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CARDIOVASCULAR DISORDERS DUE TO DYSREGULATION OF THE RENIN – ANGEOTENSIN SYSTEM AND THE VASOPRESSINERGIC SYSTEM INTERACTION

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Abstract: Angiotensin II (Ang II) is a member of the renin-angiotensin system (RAS), which forms a cascade of highly active biological compounds regulating a variety of physiological functions. Co-activation of the RAS and the vasopressinergic system (VPS) by the same stimuli, and engagement of the same post-receptor intracellular pathways by Ang II and vasopressin (AVP), favors formation of different types of interactions, which may result in additive, synergistic, or antagonistic effects. Both Ang II and AVP directly participate in the regulation of the cardiovascular system. They also have an impact on several other processes, such as metabolism, stress, emotional disorders, and inflammation, which may exert potent secondary effects on the cardiovascular functions. The main purpose of the present review is to draw attention to the interactions of Ang II and AVP in the regulation of the water-electrolyte balance and blood pressure in healthy individuals and in patients with cardiovascular diseases. Specifically, we give a description of the regulation and function of the RAS and the VPS and we focus on the mechanisms underlying the interactions of Ang II and AVP in cardiovascular regulation and on disturbances of these interactions in cardiovascular diseases.

Key words: Cardiovascular regulation, rennin, angiotensinogen, Ang II receptors.

Renin, Agt, ACE, and Ang II receptors are all present in the myocardium. Angiotensinogen is present mainly in the cardiac atria and fibers of the conductive system. The strongest expression of ACE was found in the coronary endothelial cells and cardiac fibroblasts, and weaker expression of ACE was found in the aorta, pulmonary arteries, valves, endocardium, and epicardium [2]. Angiotensin I and Ang II are synthesized de novo in the heart and their synthesis is regulated by glucocorticoids, estrogen, and thyroid hormones [4]. In the rat, endothelial cell ACE gene expression is stimulated by aldosterone [5]. Stimulation of beta receptors upregulates renin and Agt expression in the heart and mechanical stretching of the ventricular myocytes increases the release of Ang II [2]. The human angiotensin AT1 receptor gene (*at1r*) has been mapped to chromosome 3 [3]. The AT1R protein is composed of 359 amino acids and belongs to G protein-coupled receptors (GPCR) [3]. After interaction with Ang II, the AT1Rs are internalized but approximately 25% of the internalized receptors recycle back to plasma membrane. The remaining AT1R serve their intracellular functions or are degraded in lysosomes [4]. The ACE→Ang II→AT1R axis forms the vasoconstrictor/proliferation/profibrotic wing of the RAS. Angiotensin AT1Rs are widely distributed in the heart and vessels, kidney, brain, lungs, endocrine glands, and several other organs [5]. Stimulation of AT1Rs by Ang II involves activation of a broad scope of intracellular pathways, which may have different roles in specific groups of cells [6]. Homologous regulation of AT1 receptors by Ang II appears to depend on the type of cells. In a culture of vascular smooth muscle cells, Ang II downregulated AT1R mRNA and protein expression [4], whereas Ang II increased the expression of AT1R in neurons and the effect was associated with elevated expressions of NF-κB and Ets-like protein (Elk-1) [3]. In renal mesangial cells, stimulation of AT1R by Ang II stimulated stress activated protein kinase (SAPK) through the mechanism of engaging stimulation of pertussis toxin-sensitive and pertussis toxin-insensitive G proteins and activation of tyrosine kinase [4]. Significant upregulation of AT1R mRNA was found in the rat subfornical organs (SFO) and anterior pituitary

