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DOI
10.1097/00004872-199715020-00001

Publication date
1997

Published in
Journal of hypertension

Link to publication

Citation for published version (APA):
van Zwieten, P. A. (1997). Central imidazoline (I1) receptors as targets of centrally acting antihypertensives: moxonidine and rilmenidine. *Journal of hypertension*, *15*, 117-125. https://doi.org/10.1097/00004872-199715020-00001

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Central imidazoline (I_1) receptors as targets of centrally acting antihypertensives: moxonidine and rilmenidine

Pieter A. van Zwieten

Clonidine, guanfacine, guanabenz and α-methyl-dioxyphenylalanine (DOPA), the prototypes of centrally acting antihypertensives, are assumed to induce peripheral sympathoinhibition and a reduction in blood pressure via the stimulation of α_2-adrenoceptors in the brain stem. More recently, central imidazoline (I_1)-receptors have been recognized to be another target of centrally acting antihypertensive drugs. Clonidine is considered to be a mixed agonist that stimulates both α_2- and I_1-receptors. Moxonidine and rilmenidine are considered to be moderately selective I_1-receptor stimulants, although it still remains unknown whether these agents act directly on the receptor as genuine agonists.

A survey is given on the location, characteristics and functional aspects of imidazoline I_1-receptors as targets of centrally acting antihypertensives. Furthermore, the pharmacology and clinical potential of selective I_1-receptor agonists such as moxonidine and rilmenidine are discussed. Although far from perfect, these compounds have shown that it may potentially be possible to develop agents with which the well-known side effects caused by α_2-receptor agonists can be separated from the central antihypertensive mechanism.

Journal of Hypertension 1997, **15**:117–125

Keywords: imidazoline receptors, centrally acting antihypertensives, moxonidine, rilmenidine, clonidine

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Received 4 July 1996 **Revised** 18 November 1996
Accepted 26 November 1996

© Rapid Science Publishers ISSN 0263-6352

Introduction

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, serotonin, angiotensin II and 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 [1–3]. Potentially, most of these pathways and receptors could be thought to be targets of centrally acting antihypertensives.

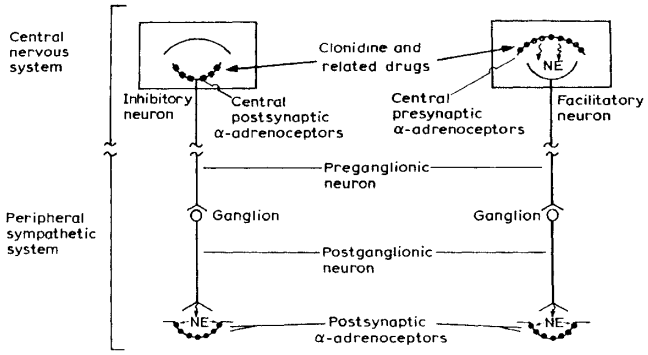
In reality, clinically useful antihypertensives with a primary target in the central nervous system are limited to a few well-known older compounds, such as clonidine, guanfacine, guanabenz and α-methyl-dioxyphenylalanine (DOPA). These classic centrally acting drugs are presumed to be stimulants of central α_2-adrenoceptors, which are located in the pontomedullary region, probably in the areas of the nucleus tractus solitarii, the hypothetic vasomotor centre [including the rostral ventrolateral medulla (RVLM)–nucleus reticularis lateralis (NRL) region], the nucleus of the vagus nerve and their various interconnecting neurons [4–7]. Stimulation of the α_2-adrenoceptors brings about a reduction in sympathetic outflow from the brain, reduced sympathetic neuronal activity in the periphery and, for that matter, a reduction of (elevated) blood pressure (Fig. 1).

