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I$_1$-IMIDAZOLINE
RECEPTORS:
FROM THE
PHARMACO-
LOGICAL BASIS
TO THE
THERAPEUTIC
APPLICATION

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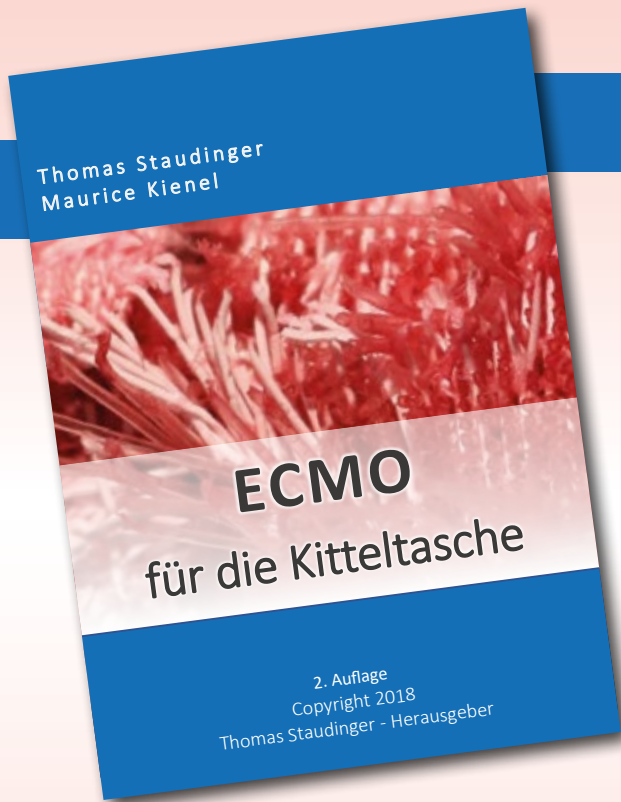# I$_1$-IMIDAZOLINE RECEPTORS: FROM THE PHARMACOLOGICAL BASIS TO THE THERAPEUTIC APPLICATION

INTRODUCTION

Imidazolines and similar centrally acting drugs are antihypertensive agents that inhibit the activity of the orthosympathetic nervous system [1]. Their site of action is located in the central nervous system, more specifically in the medulla oblongata; i.e. in the lateral reticular nucleus of the rostroventral medulla [2]. Imidazolines and related hypotensive substances are highly effective drugs. However, the first generation frequently had bothersome adverse effects, although they were generally not very severe. Pharmacologists and pharmaceutical chemists interested in these drugs had to answer at least two important questions:

- What is the pharmacological mechanism underlying the hypotensive action of these drugs?
- From a mechanistic point of view, would it be possible to differentiate the hypotensive effect from the most common adverse effect, i.e. sedation?

MECHANISM OF ACTION

It was established very early on that imidazolines and molecules with imidazoline-like structures were able to lower blood pressure by an effect on their site of action in the medulla, although catecholamines and phenylethylamines were incapable of producing such an effect at the same site [3]. This structure-activity relationship factor showed that activation of alpha-adrenergic receptors was not the prime mechanism of this action. On the basis of this, the existence of a nonadrenergic receptor specifically acted upon by imidazolines was suggested. The identification and biochemical characterization of these receptors were delayed by the fact that all the available ligands

were "hybrid", i.e. they bound not only to α_2-adrenergic receptors and sometimes α_1-adrenergic receptors but also to specific, nonadrenergic imidazoline receptors. This was particularly true in the case of clonidine [4–6]. Products belonging to the latest generation – including rilmenidine, the leading compound – exhibit a certain selectivity for nonadrenergic receptors; compared with clonidine, their selectivity has been approximately 3 to 10 times greater for imidazoline receptors than for α_2-adrenergic receptors [7]. Hence, this means that, although selective, some binding to adrenergic receptors does occur. However, rilmenidine shows sufficiently poor affinity and weak activity at α_2-adrenergic receptors for side effects associated with the activation of α_2-adrenergic receptors to be adequately diminished in terms of both frequency and severity compared with the earlier generation of drugs. This is notably true in the case of the sedative effect, dryness of the mucous membranes, bradycardia and even the rebound effect which is not observed with rilmenidine [1].

