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Review Article

Nonclassical cardiovascular effects of imidazoline receptor agonists

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Abstract

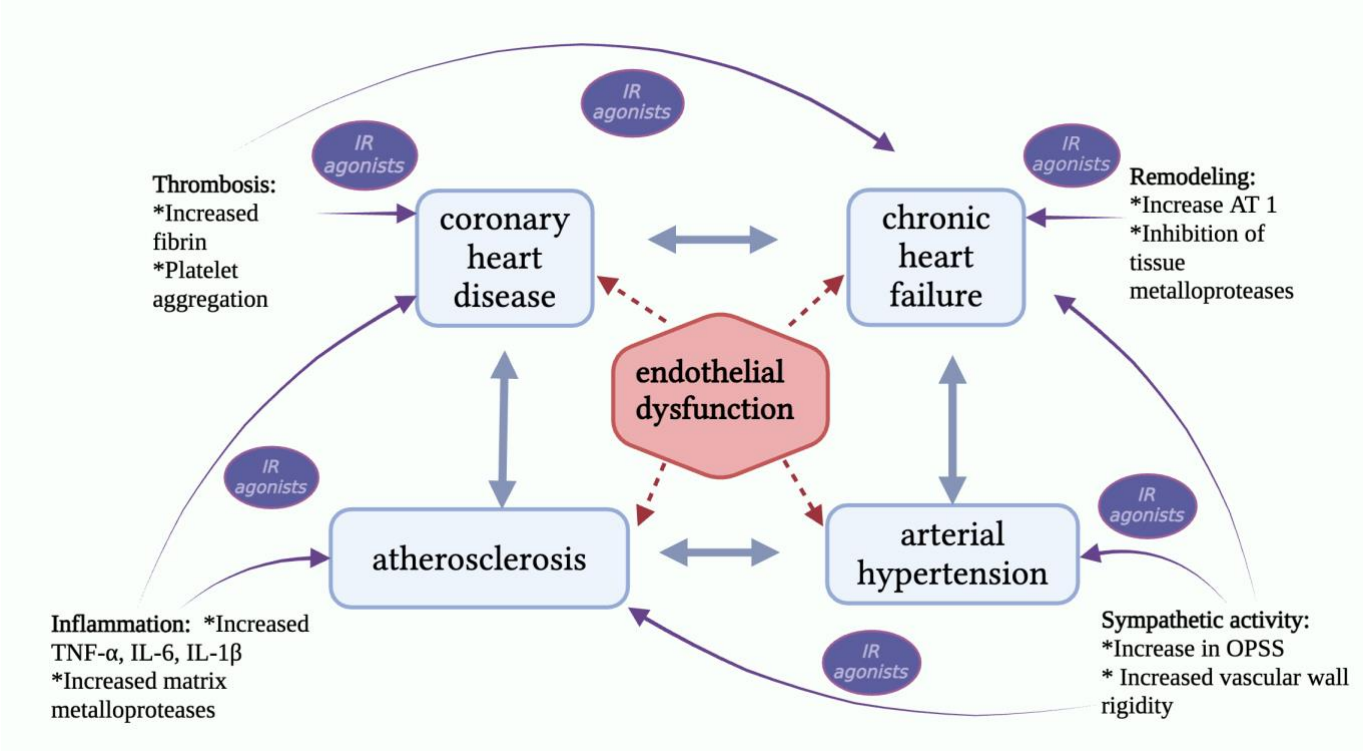
Introduction: Imidazoline receptors are a group of metabotropic receptors whose activation is associated with changes in a number of functional parameters, including hemodynamics (lowering blood pressure (BP), negative chrono-and inotropic effects), metabolic metabolism (reducing insulin resistance, increasing high-density lipoproteins (HDL) levels) and hemorheology (antiplatelet activity). In addition, the spectrum of molecular pharmacological effects of imidazoline receptor (IR) agonists includes anti-inflammatory, antioxidant, and antifibrinolytic activities.

Materials and Methods: Literature sources were searched using PubMed and Google Scholar databases, including such article types as meta-analysis, randomized controlled trial, and review. The inclusion criteria were full availability of data, scientific significance, and relevance of research.

Results and Discussion: Experimental studies in animals revealed such effects of agonists IR as a decrease in the degree of left ventricular hypertrophy (LVH) and interleukin expression. The experience of using agonists IR therapy in clinical practice has revealed its effectiveness in the treatment of patients with chronic heart failure (CHF) II-IIIof NYHA class II-III NYHA with an ejection fraction of less than 40%, arterial hypertension (AH) and microalbuminuria.

Conclusions: In general, the totality of data available to date indicates a high expediency of including imidazoline receptors in the repertoire of pharmacological targets, the impact on which can affect not only soft, but also hard endpoints in the treatment of cardiovascular pathology.

Graphical Abstract



Keywords

imidazoline receptor agonists, cardiovascular continuum, chronic heart failure, atherosclerosis

Introduction

Despite the widespread adoption of effective methods of precision and personalized therapy, the contribution of cardiovascular diseases to the overall structure of mortality and disability continues to increase permanently. The most significant cardiovascular diseases for public health are grouped into the so-called cardiovascular continuum (CVC). According to classical concepts, CVC includes such pathological conditions as atherosclerosis, hypertension, and CHF. At the same time, these conditions have such a close etiopathogenetic relationship that strategic approaches to their correction are largely similar.

