents lower blood pressure in the small group of younger hypertensive patients characterized by an elevated renin-sodium index. High renin hypertensive patients generally respond to the intravenous administration of the angiotensin II antagonist, "Saralasin," with a significant fall in blood pressure [8], a test that can be used to identify those patients with renin-dependent hypertension and in whom β-blockers are most effective [9,10]. The antihypertensive activity of β-adrenergic blockers in these patients correlated well with the degree of inhibition of renin release, and with the initial level of plasma renin activity [10,11]. When β-blockers are added to a regimen of direct vasodilator agents which raise plasma renin activity, the β-blockers may again act primarily by inhibiting the elevated renin secretion. Here again, correlation between the antihypertensive activity and the inhibition of renin release is obtained [12]. Such a correlation apparently does not hold, however, in the diuretic-induced rise in plasma renin activity when combined with β-adrenergic blocker therapy [13].

The vast majority of hypertensive patients have a normal or low renin-sodium index and the situation is more complex. Although the β-adrenoceptor blockers still lower blood pressure in most of these patients, albeit to a lesser extent than in those with high renin, no correlation with basal renin activity or a decrease in plasma renin levels is obtained. The effects on renin release occur almost immediately after the administration of β-adrenoceptor blockers, while the reduction in blood pressure may take from days to several weeks to develop. In addition, the doses needed to lower pressure are several-fold greater than those needed to inhibit renin release [14,15]. Some β-blockers, e.g. pindolol, significantly lower arterial pressure while having no inhibitory [16], and sometimes even a stimulatory [17], effect on renin release. Thus, in the majority of hypertensive patients, inhibition of the renin–angiotensin system is probably not the main mechanism of the antihypertensive activity of these agents.

Inhibition of cardiac output. The most studied and described effect of β-blockers, i.e. inhibition of cardiac β-adrenoceptors and the associated decreases in cardiac output, has been proposed as the long-sought mechanism for their antihypertensive activity in man. This is not a convincing explanation, however, since intravenous propranolol produces an immediate fall in cardiac output with almost no effect on arterial pressure due to autoregulatory compensatory increase in peripheral resistance [18]. Chronic β-blocker therapy is usually associated with decreased cardiac output which occurs well before a decrease in arterial pressure is observed [19]. Several β-blockers with intrinsic sympathomimetic activity, e.g. pindolol, alprenolol and oxprenolol, are effective antihypertensive agents but produce only minimal effects on cardiac output. Furthermore, high cardiac output hypertensive states are not particularly sensitive to the antihypertensive activity of β-adrenoceptor blockers [19–21]. Also, patients that do not respond to β-blockade by a lowering of pressure still exhibit significant decreases in cardiac output similar in magnitude to that observed in the responders [22].

Inhibition of sympathetic outflow—central effects. A central site for the antihypertensive activity of β-adrenoceptor blockers has also been suggested. This was triggered by the discovery of the strong antihypertensive activity of the α-adrenoceptor agonist clonidine (Catapres) [23]. If central α-adrenoceptor stimulation lowers arterial pressure, central β-adrenoceptor antagonists may also lower pressure via blockade of central β-receptors resulting in unopposed central α-adrenoceptor stimulation. Although adequate characterization of central β-adrenoceptors is still lacking, this hypothesis was supported by animal studies which indicated that: (a) central administration of the β-adrenoceptor stimulant, isoproterenol, in cats [24] was associated with hypertensive effects, (b) intraventricular administration of the l-isomers of a number

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of β-blockers to conscious rabbits [25], cats [26] and rats [27] reduced arterial pressure, while the *d*-isomers which possess minimal β-blocking activity were inactive, and (c) impulse traffic decreased in the splanchnic nerve in conscious rabbits after β-adrenoceptor blockade [28], an effect similar to that observed after clonidine administration. It should be noted, however, that practolol, an effective antihypertensive β-blocker, was inactive in the latter test [28]. Studies with rabbits are also open to question since the antihypertensive effects of β-blockers in this species differ significantly from their antihypertensive effects in man in time of onset and other characteristics [29]. In addition, β-blockers do not generally lower arterial pressure in the normotensive man.

The central-site hypothesis does not explain the long time-lag between the administration of β-blockers and the appearance of their antihypertensive effects, since no accumulation of propranolol in the brain appears to occur with time [30]. Also, it does not explain the good antihypertensive activity of a number of β-adrenoceptor antagonists, e.g. sotalol [31], practolol, atenolol and metoprolol [32], that seem to cross the blood/brain barrier very poorly, if at all. Although some β-blockers do cross the blood/brain barrier, as shown by their centrally mediated side effects, e.g. the frequent bizarre dreams, no good correlation appears to exist between the antihypertensive activity of β-blockers and their ability to enter the central nervous system, as determined by lipid partition coefficients. In addition, intraventricularly administered sotalol, an effective antihypertensive β-blocker, failed to lower arterial pressure in anesthetized cats [33].

