The brain renin-angiotensin system (RAS) has been extensively studied due to its role in central cardiovascular regulation and body fluid homeostasis. Much of the early work on this system was stimulated by the pioneering work of Brody, Johnson, and colleagues (1) who focused on possible interactions between circulating angiotensin II and a brain RAS promoting neurogenic hypertension. Our current understanding of the brain RAS has evolved to include multiple neuroactive peptides that have differential effects in regulating the autonomic nervous system not only in the context of hypertension but also in congestive heart failure, fetal programed cardiovascular disease, and aging (2, 4, 7, 8). Many of the advances in our understanding of the complexity of this system have been the result of new transgenic approaches that permit tissue-specific expression or deletion of important components of RAS.

In the recent publication by Littlejohn et al. (5), a sophisticated double transgenic mouse model was used to examine the effects of selective activation of the brain RAS system on blood pressure and water and electrolyte homeostasis. In this model, the brain is selectively targeted by combining two separate mouse models: one with selective overexpression of human renin driven by the neuron-specific promoter synapsin and another with human angiotensinogen driven by its own promoter. Because of the species specificity, activation of the RAS is restricted to regions where both transgenes occur. Previous studies with this model demonstrated alterations in energy metabolism, increased fluid turnover, and hypertension (3). In the more recent study, the investigators explored the mechanism mediating the changes in fluid balance produced in this model, which has led to a series of interesting observations about the mechanisms underlying the hypertension.

In the double transgenic mice, the authors observed an increase in the numbers of vasopressin-positive profiles in the supraoptic nucleus of the hypothalamus along with a significant hyponatremia. Although circulating copeptin, a vasopressin prosegment, was decreased in the transgenic mice, urinary copeptin excretion was significantly elevated, suggesting that increased activity of the brain RAS was stimulating vasopressin release. The transgenic mice displayed a significant elevation in blood pressure that was normalized by chronic infusions of a nonspecific vasopressin antagonist conivaptan. Further investigation of these effects demonstrated decreased vascular reactivity to vasopressin coinciding with reduced expression of V1A receptors in mesenteric arteries. In contrast, V2 receptors in the kidneys did not show significant changes in the transgenic mice compared with wild-type control. Chronic treatments with a V2 receptor-selective antagonist tolvaptan not only reduced the hypertension but also corrected the hyponatremia in the transgenic model. Together, these observations indicate that chronic activation of the brain RAS produces a vasopressin-dependent hypertension that is mediated primarily by the kidney. The authors indicate that their results support a greater role for vasopressin in cardiovascular regulation and that the double transgenic model may be of importance in studying the pathophysiology of dilutional hyponatremia.

These results, especially those related to hypertension in this model, may seem somewhat surprising given the role that the brain RAS plays in the regulation of autonomic function in experimental models of hypertension (6) and heart failure (8). The results of Littlejohn et al. do not necessarily preclude a role for the sympathetic nervous system in the hypertension associated with this model. They do show that one of major net effects of activation of the brain RAS is stimulation of neurohypophyseal vasopressin release, which does contribute to hyponatremia and hypertension in this model. It could be argued that the relationship between vasopressin and hypertension in this study is an epiphenomenon of the complex transgenic approach used to activate the brain RAS. The results might be better viewed in a larger context. Peptides have complex functions in the central nervous system due to their modulatory nature and participation in multiple systems. Therefore, a peptide might not be expected to have a single physiological role in the brain but several depending on how, where, and with whom the peptide is activated. In this context the results of Littlejohn et al. are an important reminder of this complexity.

DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.T.C. drafted manuscript; J.T.C. edited and revised manuscript; J.T.C. approved final version of manuscript.

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