This centrally triggered peripheral sympathoinhibition may be considered an elegant and physiological mechanism to lower blood pressure, which leaves the major circulatory reflexes intact and even facilitates them. Furthermore, it seems very likely that essential hypertension is intricately associated with the activity of the sympathetic nervous system [9–11], although many details of this association remain to be elucidated. The reduction of elevated blood pressure by drugs that cause peripheral sympathoinhibition via a primary central mechanism therefore seems a logical procedure, which might even approach remotely a causative mechanism of therapy.

The aforementioned, classic centrally acting antihypertensives are without any doubt effective drugs, with an attractive mode of action and haemodynamic pattern. However, their clinical importance has diminished greatly as a result of their unfavourable pattern of subjective adverse reactions, such as sedation, a dry mouth and, in men, impotence. α_2-Adrenoceptors also play an important role in the genesis of these adverse reactions [11,12] and for this reason it has proved virtually impossible to develop centrally acting α_2-adrenoceptor agonists largely devoid of the aforementioned side effects.

Apart from the centrally acting α_2-adrenoceptor agonists, of which clonidine is the prototype, a few drugs have been introduced that lower elevated blood pressure via serotonergic receptors in the brain. For instance the

Fig. 1



Classical schematic presentation of the role of central α_2-adrenoceptors in the antihypertensive action of clonidine, α-methyldioxyphenylalanine (DOPA) (via α-methylnoradrenaline) and related drugs. The central antihypertensive (hypotensive) activity of clonidine and related drugs is triggered by the stimulation of central α_2-adrenoceptors. Two possibilities should be envisaged: on the left-hand side, stimulation of postsynaptic α_2-adrenoceptors enhances the activity of an inhibitory neuron and hence causes peripheral sympathoinhibition; and on the right-hand side stimulation of presynaptic α_2-adrenoceptors impairs the release of endogenous noradrenaline and hence impairs the cerebral activation of the peripheral sympathetic system. The postsynaptic mechanism (the left-hand side of the scheme) is likely to be the correct one. NE, Norepinephrine. From [8], with permission.

antihypertensive effect of urapidil is caused in part via the stimulation of serotonergic 5 hydroxytryptamine $(5HT)_{1A}$-receptors in the central nervous system (CNS), as well as by peripheral α_1-adrenoceptor blockade [13,14].

Ketanserin owes its antihypertensive activity probably in part to its interaction with central $5HT_2$-receptors, although the drug is also an antagonist towards peripheral α_1-adrenoceptors [15,16]. Since urapidil and ketanserin are hybrid drugs, with both central nervous and peripheral components within their mode of action, they will not be further discussed here.

More recently, imidazoline (subtype I_1) receptors in the CNS [17,18] have been recognized as a new, potentially interesting target of centrally acting antihypertensives such as moxonidine and rilmenidine. Their mode of action involves the stimulation of central imidazoline (I_1)-receptors, thus leading to peripheral sympathoinhibition. This mode of action is very similar to that of centrally acting α_2-adrenoceptor agonists. However, the relatively lower affinity of the aforementioned I_1-receptor agonists for α_2-adrenoceptors may imply that their pattern of adverse reactions is more favourable than that of clonidine and related compounds. Ideally the development of these compounds emphasizes that it has become possible to develop centrally acting antihypertensives, causing peripheral sympathoinhibition but with fewer and less intense side effects mediated by α_2-adrenoceptors. These newer types of centrally acting antihypertensives will be the subject of the present survey, after an outline of the central imidazoline (I_1)-receptors assumed to be their targets in the brain has been given.

Central imidazoline receptors

Historical background

The concept of imidazoline receptors in the brain that may be involved in the central regulation of blood pressure was submitted by Bousquet *et al.* [19], who dissociated the centrally mediated effects of clonidine (an imidazoline compound) on blood pressure from those of catecholamines. Accordingly, this concept was initiated on the basis of structure–activity relationships and functional pharmacological experiments. In a later stage, detailed radioligand binding studies largely confirmed the existence of these receptors.

