Journal of Clinical & Experimental Cardiology

Sadowska ES, J Clin Exp Cardiolog 2014, 5:5
DOI: 10.4172/2155-9880.1000313

Review Article Open Access

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

Ewa Szczepanska-Sadowska*, Agnieszka Cudnoch-Jedrzejewska, Agnieszka Wsol and Katarzyna Czarzasta

Department of Experimental and Clinical Physiology, Medical University of Warsaw, Warsaw, Poland

***Corresponding author:** Ewa Szczepanska-Sadowska, Department of Experimental and Clinical Physiology, Medical University of Warsaw, 02-106 Warsaw, ul. Pawinski 3c, Poland, Fax: +48 225720 782, +48 22116 6201; E-mail: eszczepanska@wum.edu.pl

Rec date: Mar 20, 2014, **Acc date:** May 27, 2014, **Pub date:** May 30, 2014

Abstract

There are solid grounds for the recognition of the involvement of multiple neuronal/neurotransmitter networks in the regulation of the cardiovascular system. Clinical and preclinical studies provide evidence that heart failure is associated with significant changes in the central control of some of these systems. In 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; CVO: Circumventricular Organ; DMVN: Dorsal Motor Vagal Nucleus; GABA: Γ:Aminobutyric Acid; 5:HT: Serotonin; ICV: Intracerebroventricular; IL: Interleukin; Machr: Muscarinic Acetylcholine Receptors; MAPK: Mitogen:Activated Protein Kinase; ME: Median Eminence; MR: Mineralocorticoid Receptor; NA: Nucleus Ambiguous; Nachr: Nicotinic Acetylcholine Receptor; NF:κB: Nuclear Transcription Factor; NMDA: N-Methyl D-Aspartate Receptor; NTS: Nucleus Tractus Solitarius; NO: Nitric Oxide; OTR : Oxytocin Receptor; OVLT: Organum Vasculosum Of The Lamina Terminal; OXY: Oxytocin; PAG: Periaqueductal Gray; PBN: Parabrachial Nucleus; PVN: Paraventricular Nucleus; Ras: Progenitor Of Family Of Guanosine Triphosphatases; RAS: Renin:Angiotensin System; RVLM: Rostral Ventrolateral Medulla; SFO: Subfornical Organ; H2S2: Hydrogen Disulphide; SON: Supraoptic Nucleus; TNF: 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 innervate 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 [4,5]. 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 preganglionic parasympathetic efferents. The vasoconstrictory tone, heart rate acceleration and force of contraction are regulated by the presympathetic 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 of PVN, NTS and RVLM receive and integrate the signals from the neurons involved in the regulation of blood pressure, respiration, pain, food intake and neuroendocrine secretion [3-5,26,27].

Cardiovascular Effects of Centrally Acting Neuropeptides

The cardiovascular neurons use the majority of conventional neurotransmitters (norepinephrine, acetylcholine, serotonin, glutamate and γ-aminobutyric acid). Besides, they employ multiple non-conventional transmitters, including gasotransmitters, several neuropeptides, mineralocorticoids and cardiotonic steroids.

Among them, the neuropeptide play especially important role in the regulation of long-lasting processes in the brain. After release they are slowly metabolised 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.

All components of the renin-angiotensin system (RAS) and angiotensin receptors (AT1, AT2, AT4 and Mas) have been identified in the brain. The binding sites, protein and/or mRNA of these receptors have been identified in the majority of the brain cardiovascular regions [28-32]. The hitherto available evidence indicates that the centrally operating angiotensin II (ANG II) and angiotensin III (ANG III) both have significant hypertensive effects, their action being reinforced by the stimulation of AT1 receptors in the circumventricular organs by peripherally circulating ANG II [33-36]. Importantly, the mechanism of the central pressor action of ANG II is complex and includes activation of the sympathetic system, stimulation of vasopressin (AVP) release, enhancement of thirst and sodium appetite, and inhibition of the baroreflex [22,32,36-38]. Central administration of exogenous angiotensin II significantly potentiates the pressor responses to acute stress in Sprague Dawley rats [39].

Cooperation of Angiotensin II and Aldosterone: Angiotensin II closely operates together with mineralocorticoids. For many years, the hypertensive properties of aldosterone have been assigned exclusively to its sodium retaining properties. In recent decades, it was established that aldosterone can easily penetrate through the blood-brain barrier and is produced in the brain itself [40-43]. The mineralcorticoid receptors (MR) are well represented in the forebrain and medullary brain cardiovascular regions [42,44]. It has also been established that the central hypertensive effect of aldosterone results mainly from its interaction with the brain angiotensin system [45,46].

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 [69-72]. Cerebroventricular administration of IL-1β increases blood pressure in rats and sensitizes them to the pressor action of ANG II [73-76]. Interleukin-1β also plays a significant role in the exaggeration of the pressor response to acute stress [77]

Interaction of Neuropeptides with Gasotransmitters: Essential modulatory cardiovascular effects are attributed to nitric oxide (NO) and disulphide hydrogen (H_2S_2) [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 sympatho-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 presympathetic neurons and sympatho-adrenal activation [80,81], stimulation of renin-angiotensin-aldosteron system [82,83], release of vasopressin together with copeptin and enhanced production of pro-inflammatory cytokines [84,85]. The over-excitation of the cardiac sympathethic neurons may play a negative role as it enhances the cardiac work load and may result in disproportions between oxygen supply and oxygen uptake and in an expansion of the ischemic zone in the infarcted heart [79,80,86].

