REVIEW ARTICLE

Review Series: Basic science in hypertension research

Clarification of hypertension mechanisms provided by the research of central circulatory regulation

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Abstract

Sympathoexcitation, under the regulatory control of the brain, plays a pivotal role in the etiology of hypertension. Within the brainstem, significant structures involved in the modulation of sympathetic nerve activity include the rostral ventrolateral medulla (RVLM), caudal ventrolateral medulla (CVLM), nucleus tractus solitarius (NTS), and paraventricular nucleus (paraventricular). The RVLM, in particular, is recognized as the vasomotor center. Over the past five decades, fundamental investigations on central circulatory regulation have underscored the involvement of nitric oxide (NO), oxidative stress, the renin-angiotensin system, and brain inflammation in regulating the sympathetic nervous system. Notably, numerous significant findings have come to light through chronic experiments conducted in conscious subjects employing radio-telemetry systems, gene transfer techniques, and knockout methodologies. Our research has centered on elucidating the role of NO and angiotensin II type 1 (AT_1) receptor-induced oxidative stress within the RVLM and NTS in regulating the sympathetic nervous system. Additionally, we have observed that various orally administered AT_1 receptor blockers effectively induce sympathoinhibition by reducing oxidative stress via blockade of the AT_1 receptor in the RVLM of hypertensive rats. Recent advances have witnessed the development of several clinical interventions targeting brain mechanisms. Nonetheless, Future and further basic and clinical research are needed.

Keywords brain · oxidative stress · nitric oxide · sympathetic nerve activity · hypertension

Introduction

Sympathoexcitation plays a pivotal role in the pathogenesis of hypertension [1–5]. The brain's regulation of the sympathetic nervous system involves the rostral ventrolateral medulla (RVLM), a renowned vasomotor center situated in the brainstem [6, 7]. The basal central sympathetic outflow is determined by inputs from baroreceptors, chemoreceptors, and visceral receptors, which are relayed through the nucleus tractus solitarius (NTS) [7–12] and the paraventricular nucleus (PVN) of the hypothalamus [8, 13, 14]. Notably, NTS stimulation inhibits neurons in the RVLM through the caudal ventrolateral medulla (CVLM) pathway [15]. (Fig. 1)

Over the past five decades, extensive investigations have explored the regulatory role of various factors in the brain's modulation of sympathetic nerve activity, including nitric oxide (NO), angiotensin II type 1 (AT_1) receptor-induced oxidative stress [16–25], and inflammation [26–32]. This review provides a comprehensive summary of the research on central circulatory regulation, shedding light on the underlying mechanisms of hypertension.

NO dysfunction in the brain causes hypertension with sympathoexcitation

NO is a crucial mediator of intracellular signaling in various tissues, including the central nervous system [33–35]. However, conflicting responses have been observed in acute experiments conducted under anesthetized conditions concerning the effects of NO in the RVLM and NTS [25, 36–41]. Chronic experiments employing in vivo techniques for gene transfer of endothelial NO synthase (eNOS) into the NTS of rats have demonstrated that elevated levels of NO within the NTS lead to a reduction in blood pressure accompanied by sympathoinhibition in both normotensive and hypertensive rats [21, 25, 42]. Additionally, our findings have indicated that NO within the RVLM elicits a

