PHARMACOLOGY OF CENTRALLY ACTING HYPOTENSIVE DRUGS

P.A. van ZWIETEN

Department of Pharmacy, Division of Pharmacotherapy, University of Amsterdam, Plantage Muidergracht 24, Amsterdam, The Netherlands

- 1 A survey is given of the various aspects of centrally acting hypotensive drugs. The majority of centrally acting hypotensive agents act by way of central α -adrenoceptors, probably located in the pontomedullary region of the brain. These central receptors are stimulated by clonidine, guanfacine and various related compounds, and also by α -methylnoradrenaline, generated *in vivo* upon biotransformation of α -methyldopa within the brain. The stimulation of the α -adrenoceptors induces a decrease in peripheral sympathetic tone and thus a fall in arterial blood pressure and bradycardia.
- 2 The possibility that presynaptic α -adrenoceptors in the brain are involved in the central hypotensive action of clonidine, guanfacine and related compounds is discussed. Also, the possible involvement of central histaminergic and cholinergic receptors in central hypotensive effects is reviewed.
- 3 Various experimental compounds with a central hypotensive effect different from that of clonidine and related drugs are mentioned.
- 4 Finally, it is pointed out that the hypotensive effects of various β -sympatholytic drugs and of prazosin are probably not of central origin.

Introduction

UNTIL the 1960s all antihypertensive drugs in use owed their therapeutic activity to peripheral mechanisms. This statement holds for the ganglion blocking agents, adrenergic blocking agents (guanethidine and related drugs), peripheral α -sympatholytic drugs, diuretics and direct vasodilator drugs (hydralazine and related compounds).

Reserpine has a strong peripheral effect on the postganglionic sympathetic neurones which satisfactorily explains its blood pressure lowering properties. Nevertheless, under certain circumstances reserpine can exert central hypotensive activity in animal studies. A central mechanism is probably not of particular importance when the drug is used to treat hypertension in humans.

It was not until the late 1960s that the concept of a predominantly *central* mechanism of action for certain antihypertensive drugs could be supported by experimental evidence. This evidence was provided by the detailed pharmacological analysis of the action of clonidine (Catapresan®, Catapres®), an imidazolidine derivative designed to be used as a nasal decongestant. However, the potent blood pressure lowering properties were soon discovered and the drug was introduced for the treatment of hypertension. A predominantly *central* action of this drug could be demonstrated. A central mechanism of

action also seemed probable for several clonidine analogues, for α -methyldopa (which is converted *in vivo* into α -methylnoradrenaline, the active compound), for guanfacine (Estulic®), for a variety of experimental compounds, like xylazine (Bay 1470) or compound 44.549, and even for structures quite remote from that of clonidine, like B-HT 933 (Figure 1).

The pharmacology of the various centrally acting antihypertensive drugs is the subject of the present review. Some remarks will also be made concerning the structure-activity relationship (SAR) of clonidine and related drugs.

Clonidine and related imidazolidines: the central α -adrenoceptor

Clonidine was originally designed as a decongestant drug, chemically related to naphazoline, xylometazoline and similar drugs. Its potent antihypertensive activity was discovered accidentally. Its effect on the circulation has been the subject of various extensive reviews (Schmitt, 1971; Kobinger, 1973; van Zwieten, 1973; 1975a; Kobinger, 1978).

The influence of clonidine on arterial blood pressure and heart rate may be summarized as follows: clonidine causes an initial but transient

Figure 1 Chemical structures of a few prototypes of centrally acting hypotensive agents. (a), clonidine; (b) guanfacine (BS 100-141); (c), xylazine (Bay 1470); (d), B-HT 933.

pressor effect, which is explained by a direct activation of peripheral α -adrenoceptors. This effect is not surprising, in view of the similarity to other imidazoline compounds. After the vasoconstriction a more marked and longer lasting hypotensive effect develops, which is due to a *central* mechanism. This central mechanism has been confirmed by a series of animal experiments in which the drug has been applied to brain structures by means of various techniques, such as injections into the cisterna cerebellomedullaris, the vertebral artery, or the cerebral ventricles. After administration by way of all of these routes the drug proved more active than after intravenous injection. Also, a powerful hypotensive effect has been recorded after its stereotaxic injection into various parts of the hypothalamic region (Struycker Boudier & van Rossum, 1972).