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 [90,92]. 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].

Altered cardiovascular regulation by the brain neuropeptides in heart failure. In the last years significant attention was given to altered regulation of the cardiovascular system by the brain angiotensins, vasopressin, oxytocin and cytokines 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 nuclear 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 infarcted 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 infarcted rats reduces resting blood pressure and potentiates post-infarct hypotensin. 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 infarcted rats to the central administration of ANG II are largely mediated by AVP and the stimulation of V1a receptors [60].

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 pentoxyfilline -or etanercept reduce activation of the renal sympathetic nerves and eliminate enhanced expression of AT1 receptors in PVN of the infarcted 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 sympathetic 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 synergy 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

It is noteworthy that several neurochemical pathways, which are affected during stress or depression, manifest also altered activity in heart failure. This refers to 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 role of 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 [127] as well as in the regulation of vulnerability to stress, anxiety and depression [128-130]. 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].

Oxytoxin: Central administration of oxytocin effectively decreases the pressor and tachycardic responses to acute stress in Sprague Dawley rats [67]. The stress-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 Conclusions

The cardiovascular system is controlled by the cardiovascular neuons 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, metaboreceptors 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).

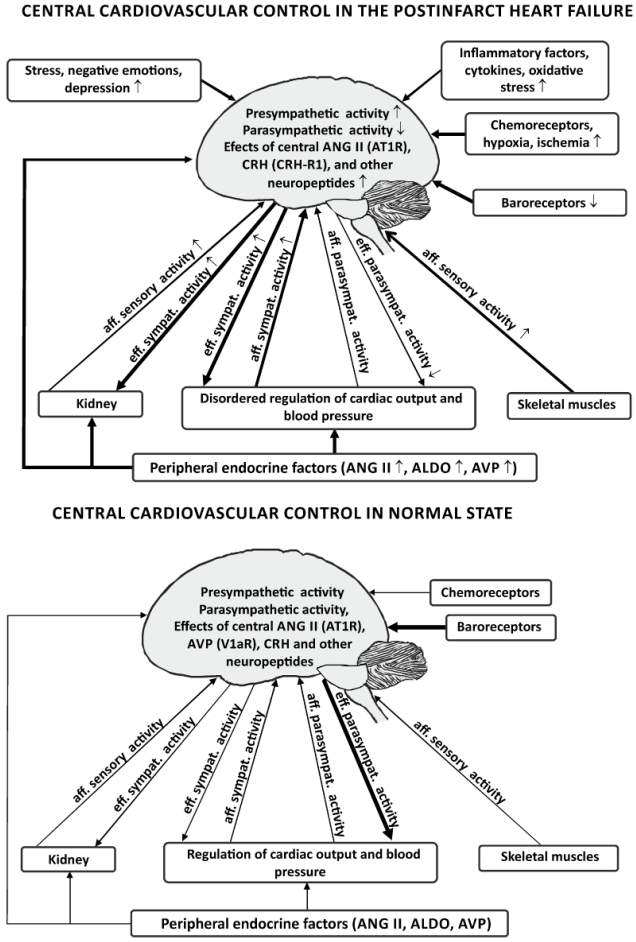

Figure 1: The schemes illustrate the main groups of central presympathetic and parasympathetic cardiovascular neurones and neurondocrine factors involved in the regulation of cardiovascular functions in the healthy subjects (A) and during the post-infarct heart failure (B). Main afferent and efferent pathways between the central nervous system and peripheral organs are shown. The direction of change is indicated by arrows and intensity of change by thickness of the lines. The Figure shows an involvement of key neuropeptides, activation of the presympathetic neurons and inhibition of the parasympathetic neurons in enhancement of cardiovascular responses to stress during post-infarct heart failure.

ALDO: Aldosterone; ANG: Angiotensin; AVP: Arginine Vasopressin; AT1R: Angiotensin AT1 Receptor; MR:

Mineralocorticoid Receptor; V1aR: Vasopressin V1a Receptor. See text for other explanations.

Acknowledgments

The work was supported by the First Faculty of Medicine of the Medical University of Warsaw (project 1MA/2013-2014).