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Graphical Abstract

Clarification of Hypertension Mechanisms
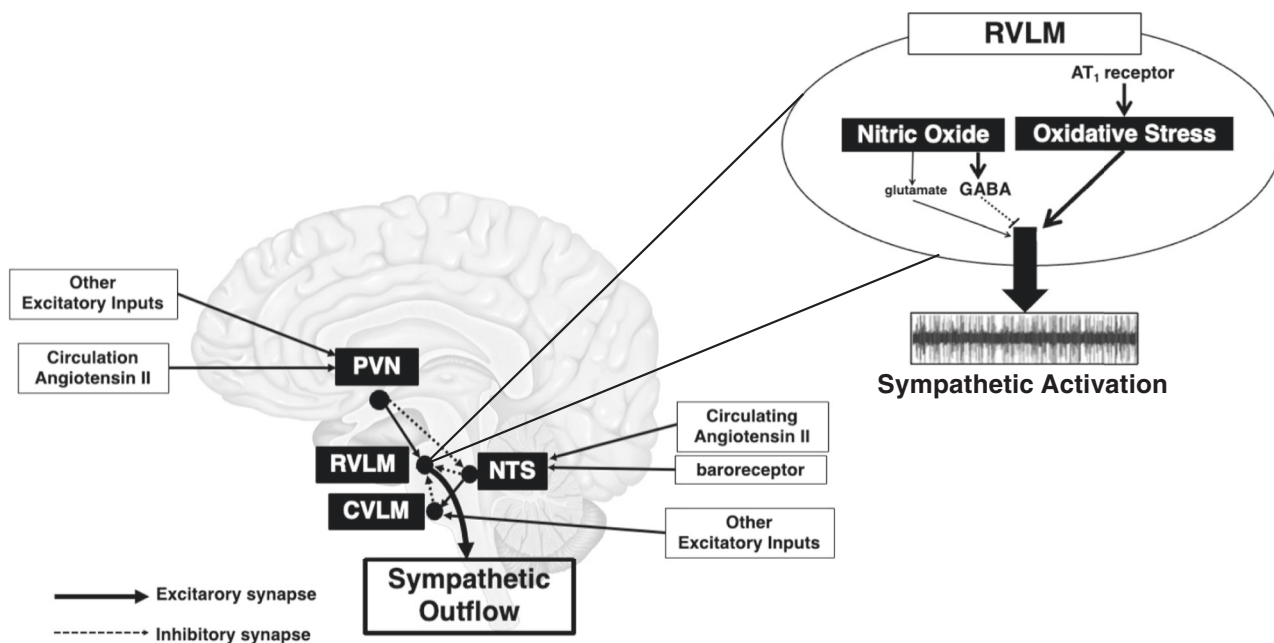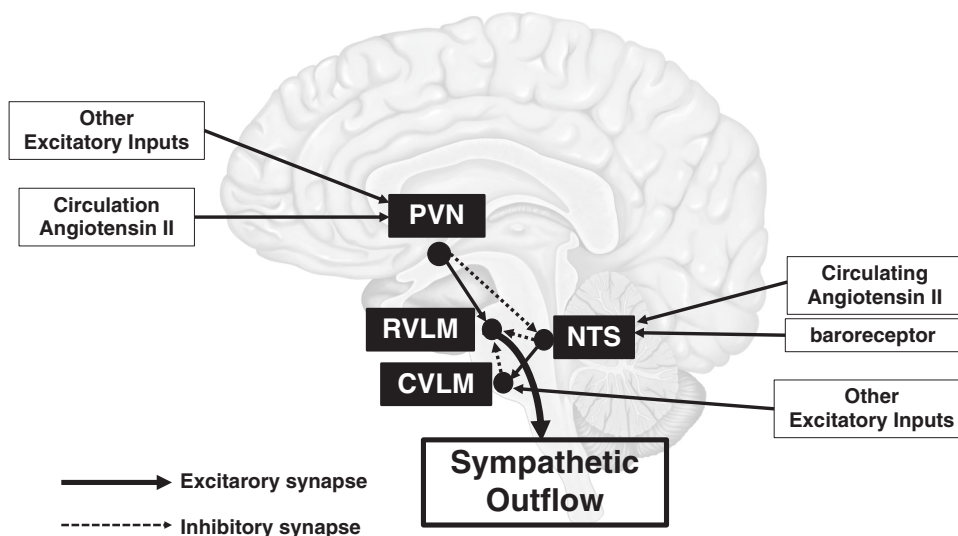# Provided by the Research of Central Circulatory Regulation

Fig. 1 The neural network of nucleus tractus solitarius (NTS), paraventricular nucleus (PVN) of the hypothalamus, rostral ventrolateral medulla (RVLM), and caudal ventrolateral medulla (CVLM)

prolonged depressor response associated with sympathoinhibition mediated by an augmented release of gamma-aminobutyric acid (GABA), an inhibitory amino acid, within the RVLM of normotensive and stroke-prone spontaneously hypertensive rats (SHRSP) [43, 44]. Moreover, NO within the RVLM improves impaired baroreflex control of heart rate in hypertensive rats [45]. These outcomes imply that dysfunctional NO signaling and subsequent

disinhibition of the RVLM may contribute to sympathoexcitation in hypertensive rats.

Accumulating evidence from animal models of hypertension and human hypertensive subjects suggests that alterations in central neural pathways within the PVN, regulated by neuronal NO, modulate sympathetic outflow. Previous investigations have demonstrated that administering an NO donor, sodium nitroprusside, into the PVN leads

to decreased sympathetic nerve activity, blood pressure, and heart rate in rats [46–49].

