Neuroimmunoendocrinological aspects of arterial hypertension

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Abstract

Article presents the latest data on the role of the immune, endocrine and sympathetic nervous system in the pathogenesis of hypertension. The authors pay attention to the interaction of regulatory systems in the mechanisms of disease development and stabilization.

Key words: sympathetic nervous system, renin-angiotensin-aldosterone system, immune cells, essential hypertension.

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Артериальная гипертензия с позиций нейроиммуноэндокринологии

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Резюме

В статье представлены последние данные о роли иммунной, эндокринной и симпатической нервной системы в патогенезе формирования артериальной гипертензии. Авторы уделяют внимание взаимодействию регуляторных систем в механизмах развития и стабилизации заболевания.

Ключевые слова: симпатическая нервная система, ренин-ангиотензин-альдостероновая система, иммунокомпетентные клетки, артериальная гипертензия.

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Hypertension (HTN) is one of the most common diseases in the world [1]. Numerous studies indicate the need for early detection of the disease and its timely correction [2–4] to prevent adverse cardiovascular events [1, 5–7]. Modern pharmacological progress allows achieving satisfactory blood pressure level (BP) in most cases. On the other hand, cardiovascular diseases still bear the palm in the causes of morbidity and mortality worldwide [7, 8]. Present problem requires new scientific research in understanding of disease pathogenesis and to develop new treatment options. Most modern publications on HTN are focused on sympathetic nervous system (SNS) activation. Its effect is due to the action of neurotransmitters (epinephrine and norepinephrine) on adrenergic receptors in vascular wall and is accompanied by vascular wall smooth muscle cells (SMC) tone up followed by elevated BP [13]. This leads to blood supply deterioration of nephron glomerulus, juxtaglomerular apparatus activation and renin-angiotensin-aldosterone system (RAAS) activation. The latter enhances and prolongs the catecholamine effect on the arterial wall greatly toning it up [9–11]. However, the data are not sufficient for learning the genesis of essential hypertension. All data should be summarized in one system to understand the mechanisms of HTN. Integration is about joint research of the role of the immune, endocrine and nervous systems in HTN pathogenesis. Thus, immune system is actively involved (inherent and acquired immunity) in HTN stabilizing mechanisms, according to modern concepts [12–14]. It is well-known that the vascular wall is composed of intima, media, adventitia and immune elements: macrophages, T lymphocytes, dendriform cells and mast cells [15]. Hyperactivity of sympathetic system increases vascular tone and leads to angiospasm, at the same time it modulates free radical oxidation and triggers ad activates macrophages and dendritic cells of the artery wall. It leads to the synthesis of the inflammatory cytokines [tumor necrosis factor-α (TNF), interleukins (IL-1α, IL-6, IL-17)] by the immune cells [14, 16]. As a result, mechanisms which are responsible for information transfer to the nucleus and various genes expression, switch on. Nuclear factor kappa B (NF-kB) is one of these intracellular mediators [16–19], which enhances oxidative stress and can lead to HTN complications [20]. Nitric oxide (NO) plays an important role in free radical formation in HTN. It demonstrates both pro-inflammatory and anti-inflammatory effects. In certain reactions of immunoendocrinological system its actions depend on location and quantity [16, 20]. Actually, NF-kB activation is one of the major factors triggering inducible nitrooxidsintetaze transcription. This leads to an excessive NO production and free radical storage [20].

Superoxide anion formed in the endothelium binds excessive NO, thus inhibiting vasodilation. Peroxynitrite is produced as a result of the process, which blocks endothelial NO-synthase (eNOS) preventing electron transfer to L-arginine in order to form NO. Peroxynitrite transports electrons to molecular oxygen, enhancing the cytotoxic effects of superoxide anion [16, 20]. Transcriptional iNOS NF-kB activation appears a trigger for endothelial dysfunction, now regarded as one of the main mechanisms of sustained HTN. Endothelial dysfunction is accompanied by a shifting in vasoconstriction-vasodilatation system in favor of vasodilatation. It is also accompanied by the endothelium barrier alteration and permeability increase. Ultimately endothelial dysfunction leads to the structural and metabolic exhaustion of endotheliocytes associated with their functional decline, loss and desquamation and inhibition of regeneration [16, 21, 22]. Moreover, endotheliocyte apoptosis increases endothelium permeability, local cytokine expression and monocyte attraction into the subendothelial space. Mentioned pro-inflammatory changes can also trigger the proliferation of vascular SMC leading to functional failure of the vascular wall [23].