References

1. Schultz SG (2002) William Harvey and the circulation of the blood: the birth of a scientific revolution and modern physiology. News Physiol Sci 17: 175-180.
2. Zimmer HG (1999) The contributions of Carl Ludwig to cardiology. Can J Cardiol 15: 323-329.
3. Dampney RA (1994) Functional organization of central pathways regulating the cardiovascular system. Physiol Rev 74: 323-364.
4. Dampney RA, Coleman MJ, Fontes MA, Hirooka Y, Horiuchi J, et al. (2002) Central mechanisms underlying short- and long-term regulation of the cardiovascular system. Clin Exp Pharmacol Physiol 29: 261-268.
5. Dampney RA, Horiuchi J, McDowall LM (2008) Hypothalamic mechanisms coordinating cardiorespiratory function during exercise and defensive behaviour. Autonom Neurosci 142: 3-10.
6. Gianaros PJ, Derbyshire SW, May JC, Siegle GJ, Gamalo MA, et al. (2005) Anterior cingulate activity correlates with blood pressure during stress. Psychophysiology 42: 627-635.
7. Kimmerly DS, O'Leary DD, Menon RS, Gati JS, Shoemaker JK (2005) Cortical regions associated with autonomic cardiovascular regulation during lower body negative pressure in humans. J Physiol 569: 331-345.
8. Lipski J, Kanjhan R, Kruszewska B, Smith M (1995) Barosensitive neurons in the rostral ventrolateral medulla of the rat in vivo: morphological properties and relationship to C1 adrenergic neurons. Neuroscience 69: 601-618.
9. Dampney RA, Horiuchi J, Killinger S, Sheriff MJ, Tan PS, et al. (2005) Long-term regulation of arterial blood pressure by hypothalamic nuclei: some critical questions. Clin Exp Pharmacol Physiol 32: 419-425.
10. Dergacheva O, Griffioen KJ, Neff RA, Mendelowitz D (2010) Respiratory modulation of premotor cardiac vagal neurons in the brainstem. Respir Physiol Neurobiol 174: 102-110.
11. Kc P, Dick TE (2010) Modulation of cardiorespiratory function mediated by the paraventricular nucleus. Respir Physiol Neurobiol 174: 55-64.
12. Kimmerly DS, Morris BL2, Floras JS2 (2013) Apnea-induced cortical BOLD-fMRI and peripheral sympathoneural firing response patterns of awake healthy humans. PLoS One 8: e82525.
13. Wong SW, Massé N, Kimmerly DS, Menon RS, Shoemaker JK (2007) Ventral medial prefrontal cortex and cardiovagal control in conscious humans. Neuroimage 35: 698-708.
14. Gianaros PJ, Sheu LK, Matthews KA, Jennings JR, Manuck SB, et al. (2008) Individual differences in stressor-evoked blood pressure reactivity vary with activation, volume, and functional connectivity of the amygdala. J Neurosci 28: 990-999.
15. Gianaros PJ, Onyewuenyi IC, Sheu LK, Christie IC, Critchley HD (2012) Brain systems for baroreflex suppression during stress in humans. Hum Brain Mapp 33: 1700-1716.
16. McDougall SJ, Widdop RE, Lawrence AJ (2005) Central autonomic integration of psychological stressors: focus on cardiovascular modulation. Auton Neurosci 123: 1-11.
17. Card JP, Swanson LW, Moore MJ (2003) The hypothalamus: an overview of regulatory systems In: Fundamental Neuroscience Squire LF, Bloom EF, McConnell SK, Spitzer JL, Zigmond MJ (eds). Academic Press, London: 897-909.
18. El Yamani FZ, Yon L, Guérin M, El Ouezzani S, Alaoui A et al. (2013) Immunocytochemical distribution of EM66 within the hypothalamic parvocellular paraventricular nucleus: colocalization with CRH and TRH but no plasticity related to acute stress and thyroidectomy in the rat. Regul Pept 183: 28-34.
19. Guo ZL, Moazzami AR, Longhurst JC (2005) Stimulation of cardiac sympathetic afferents activates glutamatergic neurons in the parabrachial nucleus: relation to neurons containing nNOS. Brain Res 1053: 97-107.
20. Hu K, Bahner U, Gaudron P, Palkovits M, Ring M et al. (2001) Chronic effects of ACE-inhibition (quinapril) and angiotensin-II type-1 receptor blockade (losartan) on atrial natriuretic peptide in brain nuclei of rats with experimental myocardial infarction. Basic Res Cardiol 96: 258-296.
21. Reaux A, Gallatz K, Palkovits M, Llorens-Cortes C (2002) Distribution of apelin-synthesizing neurons in the adult rat brain. Neuroscience 113: 653-662.
22. Szczepanska-Sadowska E (2006) Neuropeptides in neurogenic disorders of the cardiovascular control. J Physiol Pharmacol 57 Suppl 11: 31-53.
23. McKinley MJ, Johnson AK (2004) The physiological regulation of thirst and fluid intake. News Physiol Sci 19: 1-6.
24. Smith PM, Ferguson AV (2010) Circulating signals as critical regulators of autonomic state--central roles for the subfornical organ. Am J Physiol Regul Integr Comp Physiol 299: R405-415.
25. Adams JM, Bardgett, ME, Stocker SD (2009) Ventral lamina terminalis mediates enhanced cardiovascular responses of rostral ventrolateral medulla neurons during increased dietary salt. Hypertension 54: 308-314.
26. Huber DA, Schreihofer AM (2011) Altered regulation of the rostral ventrolateral medulla in hypertensive obese Zucker rats. Am J Physiol Heart Circ Physiol 301: H230-240.
27. Lonhgurst JC (2003) Neural regulation of the cardiovascular system. In: Fundamental Neuroscience. Squire LR, Bloom FE, McConnell SK, Spitzer J L, Zigmond M J (eds), Academic Press, London: 935-966.
28. Bader M, Ganten D (2002) It's renin in the brain: transgenic animals elucidate the brain renin angiotensin system. Circ Res 90: 8-10.
29. Bottari SP, de Gasparo M, Stecklings UM, Levens NR (1993) Angiotensin II receptor subtypes: characterization, signalling mechanisms, and possible physiological implications. Front Neuroendocrinol 14: 123-171.
30. Lavoie JL, Sigmund CD (2003) Minireview: overview of the renin-angiotensin system--an endocrine and paracrine system. Endocrinology 144: 2179-2183.
31. Lenkei Z, Palkovits M, Corvol P, Llorens-Cortes C (1998) Distribution of angiotensin type-1 receptor messenger RNA expression in the adult rat brain. Neuroscience 82: 827-841.
32. Wright JW, Harding JW (1994) Brain angiotensin receptor subtypes in the control of physiological and behavioral responses. Neurosci Biobehav Rev 18: 21-53.
33. Ganten D, Unger T, Lang RE (1985) The dual role of angiotensin and vasopressin as plasma hormones and neuropeptides in cardiovascular regulation. J Pharmacol 16 Suppl 2: 51-68.
34. Hoffman WE, Philips MI, Schmid PG, Falcon J, Weet JF (1977) Antidiuretic hormone release and the pressor response to central angiotensin II and cholinergic stimulation. Neuropharmacology 16: 463-472.
35. Szczepanska-Sadowska E, Szczypaczewska M (1996) Evidence that centrally released arginine vasopressin is involved in central pressor action of angiotensin II. Am J Physiol 270: H167-173.
36. Phillips MI, Sumners C (1998) Angiotensin II in central nervous system physiology. Regul Pept 78: 1-11.
37. DiBona GF (1999) Central sympathoexcitatory actions of angiotensin II: role of type 1 angiotensin II receptors. J Am Soc Nephrol 10 Suppl 11: S90-94.
38. Johns EJ (2005) Angiotensin II in the brain and the autonomic control of the kidney. Exp Physiol 90: 163-168.
39. Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Dobruch J, Puchalska L, Ufnal M et al. (2008) Differential sensitization to central cardiovascular effects of angiotensin II in rats with a myocardial infarct: relevance to stress and interaction with vasopressin. Stress 11: 290-301.
40. Connell JM, Davies E (2005) The new biology of aldosterone. J Endocrinol 186: 1-20.

