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SYMPATHOADRENAL ACTIVITY, CATECHOLAMINES, AND THE PATHOGENESIS OF VASCULOPATHIC HYPERTENSIVE AMONG POPUPALTION

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Abstract: Exaggerated cardiovascular response to acute and stresses increases the risk for hypertension and cardiovascular disease. Stress also can be broadly defined as a disruption of homeostasis. The re-establishment and maintenance of homeostasis entail the coordinated activation and control of neuroendocrine and autonomic stress systems. Stressor-related information from all major sensory systems is conveyed to the brain. Brain activates neural and neuroendocrine systems to minimize the harmful effects of stress. Stress is generally thought to contribute to the development of hypertension. On the other hand, the evidence is still inconclusive. It is generally accepted that stress-induced hypertension occurs because of increases in sympathoadrenal activity, which enhances vascular tone, but complete α-adrenoreceptor blockade cannot prevent the long-lasting vasoconstriction induced by sympathetic nerve stimulation. That is why it is suggested that sympathetic nerve-mediated vasoconstriction may also be mediated by factors other than catecholamines. In this review, we aim to present the relationship between blood pressure effectors and stress altogether, along with evaluating the relationship between stress and blood pressure.

Key words: Hypertension, vascular tone, sympathoadrenal activity, stress.

High blood pressure is one of the established risk factors for cardiovascular diseases. Cardiovascular diseases associated with high blood pressure are more consistent and independent than other risk factors. The frequency of hypertension worldwide directly reflects the frequency of cardiovascular disease and heart attack[1].. Hypertension is an important risk factor because it takes first place worldwide as a preventable cause of death, in addition to its high prevalence. At the same time, hypertension ranks third place among the factors that adversely affect patients' quality of life. That is why reducing the risk of hypertension, which is a predicted risk factor, has importance for protection from disease and death[2]. Stress factors cause a series of reactions that change the dynamic steady-state condition in living organisms. The survival and welfare of all species require an appropriate physiological response to environmental and homeostatic problems. Acute stress is defined as a type of stress in which "fight or flight" response is observed as a result of exposure to stress by activation of the sympathetic nerve system (SNS). This response increases heart rate, contractility, vasoconstriction, the level of epinephrine and norepinephrine secreted by the adrenal medulla and sympathetic nerves, respectively[3,4]. Daily events cause chronic stress and have detrimental effects on the body (allostatic load) beyond the creation of "fight or flight" response against to acute stress. However, the hormones associated with stress protect the body in the short term and regulate adaptation[5]. Initially, heart failure was described as a clinical syndrome induced by reduced capacity of the heart. Later on, it was described as myocardial dysfunction and the continuous interaction between neurohormonal and activated balancing mechanisms. SNS, RAAS and cytokine systems are included in neurohormonal mechanisms. These systems can balance myocardial function, which is suppressed at acute phase and cardiovascular homeostasis. However, long-term activation of these systems has adverse effects on cardiac structure and function, which cause cardiac decompensation and progression of heart failure[7]. In the last two decades, important changes have emerged in the field of cardiology on the recognition of the effects of several activated

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neurohormonal axes including mainly SNS and RAAS, on the developmental process of cardiovascular diseases, besides the pathologic changes of the integrity of the myocardial and vascular structures. Cardiovascular diseases, which are promoted by atherosclerosis and left ventricular hypertrophy, cause a series of events such as thrombosis and myocardial infarction (MI), show progression in patients, and often cause death by heart failure. All these events have progressed before MI and heart failure, and are mediated by components of the neurohormonal system such as norepinephrine, angiotensin II (AngII) and aldosterone, which are components of SNS and RAAS. Recognition of the importance of these neurohormones provides great advantages for the treatment of the development of several diseases, which occur during cardiovascular processes. Therefore, the modulation of activation and inhibition of neurohormones has particular importance for the development of new and effective treatments for heart diseases. Pathophysiological changes, which are affected by RAAS and SNS in heart diseases, include sodium retention, decreased cardiac contractility, and myocardial hypertrophy[8]. SNS is involved in the regulation of the cardiovascular system in the acute phase. On the other hand, the long-term activation of SNS causes heart failure. Increased sympathetic activity in heart disease results from various pathophysiological changes, including ventricular hypertrophy, sodium retention and vasoconstriction [8]. Increased plasma levels of norepinephrine, which result from central sympathetic outflow and activated sympathetic nerves, have been shown as evidence of sympathetic hyperactivity. At the same time, it has been emphasized that hyperactivity of SNS can increase the risk of cardiovascular disease, such as left ventricular diastolic dysfunction, in patients with hypertension. The importance of cardiac toxicity, which occurs depending on catecholamines, was mentioned. Additionally, the importance of the hypothesis stating that "prolonged sympathetic activation causes myocardial toxicity" has been emphasized. An excessive amount of norepinephrine causes hypoxia, increased cyclic adenosine monophosphate (cAMP), formation of catecholamine metabolites and intracellular calcium overload, which occurs due to increased sarcolemmal permeability and ends in death of cardiomyocytes directly. Sympathetic activation, which occurs by increased secretion of norepinephrine, causes myocardial hypertrophy, increased apoptosis of the cardiomyocytes, and deleterious changes in contractile and metabolic proteins by differentiation of gene expression in cardiomyocytes, via enabling activation of adrenergic receptors [9]. Additionally, it has been shown that chronic administration of catecholamines in rats causes interstitial fibrosis, beta-adrenergic receptor-mediated decrease in inotropic responses, myocyte apoptosis and increased pumping function disturbances that occur via particularly left ventricular dilatation[7]. Sympathetic hyperactivity that is observed in heart diseases is closely related to abnormalities in cardiovascular reflexes. Sympathoinhibitory cardiovascular reflexes, such as the arterial baroreceptor reflex, are suppressed significantly along with sympathoexcitatory reflexes such as cardiac sympathetic afferent and the arterial chemoreceptor reflex that are increased in case of sympathetic hyperactivity [6]. The central nervous system receives information from different sources of the body and active mechanisms, which play a major role in cardiac remodeling and in the development of dysfunction. Additionally, it causes the development of systolic heart failure, which occurs by production of AngII and aldosterone locally in the brain and by activation of sympathetic nerve system. AngII causes increased production of superoxide anion, mediated by increased AngII type 1 receptor (AT1-R), inhibited nitric oxide (NO) and reduced nicotinamide adenine. It will also lead to increased development of disease mediated by increased sympathetic stimulation [9]. It is reported that prolonged activation of the sympathetic nervous system negatively affects the excitation-contraction matching and activates the apoptotic ways, which play a central role in the development of chronic heart failure. It is supported by the fact that although human beta1-adrenergic receptors (ADRβ1) initially improve cardiac function, this event causes

