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Effect of Aging on Urinary Excretion of 19-Noraldosterone and 18,19-Dihydroxycorticosterone

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19-Noraldosterone, recently shown to be produced in the human adrenal gland, possesses potent mineralocorticoid and hypertensinogenic activity. A possible precursor, 18,19-dihydroxycorticosterone, has been identified in human urine, with both steroids acutely regulated by the renin–angiotensin system. The secretion of aldosterone declines with advancing age. To elucidate the effect of aging on the urinary excretion of 19-noraldosterone and 18,19-dihydroxycorticosterone, we measured their urinary concentrations in 51 normotensive subjects aged 20–70 years. We observed significant negative correlations between age and the urinary excretion of 19-noraldosterone and 18,19-dihydroxycorticosterone ($r = -0.69$, $r = -0.65$, $P < 0.05$, respectively). Urinary and plasma aldosterone and PRA similarly decreased with aging. These results suggest that 19-noraldosterone may be chronically regulated in part by the renin–angiotensin system.

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INTRODUCTION

19-Noraldosterone, a potent mineralocorticoid, produced in the adrenal gland, has been isolated from human urine [1]. It is hypertensinogenic [2] and has a high affinity for mineralocorticoid receptors [3]. 18,19-Dihydroxycorticosterone [18,19-$(OH)_2$-B], a possible precursor for 19-noraldosterone, has also been identified in human urine [4]. We previously reported that these mineralocorticoid hormones are acutely regulated by the renin–angiotensin system [5]. Aldosterone secretion declines with advancing age [6], and plasma renin activity (PRA) is also decreased in aged subjects [7]. We have thus investigated the effect of aging on the urinary excretion of 19-noraldosterone and 18,19-$(OH)_2$-B in normal subjects.

EXPERIMENTAL

Steroid analysis

The urinary excretion of aldosterone was determined by RIA after hydrolysis at pH 1 for 24 h [8]. Urinary free 18-hydroxycorticosterone (18-OH-B), free 18,19-$(OH)_2$-B, free 19-noraldosterone and free cortisol were measured by RIA after purification of urine extracts by HPLC, as previously described [9, 10]. Briefly 10–50 ml of urine containing [^{3}H]-labelled each steroid (3000 cpm) was extracted with Sep-pak C18 cartridge (Waters, Milford, MA, U.S.A.) and chromatographed in a reversed-phase HPLC system, followed by radioimmunoassay using a specific antibody and individual recovery measurements. The sensitivity of each assay was 30 fmol per tube. The overall recovery was 60–70% for 19-noraldosterone and 50–60% for 18,19-$(OH)_2$-B. The interassay variations were 13.5% for 19-noraldosterone and 14.5% for 18,19-$(OH)_2$-B. The intraassay variations for 19-noraldosterone and 18,19-$(OH)_2$-B were 9.2% and 9.5%, respectively. PRA and plasma aldosterone were measured by RIA, as previously described [11].

Study protocol

Fifty-one urine samples were obtained from healthy members of the laboratory staff and their healthy adult relatives aged 20–70 years. They were allowed to eat an unrestricted diet, but all were advised to limit their daily sodium intake to 180–200 mmol/day. They have no known endocrine disorders, renal disease, hepatic disease, or hypertension for which they were receiving medical attention. Twenty-four-hour urinary samples were collected on several occasions,

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and on each occasion serum and urinary creatinine, β_2-microglobulin, and urinary electrolytes were measured.

Data are expressed as mean ± SEM. The relationships between age and urinary 19-noraldosterone, 18,19-$(OH)_2$-B, aldosterone, 18-OH-B, free cortisol, PRA, or plasma aldosterone were analyzed by linear regression. Statistical significance was accepted for a level of $P < 0.05$.

RESULTS

Urinary excretion of sodium and potassium were 176 ± 63 mmol/day and 74 ± 27 mmol/day, respectively. Mean values for creatinine clearance and urinary β_2-microglobulin slightly but not significantly decreased with aging in our experiments, and urinary excretion of neither sodium (Fig. 1) nor potassium showed a negative correlation with age (data not shown). Urinary levels of aldosterone and plasma aldosterone concentration showed a significant negative correlation with age ($r = -0.62$, $r = -0.67$, $P < 0.05$, respectively) (Fig. 1), as did basal PRA ($r = -0.63$, $P < 0.05$). Figure 2 shows a significant negative correlation between age and the urinary excretion of 19-noraldosterone ($r = -0.69$, $P < 0.05$); urinary excretion of 18,19-$(OH)_2$-B was similarly significantly correlated with age ($r = -0.65$, $P < 0.05$), as was urinary excretion of 18-OH-B ($r = -0.66$, $P < 0.05$) (Fig. 2). Urinary free cortisol was neither correlated with age nor urinary excretion of 19-noraldosterone (Fig. 2).

