Review

Interplay of Angiotensin Peptides, Vasopressin and Insulin in the Heart: Altered Interactions in Obesity and Diabetes Mellitus

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Review

Interplay of Angiotensin Peptides, Vasopressin and Insulin in the Heart: Altered Interactions in Obesity and Diabetes Mellitus

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Abstract: The heart serves as the pivotal organ generating rhythmic contractions allowing blood ejection from the ventricles and its circulation in the cardiovascular system. Contractions of the heart requires oxygen and energy consumption and removal of metabolic factors from cardiac myocytes. The mechanical performance of the cardiac muscle and production of the vasoactive factors are significantly affected in cardiovascular and metabolic diseases, especially in the heart failure, hypertension and diabetes mellitus. The processes affecting coronary blood flow and cardiac contractility in these diseases are not fully recognized. The present review draws attention to specific role of angiotensin peptides, vasopressin and insulin in the regulation of the coronary blood flow and cardiac contractions. There is evidence for intracardiac production of some of these compounds and their importance in the regulation of the cardiac tissue oxygenation, energy production and metabolism, and generation of other cardiovascular compounds, such as nitric oxide, bradykinin and endothelin. Presence of receptors for angiotensin II, angiotensin-(1-7) and insulin in the coronary vessels and cardiomyocyes sets up conditions for interaction of these factors at the signaling level. Coronary vessels and cardiac muscle possess AT1 and AT2 receptors, angiotensin-1-7 receptor, vasopressin V1 receptor, and insulin receptor substrates. Expression of these receptors and responsiveness to angiotensins, vasopressin and insulin are altered during heart failure, hypertension, obesity and diabetes mellitus, especially when these diseases occur simultaneously. The survey of the literature presented in the review provides evidence for the belief that very individualized treatment, including interactions of angiotensins and vasopressin with insulin, should be selected for patients suffering simultaneously for cardiovascular and metabolic diseases.

Keywords: angiotensin; diabetes mellitus; heart failure; hypertension; hypoxia; insulin; obesity; vasopressin

1. Introduction

In each vascular bed the blood flow depends on perfusion pressure, rheologic properties of the blood, structural and functional characteristic of the vascular wall, and action of vasoconstrictory and vasodilatory factors produced locally or inflowing from the systemic circulation. Importance of particular parameters significantly depends on specific function of the supplied organ. The fundamental role of the heart in maintenance of the blood circulation requires particularly precise regulation of the coronary blood flow (CBF). Rhythmic contractions of the heart exert direct mechanical effect on the coronary vessels that is associated with production of metabolic factors in cardiac myocytes and smooth muscle cells. The local cardiac vasoactive compounds regulate CBF in concert with cardiovascular compounds inflowing from the systemic circulation, and with the neurogenic control of the heart by the autonomic nervous system [1]. Considerable evidence shows that the mechanical performance of the cardiac muscle and production of the vasoactive factors are significantly affected in cardiovascular and metabolic diseases [2–4]. Among factors regulating CBF and cardiac metabolism are components of the renin-angiotensin system (RAS), vasopressin system (VS) and insulin [5–9]. In addition activation of RAS generates oxidative stress, which causes overproduction of reactive oxygen species (ROS) and significant disturbances of sarcolemma, sarcoplasmatic reticulum and myofibrils which contribute to development of cardiomyopathy [10–13]. Increasing number of studies provide evidence that RAS and VS participate in the regulation of

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metabolism and closely cooperate in this respect with insulin. Insulin resistance, cerebral glucose hypometabolism, cardiac autonomic neuropathy and cardiovascular disturbances, belong to serious complications of the diabetes mellitus of type 1 (T1DM) and type 2 (T2DM), and of the prediabetes (pre-DM) and metabolic (MetS) syndromes [14]; however the causative link of these disorders is not yet fully understood [15–18].

The present Review is a survey of experimental and clinical studies providing evidence that angiotensin peptides and vasopressin (AVP) play important role in the regulation of the coronary circulation and cardiac muscle properties. Cooperation of these peptides with insulin is emphasized and attention is drawn to aberrant interactions of RAS and AVP with insulin in diabetes mellitus and other metabolic disorders.

2. Renin-angiotensin system

2.1. Components of renin-angiotensin system

The RAS includes renin, angiotensinogen and angiotensin peptides. Renin is a highly potent enzyme, acting on N-terminal of angiotensinogen (AGT), which in humans is a molecule composed of 485 aminoacids. Renin removes a decapeptide angiotensin I [(Ang I, Ang-(1-10)] that can be converted either to highly active angiotensin II [(Ang II, Ang-(1-8)] by angiotensin converting enzyme 1 (ACE1) or to less active Ang-(1-9) by angiotensin converting enzyme 2 (ACE2). Ang-(1-7) can be cleaved either from Ang-(1-9) by ACE1 or from Ang-(1-8) by ACE2 (Figure 1). Other components of the RAS system [Ang III, Ang-(2-8); Ang IV, Ang-(3-8); Ang-(1-5), Ang-(5-8); Ang-(1-12)] are produced by enzymatic transformation engaging carboxypeptidases and endopeptidases.

Angiotensin peptides interact with AT1R (in some species AT1aR and AT1bR subtypes), AT2R, and MasR receptors, which are coupled with G protein. Activation of AT1R is mediated by multiple enzymatic pathways including phospholipase C (PLC), phospholipase D, phospholipase A2 (PLA2), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase and metalloproteinases. Activation of these tracks results in stimulation of highly active proteins, such as cyclooxygenases, lipooxygenases, cytochrome P450 enzymes, mitogen-activated protein kinase (MAPK), c-Jun N-terminal kinase (JNK), extracellular-signal-regulated protein kinases 1 and 2 (ERK1/2), transcription factors (NF-κB, AP-1, HIF-1α). Stimulation of AT2R results in activation of phosphotyrosine phosphatases and inactivation of protein kinases, and in activation of potassium channels, PLA2 and arachidonic acid derivatives. Ang-(1-7) activates the Mas receptor (MasR) and the ACE2 – Ang-(1-7) – MasR axis [19,20].

