Mechanisms Underlying Hypertension and Obesity
A Melanocortin Linkage in the Brain

Scott H. Carlson, J. Michael Wyss

See related article, pp 435–441

Hypertension significantly contributes to cardiovascular disease, renal dysfunction and stroke, and it greatly enhances diabetes-related morbidity and mortality. Despite these significant interactions, research has yet to fully elucidate the underlying mechanisms. Elevated sympathetic nervous system activity appears to contribute to many forms of the disease, but it is unclear which factors lead to enhanced sympathetic output. Circulating factors such as angiotensin II (Ang II) and leptin are sympathoexcitatory in several rodent models of hypertension, although their contribution to hypertension in humans is less clear. Similarly, elevated insulin levels increase sympathetic nervous system activity and blood pressure in rodent models of diabetes, but again, the contribution of insulin to diabetic-induced hypertension in humans remains to be established. The study by Ward et al1 strongly suggests that circulating insulin activates a specific melanocortin-dependent pathway within the central nervous system (CNS) that alters hypothalamic paraventricular nucleus activity, thereby increasing glutamatergic drive to the rostral ventrolateral medulla and raising arterial pressure.

The rostral ventrolateral medulla (RVLM) is the final major brain region that controls sympathetic nervous system activity. RVLM neurons display spontaneous discharge, and their neuronal activity strongly correlates with sympathetic nervous system activity.2 RVLM neuronal activity is modulated by other cardiovascular regions in the CNS,3 one of which is the hypothalamic paraventricular nucleus (PVN). The PVN projects to both the RVLM and directly to the spinal sympathetic intermediolateral nucleus, and stimulation of PVN neurons increases RVLM activity and arterial pressure. Many PVN neurons that project to RVLM also display an intrinsic autorhythmicity, and the discharge frequency correlates closely with sympathetic discharge rate.4 The relation of PVN neurons to sympathetic control suggests that the spontaneous discharge can be modified through either changes to the intrinsic rate of depolarization or alterations in the balance of excitatory and inhibitory afferent input.

Given the role of the PVN in controlling sympathetic activity and its potential contribution to hypertension, research is exploring how PVN activity may be modified by extrinsic inputs. The PVN receives extensive neuronal input from a large number of regions in the brain, including those associated with osmotic control (the subfornical and median preoptic nuclei), appetite and energy metabolism (lateral hypothalamic), limbic nuclei, and other areas that exert effects on blood pressure (eg, lateral parabrachial nucleus, nucleus tractus solitarius, dorsal motor nucleus of the vagus).4 Thus, altered input from any of these areas may alter PVN activity, elevate sympathetic outflow, and contribute to neurogenic hypertension. One such example is seen in the spontaneously hypertensive rat, in which PVN-induced stimulation of RVLM neurons elevates arterial pressure through excess glutamatergic signaling and decreased gamma-aminobutyric acid input.5

PVN and RVLM neurons also respond to endocrine factors, of which the renin-angiotensin is perhaps the best studied. Ang II affects arterial pressure through its action as a hormone throughout the body, including brain areas outside the blood-brain barrier. Additionally, Ang II generated within the CNS through an endogenous renin-angiotensin system also appears to directly alter sympathetic activity through neurotransmitter/neuromodulatory actions at the RVLM and PVN neurons.6

The study by Ward et al1 focuses on a second CNS neuromodulator/neurotransmitter system that appears to be involved in arterial pressure regulation, ie, the melanocortin system. The melanocortins are derived from proopiomelanocortin in the arcuate nucleus and are involved in the regulation of food intake and weight control. The effects of melanocortins are mediated by G protein-coupled melanocorticotid receptors, including the MC3R and MC4R, which are distributed in several CNS nuclei, including the PVN. Rodent studies and clinical observations support a linkage of the melanocortins to regulation of food intake, leptin, weight control, and now blood pressure. In normotensive rats, intracerebroventricular administration of a melanocortin MC3/4R agonist increases arterial pressure, in part through sympathoexcitation.7 The melanocortin pathway appears to contribute to hypertension in the Dahl salt-sensitive rat8 and spontaneously hypertensive rat,9 and may also play a role in leptin-induced sympathoactivation. In Sprague-Dawley rats, intracerebroventricular administration of leptin increases sympathetic activity, and this is blocked by administration of a MC4R antagonist.10 Similarly, intracerebroventricular administration of leptin and melanocortin increases sympathetic nerve activity in wild-type mice, but not in db/db mice that lack the leptin receptor.11 Interestingly, this melanocortin-induced sympathoexcitation is markedly decreased in db/db mice, while the
leptin-induced increase in sympathetic activity is abolished in homozygous MC4R knock-out mice. Taken together, these results suggest that the melanocortin system is necessary for leptin and insulin-dependent sympathoexcitation. Finally, melanocortin appears to play a similar role in humans. Greenfield and colleagues have demonstrated that hypertension is markedly lower in patients with a genetic deficiency of MC4R, in part from a reduction in sympathetic activity. Thus, the melanocortin pathway appears to contribute to alterations in sympathetic outflow and elevations in arterial pressure associated with leptin, insulin, and other obesity-related factors.

The study by Ward et al expands on current understanding of hyperinsulinemia and sympathoexcitation. Using Sprague Dawley rats, they find that circulating insulin activates a melanocortin-dependent pathway to the PVN, thereby increasing excitatory glutamnergic projections to the RVLM and increasing sympathetic activity and arterial pressure. Such a role is supported by newly published findings in which melanocortin-induced excitation of RVLM-projecting PVN neurons is potentiated in hyperinsulinemic obese Zucker rats (compared to lean controls), as well as in the clinical study by Greenfield discussed above. Taken together, these results demonstrate a potential for the central melanocortin system in elevating sympathetic outflow and arterial pressure in hyperinsulinemic conditions.

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**References**

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