The Regulation of Sympathetic Nerve Activity by Angiotensin II Involves Reactive Oxygen Species and MAPK

Irving H. Zucker, Lie Gao

The central regulation of sympathetic nerve activity has been extensively investigated in normal and disease states since the detailed description of the cardiovascular pressor area by Alexander in 1946. This so called "pressor area" we now know to be the rostral ventrolateral medulla (RVLM). The neurons of the RVLM constitute the primary motor neuron pool from which sympathetic projections to the spinal cord arise. Importantly, the RVLM also receives inputs from a variety of integrative areas in the hypothalamus and medulla. The net sympathetic outflow of various cardiovascular reflexogenic areas have a common pathway which exits the brain from the RVLM. In addition to the neural modulation of these reflexes from hard wired areas in the hypothalamus, medulla, and forebrain, it has become increasingly more recognized that autocrine, paracrine, and endocrine influences on these sympathetic neurons are important for the regulation of arterial pressure, myocardial function, salt and water balance, and general cardiovascular homeostasis in the normal resting state and during the extremes of cardiovascular function such as exercise, heart failure, hypertension, etc.

Neuronal excitability in the RVLM is not only modulated by classical neurotransmitters such as glutamate and gamma amino butyric acid (GABA) but appears also to be regulated by the ubiquitous octapeptide angiotensin II (Ang II). In fact, Ang II, in addition to its myriad of cardiovascular and endocrine effects, has been known for many years to modulate sympathetic function at various sites in the central and peripheral nervous systems. One of the earliest works in this area came from Mangiapane et al, who found that direct administration of Ang II into the subfornical organ elicited cardiovascular and dipsogenic effects. These investigators have demonstrated in an elegant series of experiments that part of the Ang II–AT1 signaling pathway in the RVLM requires activation and phosphorylation of the p38 mitogen-activated protein kinase (p38MAPK) and the extracellular signal-regulated protein kinase (ERK1/2). Furthermore, this process requires activation of the NAD(P)H oxidase enzyme complex and the generation of superoxide anion (O2−). The relationship of Ang II to O2− generation in the cardiovascular system in normal and disease states largely comes from the work of Harrison and Griendling. The role of vascular NAD(P)H oxidase in the generation of O2− has been well appreciated because of these studies. Neuronal signaling by Ang II and AT1 receptors has not been as extensively investigated but has still been well demonstrated in cardiovascular areas of the brain that are associated with sympathetic regulation. What has not been as well appreciated in the regulation of sympathetic outflow by Ang II is the altering signaling pathway mediated by p38MAPK and ERK1/2. The study by Chan et al. raises an important issue concerning the modulation of p38MAPK and ERK1/2 phosphorylation by a NAD(P)H oxidase–dependent mechanism. The stress related proteins, SAPK and JNK, were not activated by Ang II in this study. Although the article by Chan et al. may be the first to describe this mechanism in neural tissue, a similar mechanism has been demonstrated in human neutrophils and vascular smooth muscle. Many transcription factors encompassing a broad range of action have been shown to be phosphorylated and subsequently activated by p38MAPK. This may include activation of transcription factor 1, 2, and 6 (ATF-1/2/6), SRF accessory protein (Sap 1), and CHOP (growth arrest and DNA damage inducible gene 153, or GADD153). Activation of p38MAPK by this mechanism may thus be responsible for modulation of gene transcription of several proteins important in neuronal excitability such as the potassium channel family of ion channel proteins. Furthermore, O2− itself has been shown to modulate calcium channel function and thereby neuronal excitability. Although the experiments described in this study reflect an important short-term effect of Ang II–O2−–MAPK, the chronic effects of Ang II–NAD(P)H oxidase–O2− may be of great importance in defining the activity of RVLM neurons in disease states. For instance, in chronic heart failure (CHF), sympathetic nerve activity to the heart and the peripheral circulation is increased. Central Ang II and AT1 receptors have been shown to play an important role in this sympathoexcitation. For instance, in a recent study from our laboratory...
we demonstrated that chronic (7 days) infusion of Ang II into the brain of normal rabbits resulted in sympatho-excitation, upregulation of AT1 receptors in the RVLM, and increased oxidative stress.23 More importantly, Ang II infusion caused an upregulation of several of the protein subunits of NAD(P)H oxidase including gp91phox. All of these effects were inhibited by losartan. In a study performed in rabbits with CHF, central administration of losartan, tempol, or apocynin reduced sympathetic nerve activity, oxidative stress, and NAD(P)H oxidase activity.36

Finally, an important issue in this pathway relates to the mechanism by which the AT1 receptor is upregulated in hyperangiotensinergic states. There is evidence that the transcription factor AP-1 can modulate AT1 receptor expression.37 There is now good evidence that p38MAPK can activate AP-1,38,39 thus potentially controlling AT1 receptor expression.

The relationship between Ang II, the AT1 receptor, NAD(P)H oxidase, superoxide anion, and potassium channel regulation is depicted as a schematic representation in the Figure. p38MAPK may play an integral role in the regulation of neuronal excitability in the RVLM and thus modulate sympathetic nerve activity in disease states characterized by hyperadrenergic activity.

Acknowledgments

The studies reported here from the author’s laboratory were supported by National Institutes of Health grant PO-1 HL-62222 and by a postdoctoral fellowship (Award 0425680Z) from the American Heart Association (Heartland Affiliate).

References


**KEY WORDS:** autonomic nerve activity ■ ROS ■ superoxide ■ RVLM
The Regulation of Sympathetic Nerve Activity by Angiotensin II Involves Reactive Oxygen Species and MAPK
Irving H. Zucker and Lie Gao

Circ Res. 2005;97:737-739
doi: 10.1161/01.RES.0000188261.94569.1f

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circres.ahajournals.org/content/97/8/737

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation Research can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation Research is online at:
http://circres.ahajournals.org//subscriptions/