41. Gomez-Sanchez EP, Gomez-Sanchez CE (2003) Is aldosterone synthesized in the CNS regulated and functional? Trends Endocrinol Metab 14: 444-446.
42. Gomez-Sanchez EP, Gomez-Sanchez CE (2012) Central regulation of blood pressure by the mineralocorticoid receptor. Mol Cell Endocrinol 350: 289-298.
43. Gomez-Sanchez EP, Ahmad N, Romero DG, Gomez-Sanchez CE (2005) Is aldosterone synthesized within the rat brain? Am J Physiol Endocrinol Metab 288: E342-346.
44. Jackiewicz E, Szczepanska-Sadowska E (2005) Expression of mineralocorticoid receptors mRNA in the brain, heart and kidney of Sprague Dawley rats with renovascular hypertension. Brain Res Bull 65: 23-29.
45. Zhang ZH, Yu Y, Kang YM, Wei SG, Felder RB (2008) Aldosterone acts centrally to increase brain renin-angiotensin system activity and oxidative stress in normal rats. Am J Physiol Heart Circ Physiol 294: H1067-1074.
46. Yu Y, Wei SG, Zhang ZH, Gomez-Sanchez E, Weiss RM, et al. (2008) Does aldosterone upregulate the brain renin-angiotensin system in rats with heart failure? Hypertension 51: 727-733.
47. Berecek KH, Webb RL, Brody MJ (1983) Evidence for a central role for vasopressin in cardiovascular regulation. Am J Physiol 244: H852-859.
48. Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Dobruch J, Gomolka R, Puchalska L (2010) Brain vasopressin V(1) receptors contribute to enhanced cardiovascular responses to acute stress in chronically stressed rats and rats with myocardial infarcton. Am J Physiol Regul Integr Comp Physiol 298: R672-680.
49. Dobruch J, Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E (2005) Enhanced involvement of brain vasopressin V1 receptors in cardiovascular responses to stress in rats with myocardial infarction. Stress 8: 273-284.
50. Noszczyk B, Lon S, SzczepaÅ„ska-Sadowska E (1993) Central cardiovascular effects of AVP and AVP analogs with V1, V2 and 'V3' agonistic or antagonistic properties in conscious dog. Brain Res 610: 115-126.
51. Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Ufnal M, Zera T (2010) Brain and cardiovascular diseases: common neurogenic background of cardiovascular, metabolic and inflammatory diseases. J Physiol Pharmacol 61: 509-521.
52. Szczepanska-Sadowska E, Paczwa P, Lon„ S, Ganten D (1998) Increased pressor function of central vasopressinergic system in hypertensive renin transgenic rats. J Hypertens 16: 1505-1514.
53. Buijs RM (1990) Vasopressin and oxytocin localization and putative functions in the brain. Acta Neurochir Suppl (Wien) 47: 86-89.
54. Hallbeck M, Larhammar D, Blomqvist A (2001) Neuropeptide expression in rat paraventricular hypothalamic neurons that project to the spinal cord. J Comp Neurol 433: 222-238.
55. Kalsbeek A, Palm IF, Buijs RM (2002) Central vasopressin systems and steroid hormones. Prog Brain Res 139: 57-73.
56. Martin SM, Malkinson TJ, Veale WL, Pittman QJ (1985) The action of centrally administered arginine vasopressin on blood pressure in the conscious rabbit. Brain Res 348: 137-145.
57. Milik E, Szczepanska-Sadowska E, Cudnoch-Jedrzejewska A, Dobruch J (2011) Down-regulation of V1a vasopressin receptors in the cerebellum after myocardial infarction. Neurosci Lett 499: 119-123.
58. Budzikowski AS, Paczwa P, SzczepaÅ„ska-Sadowska E (1996) Central V1 AVP receptors are involved in cardiovascular adaptation to hypovolemia in WKY but not in SHR. Am J Physiol 271: H1057-1064.
59. Koshimizu TA, Nasa Y, Tanoue A, Oikawa R, Kawahara Y, et al. (2006) V1a vasopressin receptors maintain normal blood pressure by regulating circulating blood volume and baroreflex sensitivity. Proc Natl Acad Sci U S A 103: 7807-7812.
60. Cudnoch-Jedrzejewska A, Dobruch J, Puchalska L, SzczepaÅ„ska-Sadowska E (2007) Interaction of AT1 receptors and V1a receptors-mediated effects in the central cardiovascular control during the post-infarct state. Regul Pept 142: 86-94.