In light of these investigations, we can postulate that NO within the RVLM, NTS, and PVN induces a depressor response with sympathoinhibition and that NO dysfunction within the brain contributes to hypertension characterized by sympathoexcitation.

Oxidative stress in the brain causes hypertension with sympathoexcitation

Oxidative stress in the brain has been identified as a significant contributing factor to sympathoexcitation, complementing the role of NO. We quantified oxidative stress in the RVLM using the electron spin resonance or thiobarbituric acid-reactive substances method. Our findings revealed an elevation in oxidative stress levels within the RVLM of SHRSP [50–58] and spontaneously hypertensive rats (SHR) [59, 60]. Notably, we conducted microinjections of tempol, a membrane-permeable superoxide dismutase (SOD) mimetic, into the RVLM, resulting in reduced blood pressure and heart rate solely in SHRSP, while normotensive rats showed no response [50]. We also employed adenovirus vectors encoding the manganese SOD (MnSOD) gene to transfect the RVLM in SHRSP. The overexpression of MnSOD in the RVLM elicited decreased blood pressure, heart rate, and urinary norepinephrine excretion exclusively in SHRSP, with no effect observed in normotensive rats [50]. Moreover, our investigation revealed reduced SOD activity within the RVLM of SHRSP compared to normotensive rats, impairing the capability to scavenge superoxide anions [50]. These observations highlight the role of oxidative stress in the RVLM as a causative factor in sympathoexcitation, thereby contributing to the neural pathophysiology of hypertension in SHRSP. Additionally, we demonstrated that oxidative stress in the RVLM induces sympathoexcitation in various other hypertensive models, including salt-induced hypertension [59], dietary-induced hypertension [54, 61], and experimental jet lag [53]. These results align with previous studies conducted by other researchers [19, 20, 22, 62, 63]. Furthermore, in renovascular (two-kidney one-clip) hypertensive rats, sympathoexcitation is associated with oxidative stress in the RVLM and PVN [64–66]. These findings strongly support the notion that the upsurge in oxidative stress within the RVLM is a primary cause rather than a consequence of sympathoexcitation, ultimately leading to hypertension. Several investigations have also demonstrated that oxidative stress within the NTS or PVN contributes to hypertension via sympathoexcitation [67–70].

Sources of oxidative stress in the brain

Within the brain, various sources of oxidative stress, including nicotinamide adenine dinucleotide phosphate (NAD(P)H) oxidase, xanthine oxidase, uncoupled NOS, and mitochondria, activate the AT_1 receptor/NAD(P)H oxidase pathway. This activation primarily induces oxidative stress in the RVLM of SHRSP [55, 71, 72]. The renin-angiotensin system in the brain is associated with augmented central sympathetic outflow [73–79]. Notably, it has been established that mitochondria-derived oxidative stress mediates angiotensin II-induced sympathoexcitation in the brain [80, 81]. Administration of exogenous angiotensin II into the RVLM elicits a pressor response through sympathoexcitation [82, 83]. In hypertensive rats, the inhibition of the AT1 receptor in the RVLM by AT1 receptor blockers induces sympathoinhibition [54–56, 59, 61, 72, 82]. Furthermore, the overexpression of MnSOD attenuates angiotensin II-induced pressor response associated with oxidative stress in the RVLM [71]. These findings collectively suggest that the AT_1 receptor/NAD(P)H oxidase pathway is the primary source of oxidative stress in the RVLM of hypertensive rats. Additionally, Rac1, a small G protein involved in intracellular signaling pathways leading to NAD(P)H activation, requires lipid modifications to translocate from the cytosol to the cell membrane. Rac1 is associated with the activation of NAD(P)H oxidase [21, 23–25, 52, 80]. Inhibition of Rac1 through the transfection of adenovirus vectors encoding a dominant negative Rac1 into the RVLM or NTS results in decreased blood pressure, heart rate, and sympathetic nerve activity in SHRSP but not in normotensive rats [23, 80]. Moreover, blocking the translocation of Rac1 from the cytosol to the membrane in the RVLM of SHRSP induces sympathoinhibition by reducing NAD(P)H oxidase activity and oxidative stress [52]. These findings suggest that activating the AT_1 receptor/NAD(P)H oxidase pathway, associated with Rac1, predominantly contributes to oxidative stress in the RVLM or NTS in hypertension.

