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BLOOD PRESSURE MECHANISM

Sympathetic Nervous System and Hypertension

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ABSTRACT

Aim: The review emphasizes on the sympathetic and parasympathetic abnormalities in essential hypertension, the possible mechanisms underlying these abnormalities, and their importance in the development and progression of the structural and functional cardiovascular (CV) damage that characterizes hypertension.

Background: Apart from being a hemodynamic phenomenon, primary hypertension is a vicious syndrome involving abnormal adiposity, overactivation of the adrenergic system, metabolic abnormalities, and activation of the immune system. Physiological studies have established the key role played by the autonomic nervous system in modulating CV functions and in controlling arterial pressure values. Many factors contribute to increased sympathetic nerve activity in metabolic abnormalities including obesity, impaired baroreflex sensitivity, hyperinsulinemia, and elevated adipokine levels.

Review results: Experimental and clinical investigations clearly indicate that the origin, progression, and outcome of hypertension are related to dysfunction of the autonomic CV system, especially to abnormal activation of the adrenergic division. The activation of the sympathetic nervous system is essential in energy homeostasis and can exert intense metabolic effects. Accumulating data from a number of studies suggest that central sympathetic overactivity plays a crucial role in the causative factors and complications of several metabolic conditions that can cluster to form the metabolic syndrome.

Conclusion: This review provides an evidence of attenuation of autonomic CV control in essential hypertension and that sympathetic overdrive is a major component of this autonomic dysregulation. Arterial pressure control requires complex integration of regulatory mechanisms across multiple physiological systems. A continuous increase in blood pressure therefore, reflects a failure of one or more of these controls.

Clinical significance: The findings discussed herein provide a rationale for pursuing sympathetic deactivation by nonpharmacological as well as pharmacological interventions aimed at lowering elevated blood pressure values and protecting patients from hypertension-related complications.

Keywords: Hypertension, Neural regulation, Sympathetic nervous system.

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BACKGROUND

Arterial hypertension has been recognized as a major killer and cause of the global cardiovascular (CV) morbidity. Despite clinical and research advances in hypertension prevention and management,[1] hypertension is present in one-third adults, with a growing incidence and prevalence worldwide.[2] Despite the increase in hypertension awareness and the use of blood pressure (BP)-lowering drugs, patients with a higher CV risk have less controlled pressure in comparison to average risk patients.[3]

In this review, our focus is limited to the relation of autonomic nervous system (ANS) to essential or primary hypertension, with no obvious reference to the secondary hypertension because its prevalence is less,[4] and its causes do not include alterations of central or reflex autonomic drive.

The sympathetic nervous system (SNS) is part of the ANS which is important for the regulatory mechanisms of blood pressure, electrolyte balance, and maintenance of homeostatic state. The SNS is instrumental in the regulation of daily energy expenditure through the control of resting metabolic rate and thermogenesis in response to various physiological stimuli, changing states of energy, intake of food, consumption of carbohydrate, and hyperinsulinemia. Furthermore, the activation of sympathetic nerves in various target organs including pancreas, liver, skeletal muscle, and adipose tissue can elicit acute catabolic responses like glycogenolysis and lipolysis. Overactivation of SNS is strongly associated with at least two components of the metabolic syndrome, i.e., hypertension and obesity.

In the last 40 years, the relationship of SNS to development, progression, and complications of hypertension has been investigated extensively. Enhanced sympathetic activation is the key mechanism involved in human hypertension, and its deleterious CV consequences are well recognized.[5-8] Increased sympathetic nerve activity of muscle[4] and augmented cardiac and renal noradrenaline release from the sympathetic nerves[5,9,10] feature in essential hypertension. Sympathetic overactivity starts early in course of time and has been reported even in very low-risk subjects with high-normal BP.[7] The magnitude of this sympathetic overdrive has been closely related to hypertension-related end-organ damage.[8,11,12]

RESULTS

Sympathetic activation in hypertension arises from either compromised peripheral regulatory mechanisms or a primary increase in sympathetic outflow within the central nervous system.[13] Peripheral regulators of sympathetic activation and CV function include cardiopulmonary mechanoreceptors, arterial baroreceptors, and chemoreceptors.

