PROBLEMS AND PROSPECTS FOR FINDING NEW PHARMACOLOGICAL AGENTS AMONG ADENOSINE RECEPTOR AGONISTS, ANTAGONISTS, OR THEIR ALLOSTERIC MODULATORS FOR THE TREATMENT OF CARDIOVASCULAR DISEASES

V.N. Perfilova[1,2], E.A. Muzyko[1]*, A.S. Taran[1], A.A. Shevchenko[1], L.V. Naumenko[1]

[1]Volgograd State Medical University,
1 Pavshih Bortsov sq., Volgograd, 400131 Russia; *e-mail: muzyko.elena@mail.ru
[2]Volgograd Medical Research Center, 1 Pavshih Bortsov sq., Volgograd, 400131 Russia

A1-adenosine receptors (A1AR) are widely distributed in the human body and mediate many different effects. They are abundantly present in the cardiovascular system, where they control angiogenesis, vascular tone, heart rate, and conduction. This makes the cardiovascular system A1AR an attractive target for the treatment of cardiovascular diseases (CVD). The review summarizes the literature data on the structure and functioning of A1AR, and analyzes their involvement in the formation of myocardial hypertrophy, ischemia-reperfusion damage, various types of heart rhythm disorders, chronic heart failure, and arterial hypertension. Special attention is paid to the role of some allosteric regulators of A1AR as potential agents for the CVD treatment.

Key words: A1-adenosine receptors; cardiovascular diseases; agonists; antagonists and allosteric modulators of A1-adenosine receptors

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INTRODUCTION

Cardiovascular disease (CVD) remains a major cause of premature mortality and rising healthcare costs [1]. Despite the wide choice of drugs for CVD treatment, the number of patients and adverse patient outcomes increase from year to year thus indicating the insufficient effectiveness the existing arsenal of drugs. In addition, these medications have significant side effects. For example, calcium antagonists may increase heart failure, bradycardia, and atrioventricular conduction disorder. Beta blockers can induce rhythm and conduction disturbances and cause the development of heart failure, and a decrease in blood supply to the extremities. Angiotensin-converting enzyme (ACE) inhibitors may cause cough, hypotension, fever, palpitations, and chest pain. Side effects of angiotensin II receptor blockers are less pronounced and manifest themselves in the form of weakness, dizziness, headache and dyspeptic symptoms, which, however, require medication discontinuation in 2-3% of patients. Antiarrhythmic drugs cause proarrhythmic effects. All this dictates the need to search for new targets for the development of effective and safe drugs for the CVD treatment.

In this context, agonists and antagonists of adenosine receptors (AR) and especially allosteric modulators of AR attract much interest and the AR orthosteric site has long been used for drug development. However, its high similarity among different AR subtypes prevents its agonists from entering clinical trials due to side effects. Allosteric regions have been identified in AR [2]; their discovery opens possibilities for the development of modulator drugs that can maintain the specificity of receptor subtypes, because these regions are not as conserved as orthosteric ones. It is clear that allosteric modulators may provide therapeutic advantages over active-site receptor-binding agonists in terms of greater selectivity for receptor subtypes and fewer side effects [3].

Adenosine is a nucleoside found in all cells of the body; it performs pleiotropic functions. In the central nervous system, adenosine modulates the release of neurotransmitters, synaptic plasticity [4], and provides neuroprotection during ischemic and hypoxic brain damage and oxidative stress [5–7]. In addition, adenosine regulates T-cell proliferation and cytokine production; it also inhibits lipolysis and stimulates bronchoconstriction. In the cardiovascular system, it causes either vasoconstriction or vasodilation of veins and arteries; it is involved in the regulation of heart rate (HR) and conductivity; adenosine also affects the adrenergic system and coronary circulation, the growth of the heart and blood vessels [8].

Adenosine realizes its biological effects through four subtypes of receptors, which have been cloned and identified in different tissues: A1AR, A2AAR, A2BAR and A3AR [9, 10]. A1AR and A2AAR have high affinity for adenosine, while A2BAR and A3AR show relatively lower affinity. ARs constitute a group of G-protein-coupled receptors (GPCRs). $G_{i/o}$-coupled A1AR inhibits adenylate cyclase (AC) activity (and reduces cAMP production), suppresses Ca^{2+} conductance and increases K^+ conductance, increases the activity of phospholipase C, phosphoinositide 3-kinase (PI3K) and mitogen-activated protein kinase (MAPK) [11]. A2AAR is coupled to the G_s protein, which activates AC and thus activates cAMP-dependent protein kinase A (PKA),

as well as protein kinase C (PKC), MAPK and ion channels [12]. A2BAR interacts with G_s and G_q, and, like the A2AR, induces an increase in cAMP levels and PKA activity, stimulates MAPK and phospholipase C [13]. G_i protein-coupled A3AR inhibits AC, resulting in decreased cAMP production and PKA activity. In addition, A3AR can bind to the G_q protein, resulting in phospholipase C stimulation, increased Ca^{2+} levels, and modulation of PKC activity. A3ARs can activate phospholipase C through the $G_{\beta\gamma}$ subunits [14].

Alteration of AR expression and function has been shown in many diseases, making these receptors a potential target for therapy:

A1AR — in CVD (ischemia/reperfusion, myocardial infarction, angina pectoris, hypertension, cardiomyopathy, arrhythmia, chronic heart failure [15–22], obesity [23], cancer [24], increased intraocular pressure (glaucoma) [25]);

A2AAR — in CVD [26], obesity [23], Parkinson's disease (PD) [27], and cancer [24];

A2BAR — in inflammation [28], chronic obstructive pulmonary disease [29], and diabetes [30];

A3AR — in inflammation [31], glaucoma [32], rheumatoid arthritis [33], and stroke [34].

The aim of this review was to evaluate the role of A1AR in the development of CVD as well as the role of agonists, antagonists and allosteric regulators of these receptors as promising cardioprotective drugs.

1. STRUCTURE, LOCALIZATION AND FUNCTIONS OF A1 ADENOSINE RECEPTORS

A1ARs are highly expressed in adipose tissue, the brain (especially in excitatory nerves), kidneys, and also in the cardiovascular system. They are present in all parts of the heart; the highest density is observed in the atria [35]. In addition, A1ARs have been shown to be located in smooth muscle and endothelial cells of the coronary arteries [36], aorta, mesenteric [20], and renal vessels [37]. It should be noted that the intensity of A1AR expression depends on age. In a study by Jenner et al. it was shown that in 52-54-week-old male Wistar rats the level of A1AR in the heart was significantly reduced (5.5 times) as compared to young animals [38].

