



Imidazoline receptors agonists: possible mechanisms of endothelioprotection

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Abstract

Imidazoline receptor agonists are one of the groups of contemporary antihypertensive drugs with the pleiotropic cardiovascular effects. In this review, the historical, physiological, pathophysiological aspects concerning imidazoline receptor agonists and possible mechanisms for their participation in endothelioprotection were considered. Illuminated the molecular biology of each subtype of imidazoline receptors and their significance in the pharmacological correction of cardiovascular disease.

IR type 1 are localized in the brain nucleus, carrying out the descending tonic control of sympathetic activation, as well as in the endothelial cells of the vessels and kidneys. Their activation leads to a decrease in blood pressure, slowing the remodeling of the vascular wall and increasing sodium reabsorption. IR type 2 is expressed predominantly in the adrenal gland, fat and muscle tissues. The physiological effects of their stimulation are associated with an increase in glucose utilization by peripheral tissues. IR type 3 are mainly present in pancreatic cells and are associated with the regulation of insulin secretion. Their stimulation leads to an increase in insulin liberation. Thus, IR agonists are able to improve endothelial function through various mechanisms, including blood pressure reduction, improvement in metabolic profile, and direct positive effects on the vascular wall.

Current information on the pharmacological effects of this group compounds allows us to conclude that they are a promising group for correcting endothelial dysfunction and complications associated with it.

Keywords

endothelial dysfunction, imidazoline receptors agonists, rats, atherosclerosis, blood pressure.

Introduction

The permanent growth of cardiovascular diseases and the socioeconomic damage they cause dictates the necessity for constant improvement of strategies aimed at

the prevention and treatment of this nosological group. Improving the data about the pathogenetic basis of atherogenesis and endothelial dysfunction allows developing existent and creating new strategies for the cardiovascular pathology prevention and correction.

Modern arsenal of remedies for the pharmacotherapy of essential hypertension and associated vascular injury can affect various pathophysiological contours: renin-angiotensin-aldosterone system, intracellular calcium concentration, sympathetic tone, lipid metabolism. A certain advantage is possessed by drugs having application points in several pathological cascades. Drugs which can be applied to several pathological cascades have certain advantage. These drugs include imidazoline receptor (IR) agonists.

History of discovery and general information about imidazoline receptors

The use of IR agonist in medical practice has a long history. In 1945, the cases of hypotension among teenagers and children who had been taking nasal congestants of imidazoline nature led to the synthesis of a number of drugs with antihypertensive activity, the first of which was clonidine. Then it was found that the mechanism of their action is caused by the central sympatholytic activity (Lowry et al. 2014). Further studies have shown that α_2 -adrenergic receptors (α_2 -AR) are their primary target (Timmermans et al. 1981).

However, in a comparative study of the derivatives of β -phenylethylamine and imidazoline activity Ruffolo et al. (1982) obtained the evidence that the binding sites for these compounds are not the same. This indicated either the existence of different binding sites on α_2 -AR, or the interaction of imidazoline derivatives with some other receptor. Since the application of imidazoline derivatives to the lateral reticular nucleus without α_2 -adrenoreceptors caused a decrease of blood pressure, it was predicted that there are specific receptors with a resemblance for a given chemical group. (Bousquet et al. 1986, 1989).

A further search led to the discovery of their endogenous ligand of agmatin, which is decarboxylated arginine (Li et al. 1994). A study of its phenotypic effects has formed the idea of the existence of three types of IR. While the hypotensive effect is mediated by I_1 R (Ernsberger et al. 1995), I_2 R and I_3 R mainly control metabolic processes. Presently, only the gene of the first type receptors has been cloned, therefore, detailed information on the domain and molecular structure was obtained only for them.

Imidazoline receptors type 1

According to existing ideas, imidazoline receptors of type 1 (I_1 R) being localized in the ventrolateral region of the medulla oblongata, are responsible for tonic and reflex control of the sympathetic nervous system.

The I_1 R molecule is encoded by the *NISCH* gene (also known as *I-1*; *IR1*; *IRAS*; *hIRAS*) which is located on third chromosome and widely expressed in many body

tissues but most active in the prefrontal cortex, epiphysis (at night), tonsils, pituitary gland, kidneys, prostate and testes (Fagerberg et al. 2014) (Fig. 1).