Baroreceptor dysfunction has been found in patients with hypertension as well as in subjects with a positive family history of hypertension with normal BP levels.[14] Likewise, gain of the cardiopulmonary baroreflex regulation of sympathetic activity is higher in hypertensive patients in comparison to their normal counterparts and the augmentation is not related with attenuation of the arterial baroreflex.[15]

Another causal mechanism leading to higher sympathetic activation is potentiated sensitivity of vascular chemoreceptors. The impairment of arterial chemoreceptors contributes to the pathogenesis of human hypertension.[16] Microneurography-based studies have confirmed an exaggerated hypoxic sympathetic drive in hypertension;[17] the deactivation of peripheral chemoreceptors resulted in BP and muscular sympathetic nerve activity (MSNA) reduction in essential hypertension.[16,18] Persistent generalized sympathetic activation evident in arterial hypertension is critical in progression of disease leading to increased CV morbidity and mortality.

Hypertension is the chronic derangement of autonomic CV regulation. These sympathetic and parasympathetic CV influences play a vital primary role in homeostatic control of the CV system. In animal models of hypertension, not only increased sympathetic nerve activity but also decreased parasympathetic tone is associated with and responsible for the causation and maintenance of high BP, and even hypertension-related sequelae.[19-21] Abnormal increase in circulating plasma levels of the sympathetic neurotransmitters has been demonstrated repeatedly in normotensive persons with a family history of hypertension. Moreover, these abnormalities are traceable when measured during various maneuvers that activate sympathetic CV control.[22-26] Pressor responses to a variety of laboratory stressors have also predicted for the subsequent development of hypertension.[27,28]

Further, to strengthen the concept, a more refined experimental approach (measurement of the clearance of neurotransmitter norepinephrine after the infusion of small amounts of its radiolabeled form) demonstrated that the rise in norepinephrine is not due to its reduced tissue disposal but rather due to an increased spillover rate from neuroeffective junctions and thus to enhance norepinephrine secretion from sympathetic nerve terminals.[29] In the microneurographic studies which were originally aimed to find out postganglionic sympathetic nerve traffic to the circulation of skeletal muscle, including controls with normal blood pressure, both the quantity and amplitude of sympathetic bursts were higher in individuals with family history of hypertension[30] as well as in those with white-coat and masked hypertension,[31-33] i.e., subjects with greater risk of progressing to true hypertension.[34] Thus, it suggests that a central sympathetic oversecretion is present in individuals predisposed to developing high BP, which can be because of either a genetic background or a specific BP phenotype.

Interestingly, this sympathetic hyperactivity is likely to be accompanied by an impaired (decreased) vagal influence on the heart. Evidence for this has arrived from studies of the normotensive offspring of hypertensive parents. In this study, spectral analysis of the R–R interval showed a reduction of low-frequency fluctuations in heart rate;[35,36] these are known to be a component of heart rate variability (HRV) act by vagal modulation of the sinus node.[37] Thus, both sympathetic and parasympathetic divisions may be altered in greater risk individuals, even when an overt BP abnormality is not yet visible. This explains the important role of the SNS in the development of hypertension.

Further support for a causative role of sympathetic dysfunction in high BP comes from the multiple lines of evidence showing the association of increased sympathetic tone along with decreased cardiac vagal drive to young hypertensive individuals even in the early stages of hypertension. Seminal studies revealed that in young patients with hyperkinetic syndrome (increase in systolic BP, increase in cardiac output, and a resting tachycardia),[38] the elevations in heart rate depended on a reduced vagal inhibitory influence on the sinus node because the IV administration of atropine (which selectively blocks the effect of the vagal neurotransmitter acetylcholine on muscarinic receptors) restored both heart rate and BP to the normal values of the control group.[39] A smaller reduction in glandular secretions under parasympathetic control, such as salivary flow,[40] in borderline hypertensive individuals suggest that in early hypertension, parasympathetic impairment is not confined to the heart or to the CV system; rather, it is generalized to all functions involving parasympathetic division of ANS.

A reduction in sympathetic nerve activity and an enhancement in cardiac vagal drive have also been attributed as an explanation for the lifestyle interventions used in clinical practice to lower an elevated BP, such as physical exercise and loss of body weight.[41,42] The decrease in pressure is accompanied in either case by a reduction of muscle sympathetic nerve traffic and the

increased plasticity of baroreceptor activity to regulate the sympathetic drive.