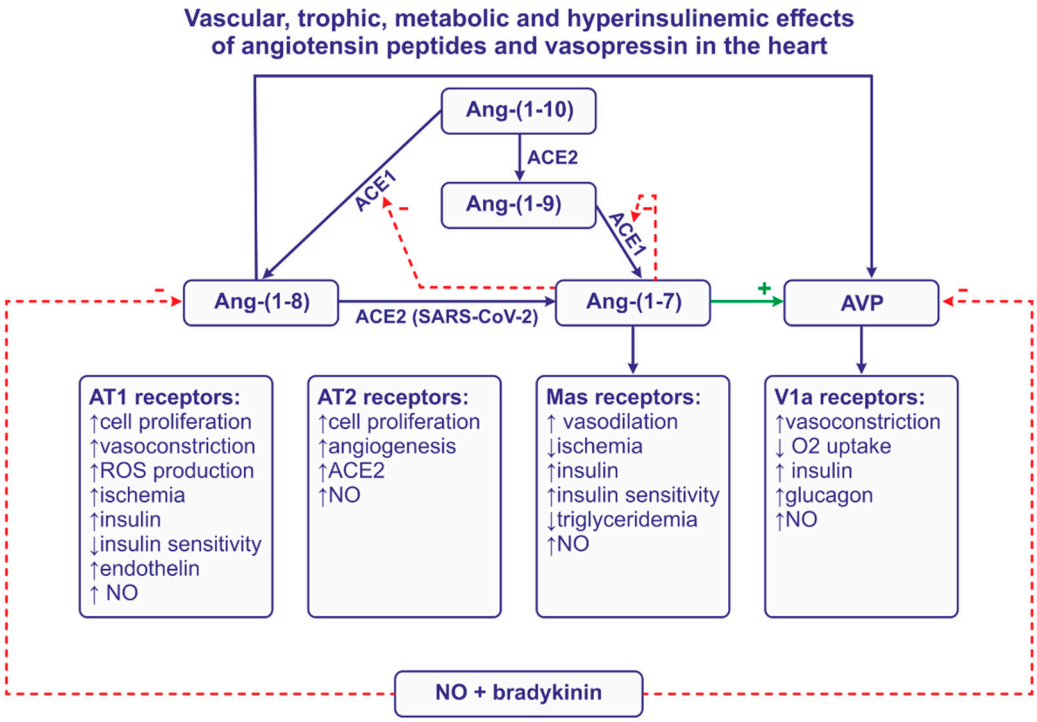

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Figure 1. Figure illustrates the role of angiotensin converting enzyme -1 (ACE1), angiotensin converting enzyme-2 (ACE2), nitric oxide (NO) and bradykinin in formation and release of angiotensin II (Ang-(1-8) and Ang-(1-7). The Figure summarizes also effects of Ang-(1-8), Ang-(1-7) and vasopressin (AVP) on constriction of coronary vessels, formation of NO and trophic and metabolic processes in the heart.

2.2. Cardiac effects of Angiotensin II

*2.2.1. Action of Ang II in cardiac muscle and coronary vessels***.**

Angiotensin receptors are present both in the coronary vessels and in the cardiac muscle (Figure 2). Demonstration of autocrine release of Ang II from mechanically stretch cardiomyocytes suggested that Ang II may be produced in the heart and may contribute to development of stretch-induced hypertrophy [21]. Essential role of AT1R in appropriate function of the heart was confirmed in studies on control mice and mice with knockout of AT1aR and AT1bR, because the knockout resulted in the atrophic changes of the myocardium and in abolishement of Ang II – induced decrease of the coronary blood flow, as well as in reduction of the left ventricle pressure [22].

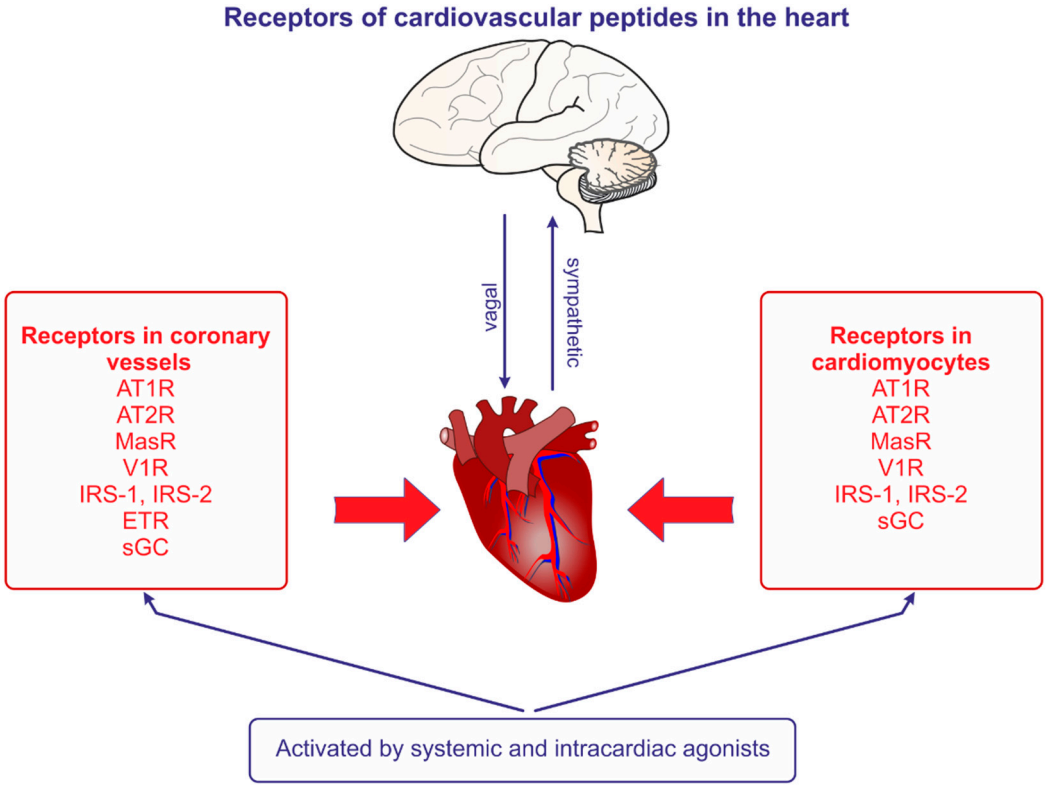

Figure 2. Figure shows presence of angiotensin II receptors of type 1 (AT1R) and type 2 (AT2R), angiotensin- (1-7) receptor (MasR), vasopressin V1a receptor (V1aR), endothelin receptor (ETR), nitric oxide receptor (sGC, soluble guanylyl cyclase), insulin receptor substrate of type 1 (IRS-1) and insulin receptor substrate of type 2 (IRS-2) in the coronary vessels and the cardiomyocytes of the heart.

It is likely that Ang II induces apoptosis of the cardiac cells through actions exerted in mitochondria. Exposure of neonatal cardiomyocytes to high Ang II concentration elicited mitochondrial damage with downregulation of NADPH dehydrogenase subunit, which is a component of the electron transport chain [23,24]. Furthermore, it has been shown that Ang II enters mitochondria, where it stimulates NADPH oxidase 4 (NOX4) and promotes electron leak and ROS production, which may cause damage of mitochondrial DNA. In the mitochondria Ang II stimulates also other destructive processes, such as oxidation of components of the membrane permeability transition pore, and activation of the mitochondrial ATP-sensitive K^+ channel. Accordingly, it has been suggested that the above processes play pivotal role in Ang II-induced cardiac hypertrophy and endothelial dysfunction, and that an inappropriate mitochondrial action of Ang II contributes to development of cardiac and metabolic diseases [24–26].