The initial, peripheral pressor effect of clonidine is usually accompanied by moderate reflex bradycardia. The central hypotensive action is also accompanied by modest or pronounced bradycardia, its intensity being dependent on the animal species and the route of the drug's administration. Like the hypotension, bradycardia is also of central origin. Moreover, clonidine and related drugs have been demonstrated to enhance reflex bradycardia via an enhancement of vagal reflexes, which is also initiated by a central mechanism (Kobinger & Walland, 1971; 1972a; 1972b; 1973).

The precise localization of the central hypotensive and bradycardic mechanisms has not yet been elucidated, in spite of a considerable effort in neuropharmacological research. It seems likely, however, that the pontomedullary area in the brain stem is the most important target for the centrally induced hypotensive and bradycardic effects, although a few authors consider the hypothalamic region to be the main site of action (Struycker Boudier & van Rossum, 1972). Within the pontomedullary region, the nucleus tractus solitarii

has been proposed as the main site of action (Schmitt, 1971). This assumption is not supported by experiments in which clonidine is directly injected into the area of the nucleus tractus solitarii. Clonidine thus administered displayed but a weak hypotensive activity (de Jong, 1974; de Jong & Nijkamp, 1976). Thus far, a more precise localization than the pontomedullary region as the site of action of clonidine and related drugs cannot be indicated.

Quantitative correlation studies of a series of clonidine derivatives have yielded information on the properties of the central α -adrenoceptor involved in the hypotensive effect of these drugs. For a series of clonidine-related imidazolidines quantitative structure-activity relationship studies have permitted equations to be derived which describe the potency of the various drugs as a function of their steric and electronic properties (Timmermans & van Zwieten, 1977a). By means of careful determination of the drug concentrations in the pontomedullary region, assumed to be the receptor site, kinetic and distribution phenomena can be elucidated (Timmermans, Brands & van Zwieten, 1977). It goes without saying that lipophilicity is also a very important factor concerning the central hypotensive activity: drugs presumed to act within the central nervous system must be able to penetrate the brain to a significant degree before any pharmacological effect can occur. Apart from the lipophilicity certain steric and electronic properties of the drug molecules are required. The extrapolation of these properties has led to a hypothetical model of the central α -adrenoceptor (Timmermans & van Zwieten, 1977a), similar to the model put forward by Belleau (1964) for peripheral α -adrenoceptors.

Pre- and postsynaptic activity of clonidine

In recent years, the concept of presynaptic α -adrenoceptors being involved in adrenergic

neurotransmission has attracted a great deal of interest (review by Starke & Endo, 1976). Accordingly, the α -adrenoceptor-stimulating drugs with a peripheral action can be divided in compounds with a predominantly postsynaptic activity (phenylephrine), a mainly presynaptic effect (clonidine) or a mixed pre- and postsynaptic potency (noradrenaline) (Starke & Montel, 1973; Starke & Endo, 1976).

Similarly, peripherally acting α -adrenoceptor-blocking agents can be classified according to this principle: The peripherally acting compound prazosin is an almost pure postsynaptic α -adrenoceptor blocker; yohimbine and piperoxan display predominantly presynaptic activities, whereas phentolamine and phenoxybenzamine are both pre- and postsynaptic blocking agents. These findings, relevant to the peripheral sympathetic system, have been extrapolated, although speculatively, to the adrenergic receptors of the central nervous system involved in blood pressure regulation and in the initiation of central hypotensive effects of drugs like clonidine (Starke & Montel, 1973). Andén, Grabowska & Strömbom (1976) have demonstrated that clonidine reduces noradrenaline turnover in the brain by way of negative feedback in central noradrenergic neurones. Moreover, Starke & Montel (1976) have shown that clonidine diminishes the release of noradrenaline, induced in isolated cerebral cortex slices of rats by electrical field stimulation.

The findings by Andén *et al.* (1976) and by Starke & Montel (1976) argue in favour of a presynaptic action of clonidine in the brain. However, Haeusler (1974) and Kobinger & Pichler (1974; 1976) have shown that the central hypotensive and bradycardic effects of clonidine are not diminished after a partial destruction of the adrenergic system by 6-hydroxydopamine or reserpine. These findings would rather suggest a postsynaptic effect of clonidine in the brain, as a mainly presynaptic mechanism would require the integrity of the endogenous transmitter system. In this connection the experiments by Dollery & Reid (1975) are at variance with those by the aforementioned investigators.

A final answer to the question of whether the central hypotensive effect of clonidine and related drugs is due to a post- or a presynaptic mechanism cannot yet be given. Both mechanisms can be supported by experimental findings, but a conclusive decision cannot be drawn at the present stage. Psychologically, a hypotensive effect due to α -receptor stimulation, involved in the postsynaptic mechanism, seems more difficult to accept than the presynaptically induced inhibition of noradrenaline release in the brain. However, in the author's personal view a postsynaptic mechanism is supported by strong experimental evidence.