Currently, the main line of therapy in patients with hypertension, atherosclerotic vascular lesions and CHF is the suppression of RAAS (renin-angiotensin-aldosterone system) and suppression of catecholaminergic activation. Drugs of the first stage with such activity include: ACE inhibitors, beta-blockers, diuretics, calcium antagonists, and alpha-1 blockers. The positive effect of these drugs on prognosis and hard endpoints has been proven in numerous prospective and retrospective clinical studies. Nevertheless, the search for new (or additional) ways of therapeutic influence on CVC remains an urgent task. Among others, a pharmacological group with more than half a century of study – imidazoline receptor agonists-is of particular interest.

Currently, the role of imidazoline receptors (IR) in practical medicine remains quite modest. For example, the description of the physiology and pharmacology of agonists IR in the 12th edition of Goodman and Gilman is presented in just a few paragraphs (Brunton et al. 2011). This group is not widely used in medical practice and is used only as an auxiliary antihypertensive therapy in people with a combination of hypertension and metabolic syndrome, as well as for emergency reduction of blood pressure (Chan and Morgan 1998). Nevertheless, the most important physiological role of agonists IR in the regulation of hemodynamics and a number of

other vital processes allows us to consider them as an important target for the development of drugs aimed at the treatment of CVC. Here we tried to summarize the available information on the role of agonists IR in the development and progression of CVC, as well as to analyze clinical and experimental data on the pharmacological effectiveness of agonists IR.

Materials and Methods

The authors analyzed and selected relevant articles for review for the period from 1981 to 2024. Literature sources were searched using the PubMed and Google Scholar databases and the Web of Science/Scopus citation index, including the article type as systematic reviews and meta-analyses, randomized controlled trials, clinical case descriptions, and clinical literature reviews. The inclusion criteria were full availability of data, scientific significance and relevance of studies, and the following keywords were used for the search: imidazoline receptor agonists, beta-phenylethylamine and imidazoline derivatives, arterial hypertension, metabolic syndrome, diabetes mellitus, obesity, Moxonidine, Metformin, Rilmenidine, Clonidine, type I IR (IR1), IR second type (IR2), and third type IR (IR3). A total of 232 articles were found in the above databases, but according to the inclusion criteria, 181 articles did not meet them and were excluded from processing and further analysis of the review.

Results and Discussions

Basic information about agonists IR

For many years, IR agonists have been trying to gain their place in clinical practice. If we go deeper into history, the first recorded ”case-control” clinical trials date back to the 1940s (Bylund and Martinez 1981; Lowry and Brown 2014; Bousquet et al. 2020). Later, scientists, when comparing the activity of β-phenylethylamine and imidazoline derivatives, found that there are different binding sites for both α2-AR and the place of interaction of imidazoline derivatives with another type of receptor, as a result of which the hypothesis of the existence of some other receptors with affinity for this group of chemical compounds was suggested (Ruffolo et al. 1982; Bousquet et al. 1989).

In parallel, the agmatine ligand decarboxylated arginine was discovered in the 1990s (Li et al. 1994). Since the assessment of the pharmacological properties of agonists IR allowed us to form an idea of the existence of three different types of these receptors. In particular, it was found that the antihypertensive effect associated with IR activation is mainly mediated through the first type of IR (IR1), while the second type of IR (IR2) mediates neuroprotective, anti-apoptotic and anti-inflammatory effects, and the third type of IR (IR3) is mainly involved in the regulation and control of various metabolic processes occurring in the body. To date, only the gene encoding the first type of receptor (IR1) has been cloned, which means that detailed and structural information related to the domains and molecular organization of these receptors has been obtained exclusively for IR1. At the same time, as of today, information on the molecular structure and domain features of IR2 and IR3 is quite scant, since their genes have not yet been fully identified and cloned, which makes it difficult to better understand their functions and mechanisms of action (Ernsberger et al. 1995).

To summarize from the above, there are currently 3 types of IR:

Type 1 – localized mainly in the medulla oblongata (pallidum, hippocampus, striatum, amygdala and substantia nigra), exerting a hypotensive effect, reverse development of left ventricular hypertrophy and reduction of signs of left ventricular remodeling; in the liver, it leads to an increase in HDL and a decrease in low-density lipoproteins (LDL) and triglycerides (TG) levels; on platelet membranes (Bousquet et al. 1984);

Type 2 – widespread in various structures of the central nervous system (CNS), including the inter-leg and arched nuclei, as well as the pineal gland. In addition, it is found in the brain matter of parenchymal internal organs, in the large intestine, placenta, urethra and prostate. In addition, it is present in immunocompetent cells located in the central nervous system, such as astrocytes and microglia, as well as in platelets, vascular smooth muscle cells, and other tissue structures. This mechanism mediates neuroprotective activity, including reduction of neuroinflammation and apoptosis, inhibition of excitotoxicity, and reduction of brain edema. In addition, it has a pronounced analgesic activity-contributing to the weakening of mechanical allodynia and thermal hyperalgesia, while simultaneously showing a hypothermic effect (Gongadze et al. 2008);

Type 3 – present in beta cells of the pancreatic Langerhans islets and controls insulin secretion (Mahmoudi et al. 2018). In more detail, the endogenous ligand is clonidine-containing compounds (an example is β-carboline), which are involved in the regulation of insulin

production and have a positive effect on the integrity of the vascular endothelium. It is also important to provide an anti-inflammatory effect by activating hemoxynenase-1 (HO-1), which contributes to the inhibition of lipopolysaccharide-induced production of nitric oxide (NO), prostaglandin E2 and interleukin-6, which induce a shift in the cardiomyocyte cell cycle towards apoptosis, remodel the heart muscle, and disrupt the collagen ratio (Morganet al. 1999; Morgan et al. 2003). With the predominant activation of collagen I and inhibition of collagen III, further hypertrophic and atrophic processes of the dilated parts of the heart are inhibited (Nguyen et al. 2016).

