

Review article

E. SZCZEPANSKA-SADOWSKA, A. CUDNOCH-JEDRZEJEWSKA, M. UFNAL, T. ZERA

BRAIN AND CARDIOVASCULAR DISEASES: COMMON NEUROGENIC BACKGROUND OF CARDIOVASCULAR, METABOLIC AND INFLAMMATORY DISEASES

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

In spite of significant progress in pharmacotherapy the incidence of newly diagnosed cases of cardiovascular diseases and cardiovascular morbidity is alarmingly high. Treatment of hypertension or heart failure still remains a serious challenge. Continuous attempts are made to identify the mechanisms that decide about susceptibility to pathogenic factors, and to determine effectiveness of a specific therapeutic approach. Coincidence of cardiovascular diseases with metabolic disorders and obesity has initiated intensive research for their common background. In the recent years increasing attention has been drawn to disproportionately greater number of depressive disorders and susceptibility to stress in patients with coronary artery disease. An opposite relationship, *i.e.* a greater number of sudden cardiovascular complications in patients with depression, has been also postulated. Progress in functional neuroanatomy and neurochemistry provided new information about the neural network responsible for regulation of cardiovascular functions, metabolism and emotionality in health and under pathological conditions. In this review we will focus on the role of neuromodulators and neurotransmitters engaged in regulation of the cardiovascular system, neuroendocrine and metabolic functions in health and in pathogenesis of cardiovascular diseases and obesity. Among them are classical neurotransmitters (epinephrine and norepinephrine, serotonin, GABA), classical (CRH, vasopressin, neuropeptide Y) and newly discovered (orexins, apelin, leptin IL-1beta, TNF-alpha, ghrelin) neuropeptides, gasotransmitters, eicozanoids, endocannabinoids, and some other compounds involved in regulation of neuroendocrine, sympatho-adrenal and parasympathetic nervous systems. Special attention is drawn to those factors which play a role in immunology and inflammatory processes. Interaction between various neurotransmitter/neuromodulatory systems which may be involved in integration of metabolic and cardiovascular functions is analyzed. The survey gives evidence for significant disturbances in release or action of the same mediators in hypertension heart failure, obesity, diabetes mellitus, metabolic syndrome, starvation, chronic stress, depression and other psychiatric disorders. With regard to the pathogenic background of the cardiovascular diseases especially valuable are the studies showing inappropriate function of angiotensin peptides, vasopressin, CRH, apelin, cytokines and orexins in chronic stress, cardiovascular and metabolic diseases. The studies surveyed in this review suggest that multiple brain mechanisms interact together sharing the same neural circuits responsible for adjustment of function of the cardiovascular system and metabolism to current needs.

Key words: *angiotensin, apelin, cardiovascular diseases, cytokines, endocannabinoids, gasotransmitters, neuropeptides, orexin, vasopressin*

INTRODUCTION

Recent progress in experimental and clinical physiology brought an impressive increase in knowledge of the molecular processes underlying function of cells and regulatory systems of the living organisms. At the same time, it became increasingly evident that several factors, originally thought to affect one class of cells or exert one type of regulatory action, may in fact exert pluripotent effects on distant organs of the body. Research into interaction of different regulatory mechanisms markedly improved understanding of many vital physiological processes and the reasons of frequent therapeutic failures in patients suffering from two or more diseases. The purpose of the present review is to highlight some common neurogenic mechanisms that may be affected in the cardiovascular, metabolic, inflammatory and affective diseases. For detailed information

regarding particular disorders we refer to other reviews and experimental studies.

FUNCTIONAL NEUROANATOMY

Network related to cardiovascular neurons

For decades it was thought that the neural command to the cardiovascular system originates in the cardiovascular neurons of the brain stem. Discovery of the first synapses for the baroreceptor and chemoreceptor reflexes in nucleus of the solitary tract (NTS) reinforced this belief. During last fifty years multiple neuroanatomical, neurochemical and neuroimmunocytological studies revealed that the neurons responding to changes in blood pressure or heart rate form an extensive and complex network

extending from the cerebral cortex to the spinal cord (1-21). Analysis of afferent and efferent connections between the particular groups of the cardiovascular neurons revealed that they receive continuous information about the external and internal environments by means of variety of receptors (visual, olfactory, auditory, tactile, pain, and cardiovascular, respiratory, renal, digestive and kinetosensory) (1, 22). Activity of the cardiovascular neurons is also affected by impulses generated in the brain structures engaged in the control of conscious and subconscious behavior, emotional and motivated activity. Among them are the motor, medial prefrontal, anterior cingular and insular cortex, and several other regions located in the forebrain, midbrain, medulla oblongata, and the circumventricular organs (*Fig. 1*) (1, 5-7, 11, 14, 21, 23-27). Importantly, individual parts of the heart or vascular beds were found to be innervated by topographically arranged groups of neurons (5, 28-30). Several shortcut connections through the presympathetic or parasympathetic pathways allow for rapid adjustment of the cardiovascular system to the changing environment (5, 7). Integration of those multiple inputs allows for adjustment of blood flow to requirements (energy supply, metabolites removal) of particular organs and the whole body.

Activity of the neuronal network controlling the cardiovascular system is regulated by classical neurotransmitters, neuropeptides, gasotransmitters and purines (31-40). The regulatory effect of neurotransmitter/neuromodulator depends on place of its release and availability of specific receptors. Thus, each regulatory factor may exert either stimulatory or inhibitory effect, depending on the particular place of release.

