World Bulletin of Public Health (WBPH)
Available Online at: https://www.scholarexpress.net
Volume-28, November 2023
ISSN: 2749-3644

POTENTIAL OF IMIDAZOLINE RECEPTOR AGONISTS IN THE TREATMENT OF ARTERIAL HYPERTENSION

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Article history:

Received: September 17th 023
Accepted: October 17th 2023
Published: November 24th 2023

Abstract:

The review is devoted to the new generation of sympatholytics—selective agonists of I1-imidazoline receptors (AIRs). An analysis of Russian and foreign studies is presented, which convincingly indicate that this class of drugs not only provides adequate and long-term control of blood pressure, but also has a number of positive metabolic effects: it helps reduce insulin resistance (weight loss) and has organoprotective properties (improves endothelial function , promotes regression of left ventricular hypertrophy, reduction of microalbuminuria). At the same time, AIRs are much less likely to cause side effects characteristic of older generation sympatholytics. This class of drugs invariably finds its place in Russian recommendations for the diagnosis and treatment of hypertension. The review focuses on moxonidine. Of particular interest is the analysis of data on the metabolic effects of AIR. It is known that I1-imidazoline receptors regulate insulin secretion by pancreatic β-cells, which causes additional effects of AIR on carbohydrate metabolism. One of the mechanisms of the positive effect of AIRs on carbohydrate metabolism is their ability to induce the expression of β-subunits of the insulin receptor and IRS-1 protein in tissues, which is accompanied by improved functioning of the insulin signaling pathways in skeletal muscles and liver.

Keywords: imidazoline receptor agonists, insulin resistance, antihypertensive effect, metabolic effects, organ protection.

INTRODUCTION

Centrally acting drugs were among the first to be used in clinical practice to lower blood pressure (BP). This is not surprising, since the sympathetic nervous system (SNS) has been given great importance in the pathogenesis of arterial hypertension (AH) since the time of the neurogenic theory of G.F. Langa. It has been proven that a long-term increase in SNS tone leads to multiple organ lesions in patients with hypertension [11], therefore, early and adequate correction of the SNS condition is pathogenetically justified. However, it later became clear that first-generation sympatholytics (clonidine, methyldopa, reserpine) cannot be used for long-term antihypertensive therapy, since they often cause serious side effects such as drowsiness, depression, sexual dysfunction and the rebound phenomenon. In this regard, they are mainly used either for hypertensive crises or for economic reasons due to their relatively low cost. Nevertheless, the understanding of the significant role of the SNS in the genesis of hypertension is so ingrained in the consciousness of the medical community that attempts to create new, effective and safe sympatholytics have not stopped. The relevance of creating such drugs increased even more when it became clear that activation of the SNS leads not only to an increase in blood pressure, but also to a number of other negative effects: myocardial hypertrophy, endothelial dysfunction, platelet activation, insulin resistance and dyslipidemia, which significantly increase the risk of complications in patients. persons with hypertension [2]. Therefore, hopes were pinned on the creation of new, effective and safe centrally acting drugs related not only to adequate blood pressure control, but also to the correction of metabolic disorders and organ protection.

Imidazoline receptor agonists

With the discovery of imidazoline receptors and the creation of their selective agonists, the prospect of creating new, effective and safe sympatholytics opened up. It was found that imidazoline receptors are located in two of the most important organs regulating blood pressure - in the brain and kidneys [3, 4]. They are located in the lateral reticular nuclei of the rostral medulla oblongata and in the proximal tubules of the kidneys. It turned out that these receptors do not respond to catecholamines, but to chemical compounds similar to imidazoline. Therefore, they are called

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Volume-28, November 2023
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imidazoline receptors. Activation of these receptors at the level of the brain causes modulation of sympathetic impulses and a decrease in blood pressure, and in the kidneys - a decrease in the activity of the H+/Na+ pump and a slowdown in the reabsorption of salt and water. Imidazoline receptor agonists (AIRs) have a structure similar to imidazoline and bind to these receptors in the brain and kidneys. In the first case, they reduce sympathetic activity, which leads to a decrease in peripheral vascular resistance, the activity of the renin-angiotensin system and the reabsorption of salt and water. Due to their high affinity for imidazoline receptors, AIRs practically do not bind to other adrenergic receptors, for example α2, as a result of which, in therapeutic doses, they are much less likely to cause side effects characteristic of other centrally acting drugs. As is known, the occurrence of these side effects is associated with stimulation of α2-adrenergic receptors, through which both selective (methyldopa) and non-selective (clonidine) α2-adrenergic receptor agonists exert their antihypertensive effect [4].

