Growing number of studies reveal that the brain neural network plays significant role in the short-term and long-term regulation of the cardiovascular functions. The neurons involved in the complex neurogenic control of the cardiovascular system use classical neurotransmitters and nonconventional mediators such as peptides (angiotensin II, vasopressin, natriuretic peptides, endothelins, opioids, cytokines), steroids, ouabaine-like factors and gaseous compounds. Among them the neuropeptides form a group of substances arising significant interest. Thanks to wide distribution of peptidergic neurons in the central nervous system, location of peptide receptors on neurons and glial cells, versatile but frequently overlapping mechanisms of activation of the intracellular processes the neuropeptides play significant role in short-term and long-term regulation of excitability and remodeling of the neurons. In several instances they modulate effects of the classical transmitting systems involved in regulation blood pressure, heart rate, water-electrolyte balance, metabolism, stress, pain, mood and memory. Prolonged activation or inhibition of specific neuropeptide pathways frequently results in long-lasting disorders of several regulatory systems. In this review this is exemplified by overactivity of angiotensin II, vasopressin and cytokines in the brain during hypertension, heart failure and stress. Multifarious actions of angiotensin II and vasopressin, and their mutual interaction with cytokines make of these neuropeptides excellent candidates for the compounds responsible for long-term resetting of the central cardiovascular control, and forming a link between the cardiovascular diseases, stress and mood disorders.

**Key words:** angiotensin peptides, vasopressin, cytokines, IL-1β, TNFα, cardiac failure, hypertension
INTRODUCTION

In broad sense the term neuropeptides refers to the group of versatile bioactive peptides which may be synthesised in the brain or in the peripheral nervous system and which are able to influence function of the neurones (1 - 3). Although in many respects the neuropeptides differ from the classical neurotransmitters, the most essential function of both classes of these neuroactive substances serve to the same purpose, i.e. to carry on information between the neurones and regulate the efficacy of the neuronal network. Frequently the classical neurotransmitters and neuropeptides are co-localised in the same neurones and synapses (4, 5). Biosynthesis of neuropeptides significantly differs from that of the conventional neurotransmitters. The main findings which help to understand the most essential properties of neuropeptides which enable them not only to modulate the process of neurotransmission but also to play a key role in long lasting remodeling of neurons and glial cells can be summarized as follows. The neuropeptides are synthesised in the course of multistage process of transcription, posttranscriptional processing, translation, posttranslational processing, and intracellular segregation and processing of prohormones in the trans-Golgi network (TGN). In the TGN they are subjected to a complex process of intracellular trafficking including transport along the axonal microtubules to the specific places of destination located in the appropriate membrane domains (1 - 3). The process of synthesis of the final active product (or products) requires presence of a whole constellation of other proteins (transcription factors, enzymes and other). It is frequently emphasised that the process of synthesis of neuropeptides is very plastic, i.e easily adjusted to activity of the neuronal pool within which they are operating. From the point of view of long-lasting, sustained processes of adaptation to the prolonged changes in the environment or in the excitatory input from the other neurones the plasticity in synthesis of neuropeptides is an especially important property; the synthesis of neuropeptides and the function of cells which they control can be easily adjusted to changes in activity of the other cells, or in the environment (1, 2).

In general, the concentration at which the neuropeptides exert their biological effects is much lower (fmol/L, pmol/L) than that of the classical neurotransmitters (pmol/L, nmol/L). In addition much smaller increase in calcium concentration is required for release of neuropeptides than for release of the conventional neurotransmitters (1, 2). Accordingly, the release of neuropeptides may be provoked by relatively small changes in membrane potential which may be subthreshold for generation of series of action potentials, needed for release of the conventional neurotransmitter during the classical process of synaptic neurotransmission. The process of enzymatic degradation of neuropeptides occurs with some delay. Thus, the neuropeptides are available for receptors for relatively longer time in comparison to the classical neurotransmitters. The neuropeptides can be released not only to the synaptic cleft but also outside of the synapses in the other domains of the cellular membrane (but see also below).
Finally, one of the essential properties of neuropeptides is their ability to activate, though with different intensity, the nuclear post-receptor mechanisms, and therefore they may regulate synthesis of those proteins which are essential for processes of neuronal and glial plasticity.

