Potential Clinical Application of Recently Discovered Brain Mechanisms Involved in Hypertension

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Accumulating evidence indicates that central activation of the sympathetic nervous system plays an important role in hypertension. The aim of this review is to inform clinicians about the involvement of brain mechanisms in clinical hypertension and the applicability of recent findings to clinical practice. Clinicians, particularly cardiologists and nephrologists, are now initiating clinical treatment of hypertension that targets the sympathetic nervous system using novel techniques, such as catheter-based renal denervation and carotid baroreflex activation therapy. Renal denervation reduces efferent renal sympathetic activity, thereby decreasing renal tubular sodium reabsorption, supporting renal blood flow, and inhibiting the renin–angiotensin–aldosterone system, which has a blood pressure-lowering effect. In addition, it has been proposed that inhibition of central sympathetic outflow via reduced renal afferent input to the brain leads to a long-term reduction in blood pressure. Carotid baroreflex activation therapy reduces blood pressure and central sympathetic outflow, and the sympathoinhibitory action lasts for a much longer period than previously thought, without rapid adaptation. In addition, the currently used antihypertensive drugs are suggested to act on the central nervous system.

Neural Mechanisms Are Re-Emerging as a Pathogenesis and Pathophysiology of Hypertension

The brain is essential for processing and integrating various stimuli from the periphery to maintain blood pressure and fluid homeostasis. The circumventricular organs, hypothalamus, and brain stem are major brain regions contributing to this function. During the past several decades, however, neural mechanisms, such as arterial baroreflex function, have been considered to be involved in short-term blood pressure regulation, but not in long-term blood pressure control (i.e., hypertension). Arterial baroreceptors adapt and thus cannot provide accurate negative feedback signals to the brain to maintain normal arterial pressure. Importantly, surgical removal of the afferent projections of arterial baroreceptors (sinoaortic denervation) results in a transient increase in arterial pressure but does not lead to chronic hypertension. These findings suggest that the renin–angiotensin system and kidney are major contributors to the pathogenesis of hypertension.

Several important series of studies revealed that arterial baroreflexes have a role in long-term blood pressure regulation. First, Thrasher produced chronic unloading of arterial baroreceptors in dogs, in which 1 carotid sinus and the aortic depressor nerve were cut, and the carotid sinus from the remaining innervated region was isolated from the systemic arterial pressure. Baroreceptor unloading was then induced by ligating the common carotid artery proximal to the innervated sinus, which led to an increase in arterial pressure that lasted for several weeks; although the initial increase in arterial pressure was not sustained, the level remained above control levels. Lohmeier et al subsequently observed that electric stimulation of the carotid baroreceptors for 7 days and 2 weeks elicits a sustained reduction in arterial pressure and heart rate associated with a decrease in plasma norepinephrine and renin although the effect may be model dependent and renal nerve independent. In addition to these important observations, a growing body of evidence from recent studies suggests that activation of the sympathetic nervous system has an important role in both the occurrence and the progression of hypertension, as well as target organ damage. Several studies have demonstrated abnormalities of baroreceptor function, but it is unclear why enhanced sympathetic activity occurs in hypertension. These findings have attracted the interest of many researchers in the brain mechanisms leading to enhanced central sympathetic outflow in hypertension.

What Are the Brain Mechanisms of Hypertension?

Specific Brain Pathway for Activation of the Sympathetic Nervous System in Hypertension

