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SHORT REVIEW

The central action of antihypertensive drugs, mediated via central α-receptors

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The aim of this brief review is to attempt to describe and as far as possible explain the central action of some well-known antihypertensive agents by a common mechanism of action. At present, different groups of antihypertensive agents are known and used in the treatment of arterial hypertension of varied origin. It is generally assumed that most categories of these drugs reduce peripheral sympathetic tone so that a decrease in arterial pressure results, brought about by either a reduction in peripheral vascular resistance or a diminished cardiac output.

A primarily peripheral effect leading to a decrease in sympathetic tone has been assumed to exist with a number of well known antihypertensive agents, e.g. the ganglion blocking drugs; guanethidine, cyclazenin, guanoxan, reserpine, α-methyldopa.

The hypotensive action of ganglion-blocking agents is almost certainly peripheral, although some of these drugs may influence the central nervous system (Freis, 1959).

Guanethidine and related compounds act at the nerve ending. The changes in noradrenaline storage and release induced by these compounds only occur in the peripheral nervous system and not in the cns (Boura & Green, 1965).

The influence of reserpine on the peripheral sympathetic nervous system is well known; the granular stores of noradrenaline are disrupted leading to its enyzmic degradation and finally to its depletion. The diminished amount of transmitter substance is believed to impair the function of the peripheral sympathetic system, thus causing a fall in blood pressure. However, the extragranular stores of noradrenaline are hardly affected by reserpine, so that this part of the transmitter stores remains available.

This explanation for the hypotensive action of reserpine has been subject to debate. The opponents of this hypothesis maintain that the incomplete loss of noradrenaline does not account for sufficient loss of peripheral adrenergic function and therefore it seems an unsuitable explanation for the drug's hypotensive action (Alper, Flacke & Kraijer, 1963).

The action of α-methyldopa, a widely used drug in the therapy of hypertension, also remains difficult to explain. The original hypothesis, i.e. the inhibition of noradrenaline biosynthesis as a result of the blockade of dopa-decarboxylase, cannot explain the antihypertensive action satisfactorily (Muscholl, 1966). The subsequently developed hypothesis of the "false transmitter substance" (Day & Rand, 1963) has also been subject to severe criticism (Henning, 1969). There is no doubt about the conversion of α-methyldopa to α-methylnoradrenaline (via α-methyldopamine) in peripheral organs. However, the existence of a causal relation between metabolic conversion in the periphery and the pharmacological effect has been strongly doubted (Henning, 1969). For these reasons alternative explanations for the hypotensive or, more general,

sympathetic system depressant actions of α-methyldopa and reserpine have been the subject of several investigations.

THE CONCEPT OF CENTRAL α-ADRENOCEPTORS

Clonidine

Clonidine [Catapresan, 2-(2,6-dichlorophenylamino)-2-imidazoline hydrochloride], a derivative of imidazoline, was originally designed to be an α-adrenoceptor stimulating agent. The original aim of its development was to find a new decongestive agent for the local treatment of rhinitis or conjunctivitis. However, soon after its introduction, its potent blood pressure lowering activity was discovered. Intravenously administered clonidine initially causes a transient rise in arterial pressure that is followed by a prolonged hypotensive action. The initial hypertensive effect is the expression of peripheral α-adrenoceptor stimulating properties of the drug (Hoefke & Kobinger, 1966). Several authors have presented evidence that the subsequent decrease in pressure is due primarily to a *central* action that causes a reduced activity of the peripheral sympathetic nervous system (Schmitt, Schmitt & others, 1967; Sattler & van Zwieten, 1967; Kobinger, 1967; Kobinger & Oda, 1969; Klupp, Knappen & others, 1970).