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Coronary vessels. The first study exploring effects of systemic administration of Ang II on coronary vessels was performed in 1976 by Giacomelli et al. [27] on Holtzman rats. The study demonstrated that Ang II delivered in hypertensive dose (1.7 μg/min/kg) for 4 hours induced injury of coronary vessels that was manifested by increased permeability of epicardial arteries and lesions of intramural arteries and arterioles. Next, experiments on Wistar Kyoto rats showed that infusion of Ang II at the same rate for 2 hours increased blood pressure and elicited vasoconstriction of intracardiac intramural arteries and arterioles that were associated with endothelial cell vascuolization, smooth muscle cell fragmentation and necrosis [28]. Experiments on trained rats revealed that administration of Ang II prominently reduced left ventricle (LV) vessels density of the trained animals performing repetitive exercise for 10 weeks [29].

Experiments on human cultured coronary artery smooth muscle cells showed that Ang II enhances migration and proliferation of the cells and that this process can be blocked by AT1R antagonist valsartan [30]. There is evidence that the growth-promoting action of Ang II on smooth muscle cells of human coronary vessels requires activation of mammalian target of rapamacine (mTOR) sensitive signaling pathway and activation of phosphatidylinositol 3-kinase, p70(s6k) and eukaryotic inhibitor factor-4E [31]. Human coronary artery endothelial cells (HCAECs) respond also to moderate concentrations of Ang II with up-regulation of genes that promote tube formation, such as signal transducer and activator of transcription 3 (STAT3) and mir-21 and presumably are involved in the process of vasculogenesis [19,32].

With regard to potential role of intracardiac Ang II in the coronary vessels there is evidence for presence of some of the components of RAS in the heart. Experiments on cultured bovine aortic endothelial cells provided evidence that these cells are able to synthesize and secrete angiotensin peptides and the authors suggested that the coronary endothelial cells may possess likewise property [33]. In this line, employment of quantitative *in vitro* autoradiography in the rat allowed to demonstrate presence of ACE in the endothelium and smooth muscle of coronary vessels, aorta and pulmonary artery [34–36]. Studies on the rat coronary endothelial cells (CES) and vascular smooth cells (VSMC) visualised AT1R in endothelial cells, and AT2R in both types of cells. Ang II induced AT1R-dependent proliferation of VSMC whereas in CES the proliferative effect could be observed after blockade of AT2R. In addition in CES the antiproliferative action could be observed after administration of a selective agonist of AT2R (CGP 42112). Altogether the results suggested that Ang II is able to promote proliferation of VSMC, and can suppress proliferation of CES [37]. AT1R and AT2R were demonstrated in smooth muscle cells of porcine coronary artery explants and both types of these receptors participated in stimulation of migration of smooth muscle cells by Ang II [38] (Figure 1).

Angiotensin II, nitric oxide and hypoxia. Strong evidence points to important role of nitric oxide (NO) in regulation of the coronary vessels by Ang II. Earlier studies indicated that long-term inhibition of NO synthesis by administration of N(ω)-nitro-L-arginine methyl ester (L-NAME) in Wistar Kyoto rats enhanced activation of ACE and induced increase of wall-to lumen ratio and elevation of perivascular fibrolysis, showing therby remodeling of coronary vessels. These effects were markedly reduced by administration of ACE inhibitor (tamocapril) and by blockade of AT1R [39,40]. Other studies confirmed important role of bradykinin and NO in ACE-mediated vasodilation of coronary vessels [41,42]. *In vitro* studies on endothelial cells of male Wistar rats showed that Ang II increases NO production in the proliferating cells and that this effect is mediated both by AT1R and AT2R [43].

It is likely that interaction of Ang II with NO plays a role in adaptation of coronary endothelial cells to hypoxia. Experiments on mice provided evidence that under hypoxic conditions Ang II acting on AT2R induces endothelial sprout formation and that this effect is mediated by bradykinin and NO [44]. Furthermore, it has been shown that exposure of human coronary endothelial cells to hypoxia increases phosphorylation of JNK and activity of hypoxia-inducible factor-1α (HIF-1α). Moreover, together with hypoxia Ang II increases secretion of visfatin, which is an adipocytokine with angiogenic properties. The authors found that hypoxia or hypoxia combined with application of hyperbaric oxygen increases glucose uptake and promotes migration and tube formation in the cells. These effects could be blocked by AT1R antagonist losartan [45].

Interaction of angiotensin II and endothelin. There is evidence that Ang II cooperates with endothelin (ET) in the regulation of CBF. The majority of endothelin-1 (ET-1) originates from

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endothelial cells where its synthesis is stimulated by Ang II, thrombin and inflammatory cytokines [46,47]. It has been found that cultured endothelial coronary cells co-express Ang II and ET-1 and that exposure of these cells to isoproterenol or high potassium concentration induces co-expression of both peptides, whereas exposure to sodium nitroprusside or S-nitroso-N-acetyl penicillamine (SNAP) decreases Ang II and ET-1 secretion [36]. Other study showed that stimulation of α1 adrenergic receptors in rat cardiomyocytes increased production of Ang II, which subsequently stimulated formation of ET-1 through activation of NADP oxidase [47]. In healthy awake swine separate blockade of AT1R and ETA/ETB receptors produced similar vasodilatory responses as combined blockade of these receptors, however after the myocardial infarction responsiveness to both peptides was significantly altered [48].

Angiotensin II and epicardial adipose tissue. The electrical and mechanical function of the heart as well as the coronary blood flow can be also regulated by bioactive compounds generated in the epicardial adipose tissue (EAT) [49]. The pericardial fat is a source of adipokine, anti-inflammatory cytokine (IL-10), pro-inflammatory cytokine (IL-6) and other pro-inflammatory factors, (IFNγ, MCP1) regulating function of the cardiac muscle and coronary blood vessels. In patients with cardiovascular diseases production of ROS in EAT is higher than in the subcutaneous adipose tissue [50]. There is also evidence for activation RAS in the EAT [51,52].

2.3. Cardiac effects of Ang-(1-7)and other angiotensins

In many instances Ang (1-7) acting on MasR exerts similar effects to those observed after stimulation of AT2R by Ang II, and serves a role of the cardioprotective factor (Figure 1). The mechanism of the cardioprotective action of Ang-(1-7) is not yet fully recognized, however it appears that it depends on generation of NO [53–56]. There is also evidence that Ang-(1-7) acts as an ACE1 inhibitor, and that it potentiates vasodilatory effect of bradykinin via B2 receptors [57]. The possibility that the vasodilatory action of Ang-(1-7) in the coronary vessels is mediated by bradykinin and NO has been confirmed in experiments on the hearts isolated from the guinea pigs and Wistar rats [58,59]. Also other angiotensin peptides [Ang-(1-2), Ang-(1-3), Ang-(1-4), Ang-(1-5)] reduce pressure perfusion of the rat coronary vessels and it is likely that their action depends on stimulation of Mas receptor and release of NO [60].

2.4. Central effects of angiotensin peptides

Local action of Ang II in the heart may be potentiated by its interaction with cardiovascular neurons in the central nervous system. Although the systemic Ang II does not cross the blood-brain barrier, it can act in the subfornical organ (SFO), and it can activate neural pathways projecting from the SFO to the paraventricular nucleus (PVN) where it can stimulate AVP secretion and activation of the sympathetic outflow [61–63]. Systemic administration of relatively small doses of Ang II in mice was found to elevate blood pressure, and plasma AVP and endothelin-1 (ET1) levels and to decrease cerebral blood flow (CBF). As the above effects were significantly reduced by the intrabrain applications of AT1R antagonist (losartan), AVP V1a receptors (V1aR) antagonist (SR49059) and ROS scavenger (MnTBAP), it was suggested that they were mediated by AT1R, V1aR and ROS [64].