Many brain mechanisms of hypertension related to activation of the sympathetic nervous system have been discovered. The most investigated factor is the brain renin–angiotensin system, which markedly contributes to the central regulation of blood pressure. Circumventricular organs, such as the subfornical organ (SFO), organum vasculosum lamina terminalis, and median eminence, lack a blood–brain barrier and, importantly, contain a high density of angiotensin type 1 (AT1) receptors. Therefore, these areas can access circulating angiotensin II and are also activated by locally produced angiotensin II. In addition, these regions send efferent...
 projections to the paraventricular nucleus (PVN) of the hypothalamus, the median preoptic nucleus, and the rostral ventrolateral medulla (RVLM) in the brain stem. In hypertension, the SFO/organum vasculosum laminae terminalis–PVN–RVLM pathway is activated in association with AT1 receptor activation. Other brain sites, such as the median preoptic nucleus, which receives the input from the SFO and organum vasculosum lamina terminalis, are also essential to the pathogenesis of angiotensin II–induced hypertension. AT1 receptors and glutamatergic receptors in the RVLM support blood pressure in hypertensive rats. Because AT1 receptors in the brain are responsible for sympathoexcitation, which are also activated independent of circulating angiotensin II, it is not clear how these pathways become activated in hypertension. One possibility is genetic predetermination, such as in spontaneously hypertensive rats (SHRs). Another possibility is that environmental factors, such as stress, obesity, and high-salt intake, activate the AT1 receptors responsible for autonomic functions. The role of oxidative stress in hypertension has been studied extensively in various tissues. Angiotensin II stimulates NAD(P)H oxidase, thereby producing superoxide. In the brain, superoxide mediates the angiotensin II–induced pressor response. Circulating angiotensin II can act on AT1 receptors in the SFO, the action of blood-borne angiotensin II on the SFO involves superoxide production. Thereafter, superoxide and related reactive oxygen species (ROS) generation in the PVN and RVLM increase sympathetic activity in hypertensive rats.

In our series of studies, we focused on the imbalance of central nitric oxide (NO) and ROS in the regulation of sympathetic activity as a cause of hypertension, as well as its progression. This concept is now established in this field of research although some details remain controversial. NO synthase isoforms may have different actions in autonomic control. The role of ROS production in the normal state is not clear, but in general NO in the brain has sympathoinhibitory actions, even in the normal state. A critical question is which cells in which nuclei are key players in the whole system? A greater understanding of how these signaling pathways affect central sympathetic output as a final pathway is important. Basically, the signaling pathways seem similar to those of other organs, such as the kidney and heart and the vasculature. Persistent activation of the sympathetic nervous system also affects target organs, such as the brain, heart, kidney, and vasculature. Accumulating evidence indicates that upstream of the imbalance of NO and ROS production, activation of the renin–angiotensin–aldosterone system has a crucial role in eliciting abnormalities, thereby causing increased sympathetic activity.

**What Are the Targets for Central Sympathetic Outflow?**

**Brain AT1 Receptors as a Target for Reducing Central Sympathetic Outflow**

In hypertensive rats, oxidative stress is increased in both the PVN and the RVLM. AT1 receptor stimulation in the RVLM induces activation of the NAD(P)H oxidase/rac1 pathway leading to ROS generation. Further, caspase-3 activity in the RVLM is significantly higher in stroke-prone SHR (SHRSP) than in Wistar-Kyoto rats. Intracerebroventricular infusion of an AT1 receptor blocker in SHRSP inhibits the caspase-3 pathway in the RVLM. It is not clear how increased apoptotic signaling activates sympathetic activity at this stage. Further investigation is warranted, however, to examine which cells are affected and the type of signals, including cytokines, that have a role in this phenomenon. Intracerebroventricular infusion of angiotensin II also elicits toll-like receptor-4 activation as the innate immune system, which might be related to the concept connecting the immune system and renin–angiotensin system in the brain, as previously described. In mice with heart failure, intracerebroventricular infusion of losartan reduces the enhanced sympathetic outflow through the toll-like receptor-4 pathway. A recent study suggests that activation of toll-like receptor-4 contributes to blood pressure regulation and vascular function in SHRs.