For a long time three dogmas have dominated in distinguishing the neuropeptides from the classical neurotransmitters: First, it has been claimed that in contrast to the classic neurotransmitters the neuropeptides are not released to the synaptic cleft, second, that the neuropeptides can be replaced in the neurons exclusively by means of the axonal transport from the cell body, and third that the neurotransmitters are responsible for transmission of rapid information between the neurones while neuropeptides play a role of neuromodulators. According to Florey (6), who proposed the term neuromodulation for the first time in 60s the term neuromodulator refers to the substance of cellular and non synaptic origin which affects the excitability and performance of neurones through actions exerted outside of the synaptic region. Thus, in contrast to the neurotransmitters, whose release is determined by generation and duration of the action potentials and is restricted to the synaptic membrane, the neuromodulators could affect significantly larger neuronal surface and act during a longer time. The above cannons have been questioned by recent investigations demonstrating that some neuropeptides can be released from the presynaptic membrane and can stimulate receptors in the postsynaptic membrane (1, 7 - 9). Furthermore, it has been reported that after release from the neurones some neuropeptides can be taken up to the neuronal endings and used again during the next excitation (1, 2). Surprisingly, it has been also documented that the classical neurotransmitters have the neuromodulatory properties. Thus, they can be released not only from the presynaptic membrane but also from the other portions of the axon and/or undergo spillover from the synapse. In both cases they may reach several neuronal and glial cells through the process known as diffuse or volume transmission and act as neuromodulators (2, 9 - 11). It is also important to emphasise that those neuropeptides which act as neuromodulators have receptors not only on neurons but also on glial cells and vessels (12). Acting on the extraneuronal receptors the neuropeptides are able to influence metabolic processes (including enzymatic activation or inactivation of the other neuroactive compounds), regulate buffering of ionic concentration and blood flow-dependent supply of substrates as well as removal of metabolites (12). Beside, the glial cells produce also substrates necessary for production of the neuroregulatory compounds.

Majority of the classical neurotransmitters is produced by distinct subsystems, which consist of the neuronal bodies located in the separate nuclei and sending widely spread fibers protruding to a long distance and innervating the other regions of the brain. This does not refer to excitatory and inhibitory neurotransmitters, such as glutamate and GABA which are released by widely dispersed neurones that are not grouped in the distinct nuclei. The neuropeptides can be synthesized by the groups of neurones located in the
distinct nuclei and sending axons to the other brain regions (for example neurones producing vasopressin, oxytocin, CRH, TRH, GHRH, β-endorphin and projecting from the hypothalamus to the neurohypophysis or median eminence), by dispersed neurones (for example neurones producing enkephalins, angiotensins and natriuretic peptides) or by both (nerones synthesising vasopressin, oxytocin, β-endorphin, CRH, TRH, GHRH).

Mechanisms of neuroregulatory actions of neuropeptides

The first studies demonstrating presence of neuroactive peptides in neurones were published in the 1970s - 1980s. Initially the neuropeptides were determined by means of radioimmunoassay techniques. Subsequently, development of electron microscopy and immunocytochistochemical methods allowed for determining distribution of neuropeptides in the intracellular compartments while rapid progress in the molecular biology tools permitted monitoring of expression of mRNA levels of specific neuropeptides and their receptors. The method of cloning of the neuropeptides receptors and its combination with in situ hybridisation and immunohistochemistry opened a new field which markedly accelerated research on the mechanisms determining cellular responsiveness to neuropeptides (1).

The neuropeptides act by means of stimulation of several different types of receptors which are frequently located on the same neurones. They are able to exert both instantaneous changes in ionic permeability as well as long lasting effects resulting from changes in gene expression. Thanks to diversity of the modes of action and multiplicity of the targets the neuropeptides are able to regulate the synthesis, storage, release and reuptake of the other neurotransmitters and modulators as well as the number, trafficking and targeting of receptors in the cells. They can also influence the process of phosphorylation of receptors and their affinity for the ligand, interaction between the receptors and initiation of the post-receptor events (1). This is possible due to activation (or inhibition) by neuropeptides of several steps of chemical transmission at the cellular level, beginning with regulation of synthesis of auto-and hetero-receptors through generation of the second messengers and activation of transcription factors in the nucleus.