2.5. Angiotensin peptides in regulation of the heart in cardiovascular diseases

Multiple experimental studies studies provide evidence that excessive activation of the RAS pathway importantly contributes to development of pathogenic responses in the heart.

Significance of ACE and Ang II. Experiments on sham-operated rats and rats with myocardial infarction revealed that prolonged administration of ACE inhibitor quinapril helps to preserve high energy phosphate metabolism in the infarcted rats, which suggested that endogenously produced Ang II exerts negative effect on metabolism of the infarcted heart [65]. Administration of ACE inhibitor (enalaprilat) in a porcine model of myocardial infarction significantly reduced the area of necrosis and impaired regional cell motion [66]. The positive effects of ACE inhibition and AT1R blockade during myocardial ischemia could be also caused by increased production of NO and bradykinin [67–69]. Studies on dogs with pacing-induced heart failure revealed that the vasoconstrictory effect of AT1R stimulation on the coronary vessels is markedly attenuated in the cardiac heart failure, which suggested desensitization of the coronary vessels to vasoconstrictory effect of Ang II. The authors suggested that desensitization to Ang II may be caused by accumulation

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of some vasodilatory compounds, for instance bradykinin and/or NO [70]. Indeed, inhibition of ACE and blockade of AT1R increased cardiac bradykinin and NO levels, and elevated coronary blood flow in another study on dogs with myocardial ischemia induced by reduction of the coronary perfusion pressure [71]. Blockade of AT1R restored endothelial NO synthase, contractile-type myosin heavy chain isoform SM2 and calponin and Gata-6 levels in the coronary vessels of SHR rats [72]. Subsequent studies showed that blockade of AT1R by losartan in rats with the myocardial infarction improved cardiac performance and reversed several negative biochemical alterations, such as elevated sarcoplasmic reticulum Ca^{2+} uptake, Ca^{2+} pump protein, phospholamban protein, and myofibrils (MF) Ca^{2+} stimulated ATPase, myosin heavy chain (α-MHC) mRNA and β-MHC mRNA [73]. There is evidence that the myocardial infarction modulates interactions between AT1R and ETA/ETB receptors in the coronary vessels. For instance it was shown that in healthy awake swine the separate blockade of AT1R and ETA/ETB receptors produced similar vasodilatory responses as combined blockade of these receptors [48**]**, however, 2-3 weeks after the myocardial infarction the coronary vasodilatory responses to individual blockades of AT1R and ETA/ETB receptors were abolished in spite that the expression of AT1R and ETA receptors was not altered. In addition blockade of ETA/ETB receptors in presence of blockade of AT1R was able to produce coronary vasodilation in the infarcted swine. Thus, the authors postulated that under control conditions Ang II and endothelin act in the coronary vessels as independent vasoconstrictory peptides, whereas the myocardial infarction initiates cross-talk interactions between these compounds at the post-receptor level [48]. Effectiveness of stimulation of AT1R may depend on accessibility of AT1R-associated protein (ATRAP) which is able to enhance internalization of AT1R from the cell surface to cytoplasm and to reduce action of Ang II [74]. More recently studies performed on non-culprit arteries harvested from the rabbit model of myocardial ischemia-reperfusion provided evidence that expression of AT1R was higher in the ischemia-reperfusion group than in the sham group but expressions of AT1R, connexin 43 and β-tubulin were lower in the ischemic postconditioning group than in the ischemia reperfusion group [75].

There is also evidence for enhanced involvement of central AT1R in blood pressure regulation in hypertension. Blockade of central AT1R with losartan significantly reduced the hypertension of renin transgenic rats although it was not effective in normotensive SD rats [76]. Furtheromore, it was show that the cardiac sympathetic afferent reflex and renal sympathetic activity were enhanced in SD rats with the myocardial infarction and these effects were associated with elevated stimulation of AT1R receptors by Ang II in the PVN [77]. The central effects of angiotensin peptides may play especially significant role when the cardiovascular disease is associated with stress. For instance it has been found that prolonged (2 weeks) restraint stress of C57BL/6J mice enhanced expression of the mRNA levels of angiotensinogen, TNF-α, IL-6, monocyte chemoattractant protein-1 (MCP-1), insulin receptor substrate (IRS-1), and glucose transporter 4 (GLUT4) and could promote in this way synthesis of angiotenasin peptides and cytokines as well as development of insulin insensitivity [78].

Positive effects of ACE inhibition and AT1R blockade were also found in human patients with cardiac failure. In patients undergoing coronary arteriography blockade of AT1R with losartan improved epicardial blood flow during stress-induced cold pressure test and during exercise [79**]**. Moreover, prolonged therapy with ACE inhibitors promoted development of collateral circulation in patients with coronary artery stenosis, presumably due to coronary artery angiogenesis [80]. Studies analyzing expression of ACE in samples of coronary vessels obtained from patients suffering from coronary disease revealed presence of ACE in the atherosclerotic plaques [81]. In addition, experiments on coronary arterioles obtained from patients suffering from atherosclerosis showed that incubation of these vessels with ACE inhibitor (Lisinopril) significantly ameliorated vasodilatory responses to several endothelium-dependent agonists. The latter effect could be abolished by pretreatment with NO synthase inhibitor [82]. In patients with chronic heart failure combined application of ACE1 inhibitor (enalapril) and losartan for 16 weeks significantly reduced plasma insulin level, and homeostatic model assessment –insulin resstance (HOMA-IR) factor, serum tumor necrosis factor alpha (TNF-α), interleukin- 6 (IL-6), and monocyte chemoattractant protein-1 (MCP-1) levels. Correlations were found between reduction of HOMA-IR and decreases of IL-1 and MCP-1, which suggested significant role of activation ACE1 and AT1R in regulation of cytokines and insulin secretion [83].

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Significance of ACE2 and Ang-(1-7). There is evidence that the cardiac failure causes activation of ACE2 and stimulation of Ang-(1-7) pathway. Experiments on control and infarcted Wistar rats, which were treated or non-treated with selective Ang-(1-7) agonist, Ang-(1-7) antagonist and with N(G)nitro-l-arginine methyl ester (L-NAME), provided evidence that Ang-(1-7) improves hemodynamic parameters of the heart and decreases the infarcted area trhough actions mediated by NO [84]. Prolonged blockade of ACE2 activity in male Wistar rats was found to increase the myocardial infarct size and to reduce the left ventricle percentage shortening [85]. Studies *in vitro* using the model of endothelium–denuded coronary vessels revealed that levels of AT1R mRNA and AT2R mRNA were lower in smooth muscle cells of patients with heart failure than in control subjects [86]. Expression of AT2R was demonstrated in atherosclerotic plaques isolated from the internal coronary artery of human patients [87].