Based on these findings, we tested the effects of oral treatment with AT1 receptor blockers (ARBs) to reduce oxidative stress within the brain and decrease blood pressure via sympathoinhibitory effects in SHRSP. Interestingly, telmisartan and olmesartan decreased blood pressure in association with antioxidant effects in the brain. Despite the fact that baroreflex-mediated sympathoexcitatory responses were observed after hydralazine and diuretic treatments, ARBs did not increase sympathetic activity measured by urinary norepinephrine excretion. Because these effects were not observed for all ARBs, however, it is likely that the effects of various ARBs differ with regard to their sympathoinhibitory and antioxidant effects in the brain. Furthermore, the pressor response evoked by microinjection of angiotensin II is markedly attenuated in SHRSP treated with telmisartan. In addition, the depressor response evoked by tempol or apocynin is attenuated in SHRSP treated with telmisartan. Together, these findings indicate that oral treatment with telmisartan affects AT1 receptors in the RVLM and reduces oxidative stress via the NAD(P)H oxidase/rac1 pathway, thereby causing sympathoinhibition. In support of our findings, Golik et al demonstrated that peripheral administration of telmisartan penetrates the blood–brain barrier in a dose- and time-dependent manner to inhibit the centrally mediated effects of angiotensin II, probably because of its pharmacokinetics and lipophilicity. It remains unknown, however, whether other mechanisms contribute to this action, such as the effect of transporters and the blood–brain barrier damage observed in SHRSP. If damage to the blood–brain barrier allows ARBs to access the RVLM, every ARB should have a similar effect, but this is not the case, indicating the complexity of the mechanisms. It seems that there might be differences in the capability of acting on the autonomic nuclei, such as the RVLM. If the effects of ARBs are mediated mainly by the SFO, which lacks a blood–brain barrier, however, each ARB might have a similar effect on the brain, which does not explain the different effects of each ARB. We cannot exclude the possibility that the SFO has a role in angiotensin II–induced oxidative stress and hypertension. The SFO receives input from circulating angiotensin II, which leads to an increase in sympathetic activity and vasopressin release via oxidative stress.
acting on the cerebrovascular AT1 receptors. The strong sympathoinhibitory effect of each ARB administered intracerebroventricularly into the brain indicates that the brain is the target site for the sympathoinhibitory effects of ARBs. L-Type calcium channels are important for ROS generation after NAD(P)H oxidase activation. Long-acting calcium channel blockers are suggested to act on the brain to reduce oxidative stress, which in turn inhibited sympathetic activity. In particular, azelnidipine is more lipophilic than amlodipine and activates copper/zinc-superoxide dismutase (SOD) and Mn-SOD in the RVLM. In patients with hypertension, azelnidipine reduces heart rate, whereas amlodipine slightly increases heart rate, which might be related to differences in the antioxidative effects of the drugs. Interestingly, we found that exercise training for 6 weeks on a treadmill inhibits sympathetic activity and blood pressure with antioxidative effects in the RVLM of SHRSP. We, therefore, conclude that AT1 receptors and oxidative stress in the RVLM could be important therapeutic targets for hypertension.

Are Brain Mineralocorticoid Receptors Involved in Sympathoeoxcitation?