61. Japund N (2013) Vasopressin and oxytocin in control of the cardiovascular system. Curr Neuropharmacol 11: 218-230.
62. Stojici S, Milutinovi-Smiljani S, Sarenac O, Milosavljevi S, Paton JF, et al. (2008) Blockade of central vasopressin receptors reduces the cardiovascular response to acute stress in freely moving rats. Neuropharmacology 54: 824-836.
63. Ivell R, Russell JA (1996) Oxytocin: cellular and molecular approaches in medicine and research. Rev Reprod 1: 13-18.
64. Zingg HH, Laporte SA (2003) The oxytocin receptor. Trends Endocrinol Metab 14: 222-227.
65. Akerlund M, Bossmar T, Brouard R, Kostrzewska A, Laudanski T, et al. (1999) Receptor binding of oxytocin and vasopressin antagonists and inhibitory effects on isolated myometrium from preterm and term pregnant women. Br J Obstet Gynaecol 106: 1047-1053.
66. Gimpl G, Reitz J, Brauer S, Trossen C (2008) Oxytocin receptors: ligand binding, signalling and cholesterol dependence. Prog Brain Res 170: 193-204.
67. Wsol A, Cudnoch-Jedrzejewska A, Szczepanska-Sadowska E, Kowalewski S, Dobruch J (2009) Central oxytocin modulation of acute-stress-induced cardiovascular responses after myocardial infarction in the rat. Stress 12: 517-525.
68. Wsol A, Szczepanska-Sadowska E, Kowalewski S, Puchalska L, Cudnoch-Jedrzejewska A (2014) Oxytocin differently regulates pressor responses to stress in WKY and SHR rats: the role of central oxytocin and V1a receptors. Stress 17: 117-125.
69. Petersson M, Alster P, Lundeberg T, Uvnäs-Moberg K (1996) Oxytocin causes a long-term decrease of blood pressure in female and male rats. Physiol Behav 60: 1311-1315.
70. Petersson M, Uvnäs-Moberg K (2007) Effects of an acute stressor on blood pressure and heart rate in rats pretreated with intracerebroventricular oxytocin injections. Psychoneuroendocrinology 32: 959-965.
71. Francis J, Weiss RM, Wie SG, Johnson AK, Beltz TG et al. (2001) Central mineralocorticoid receptor blockade improves volume regulation and reduces sympathetic drive in heart failure. Am J Physiol Heart Circ Physiol 281: H2241-2251.
72. Francis J, Chu Y, Johnson AK, Weiss RM, Felder RB (2004) Acute myocardial infarction induces hypothalamic cytokine synthesis. Am J Physiol Heart Circ Physiol 286: H2264-2271.
73. Liu H, Luiten PG, Eisel UL, Dejongste MJ, Schoemaker RG (2013) Depression after myocardial infarction: TNF-a-induced alterations of the blood-brain barrier and its putative therapeutic implications. Neurosci Biobehav Rev 37: 561-572.
74. Pitossi F, del Rey A, Kabiersch A, Besedovsky H (1997) Induction of cytokine transcripts in the central nervous system and pituitary following peripheral administration of endotoxin to mice. J Neurosci Res 48: 287-298.
75. Ufnal M, Dudek M, Zera T, Szczepanska-Sadowska E (2006) Centrally administered interleukin-1 beta sensitizes to the central pressor action of angiotensin II. Brain Res 1100: 64-72.
76. Zera T, Ufnal M, Szczepanska-Sadowska E (2008) Central TNF-alpha elevates blood pressure and sensitizes to central pressor action of angiotensin II in the infarcted rats. J Physiol Pharmacol 59 Suppl 8: 117-121.
77. Ufnal M, Sikora M, Szczepanska-Sadowska E (2008) Interleukin-1 receptor antagonist reduces the magnitude of the pressor response to acute stress. Neurosci Lett 448: 47-51.
78. Ufnal M, Sikora M (2011) The role of brain gaseous transmitters in the regulation of the circulatory system. Curr Pharm Biotechnol 12: 1322-1333.
79. Blumenthal JA (2011) New frontiers in cardiovascular behavioral medicine: comparative effectiveness of exercise and medication in treating depression. Cleve Clin J Med 78 Suppl 1: S35-43.