A1ARs are proteins consisting of 326 amino acid residues (aa) and containing 7 transmembrane domains (TM1–7), which include α-helices connected to each other by three extracellular (EL1, EL2, EL3) and three intracellular (IL1, IL2, IL3) loops [26]. The N-terminus is relatively short and is exposed extracellularly; the cytoplasmic C-terminus contains a α-helix (Hx8) parallel to the cell membrane [39]. In ARs, the main role in ligand binding is assigned to the NPXXY regions in TM7, the DRY (Asp-Arg-Tyr) motif of TM3, the ion lock and the TDY (Thr-Asp-Tyr) triad [40]. The active conformation of A1AR, interacting with an agonist without binding to a G protein, is unstable and the regulatory effects of the G protein differ depending on its type: they are significantly enhanced when A1AR is coexpressed with $G_{\alpha i1}G_{\beta 1}G_{\gamma 2}2$ (G_{i1}) or $G_{\alpha qi5}G_{\beta 1}G_{\gamma 2}2$ (G_{qi5}), but not with $G_{\alpha o}G_{\beta 1}G_{\gamma 2}2$ (G_o) [41]. A study of the structure of the A1AR-G_i complex (inhibitory G protein) using cryoelectron microscopy has shown that when adenosine binds to it, TM1 and TM2 change shape; this results in a conformational change in the orthosteric binding site on the extracellular surface of the membrane. On the intracellular side, the G protein interacts with A1AR mainly through the C-terminal residues. α5-helix $G_{\alpha i}$, which is accompanied by an outward movement of TM6 by 10.5 Å. In this case, receptor activation is accompanied by adjustments of TM7, helix 8 (H8), extracellular loops (EL), and the ligand-binding pocket [42].

Molecular modeling of A1AR has shown that the allosteric center is located next to the orthosteric center within the EL2 receptor [43], which was later confirmed [44]. $E172^{EL2}$ is a key determinant of ligand interaction, and substitution of glutamate for alanine reduces the affinity of the allosteric modulators PD81723 and VCP171 for free A1AR [45]. In addition, it has been found that allosteric effectors can modulate the binding and/or signaling properties of the orthosteric ligand and alter the activity of G protein-coupled receptors, even in its absence [46]. Recently, a multisite binding model for allosteric modulation of A1AR has been proposed; according to this model there is not only a single pocket, but also several extracellular sites capable of binding the modulator [47].

When adenosine interacts with A1AR, the subunits of the G_i-protein associated with it dissociate, and the α-subunit inhibits AC. This leads to a decrease in the cAMP level followed by a decrease in PKA activity, phosphorylation of the transcription factor CREB (cAMP response element-binding protein) and, accordingly, a attenuation of the transcriptional activation of various genes necessary for cell proliferation, differentiation, adaptation, and survival [48].

Inactivation of CREB plays an important role in the development of CVD. For example, it was found that in aortic smooth muscle cells of low-density lipoprotein receptor gene knockout mice, in addition to hyperlipidemia, and also insulin resistance and hypertension, modelled by aging, the amount of CREB protein was reduced [49]. Mice deficient in cardiac natriuretic peptides show decreased phosphorylation of CREB in cardiac cells and an increased incidence of ventricular arrhythmias and sudden death due to acute myocardial stress [50].

Activation of A1AR leads to the dissociation of the G_q protein α-subunit and stimulation of phospholipase C, which catalyzes the formation

of diacylglycerol and inositol-1,4,5-trisphosphate from phosphatidylinositol diphosphate. Inositol-1,4,5-trisphosphate induces an increase in intracellular Ca^{2+} levels, which activates calcium-dependent PKC and/or other calcium-binding proteins. It should be noted that the β and γ subunits of the G_i protein are also involved in PKC activation [51]. In addition, A1AR is involved in the regulation of ATP-dependent potassium channels expressed in the myocardium and nervous tissue cells, as well as Q-, P- and N-type Ca^{2+} channels [48] (Fig. 1).

Recently, a new approach to full activation of A1AR has been developed; it includes adenosine binding to the extracellular site of A1AR, leading to conformational changes and preactivation of the receptor, and the interaction of G_{i2} with the intracellular site of A1AR, causing a decrease in the volume of the extracellular orthosteric site and stabilization of the association of adenosine with the receptor. It provides additional, more detailed structural characterization of A1AR throughout the activation process (intermediate states), which can be used to optimize drug development [52].

A1ARs can heterodimerize with other GPCRs, such as dopamine D1 receptors [53]. There is evidence of cross-talk with purinergic P2Y1 receptors [54]. During realization of cardiovascular responses, A1AR is associated with other AR subtypes: for example, it counteracts A2AR-mediated vasodilation [55]. There is evidence of interaction between A1, A2A and A2B ARs in the mechanisms of cardioprotection [17, 42]. At the same time, it should be noted that the AR heteromers A1/A2A have not yet been studied in the cardiovascular system. ARs also interact with opioid receptors to limit cell damage and death during ischemia-reperfusion injury [56]. Thus, ARs exhibit complex interactions with each other and with other GPCRs. This is not surprising, because purinergic receptors represent one of the earliest systems [57] that provide long-term evolution and complex signaling connections between cell functions and their energy state.

2. THE ROLE OF ADENOSINE A1 RECEPTORS IN THE DEVELOPMENT OF CARDIOVASCULAR DISEASES

As mentioned above, A1ARs are actively expressed in cardiac cells and blood vessels and play an important role in regulating the activity of the cardiovascular system under normal and in various pathological conditions.