In hypertensive individuals with their normal salt intake (9–18 gm/day), the concentrations of plasma sodium and cerebrospinal fluid (CSF) sodium are slightly raised as compared with values observed in the same individual on a low-salt (3–4 gm/day) intake. Studies performed by using the animal models hypothesized that these increased plasma sodium and/or CSF sodium concentrations activate brain's sodium/osmoreceptors, which are located mainly at the hypothalamus, to trigger sympathoexcitation.[43,44] These osmoreceptors do not have ability to reset significantly with prolonged change in osmolality and thus can provide a continued signal to chronically increase sympathetic tone.[44] Similarly, dehydration-induced increase in osmolality also acts in the hypothalamus to promote sympathoexcitation and support BP.[45,46]

In established cases of hypertension, dietary sodium restriction seems to further alter autonomic balance, i.e., to impair reflex sympathetic control, and to side by side further enhance the number of sympathetic bursts to the skeletal muscle circulation. The effect is more when the sodium restraint is marked but present even with moderately low-sodium intake (80 mmol NaCl/day), suggesting that a low-sodium diet, as usually implemented in daily life, enhances the hypertension-related alterations of autonomic CV control.

The adrenergic hyperactivity accompanying early hypertension has both a central and a peripheral component that can further amplify the CV effects of adrenergic stimuli. This may change in the subsequent phase of the disease, however, because a permanent increase of sympathetic drive generates a downregulation of adrenergic receptors[47] that may partly offset the consequences of sympathetic hyperactivation. The downregulation of peripheral β-adrenergic receptors has been observed in stage 1 hypertension, thus generating the hypothesis that its occurrence leads to an alteration of energy balance that favors weight gain.[48]

The adrenergic overdrive that characterizes hypertension is not stable but instead follows the blood pressure increase and the progression from uncomplicated to complicated stages that may occur in the course of the disease.[49,50] A number of studies revealed that sympathetic activation is normally more pronounced in complicated than in noncomplicated stages of hypertension. As compared with the respective controls, sympathetic activations has been shown to be more pronounced in hypertensive patients with (1) left ventricular hypertrophy,[51-53] (2) impaired left ventricular diastolic function,[54] (3) systolic heart failure,[55] and (4) advanced ventricular arrhythmias. There are consistent data to suggest that activation of the adrenergic nervous system evolves from less to more severe hypertensive states, i.e., it increases with the increase in blood pressure values, the development of organ damage, and the appearance of clinically apparent renal or cardiac disease or of treatment ineffectiveness.

The sympathetic overactivity associated with the established hypertensive phase is not uniformly distributed throughout the body; rather, regional differences are such that it is marked in some districts and modest or even absent in others. For example, radiolabeling studies have shown that in established hypertension, there is increased norepinephrine spillover into the cerebral, coronary, and renal circulation but not at the level of the splanchnic and pulmonary vascular districts.[56,57]

Most importantly, sympathetic nerve activity may be, either directly or indirectly, a predictor of CV morbidity and mortality. First, sympathetic activity is associated with and is probably a determinant of blood pressure variability,[58,59] which itself is a CV risk factor independent of average blood pressure values.[60] Second, sympathetic hyperactivity, as measured by plasma norepinephrine, systemic norepinephrine spillover, or microneurography, is known to be an independent prognostic factor for CV-related morbid or fatal events in patients with heart failure, end-stage renal failure, major cardiac arrhythmias, obstructive pulmonary disease, or after an acute stroke.[61-67]

Several mechanisms have been proposed to explain the sympathetic overdrive seen in individuals with essential hypertension. An attractive hypothesis is that overdrive depends on an excessive adrenergic response to environmental stimuli, leading initially to greater blood pressure variability and later to a sustained hypertensive state.[68] It has also been proposed that sympathetic overdrive originates from a reduced inhibitory influence of the arterial baroreceptors because cellular impairment or a stiffening of the arterial wall where these baroreceptors are located attenuates their responsiveness to blood pressure changes. Furthermore, in hypertensive humans, the arterial baroreflex loses much of its ability to control the heart rate, but it continues to effectively modulate blood pressure and sympathetic activity.[50] As the blood pressure increases, so does the range of blood pressure and sympathetic modulation exerted by the baroreflex; this resetting phenomenon helps to stabilize both blood pressure and sympathetic activity at the higher values.[41] Secondly, an increased sympathetic drive may be favored by the reduced inhibitory influence of cardiac stretch receptors, which occurs when hypertension-related diastolic dysfunction and left ventricular hypertrophy

reduce the stimuli (changes in cardiac volume and myocardial contractility) to which these receptors respond.[69]