Pathobiology of CVC

To understand the potential role of agonists IR in influencing the pathological cascades of CVC, basic information about the key mechanisms of hypertension, CHF, and atherosclerosis is presented below. Sympathetic activation, ED, chronic inflammation of the vascular wall and myocardium, and an increase in the pro-apoptotic orientation of cells can be distinguished among the basic pathological processes involved in the formation of all CVC links.

Endothelial dysfunction

The key and, of course, one of the most significant links in pathogenetic cascades underlying the development of various forms of cardiovascular diseases is a violation of the physiological function of endotheliocytes. These cells play a critical role in ensuring the regulation of vascular tone, as they are responsible for the balance between vasodilation and vasoconstriction, which is necessary to maintain adequate blood flow and blood pressure. In addition, endothelial cells are involved in the regulation of the hemostatic system, since they are involved in the synthesis of various factors in the process of fibrinolysis and platelet antiaggregation. Additionally, these cells play an important role in modulating local inflammation, since they are able to produce and secrete both pro-inflammatory and anti-inflammatory cytokines, which provides dynamic regulation of inflammatory responses in the tissues of the vascular system. Along with this, the endothelial cell regulates the anatomical structure and morphology of blood vessels, controlling the synthesis and inhibition of factors that are responsible for reducing proliferative factors, which subsequently affects vascular remodeling, the development of atherosclerotic plaques, and other pathological changes in the vascular walls (Li et al. 1994; Chaikijurajai et al. 2020). The leading humoral factor produced by endothelial cells is nitric oxide (NO) (Bousquet et al. 1984; Ernsberger et al. 1995; Wang and He 2024).

Direct contact of endothelial cells with the bloodstream means that they are particularly vulnerable to damage by circulating molecules in the blood, on the one hand, and that they play a crucial ”protective” role, on the other hand. The main mechanisms of endothelial cell damage include inflammatory hyperactivation, oxidative stress, hyperhomocysteinemia, hyperglycemia, etc. The death of endotheliocytes leads, on the one hand, to an increase in the permeability of the vessel wall for inflammatory cells and lipids, and on the other, to a violation of hemorheology and a decrease in tissue perfusion.

Sympathetic activation

The catecholaminergic system also plays a key role in the pathogenesis of cardiovascular diseases and is an important mechanism that ensures the body’s adaptation to stressful situations. Catecholamines such as norepinephrine, epinephrine, and dopamine are produced by the adrenal glands and nerve endings of the sympathetic nervous system. These molecules are important neurotransmitters that provide increased oxygen delivery to the tissues, which is achieved by increasing cardiac output and optimizing myocardial perfusion. With the progression of CVC diseases, an increase in the concentration of catecholamines in blood plasma is observed. This change occurs as the myocardium is depleted, and its function is impaired, which is especially characteristic of the development of heart failure. Elevated levels of catecholamines, although being an adaptive response of the body, can have a negative impact on the cardiovascular system over time. In particular, sympathetic activation leads to significant stimulation of vascular endothelial smooth muscle cells, which contributes to their excessive activity, leading to the formation of active radicals and triggering the processes of oxidative stress, apoptotic activation of endotheliocytes, cardiomyocytes, and fibroblast proliferation. Ultimately, all these pathological changes lead to the progression of conditions such as atherosclerosis and chronic heart failure (Proshaev et al. 2012; Danilenko et al. 2025).

Remodeling

During the progression of heart failure, a cascade of specific reactions of adhesion and infiltration of monocytes into the intima is triggered, contributing to hypoxia inside the plaque, which

ultimately leads to its revascularization and necrosis. Its progressive growth leads to a weakening of the compensatory properties of the musculoelastic framework of the blood vessel, causing remodeling and dilation. One of the key processes contributing to myocardial remodeling is inhibition of tissue metalloproteinases, as well as changes in the expression of matrix metalloproteinases. These changes lead to a violation of the balance of collagen structures in myofibrils, which in turn significantly affects the mechanical properties of the myocardium and its functionality (Maslovet al. 2015). In the context of the renin-angiotensin-aldosterone system (RAAS), special attention should be paid to the angiotensin 1 receptor (AT1), which plays a central role in the pathophysiology of various cardiovascular diseases. Activation of this receptor is carried out through several intracellular signaling pathways, which, in turn, trigger a cascade of biochemical reactions. Among them, a certain role is played by the activation of the protein kinase system, which involves NADP-oxidase subunits, as well as various growth factor receptors. AT1 also interacts directly with proteins that activate signaling pathways such as Janus kinase 2 and phospholipase C. For example, one of the effects of activating the AT1 receptor is its binding to filamine A, which leads to actin remodeling and maintenance of the structure and functions of myocytes, since the actin-myosin system ensures the contractility of the heart. In addition, AT1 interacts with prostaglandin F receptors, which increases vasoconstriction and, consequently, leads to an increase in blood pressure. This interaction becomes especially important in conditions of cardiovascular insufficiency, when redistribution of blood flow and increased vascular resistance can worsen the course of the disease (Stepenko et al. 2024). It is also worth noting that the interaction of AT1 with the epidermal growth factor (EGF) receptor plays a key role in vascular remodeling. This interaction contributes not only to changes in the structure of the vascular wall, but also contributes to the processes of angiogenesis, which can affect the mitochondrial respiration of myocardiocytes, including in conditions of coronary heart disease.

