ACTIVATION OF THE SYMPATHETIC nervous system is critically involved in the pathogenesis of hypertension, from initial occurrence to the development of target organ damage, such as heart failure, stroke, and renal failure (35, 36). The importance of the effects of the renin-angiotensin system on the sympathetic nervous system in the pathogenesis of hypertension is recently highlighted (30, 31). This is not surprising because both the autonomic nervous system and hormonal factors are the major regulators of blood pressure; therefore, abnormalities of either system are likely to be involved in the pathogenesis of essential hypertension (30, 31, 37). Esler (30) reported that the sympathetic nervous system is activated in 50% of patients with hypertension, particularly in patients with essential hypertension. Central sympathetic outflow is determined by several important nuclei and their circuits in the central nervous system (CNS) (9, 81). These pathways involve many neurotransmitters and neuromodulators (16, 25, 38, 99). In particular, the brain stem circuitry is now considered crucial for the pathogenesis of hypertension, including both excitatory and inhibitory inputs from the supramedullary nuclei and the baroreceptors (16, 25, 38, 100, 115). In this review, we focus on the role of NO and ROS in the regulation of sympathetic activity and neural mechanisms of hypertension.

Nitric oxide (NO) and reactive oxygen species (ROS) play important roles in blood pressure regulation via the modulation of the autonomic nervous system, particularly in the central nervous system (CNS). In general, accumulating evidence suggests that NO inhibits, but ROS activates, the sympathetic nervous system. NO and ROS, however, interact with each other. Our consecutive studies and those of others strongly indicate that an imbalance of NO and ROS in the CNS, including the brain stem, activates the sympathetic nervous system, and this mechanism is involved in the pathogenesis of neurogenic aspects of hypertension. In this review, we focus on the role of NO and ROS in the regulation of the sympathetic nervous system within the brain stem and subsequent cardiovascular control. Multiple mechanisms are proposed, including modulation of neurotransmitter release, inhibition of receptors, and alteration of intracellular signaling pathways. Together, the evidence indicates that an imbalance of NO and ROS plays a pivotal role in the pathogenesis of hypertension.

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ronic blockade elicits a greater fall in blood pressure in L-NAME-treated rats compared with controls, suggesting that the level of central sympathetic outflow in L-NAME-treated rats is greater than that in control rats. Microinjection of an ANG II type 1 (AT1) receptor blocker (candesartan), but not that of an AT2 receptor blocker (PD123319), into the nucleus tractus solitarius (NTS) elicits a greater decrease in blood pressure, heart rate, and renal sympathetic nerve activity (RSNA) in L-NAME-treated rats than in control rats. These results suggest that increased RSNA contributes to hypertension induced by chronic NOS inhibition and that activation of the renin-angiotensin system in the NTS is involved, at least in part, in the increased RSNA via AT1 receptors (29). The rostral ventrolateral medulla (RVLM), the vasomotor center, is also activated in this model of hypertension, suggesting enhanced central sympathetic outflow (9). Pharmacological inhibition of NOS evoked by Nω-monomethyl-L-arginine (L-NMMA) or L-NAME also induces large increases in blood pressure that are partially sympathetically mediated in humans (109).