80. Grassi G, Mancia G (1999) Sympathetic overactivity and exercise intolerance in heart failure: a cause-effect relationship. Eur Heart J 20: 854-855.
81. Notarius CF, Ando S, Rongen GA, Floras JS (1999) Resting muscle sympathetic nerve activity and peak oxygen uptake in heart failure and normal subjects. Eur Heart J 20: 880-887.
82. Brandimarte F, Blair JE, Manuchehry A, Fedele F, Gheorghiade M (2008) Aldosterone receptor blockade in patients with left ventricular systolic dysfunction following acute myocardial infarction. Cardiol Clin 26: 91-105, vii.
83. Ma TK, Kam KK, Yan BP, Lam YY (2010) Renin-angiotensin-aldosterone system blockade for cardiovascular diseases: current status. Br J Pharmacol 160: 1273-1292.
84. Lipinski MJ, Escárcega RO1, D'Ascenzo F2, Magalhães MA1, Baker NC1, et al. (2014) A systematic review and collaborative meta-analysis to determine the incremental value of copeptin for rapid rule-out of acute myocardial infarction. Am J Cardiol 113: 1581-1591.
85. Chen Y, Fu L, Han Y, Teng Y, Sun J, et al. (2012) Testosterone replacement therapy promotes angiogenesis after acute myocardial infarction by enhancing expression of cytokines HIF-1a, SDF-1a and VEGF. Eur J Pharmacol 684: 116-124.
86. Cohn JN, Levine TB, Olivari MT, Garberg V, Lura D, et al. (1984) Plasma norepinephrine as a guide to prognosis in patients with chronic congestive heart failure. N Engl J Med 311: 819-823.
87. Felder RB (2010) Mineralocorticoid receptors, inflammation and sympathetic drive in a rat model of systolic heart failure. Exp Physiol 95: 19-25.
88. Zucker IH (2006) Novel mechanisms of sympathetic regulation in chronic heart failure. Hypertension 48: 1005-1011.
89. DiBona GF, Sawin LL (1994) Reflex regulation of renal nerve activity in cardiac failure. Am J Physiol 266: R27-39.
90. Gao L, Schultz HD, Patel KP, Zucker IH, Wang W (2005) Augmented input from cardiac sympathetic afferents inhibits baroreflex in rats with heart failure. Hypertension 45: 1173-1181.
91. Kaye DM, Lefkovits J, Jennings GL, Bergin P, Broughton A, et al. (1995) Adverse consequences of high sympathetic nervous activity in the failing human heart. J Am Coll Cardiol 26: 1257-1263.
92. Grassi G, Seravalle G, Giannattasio C, Saino A, Turri C, et al. (1999) Baroreflex and non-baroreflex modulation of vagal cardiac control after myocardial infarction. Am J Cardiol 84: 525-529.
93. Hirsch AT, Dzau VJ, Creager MA (1987) Baroreceptor function in congestive heart failure: effect on neurohumoral activation and regional vascular resistance. Circulation 75: IV36-48.
94. Szczepanska-Sadowska E (2013) Brain and cardiovascular diseases. Molecular aspects. In: Metabolic Syndrome and Neurological Disorders. Farooqui T and. Farooqui AA (eds) Wiley-Blackwell: 439-460.
95. Wang WZ, Gao L, Wang HJ, Zucker IH, Wang W (2009) Tonic glutamatergic input in the rostral ventrolateral medulla is increased in rats with chronic heart failure. Hypertension 53: 370-374.
96. Wang RJ, Zeng QH, Wang WZ, Wang W (2009) GABA(A) and GABA(B) receptor-mediated inhibition of sympathetic outflow in the paraventricular nucleus is blunted in chronic heart failure. Clin Exp Pharmacol Physiol 36: 516-522.
97. Tan J, Wang H, Leenen FH (2004) Increases in brain and cardiac AT1 receptor and ACE densities after myocardial infarct in rats. Am J Physiol Heart Circ Physiol 286: H1665-1671.
98. Gao L, Li Y, Schultz HD, Wang WZ, Wang W, et al. (2010) Downregulated Kv4.3 expression in the RVLM as a potential mechanism for sympathoexcitation in rats with chronic heart failure. Am J Physiol Heart Circ Physiol 298: H945-955.
99. Mitra AK, Gao L, Zucker IH (2010) Angiotensin II-induced upregulation of AT(1) receptor expression: sequential activation of NF-kappaB and Elk-1 in neurons. Am J Physiol Cell Physiol 299: C561-569.
100. Felder RB1, Yu Y, Zhang ZH, Wei SG (2009) Pharmacological treatment for heart failure: a view from the brain. Clin Pharmacol Ther 86: 216-220.