Receptors mediating action of neuropeptides

The methods available to investigate the role of different neuropeptides are based on administration of specific agonists, inhibition of their receptors by peptide and nonpeptide antagonists, use of peptidase inhibitors to block metabolism of neuropeptides or on temporary inhibition of the neuropeptide (or its receptor) gene expression by means of the antisense probes. The latter method is based on administration of oligonucleotides with a complementary sequence (antisens) to the sequence of mRNA of the target peptide (or its receptor). Such
procedure results in inhibition of translation of mRNA of the specific gene. These methods have been substantially enriched by introduction of genetically modified animals with mutations, knockout or over-expression of specific genes (13 - 15). In several instances expression of genes for the peptides and peptide receptors may be significantly affected by changes of the environment (ionic concentration, changes of interstitial pressure, changes of pH, hypoxia), intensity of stimulation or by injury of the neurones or glial cells.

**Regulatory effects of neuropeptides in the central nervous system**

Application of the techniques described above markedly enriched the knowledge of the role of neuropeptides. Peripheral and central administration of neuropeptides results in multiple effects which are specific for a particular neuropeptide. Because of presence of the circumventricular organs peripherally administered neuropeptides can also affect function of the neurones located in these organs and through their connections with the other neurones they may influence activity of neurones in the other regions of the brain (16). It is also postulated that some neuropeptides can be transported to the brain by special carriers in the blood-brain-barrier or by retrograde transport via the vagal afferents (17). However, it should be stressed that the prevailing number of neuropeptides present in the brain are synthesised by neurones and glial cells located in the brain.

The first studies demonstrating that neuropeptides influence function of the brain appeared at the beginning of seventies of the previous century. In sixties Fitzsimons and collaborators (18) have reported that systemic administration of renin and angiotenin II causes stimulation of thirst in water satiated rats. In 1970 Epstein and coworkers (19) reported that copious drinking can be also elicited in the rat by administration of renin, angiotensin II and other angiotensin peptides introduced directly into the cerebroventricular system. This study opened the possibility that the dipsogenic effect of renin and angiotensin peptides, which have been previously ascribed exclusively to the blood-born renin and angiotensin peptides may be also caused by stimulation of angiotensin receptors in the brain by brain-born angiotensin peptides (see below). The studies of Fitzsimons et al. (18) and Epstein et al. (19) have resulted in explosion of multiple investigations aimed at exploring central effects of angiotensin II and the other neuropeptides. It has been demonstrated that neuropeptides are involved in regulation of neural circuits involved in regulation of several vital functions: learning and consolidation of memory, cognitive processes, emotions, temperature regulation, thirst, sodium appetite, food intake, metabolism, secretion of hypothalamic neurohormones, cardiovascular and respiratory functions. Importance of neuropeptides becomes especially apparent during prolonged, intense stimulation such as that occurring during various pathological
processes (for example: addiction, cardiovascular diseases, disorders in energy or water-electrolyte balance).

**Neuropeptides involved in regulation of the cardiovascular system**

During past two decades an intense research based on activation of the cardiovascular reflexes, hemodynamic challenges, and use of the electrophysiological and c-Fos functional mapping techniques, allowed for identification of the central pathways involved in regulation of cardiovascular functions (20 - 25). It is now well established that activity of the brain cardiovascular neurones is regulated both by the neural inputs from the cardiovascular receptors and by multiple neuroactive factors which are either penetrating through the brain barriers or are synthesised locally in the brain. The list of neuropeptides that have been found to produce cardiovascular effects after administration directly into the central nervous system, in the doses which are not effective when applied peripherally includes angiotensins (angiotensin II, angiotensin III, angiotensin IV, angiotensin-1-7), vasopressin, corticotrophin releasing hormone (CRH), thyrotrophin releasing hormone (TRH), neuropeptide Y (NPY), natriuretic peptides (ANP, BNP), endothelins (mainly ET3) opioid peptides (ß-endorphin, enkephalins), adrenomedullin, cytokines (interleukin 1-beta, IL-1ß, tumor necrosis factor alpha, TNF-α), orexins and ghrelin. Basing on the current knowledge it appears that the most interesting of them are arginine vasopressin (AVP), angiotensin peptides and some cytokines (especially IL-1ß and TNF-ß). Strong evidence indicates that the above peptides and their receptors are synthesised in the brain and can produce central cardiovascular effects in relatively low concentrations (see below). Beside, Ang II and AVP exert significant effects on emotional behaviour and adaptation to stress. Therefore, there may constitute an essential link between the neurogenic component of the cardiovascular diseases and an enhanced susceptibility to stress and depression (see also the article of Johnson and Grippo in this supplement).

