In the current issue of Hypertension, Gonzalez et al describe the modulation of mesenteric vascular angiotensin type 2 receptor (AT2R) expression by aldosterone.1 The principal findings are as follows: (1) AT2R activation dilates phenylephrine preconstricted mesenteric arterioles; (2) 4 days of oral salt loading eliminates AT2R-mediated dilation and reduces expression of AT2R mRNA and protein; (3) an adrenal hormone is implicated because the effects of salt loading are mimicked by adrenalectomy; (4) of the candidate adrenal hormones, aldosterone is identified because mineralocorticoid replacement prevents the effects of adrenalectomy; and (5) aldosterone upregulates AT2R expression in explanted mesenteric arterioles. These well designed series of experiments strongly support a role for aldosterone to stimulate expression of AT2R and adds to the growing repertoire of roles that aldosterone plays in vasculature physiology.

The AT2R-mediated vasodilation observed by Gonzalez et al elegantly reproduces similar effects reported in the mesentery and other vascular preparations.2-5 AT2R induced vasodilation of mesenteric arterioles appears as endothelium-dependent,6 acts through kinin and nitric oxide (NO) generation,7 and involves myocyte hyperpolarization through stimulation of large-conductance Ca2+-dependent potassium channels.8 Such AT2R-mediated reduction of vascular resistance generalizes beyond the mesenteric vascular bed. Systemic AT2R activation through infusion of angiotensin II plus AT1 receptor blockers lowers blood pressure9 and AT2-null mice have mild hypertension with an exaggerated blood pressure response to deoxycorticosterone acetate plus salt.10,11 Carotid arteries,12 coronary arterioles,13 renal afferent arterioles,14-16 and descending vasa recta17 are dilated by AT2R activation. The participation of bradykinin B2 receptor activation and NO generation in AT2R-mediated vasodilation is a common finding but it is not uniform in all experimental preparations. Disruption of bradykinin B2 receptor fails to eliminate AT2R-stimulated cGMP and NO generation in the murine kidney.18 AT2R activation in the renal afferent arteriole may be largely tied to generation of vasodilatory cytochrome P450 epoxygenase products rather than NO.19 In descending vasa recta, AT2R activation vasodilates by facilitating endothelial cytoplasmic Ca2+ responses that are otherwise inhibited by AT1 receptor stimulation. In that preparation, AT2R activation increases NO bioavailability by inhibiting generation of reactive oxygen species.17,19 Taken together, the finding by Gonzales et al1 that AT2R activation is vasodilatory largely supports previous observations.

The ability of aldosterone to regulate AT2R transcription in mesenteric arterioles1 is novel and adds to a growing literature that demonstrates direct microcirculatory effects of mineralocorticoids. Aldosterone is well recognized for its ability to stimulate distal sodium reabsorption in the kidney, a process that partially occurs through increased expression of transporters in distal tubule and collecting duct. That “genomic effect” takes place when ligand-bound mineralocorticoid receptor translocates to the nucleus and stimulates transcription. In addition to long-term regulation in the kidney, aldosterone has been found to have “nongenomic” effects to constrict and dilate microvessels. Such acute effects on the vasculature have been recognized for some time20 and have become the subject of recent mechanistic investigations. In the presence of NO synthase inhibition, aldosterone facilitates blood flow reduction to the human forearm by phenylephrine.21 A report of constriction of renal glomerular arterioles through spironolactone-insensitive surface receptor binding has been provided.22 Aldosterone has also been found to dilate renal afferent arterioles through a spironolactone-sensitive mechanism.23 Most studies favor a role for aldosterone to stimulate compensatory NO production.21,23,24 Whether the reduced expression of AT2R observed by Gonzalez et al1 is because of mineralocorticoid receptor-mediated signaling or lies downstream of cytoplasmic Ca2+ elevation, NO, or other pathways is currently unexplored. Based on the presence of appropriate response elements in the AT2R promoter, the authors make cogent arguments for the former. This remains to be sorted out and the signaling pathways involved will undoubtedly be a focus for further studies.

Apart from the signaling that modulates AT2R expression, one is led to ponder its physiological role. Salt loading is expected to reduce and increase expression of angiotensin II (Ang II) AT2 and AT1 receptors, respectively.25 That pattern of receptor regulation might augment rather than blunt the tendency toward salt-induced hypertension. Net effects are likely to be governed by local tissue concentration of Ang II and the sensitivity conferred by balance of receptor subtype expression. Local tissue Ang II concentration can differ from circulating plasma Ang II concentration by orders of magnitude, particularly in the kidney.26 Ang II is generated in many locations and the extent to which AT2R downregulation by aldosterone favors hypertension might hinge on the degree of
suppression of circulating renin and the local tissue Ang II generation. The physiological role of AT2R regulation by suppression of circulating renin and the local tissue Ang II generation. The physiological role of AT2R regulation by aldosterone seems uncertain and it is possible that additional effects of mineralocorticoids on the vasculature, yet to be discovered, may be needed to resolve the issue.

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References

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