Thus, myocardial remodeling is not an isolated process, but is a complex mechanism involving many regional and systemic interactions, each of which makes a significant contribution to adaptation and, often, pathological changes in the cardiovascular system (Kawai et al. 2017).

Inflammation

Vascular wall inflammation is a complex biological process, mainly initiated by the activation of pro-inflammatory cytokines. These molecules are not just signaling substances, but have unique and specific pathways of action that ultimately lead to the development of endothelial dysfunction. For example, tumor necrosis factor alpha (TNF-alpha) plays an important role in the pathogenesis of inflammatory processes. It increases the concentration of angiotensin II type 1 (AT1) in the heart, which leads to the activation of a number of pathogenetic mechanisms. Elevated levels of AT1, in turn, increase vasoconstriction and contribute to myocardial overload, which can negatively affect its function. In addition, TNF-α increases the activity of matrix metalloproteinases, which can lead to degradation of the extracellular matrix and disruption of the structural integrity of the vascular wall, aggravating the remodeling process and contributing to the progression of cardiovascular diseases. Meanwhile, interleukin-6 (IL-6) is also important in the pathogenesis of the inflammatory process. It can have a negative inotropic effect on the myocardium, which is expressed in a decrease in the contractility of the heart muscle. This occurs through increased regulation of nitric oxide synthetase (NO), which in turn affects the level of NO in myocardial tissue. An increase in NO leads to activation of cyclic guanosine monophosphate (cGMP), which may weaken the mechanisms of myocardial contraction. It should be noted that IL-6 reduces the activity of Ca2+ - ATPase in the sarcoplasmic reticulum of the myocardium. This leads to a violation of the utilization and release of calcium, which is critical for the normal contractile function of the myocardium. A decrease in free calcium for contraction leads to a decrease in the strength of heart contraction, which subsequently initiates apoptotic reactions in the myocardium. This process is activated through the Janus kinase system (JAK) and mitogen-activated protein kinase (MAPK) (Bousquet et al. 1984).

Thus, vascular wall inflammation initiated by pro-inflammatory cytokines is a multicomponent process in which each cytokine plays its own unique role, contributing to the development of endothelial dysfunction and worsening myocardial function. As a result of this negative interaction, the risks of cardiovascular disease increase, which underscores the importance of understanding these mechanisms for developing effective therapeutic strategies.

Non-classical effects of agonists IR according to experimental and clinical data

In an experimental model of CHF in hamsters, Moxonidine c demonstrated anti-inflammatory, antioxidant, and antifibrotic effects by inhibiting TNF-α, IL-1β, NF-KBp65, and iNOS, and changing the ratio of collagen I/III. Simultaneously in the preclinical study of Stabile A. when

modeling cardiomyopathy in hamsters, Moxonidine had a direct sympatho-inhibitory effect, preventing left ventricular hypertrophy and myocardial remodeling (Lijnen et al. 2002). The cardiomyotropic effect of three-week administration of Moxonidine at doses of 3 and 6 mg/kg was also evaluated in a rat model of CHF, where its antifibrotic and negative chronotropic activity was confirmed (Alteret et al. 2012). In Honsho et al. (2009), bolus intravenous administration of Moxonidine to rats, in addition to the basic hypotensive effects, increased the level of atrial natriuretic peptide in plasma and cGMP in the cytosol, and also led to a decrease in the degree of LVH and IL-1b expression in the myocardium in the long-term follow-up period. In the course of experimental work on L-NAME-induced ED in rats, Moxonidine and Metformin demonstrated a complex effect on the pathogenesis of endothelial-associated diseases, due to the correction of nitric oxide deficiency. Radwanska et al. (2009) investigated the effect of agonists IR on rat isolated atria of the heart, and it was shown that Clonidine is characterized by the greatest positive inotropic effect in the Clonidine-Rilmenidine-Moxonidine series. The transgenic SHROB rat line with the faK mutation to the leptin receptor shows a triad of symptoms: arterial hypertension, glucose intolerance, and insulin resistance, but when pharmacocorrected with Moxonidine, blood pressure, insulin levels, and free fatty acids in blood plasma were reduced. Similar results were obtained when using Rilmenidine in the above-mentioned animal model, in addition, triglyceride and cholesterol concentrations were reduced (Velliquette et al. 2006). In an experimental study on Holtzmann rats, the cardiogenic effects of Moxonidine were compared when the site of drug administration was changed – this is the 4th ventricle and the lateral ventricle of the brain (GM). The first route of administration of Moxonidine – 4th ventricle GM – showed the following effects: a decrease in blood pressure, heart rate (HR), as well as renal and mesenteric vascular resistance. The second route of administration, the lateral ventricle of GM, showed other effects than those listed above, such as a decrease in renal vascular resistance, without changes in blood pressure, heart rate, and mesenteric vascular resistance (Moreiraet et al. 2007).

