A Cross-Talk between the Renin-Angiotensin and Adrenergic Systems in Cardiovascular Health and Disease

Ana Stupin[1], Ines Drenjancevic[1], Lidija Rasic[1], Anita Cosic[1], Marko Stupin[1,2]

[1] Department of Physiology and Immunology, Faculty of Medicine Josip Juraj Strossmayer University of Osijek, Osijek, Croatia

[2] Department for Cardiovascular Diseases, Osijek University Hospital, Osijek, Croatia

Corresponding author: Ana Stupin, MD, PhD - cavka.ana@gmail.com, anacavka@mefos.hr

Abstract

It is well accepted that a number of cardiovascular (CV) and renal diseases are characterized by the long-term activation of both the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS), which also contribute to the pathophysiology of structural and functional CV abnormalities as well as to the final clinical outcome. Moreover, there is a growing body of conclusive evidence that these systems do not operate independently, but interact at different levels throughout the CV system. The mediation of renin release from juxtaglomerular epithelioid (JGE) cells in kidney by SNS is well established and accepted. On the other hand, in recent years it became evident that RAS, by its main effect or angiotensin II (Ang II), induces SNS activity in various organs and tissues. Thus, there is a growing effort to clarify pathophysiological mechanisms of interaction and a more evident mutual potentiation of these two systems in different pathological states. Since it became evident that a high salt (HS) intake, which is a major risk factor for hypertension development, has a deleterious impact on vascular and endothelial functions (even in the absence of blood pressure changes), it became necessary to investigate and clarify the effect of HS loading on major regulating systems—RAS and SNS—precisely in healthy individuals. The present review aimed to summarize the interactions between the RAS and SNS in health and diseases (e.g. cardiovascular, renal), with a special focus on these two systems' interaction during HS intake in a healthy normotensive population.

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Introduction

This review aimed to present the interactions between the renin-angiotensin system (RAS) and the sympathetic nervous system (SNS) in health and diseases (e.g. cardiovascular, renal), with a special focus on these two systems interaction during HS intake in healthy

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individuals. The mediation of renin release from JGE cells in kidney by β1-adrenergic receptors activation is well established and accepted (1). However, there is a growing interest to understand how RAS affects SNS activity, and to evaluate whether these two systems potentiate each other's effects. It became evident that RAS, by its main effector, angiotenin II (Ang II), increases SNS activity in various organs and tissues (e.g. the central nervous system, the adrenal medulla, the sympathetic ganglia and the sympathetic nerve endings), and that this interaction is mediated mostly by the Ang II receptors type1 (AT1 receptors) located at the sympathetic nerve endings (2). The suggested physiological feedback loop in RAS-SNS interrelation is summarized in Figure 1. Most of these findings were brought by studies investigating the activity of these two systems in hypertension, chronic heart failure and/or chronic kidney disease (3, 4). Even though HS intake unequivocally suppresses RAS activity, the effect of HS intake on SNS activity that is independent of blood pressure changes is still not completely understood.

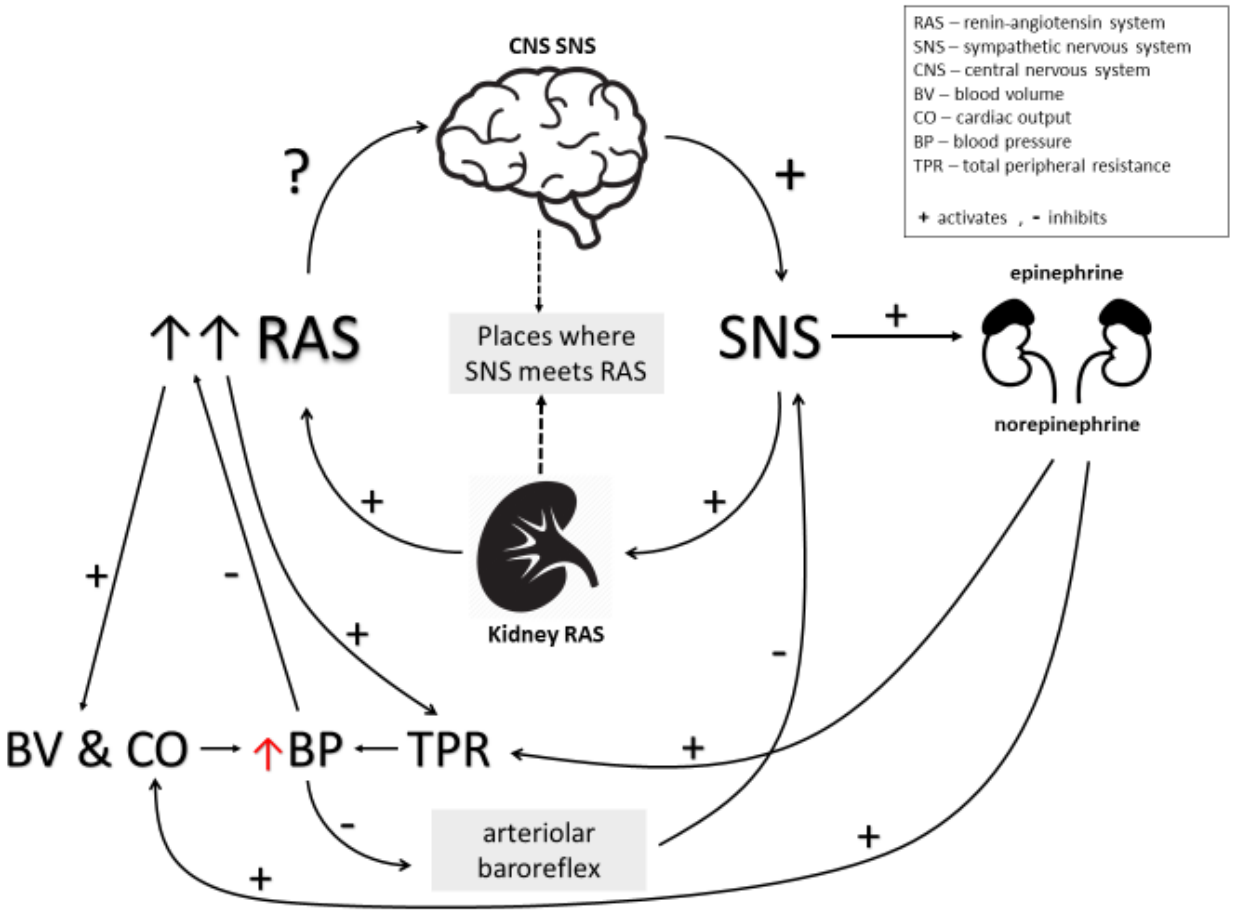
The role of the renin-angiotensin system in the cardiovascular physiological control system