101. Muders F, Riegger GA, Bahner U, Palkovits M (2002) The central vasopressinergic system in experimental left ventricular hypertrophy and dysfunction. Prog Brain Res 139: 275-279.
102. Muders F, Elsner D, Schunkert H, Riegger GA, Palkovits M (1999) Central vasopressin is modulated by chronic blockade of the renin-angiotensin system in experimental left ventricular hypertrophy. Am J Hypertens 12: 311-314.
103. Sivukhina EV, Lu E, Dolzhikov AA, Jirikowski GF, Grinevich V (2010) Comparison of vasopressin and oxytocin expressions in the hypothalamo-neurohypophysial system of patients with chronic heart failure. Horm Metab Res 42: 56-60.
104. Kang YM, He RL, Yang LM, Qin DN, Guggilam A et al. (2009) Brain tumour necrosis factor-alpha modulates neurotransmitters in hypothalamic paraventricular nucleus in heart failure. Cardiovasc Res 83: 737-746.
105. Kang YM, Wang Y, Yang LM, Elks C, Cardinale J, et al. (2010) TNF-Î± in hypothalamic paraventricular nucleus contributes to sympathoexcitation in heart failure by modulating AT1 receptor and neurotransmitters. Tohoku J Exp Med 222: 251-263.
106. Dimsdale JE (2008) Psychological stress and cardiovascular disease. J Am Coll Cardiol 51: 1237-1246.
107. May HT, Horne BD, Carlquist JF, Sheng X, Joy E, et al. (2009) Depression after coronary artery disease is associated with heart failure. J Am Coll Cardiol 53: 1440-1447.
108. Davidson KW, Bigger JT, Burg MM, Carney RM, Chaplin WF, et al. (2013) Centralized, Stepped, Patient Preference-Based Treatment for Patients with Post-Acute Coronary Syndrome Depression: CODIACS Vanguard Randomized Controlled Trial. JAMA Intern Med 173: 997-1004.
109. de Jonge P, Rosmalen JG, Kema IP, Doornbos B, van Melle JP, et al. (2010) Psychophysiological biomarkers explaining the association between depression and prognosis in coronary artery patients: a critical review of the literature. Neurosci Biobehav Rev 35: 84-90.
110. Gottlieb SS, Khatta M, Friedmann E, Einbinder L, Katzen S, et al. (2004) The influence of age, gender, and race on the prevalence of depression in heart failure patients. J Am Coll Cardiol 43: 1542-1549.
111. Grippo AJ, Johnson AK (2009) Stress, depression and cardiovascular dysregulation: a review of neurobiological mechanisms and the integration of research from preclinical disease models. Stress 12: 1-21.
112. Rutledge T, Reis VA, Linke SE, Greenberg BH, Mills PJ (2006) Depression in heart failure a meta-analytic review of prevalence, intervention effects, and associations with clinical outcomes. J Am Coll Cardiol 48: 1527-1537.
113. van Melle JP, de Jonge P, Ormel J, Crijns HJ, van Veldhuisen DJ, et al. (2005) Relationship between left ventricular dysfunction and depression following myocardial infarction: data from the MIND-IT. Eur Heart J 26: 2650-2656.
114. Denollet J, Conraads VM (2011) Type D personality and vulnerability to adverse outcomes in heart disease. Cleve Clin J Med 78 Suppl 1: S13-19.
115. van den Broek KC, Nyklícek I, van der Voort PH, Alings M, Meijer A, et al. (2009) Risk of ventricular arrhythmia after implantable defibrillator treatment in anxious type D patients. J Am Coll Cardiol 54: 531-537.
116. Whooley MA, de Jonge P, Vittinghoff E, Otte C, Moos R, et al. (2008) Depressive symptoms, health behaviors, and risk of cardiovascular events in patients with coronary heart disease. JAMA 300: 2379-2388.
117. Davydov DM, Shapiro D, Cook IA, Goldstein I (2007) Baroreflex mechanisms in major depression. Prog Neuropsychopharmacol Biol Psychiatry 31: 164-177.
118. Carnevali L, Mastorci F, Audero E, Graiani G, Rossi S, et al. (2012) Stress-induced susceptibility to sudden cardiac death in mice with altered serotonin homeostasis. PLoS One 7: e41184.
119. Pattij T, Groenink L, Oosting RS, van der Gugten J, Maes RA, et al. (2002) GABA(A)-benzodiazepine receptor complex sensitivity in 5-HT(1A) receptor knockout mice on a 129/Sv background. Eur J Pharmacol 447: 67-74.

