Significance of Neuropeptides for Coexistence of Disturbances in Central Cardiovascular Control in Heart Failure, Stress and Depression

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Abstract

There are solid grounds for the recognition of the involvement of multiple neuronal/neurotransmitter networks in the regulation of the cardiovascular system...
addition, it has been shown that some of the brain's neurochemical pathways, which are involved in the central control of blood pressure, play a role in the regulation of emotions and cognitive functions. Stress and depression are regarded as potential challenges for the cardiovascular system, causing inappropriate regulation of cardiovascular parameters and worsening the prognosis of heart failure. There is also evidence that heart failure increases sensitivity to stress and depression. Recently, knowledge of the neurochemical background of comorbidity of stress, depression and heart failure has increased markedly. Our studies and those of other authors provided evidence for significant role of the improper function of neuropeptides, and in particular of the angiotensinergic, vasopressinergic and oxytocinergic systems in the exaggerated responsiveness of the cardiovascular system to stress in heart failure and depression. Current evidence indicates that the inappropriate regulation of the release of these neuropeptides and/or expression of their receptors play a particularly important role in long-term changes of central cardiovascular control during post-infarct heart failure.

Keywords
Angiotensin, Cytokines, Oxytocin, Stress, Vasopressin, CRH

Abbreviations
ACTH: Adrenocorticotropic Hormone; ANG: Angiotensin; AP: Area Postrema; AVP: Vasopressin; AV3V: Anteroventral Wall Of The Third Ventricle; ATR: Angiotensin Receptor; CRH: Corticotropin Releasing Hormone; CNS: Central Nervous System; CSF: Cerebrospinal Fluid; CVLM: Caudal Ventrolateral Medulla; CVN: Cervical Ventral nucleus; H2S2: Hydrogen Disulphide; SON: Supraoptic Nucleus; TNF: Tumor Necrosis Factor; V1R: Vasopressin V1 Receptor; OXY: Oxytocin; PAG: Periaqueductal Gray; PBN: Parabrachial Nucleus; PVN: Paraventricular Nucleus; MAPK: Mitogen:Activated Protein Kinase; ME: Median Eminence; MR: Mineralocorticoid Receptor; NA: Nucleus Ambiguus; Nachr: Nicotinic Acetylcholine Receptor; NF-kB: Nuclear Transcription Factor; NMDA: N-Methyl D-Aspartate Receptor; NTS: Nucleus Tractus Solitarii; NO: Nitric Oxide; OTR: Oxytocin Receptor; OVLT: Organum Vascularosum Of The Lamina Terminalis; RAS: Renin:Angiotensin System; RVLM: Rostral Ventrolateral Medulla; SFO: Subfornical Organ; H2S2: Hydrogen Disulphide; SON: Supraoptic Nucleus; TF: Tumor Necrosis Factor; V1R: Vasopressin V1 Receptor

Introduction
For many years, anecdotal observations indicated that sudden stress or prolonged emotional discomfort may provoke myocardial infarction or aggravate the post-infarct heart failure. It has also been reported that patients with post-infarct heart failure manifest a greater vulnerability to stress and depression. Recent progress in the exploration of the neuroanatomy and the neurochemistry of the central nervous system (CNS) has made it possible to identify the regions of the brain and chemical molecules involved in the cardiovascular and emotional regulations and has markedly increased the knowledge of the neurochemical background underlying the mutual links between stress, depression and disturbances in the circulatory control in cardiovascular diseases. The present review focuses on the special role of some of the neuropeptides in generating disordered regulation of cardiovascular functions during post-infarct heart failure associated with neurogenic stress and/or depression.

Neuroanatomical Association of the Cardiovascular and Emotional Regulations
Previously, cardiovascular neurons have been identified in the brain stem [1,2]. However, recent evidence has shown that significant disturbances in cardiovascular functions can be evoked during stimulation (or after destruction) of multiple groups of neurons located in other structures of the brain, including the cerebral cortex and cerebellum. Detailed information about the location of these neurons can be found in the experimental studies and reviews of the other investigators [3-8]. In this review we concentrate mainly on those regions which are involved in the regulation of the central and peripheral release of cardiovascular neuropeptides, and are activated during emotional stress or depression.