Network related to energy balance and metabolism

Alarming growth prevalence of obesity stimulated intensive research on its causes, comorbidities, and methods of prevention and treatment. Early models of caloric homeostasis have focused on stimulation and inhibition of food intake by signals arising in digestive system and on the unique role of glucose, which is the main substrate for neurons in regulation of food intake (18, 41, 42). At present it has been well established that regulation of food intake is closely linked to the regulation of energy stores and that the central nervous system plays a primary role in coordination of food intake with regulation of metabolism by the autonomic nervous system and neuroendocrine factors (43-49).

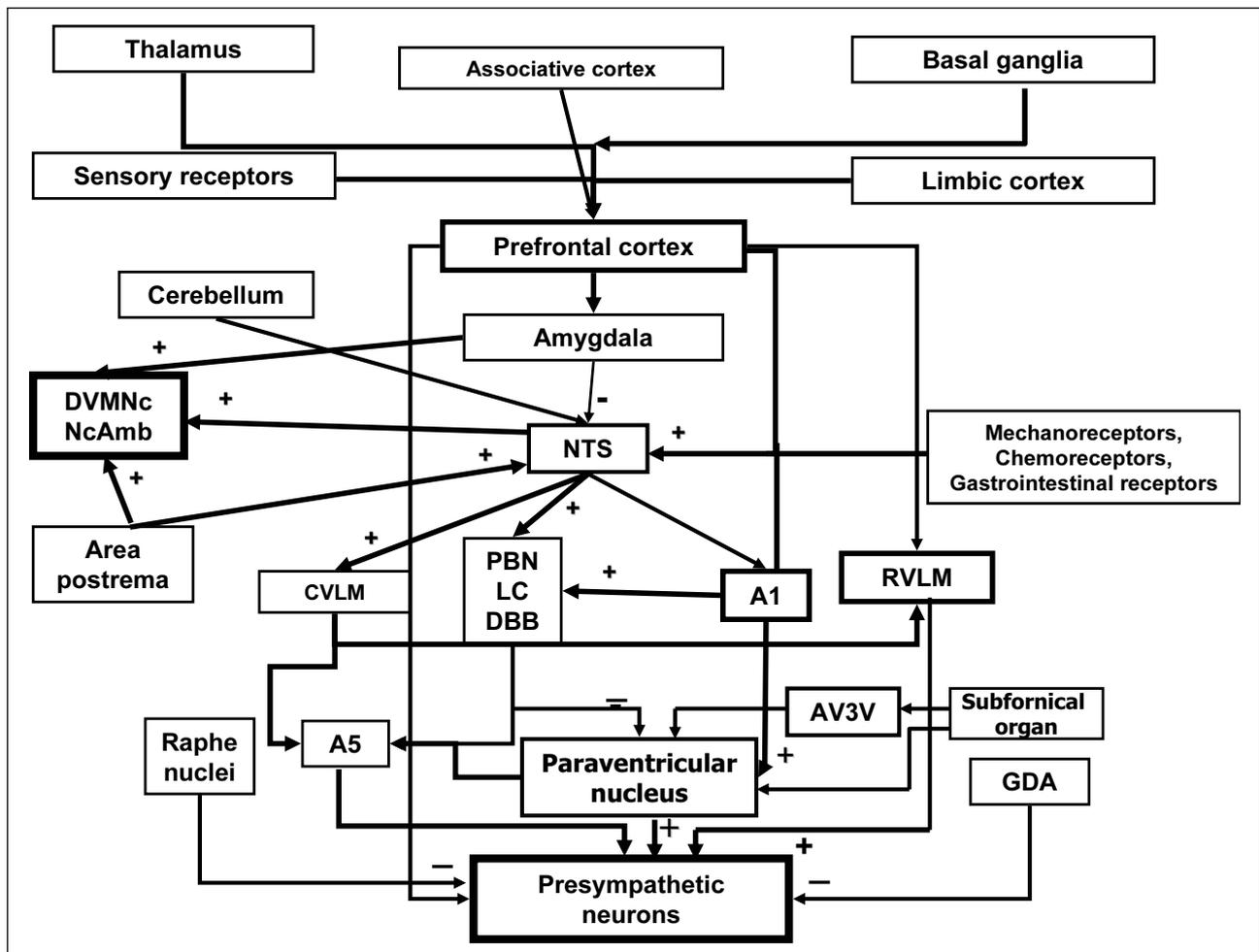


Fig. 1. Main structures in the brain involved in the regulation of the cardiovascular system. A1, A5 - noradrenergic regions, AV3V - anteroventral 3rd ventricle region, CVLM - caudal ventrolateral medulla, DBB - diagonal band of Broca, DVMNc - dorsal motor nucleus of the vagus, GDA - gigantocellular depressive area, LC - locus coeruleus, NTS - nucleus of the solitary tract, PBN - parabrachial nucleus, RVLM - rostral ventrolateral medulla.

Modified from Szczepanska-Sadowska E, Stanislaw Kowalewski "Organization of the brain and spinal cord neurons involved in the regulation of the cardiac work and blood pressure", In: Nervous System and Diseases of the Cardiovascular System, E Szczepanska-Sadowska, W Ruzyllo, W Januszewicz, A Januszewicz. Medycyna Praktyczna, Cracow 2009 (in Polish).