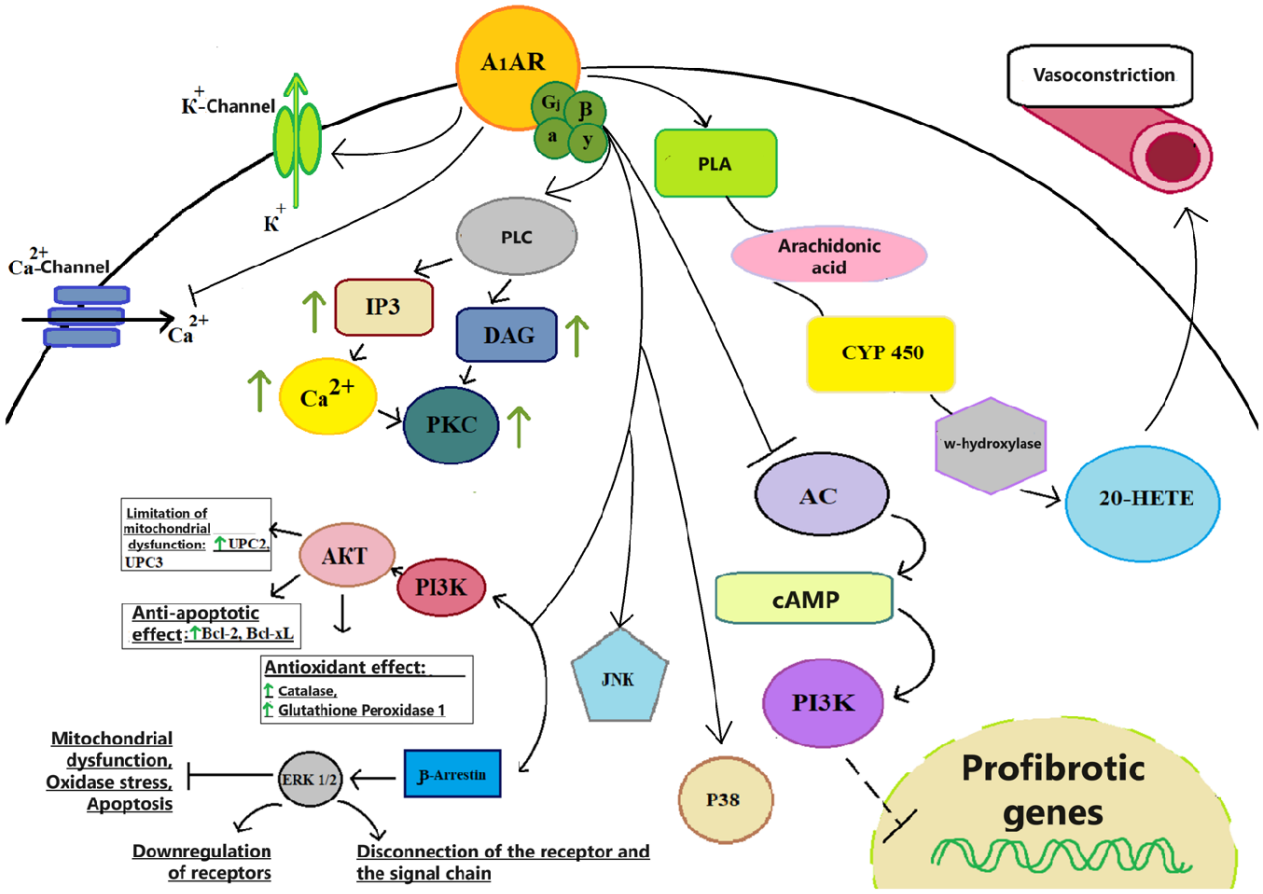

Figure 1. Schematic representation of adenosine A1 receptor signaling pathways. AC – adenylate cyclase, cAMP – cyclic adenosine monophosphate, PI3K – phosphoinositide 3-kinase, DAG – diacylglycerol, IP3 – inositol triphosphate, PKC – protein kinase C, JNK – C-Jun N-terminal kinase, ERK – extracellular signal-regulated kinase; AKT – protein kinase B; 20 HETE – ω-terminal hydroxyeicosatetraenoic acids; CYP450 – cytochrome P450.

2.1. The Cardioprotective Effect of A1AR Activation

AR activation has a cytoprotective effect, as evidenced by the protective effect of the A1AR agonist 2-chloro-N^6-cyclopentyladenosine, mediated by p38 MAPK phosphorylation, on cultured cardiomyocytes after hypoxic exposure [58]. The A1AR agonist N^6-cyclopentyladenosine also has a cardioprotective effect; it stimulates p38, ERK (extracellular signal-regulated kinase) and JNK (c-Jun N-terminal kinases) phosphorylation, which leads to the activation of tissue transglutaminase 2 (TG2) in H9c2 cardiomyoblasts [59]. TG2 catalyzes inter- and intramolecular cross-linking, promoting the formation of insoluble protein structures that form barriers resistant to proteolysis and increase the resistance of cells and tissues to chemical, enzymatic, and mechanical destruction.

One of the mechanisms of the cardioprotective effect upon activation of the adenosine system is the limitation of excessive adrenergic stimulation; this process is mediated by A1AR. In experimental model of compensated cardiac hypertrophy due to chronic overload caused by high blood pressure, the synthesis of A1AR mRNA and the receptor protein in the left ventricle was significantly higher (37% and 77%, respectively, $p<0.01$) in rats with the experimental pathology as compared with sham-operated animals. This mechanism should be considered as protective, because increased expression of A1AR mRNA was not found in rats with a decompensated form of hypertrophy [60]. The effects of A1AR in the development of this pathological process can be realized with the participation of zinc finger proteins (ZFP91), which regulate the expression of A1AR mRNA and affect myocardial homeostasis under conditions of excessive cardiac overload. ZFP91 deletion is accompanied by a decrease in A1AR mRNA synthesis and development of left ventricular hypertrophy [61].

Stimulation of adenosine A1 receptors leads to inhibition of angiotensin II (Ang II)-induced cardiomyocyte hypertrophy by suppressing ERK signaling pathways and reducing intracellular Ca^{2+} [62]. A1AR agonist VCP746 prevents hypertrophy of cardiac muscle cells in newborn rats caused by interleukin 1β (IL-1β, interleukin-1-beta) and tumor necrosis factor-α (TNF-α, tumor necrosis factor-alpha). IL-1β and TNF-α also play a significant role in cardiac remodeling as evidenced by an increase in the expression of mRNA markers of hypertrophy: atrial natriuretic peptide (ANP), β-myosin heavy chains (β-MHC), and α-smooth muscle actin (α-SMA) in animals [63]. The antihypertrophic effect of adenosine and A1AR agonists may be due to the limitation of the cardiomyocyte TNF-α synthesis [64], which affects expression and activation of matrix metalloproteinase 2, an important inducer of ventricular dilatation and extracellular matrix degradation, and leading to the development of cardiac fibrosis [65].

A1AR receptors mediate the resistance to ischemic heart damage. Experiments performed on the *A1AR* gene knockout (KO) mice revealed that tolerance to 25 min global ischemia (followed by 45 min reperfusion) was significantly limited by *A1AR* KO, with impaired contractile recovery (reduced by 25%) and enhanced lactate dehydrogenase (LDH) efflux (increased 2-fold). In contrast, *A1AR* overexpression improved ischemia tolerance, primarily through its effect on diastolic function [66]. *A1AR* gene deletion had a significant impact on tolerance of mouse heart to 25-min ischemia / 45-min reperfusion, which was accompanied by worsened contractility, and increased LDH efflux, as well as increased level of lipid hydroperoxides and hydroxides, α-tocopherylquinone (the oxidation product of α-tocopherol) and also by a decrease in the redox potential of glutathione [16].

The protective effect of A1AR is due to improved functioning of cardiomyocyte mitochondria and changes in the functioning of the NO-ergic system. After remote ischemic preconditioning, ischemia-reperfusion injury in isolated rat hearts is accompanied by activation of A1AR after 10 min of reperfusion, further phosphorylation of endothelial nitric oxide synthase (eNOS) by AKT kinase, and increased mitochondrial respiration, thus leading to a decrease in the myocardial infarction area [67]. The A1AR agonist N^6-cyclohexyladenosine, administered prophylactically to mice, promoted recovery of cardiac function after ischemic injury through intensification of phosphorylation and activation of AKT and eNOS, as well as S-nitrosylation of proteins [68], the covalent attachment of the NO fragment to sulfhydryl residues, leading to the formation of S-nitrosothiols (SNO). This process is the predominant post-translational modification of proteins involved in intracellular redox signaling and provides protection by preventing the development of oxidative and nitrosative stress.

Activation of A1AR by N^6-cyclopentyladenosine leads to attenuation of H_2O_2-induced intracellular and mitochondrial reactive oxygen species (ROS) production and limits apoptosis. The cardioprotective effect of the agonist is mediated by PI3K/Akt- and ERK1/2-dependent signaling pathways and stimulation of the expression of antioxidant enzymes catalase and glutathione peroxidase-1, as well as the anti-apoptotic proteins Bcl-2 and Bcl-xL [69].