Nevertheless, using these tools, it was possible to distinguish two or even three subtypes of imidazoline receptors. Subtype I$_1$, involved in cardiovascular effects, is sensitive to clonidine and idazoxan (an antagonist of central antihypertensive effects) whereas subtype I$_2$ is insensitive to clonidine but sensitive to idazoxan. The I$_2$-imidazoline receptor was identified as a site for monoamine oxidase regulation [8, 9]. As for subtype I$_3$, it is currently the most puzzling receptor; its existence was suggested on the basis of functional studies which demonstrated that certain imidazolines exerted a regulatory action on the pancreatic secretion of insulin. These pharmacological effects fail to correspond with the pharmacology of either I$_1$- or I$_2$-imidazoline receptors [10]. However, it has so far been impossible to detect any nonadrenergic specific binding of imidazoline-like or related compounds in the

pancreas. Ongoing research in this exciting field is designed to achieve this end. The remainder of this update will be devoted solely to describing advances made concerning receptors involved in the regulation of sympathetic tone, namely I$_1$-imidazoline receptors [11].

I$_1$-imidazoline receptors have been identified in several different species, and in several different tissues, organs and cell lines. We have shown that they are present at a fairly high density in the region of the medulla oblongata which contains the site of hypotensive action for imidazoline-like and related drugs. We also demonstrated that they were located on the plasma membrane of neurons.

Various teams have made attempts to clone the receptors. For the moment, these have not been entirely successful, probably because the receptor protein is unstable in the case of attempts that require purification of the receptor, and because the molecular tools are not sufficiently selective in the case of attempted cloning that relies on expression. New cloning strategies are being developed. There are several experimental arguments in favour of coupling the receptor to one or more G proteins. Two mechanisms of signal transduction associated with I$_1$-imidazoline receptors have recently been identified: phosphatidylcholine-sensitive phospholipase C and adenyl cyclase [12, 13].

Much information has already been obtained concerning I$_1$-imidazoline receptors. However, ligands which would only bind to and therefore only act upon these receptors – specifically ignoring alpha$_2$-adrenergic receptors – have been sadly lacking not only for use in the continued analysis of this nonadrenergic receptor system but also for the exploration of potential new therapeutic pathways which would rely exclusively on such a system.

The synthesis of pyrroline analogues of imidazolines and reference oxazolines led to an appreciable increase in selectivity for I$_1$-receptors compared with α_2 and I$_2$. A few of these compounds will be mentioned: S23515, S23757, LNP 509 and LNP911. Table 1 indicates the affinities of these compounds for I$_1$-, I$_2$- and α_2-adrenergic receptors and their selectivity ratios [14–16].

These compounds are the first imidazoline analogues described which are devoid of any significant affinity for α_2-adrenergic receptors, and we have confirmed that they do not exhibit any agonist or antagonist activity at these receptors. Some of these compounds have allowed us to answer one crucial question concerning this research topic: are imidazoline analogues which are totally without effect on adrenergic receptors capable of affecting blood pressure? In fact, we recently reported that compounds S23515 and LNP509 induce a dose-dependent hypotensive effect in the anaesthetized rabbit when they are administered directly in the vicinity of the medulla oblongata, i.e. intracisternally [14, 17]. These drugs do not cross the blood-brain barrier and must be injected directly into the brain. We showed that LNP509 is as active in genetically modified D79N mice (whose α_2-adrenergic receptors have undergone mutation so that they are no longer functional) as in wild-type mice (i.e. those having normally functioning α_2-adrenergic receptors) [17].

From now on, similar products which cross the blood-brain barrier and can therefore be administered systemically are also available. S23757, which has no intrinsic effect on blood pressure when used under the same experimental conditions, totally inhibits the hypotensive action of S23515 and LNP509; it is the first antagonist which is truly selective towards imidazoline receptors; it has no inhibitory effect whatsoever on

Table 1: Affinities (Ki $\pm$ s.e.m (nM))			
	α_1AR	α_2AR	I$_1$R
LNP 509	>10 000	> 10 000	538 ± 163
S23515	1.710 ± 474	> 10 000	6.40 ± 1.94
S23757	> 10 000	> 10 000	5.30 ± 1.48
LNP 911	> 10 000	> 10 000	0.2 ± 0.1

the hypotensive effect of a purely α_2-adrenergic agonist, α-methylnoradrenaline [14].

