The Hypotensive Activity and Side Effects of Methyldopa, Clonidine, and Guanfacine

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SUMMARY Clonidine (Catapres, Catapresan), guanfacine (Estulic), and methyldopa (Aldomet) are the prototypes of centrally acting antihypertensive drugs. Clonidine and guanfacine are lipophilic drugs that readily penetrate into the brain, where they stimulate a-adrenergic receptors in the pontomedullary region. The stimulation of these central a-adrenergic receptors has been shown to activate an inhibiting neuron, which causes a reduction of peripheral sympathetic tone and a subsequent fall in arterial blood pressure and heart rate. Both a centrally initiated reduction of vagus reflex activity and the activation of presynaptic \( \alpha \)-adrenergic blocking agents in the heart may contribute to the bradycardia. Studies indicate that methyldopa also penetrates into the brain, where it is converted into a-methylnorepinephrine. This amine may stimulate the same central a-adrenergic receptors as those activated by clonidine, which will result in a hypotensive effect. Possibly, a-methyldopamine might also play a role. Accordingly, the modes of action of clonidine and a-methyldopa probably are very similar at a basic level. The central adrenergic receptors probably are located postsynaptically. Their receptor demand corresponds more closely to that of the \( \alpha_2 \)-subtype. Central a\(_2\)-adrenergic receptors might possibly play a part in the modulation of vagally induced baroreflex bradycardia. A discussion on the pharmacological basis of the side effects of the centrally acting antihypertensives has been limited to those adverse reactions that are somehow related to a-adrenergic receptors. Sedation, a common side effect, appears to be mediated by central \( \alpha_2 \)-adrenergic receptors, at least in animal models. The withdrawal syndrome, observed on abrupt cessation of treatment with clonidine, apparently also involves a-adrenergic receptors; however, why methyldopa does not precipitate a withdrawal phenomenon in the same animal model where clonidine was studied cannot be explained at present.

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KEY WORDS • methyldopa • central hypotensive activity • clonidine • guanfacine • a-adrenergic receptors

The central nervous system, in particular structures in the brain stem, is known to play a major part in the regulation of the peripheral circulation. For this reason it can be supposed that drugs could interfere with blood pressure regulation at the level of the CNS. It has indeed been shown that certain antihypertensive drugs owe their hypotensive action primarily to an interference with receptors located in the brain stem, the region of the CNS where circulatory regulation predominantly is located.

Clonidine, guanfacine, and methyldopa are the prototypes of centrally acting antihypertensive drugs, which are known to act primarily via a-adrenergic receptors in the brain. These drugs have found wide clinical application. In particular, methyldopa has been used extensively for many years. Guanabenz, tiamenidine, lofexidine, and azepexole are experimental compounds with a similar mode of action, but their therapeutic values have not been established in detail. Several compounds also have been developed that decrease blood pressure via central mechanisms that do not involve the central a-adrenergic receptors. Cholinergic, opioid, dopaminergic, serotoninergic, and gamma-aminobutyric acid (GABA)-ergic compounds with central hypotensive activity have been developed. None of these latter compounds, however, have yet proved of therapeutic value, and the introduction of these types of drugs in the treatment of arterial hypertension does not seem to be imminent. For this reason the present survey shall remain limited to the mode of action and applications of clonidine, guanfacine, and methyldopa, with an emphasis on the characteristics of the central a-adrenergic receptors involved in the mediation of the central hypotensive action of these drugs.
The discovery of the centrally acting antihypertensive drugs, which act on the central a-adrenergic receptors, has given strong impetus to the study of the central regulation of peripheral blood pressure. This impetus, of particular value in fundamental physiology, pharmacology, and pathophysiology, may be as important as the therapeutic application of the centrally acting drugs in hypertensive disease.

Centrally Acting Antihypertensive Agents
Compounds Interacting with a-Adrenergic Receptors
Reserpine is the oldest antihypertensive drug that owes at least part of its antihypotensive potency to a central mechanism.1 It should be realized that the major mechanism contributing to the drug’s hypotensive potency is the depletion of norepinephrine from peripheral storage sites in postganglionic sympathetic nerve endings. The central mechanism of reserpine probably involves the stimulation of central a-adrenergic receptors by endogenous norepinephrine released from presynaptic storage sites.