This effect was observed in various species. Clonidine was administered either into the cisterna cerebellomedullaris or into a vertebral artery in such low doses that any peripheral action could be excluded. Since these low doses invariably caused a decrease in blood pressure and other features of decreased sympathetic activity, a primary influence on the cns had to be assumed as the origin of the peripheral changes. Clonidine possesses several direct peripheral effects (Nayler, Rosenbaum & others, 1966; Nayler, Price & others, 1968) but it seems hardly possible that these effects contribute significantly to the drug's blood pressure lowering action. Evidence for a significant influence of clonidine on biogenic amines in the brain has not been forthcoming. The central effect of clonidine could be abolished by some α-adrenoceptor blocking agents like yohimbine and piperoxan, although phentolamine, which penetrates less readily into the cns, remained ineffective (Schmitt, 1971; Schmitt, Schmitt & Fénard, 1971). The paradoxical situation thus arises that the action of a blood pressure lowering drug is counteracted by that of an α-adrenoceptor blocking agent that also has hypotensive properties. This observation led Schmitt & others (1971) to postulate that some structure in that part of the brain reached by clonidine (administered via a central route) contains α-adrenoceptors that can be activated by clonidine and by other drugs with central hypotensive properties. It had to be further postulated that the central α-adrenoceptors are connected to an inhibitory neuron (possibly the bulbo-spinal sympathetic neuron), the activation of which brings about the depression of the peripheral sympathetic nervous system and thus a fall in blood pressure.

The anatomical localization of the central α-adrenoceptors remains to be elucidated. According to Schmitt (1971) the following pathway might be involved: the baroreceptor fibres initiating in the carotid sinus have a synapse in the nucleus tractus solitarii (Seller & Illert, 1969) which has been demonstrated to contain noradrenergic fibres and the subsequent second neuron would be noradrenergic (Dahlström & Fuxe, 1964, 1965). Accordingly, the α-adrenoceptors could be situated on the membrane of the third neuron.

Thus, stimulation of these receptors with centrally acting sympathomimetic agents could influence the bulbo-spinal sympathetic neuron and accordingly depress peri-

pheral sympathetic activity. Such a stimulation of the receptors with drugs like clonidine would exert an effect similar to that of stimulation of the carotid nerve which is known to provoke decreased peripheral sympathetic activity and a fall in blood pressure. This speculation seems attractive but as yet experimental evidence for its support is lacking (Struyker Boudier & van Rossum, 1972).

According to the aforementioned hypothesis, clonidine would indeed be an α-adrenoceptor stimulating agent with predominantly central actions. The direct peripheral α-adrenoceptor stimulant action of this drug is transient and seems far less important than its central properties. So far, several sympathomimetic agents with some kind of organ specificity have been developed. In recent years, agents that predominantly influence either the heart, blood vessels or bronchi have become available so that the existence of a sympathomimetic agent that mainly affects central adrenergic properties is conceivable. Several imidazoline derivatives related to clonidine are also known to possess hypotensive activity (Klupp; Kobinger, personal communications).

One compound that is not an imidazoline derivative, 2-(2,6-xylidino)-5,6-dihydro-4H-1,3-thiazine (BAY, 1470), has been shown to possess central hypotensive action and it seems possible that its effect, which can be abolished by α-adrenoceptor blocking agents, is also due to a stimulation of central α-adrenoceptors (Heise, Kroneberg & Schlossmann, 1971).

Apart from the influence on peripheral sympathetic activity mediated via the α-adrenoceptors by clonidine as just discussed, the drug also brings about a significant effect on vagal activity (Kobinger & Walland, 1971). According to these authors, the effect is also due to the stimulation of α-adrenoceptors in the cns. It might be possible that virtually the same mechanism is involved.

Several other primarily central effects of clonidine, like sedation (Holman, Shillito & Vogt, 1971), inhibition of water intake (Le Douarec, Schmitt & Lucet, 1971), central hyperglycaemia (Bock & van Zwieten, 1971) have been described and they could all be blocked by α-adrenoceptor blocking agents.

Since the present review is limited to circulatory aspects of the problem the possible explanation of these phenomena will not be discussed, but these observations point in the same direction.

The nature of the central α-adrenoceptors is probably different from peripheral α-adrenoceptors but the unknown central localization makes further characterization difficult. The activity of α-adrenoceptor stimulating and blocking agents on the central receptors is certainly different from that on those in the periphery. However, differences in distribution in the cns may play a part as well so that a direct comparison of various drugs is hardly possible (compare the central action of L-dopa, see later).