Constrictor agents should be mentioned when describing vasoregulatory system. Endothelin-1 is an important proinflammatory and vasoconstrictive peptide. It is mostly produced by endothelial cells, but can also be synthesized by vascular SMC [21]. Expression of adhesion molecules, endothelial leukocyte infiltration and activation of inflammatory kinases including protein kinase C (it regulates cell cycle, growth, differentiation and apoptosis) are considered to be the main pro-inflammatory actions of endothelin-1 [24]. Negative vascular effects of edothelin-1 at early HTN stages are primarily due to the activation of Ca 2+ channels

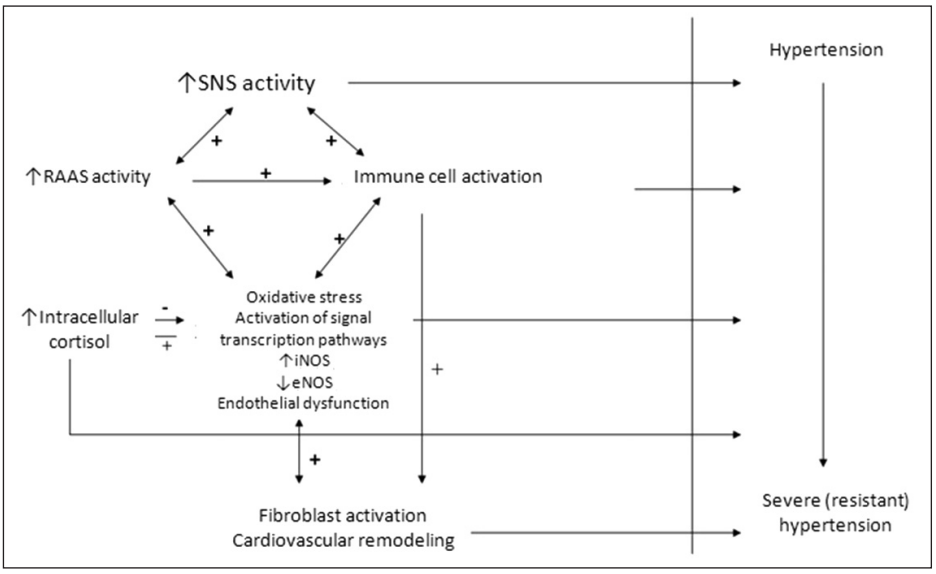
and subsequent vasoconstriction. Later on, this peptide contributes to the obliteration of the lumen due to SMC hypertrophy stimulation consequently promoting vascular wall changes through the fibroblast activation [21, 24]. Fibroblasts may occur from their precursors: circulating fibrocytes, or monocyte-macrophages, or epithelial (and endothelial) cells [25, 26]. Cell activation promotes transformation of fibroblasts into myofibroblasts with subsequent production of metalloproteinases and the synthesis of extracellular matrix key elements, including collagen 1, 3, 4, 5, and 7 types. These play an important role in cell migration and matrix remodeling [25, 27].

RAAS also has a powerful pro-inflammatory effect on hormones of cardiovascular homeostasis. Published data indicate the existence of renin receptors in target organs (heart, blood vessels, kidney, brain), as well as in liver, adipose tissue, adrenal glands, ovaries, reflecting the presence of the local angiotensin II releasing in these organs [28]. Receptor activation stimulates mitogen-activated kinase, which regulates the processes of proliferation and apoptosis subsequently forming vascular dysfunction [29, 30]. However, the most profound cardiovascular changes are mediated by angiotensin II activation. Recent studies have shown the alternative way of angiotensin I to angiotensin II conversion instead of angiotensin-converting enzyme-dependent pathway (ACE-dependent). This pathway depends on chymases, cathepsin G, and other serine proteases. Moreover, in different organs and tissues predominates either ACE-dependent way or alternative ways of angiotensin II conversion. ACE is considered to be responsible for angiotensin II generating in the lumen, while chymase mediates its production in myocardial interstitium, media and adventitia and modulates sympathetic nervous system functioning as well as smooth muscles contraction [31–33]. Chymase has been recently shown to play an important role in cardiovascular remodeling through matrix metalloproteinases induction [34]. Furthermore, cardiac mast cell degranulation accompanied by the chymase release [34–36], associated with angiotensin II overproduction and subsequent relevant cardiovascular changes. Manifest pro-inflammatory effects of angiotensin II are mediated by its I type receptors (AP-1). A cascade of immunopathological reactions triggered by proinflammatory signaling pathways (including NF-kB) is activated through this receptor [21]. An immune cell attraction into the vessel wall is supported by macrophage monocyte chemoattractant protein-1 and adhesion molecules (VCAM-1, ICAM-1). This leads to even more marked cytokine release and NF-kB overstimulation [37–39].