In clinical practice, Moxonidine and Rilmenidine are used to reduce blood pressure, while Moxonidine does not significantly affect the heart rate, unlike Rilmenidine, which exhibits a negative chronotropic effect due to the activation of the vagus nerve (Siwiket et al. 2000). A clinical trial of Moxonidine in doses of 0.1 mg, 0.2 mg, and 0.3 mg, conducted in 97 patients with II-IIINYHA class II-III CHF NYHA and an ejection fraction of less than 40%, resulted in a significant reduction in SBP and plasma norepinephrine levels (Kerckhoven et al. 2000). During a clinical trial of Moxonidine at a dose of 0.4 mg; 0.6 mg, conducted on 32 patients with class II-III CHF (according to NYHA) receiving classical therapy: ACE inhibitors, diuretics, digitonin. Moxonidine at a dose of 0.6 mg reduced mean systemic BP ($p < 0.0001$), mean pulmonary BP ($p < 0.01$), and heart rate ($p < 0.05$) (Swedberg et al. 2000; Mukaddam-Daher et al. 2004).

To study the effect of Clonidine on the heart rate, 18 patients with CHF were selected in a clinical study. The RR interval for sinus beats was 822±125 MS ($p=0.001$), and the distance covered during the 6-minute walk test was 1255±359 feet ($p=0.042$). The study revealed a decrease in SBP from 139±15 to 119±10 mm Hg; the average value of all RR intervals for 24 hours: 116±94 to 130±19 MS, $p=0.033$; Clonidine improved heart rate variability in patients with congestive heart failure by increasing parasympathetic tone (Girgis et al. 1998; Dickstein et al. 1999).

Since special interest is paid to RAAS in the application of pharmacotherapy points, it can be stated that in clinical studies on healthy volunteers, Rilmenidine proves its nephroprotective effect and normalizing effect on the endothelial hemostasis system. Contraindications to use are patients with chronic renal failure due to the main route of elimination of the drug (Messerli 2000). In a study by Krespi et al. (1998), patients with hypertension and microalbuminuria were given standard antihypertensive therapy in combination with Moxonidine, which demonstrated an effect on renal and endothelial functions. This was due to a decrease in urinary excretion of albumin, thrombomodulin, and plasminogen activator inhibitor-1, which further improved the prognosis and quality of life of patients (Karlafti et al. 2013, Maslov et al. 2015).

In terms of the frequency of development of undesirable side effects, Clonidine is almost 3 times inferior to Rilmenidine, as it causes drowsiness, impaired concentration, and dry mouth in patients. Rilmenidine has proven itself well among the elderly, thereby ensuring the absence of withdrawal effects, orthostatic hypotension, and metabolic tolerance (Britov and Orlova 2006).

Conclusion

Thus, the results of Russian and foreign studies allow us to judge imidazoline receptors as promising targets in the treatment of cardiovascular diseases, the effect on which allows not only

adequate, but also long-term control of blood pressure, regulate the metabolic profile (reducing insulin resistance, increasing HDL levels, suppressing lipolysis), improve endothelial function and normalize hemorheology (Ristovska et al. 2006). Currently, in clinical practice, patients with cardiovascular diseases, in certain cases, such as emergency pharmacotherapy for hypertensive crises and when standard antihypertensive therapy is ineffective, are prescribed agonists IR. Thus, the question of the possibility of including agonists IR in standard treatment regimens remains open and requires further study. This paper provides evidence of the prospects of such research.

Additional Information

Conflict of interest

The authors declare the absence of a conflict of interests.

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Data availability

All of the data that support the findings of this study are available in the main text.