The cardioprotective effect upon A1AR activation is associated with stimulation of A2AR and A2BR, as evidenced by the lack of the protective effect of the N^6-cyclohexyladenosine agonist during ischemia-reperfusion injury in isolated perfused hearts of *A2AR* and *A2BR* gene knockout mice. In a group of wild-type mice with a modelled pathology, which were treated with N^6-cyclohexyladenosine, the pressure developed by the left ventricle significantly increased and the infarct size decreased [70]. In *A2AR* gene knockout mice the cardioprotective effect during

ischemia/reperfusion was also absent in the case of treatment with N^6-cyclopentyladenosine and specific A2AR and A2BR antagonists. Moreover, in wild-type animals, N^6-cyclopentyladenosine significantly improved cardiac contractility, increased left ventricular pressure and end-diastolic pressure, and reduced infarct size and damaging reperfusion effects. The cardioprotective effect of N^6-cyclopentyladenosine was due to stimulation of ERK phosphorylation [26].

Modeling of myocardial infarction with preserved left ventricular ejection fraction in mature male pigs by means of surgical ligation of the left anterior descending coronary artery has shown that the expression of A1AR mRNA in the infarction zone in animals of the experimental group was significantly lower than in intact animals. This is due to the adaptive mechanisms: a high concentration of adenosine during myocardial ischemia promotes desensitization of A1AR and a decrease in the synthesis of its mRNA [71].

Activation of A1AR has a protective effect against ventricular arrhythmias caused by cardiac ischemia-reperfusion injury. The A1AR agonist 1-cyclopropyl isoguanosine, administered to rats 10 min before occlusion of the left coronary artery, slowed the onset of ventricular arrhythmias, reduced the total number of ventricular extrasystoles and tachycardias, and reduced the frequency of fibrillations and mortality during the first 30 min after ligation. The agonist also helped to normalize the rhythm and increased survival in isoprenaline-induced ventricular fibrillation [72]. Activation of A1AR by the highly selective agonist trabodenozone (INO-8875) in rats led to a dose-dependent and long-lasting (up to 2.5 h after administration) decrease in heart rate, atrial refractoriness, and slowing of atrioventricular conduction [73].

The antiarrhythmogenic effect of adenosine and A1AR agonists is due to counteracting catecholamine-induced activation of intracellular cAMP production and limiting the slow calcium current across the myocardial cell membrane; this leads to a decrease in the force of cardiac contraction during excessive adrenergic exposure [72]. Adenosine, through A1AR, attenuates β-adrenergic reactions in mouse cardiomyocytes as a result of sequential activation of phospholipase C, PKC-ε and p38 MAPK, which mediates the cardioprotective effect [51].

Currently, partial A1AR agonists represent a promising direction in the search and development of drugs for the treatment of chronic heart failure (CHF) in combination with the main therapy. Their main advantage over full agonists is the absence in most cases of side effects — bradycardia, atrioventricular blockade and sedation [74]. Stimulation of A1AR by capadenoson, a partial A1AR agonist, in dogs with heart failure induced by repeated intracoronary microembolization at 1 to 2 week intervals improved left ventricular systolic function and prevented progressive enlargement after 12 weeks of monotherapy. The results showed a significant improvement in ejection fraction and no significant increase in left ventricular end-diastolic volume as compared with the control group. The drug reduced the volume fraction of interstitial fibrosis, contributed to the normalization of Ca^{2+}-ATPase activity of the sarcoplasmic reticulum and the expression of mitochondrial uncoupling proteins UCP-2 and UCP-3, as well as glucose transporters GLUT-1 and GLUT-2. In addition, it statistically significantly decreased plasma levels of norepinephrine and brain natriuretic peptide (N-terminal fragment of brain natriuretic peptide precursor, NT-proBNP). Capadenoson did not affect heart rate, did not cause atrioventricular block, did not have sedative and antidiuretic effects, and did not lead to impairment of renal function [75]. In male Sprague-Dawley rats this partial A1AR agonist caused dose-dependent bradycardia [76], but clinical trials it had insignificant effect on resting heart rate in healthy volunteers or patients with atrial fibrillation [77, 78]. Recently, it has been found that the drug can bind not only to A1AR, but also to A2BAR in cardiac fibroblasts and myocytes, exerting a cardioprotective effect [79].

A randomized, double-blind, placebo-controlled trial of the oral A1AR partial agonist neladenoson bialanate performed in 305 patients with heart failure with preserved ejection fraction has shown that the drug contributed to a trend toward increased distance in the 6-min walk test after 20 weeks of treatment as compared with the placebo group [80]. The safety of neladenoson bialanate was demonstrated in two pilot studies in patients with heart failure with reduced ejection fraction; no changes in heart rate, blood pressure (BP), atrioventricular conduction, or neurological side effects were noted [81].

The anti-ischemic effect of A1AR stimulation was demonstrated in patients with stable angina in a randomized, double-blind, placebo-controlled, multicenter clinical trial involving 62 male patients. This trial has shown that the partial A1AR agonist capadenozone reduced heart rate during physical activity and extended its total duration, as well as the latent period of ischemia [18]. During phase 3 clinical trial the selective A1AR agonist tecadenoson (CVT-510) normalized the rhythm in 91% of patients with paroxysmal supraventricular tachycardia. In contrast to non-selective A1AR agonists, the drug did not have such adverse reactions as atrial fibrillation, hot flashes and shortness of breath [19, 82].

2.2. The Negative Impact of A1AR Activation on the Cardiovascular System

Despite convincing evidence of the cardioprotective effect of A1AR activation, there are a number of clinical and experimental studies showing the opposite effect.

Hyperactivation of A1AR inhibits cardiomyocyte division, leading to cardiac hypoplasia [83]. The offspring of mice treated with N^6-cyclopentyladenosine during pregnancy had markedly reduced ventricular size and showed signs of heart failure [84]. The nonspecific adenosine receptor antagonist caffeine given to pregnant mice, acting through the A1AR, increased left ventricular posterior wall mass and thickness and decreased cardiac output in male offspring at 10–12 weeks of age. The results obtained are associated with changes in DNA methylation of regions of genes encoding sarcomeric and structural proteins of the myocardium; this can cause cardiac hypertrophy and other cardiac diseases [85]. However, it should be noted that the complete absence of A1AR in the fetal heart under hypoxic conditions caused a significant viability decrease [86].

Overexpression of A1AR in mice caused cardiac dilatation, accompanied by impairment of ventricular function and a decrease in heart rate, ultimately leading to death within 6–12 weeks. Induction of A1AR synthesis caused cardiomyopathy in animals at 20 weeks of age, cardiac hypertrophy and dilatation after aortic ligation. In contrast, when A1AR expression was inhibited before 3 weeks of age, mice were phenotypically normal at 6 weeks, and more than 90% of mice survived to 30 weeks. Such events were associated with changes in the expression of genes encoding atrial natriuretic peptide, collagen, sarco/endoplasmic reticulum Ca^{2+}-ATPase, and phospholamban [87].