The protein product of the *NISCH* gene (Video 1), also called nischarin (Zhang et al. 2006), is located in the cytosol, cytoplasm, endosomes, or cytoplasmic membrane and, depending on localization, can participate in the processes of intracellular signal transmission, formation of the cytoskeleton (binding integrins), regulation of apoptosis, proliferation, cell migration and some others (MGC 2002). It is the transmembrane form that performs the receptor function and is the classical I_1 R-receptor.

Connecting of this form with ligands leads to conformational changes which promote its interaction with phosphatidylinositol and phosphorylation of mitogen-activated protein kinases (MAPK-1 and MAPK-3). An important molecular effect of I_1 R is its ability to suppress the activation of GTPase Rac1 triggering cell death processes (Alahari et al. 2000).

The arginine decarboxylase enzyme synthesizing agmatin from the amino acid L-arginine is widely expressed in brain. To some authors point of view, agmatine, synthesized locally, is an endogenous imidazoline receptor agonist, and it is associated with neurotransmitter control of descending sympathetic activation (Li et al. 1994).

It is considered that besides the participation in the regulation of vascular tone, neurogenic stimuli mediated by I_1 R also control adrenal function (increasing the release of catecholamines) and kidneys (reducing natriuresis) (Smyth et al. 1999). In addition, broad expression of imidazoline receptors in the kidney and endothelium allows them directly influence on the functional state of these tissues.

Imidazoline receptors type 2

I_2 R mediates the utilization of glucose by muscle tissue (through the activation of AMPK) (Lui et al. 2010, Chang et al. 2010). It has also been shown that this type of receptors has an affinity for guanidine and guanidino-like compounds, one of which is metformin. It is considered that most of metabolic effects of metformin are mediated by its antagonism to these receptors. Thus, the use of selective I_2 R-agonist BU224 neutralized such its effects as glycemia decrease, sensitivity of cells to insulin increasing, and the adrenal secretion of β -endorphin - a molecule that increases glucose uptake by peripheral tissues (Lee et al. 2011).

It has been shown that the amiloride injection to rats with streptozotocin-induced diabetes mellitus highly neutralizes the pharmacological effects of metformin. This effect is explained by its metformin's affinity for I_2 R, as a guanidine structure compound. Based on the fact that I_2 R with high (placenta) and low (brain) affinity for amiloride were identified in humans, it was suggested that I_2 R are heterogeneous and represented by types A and B (Diamant et al. 1992, Miralles et al. 1993). I_{2A} R controls the release of β -endorphin (blocked by low concentrations of