DISCUSSION

The 19-normineralocorticoids often exhibit marked mineralocorticoid and hypertensinogenic activity [12, 13]. We previously reported that 19-noraldosterone and 18,19-$(OH)_2$-B were produced by both normal adrenal tissue and by aldosterone-producing adenomas [1], and found an elevated urinary excretion of these steroids in patients with primary hyperaldosteronism [8]. Griffing *et al.* demonstrated that patients with primary hyperaldosteronism have an elevated urinary level of free 19-nordeoxycorticosterone (19-nor-DOC) [14]. This hormone was also reported to be produced by aldosterone-producing adenomas [15].

We measured urinary free 19-noraldosterone and 18,19-$(OH)_2$-B, which in fact may account for only a minor proportion of total excretion. However, tetra-

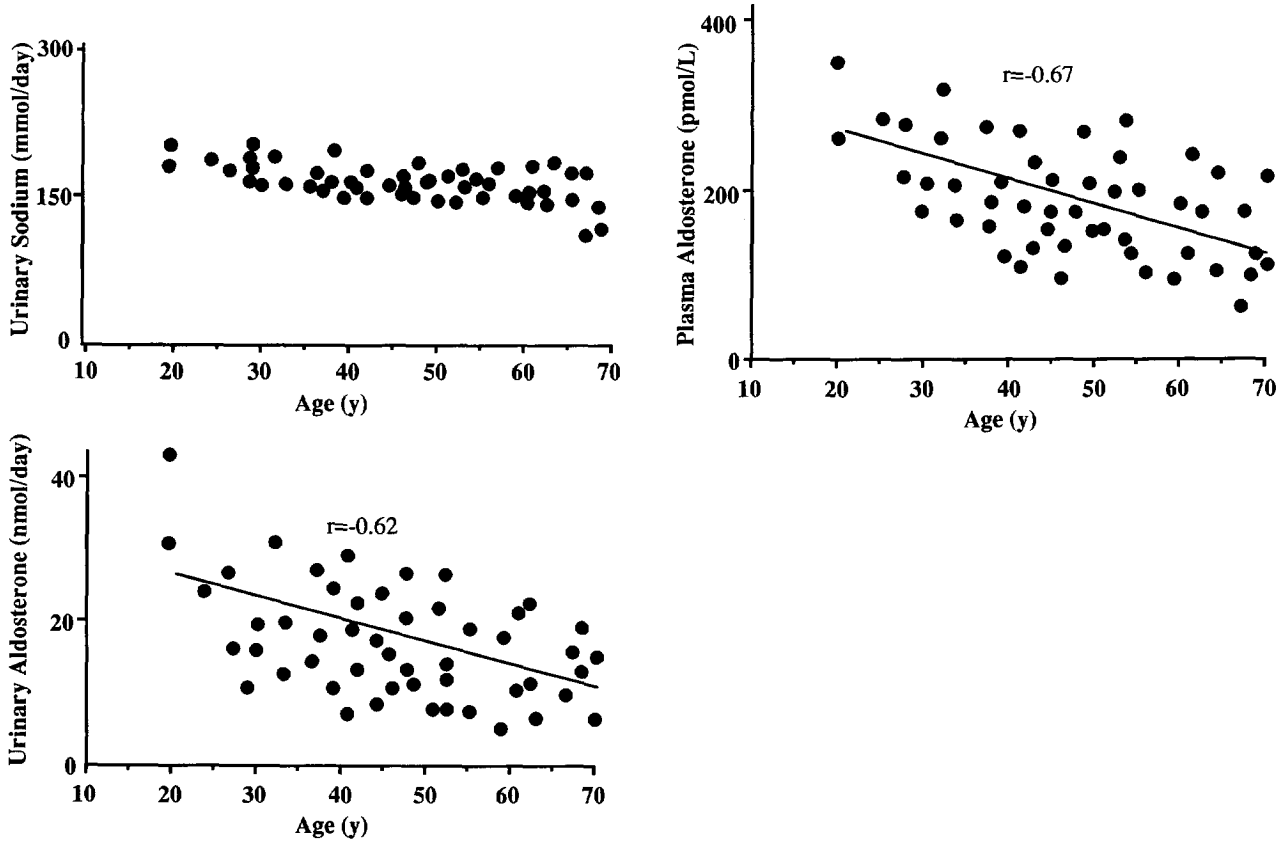

Fig. 1. Correlation between age and urinary excretion of sodium, urinary aldosterone, and plasma concentration of aldosterone, in normal subjects. There was a significant negative correlation between age and urinary or plasma aldosterone ($r = -0.62$, $r = -0.67$, respectively, $P < 0.05$). Urinary excretion of sodium did not correlate with age.