Excessive stimulation of A1AR promotes development of arrhythmias: treatment of 4-day-old chick embryos with adenosine and specific A1-adenosine receptor agonist 2-chloro-N^6-cyclopentyladenosine caused transient atrial ectopy and second-degree atrioventricular block (Mobitz type I), respectively. Both agents transiently increased ERK phosphorylation and induced arrhythmias in isolated atria that were reversed by the A1AR antagonist 8-cyclopentyl-1,3-dipropylxanthine (DPCPX). Interestingly, the proarrhythmic effect was induced through A1AR by simultaneous stimulation of NADPH oxidase and phospholipase C, followed by activation of ERK, PKC, or L-type calcium channels [88].

Adenosine leads to a decrease in the duration of the atrial action potential (AP) upon activation of A1AR, followed by subsequent opening of inward rectifying G protein-coupled K^+ channels, and promotes the occurrence of cardiac arrhythmias. In an experiment performed using isolated Langendorff heart preparation, the A1AR agonist 2-chloro-N^6-cyclopentyladenosine (CCPA) reduced the duration of AP and the effective refractory period of the atria (cases of atrial fibrillation were noted). On the contrary, the antagonist 1-butyl-3-(3-hydroxypropyl)-8-(3-noradamantyl)xanthine and ecto-5′-nucleotidase inhibitor (CD73) 5′-(α,β-methylene) diphosphate sodium salt, reducing the release of adenosine, increased these indicators and prevented atrial fibrillation and its duration [89, 90].

In the sinoatrial node cells, adenosine, interacting with A1AR receptors, increases the average duration of the action potential and its variability, directly and indirectly affecting the membrane and intracellular calcium oscillators ("membrane and Ca^{2+} clocks", that provide a stable mode of AP generation in the cardiac pacemaker cells even under conditions of stochastic Ca^{2+} dynamics), disrupting their synchronous action. The mechanism of its effect is associated with activation of $G_{\beta\gamma}$ and I KACh, hyperpolarization of the cell membrane and increase in diastolic depolarization time, as well as stimulation of $G_{\alpha i}$, suppression of adenylate cyclase activity and reduction of cAMP-mediated, PKA-dependent phosphorylation of downstream target proteins of circulating Ca^{2+}. The uncoupling of two cellular oscillators promotes the development of arrhythmias [91].

In a pilot study Jackson et al. have found that A1ARs increased blood pressure. In female Dahl SS salt-sensitive rats with a knockout of the *A1AR* gene, average, systolic and diastolic blood pressure at week 2 of a 4% salt diet were statistically significantly lower than in wild-type animals kept on a similar diet (176±5 mm Hg, 209±5 mm Hg, and 147±4 mm Hg versus 202±4 mm Hg, 240±5 mm Hg, and 172±3 mm Hg, respectively).

Increasing the amount of salt in the diet to 8% in females increased blood pressure in both knockout rats and control rats. This suggests that extremely high dietary sodium may offset the benefit of A1AR blockers for the treatment of hypertension and should be taken into account in future clinical trials [92]. In rats of the same strain, the A1AR antagonist 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902) exhibited an antihypertensive effect [93]. In mice with L-NAME-modeled hypertension, A1AR expression in the aorta and mesenteric arteries increased as compared to the control group. At the same time, an increase in vascular tone was associated with a slight decrease in the synthesis of eNOS responsible for the formation of the vasodilator nitric oxide. In addition, an increase in the expression of cytochrome P450-4A (Cyp450-4A) was observed in the aorta and mesenteric arteries.

A1AR can interact with CYP450 enzymes, such as CYP450 epoxygenases, CYP450 ω-hydroxylases, soluble epoxide hydrolases, as well as with polyunsaturated fatty acids and their derivatives oxylipins in the regulation of cardiovascular functions. CYP450 epoxygenases play an important role in the metabolism of arachidonic and linoleic acid with formation of epoxyeicosatrienoic, epoxyoctadecaenoic and other acids involved in vasodilation and cardioprotection [94, 95]. Soluble epoxide hydrolase converts epoxyeicosatrienoic acid into

dihydroxyeicosatrienoic acid, epoxyoctadecaenoic acid into dihydroxyoctadecaenoic acid; they cause vasoconstriction, proinflammatory effects, increased prothrombotic processes and decreased cardioprotective effects. In addition to soluble epoxide hydrolase, ω-hydroxylases (CYP450-4A11 and CYP450-4F2) catalyze formation of ω-terminal hydroxyeicosatetraenoic acids (19-, 20-HETE), lipoxygenases form medium-chain hydroxyeicosatetraenoic acids (5-, 11-, 12-, 15-HETE), cyclooxygenases form prostanoids (prostaglandins: PGD 2, PGF 2α; thromboxane: Txs, oxylipins), which are also involved in vasoconstriction, hypertension, pro-inflammatory processes and negative effects on the heart [94, 95].

When adenosine A1 receptors are activated, CYP450-4A through PKC-α and MAPK, in particular p44/42 MAPK, causes contraction of vascular smooth muscle [20, 95] and vasoconstriction; thus CYP450-4A promotes the formation of 20-hydroxyeicosatetraenoic acid from arachidonic acid. 20-Hydroxyeicosatetraenoic acid activates PKC-α, causing ERK1/2-dependent vascular contraction and the development of hypertension [96]. Together with PKC, it can also inhibit large conductance Ca^{2+}-activated K^+ channels involved in the regulation of smooth muscle tone [97]. Clearly, more research is needed to better understand the interaction between A1AR and eicosanoids for the development of diagnostic systems and drugs for the CVD treatment.

Blood pressure regulation is also carried out through A1AR in the nuclei of the solitary tract (NST). A1ARs are most densely located mainly in the dorsomedial/dorsolateral as well as subpostremal subnuclei of the caudate nucleus of the solitary tract [98]. Microinjections of adenosine (1.25 nmol/50 nl) into the the lateral aspect of the commissural NTS of awake rats led to a significant increase in blood pressure (119±3 mm Hg, 122±4 mm Hg, and 117±4 mm Hg after 30 s, 1 min, and 2 min, respectively) as compared to the control (102±3 mm Hg). Pretreatment with the A1AR antagonist DPCPX and then adenosine insignificantly influenced blood pressure in control animals thus suggesting participation of this particular receptor subtype in vasoregulation [99]. Despite the predominant pressor response upon activation of A1AR by the specific agonist N^6-cyclopentyladenosine, in some cases low doses of this compound have a depressor effect. It is assumed that the difference depends on the level of current reflex activity at the time of A1AR stimulation [100].

Another mechanism that contributes to the formation of hypertension is stimulation of A1AR in the nephrons; this stimulation is associated with an increase in resistance in the afferent renal arterioles, as well as changes in the reabsorption of water and sodium in the tubules. Basal interstitial adenosine levels were found to influence Ang II and norepinephrine-induced renal vasoconstriction via A1-adenosine receptors. A1AR blockade with 8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902; 10 μg/kg/min) results in a significant attenuation of renal vasoconstriction [37].