Experiments on human coronary endothelial cells provided evidence that stimulation of AT2R increases expression of ACE2 and that stimulation of ACE2 and AT2R results in inhibition of stimulatory effect of TNF α on IkB and NF-kB signaling, which may suggest that activation of ACE2 and AT2R exerts anti-inflammatory action in these cells [88]. Recently, it has been found that circulating levels of ACE2 and Ang-(1-7) are significantly elevated in patients suffering from coronary artery disease and that the levels of ACE2 are significantly higher in female than in male group of the patients [89].

It should be noted that ACE2 acts as a receptor for SARS-CoV-2 (Figure 1) and that altered activity of ACE2 and/or SARS-CoV-2 may interfere with development of atherosclerotic lesions in COVID-19 infections; indeed, SARS-Cov-2 viral mRNA is present in atherosclerotic plaques [90]. Moreover, SARS-CoV-2 infection increases production of pro-atherogenic and proinflammatory cytokines, such as IL-1β, IL-6 [90,91]. Recently, it has been reported that patients infected with SARS-COV-2 produce autoantibodies that are able to inhibit ACE2 activity and intensify severity of COVID-19 [92].

Genotypes of ACE and angiotensin receptors as determinants of coronary diseases. There is evidence that to some extent the susceptibility to the myocardial infarction and coronary artery disease may be determined by specific polymorphism of ACE constituents genotype. The study comparing distribution of ACE genotype in the Korean patients suffering from the acute coronary syndrome and in the healthy subjects indicated that the genotype DD of ACE gene may be an independent risk factor of acute coronary syndrome [93] There is evidence for association of insertion/deletion (ID) polymorphism of ACE with responsiveness of coronary vessels to NO-mediated vasodilation, i.e., patients with ACE DD genotype responded with significantly lower vasodilatory response to sodium nitroprusside (SNP) than the other groups of patients [94]. Detection of ACE polymorphism in leukocytes of patients suffering from coronary artery disease provided evidence that ACE genotype polymorphism may be associated with development of atherosclerotic plaques. Specifically, it has been shown that DD and ID genotypes manifest higher number of diseased coronary vessels, whereas the genotype I is showing smaller number of atherosclerotic lesions [95]. D allele of ACE gene was also found to be strong and independent risk factor for coronary artery disease in patients with non-insulin dependent diabetes mellitus [96].

Polymorphism of angiotensinogen M235T genotype occurs more frequently in patients with acute myocardial infarction than in the healthy control subjects [97]. Role of specific genotype of AT1R in susceptibility of human coronary vessels to vasoconstrictory factors was determined in patients undergoing arteriography, among whom it was found that the subjects with CC genotype of AT1R manifested significantly greater responsiveness to methylergonovine maleate, which is a potent vasoconstrictor [98].

2.6. Interaction of angiotensin peptides with insulin

Experimental and clinical studies provide evidence for complex interactions between angiotensin peptides and insulin in the regulation of the coronary blood flow and the myocardial function [6,99]. Prolonged (7 weeks) hyperinsulinemia decreased expression of AT1R and increased expression of AT2R in the atrium of SD rats, whereas it enhanced expression of both types of these receptors in the left ventricle [99]. Moreover, hyperinsulinemia elicited an increase of the LV mass and relative wall thickness, and reduced stroke volume and cardiac output. These changes were associated with hypertrophy of myocytes, interstitial fibrosis, and increased phosphorylation of IRS-

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1, ERK 1/2, MEK1/2, Akt and PI3K. It is likely that insulin could cooperate with the sympathetic system, because its effects could be significantly attenuated by application of metoprolol, an antagonist of beta-adrenergic receptors [99].

On the other hand, Ang II was found to participate in development of insulin resistance and endothelial dysfunction in atherosclerosis, whereas inhibition of ACE exerted positive effects in animal models of cardiometabolic syndrome [100]. In SD rats maintained on fructose rich diet, which promotes development of hypertension and insulin resistance, administration of ACE inhibitor or AT1R blocker (olmesartan) significantly reduced blood pressure, improved insulin sensitivity and reduced adipocyte size [101]. Further study revealed that blockade of AT1R in insulin-treated rats significantly potentiated NO-mediated vasodilation [102].

Ang-(1-7) appears to interact with insulin in opposite way than Ang II. Subcutaneous (sc) infusion of Ang-(1-7) was found to reduce insulin resistance, hypertriglyceridemia, obesity and hepatic fat accumulation in rats maintained on high fructose/low-magnesium diet, which imitates the metabolic syndrome [103]. Similarly, sc administration of Ang-(1-7) improved insulin sensitivity in C57BL/6J mice maintained on high-fat diet and this effect was associated with increased glucose uptake into the skeletal muscle [104]. Ang-(1-7) may also exert other effects, that may potently contribute to the regulation of metabolism by insulin. For instance it has been found that Anh-(1-7) induces proliferation of pancreatic β-cells, increases insulin secretion, amelioratates sensitivity of skeletal muscle and adipose tissue to insulin and improves metabolic function of the liver [105].

Finally, it should be noted that insulin receptors and insulin-like growth factor 1 receptor are present in the central nervous system, in the regions involved in the regulation of the sympathetic nervous system, metabolism and blood pressure [106,107]. Systemic and central administration of insulin into the RVLM increases lumbar sympathetic nerve activity and this effect can be reversed by blockade of glutamatergic NMDA receptors [106]. Therefore, it is likely that the direct interaction of insulin with angiotensin peptides in the heart may be potentiated by its action mediated by the sympathetic nervous system.

2.7. Role of angiotensin peptides in the heart in obesity, diabetes mellitus and hypertension

Multiple experimental and clinical studies report that high fat diet, obesity and dibetes mellitus significantly influence activity of the RAS.

Experimental studies. Enhanced ACE activity associated with diminished responsiveness to vasodilatory action of bradykinin, was found in coronary arterioles of rats maintained on high fat diet [108]. Treatment of type 2 diabetic KK-Ay mice, which serves as an experimental model of T2DM, with AT1R antagonist (valsartan) significantly improved insulin sensitivity and reduced plasma glucose level. This was associated with phosphorylation of IRS and translocation of GLUT 4 to the plasma membrane. In addition, application of valsartan reduced expression of TNF-α and production of superoxide. Treatment of KK-Ay mice with AT2R antagonist (PD123319) did not have significant effect on insulin sensitivity in this study [109]. Positive effects on metabolism by means of AT2R were found in another study on KK-AY mice, in which intraperitoneal injections of AT2R agonist (compound 21, C21) reduced insulin resistance [110].

Experiments on db/db mice, which is another model of T2DM, provided evidence that activation AT1R plays a role in remodeling of coronary vessels in diabetes mellitus. At 16 weeks of age db/db mice exhibited hyperglycemia, hyperlipidemia, obesity, insulin resistance and coronary remodeling [111], whereas prolonged administration of losartan in db/db mice in the dose which does not alter systemic blood pressure, significantly decreased number of VSMC, reduced remodeling of the coronary vessels and increased the coronary flow reserve [112].