The RAS is one of the most important hormonal systems which plays a key role in the arterial blood pressure, tissue perfusion, and extracellular volume homeostatic regulation, as well as in the regulation of neuronal and endocrine functions related to CV control (5, 6). RAS consists of a cascade of functional proteins and exhibits its effects through the effector molecule Ang II. In this cascade, the first is a release of an aspartyl protease called renin, which is synthesized and released from renal JGE cells located in the afferent and efferent arterioles of the renal glomerulus (1). Renin release is stimulated by various stimuli including decreased renal perfusion pressure (1), increased renal sympathetic nerves activity and decreased NaCl delivery to the macula densa of the juxtaglomerular apparatus (5, 6). Renin cleaves angiotensinogen, which is synthesized by hepatocytes, to form the inactive decapeptide angiotensin I (Ang I) (7, 8). Ang I is converted to the active octapeptide Ang II by angiotensin-converting enzyme (ACE) and non-ACE pathways (9, 10). Non-ACE pathways include Ang II production viae.g. chymase, which can be manifested in hypertensive patients treated with ACE inhibitors who have increased Ang II levels despite their therapy, a phenomenon called 'angiotensin escape' (11). To carry out its biological functions, Ang II binds to two specific and ubiquitous G-protein coupled receptors, Ang receptor type I (AT1) and type II (AT2) (12, 13).AT1 receptors mediate most of the established physiological effects of ANG II including actions on CV system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), kidneys (sodium reabsorption in renal tubule, inhibition of renin release), adrenal cortex (aldosterone synthesis) and SNS (1, 5, 6). AT2 receptors are generally assumed to counteract the vasoconstrictor and growth-stimulatory actions of AT1 receptors (14). There are several biologically active angiotensin metabolites, including angiotensin III, angiotensin IV and angiotensin-(1–7), which stimulate the AT2 receptors (but with low affinity), and/or newly discovered putative receptors (14, 15). The physiological relevance of these metabolites in various tissues is still under investigation. Aldosterone is another effector molecule of the RAS, whose synthesis and secretion is stimulated by the Ang II mediated activation of AT1 receptors in the adrenal zona glomerulosa cells. Aldosterone promotes sodium reabsorption, water retention, and potassium and magnesium loss and modulates blood pressure (16).

Circulating and local (tissue) RAS

Generally, RAS can be divided to the circulating and local (tissue) RAS (17). However, it is very hard to differentiate these two systems because of their extensive overlap (18). The circulating RAS implies renin produced in kidneys, which cleaves liver-derived angiotensinogen to generate Ang I that is converted by ACE into Ang II. On the other hand, a key feature of local RAS is the local synthesis of RAS components (e.g.

Figure 1. *Physiological feedback loop in renin-angiotensin system – sympathetic nervous system (RAS-SNS) interrelation.*



angiotensinogen, Ang peptides) independently of the circulating RAS. AT1 and AT2 receptors are invariably locally synthesized and are components of both circulating and local RAS systems (19). In recent years, it has been demonstrated that the local RAS includes many other potential components that may contribute to tissue-specific mechanisms of Ang peptide formation, and subsequently may participate in the pathophysiology of various diseases or contribute to the mechanisms that protect from tissue injury. These include the (pro)renin receptor(20), Ang generation from Ang-(1-12) that is independent of renin (21), intracellular (or intracrine) RAS that may contribute to CV disease (22, 23), and AT2 receptors and the ACE2/Ang-(1-7)/Mas receptor pathway that may mediate therapeutic benefit in CV disease (22, 23). Furthermore, several novel angiotensin peptides have been described, including angiotensin IV, angiotensin A, alamandine, and angioprotectin (22, 23), which are suggested to have the potential to contribute to disease or to protective mechanisms. The challenge of future research regarding the RAS is to investigate to what extent these two components of the RAS system are independent of each other, and what is the clinical relevance of the local RAS in CV disease development and progression.