Radioligand binding studies

The concept of the existence of imidazoline receptors different from α_2-adrenoceptors was substantiated by detailed radioligand binding studies, in particular those performed in homogenates of bovine brain [20,21]. The RVLM contains a high density of imidazoline binding sites. [^{3}H]-clonidine was originally used as a radioligand for these binding sites, but it should be realized that this compound has comparable affinity for α_2-adrenoceptors and imidazoline binding sites (see Table 1). In a later stage, [^{3}H]-moxonidine was introduced as a more, albeit moderately, selective ligand for imidazoline binding sites [22,23]. At present a distinction is made between I_1- and I_2-receptors and -binding sites. [^{3}H]-moxonidine and [^{3}H]-*p*-aminoclonidine are used as selective ligands for I_1-binding sites, whereas [^{3}H]-idazoxan labels predominantly I_2-binding sites [22], although it also binds to α_2-adrenoceptors. [^{125}I]-2-(3-amino-4-iodophenoxyl)-methyl-imidazoline and [^{3}H]-2-(2-benzofuranyl)-2-imidazoline are recently introduced radioligands for I_2-binding sites, which do not interact with α_2-adrenoceptors [22]. These ligands are therefore potentially attractive for the study of I_2-binding sites.

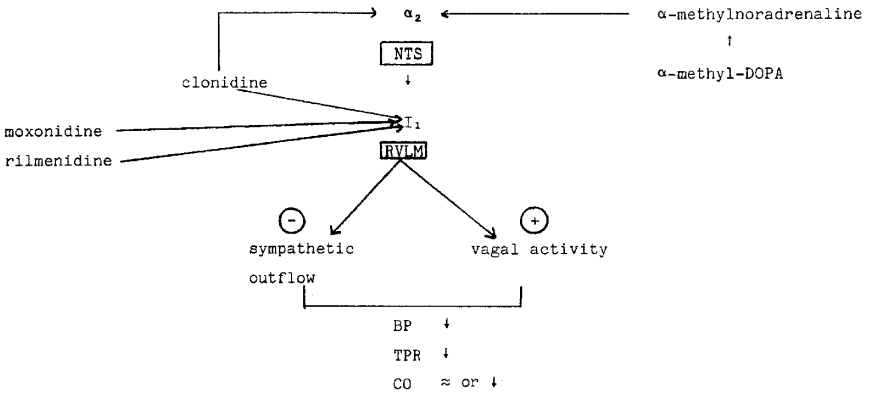
I_1-binding sites have been demonstrated to occur in the brain of various species (human, cow and rat) and also in the peripheral nervous system, including in adrenomedullary chromaffin cells, in the carotid body and in

Table 1 Central nervous system receptors as targets of centrally acting antihypertensives

Compound	Receptors
α-Methyl-DOPA (through α-methylnoradrenaline)	α_2
Guanfacine	α_2
Guanabenz	α_2
Clonidine (mixed agonist)	$\alpha_2 + I_1$
Moxonidine	$I_1 > \alpha_2$
Rilmenidine	$I_1 > \alpha_2$

DOPA, dioxyphenylalanine.

Fig. 2



Sites of action of centrally acting antihypertensives. Central α_2-adrenoceptor agonists and imidazoline (I_1)-receptor agonists have differential initial targets, whereas the final pathways inducing peripheral sympatho-inhibition are probably the same for both types of drugs. NTS, nucleus tractus solitarii; RVLM, rostral ventrolateral medulla; BP, blood pressure; TPR, total peripheral resistance; CO, cardiac output; DOPA, dioxyphenylalanine.

clonal neuron-like cell lines such as NG 108-15 neuroblastomaglioma and PC12 cells [23–27]. I_1-binding sites in bovine RVLM proved identical to those in comparable human brain tissue [28]. Autoradiographic receptor binding assays with brain and kidney tissues have been performed as well to identify I_1-imidazoline sites [29].

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 functional experiments. However, both receptors are rather similar in many ways and therefore difficult to distinguish. It has been suggested that I_1- and α_2-adrenoceptors are located in series along the same cardiovascular pathway in the medulla [30]. The amino acid sequence of the I_1-receptor has so far not been elucidated and, strictly speaking, conclusive evidence for its existence is therefore still lacking.