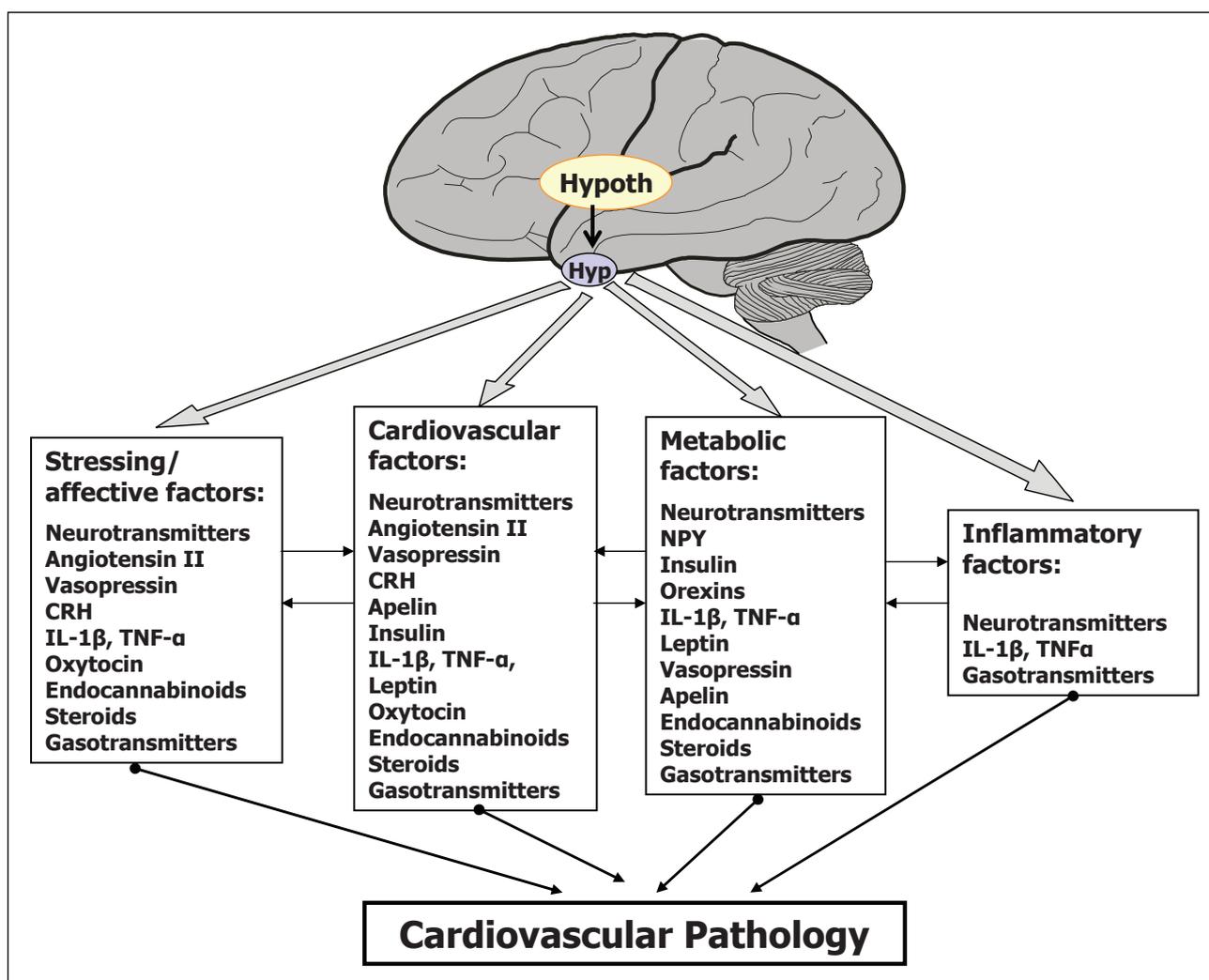


Fig. 2. Main factors contributing to the neurogenic regulation of the cardiovascular system, metabolism, inflammatory processes and affective disorders and their mutual interaction. It is proposed that the cardiovascular pathology starts when the production of these factors in the brain exceeds the critical point. See text for further explanations. Hyp - hypophysis, Hypoth - hypothalamus, IL - interleukin, TNF - tumor necrosis factor.

Main groups of neurons involved in regulation of energy stores are located in the paraventricular, ventromedial, arcuate and suprachiasmatic nuclei of the hypothalamus, and in the lateral hypothalamic area, septum, amygdala, NTS and area postrema (41-43). Recent studies employing electrical neuroimaging, functional magnetic resonance, single photon emission computed tomography (SPECT) and positron emission tomography (PET) revealed engagement of prefrontal, orbito-frontal, visual association, and occipital cortex as well as some subcortical structures (subcortical rewarding system, amygdala) in the evaluation of rewarding and energetic value of food (48). Transmission of signals between the groups of neurons regulating food intake and metabolism is executed by the classical neurotransmitters (serotonin, norepinephrine, histamine, glutamate, GABA, dopamine), neuropeptides, and gasotransmitters. Several regulatory factors are synthesized in peripheral organs, and in particular in the gastrointestinal system, liver, pancreas, and in the adipose tissue (41, 43, 45-47, 49, 50).

Network related to stress and depression

Growing number of evidence indicates that chronic stress, depression and anxiety disorders should be placed on the list of

the cardiac risk factors (51). Chronic stress and depression are also frequently associated with obesity (52, 53).

