

MINIREVIEW

# Contribution of Central Nervous System to Hypertension: role of Angiotensin II and Nitric Oxide

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**Abstract**

The contribution of the central nervous system (CNS) to the development and maintenance of high blood pressure is well established. Increased activity of the sympathetic nervous system during hypertensive conditions has been demonstrated experimentally and clinically. Different types of dysregulation in CNS, as seen by alterations in neurotransmitter production and baroreceptor reflex function, have been detected in early stages of hypertension. It was demonstrated that centrally acting drugs such as  $\alpha$ -methyl dopa, clonidine or reserpine effectively lower blood pressure. Moreover, in animal experiments renal hypertension could be prevented by central chemical sympathectomy. And psychosocial stress-induced sustained hypertension is well-known present phenomenon. The biochemical mechanisms contributing to the blood pressure increase by means of CNS are however lesser-known. Since lowering of blood pressure by the inhibition of the renin-angiotensin-aldosterone system within peripheral but also central nervous system was documented by several studies, it seems that brain angiotensin II may play a key role in the contribution of CNS to hypertension. On the other hand, sufficient production of nitric oxide within the system may effectively prevent increase in blood pressure.

**INTRODUCTION**

The renin-angiotensin system (RAS) plays an important role in both the short-term and long-lasting regulation of blood pressure, as well as in fluid and electrolyte balance. The RAS is a dual hormone system, serving as both a circulating and a local tissue hormone system with important neuromediator functions in the central nervous system (Jagadeesh 1998).

Now it is well established that the brain has its own intrinsic RAS with all respective components present in the central nervous system (Wilms *et al* 2005). The RAS involves a family of bioactive angiotensin peptides with variable neurobiological activities. These include angiotensin-1-8 (angiotensin II), angioten-

sin-3-8 (angiotensin IV), and angiotensin-1-7. Angiotensin II acts through two different specific receptors, termed AT1 and AT2. Neuronal AT1 receptors mediate the stimulatory actions of angiotensin II on blood pressure, water and salt intake, and the secretion of vasopressin. On the other hand, neuronal AT2 receptors have an antagonistic role to AT1 ones. Among the many potential effects mediated by stimulation of AT2 are neuronal regeneration after injury and the inhibition of pathological growth. Angiotensin-1-7 mediates its antihypertensive effects by stimulating the synthesis and release of vasodilator prostaglandins and nitric oxide and by potentiating the hypotensive effects of bradykinin (von Bohlen und Halbach & Albrecht 2006.)

Nitric oxide antagonizes the effects of angiotensin II on vascular tone, cell growth, and renal sodium excretion, and also down-regulates the synthesis of angiotensin-converting enzyme and AT1 receptors. Moreover, angiotensin II decreases nitric oxide bioavailability by promoting oxidative stress (Zhou *et al* 2004).

## ANGIOTENSIN II IN CNS

Angiotensin II has profound effects in the central nervous system (CNS), including promotion of thirst, regulation of vasopressin secretion, and modulation of sympathetic outflow. Despite its importance in cardiovascular and volume homeostasis, angiotensinergic mechanisms are incompletely understood within the CNS (Wilms *et al* 2005).

A signaling mechanism for angiotensin II involving reactive oxygen species (ROS) has been identified in a variety of peripheral tissues. Recently, the involvement of ROS in angiotensin II-mediated signaling in the CNS has been reported (Zimmerman *et al* 2002). Brain especially suffers from the long-term impact of the increased production of reactive oxygen species (Schaffer *et al* 2006). Because of low activity of antioxidant defence system, brain is susceptible to oxidative stress more than other organs. Brain has low catalase activity and only moderate levels of the antioxidant enzymes like superoxide dismutase (Lau *et al* 2005). The hypothesis that superoxide is a key mediator of the actions of angiotensin II in the CNS was tested in mice using adenoviral vector-mediated expression of superoxide dismutase (AdSOD). Changes in blood pressure, heart rate, and drinking elicited by injection of angiotensin II in the CNS were abolished by prior treatment with AdSOD in the brain, whereas the cardiovascular responses to carbachol, another central vasopressor agent, were unaffected (Zimmerman *et al* 2002). Angiotensin II also stimulated superoxide generation in primary CNS cell cultures which was prevented by the AT1 receptor antagonist losartan as well as by AdSOD (Zimmerman *et al* 2002).

