How do central mineralocorticoid receptors modulate blood pressure?

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TIME WAS, and sometimes still is for those with a nephrocentric world view, when the way aldosterone elevated blood pressure was simple: renal sodium and water retention, increased blood volume causing increased cardiac output, reflex vasoconstriction, and normalization of cardiac output. We now know that aldosterone has direct vasoconstrictor effects on the vascular wall and, thanks in no small part to the work of Elise Gomez-Sanchez, that activation of central mineralocorticoid receptors (MR) is essential for aldosterone/salt-induced hypertension. In this issue of the American Journal of Physiology-Regulatory, Integrative and Comparative Physiology, Gomez-Sanchez and colleagues (2) report her latest studies in the area.

The studies are elegantly designed and at one level difficult to misinterpret: at another level they invite overinterpretation, which may not help advance the field. What they show, in male and female JR/s salt-sensitive rats, is that the characteristic accelerated rise in blood pressure when the animals are given 0.9% NaCl solution to drink is reversed by the intracerebroventricular infusion of low doses of trilostane, an inhibitor of the steroidogenic enzyme 3β-hydroxysteroid dehydrogenase/isomerase. Given that intracerebroventricular infusion of the MR antagonist RU-28318 (4) or the selective epithelial channel blocker benzamil (3) can similarly abrogate the salt-induced rise in blood pressure, it seems reasonable to infer that somehow trilostane may be lessening MR activation in the circumventricular nuclei involved.

What is, however, a leap of faith is that this represents an effect of lowered ectopic aldosterone synthesis in the relevant hypothalamic area, the result of lowered local conversion of pregnenolone to progesterone, and thus lower production of downstream products, including deoxycorticosterone, corticosterone, and aldosterone. The Gomez-Sanchez laboratory has a well-deserved reputation for sensitive and specific assays, but even in their hands, they cannot measure any change in local synthesis in the hypothalamus: even in a salt-fed rat, the overwhelming majority of brain aldosterone is adrenal derived. It is possible, of course, that the anteroventral region of the third ventricle (A3V3) region is a “hot spot” in terms of local synthesis, so that its relative contribution may be higher, but no evidence is advanced for this possibility.

It is an area fraught with difficulty in interpreting what, at face value, seem to be simple and clear-cut experiments. In a previous study, Gomez-Sanchez (5) showed that intracerebroventricular aldosterone, infused at doses totally ineffective when given peripherally, raises blood pressure in Sprague-Dawley/Wistar rats on high salt, an effect progressively antagonized by concurrent infusion of equimolar or twofold higher doses of corticosterone. This was not unreasonably interpreted as evidence for an agonist effect of aldosterone via circumventricular MR unprotected by the enzyme 11β-hydroxysteroid dehydrogenase, given the antagonist effectiveness of 1× and 2× corticosterone.

But then we need to put these findings in context. Unprotected MR are essentially always occupied by normal circulating glucocorticoid levels, given their very high affinity for physiological glucocorticoids, as high or higher than that of aldosterone. Given the demonstrated activity of intracerebroventricular aldosterone, it is presumably at a local concentration sufficient to activate circumventricular MR by competing with endogenous corticosterone. Formally, this might be a minority of MR, or at the nadir of circadian glucocorticoid levels: such an explanation is, however, unlikely given the ability of coinfused corticosterone to block the aldosterone effect. If activating a minority of receptors, or a minority of receptors for a minority of the time, were sufficient for aldosterone to have its effect, it would require much higher levels of antagonist to reverse. The most parsimonious interpretation of these apparently straightforward prior studies, then, is that the levels of intracerebroventricularly infused aldosterone are locally so high as to compete with the high levels of endogenous corticosterone.

What this does is to pose a very serious question in terms of a possible (patho)physiological role for aldosterone in modulating blood pressure via circumventricular MR. Even in Conn’s syndrome, aldosterone levels are orders of magnitude lower than those of cortisol, and the possibility that under physiological circumstances, hypothalamic levels of aldosterone are higher than those of glucocorticoids is one difficult to entertain. Second, in normal Wistar rats, intracerebroventricular injection of the MR antagonist RU-28318 lowers blood pressure for >24 h; importantly, the fall in BP (20–30 mmHg) was not significantly different between animals on a high (8%)-, normal (0.4%)-, or depleted (0%)-salt diet for 3 wk (7). Although aldosterone levels were not measured in these studies, there can be little doubt that they inversely reflected sodium intake, with no appreciable difference in their contribution to circumventricular MR activation.

Thus although there is no doubt that aldosterone can raise blood pressure by activating circumventricular MR, there are considerable barriers to accepting that it does so in vivo in normotensive or hypertension-prone rats. An alternative thesis that may reconcile all the previous data is that circumventricular MR are overwhelmingly occupied by normal levels of endogenous glucocorticoids; that these glucocorticoid-MR complexes are normally inactive but can be activated by neural input, perhaps somehow linked to whole body sodium status and/or changes in redox state; and thus that the unprotected MR in the circumventricular area, like those in cardiomyocytes for example (1), are high-affinity glucocorticoid receptors sensing cellular changes rather than alterations in aldosterone levels.

Where, then, does this leave trilostane, and the present studies? It seems unlikely that trilostane is an MR antagonist, although the only evidence comes from single-dose studies versus spironolactone in DOCA-treated adrenalectomized rats (6). The doses chosen by Gomez-Sanchez (2) were designedly at the lower end of the effective range: in addition to putatively
lowering aldosterone levels, they would also lower those of DOC, an MR agonist, but also those of progesterone and corticosterone, MR antagonists: in zero-sum terms, a net reduction in MR activation by any locally produced steroids is thus unlikely. Perhaps, at the local concentrations achieved, trilostane alters the metabolic state of the A3V3 cells, and thus their MR-mediated response to high sodium. Perhaps Gomez-Sanchez and colleagues (2) are right, and the effect is dependent on local aldosterone synthesis; but to prove this case, targeted aldosterone synthase knockouts, and/or intracerebroventricular infusion of specific aldosterone synthase inhibitors such as FAD-286, are needed. Until then, the clear effect of trilostane notwithstanding, a prudent jury must stay out.

REFERENCES