On day 12 of Ang II administration BP in A1AR knockout mice was significantly lower than in wild-type animals treated with this vasoconstrictor. During the same period, knockout animals showed a significant increase in Na^+ and phosphate excretion in the proximal renal tubules as compared to the control group [82]. Pharmacological blockade of A1AR increased diuresis and natriuresis by inhibiting proximal tubular reabsorption. Theophylline and caffeine administered via gastric tube to A1AR knockout mice ($A1R^{-/-}$) and wild-type littermates ($A1R^{+/+}$) increased fluid and Na^+ excretion after 3 h in $A1R^{+/+}$, but not in $A1R^{-/-}$ animals [100]. The A1AR antagonist Rolophylline (KW-3902 or MK-7418) marketed for the treatment of acute congestive heart failure, was able to increase glomerular blood flow and filtration and inhibit proximal tubular sodium reabsorption [101].

It should be noted that low doses of adenosine acting on A1AR were able to inhibit renin release. A similar situation was observed with agonists of this type of receptor. Activation of A1AR by N^6-cyclohexyladenosine led to an increase in Ca^{2+} concentration in juxtaglomerular cells and inhibition of renin secretion involving TRPC (Transient Receptor Potential (C — canonical)) channels. On the contrary, higher doses of adenosine stimulated the release of renin and an increase in blood pressure [102].

Modeling non-ischemic CHF in dogs was accompanied by active expression of A1ARs in the atrial myocardium and sinoatrial node: the number of receptors increased by 47±19% and 90±40%, respectively, relative to the control group. At the same time, an intensification of the fibrosis process was shown within the sinoatrial node. Heart failure progression to pathological levels was accompanied by the increase in plasma adenosine, which mediated the development of conduction defects, inhibition of automaticity and caused pacing-induced atrial fibrillation [103]. In dogs with CHF, which was modeled by a 4-month tachycardia caused by a pacemaker implanted in the apex of the right ventricle, the expression of A1AR mRNA and G-protein coupled inwardly rectifying potassium channels (GIRK, G protein-coupled inwardly-rectifying) increased in the sinoatrial node. Adenosine, acting on A1AR, caused GIRK-mediated hyperpolarization of the heart cell membrane and had a negative chronotropic effect [22].

Selective A1AR antagonists (DPCPX, theophylline) prevent adenosine-induced atrial fibrillation and sinoatrial node dysfunction by increasing greater rate of excitation in CHF [22, 103]. Combined blockade of adenosine A1 and A2B receptors by BG9928 for 24 weeks in ZSF1 rats with obesity and modeled CHF with preserved ejection fraction

led to an improvement in left ventricular diastolic function and limited metabolic syndrome, reducing plasma triglyceride levels, 24-h excretion of glucose and protein in urine, polydipsia and polyuria as compared with these indicators in animals of the control group [104].

3. AGONISTS, ANTAGONISTS AND ALLOSTERIC MODULATORS OF ADENOSINE A1 RECEPTORS AS POTENTIAL AGENTS FOR THE TREATMENT OF CARDIOVASCULAR SYSTEM DISEASES

Adenosine has significant therapeutic potential due to its multiple effects and ubiquitous expression of its receptors. However, this leads to the development of undesirable side reactions, complicates the development of effective drugs-ligands of ARs and limits their entry into the market. Currently, only the short-acting parenteral agonists adenosine and regadenoson have been approved for use in humans [105, 106]. However, new concepts and compounds are being developed and applied for preclinical and clinical evaluation. A more promising approach is the study of allosteric modulators, which have a number of advantages over orthosteric ligands and can potentially overcome their limitations [107]. Allosteric ligands can stimulate biased signaling by stabilizing the unique conformations of receptors, influencing the spectrum of pathways activated or inhibited by orthosteric ligands in such a way that only part of the signaling capabilities realized by the receptor generates a response, while other pathways are excluded. In other words, the final effect shifts to a limited and specific function. It is obvious that it is possible to create ligands that can selectively involve signaling pathways that mediate certain therapeutic effects, and not affect those responsible for unwanted side effects [107, 108].

3.1. A1AR Agonists

Adenosine, an endogenous ligand of adenosine receptors, has long been used to treat arrhythmias [109]. Various modifications, mainly at the N^6 position, C^2 position and 5′ ribose position of this molecule, have led to the creation of a variety of full and partial A1AR agonists.

According to their chemical structure, A1AR agonists include N^6-cycloalkyl-substituted (N^6-cyclohexyladenosine, N^6-cyclopentyladenosine, N^6-[(1S, *trans*)-2-hydroxycyclopentyl]adenosine), N^6-heterocyclic (tecadenozone, N^6-(2-benzothiazolyl-thioalkyl)adenosine, and etc.), N^6-aryl- and N^6-arylalkyl-substituted (R-PIA, NNC-21-0074, NNC-21-0041, NNC-21-0087), C^2-substituted adenosine derivatives (N^6-cyclopentyl-2-(3-phenylaminocarbonyltriazen-1-yl) adenosine). In addition, substances with ribose modifications (5′-methylcarboxamidoadenosine, MRS5595, MRS5607, AMP-579) and non-purinergic compounds (BR-4935) have been synthesized [110].

A1AR agonists exhibit effects on the cardiovascular system (Table 1). Activation of A1AR is associated with the limitation of ischemia-reperfusion injury, myocardial hypertrophy, various arrhythmias, and chronic heart failure [15–17, 62–68, 70, 72, 75].

It should be noted that the use of full A1AR agonists is associated with a number of adverse reactions such as bradycardia, atrioventricular block, negative inotropic and dromotropic effects, sedation, decreased glomerular filtration rate, inhibition of renin release, and vasoconstriction of the renal arteries [111].

Another problem of the use of full A1AR agonists is the possible desensitization of the receptors accompanying the long-term use of these agonists. For example, N^6-R-phenylisopropyladenosine (R-PIA), administered to rats during a continuous infusion for 7 days (200 nmol/h), attenuated inotropic and chronotropic responses in isolated atria as compared with the control group. Interaction of the antagonist radioligand interacted with A1AR revealed a 52% decrease in the radioligand binding. A competitive binding study revealed a significant loss of high-affinity A1 receptors in the atria of rats treated with R-PIA. In the ventricles of these rats, the amount of G_i proteins was reduced, and uncoupling of A1AR from G proteins was observed without a significant change in A1AR density [112]. Similar abnormalities were found in the brains. Daily intraperitoneal administration of N^6-cyclopentyladenosine at a dose of 0.25 mg/kg to adult male Wistar rats for 5 days caused a significant decrease in A1AR in the hippocampus and somatosensory cortex [113].

Attempts to overcome the above-mentioned problems have led to the development of partial agonists and allosteric modulators of A1AR.

In contrast to a full agonist, partial A1-adenosine receptor agonists are ligands that produce only a submaximal response.