A centrally acting drug that has been (and still is) widely used, is the amino acid methyldopa. In fact, this compound should be considered a prodrug, which can only act after its biotransformation to the active degradation product a-methylnorepinephrine (Figure 1). The latter compound is likely to be the active agent that interacts with the central a-adrenergic receptors,2 although others have suggested that a-methyldopamine is also a metabolite with hypotensive potency.3

A major group of centrally acting antihypertensives that has been investigated thoroughly are the imidazolines and related compounds, of which clonidine and guanfacine are clinically relevant prototypes. The structure-activity relationship for imidazolines has been studied in a quantitative manner. The subject has been reviewed see 11, 18 and 19.)

Recently, a chemical structure quite different from the imidazolines and related compounds has been acknowledged to display central hypotensive activity, mediated by central a-adrenergic receptors. Azepenole (BHT 933) and BHT 920 are azepine structures (Figure 2) that display a mode of action very similar to that of clonidine and guanfacine.8,9

Studies on structure-activity relationships in centrally acting antihypertensive drugs have been limited to clonidine and related imidazolines. Methyldopa (a-methylnorepinephrine), although acting via a similar mechanism that involves central a-adrenergic receptors, is virtually the only active compound in its own particular chemical series so that no meaningful study on structure-activity relationships can be performed.10

Mode of Action Involving Central a-Adrenergic Receptors
The concept that the central a-adrenergic receptors are the initial target of clonidine and related centrally acting antihypertensive drugs was formulated by Schmitt in 1971.11

Although methyldopa has been used against hypertension for many years, only recently has its mode of action as a centrally acting antihypertensive drug been recognized as a hypothesis (e.g., inhibition of dopa-decarboxylase, false transmitter theory) had proved erroneous. The role of central a-adrenergic receptors in the hypotensive action of guanfacine also has been recognized recently.16,17

According to Schmitt’s classical hypothesis, clonidine is an agonist of central a-adrenergic receptors.18,19 The stimulation of these receptors decreases peripheral sympathetic outflow, which causes a fall in blood pressure. The a-adrenergic receptors act as antagonists toward the same receptors. The reduction in peripheral sympathetic tone by clonidine and related drugs has been demonstrated experimentally as a diminished frequency and intensity in discharges of the splanchnic nerve: plasma catecholamines and plasma renin activity simultaneously are reduced.20,21

Guanfacine has been shown to display the same mode of action as clonidine with respect to its antihypertensive activity as clonidine.

FIGURE 1. Biotransformation of methyldopa into a-methyldopamine, which in turn is converted to a-methylnorepinephrine. a-Methylnorepinephrine generally is assumed to be the active metabolite that stimulates central a₂-adrenergic receptors and therefore reduces peripheral sympathetic tone and arterial blood pressure. (See text for details.)
Figure 2. Chemical structures of centrally acting antihypertensive agents that interact with central α-adrenergic receptors. The imidazoline derivative clonidine is the prototype of such drugs. Guanfacine is chemically related to clonidine, although it is not an imidazoline. Azepeoxole (BHT 933) and BHT 920 are new azepine derivatives that appear to be highly selective α-adrenergic receptor agonists. Their central hypotensive effect apparently is caused by the same mechanism as that of clonidine and guanfacine, which implicates the stimulation of central α-adrenergic receptors. Methtidopa has been shown to be a prodrug, which is converted in the brain to α-methyldopamine and subsequently to α-methylnorepinephrine. (See text for details.)

pertensive and bradycardic activities, however, studies have documented that its plasma and tissue half-lives are longer as compared with clonidine, which explains the longer duration of action of guanfacine.