Increased level of serum «hepatokine» (C-reactive protein) is the sign of immune system activation in hypertensive patients. On the one hand, it is associated with the inhibition of endothelial progenitor cells differentiation and their function impairment [18, 39]. On the other hand, there is an association with AP-1 receptor activation [19]. In turn, the excessive angiotensin II leads to the nicotinamide-N (NADPH) oxidase hyperactivity and overproduction of reactive oxygen species. This promotes redox-sensitive genes stimulation, thus exacerbating immunopathological process in the vascular wall [40, 41]. Moreover, angiotensin II has also profibrotic features. The content of extracellular matrix proteins is regulated by angiotensin II, macrophages through their effects on fibroblasts, and metalloproteinases as well [42]. Integrine expression (cell adhesion receptors interacting with extracellular matrix and involved in remodeling processes) is bounded with angiotensin II, according to recent data [17]. Some integrines are located on the cell surface in an inactive state. They can quickly be activated by cytokines and induce a signal transmission [43]. Angiotensin-II stimulates aldosterone secretion. In high concentration it also increases antidiuretic hormone secretion and causes SNS activation [16]. All these effects contribute to development of sustained HTN.

Aldosterone is able to activate immune cells by mineralcorticoid receptor stimulation. On the one hand, it acts as a pro-inflammatory, profibrotic and prooxidant agent by potentiating macrophages and dendritic cells to synthetize proinflammatory cytokines, which trigger NF-kB and fibrosis [44, 45]. On the other hand, aldosterone performs a mitogenic effect on mesangial and smooth muscle cells stimulating insulin-like growth factor 1 (IGF-1) receptor expression [44, 46]. Thus, inflammatory signaling pathways activation by RAAS hormones supports inflammation in the vascular wall and contributes its remodeling.

Figure. Neuroendocrinological mechanisms in hypertension development



Note: SNS — sympathetic nervous system; RAAS — renin-angiotensin-aldosterone system; iNOS — inducible nitrooxidsintetaze; eNOS — endothelial nitrooxidsintetaze.

It has been shown that pro-inflammatory cytokines, endothelin-1 and reactive oxygen species play a major role in cardiac mast cells degranulation, which is associated with myocardial remodeling in HTN. Releasing TNFα and chymase and tryptase enzymes induce matrix metalloproteinases involved in extracellular matrix degradation. Moreover, tryptase was found to convert cardial fibroblasts into myofibroblasts inducing myocardial remodeling [34]. Myocardial and vascular remodeling through angiosclerosis and cardiosclerosis (due to the activation of fibroblasts and mast cells) can be considered as one of the main mechanisms of sustained HTN.

Moreover, overproduction of pro-inflammatory cytokines and vasoactive substances is a major factor for renal damage in HTN. The main effects of TNFα, IL-1 and IL-6 are apoptosis induction of almost all types of kidney cells, intraglomerular hemodynamics impairment, increased production of reactive oxygen species and procoagulants by mesangial and endothelial cells [47]. Progressing of nephrosclerosis leads to further RAAS activation resulting in vicious circle formation [48].

Thus, NF-kB activation, triggered by immune cells in vascular wall, enhances production of cytokines, chemokines, adhesins, metalloproteinases, and inducible nitrooxidaze. NF-kB hyperactivation leads to uncontrolled inflammatory induction. A progression of the inflammatory process in HTN development is accompanied by atherosclerosis formation and cardiovascular complications. However, NF-kB regulates the expression of genes involved in mitochondrial ribonucleic acid replication (mRNA) of the type 1 anti-inflammatory enzyme 11β-hydroxysteroiddehydrogenase [49, 50]. It occurs in immune cells, adipocytes, and endothelial cells and triggers conversion of inactive glucocorticoid hormone cortisone to active cortisol, forming "intracellular" hypercorticoidism [50–53]. On the one hand, glucocorticosteroids suppress inflammation by inhibiting NF-kB and by reducing proinflammatory cytokine synthesis. On the other hand, they stimulate mineralocorticoid receptors promoting severe HTN [50].

Summary data about neuroimmunoendocrinological mechanisms of HTN development are presented on the Figure.

Thus, the mechanisms of sustained HTN development can only be understood in perspective of integrative biomedical science. It combines the idea of three regulatory systems to be brought together: the nervous, the immune and the endocrine one. This knowledge will inevitably lead to changes in understanding of HTN treatment options and complication prevention.

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Conflict of interest

The authors declare no conflicts of interest.

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