Abnormal renin-angiotensin system activity in development of cardiovascular diseases

The RAS also has a central role in mediating and regulating vascular adaptive processes (24, 25) and is a major regulatory system involved in the regulation of a myriad of CV processes. Abnormal activity of the RAS leads to the development of different CV diseases and events (24), and results in vasoconstriction, muscular (vascular and cardiac) hypertrophy and fibrosis (25). Changed RAS activity is involved in secondary hypertension, including renin-secreting neoplasms, renovascular

hypertension, malignant hypertension, pheochromocytoma and primary hyperaldosteronism, and by primary hypertension, the plasma renin activity (PRA) depending on the particular case, can be high, normal or low (26). Furthermore, numerous signaling pathways, including cell proliferation, hypertrophy and apoptosis, in response to Ang II are mediated by reactive oxygen species, and oxidative stress is deeply associated with the progression of CV disease (27). The RAS, through its physiological effectors, plays a key role in promoting and maintaining inflammation, and has proinflammatory and profibrotic effects at cellular and molecular levels. Inflammation is an important mechanism in the development and progression of CV diseases such as hypertension and atherosclerosis. A dysfunctional endothelium is leaky and facilitates migration of inflammatory cells into the vascular wall and stimulates smooth muscle cells to proliferation (28). Ang II upregulates NF-κB and related inflammatory genes and activates endothelial and endocardial NADPH oxidase, which plays a central role in the generation of reactive oxygen species (ROS) in CV disorders (29). Interestingly, in almost all of the above-mentioned states, along with the RAS hyperactivity there is increased SNS activity as well (30), which sets the potential interaction of these two systems in the pathogenesis of CV and renal diseases in the focus of recent studies in this field.

The role of the sympathetic nervous system in the cardiovascular physiological control system

Activation of the SNS has long been recognized as a manifestation of various CV diseases including hypertension and the clinical syndrome of heart failure (30). Abnormal increase in the circulating plasma catecholamines level and increased muscle sympathetic nerve activity (MSNA) were some of the first documented evidences of increased SNS activity in CV disease patients (30). Still, even though increased SNS activity was generally (systemically) manifested in those patients, recent evidences implicate that SNS hyperactivity is not uniformly distributed through the body, but rather has regional distribution differences, with hyperactivity in some areas and modest or even absent activity in others. Thus, it seems that this generalized effect of SNS on the CV system was overestimated, and that a special focus of future studies should be set on its effect on individual organs and organ systems (31).

Sympathetic nervous system in central nervous system

The regulation of SNS activity in the CNS may have a crucial role in the pathogenesis of different CV diseases. The main sympathetic activity-regulating nuclei in the CNS are the paraventricular nucleus in hypothalamus (PVN), rostral ventrolateral medulla (RVLM) and nucleus tractus solitarius (NTS) (32, 33). NTS receives signals from the cardiopulmonary afferents, including baroreceptors and chemoreceptors, and has an indirect effect on of the neuronal activity of the RVLM (32, 33). In addition, when activated, NTS leads to the PNV activation as well, which is a major integrative nucleus that can influence SNS activity and extracellular fluid volume by producing antidiuretic hormone (ADH), which also has its repercussion on the activity of the CV system (34). PVN sends signals to RVLM which contains sympathetic premotor neurons for the CV system, and participates in SNS regulation via communication with the intermediolateral column of spinal cord (IML) (33, 35). These central SNS pathways are a focus of recent studies, since it has become more evident that the abnormal sympatho-excitation of the central SNS deteriorates renal and CV function in various diseases (e.g. chronic kidney disease, hypertension, heart failure) and contributes to disease progression (30).

Peripheral sympathetic nervous system

Peripheral effects of the SNS on the CV system, such as short-term—as much as long-term—control of blood pressure, are quite well known. The terminals of sympathetic nerves release norepinephrine, which binds to α-adrenergic receptors on vascular smooth muscle causing

vasoconstriction (36, 37). Many functional studies have confirmed that cutaneous blood flow is regulated by the SNS (38, 39). Sympathetic activity increases cardiac output by releasing epinephrine and norepinephrine (40) and also has effect on heart rate, which is mediated by the release of norepinephrine from postganglionic fibers that innervates the whole heart. This effect is mediated via β-adrenergic receptors on the heart muscle cells (40). Thus, a β-adrenergic blockade is an effective treatment for elevated blood pressure. The SNS regulates short-term transitions in blood pressure by the arterial barorefex (41), but also has a significant role in long-term blood pressure regulation. Studies have shown that the pharmacological blockade of sympathetic ganglions decreases blood pressure in both hypertensive and normotensive subjects (42). Chronic carotid baroreceptor stimulation evokes long-term reduction in the SNS and blood pressure in hypertensive patients (43).

