Centrally acting antihypertensives: a renaissance of tinterest: mechanisms and haemodynamics

van Zwieten, P.A.

Publication date
1997

Published in
Journal of hypertension

Centrally acting antihypertensives: a renaissance of interest. Mechanisms and haemodynamics

Pieter A. van Zwieten

Background Classic centrally acting antihypertensives are known to stimulate α_2-adrenoceptors located in the ponto-medullary region, in the vicinity of the nucleus tractus solitarii, vasomotor centre, vagal nucleus and the various interconnecting neurones. The stimulation of these central α_2-adrenoceptors induces peripheral sympathoinhibition and hence a reduction in (elevated) blood pressure, predominantly as a result of vasodilation and a consequent decrease in peripheral vascular resistance.

Antihypertensives Clonidine, guanfacine, guanabenz and α-methyldopa (via its active metabolite α-methylnoradrenaline) are well-known examples of classic centrally acting antihypertensives. They are effective antihypertensives with an attractive haemodynamic profile. However, these agents have lost much of their clinical interest because of their subjectively unpleasant side-effects (sedation, dry mouth, impotence). Since these side-effects are also mediated, to a major extent, by α_2-adrenoceptors it is virtually impossible to separate the desired centrally induced antihypertensive effect and the adverse reactions by designing new compounds.

Drug targets I_1-Imidazoline receptors have recently been discovered as a new target of centrally acting antihypertensives. When stimulated with agonists the I_1-imidazoline receptors, located in the nucleus reticularis lateralis will trigger peripheral sympathoinhibition, following similar pathways as involved in the effects of the classic α_2-adrenoceptor stimulants. Moxonidine and rilmenidine are I_1-imidazoline receptor stimulants with little affinity for α_2-adrenoceptors. Accordingly, such agents lower elevated blood pressure in a similar manner as the aforementioned older drugs, but it may be hoped that their side-effect profile is more favourable.

Conclusion Accordingly, it would now be possible to separate the attractive haemodynamic properties and the side-effects of centrally acting antihypertensives.

Journal of Hypertension 1997, 15 (suppl 1):S3–S8

Keywords: centrally acting antihypertensives, α_2-adrenoceptors, clonidine, I_1-imidazoline receptors, moxonidine, rilmenidine

From the Departments of Pharmacotherapy and Cardiology, Academic Medical Centre, University of Amsterdam, Amsterdam, The Netherlands.

Requests for reprints to Prof. P.A. van Zwieten, Departments of Pharmacotherapy and Cardiology, Academic Medical Centre, University of Amsterdam, Meibergdreef 15, 1105 AZ Amsterdam, The Netherlands.

 ISSN 0952-1178

Introduction

Centrally acting antihypertensives were introduced in the management of hypertensive disease in the 1960s. It was recognized that part of the antihypertensive activity of reserpine was triggered within the central nervous system [1], although this well-known alkaloid also lowers blood pressure as a result of peripheral mechanisms involving the sympathetic nervous system [2]. Clonidine, a stimulant of α_2-adrenoceptors in the central nervous system was then somewhat later introduced as the prototype of centrally acting antihypertensives. Its antihypertensive activity was assumed to be triggered by the stimulation of α_2-adrenoceptors in the ponto-medullary region, thus causing peripheral sympathoinhibition and a reduction of elevated blood pressure [3–6]. Guanfacine and guanabenz were found to reduce blood pressure via similar mechanisms [7]. Somewhat later the central antihypertensive activity of α-methyldopa was discovered [8,9]: α-methyldopa, a prodrug, is converted *in vivo* into its active metabolite α-methylnoradrenaline, which stimulates the same α_2-adrenoceptors known to be activated by clonidine and related compounds, thus causing peripheral sympathoinhibition and a fall in blood pressure. A direct peripheral effect involving the 'false transmitter hypothesis' has also been submitted [8,9].

In the 1960s and 1970s clonidine and α-methyldopa were appreciated as effective anyihypertensives with an attractive haemodynamic profile. All important circulatory reflexes are left unimpaired during treatment with these agents. Furthermore, the concept of sympathoinhibition seems attractive on theoretical grounds; a relationship between essential hypertension and an activated sympathetic nervous system is widely accepted to exist [10–12], although many details concerning this association remain to be elucidated. In addition, the centrally acting antihypertensives are known to effectively suppress the left ventricular hypertrophy, associated with hypertensive disease, probably as a result of peripheral sympathoinhibition [13–15].

