Evidence that high dose Cortisol-induced Na+ retention in man is not mediated by the mineralocorticoid receptor

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IN BRIEF

Hypothesis and aims

The aim of this study was to determine the role of mineralocorticoid (type I) receptor activation in F-induced sodium retention by comparing the effects of the type I receptor agonist, 9α-fludrohydrocortisone (9αFF) and cortisol in the presence and absence of type I receptor blockade with spironolactone (Sp).

Experimental design and methods

Healthy male subjects were maintained on an average daily dietary intake of 125 mmol Na and 80 mmol K. After an initial 5 day baseline period to allow stabilisation of urinary electrolytes, subjects were divided into four treatment groups: 9αFF, 1.5 mg oral q12h; 9αFF plus Sp 100mg oral q6h; F 60 mg oral q6h and F plus Sp 10 mg oral q6h. Each treatment was continued for five days. Serum and urinary electrolytes were measured at baseline and during the treatment periods.

Results

9αFF produced significant sodium retention which was maintained over the five day treatment period associated with a mean weight gain of 1.4 ±0.4 kg. There was a kaliuresis on the first day of treatment followed by a return in urinary potassium excretion to baseline values over the next four treatment days. Serum sodium remained unaltered and serum potassium decreased. Systolic BP remained unaltered (111±6 vs 113±3 mmHg baseline vs treatment). Co-administration of Sp resulted in a reduction in cumulative sodium retention (-37±130 vs 494±51 mmol/5days, p <0.01) associated with a mean weight loss of 0.6±0.2 kg. Sp prevented the fall in serum potassium and systolic BP was unaltered (105±2 vs 106±2 mmHg baseline vs treatment).

F caused a significant reduction in urinary sodium excretion (106±10 vs 15±5 mmol/24h, baseline vs day 2, p <0.01) which was maximal on day 2 and gradually returned to baseline values thereafter. There was a transient kaliuresis on day 1 followed by modest potassium retention over the next 4 treatment days. There was a modest fall in serum potassium and no change in serum sodium. Systolic BP increased significantly (107±3 vs 119±3 mmHg, baseline vs treatment, p =0.02). Co-administration of Sp did not inhibit F-induced Na retention or alter the changes in urinary K excretion observed during F treatment. Sp prevented the reduction in serum potassium, but did not prevent the rise in BP (107±3 vs 119±3 mmHg, baseline vs treatment).

Conclusion

Sodium retention and the rise in systolic BP observed during high dose F administration are not dependent on activation of type I receptors. This study raises questions about the significance of the mineralocorticoid effects of F, and about the mechanism of F-induced hypertension.
This study complements previous data from this group demonstrating that sodium retention and increased systolic BP during treatment with F (240 mg/day) was not prevented by the administration of the glucocorticoid (type II receptor) antagonist RU486 (1). In the previous study the adequacy of glucocorticoid blockade was confirmed by amelioration of the rise in plasma glucose concentrations, prevention of hyperinsulinaemia and reduction in urinary anion gap during F treatment. Although the effects of Sp treatment were also reported, the interpretation of the Sp data was made difficult by the fact that subjects became sodium depleted in the Sp pre-treatment period prior to coadministration of F.

In the current study, stable sodium and potassium balance was established prior to drug administration by a 5 day period of fixed sodium and potassium dietary intake. The adequacy of type I receptor blockade was established by the 9αFF arm of the study. At the doses used, the cumulative positive sodium balance during 9αFF treatment was approximately twice as large as during F treatment, and Sp 400 mg daily, achieved inhibition of sodium retention indicating that adequate type I receptor blockade was achieved at this dose. Sp did not prevent F-induced sodium retention or the rise in systolic BP, suggesting that both of these events may occur independently of type I receptor activation.

This study elegantly highlights important differences between the time course of mineralocorticoid and glucocorticoid effects on blood pressure. Short-term mineralocorticoid treatment caused sodium retention via activation of type I receptors but did not elevate BP. Hypertension only develops after sustained mineralocorticoid excess, and, as in Conn’s syndrome, it is responsive to Sp treatment. In contrast short-term glucocorticoid administration caused a relatively rapid rise in BP which was not prevented by type I receptor blockade. These differences suggest a divergence between steroid effects on sodium balance and blood pressure. The implication that glucocorticoid-induced hypertension occurs independently of sodium retention is consistent with data from our own studies. We have demonstrated that the rise in blood pressure which occurs during administration of the synthetic glucocorticoids (prednisolone, methylprednisolone, triamcinolone and dexamethasone) is not accompanied by urinary sodium retention or increased plasma volume (2). In ACTH and cortisol-induced hypertension in humans, increases in extracellular fluid volume and exchangeable sodium are substantial, however, dietary sodium restriction prevents the rise in extracellular fluid volume and blunts but does not prevent the rise in BP (3). These findings suggest that while sodium retention modulates glucocorticoid-induced hypertension, it is not the primary mechanism by which glucocorticoids elevate blood pressure.

The findings of this study are intriguing given the significance attributed to the mineralocorticoid effects of F in the syndrome of apparent mineralocorticoid excess (AME) (4, 5). AME is characterised by hypertension, hypokalaemia and low plasma renin concentrations (4, 5) all of which are documented effects of F and are at least partially responsive to treatment with Sp (4-6). The hypertension and metabolic features can be reproduced rapidly in treated patients by low dose F infusion (7), and in one girl with AME the hypertension could not be reversed by treatment with RU486 (6). In AME a defect in the activity of the 11β-hydroxysteroid dehydrogenase enzyme complex results in defective conversion of F to its inactive metabolite cortisone (E) (4-6). It is hypothesised that this exposes renal type I receptors to a local excessive concentration of F and that the clinical manifestations of this syndrome results from F acting via the type I receptor.

Clearly, the findings that type I receptor blockade had no effect on F-induced sodium retention or increase in blood pressure are discrepant with the current understanding of F-action in AME. However, Montrella-Waybill et al. (8) argue that their data do not exclude a contribution of type I receptors to F-induced sodium retention. They propose that at low concentrations F may have type I effects and that these effects are blunted at high concentrations of F because of down-regulation of type I receptors. They refer to their previous observation that Sp partially reverses sodium retention observed during lower dose F treatment (120mg/day) but has no effect on sodium retention due to high dose F (240mg/day) (1) to support this hypothesis. As the authors themselves point out, the interpretation of the lower dose F study is made difficult by the fact that subjects were losing weight and were in negative sodium balance prior to addition of low dose F to Sp treatment. Thus the lower urinary sodium excretion noted on the first two days of low dose F...