Location of Cardiovascular Neurons in the Brain
The neurones receiving and transmitting information from peripheral cardiovascular receptors can be found in the associative, motor, prefrontal and cingulate cortex, insula, amygdala, hypothalamus, midbrain, medulla, cerebellum and the circumventricular organs [7,9-13].

Cardiovascular Neurons in the Paraventricular Nucleus: In the diencephalon, the main group of the presympathetic neurons controlling the cardiovascular functions is located in the paraventricular nucleus (PVN). The PVN converges also information arising in the preoptic/anterior forebrain and neocortex, and innervates multiple regions of the forebrain, brain stem and spinal cord which are involved in the regulation of blood pressure [3-5,9,11-13]. Experimental and clinical studies have revealed that in many instances the same groups of neurons show altered activity in the heart failure and in neurogenic stress and depression [6,13,14,17]. The PVN neurons express an array of biologically active neuropeptides involved in the regulation of blood pressure, such as vasopressin (AVP), oxytocin (OXY), corticotropin releasing hormone (CRH), orexin, neuropeptide Y (NPY), apelin, atrial natriuretic peptide (ANP) and others [5,17-22]. Neurons of PVN also cooperate closely with the neurons surrounding the frontal wall of the third ventricle (AV3V) and with the circumventricular organs (CVO), which play an essential role in the regulation of thirst and sodium appetite, and through which some substances circulating in the blood and not penetrating the blood-brain-barrier, can affect functions of the brain cardiovascular neurons [23,24].

Cardiovascular Neurons in the Brain Stem: In the midbrain and pons essential groups of the cardiovascular neurons are located in the parabrachial nucleus (PBN), periaqueductal gray (PAG), locus coeruleus and A5 noradrenergic region [3,4]. In the medulla they are present in the nucleus tractus solitarius (NTS), caudal (CVLM) and rostral (RVLM) ventrolateral medulla, nucleus ambiguous (NcAmb) and dorsal portion of the motor vagal nucleus (DMVN) [5,9,11,13,25-27]. The medullary nuclei integrate and process information arriving from peripheral receptors (primarily from baro- and chemoreceptors) and from the supramedullary cardiovascular regions. Importantly, the medulla is also the way of passage for the ascending and descending signals transmitted between the peripheral organs and the supramedullary regions of the brain. The neurons of NA and DMVN receive multiple inputs from the other cardiovascular regions, and at the same time they are an independent source of preganglonic parasympathetic efferents. The vasconstrictory tone, heart rate acceleration and force of contraction are regulated by the presynaptic neurons located mainly in the PVN and RVLM. Stimulation of the parasympathetic efferents causes bradycardia and vasodilation in a limited number of vascular beds. Under resting conditions the heart rate is regulated predominantly by a tonic inhibitory input from the parasympathetic neurons [9,10].

It is worth emphasizing that the cardiovascular neurons form a vast neural network, which closely cooperates with different groups of neurons regulating different homeostatic functions of the body. For instance, through the connections with the PAG, PBN, amygdala, septum and circumventricular organs (CVO) the neurons

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Among them, the neuropeptides play especially important roles in the regulation of long-lasting processes in the brain. After release, they are slowly metabolized and eliminated from the neuronal surrounding. Besides, many of them stimulate synthesis and release of other biologically active compounds, including enzymes, neurotransmitters, and other neuropeptides.

Angiotensins: Among the neuropeptides angiotensins and in particular ANG II, ANG III, ANG IV, and ANG - (1-7), vasopressin, and oxytocin have arisen particularly significant interest, due to simultaneous involvement in the regulation of cardiovascular functions, the water-electrolyte balance, and engagement in the regulation of emotions and vulnerability to stress.