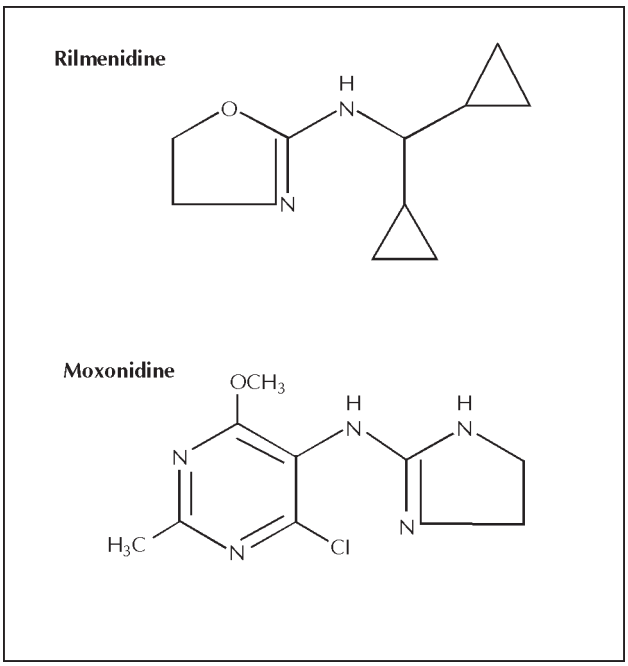
Despite these various favourable properties the centrally acting antihypertensives have lost much of their importance because of their side-effect profile. Sedation, dry mouth and

sexual impotence in men are frequently observed during treatment with such agents, and these subjectively unpleasant adverse reactions are considered as virtually unacceptable when compared with currently used antihypertensives such as β-blockers, low-dose diuretics, angiotensin converting enzyme inhibitors, calcium antagonists and α_1-adrenoceptor antagonists.

Numerous attempts have been made to develop centrally acting α_2-adrenoceptor stimulants as antihypertensives with a better profile of side-effects than that of the classic compounds. These attempts have largely failed, because most of the aforementioned side-effects are mediated by α_2-adrenoceptors as well, although located in different anatomical regions than those mediating the central antihypertensive action [16].

New light has been shed upon this problem by the discovery of I_1-imidazoline receptors in the brain, involved in the central regulation of blood pressure and recognized as targets of a novel type of centrally acting antihypertensive drugs [17–20]. Part of the antihypertensive effect of clonidine may be mediated by central I_1-imidazoline receptors (in addition to the α_2-adrenoceptor mechanism), whereas moxonidine and rilmenidine (Fig. 1) are assumed to act predominantly as I_1-imidazoline receptor agonists.

Fig. 1



Chemical structures of the I_1-imidazoline receptor agonists moxonidine and rilmenidine.

Similarly, central serotonergic receptors of the 5-hydroxytryptamine $(5HT)_{1A}$ subtype may be considered as a target of new, centrally acting antihypertensives, although this mechanism has not been explored in great detail so far. The hybrid compound urapidil, an agonist of central $5HT_{1A}$-receptors besides its peripheral α_1-adrenoceptor antagonistic activity, is the first example of a centrally acting antihypertensive involving central serotonergic receptors.

Receptors and neuronal pathways in the central nervous system as targets of antihypertensive drugs

Numerous pathways, neurotransmitters and their associated receptors are known to be involved in the central nervous regulation of the cardiovascular system, including that of arterial blood pressure. In this connection (nor)adrenaline, acetylcholine, serotonine, angiotensin II, γ-amino-butyric acid may be mentioned, and for all of these neurotransmitters neuronal pathways and receptors have been demonstrated to play a role in the central regulation of blood pressure [17–19]. Potentially, most of these pathways and receptors could be thought of as targets of centrally acting antihypertensives. In reality, α_2-adrenoceptors, I_1-imidazoline receptors and serotonergic $(5HT_{1A})$-receptors and their corresponding pathways are the only targets of clinically useful drugs.