**Vasopressin**

Arginine vasopressin (AVP) is a nonapeptide synthesised by all mammals except for the pig and hippopotamus (both are producing 8-lysine vasopressin; LVP). The neurones synthesising AVP are located in the three hypothalamic nuclei: supraoptic (SON), paraventricular (PVN) and suprachiasmaticus (SchN) as well as in the small groups of neurones which are dispersed in the amygdala, the bed nucleus of the stria terminalis and the bed nucleus of the diagonal band of Broca. Autoradiographic studies revealed presence of binding sites for labeled AVP, V1 and V1a antagonists in several regions of the brain. Intense staining was found in the septum, amygdala, hippocampus (dentate gyrus), hypothalamic sigmoid region, circumventricular organs (the area postrema, the subfornical organ), and brain stem (nucleus of the solitary tract). Less intense staining was
present in the anterior olfactory nucleus, cerebral cortex, medial preoptic and periforinal hypothalamic nuclei (25 -30).

Release of AVP into the cerebrospinal fluid and into the brain in response to various challenges has been shown in the dogs and rats (31 - 33). Arginine vasopressin was the first peptide which was reported to produce significant changes of blood pressure after administration to the central nervous system. In 1931 Cushing noted that administration of pituitrin into the lateral ventricle of neurosurgical patients causes a constellation of symptoms characteristic for stimulation of the parasympathetic system, including peripheral vasodilatation (34). This observation was neglected for 30 years until Nashold and collaborators (35) performed acute experiments on cats in which they found that lower dose of pituitrin injected into the lateral ventricle of the cat decreases blood pressure, while the higher dose causes significant pressor effect. Interestingly, both pressor and depressor effects were abolished by the prior midbrain transection. In the same study synthetic angiotensin (Hypertensin, Ciba) injected into the lateral ventricle exerted uniformly pressor effect (35).

In 1983 Martin and collaborators in the study published in Brain Research reported that injection of arginine vasopressin into lateral ventricle of the rabbit causes dose related increase of blood pressure and cardioacceleration (36). This finding was confirmed in several other studies, including those performed in our Laboratory (37-44). In addition, we have demonstrated that the central pressor effect exerted by AVP is caused by stimulation of V1 receptors (37, 38, 44) and that sensitivity to the central pressor action of vasopressin is strongly species dependent. Thus, the dose of AVP necessary to evoke significant pressor effect in the dog was 100 times lower than the threshold pressor dose in the rat (37, 38). The pressor effect of vasopressin infused into the cerebroventricular system was found by us to be buffered by nitric oxide and atrial natriuretic peptide (39 - 40).

Studies performed on healthy not anaesthetised rats maintained at rest and not subjected to any treatment apart from blockade of central V1 receptors indicate that endogenous vasopressin does not play significant role in regulation of resting blood pressure (44). However, this may not be true in the other species. For instance in the conscious dog intracerebroventricular infusion of V1 receptors antagonist produces significant pressor effect (37). Acute and chronic cardiovascular disorders cause significant activation of the brain vasopressin system. Current evidence indicates that the brain vasopressin system is involved both in regulation of pressor and depressor cardiovascular neurones. Most likely, the final effect of central action of vasopressin depends on the pool of vasopressinergic neurones which is activated by specific stimuli. Strong activation of the brain vasopressin system with engagement of its hypotensive and bradycardic components is observed during rapid hypotensive haemorrhage (45, 46).