Imidazoline I_2-receptors are expressed in several tissues including the brain, in particular in glial cells. I_2-receptors may be involved in the stimulation of insulin release, the increase in monoamine levels of the brain, a state of hyperphagia in rats and the regulation of the levels of glial fibrillary acidic protein [31–34]. Interestingly, I_2-imidazoline sites have been proposed to be allosteric sites of monoamine-oxidase enzymes [22]. Since I_2-receptors are probably not involved in the regulation of blood pressure or as a target of antihypertensive drugs, they will not be further discussed in the present survey.

Location

As mentioned previously, the I_1-receptors involved in the regulation of blood pressure and as targets of antihypertensive drugs are predominantly located in the RVLM in the brain, in various species [17–19,29]. I_1-receptors have also been identified in various other brain structures (such as the striatum and the pallidum), which are not primarily involved in blood pressure regulation [35].

I_1-receptors in the hypothalamic region are assumed to be involved in the central regulation of blood glucose levels, as concluded from the antihyperglycaemic activity of moxonidine [36]. I_1-receptors have also been identified in the kidney, predominantly in the proximal tubuli [37,38].

Functional role

When stimulated with agonists possibly acting directly, such as moxonidine or rilmenidine, the I_1-receptor will mediate a fall in blood pressure and heart rate, thus reflecting centrally induced, peripheral sympathoinhibition [17–19]. The neuronal pathway involved is probably very similar to that activated by central α_2-adrenoceptor agonists such as α-methylnoradrenaline (derived from α-methyl-DOPA) or clonidine (Fig. 2). This pathway involves, at least in part, central serotonergic neurons, in particular those in the B_3 region in the raphe (rostral ventromedial medulla) [3,39]. The possibility that I_1- and α_2-adrenoceptors are located in series along the same cardiovascular pathway [30] has already been mentioned.

The presence of I_1-receptors in neuronal pathways involved in the central regulation of blood pressure has led to speculations concerning the existence of an endogenous agonist for the activation of such receptors. Approximately a decade ago much attention was devoted to a substance isolated from bovine brain which displaces [^{3}H]-clonidine binding to rat brain membranes. This clonidine-displacing substance (CDS) also inhibited [^{3}H]-*p*-NH_2-clonidine binding in the RVLM and also exerted central hypotensive activity when injected into that brain region [40–42]. CDS was therefore proposed as an endogenous receptor stimulant, possibly involved in cardiovascular control via non-adrenergic receptors in the RVLM. Accordingly, it might be speculated that CDS

would play a role as an endogenous ligand and agonist of the I_1-receptor. However, this concept is challenged by the observation that CDS extracts, when injected directly within the rostro-ventrolateral part of the brain stem, may cause a hypertensive rather than a hypotensive effect [43,44]. Unfortunately, this concept has not been followed up in detail and the chemical structure of CDS has not been elucidated.

Agmatine, generated by the decarboxylation of L-arginine has recently been identified in brain tissues of various species. Agmatine binds to I_1-receptors and α_2-adrenoceptors [45,46].

Agmatine has been suggested to be an endogenous ligand for imidazoline receptors on the basis of in-vitro experiments [45,46]. However, agmatine increases blood pressure when it is administered centrally, via the cisterna magna or by micro-injection. When administered intravenously, high doses of agmatine cause a lowering of blood pressure, probably as a result of ganglionic blockade [47]. Accordingly, agmatine, in spite of its receptor binding profile, cannot mimic the effects of clonidine and it is therefore a dubious candidate for an endogenous ligand for I_1-receptors in the brain.