Recent studies suggest that activation of mineralocorticoid receptors (MRs) in the brain in addition to AT1 receptors plays an important role in activation of the central sympathetic outflow in hypertension and heart failure. In the case of hypertension, salt-sensitive hypertensive models are well studied with regard to the role of brain MR. Recently, we found that activation of MR in the RVLM is involved in the characteristics displayed by SHRSP. We suggest that MR/epithelial Na+ channels in the choroid plexus are also involved in the hypertensive mechanisms of SHRSP. Interestingly, the MR/epithelial Na+ channels pathway in the choroid plexus of SHRSP is activated before high salt intake and cerebrospinal fluid (CSF) [Na+] increases in SHRSP than Wistar-Kyoto rats. This might be related to the increased sympathetic activity in SHRSP. Intracerebroventricular administration of eplerenone, an MR blocker, attenuates the increase in urinary norepinephrine excretion and blood pressure, as well as in CSF [Na+] in association with a decrease in serum/glucocorticoid-inducible kinase 1 as a marker of MR activation in SHRSP fed a high-salt diet. Even in normotensive control Wistar-Kyoto rats, CSF [Na+] is higher than serum [Na+], suggesting the importance of the choroid plexus for the transport of [Na+] from the blood to the CSF and back to the blood. Although the specific mechanisms by which high salt intake actually leads to increases in blood pressure remain poorly understood, it is possible that high salt intake raises CSF [Na+], which leads to increased sympathetic activity via the Na+-sensing circumventricular organs of the brain, such as the SFO, organum vasculosum laminae terminalis, supraoptic nucleus, and median preoptic nucleus (so-called anteroventral to the third ventricle region). The PVN is considered to play a major role in the activation of sympathetic activity and relays the neuronal information to the RVLM and directly to the intermediolateral of the spinal cord. In this cascade, MR and AT1 receptor activation is important for activation of the PVN. Recently we suggested that hypothalamic AT1 receptors are required for MR-related activation of sympathetic activity. Evidence based on the results from the Randomized Aldactone Evaluation Study (RALES), the Epleronone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study (EPHESUS), and the Epleronone in Mild Patients Hospitalization and Survival Study in Heart Failure (EMPHASIS-HF) trial indicates that treatment with MR blockers for heart failure with a reduced ejection fraction is effective for preventing or reversing cardiac remodeling, reducing arrhythmogenesis, and blocking progression, thereby improving the survival ratio. Several mechanisms are involved in the beneficial effects of MR blockers in patients with heart failure, and 1 possible mechanism is the reduction of enhanced central sympathetic outflow, as shown by Zannad et al (Figure 4 in Ref. 55). A recent study demonstrated that aldosterone has benefits for the treatment of diastolic heart failure.