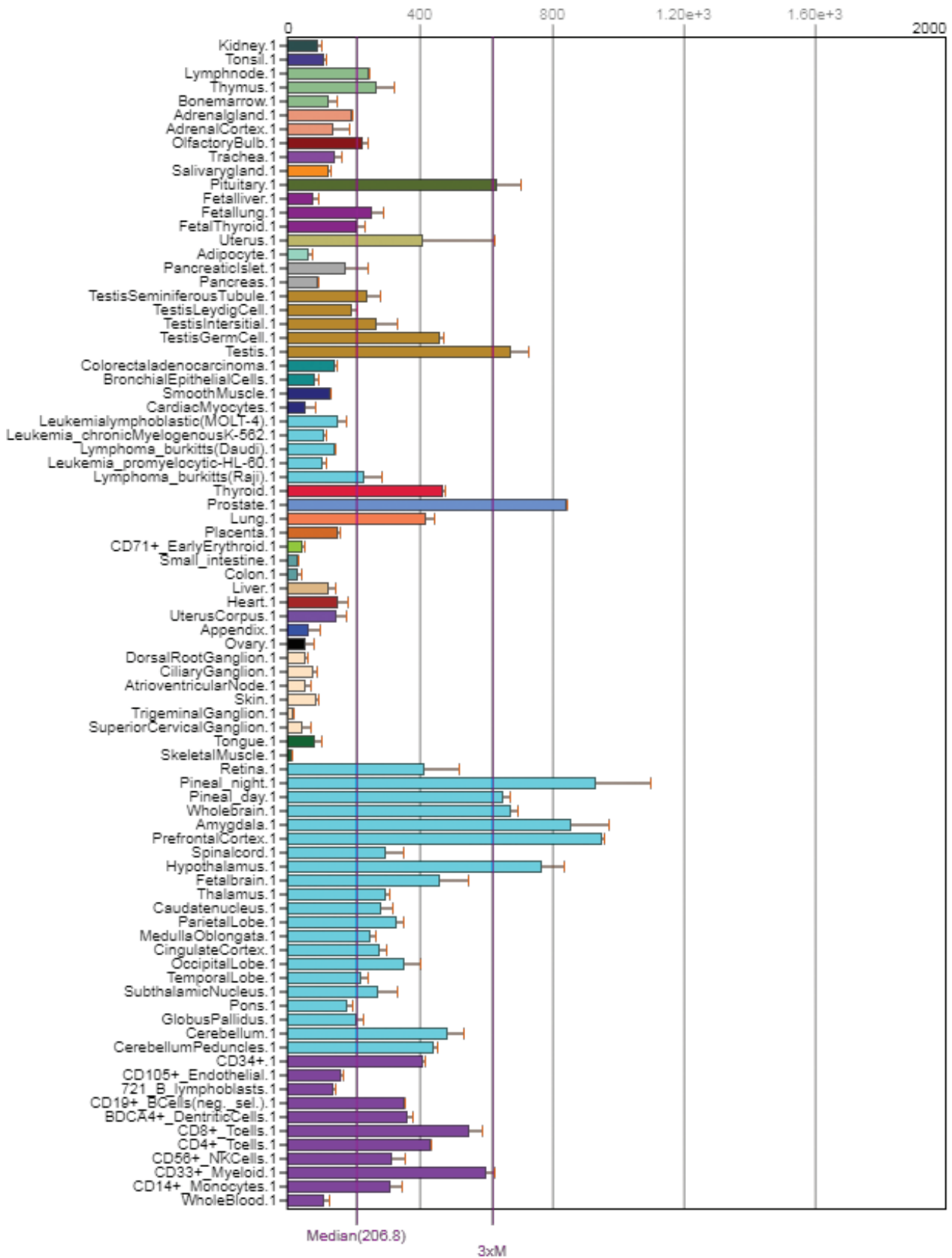
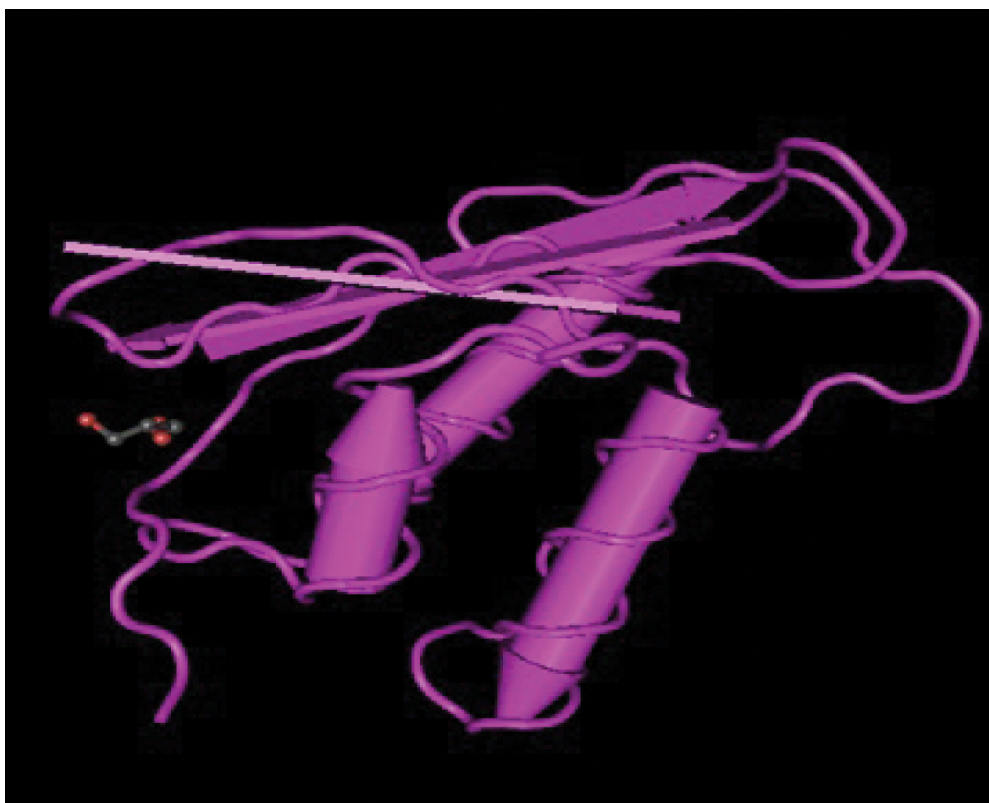


Figure 1. Tissue expression of the NISCH gene (Fagerberg et al. 2014)



Video 1. Graphic structure of I₁R (Madej et al. 2014)

amiloride), and I_{2B}R directly regulates tissue utilization of glucose (blocked by high concentrations of amiloride). Imidazoline connecting domains were found on MAO-A and MAO-B enzymes (Tesson et al. 1999). It's possible that such psychotropic effects of imidazolines as modulation of nociception, dependence and addiction formation are determined by their blocking effect on these enzymes, as they participate in the mediator systems of brain function (Gulati et al. 2009, Li et al. 2011).