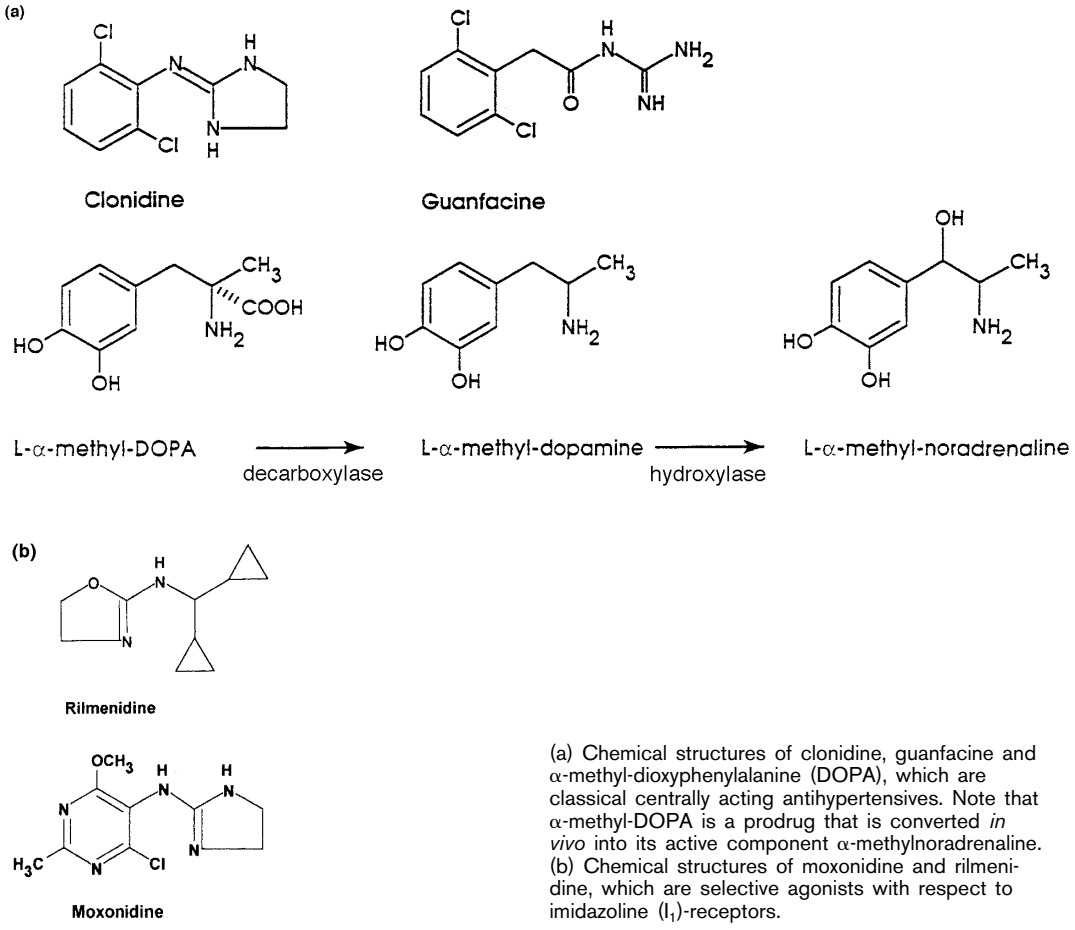
Agmatine may be involved in the central regulation of blood glucose levels and it displays antihyperglycaemic activity, mediated via central I_1-receptors [48]. This phenomenon does not necessarily imply a receptor mechanism for agmatine similar to that in the cardiovascular system.

Drugs interacting with I_1-receptors

The role of I_1-receptors as well as that of α_2-adrenoceptors as drug targets requires further differentiation of centrally acting antihypertensives. Accordingly, α-methyl-DOPA (via α-methylnoradrenaline, Fig. 3), guanfacine and guanabenz are rather selective agonists for the α_2-adrenoceptor and virtually devoid of affinity for the I_1-receptor [49].