Role of Environmental Factors in Brain Mechanisms of Hypertension

Obesity-Induced Hypertension

Obesity causes sympathoexcitation and hypertension, and the mechanisms involved in these effects are well studied. A mismatched energy balance with excess dietary calorie intake over body energy expenditure is a first step in understanding obesity-induced hypertension. As early as the 1980s, Landsberg proposed that activation of the sympathetic nervous system induced by obesity causes thermogenesis and hypertension. Grassi modified this scheme as shown in the Figure, suggesting that activation of the sympathetic nervous system increases blood pressure, but does not cause thermogenesis, and that nonsympathetic nervous system mechanisms might also play a role in increasing the blood pressure. Although the mechanisms of sympathetic activation in obesity-related hypertension have been historically debated, Esser et al confirmed sympathetic activation, particularly in the kidney, muscle, and heart. Although cardiac norepinephrine spillover is reduced in normotensive obese subjects, it is elevated in obese hypertensive patients compared with normotensive obese subjects, but not so high compared with lean hypertensive patients, suggesting an impaired reflex inhibition of cardiac sympathetic tone in obese hypertensive patients. Interestingly, they suggested that hyperinsulinemia is a secondary phenomenon, driven by central sympathetic activation and resulting from neural vasoconstriction, which reduces skeletal muscle blood flow and glucose delivery to the muscle. Because obesity is accompanied by high rates of norepinephrine spillover from the kidney, increased central sympathetic outflow is considered to be important. It is important to consider the contribution of insulin and leptin signaling for the activation of sympathetic activity. Rapid onset of renal sympathetic nerve activation is observed in rabbits fed a high-fat diet for 3 weeks. Increased plasma leptin and insulin levels may precede blood pressure elevation. Armitage et al suggested that increased leptin and insulin levels are important for the initiation of hypertension but are not required for the maintenance of blood pressure. Alterations in the response of hypothalamic neurons may play a role. Lim et al examined the relative contribution of insulin and leptin in this model. A leptin antagonist reduced renal sympathetic nerve activity in
rabbits fed a high-fat diet after 3 weeks, whereas an insulin antagonist did not, suggesting the importance of brain leptin signaling for sympathoexcitation.62 Mark and colleagues suggested the concept of selective leptin resistance in obesity-induced hypertension.63,64 In animal models of obesity-induced hypertension, increased leptin increased sympathetic nerve activity, despite metabolic leptin resistance. The major sites of action of leptin in the brain are the hypothalamic arcuate nucleus, ventromedial and dorsomedial hypothalamus, nucleus tractus solitarii, and SFO. Multiple differential signaling pathways are suggested. In his recent review article, Mark64 provided detailed discussion of this issue. In contrast, insulin in the brain acutely increases gain of baroreflex control of heart rate and lumbar sympathetic nerve activity, suggesting that postprandial insulin counteracts splanchnic vasodilation.65 Brain oxidative stress plays an important role in the increased central sympathetic outflow in obesity-induced hypertension.66,67 Nagae et al66 demonstrated that oxidative stress in the brain, particularly the hypothalamus, possibly via the activation of NAD(P)H oxidase, contributes to the progression of hypertension through central sympathoexcitation. As described above, brain oxidative stress is also important for activation of the sympathetic nervous system in salt-sensitive hypertension. The findings are supported by clinical studies suggesting that sympathoexcitation and oxidative stress are associated with metabolic syndrome and salt-sensitive hypertension. We recently demonstrated that oral treatment with the AT1 blocker telmisartan inhibits sympathetic activity through antioxidant effects via AT1 receptors and oxidative stress in the RVLM of obesity-prone rats, which also exhibit the characteristics of metabolic syndrome.67 Antihypertensive drugs with brain antioxidant effects could possibly be an effective therapeutic strategy for managing patients with metabolic syndrome. We investigated whether treatment with ARBs improves endothelial and autonomic functions in patients with metabolic syndrome and found that ARBs improve impaired endothelial and baroreflex function and increase high-molecular weight adiponectin levels.68 Interestingly, telmisartan exhibits more beneficial effects than candesartan, and telmisartan reduces sympathetic activity, despite the similar depressor effects of the 2 drugs. These findings suggest that sympathoinhibitory effects differ among ARBs, probably with regard to their actions in the brain, although it is currently difficult to examine this possibility in humans. Different sympathoinhibitory effects of various ARBs are also suggested by other studies that examined ARBs without sympathoinhibitory effects, such as eprosartan and losartan, which do not have sympathoinhibitory effects in patients with hypertension.69 although a recent review article suggested that ARBs and angiotensin-converting enzyme inhibitors have central sympathoinhibitory effects.70 Another important aspect of metabolic syndrome is the relationship between dietary therapy and blood pressure control.71 We found that calorie restriction inhibits sympathetic activity via antioxidant effects in the RVLM of obesity-prone rats.72 We also observed, however, that diet therapy has limitations for obtaining the sufficient effects in patients with metabolic syndrome.68 The limitations of the effectiveness of diet therapy have been discussed elsewhere.71

**Salt-Sensitive Hypertension**

Salt sensitivity is also an important environmental factor in hypertension.73,74 High salt intake acutely reduces circulating renin–angiotensin. Chronic high salt intake, however, particularly in patients with salt sensitivity, leads to the development of hypertension and accelerates hypertensive organ damage.73 A recent study based on direct telemetric recordings demonstrated that high dietary salt and infusion of a small dose of angiotensin II chronically increase renal sympathetic nerve activity.74 There is 1 report demonstrating that chronic high salt intake reduces renal sympathetic activity.75 In this experiment, Yoshimoto et al76 also infused chronic angiotensin II, and renal sympathetic nerve activity was decreased during angiotensin II infusion, but lumbar sympathetic nerve activity remained at control levels, and there was no change in hindlimb
norepinephrine spillover, suggesting differences in the regional sympathetic activity in angiotensin II–salt hypertensive model. It is possible that splanchnic sympathetic nerve activity is activated in this situation because overall sympathetic activation was observed. Sympathetic activation might affect venous capacitance in this regard. Also, renal denervation does not prevent the development of hypertension in Dahl salt-sensitive rats and mild deoxycorticosterone acetate-salt hypertensive rats, suggesting the importance of a renal–nervous component of salt-sensitive hypertension. A recent study demonstrated that renal denervation reduces blood pressure to some extent. Both celiac ganglionectomy and renal denervation, however, more effectively reduce blood pressure. A low dose of angiotensin II with high salt intake in rabbits induces a slow pressor response associated with increases in sympathetic activity, suggesting that the sympathetic component is affected by the circulating angiotensin II level, which leads to its vasocstrictive action.

