Is central nitric oxide essential in hypertension?
Mildred A. Pointer

It is becoming increasingly evident that central nervous system nitric oxide (NO) may be an important contributor to the development of hypertension in light of its centrally-mediated sympatho-inhibitory actions [1–3]. In this issue of the journal, Ferrari and Fior-Chadi [4] investigate the role of central neuronal nitric oxide synthase (nNOS) in the development of hypertension using the spontaneously hypertensive rat (SHR) model [4]. These authors report that nNOS message and protein levels within the nucleus tractus solitarius (NTS) are elevated in SHR relative to their age-matched Wistar-Kyoto (WKY) controls. This enhanced nNOS expression precedes the elevation in blood pressure and is observed as early as 15 days of age. The authors further note that the nNOS message and protein decreases with age in both SHR and WKY rats. These results suggest that abnormal NTS NO may play a role in the pathophysiology of hypertension in this animal model.

However, the experimental design used by these authors does not provide data that offers any definitive enlightenment on the role of central NO in the development of hypertension. If the premise is that increased sympathetic output to blood vessels contributes to the elevated blood pressure, then there are three important questions that must be considered in the experimental design to address the causative role of central NO in high blood pressure. First, what region of the brain is the source of the increased sympathetic output? Second, is the measurement of nitric oxide synthase messenger RNA and protein levels alone able to provide definitive information about NO neuromodulator levels? Finally, are the changes in neural NO neuromodulator levels causative or compensatory?

Three specific regions of the brain most frequently targeted for study in blood pressure regulation include the paraventricular nucleus (PVN), NTS and the rostral ventrolateral medulla (RVLM). Neurons in the PVN and NTS project to the RVLM [2] and neurons from the RVLM region send projections to sympathetic preganglionic neurons in the spinal cord [2,5,6]. Activation of some of the neurons within the PVN leads to the release of the neurotransmitter glutamate. Glutamate, acting through its N-methyl-D-glutamic acid (NMDA) receptor, causes an increase in blood pressure and heart rate. This cardiovascular response is through increased sympathetic output from RVLM because sympathetic nerve activity is increased following microinjection of glutamate within the PVN [1]. However, other neurons containing the inhibitory neurotransmitter γ-aminobutyric acid (GABA) also project to the RVLM region, leading to a decrease in RVLM output to the sympathetic preganglionic neurons [7]. One of the sources of the GABA inhibitory neurotransmitter is from the caudal ventrolateral medulla. The caudal ventrolateral medulla receives input from the NTS that is stimulated following blood pressure elevation [7]. Although the PVN and NTS have significant effect on sympathetic output, this occurs through modulation of the RVLM sympathetic preganglionic neurons. Therefore, it is the neuronal activity of the RVLM region that determines the sympathetic load to blood vessels. If increased sympathetic activation and output to blood vessels is the proposed mechanism of hypertension, then the RVLM site is the most appropriate region to study.

Neural NOS isoform mRNA and protein levels, NOS activity and NO levels have been examined in the SHR model. Studies that have measured NOS message and/or protein demonstrate conflicting results. More specifically, it is unclear whether NO exerts an excitatory or inhibitory action in the PVN and NTS region when NOS mRNA and protein alone are studied [8–11]. There are reports suggesting an impairment of NO actions in the PVN and NTS in hypertensive SHRs when using immunostaining and NOS activity measurement techniques [8,9]. However, other studies have shown that brainstem staining NO activity is increased in the established phase of hypertension but decreased in the prehypertensive phase in SHRs [12].

When the RVLM is specifically examined, nNOS expression appears to be increased or normal in the RVLM of SHR with established hypertension [13,14]. Interestingly, Chan et al. [14] found normal nNOS in this region but a decrease in inducible NOS (iNOS) expression in hypertensive SHR. However, in young prehypertensive SHR, nNOS levels were normal whereas inducible NOS (iNOS) levels were increased in the RVLM region in SHR relative to their WKY controls [14]. These results have been interpreted as suggesting that it is the relative proportion of nNOS to iNOS, and, consequently, the level of NO in the RVLM, that determines the blood pressure response.
Standing blood pressure regulation and, consequently, peripheral vasodilation from NO is essential for understanding the mechanism(s) of the abnormal NO levels, this information does not address the immediate question of the role of NO as initiator of hypertension.

References
2. Kantzides A, Badoer E. nNOS-containing neurons in the hypothalamus and medulla project to the RVLM. Brain Res 2005; 1037:25–34.