Clonidine, the prototype of centrally acting antihypertensives, has comparable affinity for α_2-adrenoceptors and I_1-receptors [49,50]. Its central antihypertensive effect may be triggered by both receptor types in the brain, although the neuronal pathway involved in peripheral

Fig. 3



(a) Chemical structures of clonidine, guanfacine and α-methyl-dioxyphenylalanine (DOPA), which are classical centrally acting antihypertensives. Note that α-methyl-DOPA is a prodrug that is converted *in vivo* into its active component α-methylnoradrenaline. (b) Chemical structures of moxonidine and rilmenidine, which are selective agonists with respect to imidazoline (I_1)-receptors.

sympathoinhibition is probably the same, with the exception of the initial target. The adverse reactions to clonidine are predominantly mediated by α_2-adrenoceptors in the brain (sedation) and in the periphery (a dry mouth, impotence) [11,12].

Moxonidine and rilmenidine (Fig. 3) are predominantly I_1-receptor agonists (possibly acting indirectly), with much weaker affinity for α_2-adrenoceptors [51,52].

Cirazoline, lofexidine and oxymetazoline are also (at least partially) stimulants of central I_1-receptors [22], although they have not been developed clinically as antihypertensive drugs. So far few selective antagonists for imidazoline receptors have become available. On the basis of radioligand binding data, efaroxan [53] is considered to be a selective antagonist for the I_1-receptor, whereas idazoxan may be classified as a moderately selective antagonist for the I_2-receptor [22,23,54], with additional affinity for α_2-adrenoceptors.

Since the endogenous ligand for I_1-receptors has not been identified clearly, some uncertainty will persist concerning the question of whether the various agents that interact with the receptor may be classified as genuine agonists or antagonists.

Pharmacological characteristics of moxonidine and rilmenidine

The pharmacological profiles of moxonidine and rilmenidine, which are the best known examples of selective I_1-receptor agonists, are largely comparable. The central site of action has been demonstrated convincingly for both agents by means of stereotaxic injections into regions of the CNS where central blood pressure regulation is located and also by means of administration into brain centres or via the vertebral artery, in various animal species [55–58].

The involvement of central I_1-receptors in the hypotensive/antihypertensive effect of moxonidine and rilmenidine was concluded from the radioligand binding profiles of both compounds, which indicate that there is a certain selectivity for the I_1-receptor. Furthermore, the central hypotensive effect of both agents can be antagonized by the selective I-receptor antagonists efaroxan and idazoxan [58–60]. The involvement of I_1-receptors in the effects of both compounds has been contested, however, by Urban *et al.* [61,62], who concluded from their experiments that the effects both of moxonidine and of rilmenidine predominantly involve central α_2-adrenoceptors. An interaction between I_1- and α_2-adrenoceptors in the CNS, involving the contribution of both receptor types, may be considered as well [63].

A possible role of central presynaptic α_2-adrenoceptors has been proposed in addition [61]. The antihypertensive activity of both agents was demonstrated in various animal models of hypertension. The antihypertensive activity of both drugs is caused by centrally triggered sympathoinhibition, leading predominantly to a reduction in peripheral vascular resistance and vasodilatation [55,65–69].

Cardiac output and heart rate are not much changed by both I_1-receptor stimulants, although a suppression of tachycardic episodes has been reported [70,71]. Antiarrhythmic activity in animal models has been described both for moxonidine [72] and for rilmenidine [73]. The centrally triggered peripheral sympathoinhibition caused by clonidine, moxonidine and rilmenidine is associated with a reduction in plasma catecholamines [1,7,49,58]. A decrease in cardiac and peripheral (muscle) sympathetic activity in human volunteers, assessed by means of microneurography, has recently been demonstrated to be induced by orally administered moxonidine [74].

Left ventricular hypertrophy (LVH) is considered to be an important, virtually independent risk factor in hypertensives. Moxonidine and rilmenidine both cause regression of LVH in animal models, possibly as a result of sympathoinhibition. Moxonidine stimulates imidazoline (I_1)-receptors in the kidney, thus causing significant natriuretic effects [75]. Rilmenidine has been shown to bind selectively to I_1-binding sites in the kidney [76] and it also causes a natriuretic effect [77], which may be mediated by renal I_1-receptors. It has also been suggested that the stimulation of the central nervous I_1-receptor contributes to the natriuretic activity of these agents. The clinical relevance of the natriuretic effect in hypertensive patients is so far not known, although it is potentially attractive on theoretical grounds.