NADPH oxidase has been identified as one of the major producers of ROS in the brain (Bokoch *et al* 2003). NADPH oxidase-dependent production of superoxide radical ( $O_2^-$ ) was documented to be responsible for a majority of oxidative injury in the brain (Bokoch & Knaus 2003; Kovacsova *et al* 2010). It is hypothesized that angiotensin II, similarly like in the peripheral tissues, activates NADPH oxidase leading to increased superoxide generation. Finally, the increased production of ROS may raise blood pressure via activation of the sympathetic nervous system (SNS). Angiotensin converting enzyme inhibitors and AT1 receptor antagonists, similarly like in the circulation, may represent a powerful tool in the inhibition of angiotensin II effects within the brain (Pechanova *et al* 2004; Wilms *et al* 2005).

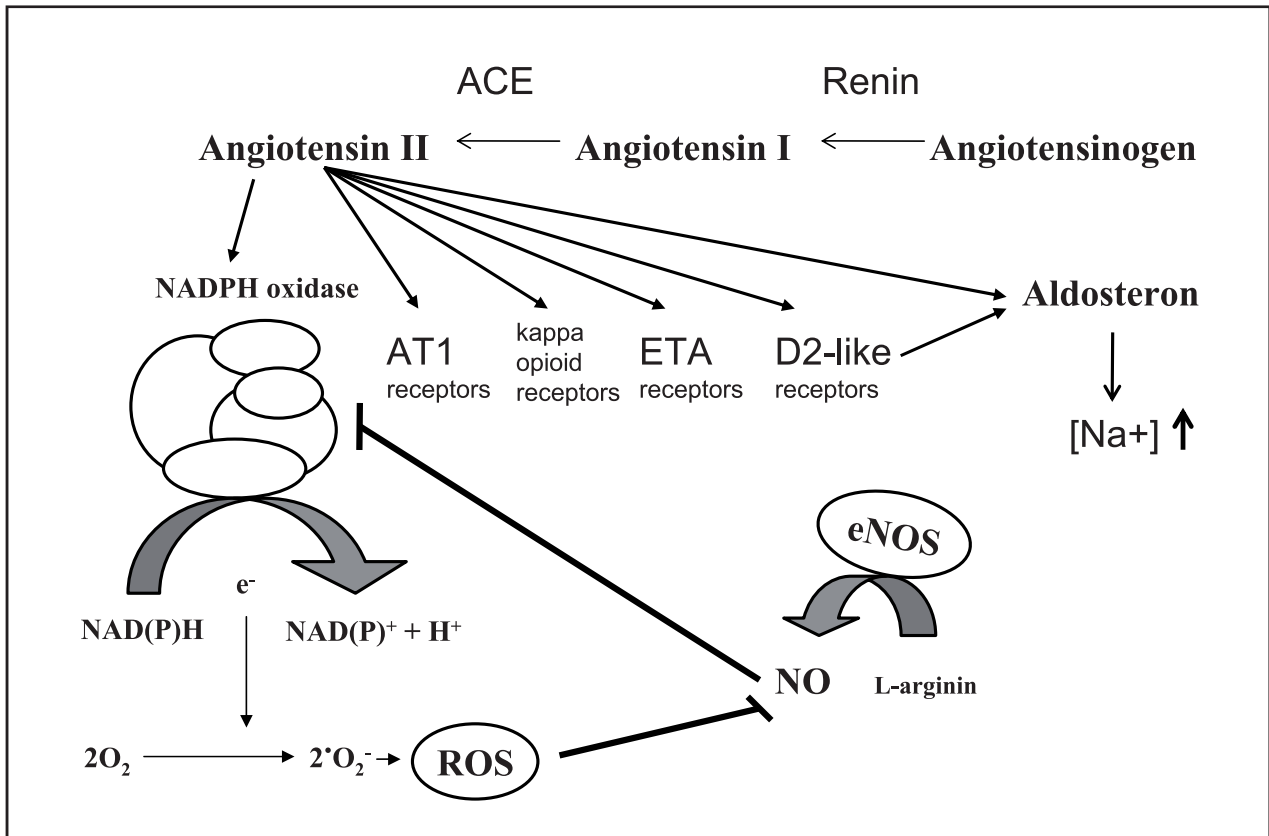
## ANGIOTENSIN II AND NON-ANGIOTENSIN II RECEPTORS

In adult spontaneously hypertensive rats, the intracerebroventricular (icv) administration of AT1 receptor antagonist – losartan induced long-lasting significant blood pressure reductions only 18h after intracerebroventricular injection. The slow development of blood pressure reduction and its persistence might be due to the formation of an active losartan metabolite, different from losartan *per se*. In older SHR, the hypotensive effect of losartan was not significant. These results suggest that in the CNS of the younger SHR, an active RAS is implicated in the establishment of the hypertensive state, and that the receptor for this function may be different from AT1, since it has a selectivity profile different from AT1 and also AT2 receptor types (Paré *et al* 1993). These observations evoked a question about other types of receptors which could be reached and affected by angiotensin II.

