Aldosterone and Mineralocorticoid Receptors
Lessons From Gene Deletion Studies
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Currently, aldosterone and mineralocorticoid receptors (MR) are generally thought of as cognate ligand and receptor, except perhaps by the neuroscientists. This fidelity is essentially true for aldosterone, which has high affinity for MR, much lower affinity for glucocorticoid receptors (GR), and negligible affinity for other nuclear transactivating factors. A number of in vitro studies requiring micromolar concentrations of aldosterone, on the principle that if a little is good, a lot must be better, have been interpreted as evidence for physiological mineralocorticoid actions. These are commonly effects mediated via GR; no (patho)physiology in vivo can realistically be ascribed to aldosterone via GR or any other nuclear receptor. Many, but not all, nongenomic effects of aldosterone are mediated via classic MR: in terms of genomic and, very possibly, nongenomic effects, aldosterone, thus, seems to solely address a particular receptor.

The same, however, is not the case for MR, which bind aldosterone, deoxycorticosterone, corticosterone, cortisol, and progesterone with essentially the same high affinity. This versatility, the >1000-fold higher circulating glucocorticoid levels and the finding of high levels of MR in such improbable aldosterone target tissues as the hippocampus, provides grounds for suspicion that MR may entertain more binding partners than aldosterone alone. These clearly include the physiological glucocorticoids, in both nonneoplastic and epithelial tissue, and possibly progesterone in tissues such as the placenta. The roles of such binding, in the brain and elsewhere, are currently part of the ongoing re-evaluation of the nonaldosterone (patho)physiology of MR.

This fundamental difference is highlighted by the non-equivalence of phenotype after gene deletion of MR or aldosterone synthase (AS), and in the present issue of the journal is thrown into stark relief by the studies by Makhnova et al on the effects of low-salt diet on the AS−/− mouse. MR knockout (MRKO) mice die 8 to 13 days postpartum of uncompensated urinary Na+/electrolyte loss, unless given NaCl by injection and, subsequently, to drink: in this dependence they resemble the time-honored adrenalectomized rat. In contrast, although AS−/− mice show some neonatal wastage, this is of the order of ∼30% rather than 100% on an unsupplemented milk intake. Thereafter, the phenotypes diverge widely in terms of salt dependence for survival; in addition, the comparisons on other parameters among −/−, +/+ and wild-type across the 2 strains may provide novel insight into the overlapping but not coterminous physiology of aldosterone and MR.

In a previous study, Makhnova et al10 showed that many of the differences between AS−/− and wild-type mice on a high normal (0.8% NaCl) intake were largely or completely abolished when the animals were given a very high (8% NaCl) diet. On this diet, AS−/− mice show no differences from wild-type mice save for a higher urinary volume and lower urinary osmolality. On this diet, AS−/− mice show exaggerated urinary volume/osmolality effects, plus a markedly (∼20%) lower body weight despite a significantly (∼30%) higher food intake on a body weight basis; in addition, they show elevated corticosterone, K+, Ca2+, and Mg2+ levels and lower plasma Cl− levels. On the higher salt intake, the plasma electrolyte levels in AS−/− mice were normalized, but the low blood pressure was unaffected.

The present study takes the comparison in the opposite direction but from a different baseline. In this study, the normal salt diet is 0.26% NaCl, and the low-salt diet is 0.05% NaCl. On this (low) normal salt diet, AS−/− mice showed a modest increase in urinary volume but not in osmolality; on the low-salt diet, the differences in both volume and osmolality seen on normal salt for AS−/− mice were exaggerated so that, for example, they showed a 2.2-fold increase in urinary volume. AS−/− mice had blood pressures equivalent to wild-type on normal chow, but 5 mm Hg lower on low salt; that of AS−/− mice fell further (from 96±2 to 85±3 mm Hg), compared with wild-type mice (108±2 to 106±2 mm Hg). The abnormalities in electrolyte status in AS−/− mice were aggravated by low salt, and the abnormalities in water handling became more severe, as noted above.

Plasma vasopressin levels did not differ between the 3 strains (wild-type, +/+ and −/−), and in all rose ∼10-fold with low salt. Both wild-type and AS−/− mice responded to desmopressin, with a comparatively blunted response in the latter group. The most striking difference between strains, however, was in water handling. As noted above, on a voluntary fluid intake, AS−/− mice passed more than double the urine volume of wild-type mice. When restricted to the same consumption level as wild-type mice, AS−/− mice showed precipitous falls in body weight (19.0±1.3 to 15.6±1.6 g on day 4), with no change in urinary osmolality, leading to the termination of the experiment. The interpretation of those findings, not unnaturally, is of a hitherto unexpected reliance on aldosterone status for vasopressin to...
be able to exert its physiological effect on urinary osmolality in the context of volume contraction.

Therefore, the differences between MRKO and AS/−/− mice are considerable. MRKO mice die unless supplemented with salt; AS/−/− mice, although they share the failure-to-thrive phenotype and some degree of neonatal mortality, can subsist on quite a low Na+ intake (0.05% NaCl). They have modestly elevated corticosterone levels, and, in the previous study,10 AS/−/− mice had increased levels of 11β hydroxysteroid dehydrogenase mRNA to 1.5-fold those in the wild-type kidney, which might be anticipated to prevent untoward renal effects of glucocorticoids via MR. That said, MR seem much more important in Na+ conservation, from the MRKO data, than does aldosterone itself; absent aldosterone, the very high levels of angiotensin might have both directly natriferic effects and effects via direct activation of MR. In contrast, salt does not seem crucial for survival of AS/−/− mice or for the lower baseline blood pressure on normal salt intakes (although salt restriction does further lower BP in this strain).

The simplest way to state the difference between phenotypes is that MRKO find salt deficiency incompatible with life, and AS/−/− mice are equivalently susceptible to fluid restriction. Classically we have focused on the role of aldosterone in sodium homeostasis, electrolytes secondary, and that of vasopressin in fluid balance. The take-home message from the elegant series of experiments in the present8 and previous articles4,5,8,9 is that these are clearly overlapping domains, and they are interrelated with a previously unforeseen complexity. Studies in comparative endocrinology (eg, the salt water–drinking marsupial quokkas, on Rottnest Island off Perth, or desert mice that can raise their urine osmolality to 5000 milliosmol) may prove illuminating. We need to thank the Smithies’ and Schultz’ laboratories for pointing the way.

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References
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