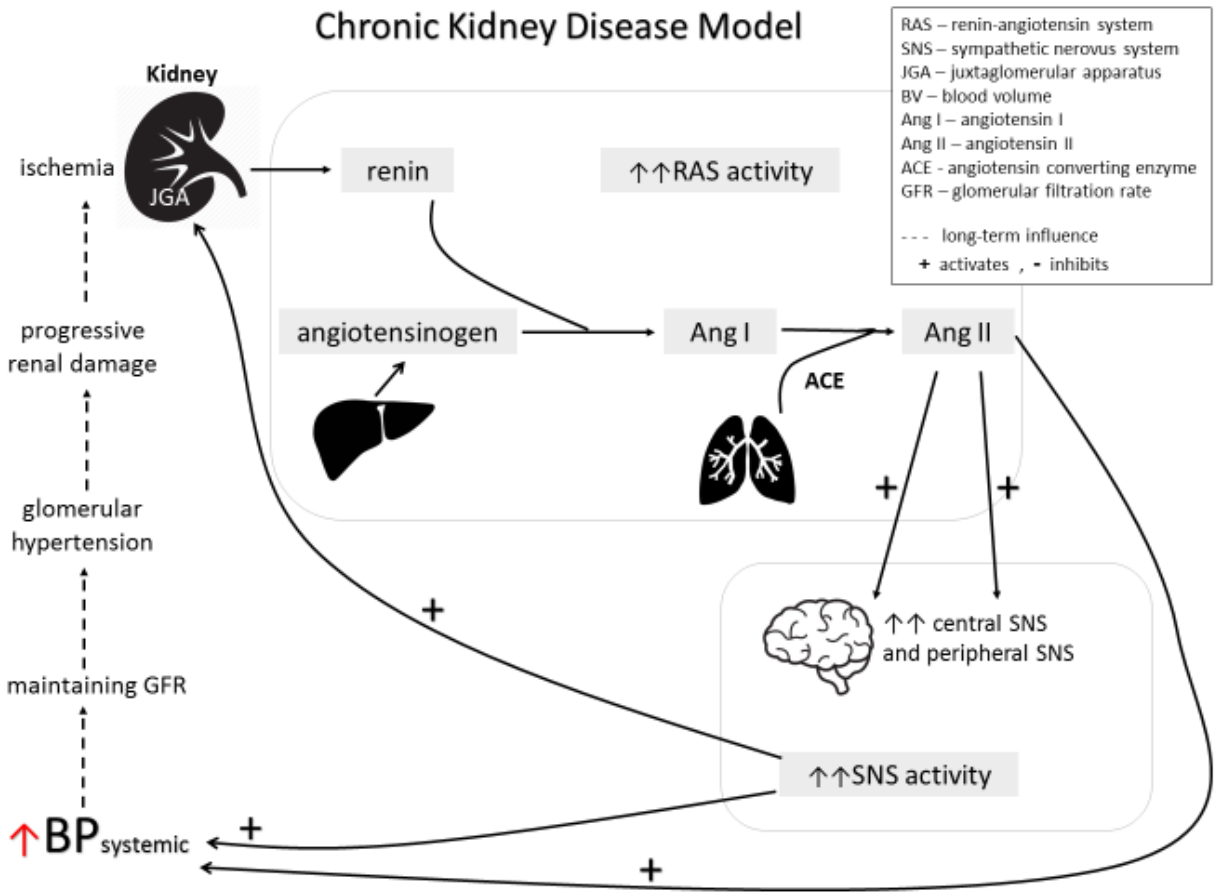
Another important part of the SNS is a muscle SNS. Muscle SNS positively correlated with total peripheral resistance, but negatively with cardiac output (44). Further, constriction of peripheral resistance vessels in the response to norepinephrine was lower in subjects with higher SNS activity, indicating that healthy people with higher muscle SNS had a second protective factor to prevent elevation in blood pressure (45). These findings may suggest that, in regulating the CV system to keep its function optimal, SNS activity affects not only well known and established pathways, but also many others not yet fully comprehensible.

The kidneys are important targets of sympathetic tone modulation in general, since the SNS is one of several factors that influences the efficiency of the renal regulation of blood pressure. Anatomical and physiological evidence has shown that the SNS innervates JGA cells, renal tubules and vasculature (46, 47).Thus, changes in renal SNS activity frequency mediate increases in urinary sodium and water excretion by regulating the renal tubular water and sodium reabsorption throughout the nephron, changes in renal blood flow and the glomerular filtration rate by regulating the constriction of renal vasculature, and changes in the activity of the RAS by regulating the renin release from JGA cells (46, 47). Increased renal SNS activity decreases renal blood flow and the glomerular filtration rate. JGA cells in the kidney have β-adrenergic receptors, which make the kidneys important targets of renal SNS activity and a place where it is generally accepted that the "SNS meets the RAS" (Figure 1). SNS activity in kidney increases renin release by activating JGA β-adrenergic receptor, along with an increase in tubular sodium reabsorption, and decreases in renal blood flow and the glomerular filtration rate (48). Furthermore, an additional effect on renal circulation is present via response to exogenous epinephrine and norepinephrine, with afferent arterioles showing higher sensitivity to the vasoconstrictive effect of circulating catecholamines than efferent arterioles (48). This reveals the importance and relevance of SNS activity on the kidney's compensatory mechanisms and management of volume expansion and high salt intake, which precedes pathological conditions such as hypertension.

The SNS also affects the immune system by contributing to leukocyte activation and extravasation, inflammation, oxidative stress and the production of chemokines and cytokines (49).