More recently still, we synthesized other imidazoline, oxazoline and pyrroline analogues which also proved to be highly selective for imidazoline receptors and had even greater affinity for the latter. Hence, they are powerful tools which can already be used for the further exploration and identification of these original receptors, and especially for further attempts at cloning, as well as in "drug design" strategies [15].

Since several experimental findings appeared to indicate that imidazoline and α-adrenergic systems might interact in the central regulation of cardiovascular function and the action of hybrid drugs, we put this hypothesis to the test using these new molecular tools. Thus, the sequential administration of a low dose of LNP509, without any intrinsic effect, followed 10 minutes later by a dose of α-methylnoradrenaline with very little effect in the anaesthetized rabbit produced a very marked effect on blood pressure. The drugs were administered intracisternally in these experiments, α-methylnoradrenaline being used as the reference "pure" α_2-adrenergic agonist. As expected, this synergistic interaction was not found in D79N mice whose α_2-adrenergic receptors are non functional [17].

Interestingly, the central hypotensive effect of rilmenidine is only obtained at high doses in the D79N mouse and the effect is less pronounced than in control wild-type mice. Only the imidazoline receptor-linked effect

persists in D79N mice; in this case, the synergistic interaction induced in normal animals only by the "hybrid" drug, rilmenidine, cannot occur in D79N mice. It is evident from these data that rilmenidine represents a valuable compromise between its necessary activity at imidazoline receptors and sufficiently weak α_2-adrenergic activity so that it has few adverse effects at the recommended doses but is adequate to trigger the synergistic interaction which is responsible for its marked hypotensive effect. It is therefore an interesting drug for normalizing blood pressure in most of hypertensive patients.

ADDITIONAL EFFECTS

The centrally acting antihypertensive drugs, such as rilmenidine, have remarkable antiarrhythmic effects in experimental models of ventricular arrhythmia associated with sympathetic hyperactivity [18]. They are also capable of producing an appreciable improvement in haemodynamic parameters in models of left ventricular dysfunction (certain forms of chronic heart failure). Some have a beneficial effect on survival in the models previously mentioned [19]. Such additional effects are extremely interesting and need to be confirmed, particularly in man. Clinical trials are being worked out with the aim of achieving this. Some drugs which are selective for imidazoline receptors retain these cardiac activities, and it should therefore be possible to develop drugs that are well tolerated:
- antihypertensive agents with addi-

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tional cardiac effects,

- antiarrhythmics at non hypotensive doses,
- drugs that can be used in the treatment of heart failure at non hypotensive doses.

Renal imidazoline-specific binding sites have also been described [20]. A direct effect of rilmenidine was observed in the rabbit as well as in the human kidney, where it inhibits the Na^+/H^+ exchanger. This effect was contrary to the one induced by the activation of renal α_2-adrenoceptors [21]. Rilmenidine was shown to increase renal blood flow, potassium excretion, natriuresis associated with inhibition of sodium reabsorption, and diuresis, whereas the sympathetic renal nerve activity was markedly decreased [22]. An attractive hypothesis would be that these effects explain the absence of any water or sodium retention in chronic treatments of hypertensive patients with rilmenidine, and account for long term benefits of the drug.

Imidazoline-related drugs are capable of decreasing the glucose-induced insulin secretion from pancreatic β-cells [23–25]. This effect seems to be specific for imidazoline compounds; it could not be reproduced with non-imidazoline α-adrenoceptor agonists. It was suggested that this action could involve receptors specific for imidazolines but different from the classic I_1 or I_2-binding sites.