Rabkin (2007) suggested the role of opioids in brain angiotensin II-mediated increase of blood pressure. The kappa opioid antagonist, MR 2266 (icv) significantly reduced and MR 2266 (icv) completely prevented the increase in blood pressure produced by angiotensin II. In contrast, the mu opioid receptor antagonist, naloxone (icv), did not significantly attenuate the blood pressure responses to angiotensin II. Also the effect of angiotensin II on baroreceptor function was significantly antagonized by the kappa opioid receptor antagonist MR 2266. These data indicate that endogenous opioids modulate the pressor response to intracerebral angiotensin II and this effect is mediated mainly through endogenous kappa opioid agonists and kappa opioid receptors rather than mu opioid receptors (Rabkin 2007).

Jose *et al* (1999) suggested that also dopaminergic system in the CNS may participate in the regulation of systemic blood pressure. They hypothesized that postsynaptic dopamine D2-like (D2, D3 and D4) receptors increase blood pressure, while presynaptic D2-like receptors produce rather the opposite effect. Indeed, aberrant dopaminergic regulation of aldosterone secretion, via D2-like receptors, has been reported to be involved in some forms of hyperaldosteronism and hypertension. Different forms of hypertension may also be caused by an aberrant renal dopaminergic system (Jose *et al* 1999).

Endothelin-1 also directly regulates central and peripheral nervous system activity, cardiac output, renal Na<sup>+</sup> and water excretion, systemic vascular resistance, and venous capacitance. Endothelin-1 mediates these effects via two types of receptors, ETA and ETB, which are expressed in the vascular smooth muscle cells, endothelial cells, intestines and brain (Piechota *et al* 2010). Increased levels of endothelin-1 have been demonstrated in the ischemic brain, and endothelin receptor antagonism has been shown to improve the



**Fig. 1: Angiotensin II and nitric oxide in CNS.** Angiotensin II in CNS may exert the pressor effects via different receptors including AT1, kappa opioid, ETA and D2-like receptors. Consequently, it could increase NADPH oxidase activity leading to increase reactive oxygen species (ROS) generation. ROS decreases bioavailability of nitric oxide (NO), a vasodilatory agent. Moreover, angiotensin II may activate aldosterone which contributes to blood pressure increase through mineralocorticoid receptors.

outcome of cerebral ischemia. A 50% increase in the ETA receptor was found in the brain of spontaneously hypertensive stroke-prone rats compared with that of the age-matched Wistar-Kyoto controls, but endothelin antagonism reversed this upregulation completely (Jesmin *et al* 2004). D'Amico *et al* (1999) demonstrated that ETA antagonist, FR139317, reduced the pressor effects of angiotensin II in the periaqueductal gray area of rats. This fact may indicate involvement of ETA receptors in pressor angiotensin II action within the brain.

The mineralocorticoid hormone aldosterone, involved in the renin-aldosteron-angiotensin system, is a major activator of mineralocorticoid receptors and epithelial sodium channels. It was documented that aldosterone can be synthesized in the brain even in adrenalectomized Wistar rats (Gomez-Sanchez *et al* 2005). Blockade of aldosterone biosynthesis in the CNS by intracerebroventricular infusion of the 3-hydroxysteroid dehydrogenase blocker trilostane prevents hypertension in Dahl salt-sensitive rats on high salt intake (Gomez-Sanchez *et al* 2005). These studies suggest that also aldosterone in the CNS may mediate some forms of hypertension, at least the form caused by high salt diet. Further, the study of Huang *et al* (2006) indicated

that in Wistar rats, a chronic increase in cerebrospinal fluid [Na+] may increase hypothalamic aldosterone and activate CNS pathways involving mineralocorticoid receptor, and ouabain-like compounds, leading to increases in AT1-receptor density and angiotensin converting enzyme (ACE) activity in brain areas involved in cardiovascular regulation and hypertension.