In the early studies investigators were mainly interested in the behavioural and neuroendocrine aspects of stress. It has been shown that stressing stimuli of different modalities activate neurons of the sympatho-adrenal, and hypothalamic-pituitary-axis (54). Later studies provided evidence that the neuroendocrine responses are under control of classical neurotransmitters/neuromodulators released by the neurons projecting from the forebrain, midbrain and brainstem, including the paraventricular and dorsomedial nuclei of the hypothalamus, periaqueductal gray, raphe pallidus, rostroventral and caudal portions of the lateral medulla, and the nucleus of the solitary tract (26, 54-61). In many instances neurones activated during stress are located in the cardiovascular regions. Chronic stressing frequently causes symptoms of depression, weight gain, excessive accumulation of visceral fat deposits, and sodium retention (52, 62-67). In patients suffering from depression PET and SPECT as well as *post mortem* examination frequently revealed presence of metabolic abnormalities or damage in the paraventricular nucleus and the prefrontal cortex - the structures engaged in the neuroendocrine and cardiovascular control, regulation of mood and analysis of the

rewarding value of the food (68, 69). Among classical neurotransmitters involved in the neuroendocrine and behavioral responses to stress are serotonin, catecholamines, dopamine, histamine, GABA and several neuropeptides that are currently investigated for their involvement in regulation of mood, behaviour and food intake (see below). Several studies implicate the anxiogenic role for CRHR1, vasopressin V1b, angiotensin II AT1 and IL- β receptors and the anxiolytic role for oxytocin (70, 10, 71-76).

EFFECTORS OF THE CARDIOVASCULAR AND METABOLIC REGULATION

Cardiovascular factors

As shown in the first part of the present survey function of the cardiovascular system is regulated by the sympathetic and parasympathetic divisions of the autonomic nervous system which are under direct and indirect control of multiple groups of the cardiovascular neurons located in several structures of the brain (Fig. 1). The cardiovascular neurons directly contacting with the preganglionic sympathetic neurons are called the presympathetic neurons (5-7). Prevailing number of these neurons are located in the rostral ventrolateral medulla (RVLM), nucleus paragigantocellularis, caudal raphe nuclei, the pontine A5 noradrenergic area of the pons and the paraventricular nucleus (PVN). Significant influence on activity of the preganglionic sympathetic neurons is also exerted by the signals from the noradrenergic A6 neurones of the locus coeruleus. The parasympathetic preganglionic neurons have been identified in the dorsal motor nucleus of the vagus (DMV), the nucleus ambiguus (AMB) and in the small groups of neurons scattered between DMV and AMB (5-7, 8, 9, 11, 14-16, 18-21, 77). Parallel and in cooperation with the autonomic system acts the hypothalamo-pituitary neuroendocrine system which produces and releases hormones regulating blood pressure, metabolism, water electrolyte balance, behavior and immunological responses to stress. At present it appears that activity of both these systems is strongly affected by impulses arising in multiple groups of neurons. The paraventricular nucleus of the brain, which is the source of a large number of the presympathetic neurones, and at the same time the place of synthesis of vasopressin, oxytocin, and the hypothalamo-pituitary releasing and inhibiting hormones is profusely innervated by the ascending and descending fibers from several regions of the central nervous system (5, 11, 77). Beside, it synthesizes a number of neurotransmitters/neuropeptides which regulate activity of the cardiovascular neurones and may affect blood pressure and/or heart rate.

Among the neuroactive substances that have been found to have impact on the cardiovascular system through action in the central nervous system are classical neurotransmitters: (acetylcholine, norepinephrine, epinephrine, dopamine, serotonin, and histamine), neuropeptides (vasopressin, angiotensins II, III, IV and 1-7, CRH, TRH, oxytocin, neuropeptide Y, leptin, natriuretic peptides, endothelins, orexins, apelin, IL-1 β , TNF- α), steroids (mineralo- and corticosteroids, estrogens, testosterone), purines, gasotransmitters (NO, SH2) and inhibitors of ATPase (12, 15, 18, 29, 36-40, 77-89). The effect of classical neurotransmitters is usually short-lasting and may be either stimulatory or inhibitory depending on the type of specific neurons and receptors and the place of their location (presynaptic or postsynaptic). Therefore their effects in different regions of the brain may be opposite, *i. e.* they may cause either a decrease or an increase in blood pressure. Effects exerted by neuropeptides

and steroids last usually longer which is related to slower rate of their metabolism and different mode of intracellular action, involving transcription-translation processes. At present, it appears that under pathological conditions neuropeptides and steroids may significantly contribute to long-lasting tuning and restructuring of the cardiovascular network. Among large group of neuroactive factors which were found to affect the cardiovascular regulation the particular attention should be given to vasopressin, angiotensin II, orexins, apelin, leptin, endocannabinoids, neuropeptide Y, IL-1 β , TNF α , because of their likely involvement in the regulation of metabolism and/or inflammatory processes, and their relevance to stress and depression.

Vasopressinergic neurons of the paraventricular nucleus innervate several regions of the brain housing the cardiovascular neurons (90). Possible involvement of vasopressin in centrally mediated regulation of blood pressure was demonstrated as early as in 1931 by Cushing who injected posterior pituitary extract to the cerebral ventricle (91). After thirty years the central pressor effect of synthetic vasopressin was proved by Pittman and collaborators (92) and subsequently confirmed in several other studies (79, 80, 82, 83, 86, 88, 93-95). Overactivation of the vasopressinergic system in the brain and altered expression of vasopressin receptors were found in several studies performed on animal models of the cardiovascular hypertension such as the spontaneous hypertension (SHR), DOCA-dependent hypertension, renin transgenic hypertension TGRmRen(2) and renovascular hypertension (85, 86, 94 96-98). Central pressor effect of vasopressin in the brain of the hypertensive animals is partly counteracted by hypotensive effects of atrial natriuretic peptide and nitric oxide (85, 99).