Other compounds, different from clonidine, with a central hypotensive action mediated by way of central α -adrenoceptors

α -methyldopa is one of the best known examples of a drug which displays central antihypertensive activity by way of the excitation of central α -adrenoceptors. However, the α -adrenoceptors are excited by α -methylnoradrenaline, the biotransformation product of α -methyldopa. The subject has been reviewed by Henning (1969), van Zwieten (1975a) and by Kobinger (1978). The older hypotheses submitted to explain the antihypertensive action of α -methyldopa, like the inhibition of dopa-decarboxylase and the 'false transmitter' concept can no longer be reconciled satisfactorily with the various experimental and clinical findings.

Little doubt remains concerning the importance of the central action of α -methyldopa, although it is difficult to rule out peripheral mechanisms completely.

The following experimental findings are the basis of the hypothesis concerning the central hypotensive effect of α -methyldopa:

(1) The drug has to be converted within the brain into α -methylnoradrenaline (Henning, 1969).

(2) An infusion of a low dose of α -methyldopa into the vertebral artery of chloralose-anaesthetized cats causes a much more pronounced hypotensive effect than the same dose applied intravenously; the effect can be blocked by α -sympatholytic drugs like yohimbine (Henning & van Zwieten, 1968; van Zwieten, 1975a).

(3) Cerebral ventricular perfusion with an α -methylnoradrenaline solution in cats causes a pronounced hypotensive effect which can be blocked by α -sympatholytic drugs (Heise & Kroneberg, 1972). So far it has not been possible to study the mechanism of the hypotensive effect of α -methyldopa in man.

A variety of compounds related to clonidine, although not imidazoline derivatives, are known to display central hypotensive activity, mediated by the excitation of the same central α -adrenoceptors as those stimulated by clonidine. From the numerous compounds which have become available we only cite the following examples: compound 44.549 (Boyajy, Manning, McIntosh, Schaefer, Herzig, Schaaf & Trapold, 1972; van Zwieten, 1975b; Timmermans & van Zwieten, 1978); xylazine (Bay 1470) (Heise & Kroneberg, 1971); lofexidine (Sjoerdsma, 1977); guanfacine (Scholtysik, Lauener, Eichenberger, Saltzmann, Müller-Schweinitzer & Waite, 1975); and most recently B-HT 933, an azepine derivative with a structure quite remote from clonidine (Kobinger & Pichler, 1977). Kobinger & Pichler (1977) have demonstrated that this compound, in spite of its

Figure 2 Central hypotensive action of clonidine 1 $\mu\text{g/kg}$ (●) and guanfacine 30 $\mu\text{g/kg}$ (■) in chloralose-anesthetized cats. The drugs were infused in low doses into the left thoracic vertebral artery according to a technique previously described in detail (Henning & van Zwieten, 1968). Note the instant and pronounced decrease in mean arterial blood pressure (MAP), which is prevented after pretreatment with piperoxan 100 $\mu\text{g/kg}$ by the same route. The same doses of clonidine and guanfacine given intravenously did not significantly reduce blood pressure. Note the more prolonged action of guanfacine when compared with that of clonidine. All experimental points represent mean values $\pm$ s.e. mean for at least six different cats; each cat only received one dose of the drug under study.

azepine structure, can excite central α -adrenoceptors, thus displaying a central hypotensive effect.

From the various compounds mentioned above, only clonidine and guanfacine have been introduced into clinical medicine; these are available as Catapresan®, Catapres® (clonidine) and Estulic® (guanfacine), respectively. The mechanism of the hypotensive action of both drugs is probably the same. Guanfacine, however, acts for longer periods than clonidine, as demonstrated by Figure 2, in which the central hypotensive effects of both compounds, after their injection into the vertebral artery of cats, have been compared. A comparison of the clinical properties of clonidine and guanfacine is discussed by Distler (1980).

Drugs which block central α -adrenoceptors and thus antagonize the hypotensive effect of clonidine and related drugs.