### ANGIOTENSIN II AND NITRIC OXIDE

It is evident that nitric oxide (NO) exerts not only its peripheral vasodilatory action but it is also involved in the central regulation of sympathetic tone (Lassegue & Griendling 2004; Parohova *et al* 2009; Bernatova *et al* 2010). The balance between angiotensin II and NO levels in the rostral ventral medulla seems to be crucial for the control of the sympathetic tone. Consequently, the reduced NO production in the central nervous system of rats with hypertension induced by NG-nitro-L-arginine methyl ester (L-NAME) treatment is reflected by enhanced sympathetic vasoconstriction as it was demonstrated by Pechanova *et al* (2004, 2009). Exaggerated sympathetic nerve activity in L-NAME hypertensive rats can be attenuated by a local increase

of NO concentration (Tsuchihashi *et al* 2000) or by a selective blockade of renin-angiotensin system in the rostral ventrolateral medulla (Bergamaschi *et al* 2002).

It is highly probable that ROS exerts similar influence on NO bioavailability formed by endothelial NO synthase in blood vessels or neuronal NO synthase in the rostral ventral medulla. Thus many antihypertensive effects of various antioxidants might be exerted not only at the level of resistant vessels but also in the CNS, influencing sympathetic tone which is the most powerful tool for blood pressure control. The results of Campese *et al* (2004) suggested that the effects of tempol, a superoxide dismutase mimetic, on SNS activity may be in part dependent and partially independent of nitric oxide. Thus, tempol may exert direct vasodilation of the peripheral circulation and also reflex activation of the SNS.

Recent findings revealed a considerable blood pressure reduction in salt-loaded Dahl rats chronically treated with N-acetylcysteine. This antihypertensive effect was almost entirely mediated by the reduction of sympathetic vasoconstriction, whereas the changes of NO-dependent vasodilation were not significant (Kunes *et al* 2004). This is in good agreement with earlier report of Cunha *et al* (1993) documented that the development of L-NAME-induced hypertension was prevented by early sympathectomy. The augmentation of the pentolinium-induced blood pressure fall appears early in the development of this form of experimental hypertension because it was already present in rats subjected to L-NAME treatment for one week only. These results indicated considerably greater contribution of the SNS than the RAS to the maintenance of high blood pressure in rats with hypertension induced by chronic L-NAME administration, although the relative contribution of both pressor systems remains unaltered compared with normotensive controls. This was true for both the early and the established phases of L-NAME-induced hypertension. These observations thus confirmed previous findings of Qiu *et al* (1994) and Zanchi *et al* (1995), who also described a greater blood pressure decrease after SNS blockade than after acute RAS inhibition.

Nevertheless, numerous studies demonstrated that chronic therapy with angiotensin AT1 receptor blockers or angiotensin-converting enzyme inhibitors prevented the development of this form of experimental hypertension (Pollock *et al* 1993; Takemoto *et al* 1997). One of the possible explanations for the high efficiency of antihypertensive drugs targeting the RAS could be based upon the interaction of nitric oxide and angiotensin II in the central regulation of sympathetic tone. Enhanced sympathetic nerve activity in animals with L-NAME-induced hypertension is ascribed to reduced NO formation and/or enhanced angiotensin II action in two brain structures: the rostral ventrolateral medulla and the nucleus tractus solitarii. The rostral ventrolateral medulla was reported to be a source

of exaggerated sympathetic nerve activity in L-NAME hypertensive rats (Bergamaschi *et al* 1999). The angiotensin II-dependent increase of sympathetic tone and blood pressure in L-NAME-induced hypertension can be attenuated by the presence of NO (Tsuchihashi *et al* 2000) or by the blockade of the RAS in this brain region (Bergamaschi *et al* 2002). The nucleus tractus solitarii represents another site in the central nervous system in which angiotensin II can activate sympathetic tone during chronic inhibition of nitric oxide synthase (Eshima *et al* 2000). The latter brain structure is rather interesting due to its involvement in baroreflex control, since augmented sympathetic tone in L-NAME hypertensive rats was ascribed to the attenuation of its baroreflex control (Scrogin *et al* 2004; Souza *et al* 2001).

## CONCLUSION

Control of blood pressure by the RAAS is exerted through multiple actions of angiotensin II, a small peptide which is a potent vasoconstrictor hormone implicated in the genesis and maintenance of hypertension within both peripheral and central nervous system. New data concerning the role of RAAS also support the existence of complex site-specific interactions between multiple angiotensins and multiple receptors in the mediation of important central functions including blood pressure regulation. The balance of angiotensin II and nitric oxide within central nervous system seems to have a key role in this important regulation.