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Vasopressin: Vasopressin is another neuropeptide, which plays an important role in the central cardiovascular regulation [35,47-52]. Pre-provasopressin mRNA or vasopressin and vasopressin receptors mRNA and protein have been identified in NTS, RVLM, CVLM, DMVN, NcAmb and other brain cardiovascular regions, including those in the cerebral cortex and cerebellum [53-57]. The central regulation of blood pressure by AVP involves activation of vasopressin V1 receptors (V1R) [22,35,52]. The primary effect of the stimulation of V1R consists of a significant increase of blood pressure, and tachycardia [50,56]. However, in some instances (for instance during rapid haemorrhage) stimulation of central V1 receptors may mediate bradycardia and hypotension [58,59]. Several studies provide evidence that the release of vasopressin is stimulated by Ang II and that centrally acting Ang II and vasopressin closely cooperate in blood pressure control [39,60]. Similarly to angiotensin II, vasopressin significantly increases blood pressure evoked by acute stress [49,61,62].

Oxytocin: Distribution of oxytocinergic innervation of the cardiovascular regions is similar to vasopressinergic innervation [53]. Oxytocin and vasopressin have similar molecules and the mechanism of activation of V1a and oxytocin receptors is similar [63,64]. There is also evidence that oxytocin receptors bind oxytocin and vasopressin with similar affinity [65,66]. Thus, oxytocin acts by its own OTR receptors but it can also stimulate V1R. It has been shown that central administration of oxytocin under resting conditions either does not exert cardiovascular effects [67,68] or elicits prolonged hypotension [69,70]. During stress endogenous oxytocin interacts with OTR and V1AR and significantly regulates the magnitude of the pressor responses [68]. It has been postulated that the role of oxytocin in the regulation of blood pressure during stress significantly depends on the proportion of V1a and OTR receptors stimulated by this peptide [68]. It appears that while activation of V1AR potentiates the pressor responses to stress, stimulation of OTR receptors by endogenous oxytocin significantly buffers these responses. The latter effect is significantly reduced in Sprague Dawley rats with post-infarct heart failure [67] and in the spontaneously hypertensive rats (SHR) [68]. Interestingly, V1AR receptors play a significant role in exaggerating the pressor responses to stress in Wistar Kyoto rats, which are closely related to SHR [68].

Cytokines: Three cytokines, namely interleukin -1β (IL-1β), tumor necrosis factor of type α (TNF-α), IL-6 and their transcripts have been detected in the brain cardiovascular regions [71,72]. Cerebroventricular administration of IL-1β increases blood pressure in rats and sensitizes them to the pressor action of ANG II [75,76]. Interleukin-1β also plays a significant role in the exaggeration of the pressor response to acute stress [77].

Interaction of Neuropeptides with Gasotransmitters: Essential buffering cardiovascular effects are attributed to nitric oxide (NO) and disulphide hydrogen (H2S) [78]. The central cardiovascular effects of gaseous neurotransmitters depend mainly on their modulatory interaction with other mediators, and in particular with neuropeptides, such as vasopressin, angiotensins and cytokines [78].

Neurochemical Remodelling in the Brain during the Post-Infarct Heart Failure

Significant activation of the sympathetic-adrenal system, inhibition of the parasympathetic system and increase in the release of vasopressin belong to typical symptoms of the post-infarct heart failure [79-81]. The pathophysiological background of these events is complex and differs at different stages of post-infarct heart failure.

Cardiovascular Events Immediately after the Myocardial Infarction

Immediately after formation of the infarct, a decrease of the stroke volume and cardiac output and the resultant hypotension cause unloading of the cardiovascular receptors and reduction of the stimulatory input to the parasympathetic neurons. This is associated with excitation of the sympathetic neurons and sympatho-adrenal activation [80,81], stimulation of renin-angiotensin-aldosterone system [82,83], release of vasopressin together with copeptin and enhanced production of pro-inflammatory cytokines [84,85]. The over-excitation of the cardiac sympathetic neurons may play a negative role as it enhances the cardiac output and exacerbates the hypotension.
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**Long Term-Cardiovascular and Neuroendocrine Disorders after the Myocardial Infarction**

Heart failure developing after myocardial infarction results in long-term changes of the central cardiovascular control by the autonomic nervous system [80,82,84,86-93]. Stimuli generated in the receptors of the infarcted heart are transmitted by the sympathetic afferents to the presympathetic neurons and significantly alter the baseline and baroreceptors-mediated regulation of sympathetic activity [80,92]. Multiple studies indicate that post-infarct heart failure is associated with significant changes in the activity of classical and non-classical transmitting systems [94]. Significant stimulation of glutamatergic neurons and NMDA- and non-NMDA receptors in the RVLM was found by Wang et al. [95]. The same group of authors found attenuation of GABA receptors-mediated inhibition of the presympathetic drive originating from the paraventricular nucleus (PVN) and the decreased expression of GABAA and GABAB receptors mRNAs [96].