More recently enhanced stimulation of the pressor component of the brain vasopressinergic system was found in the post-infarct cardiac failure and in the left ventricular hypertrophy induced by aortic constriction (79, 80, 100, 101). It has been shown in these studies that after cerebroventricular administration of V1 receptor antagonist resting blood pressure is significantly reduced in the infarcted rats but not in their sham-operated counterparts (79, 80, 100).

Growing evidence indicates that vasopressin is among key factors involved in the regulation of cardiovascular responses to stress. It is now well established that the main structures engaged in emotional aspects and mobilization of responses to stress receive extensive vasopressinergic innervation (102, 103). Moreover, it has been found that release of vasopressin in the brain is enhanced in the rats manifesting exaggerated aggressiveness or anxiety (103). Recently, it has been shown that centrally released vasopressin plays also a significant role in the regulation of the pressor responses to stress (38, 80, 100, 104).

Accordingly, significant elevation of the pressor and tachycardic responses to alarming stress was found in the post-infarct cardiac failure (79, 80) and in chronic stress (100). Closely related to vasopressin by some common regulatory mechanisms and the site of synthesis and release is another hypophysial-neurohypophysial hormone - oxytocin. Our recent studies and some unpublished data indicate that with regard to regulation of the cardiovascular responses to stress oxytocin plays the opposite role to vasopressin, *i. e.* it reduces the cardioacceleration and the pressor responses to stress. Interestingly, these effects of oxytocin are abolished in the rats with the post-infarct heart failure (105) and even reversed in SHR rats (Wsol *et al.*, unpublished).

The important role of angiotensin peptides in the central cardiovascular regulation of the cardiovascular system, and the presence of all components of the renin-angiotensin system and their receptors in the brain, and in particular in the structures involved in the regulation of the cardiovascular system have

been shown in many investigations (38, 40, 94, 106-108). Angiotensin II (Ang II) receptors AT₁R may be stimulated by Ang II which is either released from the neurons of the brain renin-angiotensin system or penetrates from the systemic circulation and acts on neurons of the circumventricular organs (94, 108, 109). Angiotensin II and angiotensin IV have been repeatedly shown to exert pressor effect after central administration by means of AT₁ (AT₁R) receptors (82, 94, 108, 110). Several studies provided evidence that excessive stimulation of AT₁R significantly contributes to development of various forms of hypertension (86, 111-115). Overstimulation of the brain AT₁R was also found in the rats with the postinfarct cardiac failure (79, 116-120). In our laboratory we have shown that vasopressin and angiotensin II closely interact in central regulation of resting blood pressure and cardiovascular responses to stress (75, 79, 82, 86). Namely, we found that the central pressor effect of angiotensin is markedly reduced or even abolished when the peptide is administered together with V₁ receptors antagonist. Moreover, in the infarcted rats the hypotensive effect of centrally applied AT₁ antagonist could not be further intensified by concomitant blockade of central V₁ receptors (79, 82, 86).

Orexins A (hypocretin-1) and B (hypocretin-2), and apelin are newly discovered neuropeptides synthesized in the brain and in the peripheral tissues. Originally they were thought to be involved exclusively in the regulation of food intake and metabolism (see below). Recently it has become evident that they may also play essential role in regulation of blood pressure. In the brain orexins and their receptors are synthesized mainly in the dorsal and ventromedial (VMN) parts of the hypothalamus. Neural projections from PVN innervate NTS and RVLM. Orexin receptors OX₁R have been found mainly in the ventromedial nucleus of the hypothalamus (VMN), while OX₂R in PVN. Administration of orexins into the cerebral ventricles, NTS or RVLM elicits long lasting pressor responses associated with strong stimulation of the renal sympathetic fibers (33, 121-126). However, bradycardia was observed when orexin A was injected directly into the nucleus ambiguus of the vagus. The effect was related to inhibition of the sympathetic system (127). Thus, the central pressor effect of orexins may be somehow restrained by its local effect in the nucleus ambiguus.

Apelin is a recently discovered novel endogenous ligand of APJ receptor (128, 129). Similarly, as orexin apelin is synthesized in several systemic organs and is also present in the central nervous system. The apelinergic system is well represented in the brain medulla and hypothalamus, and especially in the paraventricular and supraoptic nuclei. Apelin was found to stimulate neurons in the supraoptic nucleus and to cause release of vasopressin (130). It also enhances release of CRH, ACTH and corticosterone (131). Thus far, the studies aimed at determining the role of the brain apelin in regulation of blood pressure have brought contradictory results. Reaux *et al.* (132) were not able to demonstrate significant changes in blood pressure while other authors reported that intracerebroventricular injection of apelin or its topical application on NTS and RVLM causes significant increase of blood pressure (133, 134). It has been reported that in RVLM of SHR rats the expression of apelin mRNA and protein is elevated. Furthermore, the microinjection of apelin into RVLM causes elevation in blood pressure and enhances the sympathetic activity (135).