References

- Alahari SK, Lee JW, and Juliano RL (2000) Nischarin, a novel protein that interacts with the integrinα5 subunit and inhibits cell migration. The Journal of Cell Biology 15: 1141–1154. https://doi.org/10.1083/jcb.151.6.1141 [PubMed]
- Alter P, Apelt S, Figiel JH, Rominger MB, Rupp H, and Heitmann J (2012) The missing link between heart failure and sleep disordered breathing: increased left ventricular wall stress. Intetnational Journal of Cardiology 157(2): 294-297. https://doi.org/10.1016/j.ijcard [PubMed]
- Bousquet P, Feldman J, Tibirica E, Bricca G, Molines A, Dontenwill M, and Belcourt A (1989) New concepts on the central regulation of blood pressure. Alpha 2-adreno-ceptors and "imidazoline receptors'. American Journal of Medicine 87: 10-13. https://doi.org/10.1590/s0074-02761993000200024 [PubMed]
- Bousquet P, Feldman J, and Schwartz J (1984) Central cardiovascular effects of alpha-adrenergic drugs: Differences between catecholamines and imidazolines. The Journal of Pharmacology and Experimental Therapeutics 230(1): 232-236. [PubMed]
- Bousquet P, Hudson A, García-Sevilla JA, Jun-Xu L, and France CP (2020) Imidazoline receptor system: The past, the present, and the future. Pharmacological Reviews 72(1): 50-79. https://doi.org/10.1124/pr.118.016311 [PubMed]
- Britov AN and Orlova OA (2006) Place of agonists imidazol(in)e receptors in arterial hypertension patients therapy. Russian Journal of Cardiology 11(1): 95-100. [in Russian]
- Brunton L, Chabner B, and Knollman B (2011) Goodman and Gilman's Pharmacological Basis of Therapeutics. McGraw-Hill Education, 295 p.
- Bylund D and Martinez JR (1981) Postsynaptic localization of alpha 2-adrenergic receptors in rat submandibular gland. The Journal of Neuroscience 1(9): 1003-1007. https://doi.org/10.1523/JNEUROSCI.01-09-01003.1981[PubMed] [PMC]
- Chaikijurajai T and Wilson Tang WH (2020) Reappraisal of inflammatory biomarkers in heart failure. Current Heart Failure Reports 17(1): 9-19. https://doi.org/10.1007/s11897-019-00450-1 [PubMed]
- Chan SL and Morgan NG (1998) Sigma receptor ligands and imidazoline secretagogues mediate their insulin secretory effects by activating distinct receptor systems in isolated islets. European Journal of Pharmacology 350 (2-3): 267-272. https://doi.org/10.1016/s0014-2999(98)00263-5 [PubMed]
- Danilenko AP, Khentov AA, Kuznetsov AV, Shmigerova VS, Stepenko YuV, Tarasova AP, Yakushev VI, Boeva EV, Miller AV, Tatarenkova IA, Puzanova TV, Loboda YaV, Trashchenko AP, Gudyrev OS, Motailo AL, Kuzichkin VN, Milashechko VN, and Danilenko LM (2025) Predictive analysis and prediction of the main molecular targets for the N-acetyl-6-aminohexanoate derivative. Research Results in Pharmacology 11(2): 73–85. https://doi.org/10.18413/rrpharmacology.11.560
- Diamant S, Eldar-Geva T, and Atlas D (1992) Imidazoline binding sites in human placenta: evidence for heterogeneity and a search for physiological function. British Journal of Pharmacology 106 (1): 101–108. https://doi.org/10.1111/j.1476-5381.1992.tb14300.x [PMC]
- Dickstein K, Manhenke C, Aarsland T, Kopp U, McNay J, and Wiltse C (1999) Acute hemodynamic and neurohumoral effects of moxonidine in congestive heart failure secondary to ischemic or idiopathic dilated cardiomyopathy. The American of Journal Cardiology 83(12):1638-1644. https://doi.org/10.1016/s0002-9149(99)00170-8 [PubMed]
- Ernsberger P, Graves ME, Graff LM, Zakieh N, Nguyen P, Collins LA, Westbrooks KL, and Johnson GG (1995) I_1-imidazoline receptors. Definition, characterization, distribution, and transmembrane signaling. Annals of the New York Academy of Sciences 763: 22–42. https://doi.org/10.1111/j.1749-6632.1995.tb32388.x [PubMed]
- Fagerberg L, Hallstrom BM, Oksvold P, Kampf C, Djureinovic D, Odeberg J, Habuka M, Tahmasebpoor S, Danielsson A, Edlund K, Asplund A, Sjostedt E, Lundberg E, Al-Khalili C, Skogs M, Ottosson J, Berling H, Tegel H, Mulder J, Nilsson P, Schwenk JM, Lindskog C, Danielsson F, Mardinoglu A, Sivertsson A, von Feilitzen K, Forsberg M, Zwahlen M, Olsson I, Navani S, Huss M, Nielsen J, Ponten F, Uhlén M (2014) Analysis of the human

tissue-specific expression by genome-wide integration of transcriptomics and antibody-based proteomics. Molecular Cellular Proteomics 13: 397-406. https://doi.org/10.1074/mcp.M113.035600 [PubMed]