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pathological hypertrophy and heart failure in later time. The overexpression of ADRβ1 results in weakening of ventricular plasticity and left ventricular ejection fraction in animal models. It has been reported that the blockade of ADRβ1 in patients with systolic dysfunction, improves left ventricular function and reduces the sudden deaths[14,28,29](Table 1). Signalization of ADRβ2 can lead to an increase in the level of inhibitory G-protein (Gi), so that it can activate the protective anti-apoptotic pathways, which regulate the increase in catecholamines. MI size and apoptotic signalization significantly increase with selective inhibition of Gi signaling in the response, which occurs against myocardial ischemia. It is reported that the absence of ADRβ2 is associated with increased levels of catecholamine, cardiac hypertrophy, fibrosis and finally with congestive heart failure. There is no information stated on the role of beta3-adrenergic receptors (ADRβ3) in heart failure. On the other hand, the increase in ADRβ3 signalization, which shows a transient negative inotropic effect of the increase in NO production and pathways that inhibit the passage of calcium, is mentioned in heart failure. The increase in sympathetic activation during stress leads to an increase in renin production. The increase in renin production results in a higher level of blood AngII. The increase in circulating AngII increases the stimulation of physiologically active AT-1R and consequently anterior pituitary gland contributes to the formation and release of adrenocorticotropic hormone (ACTH), adrenal glucocorticoid, aldosterone and catecholamines . Although cardiovascular diseases progress in stress, especially in depression, the role of the RAAS in the stress response is generally neglected. Later studies have shown the basic role of RAAS in the development and progression of cardiovascular diseases. RAAS is one of the most important systems in the development of the pathogenesis of cardiovascular diseases. The activation of RAAS under stress conditions stimulates a series of processes such as oxidative stress related to cardiovascular damage, inflammation and insulin resistance[10]. Especially, the blockade of RAAS can stop the molecular and cellular mechanisms related to cardiovascular remodeling and the maintenance of high blood pressure. Therefore, the substances that are commonly used for the prevention of cardiovascular diseases are angiotensin converting enzyme (ACE) inhibitors and AT-1R blockers, direct renin inhibitors, and mineralocorticoid receptor antagonists. Symptoms of depression, which are related to stress and social interaction disorders, are risk factors for cardiovascular diseases. Additionally, it has been reported that the physiological response to acute stress in depressed people is not the same compared to healthy individuals. Especially, the symptoms of social isolation and depression are reported as biological and behavioral risk factors which show a negative development for cardiovascular diseases and accompanied deaths. It refers to the evidence that the activation of the hypothalamic-pituitary-adrenal (HPA) axis in depressed patients, the changes in the autonomic control of the heart, sympathoadrenomedullar system and behaviors are related to stress. The increased response to stress in the absence of sensorial information resources, which provide acute or chronic stress adaptation, is shown as the cause of increased mortality rates in socially isolated individuals. It has been shown that individuals who have depressed symptomatology and hypertension have a higher risk of mortality compared to individuals who have only one symptom. It has been suggested that the underlying mechanism for this event can be related with increased RAAS activity. The pathophysiological effects of RAAS on the cardiovascular system are formed by AngII and aldosterone

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