Several decades of investigation have provided unequivocal support for the existence of an intrinsic brain renin-angiotensin (Ang) system (RAS) and its involvement in the control of cardiovascular functions.1,2 Essential components of the RAS, ie, renin, angiotensinogen, Ang-converting enzyme, Ang-converting enzyme 2, type 1 Ang II, and type 2 Ang II receptors, as well as various aminopeptidases, are synthesized within the brain, and the hyperactivity of RAS in the brain is implicated in the development and maintenance of hypertension.1,2 Moreover, interruption of the brain RAS activity by either pharmacological or genetic means is associated with a profound beneficial outcome in hypertension.1,2 Thus, the brain RAS may be an important target for hypertension with neurogenic origin.

Many years ago it was proposed that the physiologically relevant peptide in the brain RAS that regulates blood pressure (BP) is Ang III rather than Ang II.3,4 Ang III, also called Ang-(2-8), is generated from Ang II by aminopeptidase A (APA), which cleaves the Asp1-Arg2 bond in Ang II. Persuasive evidence have been presented in support of this “Ang III hypothesis”: (1) Ang III, when centrally administered, enhances BP; stimulates vasopressin release, thirst, and sodium appetite; and decreases baroreceptor reflex function5,6; (2) Ang III displays comparable affinity to Ang II for the type 1 Ang II receptor3; (3) specific inhibitors of APA that block the conversion of Ang III from Ang II attenuate central Ang II actions4 (eg, central treatment with EC33, an APA inhibitor, attenuates ICV-administrated Ang II effects on BP); in addition, ICV injection of this inhibitor decreases brain Ang III formation7,8; and (4) APA-resistant analogs of Ang II fail to influence central actions.4 However, this Ang III hypothesis is not without its critics. Kokje et al9 performed a series of experiments using different aminopeptidase-resistant analogs of Ang II and concluded that Ang III analog is not necessary to induce central effects. Nevertheless, one important caveat of this study is that the authors used exogenous analogs. Thus, it does not eliminate the importance of endogenous brain Ang III in BP control.

It is in this regard that the study of Bodineau et al,10 in this issue of Hypertension, is of great significance. They demonstrate that RB150, a dimer of the selective APA inhibitor EC33, can cross the blood-brain barrier and can inhibit the brain APA. This results in the inhibition of Ang II conversion to Ang III and a consequent decrease in BP in the DOCA-salt rat model of hypertension (Figure). The antihypertensive effect of this prodrug is attributed to a reduction in plasma vasopressin. In fact, RB150 treatment elicited renal effects on diuresis and natriuresis compatible with a reduced release of vasopressin. Thus, these observations not only establish a method for the central delivery of an APA inhibitor but also provide further insights into the role of the brain Ang III in the regulation of vasopressin secretion and dependence of Ang III conversion from Ang II in hypertension in at least the DOCA-salt rat model.

The study is novel in many respects: (1) it strengthens the Ang III hypothesis and the role of APA in central control of BP; (2) it demonstrates that RB150, a prodrug of APA selective inhibitor, is capable of crossing the blood-brain barrier in sufficient concentrations to influence high BP (thus, the study provides a means to influence the brain APA by simple oral administration); and (3) it is an important first step in the development of oral drug-based therapeutics for neurogenic hypertension. Therefore, the study is important in consideration of a new class of central antihypertensive agents.

Many important issues, however, must be resolved, and mechanisms tested by further experimentation before this could be successfully translated into therapeutics. For example, it would be prudent to delineate the roles of Ang III and APA in various cardioregulatory brain regions in the control of cardiovascular functions, including BP control. Is a global APA inhibition, as is probably achieved in the present study, required for maximal effects on BP and vasopressin release, or would be the effects on selective brain regions such as the paraventricular nucleus, rostral ventrolateral medulla, and nucleus tractus solitarii be more effective? Would the inhibition of one brain region attenuate high BP whereas the other regions may be linked with other hypertension-linked pathophysiology, such as cardiac hypertrophy and vascular dysfunction? Would targeting of cerebral vasculature impact the preponderance of stroke-linked hypertension? There is also compelling evidence that the origin of Ang II as substrate for APA is within the brain.1,11 However, the role of circulating Ang II in the activation of angiotensinergic pathways in the circumventricular organs in pathophysiological situations remains to be worked out. Thus, information on the APA and production of Ang III in these brain regions would be critical in this respect. In addition, according to Bodineau et al,10

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1% of the administrated RB150 penetrates the brain. Although this is impressive for a lead compound in providing the “proof of principle,” it would be interesting to improve its delivery efficacy. This may lead to long-lasting antihypertensive actions. It would also be critical to extend the findings of the DOCA-salt rat to other models of hypertension, particularly those that are not brain RAS dependent, to further validate the therapeutic potential of the APA targeting. Lastly, contributions of the newer members of the RAS, including the pro(renin) receptor and Ang-converting enzyme 2, in the mechanism of APA and its inhibitors and overall activity of the brain RAS must be kept in mind.

In summary, the study provides further evidence for the involvement of the brain RAS in neurogenic hypertension. It describes the development of an APA inhibitor that is able to circumvent the blood-brain barrier, thereby inhibiting the brain APA and generation of the physiologically relevant Ang peptide, Ang III. Thus, it may turn out to be the key for the therapy of neurogenic/Ang-dependent hypertension.

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