α_2-Adrenoceptors and aminergic pathways

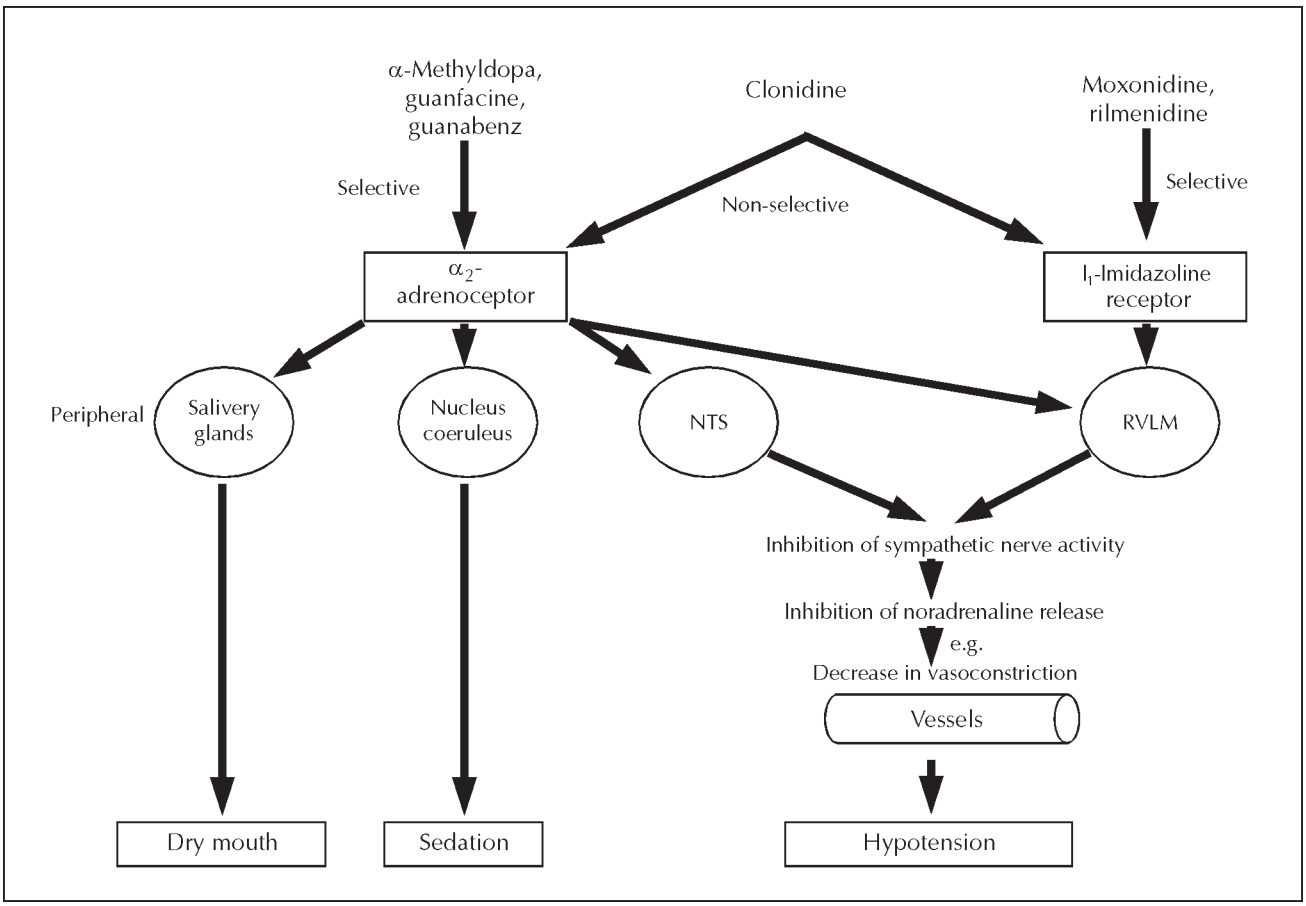
There are two main subgroups of bulbospinal sympathoexcitatory neurons in the rostral ventrolateral medulla, and the rostral ventromedial medulla. The pathway descending from the rostral ventrolateral medulla contains adrenoceptors and is linked to the peripheral sympathetic system. The other pathway coincides with the B_3-group of serotonin-containing neurons [20,21]. Centrally acting antihypertensives of the classical type (α-methyldopa, via α-methylnoradrenaline; clonidine) are known to be α_2-adrenoceptor agonists that cause peripheral sympathoinhibition. However, central serotonergic receptors lateral with respect to the midline B_3 serotonin cells in the raphe (the rostral ventrolateral medulla) are also involved in the central antihypertensive effect of the aforementioned classical centrally acting antihypertensives [22]. The α_2-adrenoceptors appear to be located in the regions of the nucleus tractus solitarii, the hypothetical vasomotor centre and the vagal centre [18,23,24].

In summary, the classic centrally antihypertensives act as α_2-adrenoceptor agonists and hence induce peripheral sympathoinhibition. Such agents also involve serotonergic neurons. As to be discussed below, clonidine as a mixed α_2-adrenoceptor and I_1-imidazoline receptor agonist probably acts in part via the stimulation of central I_1-imidazoline receptors.

