Stimulation of Aldosterone Synthesis by Angiotensin II in the Brain
Support for Positive Feedback in Hypertension?

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See related article, pp 564–571

Gomez-Sanchez et al1 published 2 crucial articles in 2005.1,2 One established that aldosterone could be synthesized in vivo in the rat brain.1 The other demonstrated that intracerebroventricular infusion of triolostane, to inhibit of aldosterone and corticosterone synthesis in the brains of Dahl salt-sensitive rats, reversed salt-induced hypertension. These carefully performed studies raised the possibility that in addition to circulating aldosterone, aldosterone synthesized locally in the brain could play a physiological role in the regulation of blood pressure. Subsequently, Huang et al3 and Gomez-Sanchez et al4 used a more selective inhibitor of aldosterone synthase, FAD286, and reported attenuation or reversal of salt-sensitive hypertension in Dahl salt-sensitive rats. Those articles provided additional support for the hypothesis that salt-induced hypertension in Dahl salt-sensitive rats is, in part, dependent on elevated expression of aldosterone synthase within the brain, resulting in increased local production of aldosterone. Was the physiological relevance of locally produced aldosterone unique to this genetic model of hypertension? In this issue of Hypertension, the article by Huang et al5 shows that intracerebroventricular infusion of either FAD286 or the mineralocorticoid receptor antagonist eplerenone attenuates the chronic phase of hypertension produced by intracerebroventricular infusion of angiotensin II. These results complement studies demonstrating that, conversely, aldosterone can act within the brain to exacerbate angiotensin-induced hypertension, and that aldosterone-induced hypertension is dependent, at least, partially, on brain angiotensin type 1 receptors.7,8 This study by Huang et al extends previous findings by this group which demonstrated that FAD286 and eplerenone could diminish hypertension produced by peripheral infusion of angiotensin II; this new study is significant because it raises the possibility that angiotensin II and aldosterone, both produced within the brain, participate in a positive feedback loop that promotes the maintenance of elevated sympathetic nerve activity in multiple forms of hypertension. Given the growing appreciation for the significant role of elevated sympathetic nervous system activity in the cause of human essential hypertension, these results have important clinical implications.

The current study by Huang et al also potentially contributes to our understanding of how ligand specificity is conferred to the mineralocorticoid receptor (MR). As recently reviewed by Gomez-Sanchez,9 aldosterone and the endogenous glucocorticoids corticosterone and cortisol bind to the MR with high affinity, but the glucocorticoids attain plasma concentrations 100 to 1000× greater than normal plasma aldosterone concentrations. The enzyme 11β-hydroxysteroid dehydrogenase 2 (11βHSD2) can metabolize cytoplasmic cortisol and corticosterone, allowing aldosterone to bind to the MR. However, for multiple reasons, coexpression of MR and 11βHSD2 cannot fully account for ligand specificity, especially within the brain. Local generation of aldosterone within the brain regions involved in cardiovascular regulation could potentially produce local concentrations of aldosterone sufficiently high to displace corticosterone or cortisol from the MR. Because corticosterone can, at least under some conditions, antagonize central nervous system–mediated hypertensive effects of aldosterone,11 uncovering the factors conferring ligand specificity for brain MR is critical for understanding mechanisms by which chronic increases in aldosterone can act in the brain to produce hypertension.

There are several aspects of this study by Huang et al that have to be considered in context of its potential significance. First, there is no way to judge the physiological relevance of the doses of angiotensin II that were used in this study. Huang et al did measure cerebral spinal fluid (CSF) angiotensin II concentration, and the intracerebroventricular infusions of 2.5 and 12.5 ng/min both produced a 10-fold increase in CSF concentration relative to intracerebroventricular vehicle controls. However, there are few studies that have measured CSF angiotensin concentration to provide a range of physiological and pathophysiological concentrations. Furthermore, normally, angiotensin II in the CSF comes from brain tissue, and therefore, brain tissue concentration would be predicted to be higher than CSF concentration. Tissue levels in brain regions mediating angiotensin-induced sympathoexcitation and hypertension will have to be measured in animals with endogenous angiotensin-dependent hypertension and in animals with intracerebroventricular infusion of angiotensin II to ascertain the physiological relevance of this study.

Aldosterone synthesis in the brain was inhibited using intracerebroventricular infusion of FAD286. Although FAD286 is certainly more selective for aldosterone synthesis that triolostane or metyrapone, it still retains the capability of inhibiting
corticosterone synthesis. In this study, intracerebroventricular administration of angiotensin II increased hypothalamic and plasma levels of both aldosterone and corticosterone. FAD286 significantly attenuated the increase in both hypothalamic and plasma aldosterone, significantly reduced plasma corticosterone concentration, and had a smaller, statistically not significant, effect to reduce hypothalamic corticosterone concentration. In any case, hypothalamic concentrations of corticosterone were 100× hypothalamic concentrations of aldosterone. Thus, as the authors point out in the discussion, a role for MR activation by corticosterone in mediating the hypertension produced by intracerebroventricular infusion of angiotensin II cannot be ruled out by the data presented in this article.

Despite the caveats discussed above, Huang et al have provided additional evidence to support the hypothesis that local synthesis of aldosterone within the brain has a physiological role in the maintenance of angiotensin-dependent hypertension. Future studies in which aldosterone synthase is selectively inhibited in discrete brain regions known to mediate angiotensin-induced hypertension are needed. Conclusive demonstration of a central endogenous angiotensin–aldosterone positive feedback loop, whereby elevated local angiotensin levels stimulate aldosterone synthesis, which in turn sensitizes the hypertensive effects of angiotensin II, would further support the use of combined therapies targeting both angiotensin II and aldosterone, even in patients without elevated plasma aldosterone concentrations.

Disclosures

None.

References

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