Methyldopa (via α-methylnorepinephrine) appears to act via a mechanism similar to that proposed for clonidine: After its oral ingestion and absorption, the drug is taken up by central nervous tissues and converted into its metabolites α-methyldopamine and α-methylnorepinephrine. α-Methylnorepinephrine, an α-adrenergic receptor agonist, stimulates the centrally located α-adrenergic receptors in a manner similar to that of clonidine and guanfacine and hence causes a hypotensive effect, associated with a reduction in peripheral sympathetic tone. α-Methyldopamine also has been discussed as being potentially involved in the central hypotensive action of methyldopa.

Central hypotensive activity involving central α-adrenergic receptors can be demonstrated experimentally for a variety of compounds that, by different mechanisms, increase the norepinephrine concentration in the pertinent brain regions, which stimulates the central α-adrenergic receptors. This type of "indirect" central hypotensive activity has been observed for the following categories of drugs when they were injected via a central route in laboratory animals: (1) tricyclic antidepressants and cocaine, which are known to inhibit reuptake of norepinephrine at presynaptic sites; (2) tyramine and ephedrine, which enhance the release of endogenous norepinephrine from the presynaptic storage sites; (3) nialamide and other inhibitors of monoamine oxidase (MAO), which inhibit the enzymatic degradation of norepinephrine and hence increase its synaptic concentration. As a rule these three groups of drugs are not used as antihypertensives. It seems, however, of some interest to mention their central hypotensive potency, to confirm the general validity of the theory of central α-adrenergic receptors involved in the drug-induced lowering of blood pressure.

Location and Character of the Central α-Adrenergic Receptors

In spite of considerable effort in neuropharmacological research, precise localization of the central α-adrenergic receptors involved in the central hypotensive effect of guanfacine, clonidine, and methyldopa cannot be indicated. Within the pontomedullary region the central α-adrenergic receptors probably are positioned in and between the following regions: the nucleus of the tractus solitarius, the vasomotor center, and the nucleus of the vagus nerve. It is conceivable that the α-adrenergic receptors are not limited to one circumscribed nucleus or center but are more or less dispersed over several brain regions in a rather diffuse manner. A hypotalamic position has been proposed but seems rather unlikely. More refined methods have to be developed to establish the precise position of the central α-adrenergic receptors.

With respect to the localization of the α-adrenergic receptors at a cellular level, both pre- and postsynaptic (postsynaptic) positions should be considered. As reviewed extensively by Kobinger, the pharmacological destruction of the central presynaptic pathways and presynaptic receptors by means of reserpine or 6-hydroxydopamine did not substantially interfere with the centrally initiated hypotensive effect of clonidine and related drugs. Accordingly, a presynaptic mechanism seems less likely and it may be assumed that the central α-adrenergic receptors are located at postsynaptic sites.
Excitation of the central α-adrenergic receptors is assumed to enhance the activity of an inhibitory neuron and will therefore depress peripheral sympathetic tone. The reduced sympathetic tone satisfactorily explains the fall in blood pressure caused by clonidine, guanfacine, and methyldopa.

By means of a careful pharmacological analysis with specific α₁- and α₂-adrenergic receptor antagonists we have been able to demonstrate that the central hypotensive effect was readily antagonized by the selective α₂-adrenergic receptor rauwolscine and yohimbine, whereas corynanthine, a selective α₁-adrenergic receptor, was much less effective (Figure 3). Corynanthine is a diastereoisomer of rauwolscine and for this reason possesses physicochemical properties very similar to that of rauwolscine, but its receptor affinity is selective for the α₁-adrenergic receptors. Similar experiments with several centrally acting α₁-adrenergic receptor agonists by Kobinger et al. have also indicated that the centrally acting α₁-adrenergic receptor involved in the hypotensive effect of drugs resembles more closely the α₁-subtype than the α₂-subtype. Moreover, compound St 587, a lipophilic, highly selective α₁-adrenergic receptor agonist when administered to the brain stem, on infusion into the vertebral artery did not induce a hypotensive effect.

Recent correlation calculations for various agonists and antagonists also point toward the involvement of α₂-adrenergic receptors at the central level. This view was challenged by some very recent studies, which suggest that the character of the central α-adrenergic receptors may not be completely compatible with either the α₂- or the α₁-subtype. Further confirmation of these views is needed.