- Feher A, Toth VE, Al-Khrasani M, Balogh M, Lazar B, Helyes Z, Gyires K, and Zadori ZS (2017) Analysing the effect of I1 imidazoline receptor ligands on DSS-induced acute colitis in mice. Inflammopharmacology 25(1): 107-118. https://doi.org/10.1007/s10787-016-0299-7 [PubMed]
- Gasparik V, Greney H, Schann S, Feldman J, Fellmann L, Ehrhardt JD, and Bousquet P (2015) Synthesis and biological evaluation of 2-aryliminopyrrolidines as selective ligands for I2 imidazoline receptors: discovery of new sympatho-inhibitory hypotensive agents with potential beneficial effects in metabolic syndrome. Journal of Medicinal Chemistry 58 (2): 878-887. https://doi.org/10.1021/jm501456p [PubMed]
- Girgis I, Chakko S, de Marchena E, Jara C, Diaz P, Castellanos A, and Myerburg RJ (1998) Effect of clonidine on heart rate variability in congestive heart failure. Journal of the American College of Cardiology 82(3): 335-337. https://doi.org/10.1016/s0002-9149(98)00329-4. [PubMed]
- Gongadze NV, Antelava NA, and Kezeli TD (2008) Imidazoline receptors. Georgian Medical News 44(7): 160-161. [PubMed]
- Honsho S, Nishikawa S, Amano K, Zen K, Adachi Y, Kishita E, Matsui A, Katsume A, Yamaguchi S, Nishikawa K, Isoda K, Riches D, Matoba S, Okigaki M, and Matsubara H (2009) Pressure-mediated hypertrophy and mechanical stretch induces IL-1 release and subsequent IGF-1 generation to maintain compensative hypertrophy by affecting Akt and JNK pathways. Circulation Research 105(11): 1149-1158. https://doi.org/10.1161/circresaha.109.208199 [PubMed]
- Karlafti EF, Hatzitolios AI, Karlaftis AF, Baltatzi MS, Koliakos GG, and Savopoulos CG (2013) Effects of moxonidine on sympathetic nervous system activity: An update on metabolism, cardio, and other target-organ protection. Journal of Pharmacy and Bioallied Sciences 5(4): 253–256. https://doi.org/10.4103/0975-7406.120067 [PubMed]
- Kawai T, Forrester SJ, O'Brien S, Baggett A, Rizzo V, and Eguchi S (2017) AT1 receptor signaling pathways in the cardiovascular system. Pharmacological Research 125: 4-13. https://doi.org/10.1016/j.phrs.2017.05.008 [PubMed]
- Kerckhoven R, Veen TA, Boomsma F, Saxena PR, and Schoemaker RG (2000) Chronic administration of moxonidine suppresses sympathetic activation in a rat heart failure model. European Journal of Pharmacology 397(1): 113-120. https://doi.org/10.1016/s0014-2999(00)00232-6 [PubMed]
- Lee J, Chen W, Wu H-T, Lin K, and Cheng J (2011) Metformin can activate imidazoline I-2 receptors to lower plasma glucose in type 1-like diabetic rats. Hormone and Metabolic Research 43(1): 26–30. https://doi.org/10.1055/s-0030-1267169 [PubMed]
- Li G, Regunatham S, Barrow C, Eshraghi J, Cooper R, and Reis DJ (1994) Agmatine: an endogenous clonidine-displacing substance in the brain. Science 263(5): 966-969. https://doi.org/10.1126 / science.7906055 [PubMed]
- Lijnen P, Petrov V, Rumilla K, and Fagard R (2002) Stimulation of collagen gel contraction by angiotensin II and III in cardiac fibroblasts. Journal of the Renin-angiotensin-aldosterone-System: JRAAS 3(3): 160-166. https://doi.org/10.3317/jraas.2002.036 [PubMed]
- Lin MH, Hsu CC, Lin J, Cheng J, and Wu M (2017) Identification of morin as an agonist of imidazoline I-3 receptor for insulin secretion in diabetic rats. Naunyn-Schmiedebergs Archives of Pharmacology 390(10): 997-1003. https://doi.org/10.1007/s00210-017-1399-7 [PubMed]
- Lowry J and Brown J (2014) Significance of the imidazoline receptors in toxicology. Clinical Toxicology 52(5): 454-469. https://doi.org/10.3109/15563650.2014.898770 [PubMed]
- Mahmoudi J, Majdi A, Lattanzi S, Napoli MD, Bershad EM, Rodrigues CM, and Divani AA (2018) Imidazoline receptor agonists for managing hypertension may hold promise for treatment of intracerebral hemorrhage. Current Molecular Medicine 18 (4): 241-251. https://doi.org/10.2174/1566524018666180926163712 [PubMed]
- Maslov MY, Wei AE, Pezone MJ, Edelman ER, and Lovich MA (2015) Vascular dilation, tachycardia, and increased inotropy occur sequentially with increasing epinephrine dose rate, plasma and myocardial concentrations, and cAMP. Heart, Lung Circulation 24(9): 912–918. https://doi.org/10.1016/j.hlc.2015.02.012 [PubMed]
- Maslov MD, Abraham EW, Pezone MJ, Edelman ER, and Lovich MA (2015)Vascular dilation, tachycardia, and increased inotropy occur sequentially with increasing epinephrine dose rate, plasma and myocardial concentrations. Heart Lung Circulation 24(9): 912-918. https://doi.org/10.1016/j.hlc.2015.02.012 [PubMed]
- Messerli F (2000) Moxonidine: a new and versatile antihypertensive drug. Journal of Cardiovascular Pharmacology 35: 53-56. https://doi.org/10.1097/00005344-200000004-00007 [PubMed]
- Miralles A, Olmos G, Sastre M, Barturen F, Martin I, and Garcia-Sevilla JA (1993) Discrimination and pharmacological characterization of I2-imidazoline sites with [3H] idazoxan and alpha-2 adrenoceptors with [3H] RX821002 (2-methoxy idazoxan) in the human and rat brains. Journal Pharmacology Experimental Therapeutics 264(3): 1187–1197. [PubMed]
- Moreira TS, Takakura AC, Menani JV, and Colombari E (2007) Involvement of central alpha1- and alpha2-adrenoceptors on cardiovascular responses to moxonidine. European Journal of Pharmacology 563 (1-3): 164-171. https://doi.org/10.1016/j.ejphar.2007.02.002 [PubMed]
- Morgan N, Chan S, Mourtada M, Monks LK, and Ramsden CA (1999) Imidazolines and pancreatic hormone secretion. Annals of the New York Academy of Sciences 881: 217–228. https://doi.org/10.1111/j.1749-6632.1999.tb09364.x [PubMed]
- Morgan N, Cooper E, Squires P, Hills C, Parker C, and Hudson A (2003) Comparative effects of efaroxan and beta-carbolines on the secretory activity of rodent and human beta cells. Annals of the New York Academy of Sciences 1009: 167–174. https://doi.org/10.1196 / annals.1304.019 [PubMed]
- Mukaddam-Daher S and Gutkowska J (2004) Imidazoline receptors in the heart: a novel target and a novel mechanism of action that involves atrial natriuretic peptides. Brazilian Journal of Medical and Biological Research 37(8): 1239-1245. https://doi.org/10.1590/s0100-879x2004000800015 [PubMed]
- Nguyen HD, Choo YY, Nguyen TD, Nguyen HN, Chau VM, and Lee J-H (2016) 7-methoxy-(9H-β-carbolin-1-il)-(E)-1-propenoic acid, a β-carboline alkaloid from Eurycoma longifolia, exhibits anti-inflammatory effects by activating the Nrf2 heme oxygenase-1 pathway. Journal of Cellular Biochemisty 117(3): 659-670. https://doi.org/10.1002/jcb.25315 [PubMed]