Immunohistochemical studies have revealed a rich distribution of nNOS in the NTS (8). Microinjection of L-NMMA into the NTS elicits an increase in blood pressure and RSNA, regardless of whether the baroreceptors are intact in anesthetized rabbits (39). The neurons in the NTS are activated by NO projecting to the caudal ventrolateral medulla, thereby activating the inhibitory neurons in the caudal ventrolateral medulla, which project to the RVLM, and may ultimately result in decreased sympathetic nerve activity (SNA). Single-unit extracellular recordings of NTS neurons in rat brain stem slices revealed that L-arginine increases neuronal activity dose-dependent, but L-arginine does not (80, 116). L-NMMA blocks the L-arginine-induced increases in the neuronal activity. Sodium nitroprusside, an NO donor, also increases neuronal activity. Consistent with the findings from the in vivo studies (39), these results suggest that NO increases the neuronal activity in the NTS through an increase in cyclic GMP. It has been proposed that NO acts in an ultrashort feedback loop, in which the release of L-glutamate activates nNOS and subsequently the production of NO (32). The NO, in turn, diffuses to presynaptic terminals, where it modulates the release of L-glutamate in response to neuronal activation. Studies using in vivo microdialysis demonstrated that activation of NMDA receptors in the NTS induces the release of NO, and NMDA-induced NO production stimulates L-glutamate release (74, 75, 82). In addition, this mechanism is involved in the depressor and bradycardic responses evoked by NMDA receptor activation in anesthetized rats (82). To determine the effects of increased NO production in the NTS for much longer periods on blood pressure, heart rate, and urinary norepinephrine excretion, we developed an in vivo technique for eNOS gene transfer into the NTS of rats (43, 44, 46, 107). In this study, the successful transfer of the eNOS gene into the NTS was confirmed by several methods, including immunohistochemistry, Western blot analysis, and nitrite/nitrate concentration measurements (107). Changes in blood pressure and heart rate were observed using a radio-telemetry system. It is important to note that we used eNOS instead of nNOS, which is normally abundant in the CNS, because the purpose of the study was to increase NO production from constitutively expressed NOS. The results indicated that NO in the NTS exerts an inhibitory effect on SNA in vivo.

Compared to studies of the NTS, studies of the RVLM in both acute and anesthetized models have produced more conflicting results (42, 53, 66, 81, 112, 120, 131). Therefore, we applied the technique described above to studies of the RVLM (57, 58). In these studies, blood pressure, heart rate, and urinary norepinephrine excretion were decreased after eNOS gene transfer. Microinjection of either L-NMMA or bicuculline, a GABA receptor antagonist, into the RVLM after eNOS gene transfer increased blood pressure to greater levels in the eNOS gene transfer group compared with the mock gene transfer control group. GABA levels in the RVLM after the eNOS gene transfer measured by in vivo microdialysis were also increased in the eNOS gene transfer group. These results indicate that the increased NO production evoked by the overexpression of eNOS in the bilateral RVLM decreases blood pressure, heart rate, and SNA in awake rats. Furthermore, these responses are mediated by an increased release of GABA in the RVLM. These studies provided convincing evidence that chronic changes in neurotransmitters/neuromodulators in the RVLM have a sustained impact on blood pressure in awake animals.

There is no clear explanation for the different modulatory effects of NO on neurons between the NTS and RVLM. NO increases both excitatory and inhibitory amino acids in the RVLM (43, 57). NO also has been shown to increase both L-glutamate and GABA in the paraventricular nucleus of hypothalamus (49). Microinjection of kynurenic acid into the RVLM, however, did not alter blood pressure after eNOS gene transfer, although microinjection of bicuculline into the RVLM augmented the increase in blood pressure (57). Therefore, we consider that GABAergic inhibition of the RVLM neurons might be more powerful than the glutamatergic activation in the resting condition (43, 57). In contrast, the glutamatergic input into the NTS neurons might be more powerful than the GABAergic input. In the NTS, there are close anatomic connections between nNOS and glutamatergic receptors (75). Furthermore, increases in NO induce L-glutamate release and microinfusion of NMDA and AMPA increase NO levels, suggesting that there are facilitatory interactions between L-glutamate and NO (27, 74, 82), although there are no studies measuring GABA levels induced by NO in the NTS. Furthermore, higher concentrations of NO are required to directly engage GABAergic inhibition, while lower concentrations of NO might be important for glutamatergic transmission in the NTS (125). Thus, it is still difficult and complicated to explain the physiological response induced by NO in the NTS (119). With regard to the action of NO on neuronal activity, NO induces both excitatory and inhibitory postsynaptic currents that likely depend on the neuron examined (6, 7, 126, 127).