Thus, it is evident that understanding of the SNS modulatory effects on CV function implies its general (systemic), central and peripheral (individual organ or tissue) effects, and its interactions as well. While these individual effects of SNS are mainly well understood, there are many intertwined pathways between different SNS components in both health and disease, which make the effect of the SNS on the CV system more complex to understand and thus a focus of most recent studies on this issue.

Figure 2A. *Enhancement of renin-angiotensin system activity by sympathetic nervous system and vice versa in cardiovascular and renal diseases (chronic kidney disease)*



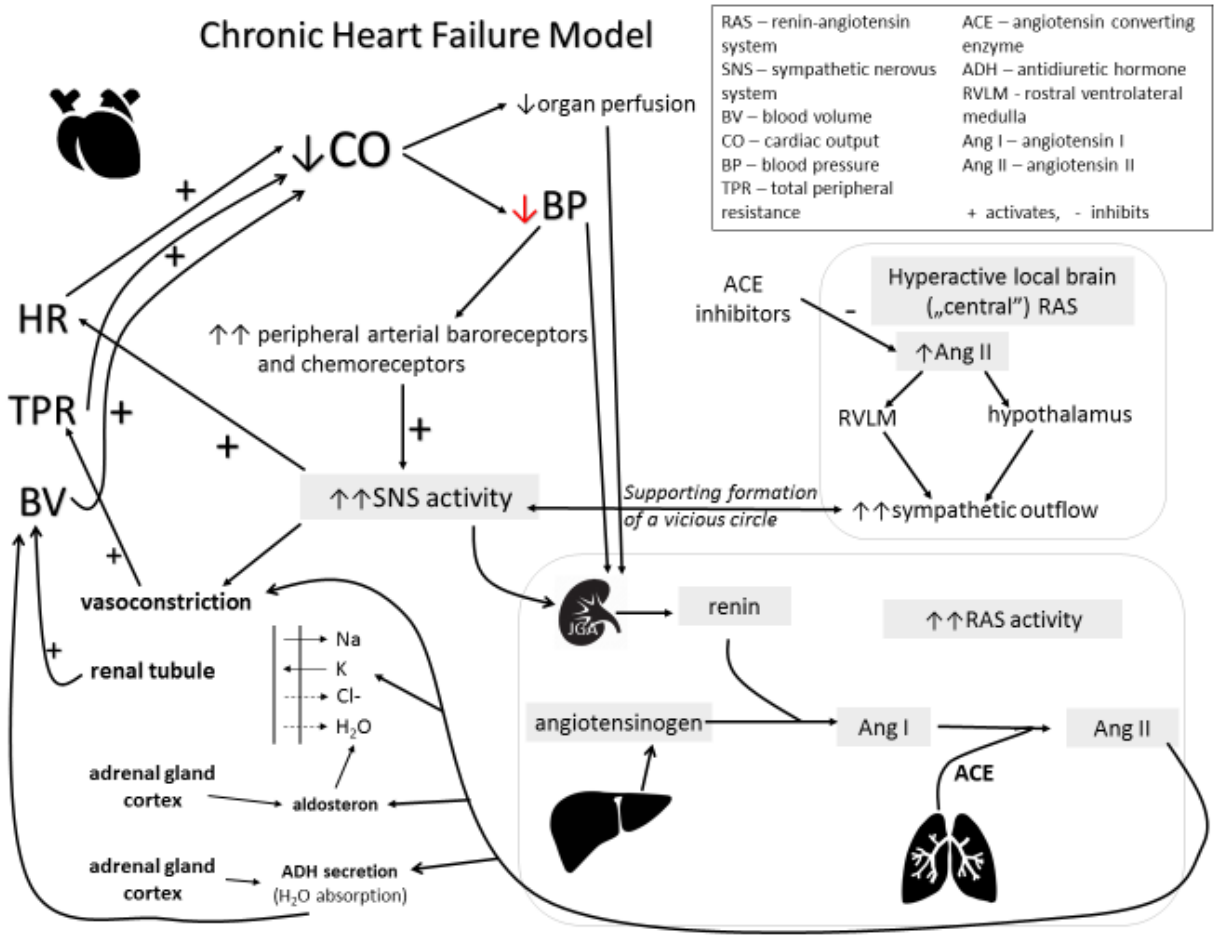
Interaction between the renin-angiotensin system and the sympathetic nervous system in the pathogenesis of cardiovascular and renal diseases

There are several CV and renal diseases characterized by both RAS and SNS activation in which these systems, beside their effect on blood pressure regulation, also contribute to the pathophysiology of both structural and functional CV abnormalities and contribute significantly to clinical outcome (4). It became evident that these systems do not operate independently, but interact at different levels throughout the CV system. Thus, there is a growing effort to clarify the pathophysiological mechanisms of interaction and more evident mutual potentiation of these two systems in different pathological states, including chronic kidney disease, essential hypertension, heart failure, obesity, metabolic syndrome, etc.