Imidazoline receptors type 3

The agonist's imidazoline receptors ability to increase insulin concentration has prompted researchers to detailed analysis of the nature of this process. As a result of a series of experiments on cell cultures of insulinoma RIN-5AH, it was shown that the insulin secretagogue function of pancreatic β -cells is increased by the action of imidazoline compounds even with selective blocking of I₁R and I₂R. This research has indicated the presence of another imidazoline-sensitive receptor and initiated the investigation of I₃R (Morgan et al. 1999; Olmos et al. 1994). Since the addition of an activator of K⁺-ATP-dependent diazoxin channels prevents insulinolysis, it is considered that I₃R performs its function through regulation of K⁺ and Ca²⁺ concentrations of Langerhans cells. Later, β -carboline Harmane was found as its selective agonist (Morgan et al. 2003).

Endothelial dysfunction

The concept of endothelial dysfunction as the central element in the development of cardiovascular pathology allows us to consider endotheliocytes as one of the main targets for the therapy and prevention of arterial hypertension, atherosclerosis, atherothrombosis and related diseases. It is known that the ability to produce the widest spectrum of biologically active substances and the strategically important localization of the endothelial monolayer determine its participation in the control of hemodynamics, rheology of blood, hemostasis, neovasculogenesis and inflammation. In connection with this, ED leads to vasoconstriction, thrombophilia, impairs vascular wall permeability and its leukocyte infiltration, activation of oxidative stress and lipid peroxidation, the appearance of anomalies in the architectonics of the vasculature. The pharmacodynamic effects inherent in the imidazoline receptor agonists are capable of conditioning the endothelioprotective effect through a number of fundamentally different mechanisms:

1) Effect on vascular tone:

Violation of the endothelium vasoregulatory function leads to the appearance of permanent vasoconstriction. At the same time, hypertension is the factor contributing to damage to the endothelial monolayer. As a result, a unique vicious circle is created, the rupture of which is one