There is evidence for enhanced involvement of angiotensin peptides in development of insulin resistance and in generation of oxidative stress in hypertension. In a model of Dahl-salt sensitive hypertension the hypertensive animals manifested insulin resistance, increased expression of AT1R mRNA and protein as well as impaired Ach-inducedced endothelium-dependent relaxation (EDR). Administration of AT1R blocker (candesartan) or antioxidant compound (tempol) reduced arterial blood pressure and insulin resistance as well as normalized EDR and O_2^- in the wall of aorta [113]. Furthermore, SHR rats maintained on high fat diet and developing diabetes of type II (SHRDI) manifested loss of body weight, hyperglycemia, reduced plasma insulin level, decreased myocardial and brain capillary vascularization and enhanced oxidative stress. The harmful effects of diabetes in

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SHRDI rats could be prevented by chronic inhibition of ACE with enalapril or by blockade of AT1R antagonist (olmesartan) [114]. Obesity, increase of blood pressure, myocardial hypertrophy and interstitial fibrosis, associated with elevated levels of ERK, PI3K and Tyr-phosphorylated β-insulin receptor subunit (βIR) and with decreased myocardial JNK expressions, were observed in Wistar-Kyoto rats fed with hypercaloric diet for 30 weeks. Several of these disorders, such as dyslipidemia and insulin resistance could be efficiently reduced by administration of losartan in drinking water [115].

It is likelt that some of the detrimental effects of Ang II in obesity and diabetes mellitus are mediated by aldosterone which closely cooperates with RAS and participates in regulation of insulin secretion. Experiments on isolated pancreatic islets revealed that aldosterone acting on mineralocorticoid receptors (MR) enhanced glucose-induced insulin secretion and ROS production. Activation of MR decreased also sensitivity to insulin in adipocytes and in skeletal muscle [116], and promoted development of inflammation, oxidative stress, lipid disorders, and insulin resistance, impairing thereby vascular insulin metabolic signaling [15,117,118].

ACE2 and Ang-(1-7) in obesity. Experimental evidence from animals maintained on high fat diet strongly suggests that ACE2 and Ang-(1-7) may partly oppose effects of activation of AT1R. Studies on ACE2 mutant (ACE2KO) mice and wild type mice provided evidence that high fat diet causes glucose intolerance, myocardial insulin resistance, cardiac steatosis, lipotoxicity and development of proinflammatory phenotype of the adipose tissue. These effects were associated with a decrease of cardiac adiponectin, which is an anti-inflammatory adipokine of adipocytes, and could be partly removed by 4 weeks lasting administration of Ang-(1-7) [119]. In the obese mice maintained on high fat diet administration of Ang-(1-7) for 28 days enlarged brown adipose tissue, upregulated thermogenesis, improved impaired glucose homeostasis, and enhanced expression UCP1 uncoupling protein-1 (UCP-1) in the brown adipose tissue [120].

Obesity and diabetes mellitus in human patients. Activity of ACE is also enhanced in coronary arterioles of obese human patients [108]. Measurements of insulin sensitivity index (ISI) and evaluations of HOMA-IR in patients with impaired glucose tolerance (IGT) and in diabetes mellitus revealed that administration of AT1R antagonist valsartan effectively reduces resting fasting insulin level, elevates ISI and adiponectin levels and decreases HOMA-IR and high sensitivity C-reactive protein (hsCRP) in the IGT group [121].

There is evidence that patients with prediabetes and type 2 diabetes have elevated pericardial and peri-aortic adipose tissue [122]. It has been shown that production of prohypertensive components of the RAS, in particular angiotensinogen mRNA and ACE mRNA, is elevated in epicardial adipose tissue of obese patients [51]. Elevated expressions of ACE2 and ADM17 (a disintegrin and metalloproteinase 17) genes have been found in epicardial fat of patients with type II diabetes mellitus and in subjects with obesity [52]. As ADM17 is a membrane bound enzyme, which participates in proteolytic cleavage of proinflammatory cytokines, such as TNF-α [123], it is possible that ADM17 elevation in obesity and in type II diabetes may signalize inflammatory processes and other detrimental changes in the heart. [124].

3. Vasopressin system

3.1. Components of vasopressin system

Arginine vasopressin is synthesized in neuroendocrine cells of the hypothalamus located mainly in the supraoptic nucleus (SON), the PVN and the suprachiasmatic nucleus (SCN) [125]. In addition, immunocytochemical and functional studies provide evidence for synthesis of AVP in the heart and lungs [126,127]. In most mammals AVP is a chief active peptide composed of Cys-Tyr-Phe-Gln-Asn-Cys-Pro-Arg-Gly-NH_2. The AVP gene is found on 20 chromosome and consists of exons encoding the sequence of 145-aminoacid polypeptide precursor forming N-terminal signal peptide, and sequences of AVP, neurophysin II (NPII) and copeptin. Copeptin is a glycopeptide, composed of 39 aminoacids released in equimolar quantities as AVP and it is frequently used as its biomarker because it is a more stable molecule [128]. Measurements of copeptin have been included into ESC guidelines on management of non ST elevation myocardial infarction [129].

Actions of AVP are mediated by V1a receptors (V1aR), V1b receptors (V1bR), V2 receptors (V2R),and oxytocin receptors (OTR) [20,130]. V1aR are found in the brain, the spinal cord, the heart and vessels, the kidneys, the lungs and the digestive system (mainly in the liver and the pancreas)

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[131–133]. V1bR are present in the pituitary, the brain, the pancreatic gland and the lungs [132,134]. Thus far, V2R have been located mainly in the kidney [131,136], however there is also some evidence for their presence in the heart [137].

3.2. Regulation of vasopressin release

Under physiological conditions release of AVP is regulated mainly by changes of blood osmolality. Among other stimulators are stress, hypovolemia, hypotension, hypoxia, hypoglycemia and several neuroactive factors, whose significance increases in cardiovascular and metabolic diseases. Angiotensin peptides, and in particular Ang II, and (Ang-1-7) belong to potent stimulators of AVP secretion [9]. Experiments on rats have shown that intracerebroventricular (ICV) infusion of insulin increases plasma AVP in a dose –dependent manner and that this effect is not associated with systemic hypoglycemia. [138]. Hypoxia and hypoglycemia are also able to stimulate AVP release, whereas vasopressin elevates blood glucose level and increases brain glucose retention. There is evidence that these effects occur with engagement of carotid chemoreceptors and NTS [139–141]. In experiments on conscious freely moving, rats it was found that central administration of glucagon-like peptide-1 (7-36) amide (GLP1) activates the parvocellular and magnocellular neurons of the PVN and SON and elevates plasma AVP level [142]. In the PVN and SON vasopressinergic neurons and GLP-1 receptors are coexpressed [143].

Significant role in regulation of AVP secretion by the hypothalamo-hypophysial neurons play gaseous molecules. NO released in the PVN inhibits secretion of AVP and plays essential role in buffering pressor responses exerted by other hypertensive compounds, such as Ang II and endothelin-1 (ET-1) [63,144]. Neuronal NO synthase (nNOS) is co-expressed with AT1R in the PVN and SON neurons and Ang II stimulates release of AVP and upregulates AVP mRNA level in PVN and SON neurons; these effects being potentiated by inhibition of nNOS activity [145]. Earlier studies suggested that during LPS-induced endotoxemia secretion of AVP is inhibited by NO and CO [146–148]. More recently experiments on the hypothalamic explants of rats provided evidence that NO reduces AVP release, whereas CO and hydrogen sulfide (H_2S) can exert an opposite effect [149].