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after sustained (5 days) dehydration [5]. In healthy human subjects, prolonged (8 days) blockade of AT1R increased PRA and Ang II concentrations, elevated urinary sodium excretion, decreased plasma aldosterone concentration, and reduced filtration fraction (FF) [6]. The gene for AT2 receptor (AT2R) is located on the X chromosome [7]. The AT2R protein belongs to a family of G protein-coupled proteins and has a low homology of amino acid sequence (~34%) with AT1R [7]. Stimulation of AT2R activates phosphotyrosine phosphatases, especially serine/threonine phosphatase 2A, protein kinase phosphatase, and SHP-1 tyrosine phosphatase. This is associated with an inactivation of MAPK (specifically p42 and p44 MAPK) and ERK[5]. The most prominent expression of AT2R was found in the kidney, heart, blood vessels, and brain, especially in the soma and dendrites of the PVN . In the cardiovascular system, activation of AT2R exerts opposite effects to those following stimulation of AT1R. After blockade of AT1R, administration of Ang II may result in hypotension, partly mediated by an increased production of BK, NO, and cGMP [8]. In addition, stimulation of AT2R exerts antiproliferative and proapoptotic effects on smooth muscle cells, and reduces expression of AT1R and transforming growth factor beta (TGF-β) receptors [9]. In the heart, stimulation of the AT2Rs inhibits growth and remodeling and induces coronary vasodilation [7]. The role of AT2R increases under pathological conditions. They play a buffering role by preventing cardiac hypertrophy and fibrosis during the administration of Ang II and participate in cardiac remodeling during post myocardial infarction. It is also postulated that they act nephroprotectively in chronic kidney diseases . Vasopressin is one of the most potent vasoconstrictors, although responsiveness of various vascular beds to its contractile action significantly differs. The most sensitive vessels to vasopressin are those of the skin, muscle, and splanchnic circulation [10]. The vasoconstrictory effect of AVP is mediated by V1aR. Vasopressin elicits contractile and growth-promoting effects in vascular smooth muscle cells, increases smooth muscle actin and SM22 promoter activities, and stimulates the JNK and p38 MAPK pathways [12]. Moreover, experiments on ring segments of gastroepiploic arteries obtained from human patients have shown that AVP is able to restore the contractile response to Ang II after tachyphylaxis . The vasoconstrictory potency of AVP may be significantly altered under pathological conditions. Experimental and clinical studies have provided evidence that blood AVP concentration is significantly elevated in hypertension and in patients with post-infarct cardiac failure. Moreover, experimental studies revealed that, in post-myocardial infarction, cardiac dysfunction is associated with increased cardiac and plasma AVP and Ang II expressions, and that AVP expression is positively correlated with left ventricular end diastolic diameter (LVEDD). The same authors have shown that, under in vitro conditions, cardiac microvascular endothelial cells respond with increased expression of AVP mRNA and protein to the application of Ang II. It has also been shown that AVP promotes proliferation of those cells. Prolonged exposure of neonatal rat cardiac fibroblasts to elevated AVP levels promoted their proliferation and induced increased expression of matrix metalloproteinases (MMP2 and MMP9). These effects were mediated by the stimulation of V1aR and activation of G protein-coupled receptor kinase 2 (GRK2) that is followed by phosphorylation of ERK1/2 . The latter effect was manifested by reduced amplitude and elongated duration of action potentials of the myocytes, and this was associated with a reduction in $[Ca2^{+}]_i$. Insulin-mediated ERK1/2 phosphorylation was enhanced whereas Akt-induced and JNK-induced hosphorylations were not altered. The cardiac effects of overexpression of V1aR were reduced by inhibition of the Gαq/11 transduction pathway. Several studies have provided evidence that the joint action of Ang II and AVP is necessary for the appropriate regulation of the vascular tone, cardiac contractility, and the release of other cardiovascular factors .The cooperative action of Ang II and AVP in the regulation of blood pressure is particularly well observed at the level of the CNS and plays a role both in the

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maintenance of resting blood pressure and in adjustments to posthemorrhagic hypovolemia, hypoxia, cardiorespiratory disorders, and stress. Several studies have provided evidence that the central pressor action of Ang II can be abolished or significantly reduced by blockade of the brain V1aR and that the combined administration of Ang II and AVP exerts greater changes of blood pressure than those changes observed after the separate application of these peptides.[10] Importantly, the interaction of Ang II and AVP is significantly enhanced in hypertension, post-infarct cardiac failure, and during chronic stress. The elevated release of AVP plays a major role in the development of hypertension in mice with brain-specific hyperactivity of the renin and angiotensinogen genes as it has been shown that the baseline blood pressure can be normalized in this strain by the administration of the nonselective AVP receptor antagonist conivaptan or the V2-selective antagonist tolvaptan. Electrophysiological studies have shown that AVP and Ang II increase the activity of the same rostrodiencephalic neurons and coactivate neurons in the SFO and organum vasculosum of the lamina terminalis (OVLT). The biochemical background of this interaction is partly clarified by studies showing that Ang II and AVP may jointly regulate calcium transits. Studies on a culture of the area postrema/NTS cells have shown that Ang II and AVP evoke a transient increase in [$Ca2^{+}$] and that this effect can be abolished by pretreatment with specific antagonists of AT1R or V1R . In in vivo experiments, blockade of central V1aR effectively abolished the central pressor action of Ang II. Although, under most circumstances, Ang II and AVP cooperate synergistically with the sympathetic nervous system, in some instances, they can act antagonisticall [11].The most evident example of such counteraction is the inhibition of the baroreceptor reflex by Ang II and potentiation of this reflex by vasopressin . There is also evidence that Ang II and AVP play different roles in the regulation of respiration during acute hypercapnia. Namely, it has been shown that Ang II acting on AT1R stimulates ventilation and increases the metabolic rate during hypercapnia and that this effect is reduced by the simultaneous stimulation of V1aR by vasopressin.

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