Left ventricular hypertrophy is caused by hypertension and often leads to diastolic heart failure associated with activation of the sympathetic nervous system. Left ventricular hypertension also activates the sympathetic nervous system, based on measurements of muscle sympathetic nerve activity and norepinephrine spillover and MRI. We recently found that mice with pressure overload produced by aortic banding acquired brain Na sensitivity via the activation of brain epithelial Na⁺ channels through stimulation of the Rho/Rho-kinase pathway and renin–angiotensin system. High salt intake leads to sympathetic activation in these mice after acquired Na sensitivity and deteriorated cardiac function. This raises an important concept suggesting new targets for the prevention and treatment of cardiac deterioration in patients with pressure overload, such as hypertensive heart disease. In previous studies, we demonstrated that activation of the Rho/ Rho-kinase pathway is involved in the sympathetic activation in hypertension. In a subsequent study, we found that activation of epithelial Na⁺ channels and AT1 receptors through MR contribute to sympatoexcitation. Both intracerebroventricular and systemic administration of eplerenone reduce sympathetic hyperactivity and prevent cardiac dysfunction. Left ventricular hypertrophy is often caused by persistent hypertension and is strongly associated with increased sympathetic activity, known as an independent outcome.

Low-Grade Inflammations and Immunity

Low-grade inflammation is now known to be critically involved in the pathogenesis of hypertension, atherosclerosis, and target organ damage. Inflammatory status is modulated by both inflammatory and anti-inflammatory cytokines. Central sympathetic outflow in hypertension and heart failure also seem to be modulated by inflammatory and anti-inflammatory cytokines. There are currently no studies, however, demonstrating that anti-inflammatory drugs reduce blood pressure.

After the discovery that an imbalance of NO and ROS in the autonomic nuclei in the brain is critically involved in the pathogenesis of hypertension, it was suggested that inflammatory processes also occur in the brain, and both circulating and brain proinflammatory cytokines affect sympathetic activation and the progression of hypertension, thereby causing target organ damage. More recently, enhanced innate and adaptive immune responses were shown to have a role in hypertension via cytokines. An increase in central sympathetic outflow induced by intracerebroventricular infusion of angiotensin II has been shown to enhance the splenic cytokine gene expression with increases in both splenic and renal sympathetic nerve activity. In prehypertensive SHR, innate immune system abnormalities may have a role in the pathogenesis of hypertension and provide a novel target for the treatment of hypertension. The immune and nervous systems interact to modulate blood pressure. T cells release cytokines, and cytokine receptors are located in T cells. The central action of angiotensin II is considered to be one of the mechanisms involved in these interactions. Other hypertensive stimuli, such as obesity and chronic stress, are also thought to be related to central angiotensin II action. Circumventricular organs activated by angiotensin II increase sympathetic activity and thereby affect peripheral lymphoid organs, such as the spleen, lymph nodes, and immune cells. T cells induce inflammatory processes in the vasculature and kidneys. In contrast, T regulatory cells, which are immune suppressors having anti-inflammatory activity, are decreased in angiotensin II–induced hypertension and high-fructose diet–induced metabolic syndrome. A recent study demonstrated that immunosenescent CD8⁺ T cells are increased in human hypertension. Thus, low-grade inflammation and oxidative stress play a role in above-mentioned abnormalities, including the brain mechanisms of hypertension. This will be a fruitful area in this field of research although it may take time to determine the clinical implications, particularly the therapeutic aspects.