The renin-angiotensin system and sympathetic nervous system interaction in chronic kidney disease

Chronic kidney disease (CKD) is often characterized by enhanced activity of the RAS and SNS (4), which is summarized in Figure 2A. It is considered that kidney ischemia represents a central stimulation for renin secretion and RAS activation that subsequently increases SNS activity. Intravenous infusion of Ang II stimulates MSNA in humans, and even a small locus of injury in one kidney leads to hypertension associated with increased central sympathetic activity. Ang II can interact with the SNS on different sites, in the kidney, in the CNS and on peripheral sites, enhancing norepinephrine release from sympathetic nerve activity (50). When taken into account that increased SNS

Figure 2B. *Enhancement of renin-angiotensin system activity by sympathetic nervous system and vice versa in cardiovascular and renal diseases (chronic heart failure)*



activity enhances RAS activation by releasing renin from JGE, it is evident that there may be a reciprocal potentiation between these two systems in the development and progression of CKD. Thus, kidney injury, which is generally characterized by an increased RAS activity, can lead to high SNS activity, hypertension and finally end organ damage (50). Moreover, there is vast experimental evidence showing that increased SNS activity contributes at several levels to the development of CV organ damage (4, 51, 52). Thus, with these pathophysiological mechanisms in mind, it seems logical to hypothesize that RAS inhibition would reduce SNS activity in CKD. Moreover, recent studies reported that a SNS blockade in addition to RAS inhibitor treatment might be beneficial in a selected patients group (51-53).

The renin-angiotensin system and the sympathetic nervous system interaction in chronic heart failure

Chronic heart failure (CHF) is a multi-factorial disease that presents the end result of various insults to the myocardium (e.g. ischemic heart disease) (3). The most significant hallmark of CHF is the continuous interaction between the underlying myocardial dysfunction (e.g. decrease of cardiac output) and activated compensatory mechanisms in order to maintain blood pressure and organ perfusion. Activation of the RAS along with the SNS plays a crucial role in the pathophysiology of CHF, which is summarized in Figure 2B. Activation of the SNS is considered a major compensatory mechanism in the development of CHF, which may be due to the changes in peripheral baroreceptors and chemoreceptors reflexes, chemical mediators

that control sympathetic outflow and central integrative sites (33) (Figure 2B). In recent years Ang II, NO and/or pro-inflammatory cytokines were described as crucial mediators controlling sympathetic outflow. On the other hand, an increase in renin release in CHF state is caused by at least two pathways including renal sympatho-excitation as well as a decrease in renal perfusion pressure (3, 33). All of these compensatory mechanisms are initially beneficial; however, they became counterproductive if sustained for a prolonged time (Figure 2B).

Areas in RVLM and in hypothalamus mediate and increase sympathetic outflow in response to a microinjection of Ang II, which was inhibited after a central infusion of AT1 blocker losartan (54-56). Interestingly, this increment in central RAS activation could be associated with an increased oxidative stress level in CHF state (57, 58). The role of the central RAS in the supporting formation of a vicious circle in the development and progression of CHF is not limited to the CNS. Francis et al. reported that a central blockade of ACE decreased renal SNS activity, improved blunted baroreflex sensitivity, and normalized sodium consumption, urine sodium and urine volume in rats with CHF (59). Furthermore, in a myocardial infarction (induced by acute coronary artery ligation) rat model with transgenic deletion of angiotensinogen (rats which express an antisense RNA against angiotensinogen), deterioration of CHF was not as progressive as in control CHF rats (60). Taken together, it became evident that a hyperactive central RAS is a contributor to global physiological changes as well as the CV dysfunction seen in CHF. On the trail of these findings there is a growing trend to consider the use of both pharmacological and non-pharmacological therapy targeting the central RAS in the treatment of CHF (3). Clearly, the described cross talk between the central RAS and increased SNS activity is only one potential mechanism explaining the regulation of SNS activity in CHF (Figure 2B).

Changes in the renin-angiotensin system and sympathetic nervous system during high-salt loading

It is generally accepted that increased dietary salt intake is associated with an increase in arterial pressure, resulting in hypertension, which makes dietary salt a leading cause for CV, cerebrovascular, and renal morbidity and mortality (61). Various mechanisms were suggested to contribute to the development and progression of salt sensitive hypertension, including increased activation of the RAS and elevated SNS activity, well established hallmarks of arterial hypertension (62). However, in recent years it became more and more evident that HS dietary intake affects vascular and particularly endothelial functions even in the absence of changes in blood pressure (BP) (63-65).Thus, it should be taken into account that the concept of salt-sensitivity is not limited only to the effect of dietary salt modulation on BP, but to its effect on vascular function and the CV system in general as well (63). There is an overall consensus that HS intake, high levels of Ang II and increased sympathetic activity are all injurious to the CV system and play a role in a multitude of CV diseases (66). However, much less is known about the role of elevated salt intake on CV functions that are independent of arterial BP, especially in healthy humans. In clarifying the pathogenic sequence in which an HS diet is on one side and impaired CV function (e.g. endothelial dysfunction, hypertension) on the other, it is necessary to investigate the effect of salt loading on major regulating systems (e.g. RAS, SNS) in healthy individuals.

