Antihypertensive effects of ACE2 in the paraventricular nucleus: a consequence of reduced neuroinflammation?

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This editorial refers to ‘ACE2 overexpression in the paraventricular nucleus attenuates angiotensin II-induced hypertension’ by S. Sriramula et al., pp. 401–408, this issue.

Angiotensin II increases arterial pressure through its multiple actions on the nervous system, the adrenal glands, the vasculature, and renal epithelial transport. In recent years, evidence has accumulated that the activation of proinflammatory mechanisms contributes to the pathogenesis of arterial hypertension by causing inflammation of tissues and organs, such as the vasculature, the kidneys, and the central nervous system (CNS). Angiotensin II is a potent stimulator of proinflammatory activity in hypertension.

The paraventricular nucleus (PVN) of the hypothalamus is intimately involved in neuroendocrine regulatory processes that affect arterial pressure. It receives inputs from osmosensitive neurons, arterial baroreceptors, and stretch receptors in the large veins and in the atria. The PVN effector neurons project to the posterior pituitary where they release oxytocin or vasopressin and to the anterior pituitary where they secrete releasing hormones into the portal circulation. Other neurons of the PVN project to CNS target neurons outside the pituitary that determine sympathetic and parasympathetic output.

Stimulation of PVN neurons by circulating angiotensin II increases vasopressin release, elevates sympathetic activity, and raises arterial pressure.

Sriramula et al. show that adenovirus-mediated overexpression of angiotensin converting enzyme 2 (ACE2) in the PVN attenuates angiotensin II-induced hypertension in rats. ACE2 is a membrane-bound carboxypeptidase that converts the octapeptide angiotensin II to the heptapeptide angiotensin-(1–7). Activation of the G-protein-coupled receptor Mas by angiotensin-(1–7) has been shown to elicit multiple cellular actions that antagonize AT1 receptor-mediated responses induced by angiotensin II.

Sriramula et al. show that angiotensin II infusion into rats increased the expression of ACE and AT1 receptors while decreasing the expression of Mas receptors, ACE2, and AT2 receptors in the PVN. These alterations in PVN receptor and enzyme expression were not observed in rats overexpressing ACE2 in the PVN. These findings indicate that ACE2 overexpression antagonizes the angiotensin II-induced alterations in the expression of renin–angiotensin system components within the PVN in addition to its blood pressure-lowering effect. The study extends previous findings in genetically modified mice showing that ACE2 overexpression throughout the brain attenuates the angiotensin II-induced rise in arterial pressure. A new finding is that ACE2 overexpression in the PVN is sufficient to significantly counteract the angiotensin II-induced effects on arterial pressure, suggesting that the PVN plays a major role in the development of angiotensin II-induced hypertension.

Angiotensin II infusion increased the expression of the proinflammatory cytokines TNF-α, IL-1β, and IL-6 as well as the chemokine MCP-1 within the PVN, confirming previous results obtained in this model and in experimental heart failure which is characterized by an activated renin–angiotensin system. Another important finding is that the local overexpression of ACE2 in the PVN prevented the angiotensin II-induced rise in proinflammatory cytokine expression in this hypothalamic nucleus, suggesting that the antihypertensive effects of ACE2 in the PVN may be due—at least in part—to its anti-inflammatory actions.

The study by Sriramula et al. does not provide data on how ACE2 transfection in the PVN lowers arterial pressure. Likely mechanisms are reduced sympathetic activity and increased sensitivity of arterial and cardiopulmonary baroreflex-dependent control of the circulation and of renal function, as suggested by data obtained in transgenic mice overexpressing ACE2 throughout the brain. The experimental rat model used in the study by Sriramula et al. readily lends itself to the study of ACE2-induced antihypertensive mechanisms, mainly because rats are more convenient to handle in complex experimental setups than mice and also because experimental data on the autonomic control of circulatory and renal function are more abundantly available in rats than in mice.

Further questions arising from this study relate to cellular mechanisms within the PVN that contribute to the beneficial effects of ACE2 transfection on angiotensin II-induced hypertension. The authors show that ACE2 overexpression is associated with increased ACE2 enzyme activity in the PVN. It remains to be clarified to what extent ACE2 enzyme activity in the PVN is a consequence of increased ACE2 receptor expression, which would indicate a reduction in angiotensin-II-mediated signaling.

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extent the observed antihypertensive action of ACE2 overexpression is due to decreased angiotensin II concentrations or increased angiotensin-(1–7) concentrations within the PVN. Mas receptor blockade abolished the protective effect of ACE2 overexpression throughout the brain in angiotensin II-induced hypertension, suggesting that angiotensin-(1–7) was important for the antihypertensive effects of ACE2. On the other hand, pharmacological Mas receptor blockade in the PVN of anaesthetized rats reduced renal sympathetic nerve activity, suggesting that endogenous angiotensin-(1–7) in the PVN may elicit sympathoexcitatory effects. The reasons for these apparently conflicting data warrant further investigation.

The precise role of elevated proinflammatory cytokines within the PVN for angiotensin II-induced hypertension remains to be clarified. This includes identification of the source of proinflammatory cytokines that may be released from both macroglia and infiltrating microglia activated by angiotensin II. Proinflammatory cytokines have been shown to facilitate excitatory neurotransmission, and one may speculate that proinflammatory cytokines contribute to sympathoexcitation via PVN neurons in angiotensin II-induced hypertension. Several findings support this concept: intracerebroventricular administration of pharmacological agents aiming to inhibit inflammatory activity in the brain reduced sympathetic activity in angiotensin II-infused rats and in heart failure rats. Furthermore, there is evidence for increased PVN neuronal activity, including elevated PVN glutamate levels, in experimental heart failure.

Recently, non-pharmacologic interventions to reduce sympathetic activity, such as renal denervation, have been successfully introduced in the treatment of severe forms of human hypertension, suggesting that elevated sympathetic activity importantly contributes to the perpetuation of pharmacotherapy-resistant hypertension. Experimental studies on neuroinflammation in hypertension and their translation to human hypertension may help better understand the role of sympathetic activation in the pathogenesis of hypertension and may provide the scientific basis for the development of novel antihypertensive treatment regimens.

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References