Metabolic and neuroendocrine factors

Obesity, atherosclerosis and diabetes mellitus have been placed on the list of the risk factors for cardiovascular pathology, such as cerebrovascular, coronary and peripheral vessels diseases. For a long time it was thought that frequent coexistence of metabolic and cardiovascular pathology results exclusively

from formation of the atherosclerotic plaque in a vascular wall and inadequate perfusion of the tissue. At present it is known that metabolism and function of the cardiovascular system are interconnected by the several neurogenic and neuroendocrine mechanisms. Among them are signals from the mechanoreceptors and chemical sensors of the gastrointestinal tract and liver, and from the visual and olfactory receptors. Jointly, they provide information about the amount, composition and attractiveness of food. The information is also provided by the pancreatic and gastrointestinal hormones. Independently from that food intake is also under control of the neural structures responsible for emotions and motivation. Integration of all these signals determines activity of the efferent vagal and sympathetic fibers and release of the gastrointestinal and pancreatic hormones responsible for digestion and metabolism (41, 49, 136-138). In addition, stimulation of the vagal efferents causes release of insulin, glucagon, and some of the gastrointestinal hormones while activation of the sympathetic fibers results in secretion of glucagon (*via* α receptors), insulin (*via* β receptors), epinephrine, cortisol, and the gastrointestinal hormones (41, 44, 46, 139). It is suggested that in some instances excessive release of norepinephrine from the sympathetic fibers may result in simultaneous secretion of glucagon and insulin; the final result being hyperglycemia. Such pathological triad is characteristic for the syndrome called "hyperinsulinism" (137). Several regulatory peptides released in the wall of the gastrointestinal system and in the pancreas are also produced locally in the brain and regulate appetite and satiation whereas some other (insulin, leptin, ghrelin) are synthesized in the peripheral cells and transported to the brain by specific carriers (44, 139). The adipose tissue is another abundant source of highly active substances regulating food intake, metabolism and blood pressure. Among them are leptin, resistin, visfatin, omentin, chemerin and some cytokines (45, 47, 140).

Several factors controlling food intake are also involved in regulation of metabolism (leptin, orexin/hypocretin, ghrelin, insulin, CRH, glucocorticoids, norepinephrine, serotonin), and blood pressure (leptin, IL-1 β , TNF α , apelin, orexin, GLP-1, ghrelin) (141-143). Studies on leptin-deficient *ob/ob* mice revealed that leptin is necessary for normal expression of several hypothalamic genes regulating food intake and metabolism.

Recently, apelin, vasopressin and endocannabinoids were placed on the list of peptides regulating both blood pressure and food intake. Apelin and its receptor APJ are synthesized in the PVN and SON in the hypothalamus and in RVLM in the brain stem. According to some studies, apelin increases food intake and sensitivity to insulin and causes hyperinsulinemia (144, 145). Intraperitoneal injection of apelin was found to enhance expression of *c-fos* in the hypothalamic and brain stem nuclei involved in regulation of food intake, blood pressure, rewarding behavior and body fluid balance (146). Interestingly, in obese rats on normal diet centrally applied apelin maintained decreased food ingestion but it was not effective in the rats receiving high fat diet (147). Because, in the latter group administration of apelin resulted in the reduction of APJ receptors in the hypothalamus, it was possible that down-regulation of these receptors could account for ineffectiveness of apelin in inhibition of food intake in the rats receiving the high fat diet. Altered regulation of systemic apelin secretion, and APJ receptors expression were reported in morbidly obese subjects with type 2 diabetes mellitus (144). Recently, stimulatory effect of apelin on angiogenesis in the adipose tissue was described and it was postulated that it may contribute to the adipogenic action of apelin (148). Apelin interacts with some hormones regulating blood pressure (see above). For instance, it has been shown that it influences activity of vasopressinergic neurons and systemic release of AVP (130). Its interaction with the angiotensin system,

and specifically with ACE2 converting enzyme has been also proposed (149).

With regard to the putative role of vasopressin in regulation of food intake and energy metabolism it has been suggested that AVP may play an important role in triggering carbohydrate appetite and stress-induced feeding (150, 151). The authors proposed that effect of AVP on food intake may be closely related to its role in mobilization of endogenous carbohydrates. Growing number of studies indicate that vasopressin contributes to the regulation of metabolism of carbohydrates by direct glycogenolytic effect in the liver, which is one of the organs possessing V1a receptors (152). Beside, by means of V1b receptors in the pituitary vasopressin stimulates ACTH-glucocorticoids axis and may indirectly influence metabolism by means of corticosteroids. Concentration of vasopressin is elevated in patients with diabetes mellitus and can be normalized after treatment with insulin (153, 154). However formerly it was thought that hypervasopressinemia in the uncontrolled diabetes mellitus is a result of dehydration. Recent studies on the mouse with knock out of V1a or V1b receptors indicate that deficiency of V1a receptors results in enhanced metabolism of fat and greater production of glucose by the liver. This is associated with diminished glycogen content in the liver, and glucose intolerance of glucose during the hyperinsulinemic-euglycemic clamp test. In contrast deficiency of V1b receptor in mouse fed with high fat diet elicited hypoglycemia and hypoinsulinemia. Combined removal of both types of receptors resulted in comparable glucose intolerance as the selective deficiency of V1a receptors (155, 156). In human subjects significant differences in the resting blood pressure and body mass index were found between the male carriers of CC and TT single nucleotide polymorphisms 10426 15 of V1a receptor gene. The carriers of the rs10426 15 T allele manifested glucose intolerance. There was also increased prevalence of diabetes in subjects on high fat diet or who were overweight. In general, the symptoms were similar to those found in the mouse with V1a receptor deficiency (157).