According to the literature, potential mechanisms of the cardioprotective action of partial A1AR agonists include improved mitochondrial functioning and increased energy supply to cardiomyocytes, limitation of ROS formation and fatty acid oxidation, protection against intracellular Ca^{2+} overload, and apoptosis. These compounds promote reverse ventricular remodeling, reduce interstitial fibrosis and myocardial hypertrophy, and have an anti-ischemic effect. In addition, they attenuate mechanical and metabolic responses to excessive adrenergic stimulation and reduce the release of catecholamines [74].

The development of partial agonist drugs is at an early stage, but it can be assumed that hemodynamically neutral therapy while improving cardiomyocyte energetics and structure may be useful in combination with basic treatment of heart failure.

Table 1. Effects of A1AR agonists in some CVDs

Agonist	Research object	*In vivo / in vitro*	Pathological state/disease	Proposed mechanism of action	Effect	Reference
N^6-R-phenyl-isopropyl adenosine (R-PIA)	Neonatal rat cardiomyocytes	*in vitro*	Ang II-induced cardiomyocyte hypertrophy	Suppression of ERK signaling pathways and reduction of intracellular Ca^{2+}	Antihypertrophic effect	[62]
VCP746	Neonatal rat cardiomyocytes	*in vitro*	Cardiomyocyte hypertrophy induced by IL-1β, TNF-α or Ang II	Suppression of mRNA expression of atrial natriuretic peptide, β-myosin heavy chains and α-skeletal actin	Antihypertrophic effect	[63]
N^6-cyclopentyl adenosine (CPA)	Neonatal rat cardiomyocytes	*in vitro*	TNF-α-induced cardiomyocyte hypertrophy	Inhibition of TNF-α synthesis in cardiomyocytes	Antihypertrophic effect	[64]
	Neonatal rat cardiomyocytes; male C57/Bl6N mice	*in vitro, in vivo*	Phenylephrine-induced compensatory hypertrophy	Activation of the mitochondrial ATP-dependent potassium channel, inhibition of the opening of the pore that changes the permeability of the mitochondrial membrane (mitochondrial permeability transition pore, mPTP), reduction of ROS production	Reduction of cardiac fibrosis, matrix metalloproteinase 2 processing and oxidative stress	[65]
	Male wild-type mice	*in vitro*	30-min myocardial ischemia followed by 60-min reperfusion	Interaction with A2A and A2B receptor subtypes, stimulation of phosphorylation	Improvement of cardiac contractility, pressure developed by the left ventricle, end-diastolic pressure, reduction of infarct size	[17]
N^6-cyclohexyl adenosine (CHA)	Isolated perfused hearts of male wild- type mice	*in vitro*	30-min myocardial ischemia followed by 60-min reperfusion	Interaction with A2A and A2B receptor subtypes (activation of AKT and ERK, mitochondrial ATP-dependent potassium channel, MAPK)	Increase in the left ventricular pressure and decrease of the infarct size	[70]

Table 1. Effects of A1AR agonists in some CVDs (continued)

Agonist	Research object	*In vivo / in vitro*	Pathological state/disease	Proposed mechanism of action	Effect	Reference
N^6-cyclohexyl adenosine (CHA)	Male and female C57BL/6J mice	*in vitro*	ischemia-reperfusion injury	Intensification of phosphorylation of AKT and eNOS, as well as S-nitrosylation of proteins	Improvement of post-ischemic functional recovery of the heart	[68]
2-Chloroadenosine	Mice	*in vitro, in vivo*	25-min normothermic myocardial ischemia followed by 45-min reperfusion	Limitation of Ca^{2+} accumulation, inhibition of oxidant production, ATP consumption and mitochondrial dysfunction	Increase of myocardial contractility and diastolic function, oxidative stress limitation	[16, 66]
1-cyclopropyl guanosine (BN-063)	Male and female Sprague Dawley rats	*in vivo*	Ventricular arrhythmia caused by left coronary artery occlusion	Suppression of catecholamine release from nerve endings, inhibition of adenylate cyclase and reduction of cAMP synthesis	Delayed onset of ventricular arrhythmias, reduction of the total number of ventricular extrasystoles and tachycardias, reduction of the incidence of ventricular fibrillation and mortality	[72]
Capadenoson (BAY68-4986)	Dogs	*in vitro, in vivo*	CHF caused by serial intracoronary microembolization with 1–2 week interval	Normalization of sarcoplasmic reticulum Ca^{2+}-ATPase activity and expression of mitochondrial uncoupling proteins UCP-2 and UCP-3, as well as glucose transporters GLUT-1 and GLUT-2	An increase in ejection fraction and the absence of a significant increase in end-diastolic volume of the left ventricle, a decrease in the volume fraction of interstitial fibrosis	[75]
Tecadenoson (CVT-510)	Humans	*in vivo,* clinical trial	Paroxysmal supraventricular tachycardia	Counteracting catecholamine-induced activation of intracellular cAMP production and limiting slow calcium current	Antiarrhythmic effect	[15]

Table 2. Effects of A1AR antagonists in some CVDs

Antagonist	Research object	*In vivo / in vitro*	Pathological state/disease	Proposed mechanism of action	Effect	Reference
8-cyclopentyl-1,3-dipropylxanthine (DPCPX)	Chicken embryos, 4 day old chicken embryo hearts	*in vitro*	Transient atrial ectopy, second degree atrioventricular block, Mobitz type I atrioventricular block	Inhibition of NADPH-oxidase, ERK, phospholipase C, PKC, and L-type calcium channels	Antiarrhythmic effect	[92]
	Male Wistar rats	*in vivo*	Hypertension induced by microinjection of adenosine (1.25 nmol/50 nl) into the lateral part of the commissural part of the nucleus of the solitary tract	Modulation of the sympathoinhibitory component of the baroreflex	Decrease in average blood pressure without changing heart rate	[99]
	Dogs, sinoatrial node cells	*in vitro*	CHF induced by tachycardia for 4 months	GIRK inhibition	Bradycardia limitation in CHF	[22]
Theophylline	Dogs, coronary-perfused preparations of the atria and sinoatrial nodes of dogs	*in vitro, in vivo*	Tachycardia-induced CHF	Antagonizes adrenergic stimulation, inhibits cAMP production, suppresses I_f current and/or L-type calcium current (I_{Ca}, L) (hypothesis)	Normalization of the sinoatrial node functioning and elimination of atrial fibrillation	[103]
Tonaphylline (BG9928)	Males of ZSF1 rats	*in vivo*	CHF with preserved ejection fraction and obesity	Combined blockade of A1AR/A2BR, inhibition of gluconeogenesis, glycogenolysis, and VEGF expression	Improvement of left ventricular diastolic function and limitation of metabolic syndrome, polydipsia and polyuria, reduction of plasma triglyceride levels, 24-hour glucose excretion and urinary protein excretion	[104]
8-(noradamantan-3-yl)-1,3-dipropylxanthine (KW-3902)	Male Dahl SS rats	*in vivo*	High NaCl diet-induced hypertension	Increase of intracellular cAMP, inhibition of Na^+-$3HCO_3^-$ cotransporter in the proximal tubules, blockade of Na^+ reabsorption	Increase of urine volume and sodium excretion, limiting cardiac hypertrophy, antihypertensive effect	[93]

3.2. Allosteric Modulators of A1AR

In contrast to conserved active centers, allosteric sites have high variability in amino acid sequences and are characterized by higher specificity, and the substances that bind to them have a pronounced selectivity of action as compared to orthosteric ligands [114].