Mechanisms of oxidative stress-induced sympathoexcitation in the brain

The interaction between superoxide and NO is pivotal, as a decrease in NO availability in the brain caused by superoxide may lead to sympathoexcitation. In SHRSP, a reduction in NO-mediated GABA release in the RVLM is partially involved in superoxide-induced sympathoexcitation [84]. Peroxynitrite is also critical in the relationship between superoxide and NO, as it exhibits excitotoxic effects [85, 86]. Reactive oxygen species and reactive nitrogen species can modulate the function of inducible nitric oxide synthase (iNOS) in a dose-dependent manner, and peroxynitrite diminishes both NO and superoxide production through enzymatic dysfunction of iNOS [85–87]. Furthermore, peroxynitrite contributes to the hypotensive effect of NO following the overexpression of endothelial nitric oxide synthase (eNOS) in SHR [88]. The role of

peroxynitrite in the RVLM in regulating the sympathetic nervous system requires further investigation.

Glutamate, one of the excitatory amino acids in the RVLM, is recognized for its ability to induce robust sympathoexcitation [6, 7]. Our recent study demonstrated that oxidative stress influences the balance between glutamate and GABA in the RVLM of hypertensive rats [60]. These findings align with a previous report indicating that NAD(P)H oxidase-derived superoxide in the RVLM contributes to the angiotensin II-induced pressor response by enhancing presynaptic glutamate release [73]. We hypothesize that glutamate in the RVLM may play a role in oxidative stress-induced sympathoexcitation.

Furthermore, we have focused on elucidating the signal transduction pathways associated with oxidative stress. Activation of the AT_1 receptor in the RVLM triggers caspase-3 activation through the Ras/mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinase (ERK) pathway, which is implicated in sympathoexcitation in SHRSP [72]. In SHRSP, the activities of Ras, p38 MAPK, ERK, and caspase-3 are elevated in the RVLM compared to normotensive rats. Phosphorylation of the pro-apoptotic proteins Bax and Bad, leading to cytochrome c release from mitochondria, activates caspase-3 [72]. Conversely, phosphorylation of the anti-apoptotic protein Bcl-2 inhibits caspase-3 activation. Intracerebroventricular infusion of a caspase-3 inhibitor reduces blood pressure and heart rate while inducing sympathoinhibition in SHRSP but not in normotensive rats. ICV infusion of an AT_1 receptor blocker also leads to sympathoinhibition and reduced activities of Ras, p38 MAPK, ERK, and caspase-3 in the RVLM of SHRSP [72]. These results are consistent with a prior report indicating that NAD(P)H oxidase-derived superoxide is responsible for p38 MAPK or ERK1/2 activation by angiotensin II in the RVLM [73]. Although the relationship between oxidative stress and kinase activation is bidirectional [89], these pathways likely exist downstream of the AT_1 receptor in the RVLM of SHRSP and contribute to the elevation of blood pressure and sympathoexcitation.

Recently, there has been a focus on exploring additional central mechanisms of sympathoexcitation associated with oxidative stress, including perivascular macrophages in the brain [90, 91], the transcription factor nuclear factor kappa-B [92], and microglial cytokines [31]. Furthermore, our recent findings have demonstrated that neuron-astrocyte uncoupling mediated by AT1 causes sympathoexcitation in SHRSP receptor-induced oxidative stress in the RVLM [93, 94].

Several unresolved matters warrant attention. Firstly, the target cells of oxidative stress in the RVLM may vary. We have yet to ascertain which specific cell types, such as presympathetic neurons, interneurons, or axon terminals originating from NTS and PVN to RVLM, are affected by oxidative stress in the RVLM. Oxidative stress triggers calcium influx in neural cells, and the subsequent accumulation of calcium in mitochondria leads to sympathoexcitation associated with mitochondrial oxidative stress production [71], similar to what has been reported previously [81]. Furthermore, our investigations have revealed that oxidative stress in the RVLM enhances glutamatergic excitatory inputs while attenuating GABAergic inhibitory inputs from PVN to RVLM [60]. Interestingly, Chan et al. demonstrated that NAD(P)H oxidase-derived superoxide in the RVLM is implicated in the angiotensin II-induced pressor response by enhancing presynaptic glutamate release to RVLM neurons [73]. Our recent results suggest that the apoptosis of astrocytes might play a role in mediating oxidative stress-induced sympathoexcitation in the RVLM [72, 93, 94]. Secondly, the precise impact of oxidative stress on the electrophysiological characteristics of RVLM neurons remains incompletely understood. Kumagai et al. revealed that RVLM bulbospinal neurons in SHR experience depolarization and an increased firing rate in response to angiotensin II. Angiotensin II induces a sustained inward current and augments the frequency and amplitude of excitatory postsynaptic currents [95–97]. These angiotensin II-mediated responses in the RVLM could be associated with oxidative stress. Angiotensin II-induced oxidative stress can downregulate the expression of a voltage-gated potassium channel in the RVLM [98, 99]. Moreover, the AT_1 receptor enhances the frequency of glutamate-sensitive spontaneous excitatory postsynaptic currents in the RVLM [73]. Further investigations are necessary to address these unresolved questions.

