Mineralocorticoid Receptor Activation and Oxidative Stress

John W. Funder

The spontaneously hypertensive rat (SHR) has been extensively used in studies of hypertension for decades. More recently, a leptin receptor–deficient SHR (SHR/NDmer-cp; SHR/cp) has been developed as a model for the human metabolic syndrome, characterized by elevated blood pressure, visceral obesity, glucose intolerance, and dyslipidemia. In this issue of Hypertension Nagase et al have used the SHR/cp to explore the role of oxidative stress and mineralocorticoid receptor (MR) activation on the renal damage that follows a forced high salt intake. The authors have examined an impressive array of markers of renal structural and functional damage, and show that the antioxidant tempol (partially) and the selective MR antagonist eplerenone (completely) block the renal damage caused by 8% NaCl as drinking solution.

In sodium deficiency states aldosterone levels are very high, and MR is very much activated, as evidenced by high levels of sodium retention; in such circumstances, however, no vascular or tubular damage is seen. In contrast, when mineralocorticoid levels are inappropriately high for sodium status—in Conn’s syndrome or experimentally (DOC/salt, aldo/salt rat models)—progressive vascular damage occurs in tissues, some of which are classic aldosterone targets (eg, kidney) and others are not (eg, heart). How MR activation in salt deficiency is homeostatic, whereas in sodium loading it is unambiguously deleterious, is a key question yet to be answered.

The data in the Nagase et al article show first that the deleterious effects of salt loading are absolutely dependent on MR activation. Secondly, they show that such activation reflects reactive oxygen species generation, in that in considerable part it can be blocked by antioxidant administration.

There are two possible mechanisms whereby MR activation may occur under such circumstances—in response to aldosterone, or in response to other ligands. There is no question that the change in plasma aldosterone levels (a fall to half) in response to salt loading in these (and other) studies is modest, in contrast with the ~20-fold higher salt intake (8% normal saline versus ~0.4% NaCl chow). The reduction in plasma renin is an order of magnitude, rather than the modest halving for aldosterone, posing the question of what sustains the aldosterone secretion rate in the face of the hypokalemia that commonly follows salt loading. The first response, then, might be that aldosterone is the culprit, and that MR are inappropriately activated by the only modestly reduced levels. Given that we do not understand how inappropriate sodium status interacts with aldosterone-mediated MR activation, it is not logically possible to exclude even reduced levels of aldosterone as the prime mover in the response seen in these studies.

Occam’s razor, however, would support the second possible mechanism, that of MR activation by normal levels of endogenous glucocorticoids under conditions of tissue damage and reactive oxygen species generation. Most of the evidence for such an interpretation is indirect, but has the advantage of deriving from both clinical and experimental studies. In the landmark RALES trial, and in subsequent studies using eplerenone (eg, EPHESUS, 4E study) starting aldosterone levels were in the low normal range, and sodium status was unremarkable. No salt loading, no administered mineralocorticoid, and yet mineralocorticoid blockade produces remarkable additional benefit to standard of care in heart failure, or very effectively reduces blood pressure in uncomplicated essential hypertension. In animal studies, eplerenone maintained coronary vascular luminal diameter 4 weeks after experimental angioplasty in pigs fed a regular diet, in contrast with the constriction seen in controls; again, no added sodium, no administered aldosterone.

There is clear evidence that glucocorticoids can activate MR, again both from clinical and experimental studies. The syndrome of apparent mineralocorticoid excess reflects deficiency/blockade of the enzyme allowing selective activation of MR in epithelia (and vessel walls) by aldosterone; when the enzyme is blocked glucocorticoids act as MR agonists, causing sodium retention and hypertension despite suppressed levels of renin and (commonly) aldosterone. Experimentally, enzyme blockade with carbenoxolone in uninephrectomised rats produces an identical coronary perivascular inflammatory response as that seen in DOC-salt rats. The effect in carbenoxolone treated rats is completely blocked by coadministered eplerenone, evidence for an effect via MR activation, putatively by normal levels of inadequate glucocorticoids in the context of inappropriate (0.9% NaCl solution to drink) salt status.

More than a decade ago it was shown that at normal plasma levels of adrenal steroids epithelial MR are ~90%, and nonepithelial MR ~99%, constitutively occupied (but not activated) by glucocorticoids. Under normal circumstances such occupancy is presumably in tonic inhibitory mode, but agonist when 11βHSD2 is blocked, in conditions of tissue damage and reactive oxygen species generation, or of inappropriate sodium status. Susie Mihailidou in preliminary studies has produced direct evidence for this bivalent action of glucocorticoids on MR. In patch clamp studies on Na+ flux across the rabbit cardiomyocyte cell membrane, aldosterone...
(10 nmol/L) rapidly (15 minutes) produces a 10-fold increase in pump current, stoichiometrically blocked down to ≈10% by 100 nmol/L cortisol. Cortisol alone has no effect, but when confused with oxidized glutathione to mimic reactive oxygen species generation becomes an MR agonist.8 The common link between 11βHSD2 blockade and ROS generation would appear to be redox change; how elevated levels of NADH, when 11βHSD2 is operating, hold MR-glucocorticoid complexes inactive, and how ROS generation activates otherwise quiescent complexes, remain to be explored.

The Nagase et al report finds no elevation of corticosterone, which is neither surprising nor necessary for inappropriate MR activation by glucocorticoids; given their ≈100-fold higher circulating levels than aldosterone (even without salt loading), and their affinity for MR as high as that of aldosterone, normal circulating levels are all that are needed. The dose of eplerenone used is uncompromising (1.25 g/kg chow) and was sufficient to lower blood pressure significantly; that this effect on blood pressure in turn accounts for the total reversal of renal structural and functional changes is inconceivable. In angiotensin II–infused rats on 0.9% NaCl, eplerenone completely blocked the perivascular inflammatory changes without reduction in blood pressure; similarly, in SHRSP rats on 0.9% NaCl, eplerenone abrogated the renal structural and functional damage with no change in blood pressure.9

In summary, Nagase et al have provided us with an unusually detailed report of the renal responses to forced high salt intake in a rat model of the metabolic syndrome, and the effects of eplerenone and tempol thereupon. The model is pushed to the limits (eg, 8% NaCl, 1.25 g/kg eplerenone) and no weights/indices of hydration status are presented. This may ultimately be important, given the clear differences between MR and aldosterone synthase gene deletion mice, and the obvious involvement of fluid balance in this difference.10 There are unexplained surprises in this model—eg, that 8% NaCl administration produced an elevation (data not shown) of measured plasma [K⁺], from 3.8±0.1 meq/L in control to 4.4±0.2 in salt loaded, and unchanged activity of renal 11βHSD2 inferred from ex vivo tissue analysis. Perhaps the most interesting point made for further reflection and investigation is that of the link between obesity and salt intolerance—in terms of unraveling the mechanisms involved, and in the treatment of the metabolic syndrome.

Disclosures
The author is a consultant to Pfizer, Merck, Daiichi-Sankyo, Schering-Plough, Speedel, and CBio.

References
Mineralocorticoid Receptor Activation and Oxidative Stress
John W. Funder

Hypertension. 2007;50:840-841; originally published online October 8, 2007;
doi: 10.1161/HYPERTENSIONAHA.107.098012

Hypertension is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 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/50/5/840

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/