Antihypertensive effect

Data from Russian and foreign studies indicate the antihypertensive effectiveness of AIRs, comparable to the effectiveness of the most well-known and widely used representatives of the main classes of antihypertensive drugs. They do not have the escape effect—the development of tolerance to treatment. AIRs are well tolerated because, as mentioned above, in therapeutic doses they do not bind to other types of adrenergic receptors [5–7]. The emergence of selective AIRs was the second birth of a class of centrally acting antihypertensive drugs (sympatholytics) in the treatment of hypertension. Thus, after a long break, sympatholytics again entered cardiological practice [8].

Metabolic effects

Of particular interest is the analysis of data on the metabolic effects of AIR. It is known that I3-imidazoline receptors regulate insulin secretion by pancreatic β-cells, which determines additional pleiotropic effects of AIR regarding carbohydrate metabolism [9]. One of the mechanisms of the positive effect of AIRs on carbohydrate metabolism is their ability to induce the expression of β-subunits of insulin receptors and IRS-1 protein in tissues, which is accompanied by an improvement in the function of insulin signaling pathways in skeletal muscles and liver [10]. In a classic study by A. Haenni et al. Using the euglycemic clamp test method, the most convincing results of the effect of AIR on insulin resistance were obtained. Moxonidine has been found to reduce insulin resistance [11]. A decrease in insulin resistance is an important feature of the action of moxonidine in addition to the leading antihypertensive effect. We conducted a study on the basis of the National Research Medical Center, which included patients with mild and moderate hypertension and compensated type 2 diabetes mellitus (DM). The results confirmed that moxonidine reduces insulin resistance [5]. After 3 months of treatment with moxonidine, insulin and blood glucose levels measured 2 hours after a standard breakfast (equivalent to a glucose tolerance test) were significantly reduced. These results indicate an improvement in tissue sensitivity to insulin, since less insulin is required to maintain lower glucose levels than before treatment after treatment with moxonidine. In a comparative randomized study, ALMAZ, involving 202 patients with insulin resistance, the effect of moxonidine and metformin on glucose metabolism was studied. Taking moxonidine helped reduce fasting glucose levels, insulin resistance, patient weight, and also increased the rate of glucose utilization [6]. The effect of these drugs on the glycemic profile in patients with excess weight, mild hypertension, insulin resistance and impaired glucose tolerance was also assessed. With the use of moxonidine, fasting glucose levels decreased less pronounced than with metformin, but insulin levels decreased significantly, while the decrease in body mass index was comparable with the use of both drugs [8]. These effects of selective AIRs have been proven in a number of international studies. The purpose of a large multicenter observational international study, MERSY (Moxonidine Efficacy on blood pressure Reduction revealed in a metabolic syndrome population), was to evaluate the long-term safety and effectiveness of moxonidine prescribed to lower blood pressure in patients with hypertension and metabolic syndrome [12]. The study included men and women (50.2 and 49.8%, respectively) with signs of abdominal obesity and hypertension degrees I–III. The duration of observation was 6 months. Moxonidine was prescribed at a dose of 0.2–0.4 mg daily in monotherapy (20%) or in combination (80%). when previous antihypertensive therapy was insufficient to achieve target blood pressure values [8]. Systolic and diastolic blood pressure decreased by an average of 24.5±14.3 and 12.6±9.1 mmHg. Art. respectively. Frequency of achieving target blood pressure <140/90 mm Hg. Art. was significantly ($P<0.001$) and significantly higher among younger patients, postmenopausal women, and patients receiving monotherapy. There was also a significant improvement in body weight (-2.1±5.4 kg), fasting plasma glucose (6.8 to 6.2 mmol/l) and triglycerides (2.4 to 2.0 mmol) /L), however, statistically significant changes in metabolic parameters could only be detected in subgroup subanalysis. In a study by