Other possible mechanisms are chemoreceptor stimulation by hypoxemia, hypercapnia, acidosis, reduction of arterial blood flow, temperature change, and low levels of glucose.[58,70-72] Reflex cardiorespiratory responses are characterized by hyperventilation and increased sympathetic discharge to the vascular beds and the heart. Tachycardia associated with hyperventilation in turn augments cardiac output, acutely raising arterial blood pressure. The carotid body (CB) chemoreceptor (glomus or type I) cells are considered the sensors of the natural stimuli.[58,70-72] Its potential role as a sympathostimulating factor has been strengthened by the observation that hypoxia is important for the increased sympathetic activity seen in individuals with sleep apnea,[73] a condition frequently associated with obesity and, as such, highly prevalent in hypertension as well.[74] Further studies revealed that insulin and leptin increase postganglionic sympathetic drive[75] and that central and peripheral sympathostimulating effects are also exerted by angiotensin II.[76,77] In these instances, the stimulation is reciprocated by the SNS in a kind of positive feedback relationship.[78] Thus, several mechanisms are potentially capable of activating sympathetic nervous influences in essential hypertension, but the relative importance of each one in the different stages or types of hypertension remains to be clarified.

Autonomic dysfunction, characterized by sympathetic hyperactivity, vagal impairment, and impaired baroreflex sensitivity (BRS), is characteristic of the metabolic syndrome and of disease conditions where the CB may be implicated, such as hypertension.[79-82] In addition, patients with metabolic disorders also have increased levels of leptin, reactive oxygen species (ROS), and proinflammatory cytokines. It is conceivable that CB chemosensory function may be compromised in the metabolic syndrome. In fact, it is known that obesity increases adipokine levels [i.e., leptin, resistin, tumor necrosis factor (TNF)-α, and interleukin (IL)-6], which through cascade of reactions contributes to the endothelial dysfunction.[83] Endothelial dysfunction is characterized by an imbalance in the release of vasoconstrictors and the endothelium-dependent relaxants. Hence, increases in endothelium-derived constriction factors (EDCFs) are common in pathophysiological conditions like hypertension.

The specific causes of the increased sympathetic activity in essential hypertension include genetic influences (family history), behavioral (salty food preference), psychosocial (mental stress), and lifestyle (physical inactivity).[84,85] Of prime importance is obesity. The prevalence of hypertension in middle-age obese subjects is 40 to 50%. Obesity increases the sympathetic (including the renal sympathetic) nervous system activity through the high sodium intake-related mechanisms and through other mechanisms, such as hyperleptinemia.[86,87] On the contrary, clinical and epidemiological studies indicate the importance of chronic mental stress in the pathogenesis of essential hypertension.[88,89] Hypertensive subjects may decrease their blood pressure with a meditation program.[90,91]

Psychosocial stress can increase the activity of the SNS by potentiating the neural mechanisms activated by a high-salt intake.[92] Race and ethnicity may also influence the predisposition to the sensitivity of blood pressure to salt. Black Africans have a higher prevalence of hypertension and more frequent severe hypertension; they also have a greater blood pressure sensitivity to salt intake than do people of other ethnic origins.[88,93] Physical inactivity also appears to be important.[84] Aerobic fitness and physical activity are each inversely related to the development of hypertension.[94] Aerobic exercise training in sedentary normotensive and hypertensive people reduces blood pressure and renal and muscle sympathetic nerve activity.[95,96]

Activation of the renal sympathetic nerves causes a change in functionality in terms of renal hemodynamic, excretory and secretory functions. At very low rates of activity, there is a prompt increase in renin secretion, a beta-adrenoceptor-mediated effect. At slightly higher levels, there is a concomitant increase in fluid reabsorption, and it is only at the highest level of sympathoexcitation that there is a reduction in renal hemodynamics. Normally, in response to everyday activities (e.g., taking in a meal containing a high content of sodium chloride), sympathetic control is exerted on renin release and fluid reabsorption to ensure that there is a smooth excretion of an appropriate proportion of the sodium load. It is only when there are acute threatening "fight and flight" situations requiring redistribution of blood that sympathetic activity increases to a level at which renal blood flow and glomerular filtration rate are reduced, but these are short-term responses that have little long-term impact on fluid balance.

The long-term increase in arterial BP often affects heart and kidneys. The higher the blood pressure, the greater is the resistance needed by heart to function. A higher blood pressure could lead to an increase in the frequency and contractile force. In the long term, this change in blood pressure could compromise cardiac function.