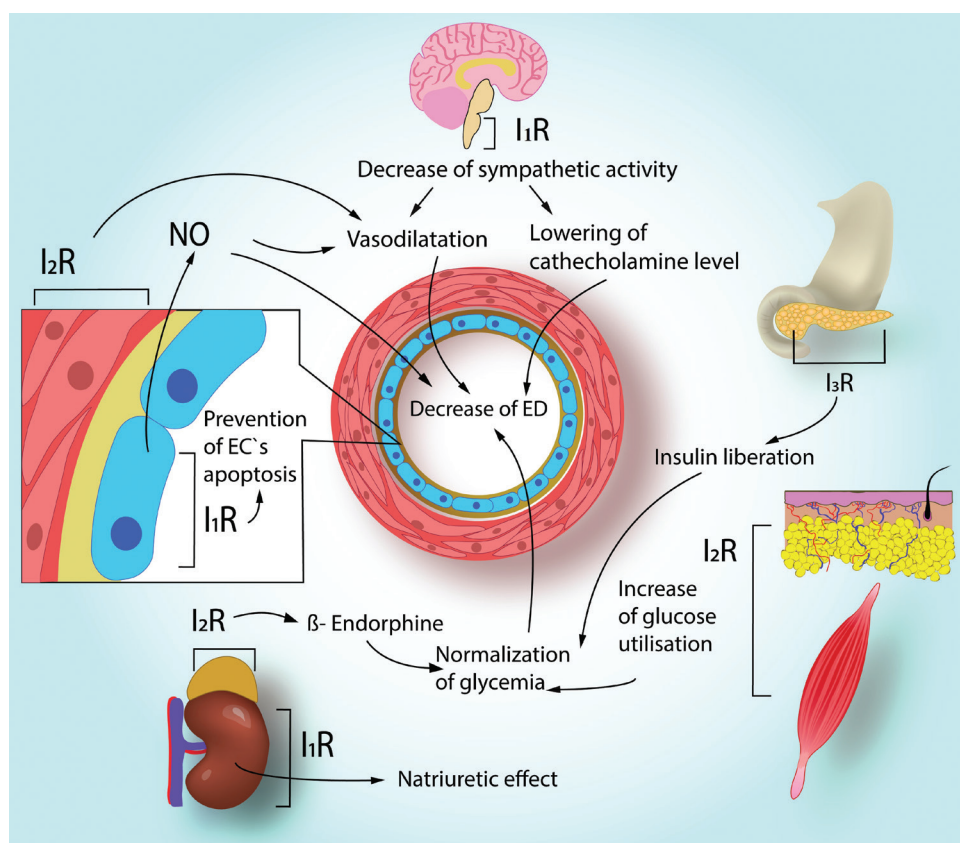


Figure 2. Ways of endothelioprotection with the participation of imidazoline receptor agonists. ED - endothelial dysfunction; EC - endothelial cells; I₁R - imidazoline receptor type 1; I₂R - imidazoline receptor type 2; imidazoline receptor type 3.

of the important tasks of pharmacotherapy. The central effects of imidazoline receptor agonists, realizing through relaxation of sympathetic tone, are considered as a basis for their hypotensive action. However, the reduction in vascular tone is also maintained when imidazolines act on the isolated aortic ring of rats. This fact indicates the presence of a peripheral component in their hypotensive effect. Wherein, this effect is blocked by the preliminary injection of BU224, it means it has been mediated by I₂R. Besides, when imidazoline receptor agonists were used in spontaneously hypertensive rats, vasodilation of peripheral arterioles was observed (Chen et al. 2014). The mechanism of this phenomenon is caused by expression on endothelial cells of I₁R, phosphatidylinositolkinase (PI₃K) activity of which leads to activation of eNOS (Joshi et al. 2007; Maltsev et al. 2013). It also matters that the activation of I₂R can reduce the voltage-dependent activation of Ca²⁺-channels of neurons innervating the vessels (Kim et al. 1999). Finally, the antihypertensive effect of imidazoline receptor agonists may be due to their nephroprotective and natriuretic activity (Smyth et al. 1999, Elkomy et al. 2018) (Fig. 2).

2) Effect on the metabolic profile:

A complex of metabolic abnormalities manifested by obesity, insulin resistance and hyperinsulinemia can be com-

bined in one term - the metabolic syndrome. This disorder is a significant risk factor of the development and progression of cardiovascular diseases.

At the same time, as a result of hyperglycemia, excessive glycosylation of proteins, disruption of intracellular metabolism and disruption of cell function occurs. With considering the peculiarities of localization of endothelial cells, it is not surprising that they are the most vulnerable to long-term increase in glucose level (Tziomalos et al. 2010; Polovina et al. 2014). Clinical investigations of imidazoline receptor agonists in groups of patients, besides the antihypertensive effects, have demonstrated their effectiveness in correction of the metabolic syndrome. Thus, the use of the imidazoline receptor agonist - moxonidine in patients with obesity and metabolic syndrome led to a statistically significant increase in the insulin sensitivity index by 21% compared with placebo. (Haenni et al. 1999). This effect is due to both hypoglycemic action associated with I₂R and I₃R (Fig. 2), and the effect on adipocytokines, such as adiponectin as well. (Zuo et al. 2015; Weiss et al. 2015)

3) Direct effect on endothelial cells:

With considering the ability of imidazoline receptors to inhibit apoptosis and inflammatory activation (mainly due to inhibition of Rac1), it seems logical to suppose that

these effects are also realized in endothelial cells. It is important that, with the action of imidazoline agonists, a change in the cellular homeostasis of endotheliocytes leads to a decrease in the concentration of molecules such as plasminogen activator inhibitor and thrombomodulin (Krespi et al. 1998).

From the point of view of direct effect on endotheliocytes, the above-mentioned ability of imidazoline compounds to effect on eNOS is the most important, since the NO-producing function of the endothelium mediates not only the vasodilation, but also such processes as regulation of the aggregate state of blood and reduction of the stiffness of the vascular wall (Fig. 2).

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Conclusion

Thus, pharmacotherapy with the use of imidazoline receptor agonists has not only an antihypertensive, but also an endothelioprotective purpose as well. Considering the presently available ideas, the described positive effects of imidazoline agonists allow us to view them as effective measures with pleiotropic effects and potentially improving the removed prognosis of patients.

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