Salt Sensitivity and 11β-Hydroxysteroid Dehydrogenase Type 2 Activity

To the Editor:
Melander et al.1 examined whether sodium intake affects 11β-hydroxysteroid dehydrogenase (11βHSD) type 2 activity and whether salt sensitivity is related to the activity of 11βHSD type 2 in healthy normotensive subjects. In their study, activity of 11βHSD type 2 was assessed by measurement of the urinary ratio of (THF+allo-THF)/THE. Although a small increase in this ratio was observed after salt loading, there was no correlation between salt sensitivity and the (THF+allo-THF)/THE ratio at baseline and even a negative correlation between this ratio and the change in mean arterial blood pressure (BP) during both the low salt and the high salt diet. On the basis of these observations, they concluded that an impaired activity of 11βHSD type 2 is not a determinant of salt sensitivity in normotensive subjects with a positive family history of primary hypertension.

It should be noted, however, that the urinary ratio of (THF+allo-THF)/THE reflects the global set point of 11βHSD activity, being determined by the combined activities of 11βHSD type 1 (acting as a reductase) and 11βHSD type 2 (acting as a dehydrogenase).2 As correctly pointed out by these investigators, the ratio of urinary free cortisol (UFF) to free cortisone (UFE) may provide a better estimate of the 11βHSD type 2 activity in vivo, but this ratio was not determined in their study.3,4

Therefore, we would like to refer to our own recently published study, in which we measured the ratio of urinary (THF+allo-THF)/THE as well as the UFF/UFE ratio in a group of healthy normotensive subjects on a low salt and high salt diet.5 Compared with the study by Melander et al.,1 the subjects in our study were younger (mean age, 23.9 ± 3.1 years) and followed a slightly different dietary protocol (50 and 200 mmol of sodium per day for 1 week, in random order). We did not observe an effect of salt loading on either the urinary (THF+allo-THF)/THE or the UFF/UFE ratio. In agreement with Melander et al.,1 we concluded that 11βHSD type 2 activity is not a determinant of salt sensitivity. Interestingly, we found that cortisol production, measured as the sum of urinary cortisol metabolites excreted, increased in salt-resistant and decreased in salt-sensitive subjects after salt loading. This is most likely due to changes in cortisol elimination, in view of the inverse relation between the changes in sum of urinary cortisol metabolites and plasma morning cortisol after salt loading (rs = −0.45, P < .05). However, these changes in cortisol metabolism did not contribute to the phenomenon of salt sensitivity, as no correlation could be demonstrated between the BP response after salt loading and changes in plasma cortisol. Notably, we did find a positive correlation (rs = 0.60, P = .001) between changes in plasma cortisol and insulin sensitivity (determined by homeostatic model assessment) after salt loading. Thus, changes in circulating cortisol might contribute to sodium-induced alterations in insulin sensitivity.

Salt sensitivity is an intriguing phenomenon with clinically important consequences, in view of the increased risk for development of hypertension and its associated mortality in salt-sensitive normotensive subjects.6 The exact pathophysiology of salt sensitivity remains to be elucidated. Changes in cortisol metabolism or 11βHSD activity do not seem to contribute to an important extent to the individual BP response to salt loading.

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References
Spironolactone for the Treatment of Isolated Systolic Hypertension

To the Editor:

Isolated systolic hypertension (ISH) is associated with a blunted nocturnal blood pressure dip and left ventricular hypertrophy.1 Treatment of ISH is effective in the prevention of congestive heart failure and cerebrovascular accidents; however, control of ISH usually requires combination therapy that is often difficult, with only 50% of patients controlled.2–5 Prior randomized, controlled ISH studies have used protocols based on diuretics, dihydropyridine calcium channel blockers, and angiotensin-converting enzyme (ACE) inhibitors that have decreased systolic blood pressure (SBP) by 23 to 27 mmHg in the treatment groups.

Spironolactone has been added for the treatment of resistant ISH in our general semi-rural, internal medicine practice for the past several years. Escrire, (Lillecorp, Albany, NY), our electronic record company, provided a list of all patients in the practice that had spironolactone on their medication list. A retrospective chart review of these patients was performed and only data from patients that were receiving spironolactone for hypertension treatment was collected. Office blood pressures (BPs) were averaged from 1 to 3 visits before treatment with spironolactone (pre-spiro) and after the addition of spironolactone (post-spiro). The office BP reflected the usual clinical practice of BP measurement; however, it was not performed in a standard manner.

Forty-eight patients were identified, with an average age of 71.6 ± 10.1 years and a pre-spiro BP of 157.7 ± 16.4/74.5 ± 11.8 mm Hg. Post-spiro BP was 141.7 ± 19.5/70.6 ± 12.6 mm Hg (P < .05 for both SBP and diastolic BP [DBP]). The addition of spironolactone decreased BP by 15.9/3.8 mm Hg (P < .05).

This group was subdivided into spironolactone responders (≥10 mm Hg decrease in SBP) and nonresponders (<10 mm Hg decrease in SBP). There were 33 responders (69%) and 15 nonresponders (31%), with similar average ages in both groups. The addition of spironolactone decreased BP by 25.3/8.1 mm Hg for the responders and by 0.6/–0.1 mm Hg for the nonresponders (P < .05 for both SBP and DBP). There were no significant differences (P > .05) between responders and nonresponders for the number of drugs before or after the addition of spironolactone, number of visits before or after spironolactone, or number of patients receiving ACE inhibitors, angiotensin receptor blockers, calcium channel blockers, β-blockers, or other drug categories.

There are many limitations to this retrospective chart review; however, the significant reduction in SBP was similar to the 13.4 mm Hg decrease with eplerenone—a selective aldosterone blocker—combined with an ACE inhibitor or the 16.0 mm Hg decrease seen with eplerenone combined with an angiotensin receptor blocker in a younger population.6 A randomized, controlled trial with spironolactone or eplerenone should be considered for the efficacy of ISH treatment.

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