Chronic resetting of activity of the brain vasopressin system occurs in various forms of hypertension and in the post-infarct cardiac failure. Upregulation of the pressor function of the brain vasopressin system was found in SHR, DOCA-salt
and renin transgenic [TGRmRen2(27) rat] hypertension (39, 42, 44, 47, 48). Namely, it was found that blockade of central V1 receptors by means of intraventricular infusion of specific V1 receptors antagonists produces significant decrease of blood pressure in the renin transgenic hypertensive rats while it is not effective in their normotensive controls (44). Increased sensitivity to the central pressor action of vasopressin in the hypertensive rats is especially well expressed after blockade of NO synthase in the brain (40, 47).

An extensive myocardial infarct results in significant disturbances of hemodynamics which cause increased activation of vasoconstrictory mechanisms aimed at maintaining an appropriate perfusion pressure within the cardiovascular system. Among them is increased release of angiotensin II, aldosterone and vasopressin and activation of the sympathetic system. Because activation of these mechanisms may cause retention of body fluids, in the later stage the post-infarct cardiac failure is associated with compensatory increase of release of the natriuretic compounds (Fig. 1).

![Diagram](https://via.placeholder.com/150)

**Fig. 1.** Figure illustrates changes in release of hormones and activity of the sympathetic system after the myocardial infarction. BP - arterial blood pressure, BV - blood volume, CO - cardiac output. Other explanations in text.
Studies performed during last years revealed that the post-infarct cardiac failure is also associated with significant alterations in regulation of the cardiovascular system by the central nervous system. Growing number of evidence indicates that neuropeptides may play a key role in these processes. Our studies on rats with the post-infarct cardiac failure reveal that significant enhancement of the pressor activity of the brain vasopressin system takes also place in the rats with the post-infarct cardiac failure (49). Thus, we have found that significant increase of blood pressure may be evoked in the infarcted rats by intracerebroventricular administration of vasopressin in the dose which is subpressor in the sham-operated controls. Moreover, significant decrease of blood pressure after intracerebroventricular administration of V1a antagonist was found in the infarcted but not in the sham-operated rats. The myocardial infarct causes significant and long-lasting changes in the neurogenic control of the cardiovascular system (50 - 54). The heart failure induced by the myocardial infarction is associated with a constellation of factors which may provoke upregulation of the brain vasopressin system. The stimulatory signals can be generated in the ischemic heart, in the cardiovascular and chemoreceptors as well as in the organs which are not adequately perfused (for instance in the kidney or the gastrointestinal system). Furthermore, the altered function of the brain vasopressin system may be caused by the systemic and brain derived components of the brain renin-angiotensin-aldosterone system and by cytokines (51 - 54, see also below and Johnson and Grippo in this supplement).

Reorganisation of the brain vasopressin system during the heart failure is also supported by the studies of Muders et al. (55) who have found significant changes in vasopressin concentration in the brain regions innervated by vasopressinergic fibers arising from the paraventricular nucleus in the rats with cardiac failure produced by the aortic constriction.

Angiotensin II

Angiotensin II (Ang II) is a key neuropeptide in regulation of the cardiovascular system (56). It is now well established that a distinct, widely distributed renin-angiotensin system (RAS) exists within the mammalian brain (57 - 59). The brain renin-angiotensin system comprises all components present in the peripheral RAS as well as AT1 and AT2 receptors (57 - 66). Extracellular recordings have shown that Ang II exerts excitatory action on neurons of the subfornical organ (SFO), supraoptic nucleus, area postrema (AP), rostral ventrolateral medulla (RVLM), nucleus of the solitary tract and lateral septum (67, 68). However, it is important to note that Ang II circulating in the blood is also able to activate the central pathways involved in regulation of blood pressure and exert some other regulatory effects by means of the neurones located in the circumventricular organs (22, 25, 69, 70) When Ang II is directly injected into the cerebroventricular system of the rat or the dog it evokes
significant and long-lasting increase of blood pressure and release of vasopressin (38, 59, 71). Beside, angiotensin II attenuates the blood pressure buffering role of baroreflex, potentiates cardiac sympathetic afferent reflex, causes centrally mediated sympathoexcitation and stimulates respiration during acute hypotension (72 - 76). Centrally-mediated pressor action of Ang II is effectively abolished by blockade of brain AT1 receptors. Thus, increase of blood pressure and release of vasopressin by centrally applied Ang II could be abolish by blockade of AT1 receptors in the brain whereas blockade of AT2 receptors was not effective (77). It appears at present that the brain Ang II probably does not play significant role in maintenance of baseline blood pressure under resting conditions in healthy, non anaesthetised rats. Such conclusion can be drawn from our own studies and those of the other authors showing that blockade of central AT1 receptors in animals without the cardiovascular disorders does not influence resting blood pressure (44, 53, 78).