THERAPEUTIC VALUE

The adverse effects of first generation imidazolines – the most common being the sedative effect – were clearly related to their ability to activate α_2-adrenergic receptors whereas their hypotensive action primarily involves a nonadrenergic mechanism. In the case of second generation central

antihypertensive agents, the development of drugs with greater selectivity for imidazoline receptors led to a considerable decrease in the incidence and severity of adverse effects [1]. Rilmenidine is foremost among such effective, well tolerated antihypertensive drugs and it has undergone extensive clinical study. In addition to its good safety profile, its antihypertensive efficacy has been deemed equivalent to that of drugs belonging to other major classes of drugs routinely employed in the treatment of essential hypertension: thiazide diuretics, beta-blockers, angiotensin converting enzyme inhibitors, and calcium channel blockers (figure 1).

Trials have shown that rilmenidine may be used in combination with other antihypertensives so as to increase the efficacy of treatment without particularly increasing the risk of adverse effects (for review see [1, 26]).

Several open or controlled clinical trials demonstrated that rilmenidine does not affect plasma glucose, plasma lipids and insulin concentrations. In addition, as noted in experimental animal models, in patients showing a metabolic syndrome associated with hypertension, sympathetic overactivity and hyperinsulinism, rilmenidine even significantly lowered the plasma fasting and 2-hour glucose levels and plasma insulin concentration after an oral glucose tolerance test. This result shows the specific potential value of sympathoinhibitory drugs in treating this common disease.

As had already been suggested by a few open trials involving small groups of patients, the echocardiographic results from a recent study carried out on a larger number of subjects were analyzed blind and showed that rilmenidine significantly decreased left ventricular mass in hypertensive patients with left ventricular hypertrophy. Another (pilot) study conducted in non insulin-dependent diabetic patients with micro-albuminuria showed that rilmenidine was as effective as captopril not only in lowering blood pressure but also in reducing microalbuminuria.

Figure 1. Controlled randomized comparative studies rilmenidine versus other major classes of drugs (De Luca N et al. J Hypertens 2000; 18: 1515–22. Scemama M et al. J Cardiovasc Pharmacol 1995; 26 (suppl 2): S34–S39. Dallochio M et al. Ach Mal Coeur Vaiss 1991; 84 (suppl): 42. Fiorentini C et al. Arch Mal Coeur Vaiss 1989; 82 (suppl): 39–46. Luccioni R. Presse Med 1995; 24: 1857–64).
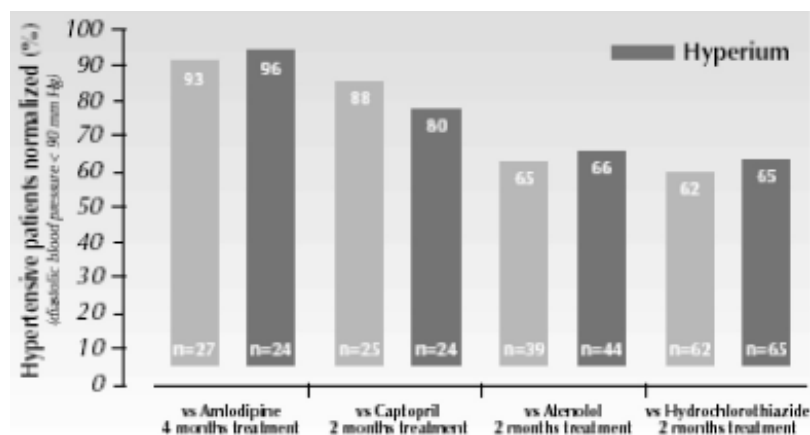
CONCLUSION

A great many new facts have recently come to light concerning both the mechanism of action and clinical efficacy of imidazoline-like drugs. New pharmacological tools and modern animal models have made it possible to develop compounds that are highly selective towards specific nonadrenergic imidazoline receptors which, in turn, has led to the resolution of important questions:

- the activation of I$_1$-imidazoline receptors in the medulla oblongata is by itself sufficient to alter blood pressure;
- the imidazolinergic system and α$_2$-adrenergic system act synergistically in the processes of regulating vasomotor sympathetic tone;
- the residual α$_2$-adrenergic activity of rilmenidine is enough for it to exert this synergistic effect but also sufficiently weak for rilmenidine to be much better tolerated than first generation drugs.

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