Increase in sympathetic activity enhances systemic and regional norepinephrine spillover and elevate resting heart rate. This condition has been linked to hypertension, obesity, and insulin resistance. Furthermore, it has been shown that high levels of fasting insulin, an index of insulin resistance, were positively associated with the low-to-high frequency (LF/HF) ratio of the heart rate

variability – an index of the sympathovagal balance at the heart level.

In view of the strong relationship among obesity, metabolic syndrome, and the development of CV risk factors, it is important to elucidate autonomic disturbances that occur in obese individuals. Though the autonomic disorders are not homogeneous in obesity, some studies have demonstrated that most individuals exhibit sympathetic hyperactivity. Both BRS and HRV are impaired in obese women. Esler et al[97] demonstrated that the sympathetic tone in obese individuals is increased in some target organs like kidney, skeletal muscle, and vessels.

Sympathetic hyperactivity in obesity indicates that obesity impairs renal-pressure natriuresis, increases renal tubular sodium reabsorption, and causes hypertension. Various studies have demonstrated increased blood pressure and serum catecholamine levels in obese individuals. The loss of weight is associated with the decrease in plasma concentration norepinephrine. Obese hypertensive children show increase in sympathetic nerve activity. However, in these patients, a low-salt diet (or hyposodic diet) is capable of promoting a decrease in arterial pressure. These studies point out the fact that sympathetic hyperactivity is related to sodium retention and increase of arterial blood pressure in obese children. Furthermore, MSNA is increased in obese (normotensive and hypertensive) as compared with nonobese normotensive individuals.

Moreover, it has been shown that the MSNA and the plasmatic norepinephrine are reduced and the BRS is increased after weight loss in normotensive obese individuals. The heart rate variations are a visible effect of the autonomic influences on the heart in cases of emotional stress. An inability to sustain varying heart rate is an important risk factor to the development of cardiovascular disease (CVD). The study of Brunner et al[98] demonstrated a relative sympathetic dominance and a lower vagal tone to the heart in MS cases, thereby indicating sympathovagal imbalance in those individuals.

Jamerson et al[99] demonstrated an inverse relationship between sympathetic vascular tone and insulin-mediated cellular consumption of glucose. Thus, the increased SNA as observed in obese individuals increases the vascular constriction and impairs the glucose transportation into the cells. Previous studies with obese models have implicated vascular constriction in insulin resistance. Specific alfa-adrenergic vasoconstriction seems to be more malefic on glucose consumption than the angiotensin-induced vasoconstriction. This suggests the sympathetic influence on glucose metabolism.

In patients with type II diabetes mellitus (T2DM), metabolic syndrome has approximately 70% of prevalence rate. The basic mechanism involved in the pathogenesis of T2DM is the insulin resistance. The insulin resistance, in turn, is strongly associated with sympathovagal imbalance. Furthermore, many data suggest the involvement of increased SNS activity in insulin resistance. Epidemiological studies have found a correlation between insulin resistance and hypertension. In patients with type I diabetes mellitus, the hypertension is usually developed after the onset of nephropathy and it is associated with renin–angiotensin-induced SNS activation. On the contrary, the prevalence of hypertension in patients with T2DM is extremely common. Thus, it can be assumed that insulin resistance and hypertension as observed in the MS are closely linked with sympathetic overactivation.

Sympathetic overload is implicated in the pathogenesis and/or deterioration of essential hypertension through the modification of heart rate, cardiac output, peripheral vascular resistance, and renal sodium retention. Some studies with essential hypertensive patients have plasmatic overflow of norepinephrine. This overflow indicates an increase in the activation of sympathetic outflow to the heart, kidneys, and cerebrovascular circulation of these individuals. These observations are evidences that some target organs are negatively affected by increased blood pressure.

DISCUSSION

The sympathetic hyperactivity with early hypertension has both central and peripheral component that further amplifies the CV effects of adrenergic stimuli. This can change the progression of the disease because a permanent increased sympathetic drive creates a downregulation of adrenergic receptors[47] that may partly offset the consequences of sympathetic overdrive. The downregulation of peripheral beta-adrenergic receptors as observed in stage 1 hypertension generates the hypothesis that its occurrence leads to an alteration of energy balance that favors increase in weight.[48]

The adrenergic overdrive, which is one of the cause of hypertension and characterizes it, follows the blood pressure increase and the progression from uncomplicated to complicated stages of hypertension that may occur in the course of the disease.[49,50] A number of studies revealed that sympathetic activation is normally more pronounced in complicated than in uncomplicated stages of hypertension. As compared with the respective controls, sympathetic activation is more pronounced in hypertensive patients with (1) left ventricular hypertrophy,[51-53] (2) impaired left ventricular diastolic function,[54] (3) systolic heart failure,[55] and (4) advanced ventricular arrhythmias. There are sufficient data to suggest that activation of the SNS evolves from less to more severe hypertensive states, i.e., it increases with the increase in blood pressure values, the development of organ damage,

and the appearance of clinically apparent renal or cardiac disease or even with treatment failure.