It is likely that NO may inhibit local cardiac release of AVP and buffer vasoconstrictory action of this peptide in the heart [126]. In support of this assumption are experiments on pressure overloaded heart of the rat in which AVP mRNA and AVP peptide were detected mainly in endothelial cells and vascular smooth muscle cells [126].

3.3. Cardiac effects of vasopressin

Earlier studies provided evidence that AVP constricts coronary vessels with diameter less than 100 μm, whereas it does not exert significant effect or it can even dilate the larger vessels [150–152]. Experiments on isolated hearts of male Long Evans rats showed that application of AVP significantly reduced coronary blood flow and myocardial oxygen consumption, and that these effects were markedly attenuated during acute hypoxia. The latter finding suggested that hypoxia may significantly modulate the vasconstrictory potency of AVP in the heart [153]. The vasoconstrictory effect of vasopressin on the coronary vessels is mediated mainly by V1R [20,154] (Figure 1, Figure 2). However, it should be noted that coronary vasoconstriction was observed in patient with spastic angina after application of desmopressin (DDAVP), which is a selective agonist for V2R [155].

Vasopressin and nitric oxide. Regulation of the coronary blood flow by vasopressin is significantly modulated by locally released NO. It has been shown that AVP and its V1a agonist [Phe2Ile3proOrn8]vasopressin] significantly increase iNOS mRNA and NO production, as well as cytosolic free Ca^{2+} level in culture of neonatal rat cardiac myocytes stimulated by IL-1β [156]. Studies on isolated coronary arteries of the monkey demonstrated that acting on V1a receptors AVP can elicit vasodilation that is mediated by NO [157]. Further studies performed on the hearts of SD rats showed that AVP is able to stimulate inducible NO synthase (iNOS), nuclear factor kappa-B (NF-kappa B) and collagen synthesis. The results suggested that in the heart AVP may participate in development of cardiac fibrosis and inflammatory processes and that these effects are attenuated by antifibrotic action of NO [158]. Negative effects of excessive stimulation of V1aR in the heart of the mice were demonstrated by Li et al. [159], who found that selective overexpression of V1aR in the heart causes cardiac dysfunction and hypertrophy, associated with ventricular dilation and overactivation of the

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$G\alpha_{q/11}$ – mediated pathway [159]. Among factors which are able to decrease the vasoconstrictory potency of vasopressin are cannabinoids acting on CB1 receptors [160].

3.4. Vasopressin in the heart in cardiovascular diseases

Some evidence indicates that responsiveness of coronary vessels to vasopressin is altered under pathological conditions. Measurements of CBF in conscious dogs with experimentally induced area of hypoperfusion of collateral-dependent myocardium showed that systemic infusion of AVP during physical exercise decreased CBF in the collateral zone and that this effects was associated with an increase of resistance in the transcollateral and small coronary vessels. Under control conditions the exercise did not have significant effect on these parameters [161]. Recent studies have shown that during cardiac ischemia AVP may play a beneficial role through its action exerted in mitochondria. For instance, experiments on male Wistar rats subjected to 30 min ischemia followed by 120 min reperfusion showed that administration of AVP decreased sensitivity of the mitochondrial permeability transition pore (MPTP) to action of MPTP openers, protecting thereby mitochondria from swelling. In addition infusion of AVP significantly reduced the infarct size and plasma levels of lactate dehydrogenase, creatinine kinase –MB and malondialdehyde [162].

Administration of AVP in patients with catecholamine-resistant vasodilatory shock exerted positive effects including elevations of blood pressure, stroke volume index and left ventricle stroke work index [163,164].

3.5. Role of vasopressin in obesity and diabetes mellitus

Links between vasopressin and insulin. Several studies provide evidence that vasopressin and insulin cooperate in regulation of glycaemia. It was found that withdrawal of insulin in patients with diabetes mellitus elevated plasma vasopressin concentration [165] whereas administration of AVP elicited hyperglycemia, which was associated with stimulation of the sympathetic system [144,166]. Moreover, it has been shown that hypoglycemia stimulates release of AVP and that the glucosensitive receptors engaged in regulation of AVP release are located inside the blood-brain barrier [167]. ICV infusion of insulin in doses, that do not cause systemic hypoglycemia increased secretion of AVP in a dose –dependent manner [138]. There is evidence that AVP participates in the regulation of glycemic responses during hypoglycemia. For instance central administration of vasopressin in rats was found to reduce the hyperglycemic and hyperglucagonemic responses to hypoglycemia induced by administration of 2-deoxy-D-glucose [168].

It has been shown that AVP actively participates in the regulation of insulin and glucagon release and closely cooperates with these hormones in the regulation and glycemia. Vasopressin has been detected in human and rat pancreatic extracts [169] and AVP receptors have been found in pancreatic islets of several species including human beings. Moreover, it has been shown that AVP stimulates release of glucagon and insulin (132,170,171]. Interestingly, AVP was able to release insulin from beta pancreatic cells and glucagon from alpha pancreatic cells, however the type of the cell stimulated strongly depended on the level of glycemia. At elevated glucose concentration AVP increased insulin secretion, whereas at reduced glucose concentrations it promoted release of glucagon [172]. The latter finding suggested that AVP may play essential role in regulation of glucagon release during hypoglycemia. The pancreatic alpha cells secreting glucagon express high level of V1bR gene and blockade of V1bR reduces AVP-dependent release of glucagon. Effectivenes of stimulation of glucagon release by AVP appears to be significantly impaired in patients with type 1 diabetes mellitus [173].

Frequently hypoglycemia and stress stimulate release of AVP together with CRH [167,174–176]. It has been also shown that increased release of AVP during hypoglycemia significantly contributes to stimulation of ACTH secretion [177–179]. It is likely that AVP plays essential role in the regulation of ACTH secretion during hypoglycemia and stress because AVP-deficient Brattleboro rats manifest reduced elevations of plasma ACTH and corticosterone levels during hypoglycemia and exposure to various types of stressors [180].

There is evidence that insulin-dependent release of AVP may be markedly dysregulated in obesity and in patients suffering from diabetes mellitus. It has been shown that administration of insulin elicits significantly higher elevations of plasma AVP and oxytocin levels in diabetic patients than in healthy subjects [181]. In addition, higher number of AVP mRNA expressing cells was found

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in the PVN of nonobese diabetic mice than in the PVN of nondiabetic mice and control C57B1/6 mice [182]. There is evidence that responsiveness of coronary vessels to vasopressin may significantly differ in diabetic males and females. In this respect it has been shown that the isolated coronary vessels of control female rats and female rats with streptozotocin-induced diabetes are less sensitive to vasoconstrictive action of AVP than the corresponding vessels of control and diabetic male rats. The study provided evidence that the reduced vasoconstrictory responsiveness to AVP in females could result from an increased production of NO [183].