Various modifications of this central hypothesis were advanced by placing the site of action on the same pathway either at the baroreceptor [34–36] or at the afferent limb [37] with the net result of decreased sympathetic outflow. However, most of the difficulties plaguing the main hypothesis still remain. Studies with pindolol failed to show a decrease in plasma norepinephrine levels concomitant with its antihypertensive effects, as was shown to occur with clonidine [38].

Regression of cardiac hypertrophy. Fitzgerald [39] suggested that prolonged cardiac β-adrenoceptor blockade, blocking the sympathetic component to cardiac activity without necessarily lowering cardiac output, would result in a reduction in the hypertension-associated cardiac hypertrophy and consequent readjustments of the circulation necessary for adequate perfusion of the kidney at significantly reduced pressures. In effect, this amounts to a reversal of the cascade of events suggested by Borst and Geus [40] to explain the vascular adjustments in hypertension. Although this hypothesis could explain the time-lag between the administration of β-blockers and the onset of their antihypertensive effects, such a hypothesis, as pointed out by Lewis [37], would not explain the rapid return of pressure to hypertensive levels after cessation of β-blocker therapy, since cardiac re-hypertrophy would be expected to be a much more gradual process. In addition, there is evidence that propranolol reduces cardiac hypertrophy with no effect on blood pressure in severe renal hypertension in rats [41].

REQUIREMENTS IN A NEW HYPOTHESIS

A hypothesis that could explain the mechanism of the antihypertensive activity of β-adrenoceptor blocking agents in the majority of hypertensives should take into consideration certain observations:

(1) The only pharmacological property of these compounds that correlates well with their antihypertensive activity is β-adrenoceptor blockade. None of the ancillary pharmacological effects, such as intrinsic sympathomimetic activity, cardioselectivity, or membrane stabilization, which may influence certain side effects, appears to play a major role in the antihypertensive action of these agents.

(2) Onset of antihypertensive activity requires from 2 days to several weeks after initiation of chronic therapy.

(3) Doses several-fold greater than those needed for β-adrenoceptor blockade are required to reduce blood pressure.

(4) The antihypertensive effects disappear at variable rates after cessation of therapy.

(5) Lowering of blood pressure by these agents occurs concomitantly with a decrease in the initially elevated peripheral resistance.

(6) There is a lack of antihypertensive activity in many animal models of hypertension.

β-ADRENERGIC RECEPTORS IN HYPERTENSION

Although the normal physiological role played by vascular β-adrenoceptors in the control of blood pressure is not well understood, decreased responsiveness of these receptors, both functionally and pharmacologically (as shown by decreased cyclic AMP synthesis), in hypertension is known. Decreased sensitivity of cardiac [42] and vascular [43,44] β-adrenergic receptors in hypertension has been described. In three forms of chronic hypertension in rats, a study of cyclic nucleotide metabolism in the heart and blood vessels revealed a lessened sensitivity of the β-adrenergic receptor, mediating cyclic AMP synthesis, to agonist stimulation [45,46]. This observation was corroborated by studies in other laboratories [47,48] and agreed well with the generalized decreased β-adrenergic receptor responsiveness in this disease. Since a decreased β-receptor sensitivity was also observed in the heart and vessels of acute, neurogenically hypertensive rats [49], it appeared that it could be mediated via excessive sympathetic stimulation. Based on these and other studies, the hypothesis was advanced [50] that increased sympathetic outflow early in the development of hypertension, possibly during periods of stress or emotionality, elicits decreased β-adrenergic receptor sensitivity. This results in predominant α-adrenergic receptor activity, increased vascular resistance and elevated arterial pressure. This could also occur at the β-receptors in the sympathetic nerve endings that stimulate norepinephrine release [51]. The β-receptor sensitivity slowly recovers in periods of normal or decreased sympathetic tone and results in the normalization of arterial pressure. These reversible changes of β-adrenoceptor sensitivity, therefore, could characterize labile hypertension. Sustained increases in sympathetic tone, resulting in continuously elevated norepinephrine

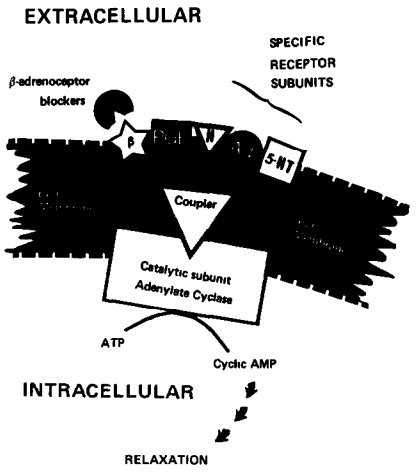

Fig. 1. Adenylate cyclase complex in vascular smooth muscle. Binding between the specific agonists and their specific receptor subunits [β: β-adrenergic; PGE: prostaglandin E; H: histamine; Ad: adenosine; and 5-HT: 5-hydroxytryptamine (serotonin)] activates the coupler subunit which in turn activates the catalytic subunit that catalyzes the conversion of ATP to cyclic AMP. β-Adrenoceptor blockers block the β-adrenergic receptor without blocking the effects of other hormonal vasodilators on the system. Cyclic AMP mediates vascular smooth muscle relaxation via a number of steps probably involving Ca^{2+} and protein phosphorylation.