**Effects of NO in the Brain System in Experimental Models of Hypertension**

Neurogenic mechanisms are dominant in the pathogenesis of essential hypertension in ~50% of patients (30). Spontaneously hypertensive rats (SHR) or stroke-prone SHR (SHRSP) exhibit increased RSNA during the development of hypertension, and blood pressure and RSNA are positively correlated (52, 79). The L-arginine-NPY pathway is disrupted in SHR and SHRSP. The depressor response to an intracerebroventricular injection of an NO donor is greater in SHRSP than in normo-
tensive control rats, whereas the pressor response to intracerebroventricular injection of L-NAME is smaller (13). Semiquan-
titative RT-PCRs and in situ hybridization in SHR and Wistar-
Kyoto (WKY) rats at 4 (prehypertensive) and 14 (established hypertension) wk of age (101) indicate that eNOS mRNA expression changes with the development of hypertension. Although there are no differences between the groups at 4 wk of age, nNOS gene expression increases in the hypothalamus, dorsal medulla, and caudal ventrolateral medulla of SHR compared with WKY rats at 14 wk of age. In the RVLM, there are no differences between the groups. In the SHRSP, there are also no differences in nNOS expression levels in the RVLM compared with WKY rats (101). A recent study demonstrated that NOS activity, measured by the ability of tissue homoge-
nate to convert [3H]L-arginine to [3H]L-citrulline in a calcium-
and NADPH-dependent manner, is impaired in the cerebral cortex and brain stem of prehypertensive SHR (104). In con-
trast, NOS activity is increased in the hypothalamus and brain stem in SHR rats with established hypertension compared with WKY rats (104). Thus, attenuated NOS activity in the cortex and brain stem of prehypertensive SHR might play a role in the pathogenesis of hypertension, and the up-regulated NOS ac-
tivity in the hypothalamus and brain stem of SHR with estab-
lished hypertension might serve to compensate for the hypotension. The expression of iNOS mRNA and protein is under the limits of detection in the hypothalamus of both WKY rats and SHR (40). Decreased NOS activity measured by the nitrite and nitrate contents was also demonstrated in the hypothalamus of SHR (1). In hypertensive SHRSP, nNOS protein expression levels in the hypothalamus and brain stem were enhanced compared with those in WKY (59). In a renovascular hypertensive rat model, mRNA expression levels of nNOS and soluble guanylate cyclase genes are reduced in the hypothalamus but not in the dorsal medulla (69). Together, these results suggest that the l-arginine-NO pathway is impaired in hypertensive rats, including SHR, possibly because of a posttranscriptional abnormality (70).

Overexpression of eNOS in the NTS results in a greater depressor response in SHR than in WKY rats in the awake state (44). In that study, eNOS was used instead of nNOS to increase NO production locally in the NTS. Findings from another study suggest that the depressed NO modulation is consistent with the lower NOS activity in the dorsal brain stem (103). Therefore, the abnormality in the l-arginine-NO pathway in the NTS might be involved in the maintenance of hypertension of SHR. A recent study by Waki et al. (121) demonstrated that endogenous eNOS activity in the NTS plays a major role in determining the blood pressure set point in SHR and contributes to maintaining high arterial blood pressure in this model, suggesting the possible in-
volvement of neurovascular coupling (96). In the RVLM of
SHRSP, overexpression of eNOS elicits greater depressor and sympathoinhibitory responses than in WKY (58). Fur-
thermore, the increase in NO production evoked by the overexpression of eNOS in the RVLM enhances the inhib-
itory action of GABA on the RVLM neurons (58). The results indicate that NO dysfunction and the resulting dis-
inhibition of the RVLM contribute to increase RSNA in
SHRSP.

Effects of NO in the Brain Stem on Baroreflex Function

As described earlier, NO activity in the NTS and RVLM influences cardiovascular regulation. We examined the role of endogenous NO in the brain stem in the rapid central adapta-
tion of baroreflex control of RSNA in anesthetized rabbits (41).
Bilateral carotid sinuses were isolated, and a stepwise increase in pressure was applied to the carotid sinuses, while arterial pressure and RSNA were recorded. The procedure was per-
fomed after intracereisternal injection of L-NAME, d-NAME, l-arginine, or the vehicle solution. l-NAME enhances the rapid adapta-
tion of the arterial baroreflex control of renal sympath-
athetic nerve activity in rabbits (41). Transmission of arterial baroreflex signals depends on NO (27, 118). It was reported that the baroreceptor reflex gain in awake animals was in-
creased by NO in the bradycardic component, although in these studies NOS inhibitors were administered systemically to ex-
amine the role of NO on baroreflex function (78, 87). Fur-
thermore, overexpression of eNOS in the RVLM improves im-
paired baroreflex control of heart rate in SHRSP (60).