Rebound activation of the sympathetic nervous system after abrupt withdrawal of clonidine therapy has been recognized to be a relevant clinical problem in connection with this classic centrally acting antihypertensive agent. This rebound phenomenon can be readily demonstrated in animal models, when prolonged treatment with clonidine via a subcutaneously implanted osmotic minipump is terminated abruptly by removing the minipump. The cessation of clonidine treatment is followed by sympathetic hyperactivation, reflected by severe tachycardia, rhythmic upswings of blood pressure and a rise in plasma noradrenaline [78–80]. Similar experiments performed with moxonidine, however, did not indicate the occurrence of such a rebound phenomenon after the abrupt cessation of treatment [58,81]. In different, less sophisticated models a certain degree of rebound sympathetic activation after rilmenidine withdrawal has been reported [82], but it is not known how relevant these experiments may be to the clinical situation.

Favourable effects on elevated plasma lipids and impaired glucose tolerance have been described for moxonidine

treatment of obese spontaneously hypertensive rats [83]. In comparative studies with clonidine both moxonidine and rilmenidine in antihypertensive doses caused significantly less sedation in various animal models [84,85], thus confirming the concept that clonidine-induced sedation is mediated preferably by central α_2-adrenoceptors rather than by I_1-receptors.

Pharmacokinetic profiles of moxonidine and rilmenidine

The pharmacokinetic profile of moxonidine may be summarized as follows [86–90].

In healthy volunteers the peak plasma concentration is reached 30–60 min after oral ingestion of a moxonidine tablet. More than 90% of the administered dose is absorbed and the absolute bio-availability can be calculated to be 88%. Hepatic first-pass metabolization does not occur. The plasma half-time of elimination amounts to approximately 2 h. About half of the administered dose is eliminated unchanged in the urine. The antihypertensive effect persists much longer than would be expected from the rather short plasma half-time of elimination, indicating that the drug's accumulation in the CNS is decisive for the long duration of the effect.

Repeated administrations of moxonidine do not alter the kinetic profile and accumulation does not occur. The kinetic profile of moxonidine was the same in patients with essential hypertension as it was in normotensives.

In patients with impaired renal function (glomerular filtration rate 30–60 ml/min) the total clearance of moxonidine is reduced and the dose should be titrated according to the requirements of individual patients. A glomerular filtration rate < 30 ml/min is considered to be a contraindication to the use of moxonidine.

In elderly volunteers moxonidine tended to accumulation and reduced clearance. The changes, however, were small and they can probably be explained in terms of the normal age-related decline in metabolic activity. If renal function is preserved (age-related) moxonidine may probably be administered without dose adjustment in the elderly.

The pharmacokinetic profile of rilmenidine may be summarized as follows [91–93].

In healthy volunteers rilmenidine is rapidly and virtually completely absorbed after oral ingestion of tablets. Maximal plasma concentrations are achieved after 1–3 h. Bioavailability is high and is claimed to approach 100%. First-pass metabolization appears not to occur. The presence of food does not influence the kinetic profile. Rilmenidine is predominantly eliminated via renal excretion. The half-time of plasma elimination amounts to approximately 8 h. Progressive renal dysfunction leads to accumulation of rilmenidine during therapy and therefore adjustment of the dosage is required.

Clinical use of moxonidine and rilmenidine

The efficacy of moxonidine as an antihypertensive agent has been established. The drug has been compared with representative agents from the major classes of antihypertensives (atenolol, hydrochlorothiazide, captopril and nifedipine) in controlled trials and found to be equally effective with respect to blood pressure control [94]. The antihypertensive effect is caused by vasodilatation and reduction of peripheral vascular resistance, whereas the basal heart rate and cardiac output remained virtually unchanged [95].