- Proschaev KI, Ilnitsky A, Bessarabov VI, Pavlova TV, Kvetnaya TV, Bolkhovitina OA, and Pozdnyakova NM (2012) Molecular foundations of the development and progression of chronic heart failure in the elderly and senile age. Molecular Medicine 6: 60-63.
- Radwanska A, Dlugokecka J, Wasilewski R, and Kaliszan R (2009) Testing conception of engagement of imidazoline receptors in imidazoline drugs effects on isolated rat heart atria. Journal of Physiology and Pharmacology 60(1): 131-142. [PubMed]
- Ristovska E, Genadieva-Dimitrova M, Todorovska B, Milivojevic V, Rankovic I, Samardziski I, and Bojadzioska M (2006) The role of endothelial dysfunction in the pathogenesis of pregnancy-related pathological conditions: A review. Prilozi 44(2): 113-137. https://doi.org/10.2478/prilozi-2023-0032 [PubMed]
- Ruffolo R, Yaden E, and Waddell J (1982) Stereochemical requirements of alpha-2 adrenergic receptors for alpha-methyl substituted phenethylamines. Journal of Pharmacology and Experimental Therapeutics 222(3): 645-651. https://doi.org/10.1016/0024-3205(82)90067-4 [PubMed]
- Siwik DA, Chang DL, and Colucci WS (2000) Interleukin-1beta and tumor necrosis factor-alpha decrease collagen synthesis and increase matrix metalloproteinase activity in cardiac fibroblasts in vitro. Circulation Research 86(12): 1259-1265. https://doi.org/10.1161/01.res.86.12.1259 [PubMed]
- Smyth D and Penner S (1999) Peripheral and central imidazoline receptor-mediated natriuresis in the rat. Annals of the New York Academy of Sciences 881: 344-357. https://doi.org/10.1111/j.1749-6632.1999.tb09378.x [PubMed]
- Stepenko YuV, Shmigerova VS, Kostina DA, Shcheblykina OV, Zhernakova NI, Solin AV, Koroleva NV, Markovskaya VA, Dudnikova OV, and Bolgov AA (2024) Study of the neuroprotective properties of the heteroreceptor EPOR/CD131 agonist of peptide structure in tau-proteinopathy modeling. Research Results in Pharmacology 10(2): 41–47. [in Russian]
- Strausberg R, Feingold E, Grouse L, Derge JG, Klausner DR, Collins FS, Wagner L, Shenmen CM, Schuler GD, Altschul SF, Zeeberg B, Buetow KH, Schaefer CF, Bhat NK, Hopkins RF, Jordan H, Moore T, Max SI (2002) Generation and initial analysis of more than 15,000 full-length human and mouse cDNA sequences. Proceeding of the National Academy of Sciences of the United States of America 99(26): 16899–16903. https://doi.org/10.1073/pnas.242603899 [PubMed]
- Strojek K, Grzeszczak W, Gorska J, Leschinger MI, and Ritz E (2001) Lowering of microalbu minuria in diabetic patients by sympaticoplegic agent: novel approach to prevent progression of diabetic nephropathy. Journal of the American Society of Nephrology 12: 602-605. https://doi.org/10.1681 /ASN.V123602 [PubMed]
- Swedberg K, Bergh CH, Dickstein K, McNay J, Steinberg M (2000) The effects of moxonidine, a novel imidazoline, on plasma norepinephrine in patients with congestive heart failure. Moxonidine Investigators. Journal of the American College of Cardiology 35(2): 398-404. https://doi.org/10.1016/s0735-1097(99)00565-3 [PubMed]
- Velliquette RA, Kossover R, Previs SF, and Ernsberger P (2006) Lipid-lowering actions of imidazoline antihypertensive agents in metabolic syndrome. Naunyn-Schmiedebergs Archives of Pharmacology 372(4): 300–312. https://doi.org/10.1007/s00210-005-0024-3 [PubMed]
- Wang X and He B (2024) Endothelial dysfunction: molecular mechanisms and clinical implications. MedComm 5(8): e651. https://doi.org/10.1002/mco2.651 [PubMed]
- Zhang J and Abdel-Rahman AA (2006) Nischarin as a functional imidazoline (I1) receptor. FEBS Letters 580: 3070–3074. https://doi.org/10.1016/j.febslet.2006.04.058 [PubMed]

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