In the last years significant attention was given to altered regulation of the cardiovascular system by the brain angiotensins, vasopressin, oxytocin and cytokotines in heart failure.

**Renin-angiotensin system:** There is strong evidence that the post-infarct heart failure results in activation of the AT1 receptors (AT1R) and tonic inhibition of the baroreflex [88,92,93]. Several studies provide evidence that post-infarct heart failure deeply affects several components of the central renin-angiotensin system. For instance, Tan et al. [97] showed that myocardial infarct increases AT1R and ACE densities in the brain. The experiments of Gao et al. [98] revealed that chronic post-infarct heart failure causes the down-regulation of the voltage-gated Kv4.3 potassium channels in the RVLM. A similar effect can be evoked by ANG II in a neuronal cell line CATH.a -the cell culture derived from the brain stem catecholaminergic neurons. It was found that the inhibition of Kv4.3 expression by ANG II may be abolished by AT1 receptors blockade evoked by the administration of losartan, as well as by the superoxide scavenger Tempol and the p38 MAPK (mitogen activated protein kinase) inhibitor [98]. Expression of the brain AT1 receptors increases after myocardial infarction and this effect is associated with the up-regulation of the neuronal transcription factor NF-κB and Ets-like protein 1 (Elk-1 protein) [99]

There is also evidence that an increased activity of the brain RAS, oxidative stress -induced activation of the MAPK-signalling pathway, and sympathoexcitation are associated with stimulation of the brain mineralocorticoid receptors MR [87,100].

**Vasopressin:** During the post-infarct heart failure ANG II closely cooperates with vasopressin. Sensitivity of the brain cardiovascular neurons to the pressor action of angiotensin ANG II and AVP is significantly elevated, as it is indicated by significantly greater increases of blood pressure after cerebroventricular administration of these peptides in infracted Sprague Dawley rats than in sham-operated rats [39,49]. The studies of Cudnoch-Jedrzejewska et al. [39,49,60] provide evidence that blockade of angiotensin AT1 and vasopressin (V1a) receptors in the brain of infracted rats reduces resting blood pressure and potentiates post-infarct hypotension. Thus, it can be speculated that the enhanced stimulation of the brain AT1 and V1a receptors in the brain of infarcted animals may prevent excessive hypotension. The same group of authors provided evidence that the enhanced pressor responses of infracted rats to the central administration of ANG II are largely mediated by AVP and the stimulation of V1a receptors [80].

There is evidence for the significant stimulation of vasopressinergic neurons and a significant role of vasopressin V1a receptors in the regulation of the cardiovascular system in heart failure [101-103]. For instance, a significant increase in AVP content in several cardiovascular brain regions was found in heart failure induced by constriction of the aorta [101]. Recently, an increase in the relative optic density of vasopressin immunoreactivity was demonstrated in the PVN, SON, and the posterior pituitary lobe of patients suffering from chronic heart failure [103]. Increased stimulation of vasopressin V1aR in the brain seems to be important for maintenance of the resting blood pressure in post-infarct cardiac failure [49]. As discussed above the increased activation of the brain V1R by vasopressin participates in the potentiation of the central pressor action by ANG II [39,60]. Recent studies from our laboratory suggest that the increased activation of the central vasopressinergic system during the post-infarct state does not result from the up-regulation of central V1a receptors as V1a receptors are down-regulated [57].