concentrations at the receptor sites, could elicit almost permanent loss of β-adrenoceptor sensitivity. This could involve permanent structural as well as functional modifications that ultimately result in sustained hypertension which usually follows the initial labile stages of the disease.

That hypothesis explained, among other things, the hypertension-associated increased contractile sensitivity of vascular smooth muscles and its decreased sensitivity to hormonal vasodilating agents. The two effects are inter-related and indicate that in hypertension there is a decreased responsiveness (relaxation) of the vasculature not only to β-adrenoceptor agonists but also to other hormonal vascular smooth muscle relaxants as well. Since cyclic AMP appears to mediate vascular smooth muscle relaxation to all these agents, an abnormality in the cyclic AMP-synthesizing system was thus strongly suspected.

As can be seen in Fig. 1, the β-adrenergic receptor is only one of a variety of hormonal receptors that trigger cyclic AMP synthesis via the same adenylate cyclase enzyme complex which is thought in most systems to consist of multiple receptor subunits, a coupler subunit and a catalytic subunit. It has been shown repeatedly in other systems [52] that if adenylate cyclase is maximally stimulated via any one of the receptors, e.g. via β-adrenoceptor stimulation, no additive effects could be produced via stimulation of another receptor, e.g. the histamine receptor; this emphasizes that we are dealing with a single enzyme responsive to a variety of specific agonists acting on their specific receptors. Specific blockade of one of the receptors, e.g. the β-receptor by β-adrenoceptor blockers, does not interfere with stimulation of cyclic AMP synthesis and the relaxation induced via another receptor.

Reduced activity in the coupler or catalytic units of the enzyme could be translated into decreased responsiveness of the system to all various stimuli acting via adenylate cyclase. Decreased responsiveness of the cyclic AMP relaxation system could be affected, independently of the catecholamines, e.g. by sustained increases in the levels of angiotensin II early in the development of hypertension. Decreased receptor responsiveness to any agonist, e.g. β-adrenergic stimulants or angiotension II, if it occurs at a level beyond the receptor subunit itself, could be associated with decreased responsiveness to other agonists as well.

In hypertension, the decreased β-adrenergic receptor responsiveness appears to occur at the level of the coupler unit (Fig. 1), since binding of norepinephrine to the vascular β-receptor is normal [53] and the enzyme adenylate cyclase is fully responsive to sodium fluoride which acts directly on the catalytic subunit [45–49]. Therefore, the defect in β-receptor responsiveness is reflected in decreased sensitivity to natural hormonal vasodilator agents other than epinephrine and norepinephrine, e.g. those involved in reflex vasodilation, as histamine and PGE_2. This may explain the observed decreased reflex vasodilation in hypertension. It must be recognized, however, that the coupler unit represents more of a conceptual than a structural component of the adenylate cyclase–receptor complex and should be viewed widely enough to include membrane components that modulate receptor to enzyme coupling. Variations in the composition and structure of vascular cell membranes in hypertension are widely recognized; changes in coupling efficiency may be a result of such disease-related lesions.

Decreased receptor sensitivity after excessive exposure to specific stimulants is a well known pharmacologic phenomenon [54–60]. Studies *in vivo*, *ex vivo* and *in vitro* indicate that this process is only slowly reversible. Thus, the receptor slowly recovers its responsiveness in the absence of the specific agonist. It may take longer for the receptor sensitivity to recover in the presence of smaller concentrations of the agonist. After it regains its responsiveness, the receptor becomes exquisitely conditioned to loss of responsiveness which now occurs at agonist concentrations lower than were needed before [61]. As discussed earlier, this correlates well with the decreased responsiveness of the β-adrenergic receptor in hypertension. In sustained hypertension, the responsiveness of the cyclic AMP relaxation system to other hormonal vasodilator agents could be kept in a lower sensitivity state by the normal or abnormal amounts of norepinephrine released at the sympathetic nerve endings.