There are several variants of allosteric modulators: positive effector PAM (positive allosteric modulators), which enhances the agonist-mediated receptor response; negative NAM (negative allosteric modulators) weakening the response; neutral modulator, which binds to the allosteric site, but does not affect the activity of the orthosteric ligand and there are molecules that are able to activate the receptor from the allosteric site even in the absence of its agonist [106]. The allosteric modulators known as BAMs (biased allosteric modulators); they interact with G-protein coupled receptors, cause conformational changes in the structure of the receptors, and activate only one of the signal transduction pathways thus preventing side effects [115, 116].

The first allosteric A1AR modulator PD 81723 [2-amino-4,5-dimethylthiophen-3-yl)(3-(trifluoromethyl) phenyl)methanone] was discovered in 1990 by Bruns et al. [45]. PAM and NAM A1AR act in the presence of orthosteric ligands and enhance or attenuate A1AR activation by stabilizing the adenosine-A1AR-G protein complex [117, 118]. PAM VCP333 improves cardiac function and reduces cardiomyocyte death after cardiac ischemia.

Another important advantage is the reciprocal connection with the orthosteric domain — the allosteric modulator affects the binding of the endogenous ligand and vice versa [119].

Therefore, compounds of this group are promising agents for the CVD correction because they have the ability to enhance only therapeutically significant signal transduction without developing side effects. Unfortunately, data on the work of allosteric A1AR modulators in CVD diseases are limited only by results of one preclinical study [120]. This study has shown that the A1AR allosteric modulator VCP333 (1 μM) and the A1AR partial agonist VCP102 (10 μM) reduced myocardial cell death after an ischemic episode in isolated mouse hearts. After 60 min reperfusion, both compounds increased left ventricular pressure and decreased cardiac troponin I levels by 25% and 6.7% (p<0.05), respectively, as compared with the control group. At the same time, during reperfusion both compounds did not affect end-diastolic pressure, coronary blood flow velocity, and dP/dtmax values [120].

Despite the promise of searching for allosteric modulators, none of them have passed clinical trials to date. Obviously, problems associated with their development lie in the unclear relationship between the structure and activity of the allosteric site, it is often unknown or difficult to detect due to changes in receptor conformation. The low degree of evolutionary conservation of allosteric sites favors the emergence of species differences that complicate their study. Another complication is that allosteric modulators can function as molecular switches, influencing the action of agonists *in vivo*. However, despite these limitations, allosteric modulators have the potential to become highly effective and safe pharmacological agents. Limited data on the role of allosteric modulators of A1-adenosine receptors in CVD opens up a wide field for the search, development and study of the cardioprotective properties of substances in this group.

3.3. A1AR Antagonists

According to their chemical structure, A1AR antagonists represent xanthines and their derivatives with an aryl or cycloalkyl group at the C^8 position. Selectivity towards A1AR was also observed in substances of this series with substitutions at positions N^1, N^3, and N^7. It should be noted that xanthine analogues often have a non-specific effect, stimulating the search and development of non-xanthine A1AR antagonists, which include represented by heterocyclic compounds (benzimidazoles, imidazopyridines, pyrazolopyridines, and thiazolopyrimidines) [110, 121, 122].

A1AR antagonists exhibit cardioprotective action and have antiarrhythmic and antihypertensive effects. Substances of this group limit CHF, cardiorenal, and metabolic syndromes (Table 2) [22, 92, 93, 99, 103, 104].

CONCLUSIONS

Convincing evidence now exists that CVD occurrence is associated with changes in the expression and functioning of A1AR, and the receptors themselves undoubtedly represent a promising target for the treatment of heart failure, hypertension, hypertrophy and myocardial ischemia/reperfusion, angina pectoris, and various arrhythmias, and etc.

However, the high abundance of AR in the body represents a serious problem. Undoubtedly, significant cardiovascular effects may be achievable, but highly selective agents and methods for their development are required to produce the desired actions in target organs/cells to avoid the occurrence of problematic off-target effects.

A significant number of *in vitro* and *in vivo* studies conducted over more than 25 years have identified compounds with different chemical structures that are full and partial agonists, allosteric modulators and antagonists of A1AR. Although ARs are considered as promising drug targets, the results so far have been disappointing: most of the drug candidates have undergone experimental preclinical studies, and only a small number of substances have entered clinical trials. This was most often due to either lack of efficacy when extrapolated to humans, or receptor desensitization and adverse renal, nervous and cardiovascular side effects.

In this regard, further search, research, and development of new highly active and safe compounds targeting A1AR for the therapeutic correction of diseases of the cardiovascular system is relevant.

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This article does not contain any research involving humans or the use of animals as objects.

CONFLICT OF INTEREST

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ПРОБЛЕМЫ И ПЕРСПЕКТИВЫ ПОИСКА НОВЫХ ФАРМАКОЛОГИЧЕСКИХ СРЕДСТВ ДЛЯ ЛЕЧЕНИЯ СЕРДЕЧНО-СОСУДИСТЫХ ЗАБОЛЕВАНИЙ СРЕДИ АГОНИСТОВ, АНТАГОНИСТОВ И АЛЛОСТЕРИЧЕСКИХ МОДУЛЯТОРОВ АДЕНОЗИНОВЫХ РЕЦЕПТОРОВ

В.Н. Перфилова[1,2], Е.А. Музыко[1]*, А.С. Таран[1], А.А. Шевченко[1], Л.В. Науменко[1]

[1]Волгоградский государственный медицинский университет,
400131, Волгоград, пл. Павших Борцов, 1; *эл. почта: muzyko.elena@mail.ru
[2]Волгоградский медицинский научный центр, 400131, Волгоград, пл. Павших Борцов, 1

А1-аденозиновые рецепторы широко распространены в организме человека и опосредуют множество разнообразных эффектов. Значительное их количество представлено в сердечно-сосудистой системе, где они контролируют ангиогенез, тонус сосудов, частоту сердечных сокращений и проводимость, что делает этот подтип рецепторов перспективной мишенью для терапии сердечно-сосудистых заболеваний. В обзоре обобщены литературные данные о строении и функционировании А1-аденозиновых рецепторов, проанализировано их участие в формировании гипертрофии миокарда, его ишемически-реперфузионного повреждения, различных видов нарушений сердечного ритма, хронической сердечной недостаточности, артериальной гипертензии. Рассмотрена роль и некоторых аллостерических регуляторов А1-аденозиновых рецепторов в качестве потенциальных средств для терапии заболеваний сердечно-сосудистой системы.

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Ключевые слова: А1-аденозиновые рецепторы; сердечно-сосудистые заболевания; агонисты; антагонисты и аллостерические модуляторы А1-аденозиновых рецепторов

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