High salt feedback on the renin-angiotensin system

It has been demonstrated unequivocally in both humans and experimental animals that salt intake is inversely related to RAS activation: low salt intake stimulates RAS activity, and HS intake suppresses it (67). Dietary salt intake modulation affects RAS activity via at least four different pathways including: 1) the macula densa mechanism, which regulates renin release in response to changes in the renal tubular salt

concentration; 2) salt-dependent changes in arterial BP; 3) circulating salt-dependent hormones, particularly atrial natriuretic peptide (ANP); and 4) the SNS (67). Still, signal pathways that adjust renin synthesis and RAS activity to changes in salt intake are still not completely understood. Recent data suggest that macula densa mechanism is involved in adjustment of renin release in response to acute changes in salt loading (68, 69). Still, its effect on RAS activation during long-term changes in salt loading is less clear: it does not appear to have a function in this situation, but rather to modulate the general responsiveness of renin release (67, 70). Furthermore, numerous studies have reported that salt-dependent regulation of RAS can occur even in the absence of changes in arterial BP, especially in healthy individuals (64, 65, 71). Thus, BP is not a general controller of salt-dependent regulation of the RAS under normal conditions, but it can modulate renin synthesis when salt modulation provokes significant changes in BP levels. It has been shown that an increase in extracellular volume, induced by oral salt intake or intravenous saline infusion, is associated with elevated plasma levels of atrial natriuretic peptide (ANP), which consequently induce natriuresis and vasorelaxation, raise glomerular filtration and have capacity to directly suppress renin release from JGE cells (72). However, whether this mechanism is relevant in physiological condition in healthy humans or animals is still unclear. Studies have reported that modest acute salt loading in both healthy humans and animals did not elevate ANP levels and did not suppress plasma renin activity, indicating that RAS inhibition is not dependent on ANP (73, 74). Thus, ANP seems inessential for RAS suppression during acute salt loading, and its role in long-term dietary salt modulation should be addressed in further investigations. A number of studies investigated the correlation between salt intake and local renal sympathetic activity, indicating an inverse relation between the salt intake and renal nerve activity. Since renin-producing JGE cells have β1-adrenoreceptors whose activation results in renin release, one of the possible mechanisms mediating RAS inhibition by HS loading could be inhibition of local renal SNS activity (75, 76). Still, evidence indicating that renal nerves have a role as a mediator of the salt-dependent regulation of renin release and synthesis are insufficient.

This indisputable connection between salt intake and RAS activity indicates that the central role in mediating salt homeostasis within the body and its effect on CV, cerebrovascular or renal function belongs particularly to the RAS. In recent years, it became more evident that, besides its crucial role in body fluid volume, electrolyte balance and blood pressure regulation, the normal function of the RAS is critical for maintaining arteriolar structure, vascular reactivity and cardiovascular health in general (5). HS-induced increased oxidative stress (5) and impairment of vascular function (that is independent of BP changes) are related to low levels of Ang II and a normally functioning RAS has a protective effect in the maintenance of vascular function (77).

In contrast to numerous animal studies reporting that RAS inhibition provoked an increased oxidative stress level and endothelial dysfunction, the effect of RAS inhibition on the vascular function in a healthy normotensive human population was set in a focus of a very few recent studies. Most of these studies have found that HS intake (RAS inhibition) impairs the flow mediated dilation of the brachial artery in the absence of BP changes (65), which was likely associated with reduced vascular NO bioactivity (78-80). Furthermore, same deleterious effect of acute salt loading was observed in skin microcirculation as well (64, 65, 79). Cavka et al. reported that one week of a low-salt diet with oral losartan (a selective AT1 receptor inhibitor) administration led to a significant increase in plasma levels of the cyclooxygenase dependent vasoconstrictor thromboxane (TXA_2) without causing any changes in BP and/or skin microvascular blood flow responsiveness in young healthy women, suggesting that an AT1 receptor blockade may play an important role in the regulation of a cyclooxygenase-dependent pathway of metabolism of arachidonic acid (81).

High salt feedback onsympathetic nervous activity

Sodium retention is link between CV and renovascular diseases together with elevated SNS activity (3, 4). Interestingly, it still remains to be investigated how salt intake affects SNS activity in healthy individuals in the absence of BP changes (does it inhibit or potentiate SNS activity), and whether this effect is uniform for both local and systemic SNS responses (Figure 1). There is a paucity of studies investigating the effect of HS loading on systemic SNS activity in physiological conditions, both in animal and human models. So far, studies in animal models (rabbits) have reported that HS alone had no effect on baseline BP, water intake or SNS activity, but in combination with low-dose Ang II infusion HS provoked sympatho-excitation (82). HS intake induces the central sensitization of sympathetic circuits to result in exaggerated CV reflexes and an increase in BP variability in normotensive salt-resistant animals (83). Furthermore, a 6-day HS diet increased the mean systolic BP, decreased heart rate, and increased vagal activity in healthy, normotensive women (age 40–70) (84). These very few studies suggest that changes in autonomic nervous system balance should be taken into account during RAS modulation by salt intake, even in young healthy normotensive individuals.

Regarding potential mechanisms that mediate interaction between salt intake and SNS activity, it is well known that acute increase of plasma osmolality of sodium concentration in both plasma and cerebrospinal fluid can cause an increase of SNS activity (85, 86), which is presumably mediated by osmosensory neurons in the organum vasculosum laminae terminalis (OVLT) in the brain (86). The most recent study by Kinsman et al. has demonstrated that OVLT neurons are activated by modest rises in plasma or cerebrospinal NaCl, and their activation elevates BP and triggers a pattern of SNS activity that presumably facilitates renal sodium excretion in Sprague Dawley rats (87). Furthermore, many other agents, such as endogenous ouabain are involved in blood pressure (BP) elevation. Elevated sodium concentrations in body fluids can induce the secretion of the ouabain by both the hypothalamus and the adrenals, suggesting that ouabain could have an important role in linking together central and peripheral hypertension occurrences (88). Ouabain acts centrally in the brain to increase the sympathetic drive (89) and in the periphery causing vasoconstriction via myocytes and endothelium (90). Still, when taken into account that in most studies (both animal and human) in which moderate HS loading provoked vascular dysfunction independently of BP changes, there was no significant increase in sodium concentration in plasma. The above suggested effects of the described conditions are disputable and remain in need of clarification.