Engagement of AVP-V1aR pathway in the regulation of glucose homeostasis was confirmed by experiments on receptor-deficient mice (V1aR(-/-), which showed significant disturbances in glucose metabolism, such as hyperglycemia, higher hepatic glucose production and decreased liver glycogen content. The mutant mice responded with elevation of plasma AVP level and developed overt obesity when they were maintained on high calorie intake, while the sam diet was not effective in the wild-type mice [184**]**. Furthermore, experiments performed on V1aR knockout mice and double V1aR/V1bR knockout mice, as well as on obese Zucker rats revealed that inappropriate activation of V1R induces significant disturbances in glucose and lipid metabolism that may have an indirect detrimental effect effect on glucose and lipid supply to the heart [185,186].

Studies on Zucker diabetic fatty (ZDF) rats, whch serve as an experimental model of diabetes of type 2, demonstrated higher levels of AVP in the PVN and SON of ZDF rats than in the PVN and SON of Zucker lean control (ZLC) rats and the pre-diabetic rats, providing thereby direct evidence that diabetes of type 2 is associated with increased secretion of AVP in the hypothalamic nuclei [187]. Higher plasma copeptin levels and higher insulin plasma concentrations were found in obese patients and patients with the metabolic syndrome [188–190]. On the other hand, diabetic patients with asymptomatic hypoglycemia responded with smaller increases of blood AVP and lower elevations of heart rate in response to hypoglycemia than the healthy subjects, which may suggest that appropriate secretion of AVP plays essential role in appropriate sensation of glycemia [191]. Decreased expression of hepatic V1aR mRNA was found in rats with streptozotocin-induced diabetes mellitus [192].

Genotypes of vasopressin receptors as risk factors of coronary diseases

Certain variations of the human AVPR1A gene are associated with specific deviations of metabolism. It has been found that the subjects carrying the T allele of rs 1042615 and male subjects carrying rs 1042615 allele demonstrate lower concentration of triglycerides and higher fasting blood glucose concentration than CC carriers [193]. It has been also reported that the allele of rs35810727 AVPR1B gene is associated with elevated body mass index and that the human subjects carrying this variance of AVPR1B gene are more prone to develop obesity and diabetes mellitus [194].

4. Conclusions

The review emphasizes the role of Ang II, Ang-(1-7), AVP and insulin in the regulation of cardiac function in health and in cardiovascular and metabolic disorders. Survey of literature provides strong evidence that these compounds, produced intracardially or inflowing to the heart from the systemic circulation act on their specific receptors in the coronary vessels and cardiomyocytes and play crucial role in the regulation of coronary blood flow and strength of cardiac contractions (Figure 2). Acting on specific receptors angiotensins, vasopressin and insulin can exert acute and prolonged synergistic or antagonistic effects and have an impact on multiple parameters and reactions that decide about the cardiac efficiency. As shown in Figure 1 among the cardiac responses are: cell proliferation [Ang II→AT1R, Ang II→AT2R], vasoconstriction [Ang II→AT1R, AVP→V1aR], angiogenesis [Ang II→AT2R], increased ischemia [Ang II→AT1R; AVP→V1aR], reduced ischemia [Ang-(1-7)], ROS generation [AngII→AT1R], increased insulin secretion [AngII→AT1R; Ang-(1-7)→MasR; AVP→V1aR], decreased insulin sensitivity [Ang II→AT1R], increased insulin sensitivity [(Ang-(1-7)→MasR], endothelin secretion [Ang II→AT1R], reduced triglyceridemia [(Ang-(1-7)], increased glucagon secretion [AVP→V1aR], and increased NO production [Ang II→AT1R, Ang II →AT2R, Ang-(1-7)→MasR, AVP→V1aR]. Cardiac failure, hypertension and diabetes mellitus (especially diabetes mellitus of type II) frequently occur together. As discussed in the review angiotensin peptides and vasopressin play significant role in the regulation of secretion of insulin and tissue sensitivity to this hormone. Subjects suffering from the heart failure and diabetes mellitus frequently manifest altered synthesis of various components of RAS and VS. Coupling of various types of

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cardiovascular diseases with metabolic disorders creates particularly challenging conditions, as it potently influences sensitivity of cells to angiotensin peptides, vasopressin and insulin and markedly influences predisposition to development of detrimental changes in the heart and vessels of diabetic patients. Accordingly, very individualized therapy, taking into account interactions of angiotensin peptides, vasopressin and insulin, should be selected for patients suffering from co-existing cardiovascular and metabolic diseases.

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Abbreviations

ACE	Angiotensin converting enzyme 1
ACE2	Angiotensin converting enzyme 2
Ach-	Acetylcholine
ACTH	Adrenocorticotropic hormone
AGT	Angiotensinogen
Ang	Angiotensin
AT1R	Angiotensin receptor of type 1
AT2R	Angiotensin receptor of type 2
AVP	Arginine vasopressin
CBF	Coronary blood flow
COVID 19	Coronavirus disease 2019
CRH	Corticotropin-releasing hormone
dDAVP	Desmopressin an analog of AVP
ERK	Extracellular signal-regulated kinase
EAT	Epicardial adipose tissue
EDR	Endothelium dependent relaxation
ESC	Coronary endothelial cell
ET	Endothelin
GLUT	Glucose transporter
HOMA	Homeostatic model assessment
HIF	Hypoxia-inducible factor
ICV	Intracerebroventricular
IL	Interleukin
IRAP	Insulin-regulated aminopeptidase
IRS	Insulin receptor substrate
ISI	Insulin sensitivity index
JNK	Jun N-terminal kinase
L-NAME	N(ω)-nitro-L-arginine methyl ester
LV	Left ventricle
MAPK	Mitogen-activated protein kinase
MasR	MAS receptor for angiotensin-(1-7)
MCP-1	Monocyte chemoattractant protein-1
MPTP	1-methyl-4phenyl-1,2,3,6-tetrahydropyridine
mTOR	Mammalian target of rapamycin
NADPH	Dinicotinamide adenine dinucleotide phosphate
NO	Nitric oxide
NTS	Nucleus of the solitary tract
PLA2	Phospholipase A2
PLC	Phospholipase C

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PVN	Paraventricular nucleus
RAS	Renin-angiotensin system
ROS	Reactive oxygen species
RVLM	Rostral ventrolateral medulla
SARS-CoV	Severe acute respiratory syndrome associated coronavirus
SFO	Subfornical organ
SHR	Spontaneously hypertensive rat
SON	Supraoptic nucleus
SNP	Single nucleotide polymorphism
TNFα	Tumor necrosis factor α
T1DM1	Diabetes mellitus of type 1
T1DM2	Diabetes mellitus of type 2
UCP	Uncoupling protein
VSMC	Vascular smooth muscle cell
V1aR	Vasopressin receptor of type 1a
V1bR	Vasopressin receptor of type 1b
V2R	Vasopressin receptor of type 2
VS	Vasopressin system
WKY	Wistar Kyoto rat
ZDF	Zucker diabetic fatty

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