In summary, NO in the brain stem, particularly in the NTS and RVLM, has a sympathoinhibitory function, thereby reduc-
ing blood pressure. NO in the brain stem also facilitates the baroreflex function. The sympathoinhibitory effects of NO are impaired in animal models of hypertension, and supplemen-
tation of NO in the brain stem in hypertensive rats attenuates the abnormality, thereby decreasing blood pressure. The facilitory release of neurotransmitters induced by NO might be involved in the synaptic transmission mechanism.

ROS in the Brain

Substantial evidence also indicates that increased oxidative stress is involved in the pathogenesis of hypertension (12, 47, 48, 94, 99). ROS, such as superoxide anions and hydroxyl radicals, increase oxidative stress. There are several sources of ROS generation, such as NADPH oxidase, xanthine oxidase, mitochondria, and NOS uncoupling (12, 47, 48, 94, 99). On the other hand, reduction of antioxidant enzymes, such as super-
oxide dismutases (SOD), also induces an increase in oxidative stress (47, 48, 99). Although the role of ROS in the regulation of blood pressure in the normotensive state is not clear, increased ROS generation in the brain stem contributes to neural mechanisms of hypertension (47, 48). For example, although there is evidence of an increase in oxidative stress in the vasculature in hypertension, we showed, for the first time, that increased ROS in the RVLM contributes to SNA, leading to the neural mechanisms of hypertension in SHRSP (61). Zimmerman et al. (133) demonstrated that hypertension caused by low doses of circulating ANG II depends on the production of superoxide in the circumventricular organs (133). It was demonstrated that physiological responses to brain ANG II involve ROS production (15, 132, 133). Considering the im-
portance of the brain ANG II system (2, 10, 26, 28, 83, 85, 86, 108), ROS play an important role in the neural regulation of blood pressure because ROS production largely depends on AT1 receptor stimulation (47, 48, 99).

Role of ROS in Neural Mechanisms of Hypertension

As described earlier, on the basis of results demonstrating that microinjection of Tempol or overexpression of manga-
Ca^{2+} profiles containing AT1 receptors (122). The potentiation of oxidase, gp91phox, is present in somatodendritic and axonal afferents (122). Importantly, the essential subunit of NADPH II failed to increase ROS production or to potentiate L-type ability and spontaneous activity in some neurons (135). ANG II on Ca^{2+} influx in the NTS neurons are caused, at least, in part, by the activation of l-type Ca^{2+} channels. It should be noted that ANG II-induced inhibition of neuronal delayed rectifying potassium current (I_{KV}) is mediated by ROS in primary neurons isolated from the hypothalamus and brain stem, because both NAD(P)H oxidase inhibition and Tempol prevented the ANG II inhibition of I_{KV} (113).

Mitochondria are another source of ROS generation in the brain. Chan et al. (21) examined the role of the mitochondrial electron transport chain in the RVLM of SHR and found that mitochondrial electron transport chain dysfunction in the RVLM of SHR depressed complex I or III activity and reduced the electron transport capacity (ETC) between complexes I and III or II and III (21). Interestingly, microinjection of coenzyme Q_{10} into the RVLM of SHR reversed the depressed ETC activity and enhanced superoxide generation. In addition, microinjection of antisense oligonucleotide against the p22phox subunit of NADPH oxidase into the RVLM reduced the enhanced ROS production in SHR (21). It is also important to note that microinjection of coenzyme Q_{10} into the RVLM of SHR decreases blood pressure (21). These results suggest that impairment of mitochondrial ETC complexes contributes to chronic oxidative stress in the RVLM of SHR, leading to enhanced central sympathetic drive and hypertension (21, 136).