Another intriguing relation is that between the SNS and RAS during HS intake. An inverse relation of HS intake and renal SNS activity was observed (91, 92), showing that HS intake can suppress renal SNS activity. Renal SNS activity also affects RAS, whereas renal SNS activity stimulates renin release via the activation of β1 adrenoceptors placed in renin-producing JGE cells (75, 93), as already described. To examine this axis, studies using β1/β2 double knockout mice fed with a HS diet were performed (94). In this study β1/β2 double knockout mice were fed with a HS diet, and surprisingly they maintained the salt-dependent regulation of renin plasma concentration, since low salt intake stimulated renin release, and HS intake suppressed it (94). Similarly, dogs were fed with a HS diet and the changes in SNS activity effects were investigated via modulating baroreceptor activity (95). The suppression of central SNS activity by electrical stimulation of baroreceptors lowered BP without affecting the RAS and without impairing the normal salt-dependent secretion of renin. This may suggest that neither renal nor central SNS activity is crucial in the salt-dependent regulation of the RAS, but surely acts as a moderator in the RAS response to changes in salt load (67). Since most organs possess a local RAS that is regulated independently and is somewhat compartmentalized from the circulation, it has been suggested that the brain RAS may play an important role in CV regulation through its ability

to modulate SNS activity (96) (Figure 1). Studies in animal models have shown that increased levels of brain Ang II and the activation of brain AT1 receptors in the RVLM mediate the sympatho-excitatory actions (96). To date, the limited data indicate that elevated dietary salt intake enhances both sympatho-excitatory and sympatho-inhibitory responses evoked by a number of neurotransmitters exogenously applied to the RVLM (97-99), but these enhanced responses could not be attributed to changes in downstream sympathetic pathways or vascular reactivity (98-100). On the other hand, results obtained in studies on experimental animals have demonstrated that the brain Ang II activates posterior hypothalamic nuclei that increase efferent renal nerve activity and BP, suggesting the presence of renal/cerebral interaction in which the brain RAS can regulate the peripheral sympathetic activity and renal RAS (101).

Taken together, the relation between SNS activity and salt intake and its role in the development and progression of hypertension is yet unclear.

Conclusions

Many separated parts and mechanisms of the RAS and SNS affecting the CV system are discovered and explained, but the interplay of these separated mechanisms seems to have a pivotal role in explaining and understanding this highly interactive network. Studies conducted so far may suggest that some parts of the RAS and/or SNS effect on the CV system are overestimated, while others are underestimated. In a situation such as HS intake, both RAS and SNS activity may have a modulatory, compensatory role, and this role can increase as the CV and renovascular diseases progress.

metabolic syndrome and a series of cardiovascular problems (35), it is very important that the values were within healthy limits. Some researches show that, similar to BMI, values for PBF and WHR rise as people age (36).

The body composition (presented in Table 1) of the subjects shows that they have appropriate mass of fat and muscles, and their body composition is in accordance to weight status based on BMI value. In other words, the prevalence of obesity based on BMI distribution would probably be similar if they were distributed according to the BF% or SLM. Results reported by Grygiel-Gorniak et al. (37) show similar values of BMI, WHR and BF% with the results of the present study, as well as the similar differences between sexes. Our findings regarding differences in BMI and BF% between men and women showed that men had higher BMI, but lower BF% compared to women. This could be ascribed to the greater muscle mass in men. However, the correlation between BF% and BMI showed a statistically significant high positive value, indicating a strong connection between those two variables. Correlation was slightly lower in men than in women. There was also high correlation between BF% and WHR in both sexes. Collins et al., in their study of association of BMI and BF% among BMI-defined non-obese middle-aged individuals, found that the BMI category was not concordant with the %BF classification for 30% of the population. The greatest discordance between %BF and BMI was observed among %BF-defined overweight/obese women (38). A strong correlation of BMI and BF% in young women was reported in the study of Bakir et al. (39). They obtained correlation coefficients between BMI and BF% of 0.74 for women aged 18-30 years.

Proportions of weight categories were not significantly different over the years in which measurements were made. Students that choose to attend the College of Applied Sciences in Vukovar are similar in weight status throughout the years. This result is different compared to predictions of increase in obesity prevalence, and shows a steady state in the weight status of first-year students during the years examined, without any increase of obesity. It is possible, however, that it might have been too short a period for potential trends to reveal themselves.

Based on the presented results, the conclusion could be made that most of the freshman students at the College of Applied Sciences fall in the category of normal weight, with an

overweight prevalence of around 19-20%, including around 5% obese persons among them. There are also 6.5% of those who are underweight. There is a higher tendency toward the prevalence of overweight persons among men, while among women there is a higher tendency for underweight prevalence. The prevalence of obesity and the overall distribution across the weight categories, as well as the body composition of the first-year students have not changed during the period from 2008 to 2016.

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