**Cytokines:** There is evidence that cytokines also participate in generation of the sympathoexcitation after myocardial infarction. The studies of Kang et al. [104,105] revealed that blockade of TNF-α in the PVN by the topical infusions of pentoxifylline -or etanercept reduce activation of the renal sympathetic nerves and eliminate enhanced expression of AT1 receptors in PVN of the infracted rats.

**Stress, Depression and Cardiovascular Regulation in Heart Failure**

Historically, neurogenic stress and depression were frequently regarded as important causes of cardiovascular diseases, especially of myocardial infarction and stroke. However, for several years, this conviction was based exclusively on incidental observations. In the last two decades a number of clinical and preclinical studies have provided experimental evidence that neurogenic stress and depression aggravate the coronary disease and increase susceptibility to myocardial infarction and the development of chronic heart failure [91,106-109]. The comorbidity of depression and heart failure in patients with the coronary artery disease has also been reported [107-113].

**Resetting of the Autonomic Cardiovascular Regulation in Stress and Depression**

It was found that the elevated activity of the sympathoemtric system, which is present during emotional stress, plays a significant negative role during heart failure [91,106]. Recent studies performed on patients with heart failure revealed an elevated risk of ventricular arrhythmia and mortality in infarcted patients with type D (distressed) personality [106,114,115]. In line with these observations are the results of the meta-analytical review of Rutledge et al. [112] who analysed the associations between the probability of development of the heart failure and clinical depression. Not all investigators agree with the postulate that depression itself is a key factor responsible for the negative prognosis in patients suffering from the heart failure. For instance, the study of Whooley et al. [116] suggests that such an association may be a consequence of an altered style of life and reduced physical activity.

The question arises which of the factors are engaged in the initiation of synergies between stress, depression and heart failure at the level of cardiovascular neurons. It is noteworthy that stress and depression result in the reduced sensitivity of the baroreflex and that in human beings this is associated with increased activity of the cingular cortex, insula, amygdala and midbrain periaqueductal gray [15,117]. It is postulated that impaired baroreflex control can account for cardioacceleration in depressed patients [117]. As discussed above impaired baroreflex sensitivity is also one of the symptoms of post-infarct heart failure. Thus, it is likely that resetting of the baroreflex in cardiac failure plays an essential role in the enhanced activation of cardiovascular neurons during stress and depression.

**Altered Neurochemical Control of Blood Pressure during Stress**
the GABA-ergic, noradrenergic and serotonergic pathways of PVN and RVLM [94,118,119]. For instance mice lacking 5HT1A receptors manifested more anxiety and were more vulnerable to sudden cardiac death [118].

There is also strong evidence that cardiac failure is associated with disordered regulation of the cardiovascular functions by the brain peptidergic systems and that some neuropeptides may play a key role in association of long term disturbances in the regulation of blood pressure in heart failure and stress.

**Angiotensins:** Angiotensin AT1 receptors are expressed in many regions of the brain, which are activated during stress [29,31,32,120,121]. In addition it has been shown that the brain angiotensin II is involved in the regulation of the hypothalamic-pituitary-adrenal axis during neurogenic stress and that it enhances cardiovascular responses to stress [39,58,120-122]. It was also found that pressor responses to acute air jet stress are potentiated by central administration of Ang II [39]. As it was shown by Zhang et al. [123] blockade of the brain AT1 receptors significantly reduces exaggerated pressor and tachycardic responses to acute stress in the post-infarct heart failure. The same group of authors has shown that exaggerated cardiovascular responses to stress are at least partly mediated by the stimulation of the sympathetic system [123] and activation of the central vasopressinergic system [49,60]. Mayorov and Head [124] have reported that the pressor effect of acute stress, evoked by the air jet stress is significantly reduced by a blockade of the AT1R receptors in the RVLM. It was also postulated that the stressogenic effect of the stimulation of the brain angiotensin AT1 receptors in the RVLM is mediated by the brain superoxide [125]. Recently, it was postulated that the inflammatory process is playing a role of the link between the acute myocardial infarction and stress and depression. Supportive to this assumption is the finding that anti-inflammatory compounds, such as TNF-α inhibitors, attenuate the depressive symptoms and improve the post-myocardial depression [126].