A certain inhibitory role of central α₁-adrenergic receptors recently has been proposed in the central modulation of the baroreceptor-reflex vagal bradycardia. In conclusion it seems justified to state that the α-adrenergic receptors in the brain stem that mediate the central hypotensive action of clonidine probably are located at postsynaptic sites; their receptor demand appears to be that of the α₂-adrenergic receptor subtype. The central α₁-adrenergic receptors that facilitate the vagally mediated bradycardia most likely are also of the α₂-type; however, an inhibitory role of central α₁-adrenergic receptors on vagal reflex bradycardia has been suggested.

Side Effects: Pharmacological Basis

The discussion of the role of central α-adrenergic-receptor-involved side effects shall be limited to the prototypes of the centrally acting hypotensive drugs: clonidine, guanfacine, and methyldopa.

It has been shown in animal experiments that sedation, a very common adverse reaction to centrally acting antihypertensives, involves the stimulation of central α₁-adrenergic receptors that are probably of the α₁-subtype; however, the pharmacological methods currently available do not allow a definite decision whether these α₁-adrenergic receptors are located at either pre- or postsynaptic sites. At least on theoretical grounds it would seem very difficult to develop new centrally acting antihypertensive drugs that do not display a substantial degree of sedation as an adverse reaction because both the central hypotensive and the sedative effects apparently are mediated by identical (or at least very similar) receptors of the α₁-subtype.

Studies have demonstrated that clonidine-induced bradycardia is caused by a complex combination of the following three phenomena: (1) the centrally induced reduction of peripheral sympathetic tone, which involves central α₂-adrenergic receptors; (2) the enhancement of vagal reflex bradycardia initiated at the level of central α₂-adrenergic receptors; and (3) the stimulation of presynaptic α₁-adrenergic receptors in

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the heart, which causes an impaired release of norepinephrine.35

The dry mouth caused by clonidine and related drugs also has been shown to involve a-adrenergic receptors: the excitation of presynaptic a,-adrenergic receptors on peripheral parasympathetic neurons causes reduced salivary flow.38

It seems likely that the corresponding and very similar side effects of guanfacine and methyldopa are caused by the same mechanisms that clonidine induces; however, these drugs have not been studied as systematically.

**Withdrawal Phenomena**

It has been reported several times that the rapid interruption of antihypertensive therapy with clonidine causes withdrawal phenomena, which are characterized by various symptoms that reflect sympathetic hyperactivity. The clinical aspects have been discussed by Reid39 and Hansson.40 Recently we have been able to develop an animal model that is suitable to demonstrate and study the withdrawal phenomena of centrally acting and other antihypertensives.41

Both clinical and animal model studies discussed in this article have suggested the following differences with respect to the three prototypes of the centrally acting antihypertensive drugs: (1) Clonidine may cause withdrawal phenomena characterized by hyper-activity of the sympathetic nervous system, on sudden cessation of antihypertensive therapy with this drug; as a rule, a genuine blood pressure overshoot does not occur. (2) Guanfacine has been found to cause withdrawal phenomena but to a very modest and clinically irrelevant degree. The limited extent of the guanfacine withdrawal syndrome in humans and rats most likely is caused by the lower elimination rate compared with clonidine.41,38 (3) Methyldopa has been reported to cause withdrawal phenomena in humans only in exceptional cases; in animal experiments this drug has not caused relevant withdrawal phenomena.41,42

Why methyldopa does not clearly cause withdrawal phenomena cannot be explained at present. Neither are we informed on the detailed mechanism of the withdrawal phenomenon of clonidine. Central a-adrenergic receptors appear to be involved, as the administration of yohimbine (an a2-adrenergic receptor antagonist) but not that of prazosin (an a,-adrenergic receptor antagonist) provoked strong withdrawal tachycardia during a 12-day continuous infusion of either clonidine or guanfacine.41,42,43 Yohimbine injected during an infusion of methyldopa did not provoke withdrawal tachycardia, which indicates that other than pharmacokinetic factors may explain the virtual absence of withdrawal phenomena after cessation of treatment with methyldopa.41

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