The concept of central α -adrenoceptors involved in the central hypotensive action of clonidine has been based on the antagonism of the depressor effect of clonidine by α -sympatholytic agents. After systemic administration tolazoline (Graubner & Wolff, 1966) and also piperoxan and yohimbine (Schmitt, Schmitt & Fénard, 1971; 1973) can reduce the hypotensive effect of clonidine; the less lipophilic α -adrenoceptor-blocking drug phentolamine is also effective when administered intracisternally in order to avoid the blood-brain barrier (Kobinger & Walland, 1971). A diminution of the central hypotensive action of a variety of derivatives of clonidine after pretreatment with piperoxan or yohimbine has recently been demonstrated (Timmermans & van Zwieten, 1977b; c). Similarly, the depressor effect of α -methyldopa (van Zwieten, 1975a), that of α -methylnoradrenaline perfused in the cat's cerebral ventricles (Heise & Kroneberg, 1972), of guanfacine (van Zwieten, this paper) and of compound 44.549 (van Zwieten, 1975b) can be diminished by piperoxan, yohimbine or other α -adrenoceptor-blocking agents.

Accordingly, it can be concluded that compounds with established peripheral α -sympatholytic activity can reduce the central hypotensive action of clonidine, α -methyldopa, guanfacine and a variety of experimental substances. However, the α -sympatholytic drugs must have sufficient access to the central α -adrenoceptors. When applied systemically, that is through the blood stream, only drugs with sufficient lipophilicity, like yohimbine and piperoxan, can penetrate into brain tissues and thus reach the α -adrenoceptors; drugs like phentolamine, which hardly penetrate into the brain, are only effective antagonists when injected intracisternally in order to avoid the blood-brain barrier (Kobinger & Walland, 1971).

Apart from known α -sympatholytic agents, various other compounds with α -sympatholytic properties can block central α -adrenoceptors and thus diminish the hypotensive effect of clonidine and similarly acting drugs. The central hypotensive effect of clonidine in man was diminished by desipramine, a tricyclic antidepressant (Briant & Reid, 1973). This finding has been confirmed in animal experiments. Extensive animal studies have shown that the central hypotensive action of clonidine is diminished by tricyclic antidepressants (imipramine, etc) and phenothiazine-neuroleptics, but not by benzodiazepine tranquilizers or by neuroleptics of the butyrophenone (haloperidol) or diphenylbutyl type (pimozide). The antagonism is explained by a competitive interference at the level of the central α -

adrenoceptor between clonidine and related drugs (the agonists) and the various psychotropic drugs with α -adrenoceptor-blocking activity. An inhibition of noradrenaline re-uptake by the psychotropic drugs can be ruled out as an explanation of the antagonism of the effect of clonidine. The subject has been discussed in the following papers (van Zwieten, 1975c; 1976; van Spanning & van Zwieten, 1973; 1975) and reviewed by the author (van Zwieten 1977b; van Zwieten & Timmermans, 1980).

Apart from the aforementioned psychoactive drugs with α -adrenoceptor-blocking properties, the central hypotensive action of clonidine is also diminished by prazosin, a new antihypertensive agent which owes its therapeutic activity to the blockade of postsynaptic α -adrenoceptors in the periphery. Although the drug is lipophilic, it does not display any central hypotensive activity (Timmermans, Lam & van Zwieten, 1979). However, when injected in appropriate dosage (3 μ g/kg) into the left vertebral artery of anaesthetized cats, the effect of clonidine, subsequently administered by the same route, is significantly diminished. This antagonism, which is dose-dependent, also occurs at the level of central α -adrenoceptors and is explained adequately by the α -adrenoceptor-blocking property of prazosin (Timmermans *et al.*, 1979).

It is not known whether the antagonism of the central hypotensive effect of clonidine by prazosin demonstrated in special conditions in cats also occurs in hypertensive patients. As the combination of both drugs is not rational, it would seem preferable to avoid their simultaneous application.

The concept of α -adrenoceptors satisfactorily explains the antagonism between clonidine and related drugs and a variety of lipophilic compounds with α -adrenoceptor-blocking activity. In some cases, especially with respect to the antagonism between clonidine and various psychotropic drugs, this example of drug interaction may be of practical importance.

Central hypotensive activity which is not mediated by way of α -adrenoceptors

Apart from the aforementioned antihypertensive drugs which owe their therapeutic effect to an interference with central α -adrenoceptors, several experimental compounds have been demonstrated to lower arterial blood pressure by other mechanisms. The majority of these compounds has not achieved any therapeutic relevance. For this reason I shall limit myself to a brief enumeration of the compounds in question and the mechanisms proposed for the explanation of their hypotensive potency.

Although the interference of clonidine with central

α -adrenoceptors seems firmly established, Karppanen, Paakkari, Paakari, Huotari & Orma (1976) have speculated about the involvement of H_2 -histaminergic receptors in the hypotensive effect of clonidine. This speculation is founded on the diminution of the hypotensive effect of clonidine by metiamide, a potent H_2 -antihistaminic. It might be extrapolated to the hypothetical involvement of H_2 -histaminergic receptors in the central regulation of arterial blood pressure.