Imidazoline receptors

The I_1-imidazoline receptor, which is assumed to play a role in central blood pressure regulation and as a target of centrally acting antihypertensive drugs can be distinguished from the α_2-adrenoceptor by radioligand binding and func-

Fig. 2



Central antihypertensive mechanisms of various types of centrally acting antihypertensive drugs. Note the different targets of α_2-adrenoceptor stimulants and I_1-imidazoline receptor agonists. The adverse reactions dry mouth and sedation are mediated by α_2-adrenoceptors but not by I_1-imidazoline receptors. NTS, nucleus tractus solitarii; RVLM, rostral ventrolateral medulla.

tional experiments. However, both receptors are rather similar in many ways and therefore difficult to distinguish. Certain authors are of the opinion that the I_1-imidazoline receptor and the α_2-adrenoceptors are located in series along the same cardiovascular pathway in the medulla [25].

So far the amino-acid sequence of the I_1-imidazoline receptor has not been elucidated. The I_1-imidazoline receptors involved in the regulation of blood pressure and the targets of antihypertensive drugs are predominantly located in the rostral ventrolateral medulla in the brain [26–28]. Furthermore, I_1-imidazoline receptors in the hypothalamic regions are assumed to be involved in the central regulation of blood glucose levels, as concluded from the antihyperglycaemic activity of the experimental I_1-imidazoline receptor agonist agmatine [29]. The renal proximal tubuli also contain I_1-imidazoline receptors, and their stimulation causes enhanced natriuresis.

When stimulated with appropriate receptor agonists such as moxonidine or rilmenidine the central I_1-imidazoline receptors will mediate a fall in blood pressure and heart rate, thus reflecting centrally induced, peripheral sympathoinhibition (Fig. 2). The neuronal pathway involved is probably very similar to that activated by central α_2-adrenoceptor agonists such as α-methylnoradrenaline (derived from α-methyldopa) or clonidine.

The existence of an endogenous agonist for the activation of I_1-imidazoline receptors is subject to a great deal of interest and speculation. Clonidine-displacing substance, a hypothetical compound [30] and agmatine [29] have been proposed as endogenous agonists for the I_1-imidazoline receptors.

Serotonergic $5HT_{1A}$-receptors

The rostral ventrolateral medulla has been identified as the site of action of experimental antihypertensive compounds such as 8-hydroxy-2-(di-n-propyl-amino)tetralin and flesinoxan. Urapidil, which is both a peripheral α_1-adrenoceptor antagonist and an agonist towards central $5HT_{1A}$-receptors owes part of its antihypertensive activity to a central mechanism, involving these $5HT_{1A}$-receptors [31]. The stimulation of central $5HT_{1A}$-receptors will cause peripheral sympathoinhibition. Furthermore, this mechanism is

assumed to enhance peripheral parasympathetic activity and to suppress reflex tachycardia, provoked by peripheral vasodilatation [31–34]. A central mode of action has also been proposed for ketanserin, a $5HT_2$-receptor antagonist with moderate α_1-adrenoceptor antagonistic activity. This mechanism has not been analysed in detail, and it is unclear which subtype of central serotonergic receptors may be involved in the drug's antihypertensive action [35,36]. We already mentioned the involvement of serotonergic pathways in the central antihypertensive activity of clonidine and α-methyldopa, although these drugs are not direct agonists of serotonergic receptors.

Receptor profiles of centrally acting antihypertensive drugs

The receptor profiles of the so far available, relevant centrally acting drugs is summarized in Table 1.

Table 1 Overview of the central nervous system (CNS) receptors as targets of centrally acting antihypertensives.

	Receptor
α-Methyldopa (through α-methylnoradrenaline)	α_2-Adrenoceptor
Guanfacine	
Guanabenz	
Clonidine (mixed agonist)	α_2-Adrenoceptor + I_1-imidazoline receptor
Moxonidine, rilmenidine	I_1-imidazoline receptor > α_2-adrenoceptor
Urapidil	5-Hydroxytryptamine type 1A receptor (CNS) α_1-adrenoceptor (periphery)

Haemodynamic profiles of centrally acting antihypertensives

Clonidine, guanfacine and guanabenz are predominantly arterial vasodilators [37] that will reduce the elevated peripheral vascular resistance, which is characteristic for essential hypertension and for other forms of hypertensive disease. In addition, heart rate is usually reduced [37]. These haemodynamic changes together with the lowering of plasma noradrenaline levels clearly reflect the reduction of peripheral sympathetic activity, which is triggered within the brain stem. α-Methyldopa also acts as an arterial vasodilator and hence reduces peripheral vascular resistance in hypertensives [38]. Although in acute animal experiments a reduction in cardiac output has sometimes been reported, long-term treatment with α-methyldopa as usual in hypertension is not associated with important changes in cardiac output or heart rate [38]. It can be imagined that the bradycardia induced via sympathoinhibition is counteracted by the β-sympathomimetic activity of α-methylnoradrenaline, the active metabolite of α-methyldopa. The aforementioned classic centrally acting antihypertensives are all known to induce regression of hypertension-induced left ventricular hypertrophy, as a result of sympathoinhibition [39,40].