The brain vasopressinergic system is another peptidergic system which is activated both during heart failure and during stress [48,49,60,61]. Vasopressin plays significant role in activation of the pituitary adrenal axis during stress as well as in the potentiation of vulnerability to stress, anxiety and depression [127-130]. Current evidence shows that both subtypes of V1 receptor (V1a and V1b) are involved in the regulation of susceptibility to stress and depression [131-133]. Our own data and that of the other authors show that vasopressin increases cardiovascular responses to stress [49,60]. Furthermore, in the model of chronic stress-induced depression blockade of central V1 AVP receptors abolishes enhancement of the pressor and tachycardic responses to acute stress [48]. This may indicate that chronic stress sensitizes the central cardiovascular neurons to the pressor action of AVP.

Interestingly, an increased expression of AVP mRNA in the PVN neurons has been found in rats exposed to early-life stress. This effect was associated with hypomethylation of the AVP promoter [134]. Relevant to these studies is the report of Sanders and Anicevic [135] who reported that neurogenic stress, which is experienced in early life, may have a significant effect on the susceptibility to stress in adult life. Specifically, borderline hypertensive rats separated from their mothers for 3 hours per day, starting from the first postnatal day, responded with significantly greater tachycardia to restraint stress in adulthood [135].

**Oxytocin:** Central administration of oxytocin effectively decreases the pressor and tachycardic responses to acute stress in Sprague Dawley rats [67]. The pressor-buffering effects of oxytocin depend on stimulation of oxytocin OTR receptors and are significantly reduced in the post-infarct state [67]. A recent study of Wsol et al. performed on normotensive WKY rats and spontaneously hypertensive (SHR) rats indicates that the reduction of the cardiovascular responses to stress by oxytocin may be abolished by the simultaneous activation of V1a receptors by this peptide [68].

**Corticotropin Releasing Hormone:** It has to be emphasized that there are also other neuropeptides which may account for inappropriate regulation of blood pressure in the heart failure stress and depression. Especially, attention was given to CRH and orexins. In the rostral region of PVN, CRH is expressed in the same neurons as vasopressin [136]. CRH, is released together with vasopressin during stress and plays a key role in the neuroendocrine response to stress [137]. It has been shown that CRH elevates blood pressure through the central effects; the pressor effect being exerted via CRH-R1 receptor [137,138]. Thus far the role of CRH in the regulation of blood pressure in the heart failure has not been determined.

**Orexins:** Orexins are also expressed in the PVN neurons and ORX-A was found to stimulate vasopressin neurons and release of CRH [139]. Centrally acting orexin A is a potent pressor compound increasing sympathoexcitatory neurons in the RVLM [140,141]. Although until now there are no studies exploring the role of orexins in the regulation of cardiovascular parameters during heart failure associated with stress, it is worth to note that orexin knockout mice show reduced defence responses and are hypotensive [142].

**Summary and Conclusion**

The cardiovascular system is controlled by the cardiovascular neurons of the central nervous system and its function is continually modified and adjusted to the actual changes in the external and internal environments (Figure 1A). The myocardial infarction results in a significant decrease of the pumping efficacy of the heart, and in the altered stimulation of the cardiovascular receptors, mechanoreceptors, melanoобразовые and chemoreceptors. The altered flow of information from the peripheral tissues results in excessive activation of the sympathetic system, reduced stimulation of the parasympathetic system and enhanced release of the vasoconstrictory and sodium and water retaining compounds, such as angiotensins, vasopressin, aldosterone and cytokines (Figure 1B). Heart failure-induced disturbances of the central cardiovascular regulation are intensified during stress and depression. Several studies indicate that cardiac failure as well as stress and depression result in the dysregulation of the neuropeptidergic system of the brain. At present, there are strong premises to hypothesize that enhanced activation of the central angiotensinergic and vasopressinergic systems and reduced stimulation of oxytocin OTR receptors, which occur during post-infarct heart failure, may play an essential role in the generation of the exaggerated cardiovascular responses to stress, and in the disordered regulation of blood pressure in depression (Figure 1B).

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### Medical & Clinical Conferences

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