ADDITIONAL COMPOUNDS THAT INFLUENCE CENTRAL α-ADRENOCEPTORS

Noradrenaline and indirectly acting sympathomimetic amines

If clonidine, assumed to be a central α-adrenoceptor stimulating agent exerts its influence on the periphery via central α-adrenoceptors, other sympathomimetic agents that reach these receptors and stimulate them should have similar properties. Classical catecholamines like noradrenaline do not penetrate the blood brain barrier when given intravenously but this problem can be avoided by intracisternal injection. Noradrenaline administered via this route indeed causes a fall in blood pressure and bradycardia (Kaneko, McCubbin & Page 1960; McCubbin, Kaneko & Page, 1960; Nashold,

Mannarino & Wunderlich, 1962; Share & Melville, 1963; Smookler, Severs & others, 1966).

Several authors have interpreted this effect as the expression of reduced local perfusion in the cns, due to the vasoconstrictor action of the administered amines. However, noradrenaline infused into a vertebral artery in sufficiently high doses does not reduce blood pressure although by this route it will certainly give rise to constriction of brain vessels (Hoyer & van Zwieten, 1972).

It seems much more likely that stimulation of the central α-adrenoceptors causes the hypotensive effect. Additional evidence for this was obtained when the central hypotensive activity of amphetamine and related drugs was demonstrated (Hoyer & van Zwieten, 1971, 1972).

Amphetamine, infused into a cat vertebral artery caused a significant and dose-dependent fall in blood pressure, whereas administration into the peripheral venous system evoked a considerable pressor effect. The central hypotensive action could be blocked by α-adrenoceptor blocking agents like yohimbine or piperoxan. This blockade occurred after intravenous or intravertebral injection of the α-adrenoceptor blocking drugs. This observation suggests that the concept of central α-adrenoceptors might also be applied to the central hypotensive action of amphetamine. Moreover, the effect could be abolished by haloperidol pretreatment which is known to block central adrenoceptors (Andén, Corrodi & others, 1970). The effect of amphetamine did not appear in reserpinized cats suggesting that it is the liberation of noradrenaline in the cns by amphetamine that causes the decrease in blood pressure.

Effects similar to those observed after infusion of amphetamine into the vertebral artery were seen when ephedrine, phentermine, chlorphentermine or fenfluramine were administered via the same route. These results probably explain the hypotension often observed in patients after oral ingestion of chlorphentermine and other anorexic agents.

α-Methyldopa, L-dopa and reserpine

The clinically important hypotensive action of α-methyldopa remains difficult to explain by the inhibition of dopa-decarboxylase or by the false-transmitter hypothesis. The search for a different explanation led to the discovery of the drug's central hypotensive action (Henning & van Zwieten, 1968; Henning, 1969; Kobinger & Oda, 1969; Ingenito, Barrett & Procita, 1970; Tauberger, Kuhn & Brus, 1970; Rubenson, 1971; Heise & Kroneberg, 1972). α-Methyldopa, an amino-acid, penetrates the blood brain barrier and in the brain it is converted into α-methyldopamine and finally, α-methylnoradrenaline.

α-Methylnoradrenaline, an α-adrenoceptor stimulating agent will be able to act on central α-adrenoceptors and thus decrease blood pressure. Heise & Kroneberg (1972) were able to block the central hypotensive action of α-methylnoradrenaline infused into brain ventricles of the cat by preinfusion with yohimbine or phentolamine. This experiment supports the concept that the central hypotensive action of α-methylnoradrenaline and therefore that of α-methyldopa will be mediated via central α-adrenoceptors. Although it cannot be proved that the central component in the depressor action of α-methyldopa is the only explanation for its clinical effect, the drug's central effect certainly makes an important contribution to its final action.

L-Dopa shows central hypotensive properties that can be inhibited by α-adrenoceptor blocking agents (Schmitt, 1971) but not by pimozide, a specific blocker of

dopamine receptors. It might be possible that dopamine formed in the cns after L-dopa administration will stimulate the postulated central α-adrenoceptors. However, Andén, Engel & Rubenson (1972) recently demonstrated that L-dopa elicits central α-adrenoceptor stimulation by release of endogenous noradrenaline, presumably by displacement of a noradrenaline store with dopamine.