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Spanish scientists J. Abellan et al. The effectiveness of moxonidine was assessed in a group of outpatients with obesity and hypertension, poorly controlled with standard antihypertensive therapy. An analysis of blood pressure control was conducted after adding moxonidine 0.4 mg to previous therapy in 112 obese patients, 25 of whom had type 2 diabetes. The study authors note a pronounced decrease in both systolic and diastolic blood pressure by an average of 23.0 and 12.9 mm Hg. Art. respectively. Data on the dynamics of creatinine clearance are noteworthy. In patients with initial hyperfiltration, as a result of treatment with moxonidine, a significant decrease in creatinine clearance was noted (which may be explained by a decrease in body weight). Additionally, moxonidine has been shown to be very well tolerated and have few drug interactions when taken concomitantly with other drugs. Thus, this study once again demonstrated the effectiveness and safety of moxonidine in patients with hypertension and concomitant metabolic disorders. The nephroprotective effect of moxonidine is also of interest. Thus, it has been shown that moxonidine reduces the level of microalbuminuria [13] and in small doses can slow down the development of glomerulosclerosis [14]. The nephroprotective effect of moxonidine was also noted in patients with hypertension and type 2 diabetes [15]. The facts stated above indicate the important positive metabolic effects of AIRs and characterize them as one of the preferred antihypertensive drugs for metabolic syndrome. It is no coincidence that back in 2007, in the European guidelines for the diagnosis and treatment of hypertension, AIRs were classified as the best class of antihypertensive drugs for their beneficial effect on tissue sensitivity to insulin [16]. 2 mmol/L) and triglycerides (2.4 to 2.0 mmol/L), but statistically significant changes in metabolic parameters could only be detected in a subgroup subanalysis. In a study by Spanish scientists J. Abellan et al. The effectiveness of moxonidine was assessed in a group of outpatients with obesity and hypertension, poorly controlled with standard antihypertensive therapy. An analysis of blood pressure control was conducted after adding moxonidine 0.4 mg to previous therapy in 112 obese patients, 25 of whom had type 2 diabetes. The study authors note a pronounced decrease in both systolic and diastolic blood pressure by an average of 23.0 and 12.9 mm Hg. Art. respectively. Data on the dynamics of creatinine clearance are noteworthy. 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Improved endothelial function

Another property of AIR that is of great clinical importance is the improvement of endothelial function. As is known, endothelial dysfunction underlies various atherogenic risk factors and serves as a universal mechanism for their implementation. Its elimination in combination with an antihypertensive effect can provide an effective reduction in the risk of cardiovascular complications during long-term therapy of hypertension. One of the indicators that allows us to assess the condition of the endothelium is the fibrinolytic activity of blood plasma. It is known that normal fibrinolytic activity is ensured by the balance of tissue plasminogen activator and its inhibitor (PAI-1), which are synthesized in endothelial cells. An increase in PAI-1 synthesis leads to a decrease in fibrinolytic activity and an increase in the risk of progression of cardiovascular diseases. During therapy with moxonidine in patients with hypertension, a significant decrease in the level of PAI-1 was found, possibly due to a decrease in insulin resistance and activity of the sympathoadrenal system [17]. A decrease in the plasma level of thrombomodulin, a glycoprotein of the cell membranes of endothelial cells, which is a receptor for thrombin and appears in the blood plasma when the endothelium is damaged, was also found. Therefore, the decrease in thrombomodulin during moxonidine therapy is probably associated with maintaining the integrity of the vascular endothelium [18].

CONCLUSION

The results of Russian and foreign studies have shown that selective I1-imidazoline receptor agonists not only provide adequate and long-term blood pressure control, but also have a number of positive metabolic effects, including: reducing insulin resistance, increasing high-density lipoprotein (HDL) cholesterol levels, improving function endothelium and fibrinolytic activity of blood plasma. The Russian recommendations for the diagnosis and treatment of hypertension note that an important property of moxonidine is its positive effect on carbohydrate and lipid metabolism. Moxonidine increases tissue sensitivity to insulin by improving the insulin-dependent mechanism of glucose transport into cells, reduces the level of insulin, leptin and glucose in the blood, reduces the content of triglycerides and free fatty acids, and increases the level of HDL cholesterol. In overweight patients, taking moxonidine leads to weight loss. Moxonidine has an organoprotective effect: it reduces LVH, improves diastolic heart function, cognitive functions of the brain, and reduces microalbuminuria [8]. Moxonidine can be prescribed for the treatment of hypertension in patients with metabolic syndrome or type 2 diabetes in combination with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium antagonists. Absolute contraindications to the prescription of AIR are sick sinus syndrome, bradycardia <50 beats/min, chronic heart failure, chronic renal failure, acute coronary syndrome [18]. Commenting on the new European recommendations on hypertension in 2018, Russian experts emphasize the need for the use of AIR for metabolic syndrome and insulin resistance [19]. Thus,

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today the positive metabolic effects and organ protection of AIR have received official recognition. A prominent representative of this group of drugs is Moxonitex (moxonidine produced by Sandoz). The relevance of using high-quality and affordable drugs in clinical practice is further emphasized in the 2018 European guidelines on hypertension to maintain patient adherence to antihypertensive therapy.

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