Significant disturbances of central regulation of blood pressure by angiotensin II and other angiotensin peptides have been described in various models of hypertension. In 1977 Hoffman et al. (79) reported that administration of Ang II into the lateral cerebral ventricle of unanesthetised spontaneously hypertensive rats produces significantly greater pressor response than in the normotensive WKY rats (79). Subsequently, numerous investigators provided evidence for significant role of the brain renin-angiotensin system in development of various models of the experimental hypertension (80, 81). Kubo et al. (81) have reported that blockade of AT1 receptors in the tissue surrounding rostral portion of the third ventricle with losartan causes significant decrease of blood pressure in SHR but not in WKY rats. Similar results were obtained after ICV administration of antisense oligonucleotide targeted to renin mRNA (82). Angiotensin II contributes also significantly to decreased sympathoinhibition, increased sympathoexcitation and impairment of baroreflex in Dahl S rats on high sodium intake (83) and in chronic 2-kidney, 1 clip hypertensive rats (2K,1C) (84). In the latter model of renovascular hypertension blockade of synthesis of angiotensinogen in the brain by ICV administration of antisense oligonucleotides (AS-ODNs) significantly decreased systolic blood pressure for 3 days after injection (84). Recently, the importance of the local brain renin-angiotensin system has been confirmed by the studies on rats with various models of transgenic hypertension (13 - 15, 44, 46, 57, 85). During last years significant attention has been devoted to the role of the brain angiotensin peptides in neurogenic regulation of the cardiovascular system during the post-infarct state (50 - 54, 86 - 88, 89 - 91, see also Johnson and Grippo, this supplement). Recently these findings have been confirmed by Cudnoch-Jędrzejewska et al. in our Department (89, 90). In addition, our studies revealed that enhanced pressor action of angiotensin II in the brain of the infarcted rats is associated with its non additive interaction with vasopressin. Specifically, selective blockade of either V1 or AT1 receptors and
combined blockade of both AT1 and V1 receptors in the brain of the infarcted Sprague Dawley rats caused significant and comparable decreases of blood pressure in the infarcted rats, while administration of the same doses of these antagonists under the same experimental conditions was not effective in their sham-operated counterparts (89, 90).

Cytokines

Initially the term cytokines refered to the group of peptides released by immune cells exposed to an antigen and responsible for immune responses. At present, it is known that cytokines comprise a large group of peptides that are synthesised by several types of cells and play significant role not only as mediators of the local immune responses but also as factors involved in the integrated control of the most essential functions of the body, including thermoregulation, food intake and metabolism, activity of the hypothalamo-pituitary-adrenocortical axis, and regulation of sympathetic and cardiovascular systems and mood and anxiety (91 - 103, see also Johnson and Grippo in this supplement).

Increasing evidence indicates that some effects observed after systemic administration of cytokines might be ascribed to their central regulatory action. Thus, it has been shown that neurones and glial cells may be affected not only by systemically but also by centrally released cytokines (104 - 111). In this line, it has been reported that at least some of systemically released cytokines are able to penetrate to the brain through the blood-brain barrier or are transported via the vagal fibers (17, 113). Beside, there is now substantial evidence that at least some cytokines are synthesised in the brain itself (114 - 115, see also Johnson and Grippo, this supplement). Although it may appear that the there is now vast literature on the central action of cytokines, it is an illusive impression in comparison to multiple number of these peptides and versatile mechanisms of their action. Determination of physiological and pathophysiological role of cytokines still encounter several difficulties. Among them are: lack of specific antagonists, and the paracrine mode of action of cytokines which means that their concentration in the blood or even in the cerebrospinal fluid does not reflect the concentration in vicinity of the receptors in the specific brain regions or cells.