Reserpine has been shown to possess central hypotensive properties (van Zwieten, Bernheimer & Hornykiewicz, 1966). The mechanism of this effect has not yet been elucidated, but it might be speculated that the endogenous noradrenaline liberated in the cns would stimulate the central α-adrenoceptors and thus reduce peripheral sympathetic activity and accordingly decrease blood pressure. In chronically reserpinized animals, Iggo & Vogt (1960) did not observe any reduction of activity in the cervical sympathetic neurons but this part of the peripheral adrenergic system is hardly involved in the regulation of blood pressure. Moreover, the depleting action of reserpine is unspecific so that it will be difficult to interpret these findings.

To summarize, reserpine certainly possesses central hypotensive properties that might be explained tentatively via the concept of the central α-adrenoceptors but in the overall depressor action of reserpine peripheral processes are probably involved as well, so that a particularly complex situation results.

MAO-inhibitors that are known to decrease blood pressure might also give rise to the stimulation of central α-adrenoceptors via a decreased breakdown of endogenous noradrenaline. Experimental evidence for this hypothesis is so far lacking (Schmitt & Schmitt, 1964; Bose, Bhaghat & Agarwal, 1967; Yamori, de Jong & others, 1972).

Schmitt & others (1971) demonstrated that the central hypotensive action of imipramine which is known to inhibit the re-uptake of noradrenaline in the cns could be blocked by α-adrenoceptor blocking agents, suggesting that central α-adrenoceptors might also be involved.

CONCLUSIONS

In the course of the past five years it has become clear that at least some of the clinically important antihypertensive drugs exert their influence via a primarily central mechanism of action. This mechanism of action requires the excitation of α-adrenoceptors located in the cns and connected to an inhibitory neuron, possibly the bulbospinal sympathetic neuron. Excitation of these receptors brings about an enhanced inhibitory activity and thus a depression of peripheral sympathetic action, resulting in a fall in blood pressure. The most effective compound in this connection is clonidine, which possesses a high central α-adrenoceptor stimulant activity.

α-Methyldopa readily penetrates the blood brain barrier. In the brain it is converted into α-methylnoradrenaline, a sympathomimetic agent that will be able to stimulate the central α-adrenoceptors and accordingly decreases peripheral sympathetic activity and blood pressure.

Reserpine, of which several central actions are well-known, mobilizes endogenous catecholamines in the brain and may thus induce excitation of the central α-adrenoceptors and hence reduce blood pressure. Moreover, the blood pressure lowering side effects of anorexic agents like amphetamine, and that of L-dopa (anti-Parkinson agent) may be explained by the concept of the central α-adrenoceptors.

Concomitantly, some kind of common central mechanism of action seems to be involved for clonidine, α-methyldopa and possibly reserpine. The anatomical localiza-

tion of the α-adrenoceptors in the cns remains unresolved but roughly, the rhombencephalon seems the most likely region. More, precisely, speculations point to the area of the nucleus tractus solitarii but experimental evidence for this view is lacking. Much additional experimental work is required to elucidate the site.

The unexpected situation that certain compounds with central α-adrenoceptor stimulant activity decrease blood pressure might also throw a different light on the pathogenesis of essential hypertension. The origin of this disease is believed to be located in the central nervous system. In this connection the findings of Yamori, Lovenberg & Sjoerdsma (1970) are of considerable interest. These authors examined the noradrenaline content of the brain of rats that developed a genetically induced spontaneous hypertension. The endogenous noradrenaline content of the brain of such animals was significantly lower than that of normal rats. Possibly, the diminished α-adrenoceptor stimulation might explain the development of spontaneous hypertension. It is certainly not possible to extrapolate these findings to clinically occurring essential hypertension but it might be worthwhile to investigate, post mortem, the endogenous noradrenaline brain contents of patients who had suffered from essential hypertension.

In the search for new antihypertensive agents, compounds with central α-adrenoceptor stimulant properties might be worthwhile investigating.

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