So far, the adrenergic system and its importance for the regulation of blood pressure have been in the focus of interest. Nevertheless, it is possible that cholinergic mechanisms may also be important. This is being studied at present by Porsius and his collaborators and by Laubie, Delbarre, Bogaievsky, Bogaievski, Tsoucharis-kupfer, Son, Schmitt & Schmitt (1977). By means of a detailed study on the structure-activity relationships in arecaidine derivatives and related compounds, the former authors have been able to demonstrate that both muscarinic and nicotinic cholinergic receptors play a part in the mediation of the central hypotensive effect of arecaidine esters. By way of speculation, it might be presumed that interference with cholinergic receptors within the brain may be of importance to the hypotensive effect of drugs and even with respect to the central regulation of arterial blood pressure. Furthermore, it may be speculated that the development of antihypertensive drugs with a central *cholinergic* mechanism can be realized (Porsius & van Zwieten, 1978; Porsius, Mutschler & van Zwieten, 1978).

The discovery of the central hypotensive effect of methysergide (Antonaccio & Taylor, 1977) has given rise to speculations concerning a possible role for 5-hydroxytryptamine receptors as mediators of central hypotensive activity of drugs. This matter has not been studied in detail and, so far, it does not seem very likely that serotonergic receptors in the brain are of vital importance in the central regulation of blood pressure, although this possibility cannot be excluded.

Finally, a compound should be mentioned for which a central hypotensive activity has been established, although the elucidation of the central mechanism remains. R28935, an experimental antihypertensive agent derived from benzodioxan, owes its blood pressure lowering property to a central mechanism (Wellens, de Wilde, van Bogart, van Bogaert, Wouters, Reneman & Janssen, 1975; van Zwieten, 1975d; Finch, 1975). However, the mechanism involved is not known. No clue has been obtained with respect to the character of possible central receptors which may be involved. Andén *et al.* (1976) have speculated that the central hypotensive activity of R28935 might be explained by its

inhibition of postsynaptic α -adrenoceptors in the brain. Conclusive evidence for this view is lacking.

The hypotensive effect of β -adrenoceptor antagonist drugs is still incompletely understood. One of the possible mechanisms discussed is an interference of these drugs with central β -adrenoceptors. The injection of propranolol into the cisterna or the cerebral ventricles causes an antihypertensive effect (Myers, Lewis, Reid & Dollery, 1975), which may be of central origin. However, in recent experiments van Zwieten & Timmermans (1979) have demonstrated that the hypotensive effect of atenolol and metoprolol is unlikely to be of central origin. Clinical experiments by Dollery, Reid, Dean & Maling (1979) have suggested that during treatment with propranolol the sympathetic tone does not diminish, although this would be expected to occur after administration of a drug with a centrally acting hypotensive effect. In view of the evidence obtained so far, it seems unjustified to postulate the existence of a central mechanism for the blood pressure lowering effect of β -sympatholytic drugs.

Prazosin, a relatively specific postsynaptic α -adrenoceptor blocking agent with clinically useful antihypertensive activity is rather lipophilic and it penetrates into the brain. Theoretically, this compound might possess central hypotensive activity. Recent experiments, in which prazosin was infused into the cat's vertebral artery did not reveal any central hypotensive activity whatsoever (van Zwieten & Timmermans, 1979b). A central mechanism is very unlikely; the drug's hypotensive activity can readily

be explained by the peripheral postsynaptic α -adrenoceptor blockade.

Conclusions

The intensive pharmacological research effort of the past decade has led to a reasonable understanding of the mode of action of centrally active hypotensive drugs in acute animal experiments. The extrapolation of this view to the mode of action of these drugs during their prolonged application in the treatment of hypertension in man, however, remains difficult and uncertain. Incidental experiments in tetraplegic subjects would suggest that at least the acute mechanism of clonidine's hypotensive effect in man has a similar basis to that in experimental animals.

Clonidine and α -methyldopa are generally recognized as the prototypes of centrally acting hypotensive drugs, which are used in the treatment of hypertension in man. Recently, guanfacine, a guanidine derivative probably acting similarly to clonidine, has been introduced into therapy.

The quantitative structure-activity relationship studies on clonidine and related compounds have led to a reasonable understanding of the interference of this type of compounds with the central α -adrenoceptors which are presumed to be the initial target of these drugs. Furthermore, the development of centrally acting antihypertensive drugs has considerably improved our understanding of the central regulation of blood pressure.

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