NEW HYPOTHESIS—A VASCULAR SITE FOR THE ACTION OF β-BLOCKERS IN HYPERTENSION; RESTORATION OF VASCULAR RELAXATION SENSITIVITY

To explain the antihypertensive activity of β-blockers, it is proposed that β-adrenoceptor blockade, if maintained, would protect the vascular β-adrenergic receptor from the insult of the reinforcing levels of the catecholamines that maintain the subsensitivity of the relaxing apparatus mediating

cyclic AMP synthesis. Chronic β-blockade therapy would allow, therefore, the adenyl cyclase–relaxation complex to slowly regain its responsiveness to other agents that normally mediate vasodilation, e.g. histamine and PGE_2, to balance the otherwise unopposed vasoconstricting α-adrenergic tone. This would allow the blood pressure to fall to near normotensive levels and may provide the basis for the antihypertensive activity of β-adrenoceptor blockers as a class.

This hypothesis agrees well with most of the properties and actions of β-adrenoceptor blockers as antihypertensive agents. Furthermore, it explains a number of observations hitherto poorly explained by other hypotheses:

(1) The only important property of these agents that correlates well with their antihypertensive activity is their β-adrenoceptor blocking property, and all β-adrenoceptor blocking agents as a class are active antihypertensive agents [62]. By definition, β-adrenoceptor blockade is the only property needed in the present hypothesis.

(2) The delay in onset of the antihypertensive effects of β-adrenoceptor blocking agents occurs because the recovery of the relaxation apparatus and receptor response is a time-consuming process. This could vary depending on the degree of receptor sensitivity loss and reversibility.

(3) Higher doses than those required for β-adrenoceptor blockade are needed to produce antihypertensive effects. Maintenance of adequate and continuous β-adrenoceptor blockade to prevent reinforcing concentrations of norepinephrine from reaching the receptor may explain the need for higher doses. This may also explain why β-blocking agents that are not excessively metabolized and which possess longer half-lives, e.g. sotalol [63], are relatively more effective antihypertensive agents than would be predicted based on β-adrenoceptor blocking potency alone.

(4) The antihypertensive activity of various β-adrenoceptor blockers is brought about primarily via a decrease in peripheral vascular resistance [18,19,64]. This hypothesis localizes the effects of these agents in hypertension to the peripheral vasculature, via a mechanism that would directly result in decreased vascular smooth muscle tone.

(5) Blood pressure returns to pretreatment levels at a variable rate after cessation of β-adrenoceptor blockade. According to this hypothesis, the β-adrenergic receptor returns to its subsensitive state as a result of exposure to catecholamines after cessation of β-blockade; the rate of return is dependent on the rate of release of catecholamines and the state of the vascular β-adrenergic receptors.

(6) The lack of antihypertensive activity in many animal models of hypertension could be due to qualitative and quantitative differences in the factors mediating vascular relaxation and the relative contribution of vascular β-adrenergic receptors to the control of vascular smooth muscle tone [65].

A number of other observations may also be explained by the present hypothesis. First, older patients with presumably less responsive adenylate cyclase [66] are less responsive to β-adrenoceptor blocking drugs [11]. Second, high doses of β-blockers with relatively strong intrinsic sympathomimetic properties, e.g. pindolol, may actually elevate arterial pressure [67] since excessive β-receptor stimulation would induce decreased receptor responsiveness. This is also true for propranolol [68] which, although devoid of intrinsic sympathomimetic activity, is metabolized to 4-hydroxy-propranolol which has strong agonist properties [69]. Third, the lack of antihypertensive activity of the *d*-isomers that also lack β-adrenergic blocking activities would be expected. Fourth, cardioselective β-blockers, e.g. practolol, are less effective antihypertensive agents [70–72] than would be expected on the basis of cardio–β-blockade, since their antihypertensive effects would result from their vascular rather than their cardiac actions. It should be noted that most of the so-called non-selective β-adrenoceptor blockers, e.g. propranolol and sotalol, are more active in blocking the effects of isoprenaline on the vasculature than on the heart. Fifth, since β-blockers would only restore the normal ability of the vascular smooth muscles to relax, excessive dosage of these drugs would not lead to severe hypotension [73].

This hypothesis can be tested by experiments designed to study vascular responsiveness to various hormonal vasodilator stimuli before and after chronic β-blockade in responsive animal models of hypertension and in hypertensive patients [74]. In fact, reserpine treatment, which reduces the concentrations of catecholamines at the receptor sites and thus catecholamine β-receptor interaction, improved the ability of the vascular smooth muscles from spontaneously hypertensive rats to relax [44]. This can be viewed as an indirect support for the proposed hypothesis.

If the present hypothesis is proven correct, it may help orient research programs directed toward the development of better adrenoceptor antagonists for the treatment of hypertension by focusing attention on the long known, poorly understood and meagerly studied vascular β-adrenoceptors as the most likely site of the lesion in hypertension.

Acknowledgement—The author is indebted to Drs. Fitzgerald, Conway, Frohlich, Tarazi, Vanhoutte, Dustan and Comer for their suggestions and stimulating discussions.

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