Molecular Target Drugs and Hypertension

Molecular target drugs are currently used to treat cancer and other diseases. Cardiovascular effects are also observed as side effects of some of these drugs. One such drug is trastuzumab, a monoclonal antibody of the ErbB receptors, which is used to treat some cases of breast cancer. We recently found that neuregulin-1/ErbB signaling in the RVLM may contribute to the neural mechanisms of hypertension. Furthermore, neuregulin-1/ErbB signaling in the RVLM may increase NO synthesis and γ-aminobutyric acid activity, thereby decreasing sympathetic activity. This is one of aspect of neuregulin-1/ErbB signaling. These findings combined with those of other studies suggest the therapeutic potential of recombinant neuregulin-1 for heart failure. Its effectiveness has been demonstrated in animal studies and is now being investigated in clinical studies.

Conclusions

Targeting the brain to reduce enhanced sympathetic outflow should be considered in the treatment for hypertension. Currently used antihypertensive drugs, particularly some ARBs, calcium channel blockers, MR blockers, and statins, have this effect. In this review, we show several animal models of hypertension, which might have different sympathetic activation. However, the effect of ganglionic blocker or renal denervation on blood pressure reduction was greater in several models of hypertension, suggesting neurogenic contribution. Furthermore, Parati and Esler describe
that neurogenic essential hypertension seems to account for >50% of hypertensive patients. The development of drugs more specifically targeting brain AT1 receptors, MR, and pro-inflammatory cytokines may be beneficial for the treatment of hypertension and cardiovascular disease (Figure). Selective centrally acting drugs, such as moxonidine and rilmenidine, 1α-imidazoline receptor agonists, are used before bedtime to treat resistant hypertension and even metabolic syndrome with few side effects. The effectiveness of recently developed and spreading device-based methods, such as renal denervation and carotid baroreflex activation therapy, strongly supports the importance of brain mechanisms and autonomic function in this disease. In particular, the application of renal denervation has become widespread and produces a better outcome in clinical trials for patients with resistant hypertension, left ventricular hypertrophy, glucose intolerance, renal dysfunction, obstructive sleep apnea, and heart failure, suggesting the importance of sympathetic activation in the clinical setting, although, based only on the usual office measurement of blood pressure and heart rate, it is sometimes difficult to determine which patients have sympathetic activation and might have better future outcomes. Inhibition of the renal afferent and renal efferent sympathetic nerves is thought to be an effective central nervous system mechanism for long-term treatment of hypertension. Animal studies have suggested that an NO/ROS imbalance causes renal afferent stimulation, leading to hypertension. The renal nerve can regenerate, however, and thus additional mechanisms contribute to the long-term blood pressure reduction, which might stop the vicious cycle of activation of the central sympathetic outflow. It is important to note that the effectiveness of renal denervation for inhibiting muscle sympathetic nerve activity and the theory of renal afferent contribution are currently under debate. Carotid baroreflex activation therapy clearly acts on the brain, where it modulates the autonomic nervous system. Clinical studies are being performed as a proof-of-principle, although the extent of the effect and whether this abnormality is significantly involved in the pathogenesis of hypertension remain unclear. For example, we do not know whether the effect of renal denervation is caused by the renal afferent blocking effect or whether circulating angiotensin and other hormonal factors are involved. In addition, activation of the central sympathetic outflow to the kidney, heart, and other organs may differ at the initiation stage of hypertension, the development stage of hypertension, or once a patient is in heart failure. A better understanding of the brain mechanisms will facilitate the development of optimal therapies for hypertension to heart failure.

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References


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