The antihypertensive activity of both moxonidine and rilmenidine (the prototypes of central I_1-imidazoline receptor agonists is associated with arterial vasodilatation and a reduction in peripheral vascular resistance [41,42]. Cardiac output and heart rate are not much changed by both I_1-imidazoline receptor stimulants, although they can suppress tachycardic episodes [41,42]. Moxonidine and rilmenidine both cause regression of left ventricular hypertrophy in animal models, probably as a result of sympathoinhibition [43,44]. Moxonidine and rilmenidine both stimulate I_1-imidazoline receptors in the kidney, thus causing significant natriuretic effects. It has also been suggested that the stimulation of the central nervous I_1-imidazoline receptor contributes to the natriuretic activity of these agents [45–47]. The clinical relevance of the natriuretic effect in hypertensive patients is so far unclear, although it is potentially attractive on theoretical grounds.

Urapidil, the α_1-blocker/$5HT_{1A}$-receptor agonist is predominantly a vasodilator, mainly as a result of its α-adrenoceptor antagonistic activity. Heart rate remains unchanged, probably because of the additional central stimulation of $5HT_{1A}$-receptors that counteracts reflex tachycardia [48,49].

Adverse reactions

The well-known unpleasant adverse effects of α-methyldopa, clonidine and related drugs, predominantly mediated via α_2-adrenoceptors were already mentioned. The general impression is obtained that moxonidine and rilmenidine in antihypertensive doses cause less psychomotoric impairment and sedation [50–52] than clonidine, α-methyldopa or related drugs, although appropriate, comparative studies have not been performed. Reduced salivation and dry mouth have also been reported for moxonidine and rilmenidine [53,54], but it is difficult to judge whether these effects are significantly less frequent or intensive as observed for clonidine and related agents. Rebound activation of the sympathetic nervous system after abrupt withdrawal of clonidine has been recognized as a relevant clinical problem in connection with this classic centrally acting antihypertensive agent [55,56]. Such rebound phenomena have so far not been reported for moxonidine and rilmenidine, neither in animal models, nor under clinical conditions. Adverse reactions to urapidil, such as dizziness, headache, tiredness and gastrointestinal problems are usually mild and rather unspecific [48,49] and quite different from those of the classic α_2-adrenoceptor agonists. Rebound phenomena have so far not been reported.

Conclusions and perspectives

From the 1970s onwards the centrally acting antihypertensives have acquired an unfavourable reputation because of their side-effect pattern, notwithstanding their efficacious antihypertensive activity. This negative profile, associated with these drugs with a clear affinity for α_2-adrenoceptors has

been challenged by the introduction of central I_1-imidazoline receptor agonists such as moxonidine and rilmenidine, which have little affinity for α_2-adrenoceptors. Central I_1-imidazoline receptors and pathways have been recognized as a novel mechanism in the regulation of blood pressure, which may also play a role in its derangements as in hypertensive disease. In this connection several detailed problems remain to be solved, in particular the precise identification of the I_1-imidazoline receptor, its amino-acid sequence and its vague distinction from the α_2-adrenoceptor. The concept of I_1-imidazoline receptor agonists has offered the possibility to design centrally acting antihypertensive drugs avoiding the α_2-adrenoceptor with all its problems in the sense of adverse reactions.

Moxonidine and rilmenidine are the first examples of centrally acting antihypertensives which are selective for the I_1-imidazoline receptor, and therefore devoid of α_2-adrenoceptor affinity. As yet they are far from being the perfect compounds and significant improvements may be anticipated. Despite this, their introduction indicates that a separation between central antihypertensive activity and side-effects (such as sedation, dry mouth) is not necessarily a hopeless enterprize. It can be well imagined that better compounds with a higher selectivity for I_1-imidazoline receptors and lower affinity for α_2-adrenoceptors will be developed in future.

The renaissance of interest in centrally acting antihypertensives is not only justified but also based on promising data, which deserve further development.

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