Mineralocorticoid Receptors and Cardiovascular Damage
It’s Not Just Aldosterone

John W. Funder

A decade before aldosterone was isolated and characterized, Hans Selye showed that administration of deoxycorticosterone acetate to rats sensitized by salt loading produced a vascular inflammatory response (polyarteritis) and tissue fibrosis. Fifty years later, Karl Weber and his colleagues showed that aldosterone and inappropriate salt intake produced cardiac hypertrophy and fibrosis; this response is bilateral, independent of blood pressure, and preceded by progressive perivascular and interstitial inflammation. Clinical, patients with primary aldosteronism are more at risk than essential hypertensive patients with comparable blood pressure elevation, similarly suggesting a pathophysiological role for aldosterone in the cardiovascular system. On the basis of this evidence, experimental and clinical, there is thus no doubt that blocking aldosterone action in such circumstances is beneficial in terms of progression and outcomes.

It is, however, not as simple as that. In the present issue of Hypertension, Nagata et al.4 show that mineralocorticoid receptor blockade attenuates cardiac hypertrophy and failure in low-renin, low-aldosterone hypertensive rats. The model is straightforward: salt sensitive Dahl rats are started at 7 weeks on an uncompromisingly high (8%) salt intake to which they not surprisingly respond by marked cardiac hypertrophy and clear signs of cardiac failure at age 19 weeks. Animals given eplerenone (30 or 100 mg/kg bw in the chow) to block mineralocorticoid receptors are progressively protected in terms of a number of cardiac/pulmonary indices. The authors conclude that in this model, mineralocorticoid receptor activation is not by the low levels of aldosterone, but by corticosterone. Levels half those in controls may be inappropriately high in rats on 8% NaCl solution. The Dahl salt sensitive (SS) rat is also produced by chronic salt loading, and plasma aldosterone levels half those of controls maintained on 0.3% NaCl chow and water: rats on a low salt diet do not show the pathological changes seen in those infused with the same dose of aldosterone but drinking 0.9% NaCl solution. The Dahl salt sensitive rats on 8% NaCl solution show plasma aldosterone levels half those of controls maintained on 0.3% NaCl chow and water: it takes no giant leap of imagination to think that aldosterone levels half those in controls may be inappropriately high in the context of an obligatory 8% salt intake. How mineralocorticoid receptor activation in a low salt context is clearly not absolutely watertight, and the present study is no exception.

Crucial to the development of coronary vascular inflammation and cardiac fibrosis is an inappropriate aldosterone/salt balance: rats on a low salt diet do not show the pathological changes seen in those infused with the same dose of aldosterone but drinking 0.9% NaCl solution. The Dahl salt sensitive rats on 8% NaCl solution show plasma aldosterone levels half those of controls maintained on 0.3% NaCl chow and water: it takes no giant leap of imagination to think that aldosterone levels half those in controls may be inappropriately high in the context of an obligatory 8% salt intake. How mineralocorticoid receptor activation in a low salt context is clearly not cardiovasculotoxic, whereas the same degree of activation with high salt is, remains enigmatic.

That said, the evidence adduced is very persuasive. The authors have made multiple determinations of cardiac structure and function that change in response to the high salt intake, and all of which are progressively improved by eplerenone. Body weight and blood pressure do not vary significantly between groups; the most sensitive markers of mineralocorticoid receptor blockade are mRNA levels for atrial natriuretic peptide, 11β...
hydroxysteroid dehydrogenase Type I, and monocyte chemotactic protein; in no case, however, does eplerenone restore levels absolutely to control.

What is important here is that cardiac myocytes do not express 11β hydroxysteroid dehydrogenase Type II and are thus not candidate physiological aldosterone target tissues. Given the 1:4000 aldosterone to corticosterone ratio of measured plasma levels in the Dahl rats on an 8% sodium intake, it is difficult to envisage how aldosterone can ever occupy cardiomyocyte MR, thus prompting the search for alternate activating ligands. There is increasing evidence that nuclear receptors as a class can be activated by agents other than their cognate ligand, and there are early reports, for instance, of mineralocorticoid receptor activation by angiotensin. This is unlikely in the present context of suppressed renin, although the authors did note increased cardiac expression of angiotensin-converting enzyme and angiotensin type I receptor genes. Occam’s razor, if nothing else, points to the activation of mineralocorticoid receptors in cardiomyocytes by corticosterone, converted from tonic inhibitor to receptor agonist by the changed cellular context.

And the changed cellular context in the cardiomyocyte in heart failure and the vascular wall in hypertension is that of the generation of reactive oxygen species and the consequent change in intracellular redox state. The present article documents the changes in GSH/GSSG ratio with high salt and its progressive normalization by eplerenone. Changes in intracellular reactive oxygen species are widely recognized as a consequence of inappropriate mineralocorticoid receptor activation; the present article, taken with previous indirect evidence, strongly suggests that in addition to being a consequence, the redox changes are also a driver, leading to a vicious cycle of spiraling tissue damage. Interrupting this vicious cycle by mineralocorticoid receptor blockade, by an obligate antagonist such as spironolactone or eplerenone, thus can be anticipated to very effectively normalize the structural and functional sequelae. This is what Nagata et al have done in their article, and in its sweep and completeness lies its strength.

As endocrinologists we almost unconsciously assign primacy to hormones, sometimes to the detriment of a broader consideration of the receptor(s) involved in hormone action. This has been the case par excellence for aldosterone and mineralocorticoid receptors and has led us essentially ignoring potential (patho)physiological roles for mineralocorticoid receptors in nonepithelial tissues unprotected by 11β hydroxysteroid dehydropregenase Type II. Mineralocorticoid receptors are present in fish and evolved well before aldosterone synthase (CYP11B2); the evolutionary driver in their distinction from the other members of the subfamily (androgen/progesterone/glucocorticoid receptors) has been cortisol, not aldosterone. The highest concentration of mineralocorticoid receptors is in the hippocampus, always occupied by glucocorticoids, with presumably a range of functions awaiting exploration. Activation of glucocorticoid-occupied mineralocorticoid receptors in the heart by redox change, as suggested by Nagata et al, may be one of a number of mechanisms whereby a bivalent ligand such as cortisol/corticosterone can switch from tonic inhibitory to agonist mode. The therapeutic implications are clear, but the subcellular mechanisms involved are still as through a glass, darkly. It should be enormous fun to find out.

References
Mineralocorticoid Receptors and Cardiovascular Damage. It’s Not Just Aldosterone
John W. Funder

Hypertension. published online February 27, 2006;
Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2006 American Heart Association, Inc. All rights reserved.
Print ISSN: 0194-911X. Online ISSN: 1524-4563

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/early/2006/02/27/01.HYP.0000203732.03784.3b.citation

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org/subscriptions/