Consistent with their observation, we also found that ANG II induced the mitochondria-derived ROS production via activation of NADPH oxidase, although we did not find differences in the mitochondrial respiratory complexes between SHRSP and WKY (91), thus suggesting a feedforward system for ROS generation (21, 91, 136) (Fig. 1). Mitochondrial-produced superoxide mediates the ANG II inhibition of I_{KV} (128). Recently, Chan et al. (22) suggested that transcriptional upregulation of mitochondrial uncoupling protein 2 (UCP2) in response to an increase in superoxide plays an active role in the feedback regulation of ROS production in the RVLM (22). Furthermore, oral treatment with rosiglitazone enhances a central antihypertensive effect via an upregulation of peroxisome proliferator-activated receptor-γ (PPAR-γ) and reduced oxidative stress in the RVLM of SHR (23). Stimulation of PPAR-γ results in the upregulation of UCP2 (23). Stimulation of PPAR-γ results in the upregulation of UCP2, thereby reducing oxidative stress. The dose of rosiglitazone used in that study,

**Sources of ROS Generation in the Brain Stem**

NADPH oxidase is a major source of ROS in hypertension (71, 72) and has a critical role in generating ROS in the brain (5, 14, 51, 90, 122, 134). ANG II is upstream of NADPH oxidase activation, which requires Rac1 (48, 90, 122, 134). NADPH oxidase-derived ROS are involved in the effects of ANG II on Ca^{2+} influx in the NTS neurons receiving vagal afferents (122). Importantly, the essential subunit of NADPH oxidase, gp91phox, is present in somatodendritic and axonal profiles containing AT1 receptors (122). The potentiation of Ca^{2+} currents indicates that ANG II increases neuronal excitability and spontaneous activity in some neurons (135). ANG II failed to increase ROS production or to potentiate l-type Ca^{2+} currents in the dorsomedial portion of the NTS neurons of mice lacking Nox2 (123). Thus, the excitatory actions of ANG II in the NTS neurons are caused, at least, in part, by the activation of l-type Ca^{2+} channels. It should be noted that ANG II-induced inhibition of neuronal delayed rectifying potassium current (I_{KV}) is mediated by ROS in primary neurons isolated from the hypothalamus and brain stem, because both NAD(P)H oxidase inhibition and Tempol prevented the ANG II inhibition of I_{KV} (113).

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however, was fairly high, and this does not necessarily relate to the clinical setting.

Downstream Signaling Pathway of the AT₁ Receptor Stimulation in the RVLM Involving ROS Production

As described above, activation of the AT₁ receptor produces superoxide anions as an initial step of ROS generation through NADPH oxidase. Thus, the signaling pathway should be pivotal for neuronal activation leading to hypertension via central sympathetic outflow. NAD(P)H oxidase-derived ROS production mediates the ANG II-induced pressor response via activation of p38 MAPK and ERK in the RVLM (18, 20). Chan et al. (20) demonstrated that intracerebroventricular infusion of ANG II elicits the long-term pressor response, and this pressor response is mediated by protein kinase C/ERK/cyclic adenosine monophosphate response element binding protein and c-fos induction (20). It should be noted that the ANG II-induced pressor response might not necessarily be related to ROS production in the RVLM. The ANG II-induced pressor response, however, is significantly inhibited by ROS scavenging, and endogenous blockade of AT₁ receptors in the brain stem of SHRSP reduces ROS and blood pressure (48, 91). Activation of caspase-3 acting through the Ras/p38 MAPK/ERK pathway in the RVLM might be involved in sympathoexcitation of SHRSP (65). In addition, the apoptotic proteins Bax and Bad are activated, and the antiapoptotic protein Bel-2 is inhibited in the RVLM of SHRSP (65). The Ras inhibitor substantially attenuated these changes, thereby attenuating caspase-3 associated with the decrease in blood pressure. In contrast, however, c-Jun N-terminal kinase activity was not altered in the RVLM of SHRSP compared with that of WKY (65). It should be noted that the possibility of caspase-3-independent neuronal apoptosis in the RVLM or of a direct link between ROS and caspase-3 activation was not examined in this study (65). However, this finding is consistent with the results demonstrating that microinjection of ANG II induces AT₁ receptor-dependent ROS production and phosphorylation of p38 MAPK and ERK, but not stress-activated protein kinase/Jun N-terminal kinase in the RVLM of Sprague-Dawley rats (18). Interestingly, this is not the case in the RVLM of heart failure rabbits (77). Stress-activated protein kinase/Jun N-terminal kinase activity was increased in the RVLM of these heart failure rabbits (77). The increased phosphorylation of Jun N-terminal kinase may lead to activation of the transcription factor AP-1, which is a dimer of Jun and c-Fos family members. It is not clear why these differences between hypertension and heart failure occur. It is possible that signal transduction changes in the progression from hypertension to heart failure, thereby leading to further enhanced central sympathetic outflow. Further studies are needed to establish a more direct link between these signaling pathways, redox sensitivity, and the development and/or progression of hypertension.

