Targeting activated mineralocorticoid receptor: Occam’s razor revisited

Andrew S. Brem

Activation of mineralocorticoid receptors (MRs) classically has been associated with electrolyte transport, but we now know that MR activation can also lead to tissue inflammation and fibrosis. Aldosterone consistently activates MR, but under selected circumstances, endogenous glucocorticoids such as cortisol and corticosterone can also trigger MR. Tissue-specific safeguards such as the enzyme 11β-hydroxysteroid dehydrogenase limit glucocorticoid-induced MR activation, while the presence of reactive oxygen species may enhance the ability for glucocorticoid-induced MR activation even in the absence of aldosterone.


More than 50 years have passed since Hans Selye first suggested that the mineralocorticoid aldosterone was a proinflammatory and profibrotic agent—actions separate from aldosterone's better-known effects on electrolyte transport. To further prove the point and expand this hypothesis, subsequent investigators often used experimental animal models involving treatment with pharmacologic doses of mineralocorticoids (aldosterone or deoxicorticosterone) given over a period of weeks in the presence of sodium loading and/or prior renal injury (usually unilateral nephrectomy). Inflammation and varying degrees of fibrotic change were almost always observed in mineralocorticoid-treated animals, especially in the heart, arteries, and kidneys. The pathologic findings induced by aldosterone or deoxicorticosterone could be attenuated if the animals were also treated with a mineralocorticoid receptor (MR) antagonist such as spironolactone, even if the animals remained hypertensive. Luther and his colleagues (this issue) now offer an alternative approach; instead of using an excess of mineralocorticoids, they took away aldosterone as an offending agent and used continuously infused angiotensin II to promote tissue injury. The angiotensin II triggered the release of aldosterone from the adrenal gland in control mice but not in the genetically altered aldosterone-deficient mice. Selected animals also received the MR antagonist spironolactone to determine whether the tissue injury was mediated through MR activation.

In brief, Luther and his associates found that angiotensin II increased cardiac mass and fibrotic changes in wild-type but not in aldosterone-deficient mice, and not in wild-type mice treated with spironolactone. The authors concluded that in the heart, many of the changes induced by angiotensin II are probably mediated through activation of MR by aldosterone. In the aorta, angiotensin II increased aortic intima-media thickness in wild-type mice but not in aldosterone-deficient and spironolactone-treated wild-type mice. Again, the angiotensin II-induced effects appeared to be mediated by aldosterone-activated MR. In the kidney, studies, the blood urea nitrogen increased with angiotensin II infusion along with an increase in glomerular diameter and some tubular atrophy. In this case, aldosterone deficiency did not prevent the observed changes, but spironolactone did. This finding was consistent with MR being activated by something other than aldosterone, possibly endogenous glucocorticoids, since their secretion was unaffected in the aldosterone-deficient mice. The common thread in all of these experiments was that pathologic changes were mediated by activated MR. Under these experimental conditions with the continuous infusion of pharmacologic angiotensin II, the adrenally released aldosterone alone appears to activate MR in vascular tissue, but in the kidney, aldosterone and other substances can serve as MR-activating agents.

On the basis of past observations, how might we explain the above findings? John Funder has referred to a 14th century friar logician named William of Occam when trying to account for variations in steroid activation of MR. Occam’s razor (principle) briefly is “entities should not be multiplied unnecessarily” or the simpler explanation among competing theories is best. Although aldosterone and endogenous glucocorticoids such as cortisol and corticosterone bind to MR with nearly equal affinity, only aldosterone consistently activates MR to induce a biologic response. This receptor selectivity is maintained, at least in part, by the actions of two enzyme isoforms of 11β-hydroxysteroid dehydrogenase (11β-HSD-1 and 11β-HSD-2). 11β-HSD-1 generally functions as a bidirectional enzyme with the direction dependent on the redox state of the cofactor NADP(H). NADP drives the forward dehydrogenase reaction, inactivating endogenous glucocorticoids, while NADPH promotes the reverse reductase reaction, regenerating glucocorticoids from their 11-dehydro-metabolites. The redox state of the cell generally drives the

1Division of Hypertension and Kidney Disease (Pediatric Nephrology), Rhode Island Hospital and Alpert Medical School at Brown University, Providence, Rhode Island, USA
Correspondence: Andrew S. Brem, Division of Hypertension and Kidney Disease, Rhode Island Hospital, 593 Eddy Street, Providence, Rhode Island 02903, USA.
E-mail: Andrew_Brem@Brown.edu
Decision in determining MR specificity and activation (Figure 1). Endogenous glucocorticoids bind to vascular MR but do not appear able to activate it like aldosterone does under normal circumstances. Endogenous glucocorticoids appear to spontaneously activate vascular MR only under conditions in which excess reactive oxygen species are present (glutathione is in the oxidized state), as occurs with tissue injury and/or after a period of excessive sodium dietary intake.

The structure and functions of 11β-HSD isoforms in the kidney are quite different (Figure 1). Mammalian renal proximal tubules contain ample 11β-HSD-1, but here the enzyme is modified and is not bidirectional as in other tissues; it functions only as a dehydrogenase. Collecting duct cells, containing MR, express ample 11β-HSD-2, which also functions exclusively as a dehydrogenase.

The net effect is that both enzyme isoforms metabolize endogenous glucocorticoids to their respective inactive 11-dehydro derivatives and play a major role in determining MR specificity for aldosterone. When these enzymes are inhibited—say, with either exogenous or endogenously produced licorice-like substances—glucocorticoids can activate MR and produce a biologic effect identical to that of aldosterone.

Luther and his associates measured mRNA expression of both renal 11β-HSD isoforms and noted that the infused angiotensin II appeared to have no effect in either wild-type or aldosterone-deficient mice. Such an analysis is limited, and conclusions drawn from that experiment may be potentially misleading. The ultimate physiologic activity of an enzyme is dependent on how much of it is present (the actual amount of protein, not message), its biochemical characteristics (Km and Vmax), the substrate concentrations, and the relative availability of the appropriate cofactor. There is supporting evidence that angiotensin II does not seem to alter the expression of either isom.10 However, angiotensin II may affect the activity of at least one of the renal 11β-HSD isoforms. Animals treated with angiotensin-converting enzyme inhibitors demonstrate an increase in renal dehydrogenase activity.11,12 This effect appears to be due to an angiotensin II-mediated decrease in 11β-HSD-2 enzymatic activity. Any local functional decrease in 11β-HSD-2 would favor MR activation by endogenous glucocorticoids.

The paper by Luther et al. provides further support for therapeutic targeting of activated MR to prevent or delay progression of cardiovascular and renal disease. The net biologic effects of both angiotensin II and aldosterone are probably mediated via activated MR. Although aldosterone has been the most obvious ligand for activating MR, it now is becoming clear that other agents, such as cortisone in humans and corticosterone in rodents, play this role under certain circumstances. Excess release of reactive oxygen species and changes in the redox state within target cells caused by prior injury, high-salt diet, and/or other hormonal agents all may affect the MR-activating process.

DISCLOSURE
The author declared no competing interests.

ACKNOWLEDGMENTS
The author thanks David Morris for his helpful editorial comments.

REFERENCES