Peripheral sympathoinhibition was reflected by reduced plasma catecholamine levels. Left ventricular hypertrophy (LVH) was reduced by long-term treatment with moxonidine [96]. Plasma lipid profiles and blood glucose are not influenced by moxonidine [97].

A major issue is the side-effect profile. Whereas no doubt exists with respect to the antihypertensive efficacy of the classic centrally acting antihypertensives (clonidine and α-methyl-DOPA), their subjective adverse reactions are judged to be unacceptable in comparison with those of more modern drugs. Moxonidine in antihypertensive doses appeared not to influence a variety of psychomotoric tests and the incidence of sedation appears to be lower than that associated with clonidine therapy [98]. However, appropriate comparative studies of the two drugs remain to be performed. Just as for angiotensin converting enzyme inhibitors and calcium antagonists, no data on an epidemiological scale concerning the potential protective effect of moxonidine treatment against strokes, myocardial infarction, heart failure and renal disease are available. A review [94] concerning the use of moxonidine in antihypertensive treatment has been published.

The antihypertensive efficacy of rilmenidine has also been established, in considerable numbers of patients. Rilmenidine's antihypertensive effect is caused by vasodilatation and reduction of peripheral vascular resistance, whereas little or no change in cardiac output or heart rate is observed [99]. Peripheral sympathoinhibition and reduced plasma noradrenaline levels have been established [99] as for moxonidine.

Treatment with rilmenidine will reduce cardiac and renal sympathetic baroreflex responses, whereas cardiac vagal baroreflex sensitivity appears to be increased. These phenomena indicate the possibility of restoring the impaired baroreflex function known to occur in hypertensives [100].

Long-term treatment with rilmenidine is associated with a reduction in LVH [101]. Rilmenidine, like moxonidine,

is considered to be a lipid-neutral antihypertensive [102]. Just as with moxonidine, rilmenidine's antihypertensive efficacy appeared not to be associated with sedation or impaired alertness in a variety of psychomotoric tests [103].

The general impression obtained is that rilmenidine in antihypertensive doses causes less psychomotoric impairment than do clonidine, α-methyl-DOPA or related drugs, although appropriate, comparative studies have not been performed. Rebound phenomena known for clonidine have so far not been reported for rilmenidine when it is used in antihypertensive treatment.

Long-term epidemiological data concerning the protective effect of rilmenidine on the sequelae of hypertension (strokes, coronary heart disease and heart failure) are not yet available. A review [104] of the antihypertensive properties of rilmenidine has been published.

Conclusions

Owing to the concept that central imidazoline receptors are targets of antihypertensives, there has been a renaissance of interest in the CNS as an important target of pharmacological intervention in hypertensive disease. This renewed interest runs parallel with the renewed attention being devoted to the sympathetic nervous system as an important mediator in the genesis and maintenance of essential hypertension.

Central imidazoline receptors and pathways have been recognized to be involved in a novel mechanism in the regulation of blood pressure, which may also play a role in its derangements, such as in hypertensive disease. In this connection several detailed problems remain to be solved, in particular the precise identification of the imidazoline (I_1)-receptor, its amino acid sequence and its distinction from the α_2-adrenoceptor. A more detailed profile of the I_1-receptor would be very useful for the design of more selective agents to interact with the receptor.

In spite of certain drawbacks and uncertainties, the concept of central imidazoline receptors has offered at least potentially the possibility of designing centrally acting antihypertensives, causing peripheral sympathoinhibition, but with a more favourable profile of side effects than those of the classic agents with high affinities for α_2-adrenoceptors.

Moxonidine and rilmenidine are as yet far from perfect compounds for therapeutic application, but their introduction indicates that a separation between central antihypertensive activity and side effects (such as sedation and a dry mouth) is not necessarily a hopeless enterprise. It seems well worthwhile to pursue this line of research further.

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