120. Saavedra JM, Benicky J (2007) Brain and peripheral angiotensin II play a major role in stress. Stress 10: 185-193.
121. Saavedra JM, Sanchez-Lemus E, Benicky J (2011) Blockade of brain angiotensin II AT1 receptors ameliorates stress, anxiety, brain inflammation and ischemia: therapeutic implications. Psychoneuroendocrinology 36: 1-18.
122. Pavel J, Benicky J, Murakami Y, Sanchez-Lemus E, Saavedra JM (2008) Peripherally administered angiotensin II AT1 receptor antagonists are anti-stress compounds in vivo. Ann N Y Acad Sci 1148: 360-366.
123. Zhang W, Huang BS, Leenen FH (1999) Brain renin-angiotensin system and sympathetic hyperactivity in rats after myocardial infarction. Am J Physiol 276: H1608-1615.
124. Mayorov DN, Head GA (2003) AT1 receptors in the RVLM mediate pressor responses to emotional stress in rabbits. Hypertension 41: 1168-1173.
125. Mayorov DN (2007) Brain superoxide as a key regulator of the cardiovascular response to emotional stress in rabbits. Exp Physiol 92: 471-479.
126. Mayorov DN, Head GA, De Matteo R (2004) Tempol attenuates excitatory actions of angiotensin II in the rostral ventrolateral medulla during emotional stress. Hypertension 44: 101-106.
127. Aguilera G, Subburaju S, Young S, Chen J (2008) The parvocellular vasopressinergic system and responsiveness of the hypothalamic pituitary adrenal axis during chronic stress. Prog Brain Res 170: 29-39.
128. Bao AM, Meynen G, Swaab DF (2008) The stress system in depression and neurodegeneration: focus on the human hypothalamus. Brain Res Rev 57: 531-553.
129. Frank E, Landgraf R (2008) The vasopressin system--from antidiuresis to psychopathology. Eur J Pharmacol 583: 226-242.
130. Landgraf R, Kessler MS, Bunck M, Murgatroyd C, Spengler D, et al. (2007) Candidate genes of anxiety-related behavior in HAB/LAB rats and mice: focus on vasopressin and glyoxalase-I. Neurosci Biobehav Rev 31: 89-102.
131. Lolait SJ, Stewart LQ, Jessop DS, Young WS 3rd, O'Carroll AM (2007) The hypothalamic-pituitary-adrenal axis response to stress in mice lacking functional vasopressin V1b receptors. Endocrinology 148: 849-856.
132. Surget A, Belzung C (2008) Involvement of vasopressin in affective disorders. Eur J Pharmacol 583: 340-349.
133. Bielsky IF, Hu SB, Szegda KL, Westphal H, Young LJ (2004) Profound impairment in social recognition and reduction in anxiety-like behavior in vasopressin V1a receptor knockout mice. Neuropsychopharmacology 29: 483-493.
134. Murgatroyd C, Patchev AV, Wu Y, Micale V, Bockmühl Y, et al. (2009) Dynamic DNA methylation programs persistent adverse effects of early-life stress. Nat Neurosci 12: 1559-1566.
135. Sanders BJ, Anticevic A (2007) Maternal separation enhances neuronal activation and cardiovascular responses to acute stress in borderline hypertensive rats. Behav Brain Res 183: 25-30.
136. Krolewski DM, Mediana A, Kerman IA, Bernard R, Burke S, et al. (2010) Expression patterns of corticotropin-releasing factor, arginine vasopressin, histidine decarboxylase, melanin-concentrating hormone, and orexin genes in the human hypothalamus. J Comp Neurol 518: 4591-4611.
137. Hashimoto K, Makino S, Asaba K, Nishiyama M (2001) Physiological roles of corticotropin-releasing hormone receptor type 2. Endocr J 48: 1-9.
138. Holsboer F, Ising M (2008) Central CRH system in depression and anxiety--evidence from clinical studies with CRH1 receptor antagonists. Eur J Pharmacol 583: 350-357.
139. Al-Barazanji KA, Wilson S, Baker J, Jessop DS, Harbuz MS (2001) Central orexin-A activates hypothalamic-pituitary-adrenal axis and stimulates hypothalamic corticotropin releasing factor and arginine vasopressin neurones in conscious rats. J Neuroendocrinol 13: 421-424.
140. Li A, Nattie E (2014) Orexin, cardio-respiratory function, and hypertension. Front Neurosci 8: 22.
141. Shahid IZ, Rahman AA, Pilowsky PM (2012) Orexin A in rat rostral ventrolateral medulla is pressor, sympatho-excitatory, increases barosensitivity and attenuates the somato-sympathetic reflex. Br J Pharmacol 165: 2292-2303.
142. Kayaba Y, Nakamura A, Kasuya Y, Ohuchi T, Yanagisawa M, et al. (2003) Attenuated defense response and low basal blood pressure in orexin knockout mice. Am J Physiol Regul Integr Comp Physiol 285: R581-593.