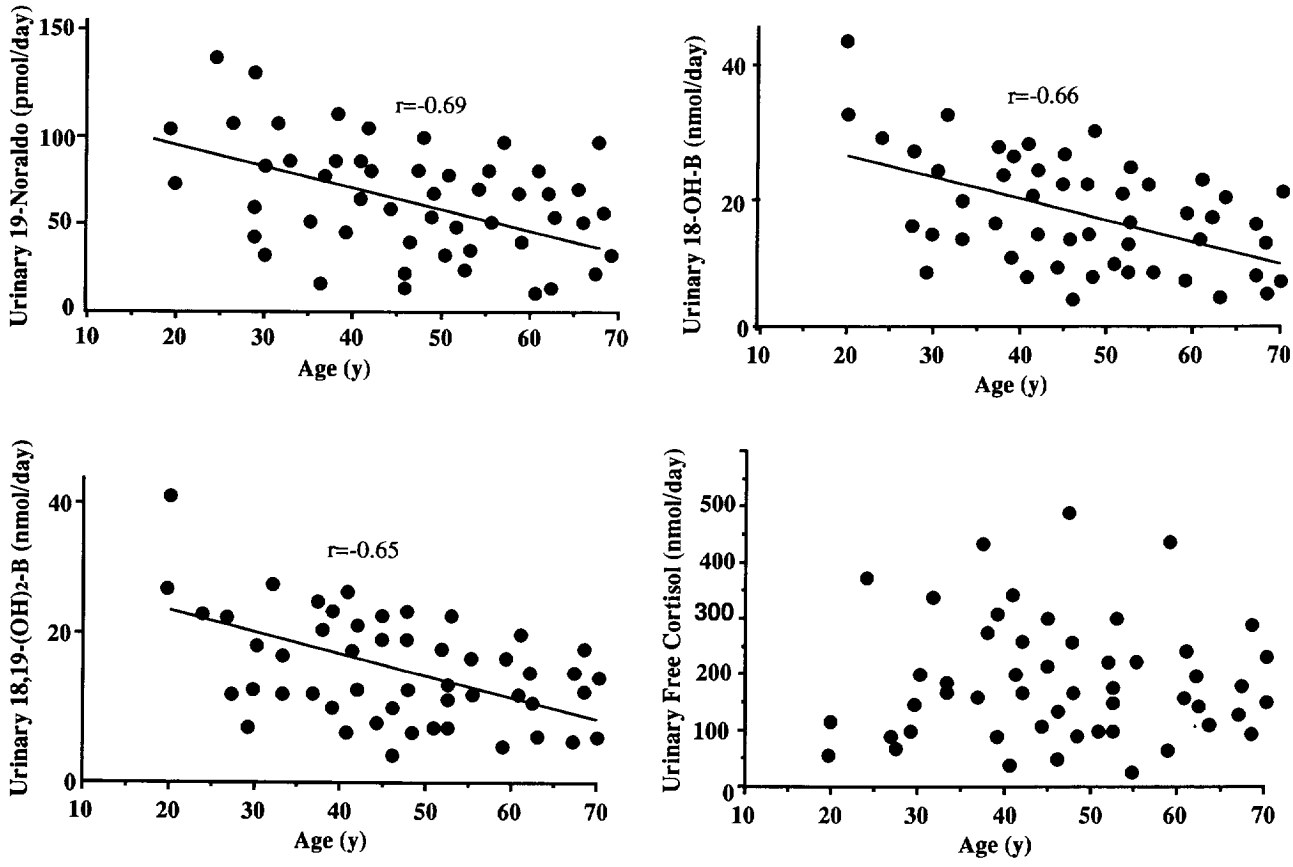

Fig. 2. Correlation between age and urinary excretion of 19-noraldosterone (19-noraldo), 18,19-dihydroxycorticosterone [18,19-$(OH)_2$-B], 18-hydroxycorticosterone (18-OH-B), and free cortisol in normal subjects. There was a significant negative correlation between age and urinary 19-noraldosterone, 18,19-$(OH)_2$-B, or 18-OH-B ($r = -0.69$, $r = -0.65$, $r = -0.66$, respectively, $P < 0.05$). Urinary excretion of free cortisol did not correlate with age.

hydroderivatives of these steroids are not available, and 19-noraldosterone is unstable in strongly acidic conditions [16].

We observed that the urinary excretion of 19-noraldosterone and that of 18,19-$(OH)_2$-B decreased with aging, in parallel with that of aldosterone and PRA. We have previously reported the effect of sodium restriction on the urinary excretion of 19-noraldosterone and 18,19-$(OH)_2$-B in normal subjects [5]. The 24 h urinary excretion of 19-noraldosterone and 18,19-$(OH)_2$-B both rose after sodium restriction, in parallel with the rise in urinary aldosterone. Based on these results, we infer that 19-noraldosterone and 18,19-$(OH)_2$-B are regulated in part by the renin–angiotensin system [5].

PRA declines with advancing age in normal subjects, and may thus be responsible for the decreased urinary level of 19-noraldosterone seen with aging. However, Radke reported that aging directly affects the basal secretion of aldosterone by the rat adrenal capsule, and that there is an age-related impairment of the threshold sensitivity and responsiveness of adrenal capsules to the secretagogues KCl and ACTH [17].

Given that there was no correlation between urinary 19-noraldosterone and free cortisol, the lack of a cortisol 19-noraldosterone relationship suggests that ACTH does not regulate 19-noraldosterone. A caveat to such an interpretation, however, is that although there is no correlation between urinary cortisol and dehydroepiandrosterone (DHEA), ACTH does in fact regulate DHEA secretion. Further study is thus necessary to clarify the effect of ACTH to the secretion of 19-noraldosterone.

In conclusion, our results suggest that 19-noraldosterone may be chronically regulated at least in part by the renin–angiotensin system.

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