The sympathetic overactivity associated with the established hypertensive phase is not in uniform distribution throughout the body; rather, regional differences are such that it is marked in some districts and modest or even absent in others. For example, radiolabeling studies revealed that in established hypertension, the increased norepinephrine spillover is restricted to the cerebral, coronary, and renal circulation but not at the level of the splanchnic and pulmonary vascular districts.[56,57]

Most importantly, sympathetic nerve activity may be a predictor of CV morbidity and mortality. First, sympathetic activity has an association with and is probably a determinant of blood pressure variability,[58,59] which itself is a CV risk factor independent of average blood pressure values.[60] Secondly, sympathetic hyperactivity is known to be an independent prognostic factor for CV-related morbid or fatal events in patients with heart failure, end-stage renal failure, major cardiac arrhythmias, obstructive pulmonary disease, or after an acute stroke.[61-67]

Several mechanisms have been proposed to explain the adrenergic overdrive seen in subjects with essential hypertension. This overdrive depends on an excessive adrenergic response to environmental stimuli, leading initially to greater blood pressure variability and later to a sustained hypertensive state.[68]

Furthermore, in hypertensive humans, the arterial baroreflex loses much of its ability to control the heart rate, but continues to effectively modulate blood pressure and adrenergic activity.[50] The increased blood pressure increases the range of blood pressure and sympathetic modulation exerted by the baroreflex; this resetting phenomenon helps to stabilize both arterial pressure and adrenergic activity at the higher values.[41] Secondly, an enhanced sympathetic drive may be favored by the reduced inhibitory influence of cardiac stretch receptors, which occurs when hypertension-related diastolic dysfunction and left ventricular hypertrophy reduce the stimuli (changes in cardiac volume and myocardial contractility) to which these receptors respond.[69]

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sive and hypertensive individuals reduces blood pressure and renal and muscle sympathetic nerve activity.[95,96]

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Jamerson et al documented an inverse relationship between sympathetic vascular tone and the insulin-mediated cellular glucose consumption. Therefore, the increased adrenergic activity as observed in obese individuals increases the vascular constriction and impairs glucose transportation into the cells. Further studies on obesity have implicated vascular constriction in insulin- resistance. Specific alfa-adrenergic vasoconstriction is more malefic on glucose consumption than the angiotensin-induced vasoconstriction, thus suggesting the sympathetic influence on glucose metabolism.

In type II diabetic patients, metabolic syndrome has approximately 70% of prevalence rate. The basic mechanism involved in the pathogenesis of T2DM is insulin resistance. In turn, the insulin resistance is strongly associated with sympathovagal imbalance. Further, numerous data suggest the involvement of increased SNS activity in insulin resistance. Epidemiological studies have found a correlation between insulin resistance and hypertension. In type I diabetic patients, the hypertension is usually developed after the onset of nephropathy and has an association with renin–angiotensin-induced SNS activation. On the contrary, the prevalence of hypertension in type II diabetic patients is extremely common. Thus, it can be hypothesized that insulin resistance and hypertension in the metabolic syndrome are closely linked with sympathetic overactivation.

Sympathetic overload is implicated in the pathogenesis as well as in the deterioration of essential hypertension through the modification of heart rate, cardiac output, peripheral vascular resistance, and renal sodium retention. Some studies documented a plasmatic overflow of norepinephrine in essential hypertensive patients, thus indicating an increase in the activation of sympathetic outflow to the heart, kidneys, and cerebrovascular circulation of these subjects. These observations conclude that some target organs are negatively affected by increased arterial pressure.

CONCLUSION

This review supports the attenuation of autonomic CV control in essential hypertension, thus concluding that adrenergic overdrive is a major component of this autonomic dysregulation. It also shows that adrenergic activation appears early in the course of the disease and becomes more prominent with the increasing severity of the hypertensive state. The adrenergic mechanisms also participate in the development of target-organ damage, which is frequently detectable in hypertensive patients.

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