Regarding regulation of blood pressure recent studies provide evidence that at least two cytokines, namely IL-1ß and TNF-α, may play significant role in regulation of blood pressure. Majority of studies show that administration of IL-1ß directly into the brain, in the doses which do not affect function of the cardiovascular system when they are applied systemically, elicits significant increase of blood pressure and sympathoexcitation (78, 110, 116, 117). The opposite effects were observed in the study of Ye et al. (118) who have found that infusion of IL-1ß into the right cerebral ventricle elicited significant decrease of blood pressure.
An essential property of cytokines is their mutual interaction with the other neurotransmitters and neuromodulators. The cytokines are not only increasing release of several neuroactive factors but they are also interacting with them (102 - 105, 119 - 122). In some instances this is a cooperative interaction, while in the other, the cytokines stimulate release of the other active compounds which mediate or attenuate their action. In the studies performed in our Department by Ufnal et al. (78, 123 - 125) it has been shown that the central pressor action of IL-1β is mediated by centrally released angiotensin II acting on AT1 receptors and by prostaglandins while it is buffered by centrally released nitric oxide. We have that the increase of IL-1β abundance in the brain sensitises brain cardiovascular neurones to central pressor action of angiotensin II (78) and TNF-α (126). Thus, it was demonstrated in these studies that the pressor effect of intracerebroventricular infusion of IL-1β is transient even when the infusion is

![Diagram](image-url)

Fig. 2. Involvement of central angiotensin II, vasopressin and cytokines in altered regulation of the cardiovascular system after the myocardial infarction. ANG - angiotensin, AP, OVLT, SFO - subfornical organs, RVLM - rostral ventrolateral medulla, NTS-nucleus of the solitary tract, VP - vasopressin. For other explanations see text.
continued, however central administration of the subpressor dose of Ang II during the period of recovery of blood pressure from action of IL-1β causes significant pressor effect (78). TNF-α infused in the subpressor doses evoked similar sensitisation to pressor action of Ang II (126).

Fig. 2 gives a synthesis of putative mechanisms involved in activation of the brain vasopressin neurones during the post-infarct state. The diagram is based on the results obtained in our Laboratory and by the other investigators cited in this review (51, 88, 115). It is postulated that two major pathways - the neural and the hormonal are potentially involved in transmission of signals from the peripheral tissues to the hypothalamic neurones producing angiotensin II and vasopressin during the post-infarct state. The neural pathway originates in the cardiovascular mechanoreceptors and chemoreceptors. The humoral pathway consists of a constellation of factors generated in the ischemic heart and produced in the other organs in response to disturbances of blood flow and tissue oxygenation. Among them are angiotensin II, cytokines and other neuroactive factors which may have access to the brain via the circumventricular organs or through the retrograde transport by means of the vagal afferents. Activation of these pathways during the post-infarct state causes significant activation of the brain angiotensin II system and through stimulation of AT1 receptors located on neurones in the PVN causes increased central and peripheral release of vasopressin. Cooperative action of angiotensin II and vasopressin in the brain during the post-infarct state results in enhanced activation of the presympathetic neurons in the brain stem. The hypothesis implicates also enhanced production of the brain cytokines (IL-1β, TNFα) in the brain stem and their participation in activation of the brain angiotensin system during the post-infarct state.