Effects of AT_1 receptor blockers on oxidative stress in the brain and sympathetic nervous system

Peripherally administered AT_1 receptor blockers can traverse the blood-brain barrier and effectively block AT_1 receptors both within and outside the brain. However, the degree of receptor blocking action within the brain may vary among different AT_1 receptor blockers [55, 61, 100–103]. Brain regions responsible for regulating the sympathetic nervous system, including the circumventricular organs outside the blood-brain barrier, exhibit a high density of AT_1 receptors. As a result, peripherally administered AT_1 receptor blockers can access these regions without being hindered by the blood-brain barrier and acting on AT_1 receptors within the brain that lies behind the blood-brain barrier [104]. Systemic administration of AT_1 receptor blockers also affects AT_1 receptors within the brain, reducing blood pressure in hypertensive rats [23, 55, 61, 101, 105–107]. The actions of AT1 receptor blockers within the brain may partly depend on their lipophilicity and pharmacokinetics [100–103].

Furthermore, we have investigated the sympathoinhibitory effect achieved by reducing oxidative stress through

inhibiting brain AT_1 receptors, and our findings align with numerous previous studies [61, 100–106]. Orally administered telmisartan or olmesartan reduced blood pressure and demonstrated sympathoinhibition in SHRSP, accompanied by decreased oxidative stress within the brainstem, including the RVLM [23, 55, 107]. Notably, orally administered telmisartan exhibited a more remarkable ability to inhibit AT_1 receptor-induced oxidative stress in the RVLM and induce sympathoinhibition in SHRSP compared to candesartan, despite producing similar blood pressure-lowering effects [55]. Similar outcomes were observed in obesity-induced hypertensive rats treated with telmisartan or losartan [61]. Therefore, it is plausible to suggest that orally administered AT_1 receptor blockers can elicit sympathoinhibition through the blockade of AT_1 receptors in the RVLM. Furthermore, the sympathoinhibitory effects of orally administered AT_1 receptor blockers may not be uniform across the class.

Sympathoinhibition by targeting oxidative stress in the brain of hypertension

3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, commonly known as statins, are potent agents that inhibit cholesterol biosynthesis and have been shown to reduce blood pressure in hypertensive patients [108]. Furthermore, the potential sympathoinhibitory effects of statins have been demonstrated [109–111]. In animal studies, orally administered atorvastatin induces sympathoinhibition. It enhances impaired baroreflex sensitivity by decreasing oxidative stress through the inhibition of the AT_1 receptor-NAD (P) H oxidase pathway and the up-regulation of MnSOD in the RVLM of SHRSP [51, 52, 110], which aligns with a previous report concerning the vasculature [112]. Additionally, orally administered atorvastatin can increase nitric oxide synthase in the brainstem of SHRSP [113]. Based on these findings, we hypothesize that statins can induce sympathoinhibition through the reduction of oxidative stress and activation of nitric oxide synthase in the RVLM.

Several calcium channel blockers have been established to cause sympathoinhibition by reducing oxidative stress in the RVLM of hypertensive rats. Orally administered amlodipine [114] or azelnidipine [58] induces sympathoinhibition by decreasing oxidative stress in the RVLM of SHRSP. We have verified that orally administered azelnidipine inhibits NAD (P) H oxidase activity and activates MnSOD in the RVLM of SHRSP [58]. Furthermore, a combination of atorvastatin and amlodipine [60] or olmesartan and azelnidipine [115] exhibits additive effects in sympathoinhibition through the reduction of oxidative stress in the RVLM.

Interestingly, calorie restriction [54] or exercise training [56] is crucial in inducing sympathoinhibition by reducing oxidative stress through the blockade of the AT_1 receptor in hypertensive rats. These findings suggest that adipocytokines and insulin resistance may influence the AT_1 receptor in the RVLM, leading to sympathoexcitation.