Imbalance of Brain NO and ROS

Superoxide derived from NADPH oxidase reacts with and inactivates NO and thereby modulates its bioavailability (32, 97, 114) (Fig. 2). The converse is also true; that is, NO reduces superoxide, which may be beneficial (32, 99) (Fig. 2). An increase in NO in the RVLM decreases blood pressure and sympathetic nervous system activity to a greater extent in SHRSP than in WKY rats (58). This might be due to a reduction in superoxide via NO in the RVLM of SHRSP, which is increased in the RVLM of SHRSP (61). All three NOS isoforms generate superoxide depending on substrate (L-arginine) and cofactor (tetrahydrobiopterin) availability (32, 97, 114). The induction of both iNOS and ROS during inflammation is well established (88, 97). A recent study suggested that ROS and reactive nitrogen species, such as peroxynitrite, dose-dependently regulate iNOS function (114). Overexpression of iNOS in the RVLM causes sympathoexcitation via an increase in oxidative stress (54). As expected, the release of more nitrite/nitrate (NO𝑥) in RVLM dialysate is induced by iNOS overexpression than by eNOS overexpression (54). Relative to the constitutive isoforms, iNOS has approximately five-fold higher NO production (97). NO release, however, is increased by approximately twofold higher by iNOS overexpression than by eNOS overexpression (54). We considered that the precursor of NO production, L-arginine, and its cofactor, tetrahydrobiopterin, might be consumed and insufficient when iNOS is chronically expressed, thereby iNOS would produce superoxide instead of NO (Fig. 2). Otherwise, chronic overexpression of iNOS increases levels of NO chronically, which, in turn, reacts with superoxide in a diffusion-limited reaction to produce peroxinitrite (Fig. 2). In fact, we found an increase in the TBARS levels in the RVLM and the pressor response after overexpression of iNOS. The increased pressor response was, however, abolished by iNOS inhibitors or Tempol. Once ROS production is increased, ROS enhance superoxide production from iNOS, indicating that ROS promote iNOS uncoupling. Further, peroxynitrite, produced from the reaction between NO and superoxide, reduces both NO and superoxide generation, indicating that peroxynitrite causes iNOS dysfunction enzymatically. In our study, we detected some iNOS-positive cells with the antinitrotyrosine antibody (54). Furthermore, iNOS expression levels were increased in the RVLM of SHRSP compared with WKY (56). Kung et al. (68) suggested that mitochondrial respiratory enzyme complexes in the RVLM were cellular targets of NO and ROS interaction after eNOS gene transfer. This concept is problematic, however, in that they suggest that superoxide and per-
oxyanitrite are produced after eNOS gene transfer into the RVLM (68). Another recent study suggested that NMDA receptor activation increases ROS production through NO and Nox2 (33). Further studies are needed to explore whether this mechanism functions via ubiquitous glutamatergic synaptic transmission in vivo.