The endocannabinoid system, comprising endogenous agonists (anandamide *i.e.* 2-arachidonoylglycerol) and their CB1 receptors is present both in the central nervous system (the hypothalamus, limbic forebrain, brain stem) and peripheral tissues. Growing evidence reveals its relevance to stimulation of food intake, dyslipidemia and decreased energy expenditure. It appears that it may play an important role in development of obesity, insulin resistance and fat storage in the liver (158-160). In addition, it is suggested that endocannabinoids may determine the hedonic aspects of food intake and that overactivation of the endocannabinoid system in the limbic forebrain (nucleus accumbens) may cause hyperphagia and obesity (161).

Inflammatory neuroendocrine factors

Cytokines are a large family of more than 100 regulatory polypeptides that includes both pro-inflammatory and anti-inflammatory mediators. Accumulating evidence suggests that cytokines play an important role not only in classical inflammatory diseases such as rheumatoid arthritis, inflammatory bowel diseases or psoriasis but also in the pathogenesis of the cardiovascular, depressive and energy balance disorders. Basing on survey of literature it may be hypothesized that the comorbidity of these diseases may be explained at least partially by their common inflammatory background in the brain. However, verification of this hypothesis may be difficult in the nearest future since cytokines exert wide spectrum of actions including the modulation of synthesis and action of a number of biological mediators. Despite the fact that the blood-brain barrier limits the access of various mediators to the brain, cytokines may easily affect the brain functions by at least three distinct pathways. First, synthesis of

cytokines is possible inside the blood-brain barrier (BBB), second, blood-borne cytokines may be transported across the blood-brain-barrier by means of specific carriers, and third, they may modulate the activity of the peripheral neuronal afferents which project to the brain (162-166); cytokines in the cerebrospinal fluid may interact with their receptors present in the glial cells and neurons of the circumventricular organs and AV3V region of the third ventricle which lack the blood-brain barrier (167). The role of inflammation in the cardiovascular and depressive diseases as well as in the obesity and anorexia has been extensively reviewed elsewhere (168-170). In the following paragraphs we will summarize current evidence on the functions of cytokines in the brain.

Cytokines and cardiovascular diseases

It is now well established that the cardiovascular diseases such as the ischemic heart disease, heart failure, arteriosclerosis and hypertension are characterized by an increased synthesis of cytokines that circulate in the blood (168, 169). Increased blood concentration of TNF- α , and TNF- α receptors, and other pro-inflammatory cytokines have been found in patients with hypertension (171, 172), heart failure (173-175) and ischemic stroke (176, 177). Recent studies have provided evidence that the myocardial infarction causes an increase in the synthesis of cytokines in the hypothalamus, and that in the heart failure the pro-inflammatory cytokines modulate neurotransmission in the PVN, contributing thereby to the sympathoexcitation in the heart failure (178, 179). Earlier, a number of studies revealed that infusions of pro-inflammatory cytokines into various brain regions result in significant hemodynamic and neurohormonal responses that are typical for cardiovascular diseases. For example, the central infusions of interleukin-1 β (IL-1 β) or tumor necrosis factor α (TNF- α), two key mediators of inflammation, were found to increase arterial blood pressure, sympathetic activity and synthesis of renin, aldosterone, atrial natriuretic peptide and vasopressin (180-182). Growing number of data indicate that under pathological conditions TNF- α acting in PVN may play a key role in regulation of the cardiovascular system. Inhibition of TNF- α synthesis by pentoxifyllin or inhibition of TNF- α by etanercept, a modified TNF- α receptor, in rats with the post-infarct heart failure resulted in reduced stimulation of the PVN neurons, decreased renal sympathetic nerve activity, and lowered plasma catecholamines (179-185). Chronic central blockade of TNF- α in the rats with heart failure reversed changes in the concentration of several neurotransmitters in the PVN back to the levels seen in control animals and prevented increases in the renal sympathetic nerve activity (186).

On the other hand, increase in the brain concentration of the anti-inflammatory cytokines, such as interleukin-1 receptor antagonist (IL-1ra) or interleukin-10 (IL-10) exerted the opposite effects. Specifically, it has been found that the cerebroventricular transfer of IL-10 gene reduces hemodynamic and humoral indices of heart failure in the infarcted rat (187), whereas the central infusion of IL-1ra decreased the hypertensive response to acute stressors in the healthy rats (187, 188).

It has been suggested that cytokines exert their action in the brain by the influence on the synthesis of other mediators including eicosanoids, nitric oxide, Ang II or their receptors. Especially interesting is a putative interaction between cytokines and the brain angiotensin system, since the increased activity of the latter has been found in animal models of hypertension and heart failure. In our laboratory, we have demonstrated that pretreatment with either IL-1 β or TNF- α , enhances the pressor response to centrally applied Ang II (189, 190). Sriramula and co-workers (191) reported that the pressor and the dipsogenic effects of Ang II in mice requires presence of TNF- α . In addition, the preliminary report by the same group revealed that blockade of

TNF- α in the brain attenuates development of Ang II- induced hypertension and reduces expression of AT1 receptors in the heart, and proinflammatory cytokines content in the PVN (192).