Inflammation in the brain exaggerates hypertension with sympathoexcitation

In the past decade, several investigations have proposed a link between brain inflammation and the occurrence of sympathoexcitation and hypertension. Haspula's research indicates that neuroinflammation and heightened sympathetic activity are pivotal in amplifying sympathetic activity in individuals with hypertension [26]. Winklewski's findings point to inflammation in the forebrain and hindbrain nuclei, which regulate the outflow of the sympathetic nervous system from the brain to the periphery, as an emerging concept in understanding the pathogenesis of neurogenic hypertension [27]. Waki's study highlights the upregulation of proinflammatory molecules in endothelial cells of the microvasculature supplying the NTS in SHR compared to normotensive rats [28]. Interestingly, macrophage infiltration into vascular walls has been implicated in the development of hypertension by promoting vascular inflammation and endothelial dysfunction [29]. Iyonaga et al. demonstrated the involvement of brain perivascular macrophages in the pathogenesis of hypertension through enhanced sympathetic activation [30]. Similarly, Shi et al. revealed that activated microglia in the PVN release proinflammatory cytokines, contributing to neurogenic hypertension [31]. These collective findings strongly suggest a causal relationship between brain inflammation and hypertension accompanied by sympathoexcitation. However, our research has demonstrated that activated microglia with morphological alterations within the PVN is not implicated in the maintenance of established severe hypertension, and inflammation within the PVN cannot be considered a therapeutic target for established hypertension [32]. Therefore, brain inflammation likely exacerbates hypertension with sympathoexcitation rather than initiating its onset.

Perspectives

Figure 2 illustrates the underlying concept of modulating the sympathetic nervous system through the action of NO derived from the overexpression of eNOS and AT_1 receptor-induced oxidative stress in the RVLM (Fig. 2). In managing subnormal sympathoexcitation in cardiovascular diseases, our investigations suggest that blocking the AT_1 receptor in the RVLM is imperative, aligning with prior research [61, 100–107]. AT_1 receptor blockers are extensively employed in treating hypertension [116]. Moreover,
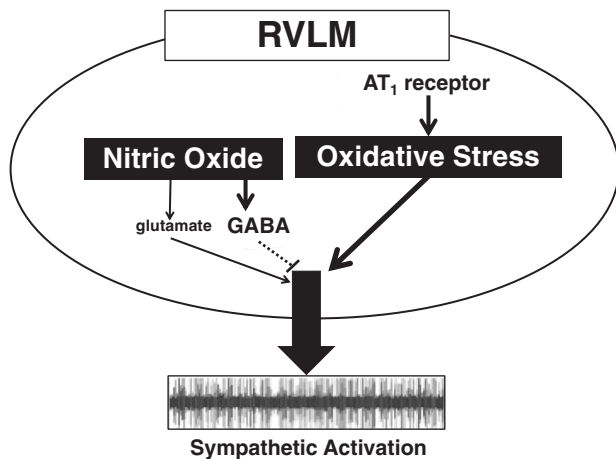
Fig. 2 A schema shows our concept in regulating sympathetic nerve activity via nitric oxide and angiotensin II type 1 (AT_1) receptor-induced oxidative stress in the rostral ventrolateral medulla (RVLM). GABA; γ-amino butyric acid

these blockers have been postulated to exert neuroprotective effects, reducing the occurrence of stroke and enhancing cognitive function [116, 117]. Notably, recent findings on renal nerve ablation in patients with resistant hypertension indicate the potential contribution of renal afferent nerves to elevated blood pressure [118–120]. These renal afferent nerves project directly to various regions within the central nervous system, including the NTS and the hypothalamus [121, 122]. In the phenol renal injury model of hypertension, which involves stimulating renal afferent nerves, oxidative stress mediates sympathoexcitation. Activation of the brain's AT_1 receptor and NAD(P)H oxidase occurs in this model. Previous research has proposed that increased production of oxidative stress and diminished expression of neuronal nitric oxide synthase may be implicated in this mechanism, resulting in alterations in brain cytokines [123, 124]. Therefore, it is reasonable to emphasize the AT_1 receptor and the associated production of oxidative stress in the RVLM as crucial therapeutic targets for addressing abnormal sympathoexcitation in hypertension.

Conclusion

Considering our investigations and prior studies, we contend that the escalation of AT_1 receptor-induced oxidative stress and the impairment of NO function in the brain, particularly in the RVLM, predominantly contribute to sympathoexcitation in hypertension [125]. Furthermore, it is plausible that targeting AT_1 receptor-induced oxidative stress and NO dysfunction in the brain could offer therapeutic prospects for hypertension. However, additional, comprehensive research is warranted at both the fundamental and clinical levels.

Compliance with ethical standards

Conflict of interest The author declares no competing interests.

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