**Sympathoinhibitory Effects of Antihypertensive Drugs and Statins**

NADPH oxidase, which is activated by AT1 receptor stimulation, is a major source of ROS (11, 17, 113, 135). The specific brain nuclei that regulate SNA, such as the anteroventral third ventricle, paraventricular nucleus of the hypothalamus, NTS, and the RVLM, are rich in AT1 receptors (2, 10, 26, 28, 83). AT1 receptor expression levels are upregulated in the RVLM of hypertensive animal models compared with normotensive controls (105). Thus, it is possible that AT1 receptor blockers reduce oxidative stress in the brain, as well as in the peripheral vasculature. It is also possible that AT1 receptor blockers inhibit ROS production by blocking AT1 receptor-mediated intracellular signaling (11, 48, 50) and that this antioxidant action accounts for the absence of reflex-induced sympathoexcitation after treatment with AT1 receptor blockers. We evaluated the effects of AT1 receptor blockers, olmesartan and telmisartan, on brain oxidative stress in SHRSP (4, 48). Both AT1 receptor blockers have antioxidant properties in the brain without stimulating reflex-mediated SNA in SHRSP. We used in vivo ESR spectroscopy to examine the effect of oral olmesartan on oxidative stress in the brain (4), because the in vivo ESR method is a powerful technique for evaluating oxidative stress (3, 110, 111). The effects of peripherally administered olmesartan or telmisartan on central sympathetic outflow have been demonstrated in other studies (34, 76). Are these antioxidant effects of olmesartan or telmisartan specific for each drug or the AT1 receptor blocker class? Other angiotensin receptor blockers, such as losartan or candesartan, have similar sympatheinhibitory effects in the CNS, although there are some differences among angiotensin receptor blockers (24, 89, 102, 124). The differences of the central effects of each angiotensin receptor blocker might depend on its lipophilicity, pharmacokinetics, and the transporter system (24, 34, 48, 124). Furthermore, systemically administered candesartan reduces brain ANG II via downregulation of the brain renin-angiotensin system (98). This finding provides new mechanistic insight into the treatment of hypertension by the AT1 receptor blockers (84). Unfortunately, however, these effects of AT1 receptor blockers, that is, reduction of brain oxidative stress and sympathoinhibitory effects, even when administered systemically, are usually ignored by researchers or clinicians, but should be considered as potential therapeutic candidates.

Considering the inhibitory effects of AT1 receptor blockers on brain oxidative stress and sympathetic nervous system activity, it would be interesting to know whether other cardiovascular drugs have similar effects. We found that atorvastatin causes depressor and sympathoinhibitory effects with upregulation of NOS in SHRSP (59), which is consistent with the effects of statins on eNOS upregulation in the vasculature (55). Atorvastatin also reduces oxidative stress in the RVLM of SHRSP (62, 63, 64). With regard to the central sympathoinhibitory effects of calcium channel blockers, lipophilic dihydropyridine calcium channel blockers, such as nifedipine, nisoldipine, and amlopidine, readily cross the blood-brain barrier, thereby presumably blocking brain L-type Ca2+ channels leading to central sympathoinhibition (73). It is generally considered that an arterial baroreflex-mediated increase in sympathetic activity is responsible for the unfavorable effects of short- and strong-acting dihydropyridine calcium channel blockers; therefore, the intrinsic sympathoinhibitory effects of calcium channel blockers have been ignored. These findings together suggest that increased NOS activity and antioxidant effects in the brain stem might be involved in the central sympathoinhibitory effects of some calcium channel blockers (45, 55, 67). The precise mechanisms involved, however, remain unknown, and further studies are required.

**Summary and Conclusions**

In summary, accumulating evidence indicates that an imbalance of NO and ROS in the CNS, particularly in the brain stem, is crucially involved in hypertension via the activation of central sympathetic outflow. Upstream and downstream consequences of the precise mechanisms are discussed. Several questions remain, however, because the interactions between NO and ROS are complex. Further studies are required to gain a better understanding of the role of brain NO and ROS in autonomic cardiovascular regulation and potential therapeutic targets.

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