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## REFERENCES

- 1 Bergamaschi CT, Biancardi VC, Lopes OU, Campos RR (2002). Effects of angiotensin blockade in the rostral ventrolateral medulla on maintenance of hypertension induced by chronic L-NAME treatment. *Brain Res.* **927**: 195–199.
- 2 Bergamaschi CT, Campos RR, Lopes OU (1999). Rostral ventrolateral medulla: a source of sympathetic activation in rats subjected to long-term treatment with L-NAME. *Hypertension.* **34**: 744–747.
- 3 Bernatova I, Kopincova J, Puzserova A (2010). Chronic stress deteriorated nitric oxide production in Wistar rats exposed to a low dose of L-NAME. *Act Nerv Super Rediviva.* **52**(3): 200–205.
- 4 Bing S Huang, Warren J Cheung, Hao Wang, Junhui Tan, Roselyn A White, Frans HH Leenen (2006). Activation of brain renin-angiotensin-aldosterone system by central sodium in Wistar rats. *Am J Physiol Heart Circ Physiol.* **291**(3): H1109–1117.
- 5 Bokoch GM & Knaus UG (2003). NADPH oxidases: not just for leukocytes anymore! *Trends Biochem Sci.* **28**: 502–508.

- 6 Campese VM, Ye S, Zhong H, Yanamadala V, Ye Z, Chiu J (2004). Reactive oxygen species stimulate central and peripheral sympathetic nervous system activity. *Am J Physiol Heart Circ Physiol.* **287**: H695–H703.
- 7 Cunha RS, Cabral AM, Velasquez EC (1993). Evidence that the autonomic nervous system plays a major role in the L-NAME-induced hypertension in conscious rats. *Am J Hypertens.* **6**: 806–809.
- 8 D'Amico M, Di Filippo C, Filippelli A, Rossi F (1999). Endothelin receptor antagonists reduce the pressor effects of angiotensin II into the periaqueductal gray area of rats. *Life Sci.* **65**(9): PL95–99.
- 9 Eshima K, Hirooka Y, Shigematsu H, Matsuo I, Koike G, Sakai K, Takeshita A (2000). Angiotensin in the nucleus tractus solitarius contributes to neurogenic hypertension caused by chronic nitric oxide synthase inhibition. *Hypertension.* **36**: 259–263.
- 10 Gomez-Sanchez EP, Ahmad N, Romero DG, Gomez-Sanchez CE (2005). Is aldosterone synthesized within the rat brain? *Am J Physiol Endocrinol Metab.* **288**: E342–E346.
- 11 Gomez-Sanchez EP, Samuel J, Vergara G, Ahmad N (2005). Effect of 3-hydroxysteroid dehydrogenase inhibition by trilostane on blood pressure in the Dahl salt-sensitive rat. *Am J Physiol Regul Integr Comp Physiol.* **288**: R389–R393.
- 12 Jagadeesh G (1998). Angiotensin II receptors-antagonists, molecular biology, and signal transduction. *Indian J Exp Biol.* **36**(12): 1171–1194.
- 13 Jesmin S, Sakuma I, Togashi H, Yoshioka M, Hattori Y, Kitabatake A, Miyauchi T (2004). Expression of endothelin receptors in the brain of SHR-SP and effects of an endothelin blocker. *J Cardiovasc Pharmacol.* **44**(Suppl 1): S156–159.
- 14 Jose PA, Eisner GM, Felder RA (1999). Role of dopamine in the pathogenesis of hypertension. *Clin Exp Pharmacol Physiol Suppl.* **26**: S10–S13.
- 15 Kovacsova M, Barta A, Parohova J, Vrankova S, Pechanova O (2010). Neuroprotective Mechanisms of Natural Polyphenolic Compounds. *Act Nerv Super Rediviva.* **52**(3): 181–186.
- 16 Kuneš J, Hojná S, Kadlecová M, Dobešová Z, Rauchová H, Vokurková M *et al* (2004). Altered balance of vasoactive systems in experimental hypertension: the role of relative NO deficiency. *Physiol Res.* **53**(Suppl 1): S23–S34.
- 17 Lassegue B & Griendling KK (2004). Reactive oxygen species in hypertension. *Am J Hypertens.* **17**: 852–860.
- 18 Lau FC, Shukitt-Hale B, Joseph JA (2005). The beneficial effects of fruit polyphenols on brain aging. *Neurobiol Aging.* **26**: 128–132.