Involvement of brain angiotensin II and vasopressin in generation of increased cardiovascular responses to stress

Increasing evidence argues for strong relationship between stress, depression and cardiovascular diseases (127 - 130, see also Johnson and Grippo this supplement). It has been established in a number of studies that the neurones responsible for behavioural and neuroendocrine responses to stress are located in the prefrontal cortex, amygdala, septum, hypothalamus and the brain stem (131- 133). It has been also documented that stress, anxiety and depression are caused by disorderly regulation of neurones by the classical neurotransmitters (134). The studies performed during last years have directed attention of several investigators towards the neuropeptides such as vasopressin, angiotensins and cytokines (see also below) as to the putative regulators of neurones involved in behavioral and affective disorders. Regarding vasopressin it has been shown that enhanced stimulation of V1a and V1b receptors plays significant role in stress, anxiety and aggressive behaviour.
As discussed above, the regions involved in regulation of behaviour, mood and anxiety express V1 binding sites and some of them are innervated by vasopressin producing neurones (27 - 30). Angiotensin II appears to be another neuropeptide which seems to be involved in the emotional response to stress (137). Recently, Zhang et al. (53) reported that the rats with the myocardial infarction respond with significantly greater increases in the sympathetic renal nerves activity, blood pressure and heart rate to the alarming stress. In addition, in the same study the authors provided evidence that the exaggerated cardiovascular responsiveness to stress can be normalised by blockade of AT1 receptors in the brain. Recent findings performed in our Department indicate that enhanced stimulation of V1a receptors by centrally released vasopressin also contributes to exaggerated cardiovascular responses to stress in the post-infarct cardiac failure. We have confirmed presence of the exaggerated blood pressure and heart rate responses to the alarming stress in the infarcted rats and have demonstrated normalisation of these responses by intraventricular infusion of V1a and AT1 receptors antagonists (49, 89, 90). On the other hand, intraventricular infusion of angiotensin II potentiated the pressor responses to stress (92). Interestingly, combined blockade of AT1 and V1a antagonists caused the same reduction of the cardiovascular responses to stress. Fig. 3. Putative mechanisms responsible for negative effects of stress during the post-infarct state. ANG II - angiotensin II, AVP - vasopressin, PVN - paraventricular nucleus, RVLM - rostral ventrolateral medulla. See also text for further explanations.
stress as the separate blockade of either AT1 or V1a receptors (90). Collectively
the above studies reveal that increased activation of angiotensin II AT1 and
AVP V1a receptors in the brain of the infarcted rats contributes to generation of
the exaggerated cardiovascular responses to stress in the infarcted rats.
Furthermore, our studies strongly suggest that the brain angiotensin II and
vasopressin interact in a non-additive manner in regulation of the
cardiovascular responses to stress. At present it seems that the pool of neurones
bearing AT1 and V1a receptors which are engaged in the exaggerated
cardiovascular responses to stress in the infarcted rats may differ from the pool
of neurones involved in regulation of resting blood pressure. This is indicated
by the results showing that blockade of central AT1 and V1a receptors in the
infarcted rats reduces stress-induced cardioacceleration while it does not affect
the heart rate under resting conditions. It should be emphasized that
enhancement of the pressor and tachycardic responses to stress imposes an
additional workload on the heart and may account for negative effects of stress
in the patients suffering from the coronary disease. In this context enhanced
activation of AT1 and V1a receptors in the brain of the infarcted rats may be
considered as a harmful change.

An exposure to stress results also in elevation of cytokines release. Growing
number of studies indicate that cytokines play significant role in activation of
the hypothalamo-pituitary-adrenocortical axis during various forms of stress
(112, 122, 138 - 140). Some investigators have proposed that cytokines may
play a key role in determining susceptibility to stress and depression (141 - 144,
see also Grippo and Johnson, this supplement). In view of the increased
production of cytokines in the brain after the myocardial infarction (see above),
it is likely that they may be also involved in regulation of the cardiovascular
responses to stress after the myocardial infarction. Beside, they may penetrate
into the brain from the circulating blood. The summary of the mechanisms
which may be involved in exaggerated cardiovascular responses to stress is
presented in Fig. 3.

In summary, the evidence available so far indicates that the neuropeptides play
significant role in long term resetting of the neurogenic control of the
cardiovascular system in pathophysiological states and during stress. Some of
them (Ang II, AVP, IL-1β and TNFα) are released both during stress and
cardiovascular diseases. Indirect evidence strongly suggests that they may play a
pathogenic role in development of increased susceptibility of patients with the
cardiac diseases to stress and depression and, *vice versa*, in the negative effects of
stress and depression on generation of serious cardiovascular complications in
patients suffering from the cardiovascular diseases.

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