Cytokines in depression and stress

Increased concentration of inflammatory cytokines in the blood, cerebrospinal fluid, and various brain regions is positively correlated with major depression, dysthymia and psychological stress in humans and in animals with depressive-like behavior (193-195). Therefore, it has been suggested that the inflammatory mediators, in particular IL-1 β and TNF- α play an important role in the pathology of depressive disorders. In this line, several clinical and experimental studies have shown that peripheral and central infusions of pro-inflammatory cytokines or lipopolysaccharide, an inflammatory inducer, cause depressive-like behavior in humans and animals. For instance, the infusions of either IL-1 β or TNF- α were found to evoke depressive-like behavior in mice (196), whereas mice lacking caspase 1, an enzyme necessary for the synthesis of IL-1, manifest reduced "sickness behavior" (197). Furthermore, Simen *et al* (197) have shown that deletion of the genes for TNF- α receptors results in anti-depressive effects (198). Several hypothesis linking depression with inflammation have been suggested including the modulation of synaptic plasticity and changes in synthesis, reuptake and metabolism of neurotransmitters involved in mood regulation (199). In the animal model of depression Grippo and co-workers (200) showed that rats, which were subjected to chronic mild stressing developed an anhedonia accompanied by dysfunction of the hypothalamic-pituitary axis, and increased expression of TNF- α and IL-1 β in the hypothalamus, pituitary and plasma (200). Similar disturbances were found in rats with the post-infarct heart failure. In addition, peripheral inhibition of TNF- α attenuated symptoms of anhedonia that are present in the infarcted rats (201), and decreased expression of AT1 receptors in the brain and sympathetic drive in the infarcted rats (184).

Interleukin-1 β is also an important modulator of hormonal and behavioral components of stress. O'Connor and collaborators have demonstrated that an acute stressor increases IL-1 β mRNA and/or protein not only in a variety of peripheral tissues but also in the brain, including hypothalamus and hippocampus (202). Moreover, it has been shown that IL-1 β plays a critical role in the activation of the hypothalamo-pituitary-adrenal axis after stress and adrenalectomy (194). There is also some evidence that the central infusion of the IL-1ra reduces the circulatory response to stressors (188, 203).

Obesity and anorexia

Cytokines have been traditionally linked to negative energy balance. This approach originates from the discovery that TNF- α (also known as cachexin) is an important mediator of cancer anorexia and cachexia. Furthermore, results from many experimental studies have shown that either peripheral or central infusions of inflammatory mediators including TNF- α , IL-1 β and IL-6 produced several responses, such as anorexia, fever, and activation of the hypothalamo-pituitary-adrenal axis and autonomic nervous system which may promote negative energy balance (204). However, the study of Amaral *et al.* (205) provided evidence that the regulatory role of TNF- α in the hypothalamus may be very complex. Specifically, they found that administration of TNF- α into the cerebral ventricle of the rat triggered signal transduction in the hypothalamic cells and enhanced expression of several factors, including other proinflammatory cytokines, orexigenic (NPY, MCH) and anorexigenic (POMC, CRH) neuropeptides, with greater effect

on the latter. The anorexigenic effect of TNF- α was also manifested, as shown by inhibition of food intake (205).

Interestingly, other studies have shown that the inflammatory process in the brain may result in positive energy balance. Thus, research performed on the rats and mice models of obesity revealed increased concentration of inflammatory mediators both in the adipose tissue and the hypothalamus (206, 207). Moreover, it has been shown, that peripheral blockade of TNFR1 receptor prevents diet-induced obesity in the rats (208). In the leptin-resistant mice development of obesity is accompanied by the increased expressions in mRNA of TNF- α and TNFR2 receptors in the hypothalamus that are not associated with changes in expression of TNFR1 receptor (209). Pharmacological and genetic inhibition of the inflammation cascade within the hypothalamus resulted in reduced body weight in the mice fed high-fat diet (206). Presumably, the mechanisms underlying this phenomenon include development of the resistance to leptin and insulin in the hypothalamus (206, 207).

Therefore it has been suggested that alterations in the activity of cytokines in the brain may result in the development of both obesity and anorexia/cachexia-like behavior, depending on presence of other pathogenic factors (210).

PERSPECTIVES

In the present survey we emphasized overlapping regulatory actions of the key biological compounds participating in the neurogenic control of the cardiovascular system, and metabolism, with relevance to their role in cardiovascular, metabolic, affective and inflammatory disorders. As shown in *Fig 2.* in many instances the same factors are involved in regulation of seemingly remote physiological processes. Appropriate action of all these compounds is probably necessary for optimum functioning of the body. At present it is not possible to propose which of these factors may be responsible for initiation of the pathological process. Most likely under physiological conditions all of them serve positive role in regulation of vital functions and adaptation to the environment. It may be hypothesized that simultaneous increase in production of several of these factors is necessary so as to reach some critical point at which they jointly start to initiate the pathological processes. It is likely that cytokines may play a role of "executor" in propagation of the pathological process. To have better insight to this complex issue future studies should focus on more comprehensive knowledge of the regulation and action of the particular regulatory factors and their mutual interactions under physiological and pathological conditions. Undoubtedly, more attention should be given to the role of the pathological processes in the gastrointestinal system in initiation of the inappropriate regulation of the metabolism and cardiovascular functions by the brain neurons. Such integrative approach should allow for better understanding of therapeutic failures in patients suffering from two or more diseases and elaboration of more efficient treatments in the cardiovascular, metabolic, inflammatory and affective disorders.

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Author's address: Prof. Ewa Szczepanska-Sadowska, Department of Experimental and Clinical Physiology, The Medical University of Warsaw, 26/28 Krakowskie Przedmiescie Street, 00-927 Warsaw, Poland; E-mail: eszczepanska@wum.edu.pl