- 19 Paré MC, Maltais S, Escher E (1993). The neurogenic origin of hypertension in SHR may be mediated by angiotensin II through a receptor different from AT1 and AT2. *Regul Pept.* **47**(1): 81–86.
- 20 Parohova J, Vrankova S, Barta A, Kovacsova M, Pechanova O (2009). The cross-talk of nuclear factor kappa B and nitric oxide in the brain. *Act Nerv Super Rediviva.* **51**(3–4): 123–126.
- 21 Pechanova O, Dobesova Z, Cejka J, Kunes J, Zicha J (2004). Vasoactive systems in L-NAME hypertension: the role of inducible nitric oxide synthase. *J Hypertens.* **22**: 167–173.
- 22 Pechanova O, Jendekova L, Vrankova S, Barta A, Bartko D (2009). The time-dependent effect of Provinols on brain NO synthase activity in L-NAME-induced hypertension. *Act Nerv Super Rediviva.* **51**(1–2): 93.
- 23 Piechota A, Polańczyk A, Goraca A (2010). Role of endothelin-1 receptor blockers on hemodynamic parameters and oxidative stress. *Pharmacol Rep.* **62**(1): 28–34.
- 24 Pollock DM, Polakowski JS, Divish BJ, Opgenorth TJ (1993). Angiotensin blockade reverses hypertension during long-term nitric oxide synthase inhibition. *Hypertension.* **21**: 660–666.
- 25 Qiu C, Engels K, Baylis C (1994). Angiotensin II and  $\alpha$ 1-adrenergic tone in chronic nitric oxide blockade-induced hypertension. *Am J Physiol.* **266**: R1470–R1476.
- 26 Rabkin SW (2007). Endogenous kappa opioids mediate the action of brain angiotensin II to increase blood pressure. *Neuropeptides.* **41**(6): 411–419.
- 27 Schaffer S, Eckert GP, Schmitt-Schillig S, Muller WF (2006). Plant foods and brain aging: a critical appraisal. *Forum Nutr.* **59**: 86–115.
- 28 Scrogin KE, Veelken R, Luft FC (1994). Sympathetic baroreceptor responses after chronic NG-nitro-L-arginine methyl ester treatment in conscious rats. *Hypertension.* **23**: 982–986.
- 29 Souza HCD, Ballejo G, Salgado MC, Da Silva VJ, Salgado HC (2001). Cardiac sympathetic overactivity and decreased baroreflex sensitivity in L-NAME hypertensive rats. *Am J Physiol.* **280**: H844–H850.
- 30 Takemoto M, Egashira K, Tomita H, Usui M, Okamoto H, Kitabatake A *et al* (1997). Chronic angiotensin-converting enzyme inhibition and angiotensin II type 1 receptor blockade: effects on cardiovascular remodeling in rats induced by the long-term blockade of nitric oxide synthesis. *Hypertension.* **30**: 1621–1627.
- 31 Tsuchihashi T, Kagiyama S, Matsumura K, Lin Y, Abe I, Fujishima M (2000). Cardiovascular responses to glutamate and angiotensin II in ventrolateral medulla of hypertension induced by chronic inhibition of nitric oxide. *Hypertens Res.* **23**: 359–364.
- 32 von Bohlen und Halbach O & Albrecht D (2006). The CNS renin-angiotensin system. *Cell Tissue Res.* **326**(2): 599–616.
- 33 Wilms H, Rosenstiel P, Unger T, Deuschl G, Lucius R (2005). Neuroprotection with angiotensin receptor antagonists: a review of the evidence and potential mechanisms. *Am J Cardiovasc Drugs.* **5**(4): 245–253.
- 34 Zanchi A, Schaad NC, Osterheld MC, Grouzmann E, Nussberger J, Brunner HR, Waeber B (1995). Effects of chronic NO synthase inhibition in rats on renin-angiotensin system and sympathetic nervous system. *Am J Physiol.* **268**: H2267–H2273.
- 35 Zhou MS, Schulman IH, Raij L (2004). Nitric oxide, angiotensin II, and hypertension. *Semin Nephrol.* **24**: 366–378.
- 36 Zimmerman MC, Lazartigues E, Lang JA, Sinnayah P, Ahmad IM, Spitz DR, Davisson RL (2002). Superoxide mediates the actions of angiotensin II in the central nervous system. *Circ Res.* **91**(11): 1038–1045.