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Effect of Aging on Urinary Excretion of 18-Hydroxycortisol

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The secretion of aldosterone declines with age. We reported that sodium depletion increased urinary excretion of 18-hydroxycortisol (18-OH-F). To elucidate the effect of aging on urinary excretion of 18-OH-F, we measured urinary 18-OH-F in 30 normotensive subjects aged 20–70 yr. There were significant negative correlations between age and urinary excretion of 18-OH-F or of aldosterone ($r = -0.49$, $r = -0.58$, $P < 0.05$, respectively) but not of urinary free cortisol. These results suggest that angiotensin may contribute to chronic regulation of 18-OH-F.

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INTRODUCTION

The zona glomerulosa of the adrenal cortex contains a cytochrome $P\text{-}450_{aldo}$ ($P\text{-}450_{c18}$, $P\text{-}450_{cmo}$) that transforms corticosterone to 18-hydroxycorticosterone and aldosterone [1]. This enzyme also transforms 18-hydroxycortisol (18-OH-F) from cortisol [2]. The activity of cytochrome $P\text{-}450_{aldo}$ is regulated by angiotensin II and potassium [3]. Aldosterone secretion declines with advancing age [4]. Plasma renin activity (PRA) is also decreased in elderly subjects [5]. We reported that sodium depletion increased urinary excretion of 18-OH-F [6]. In order to clarify whether angiotensin may contribute to chronic regulation of 18-OH-F, we investigated the effect of aging on the urinary excretion of 18-OH-F in normal subjects.

EXPERIMENTAL

Study protocol

Thirty urine samples from healthy members of the laboratory staff and their adult relatives (age range, 20–70 yr) were collected. These individuals were allowed an unrestricted diet, but all were advised to limit their daily sodium intake to 180 to 200 mmol/day. They have no complications with endocrine disorder, renal disease, hepatic disease or hypertension. They received no medical attention. Twenty-four urinary samples were collected repeatedly. At the same time serum and urinary creatinine were measured.

Urinary excretion of aldosterone was measured by RIA after hydrolysis at pH 1 for 24 h [6]. Urinary 18-OH-F was measured by RIA after purification of the urine extract by high performance liquid chromatography (HPLC) [7]. Urinary free cortisol (F) was measured by RIA after purification of the urine extract by HPLC [8]. PRA and plasma aldosterone were measured by RIA, as previously described [6].

The relationships between age and urinary 18-OH-F, aldosterone or free cortisol were analyzed by linear regression. Statistical significance was accepted at a level of $P < 0.05$.

RESULTS

Figure 1 shows a significant negative correlation between age and urinary excretion of 18-OH-F in normal subjects ($r = -0.49$, $P < 0.05$). No significant correlation was found between age and urinary free cortisol (Fig. 2). Urinary excretion of aldosterone and plasma aldosterone concentration showed a significant negative correlation with age ($r = -0.58$, $r = -0.62$, $P < 0.05$, respectively). Basal PRA was decreased with aging ($r = -0.61$, $P < 0.05$). Urinary sodium excretion was 182 ± 52 mmol/day.

DISCUSSION

18-Hydroxycortisol (18-OH-F) was first isolated as the major free cortisol in the urine of patients with

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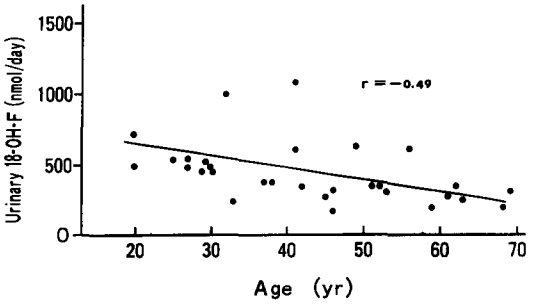

Fig. 1. Correlation between age and urinary excretion of 18-hydroxycortisol (18-OH-F) in the normal subjects. A significant negative correlation ($r = -0.49$, $P < 0.05$) was observed.

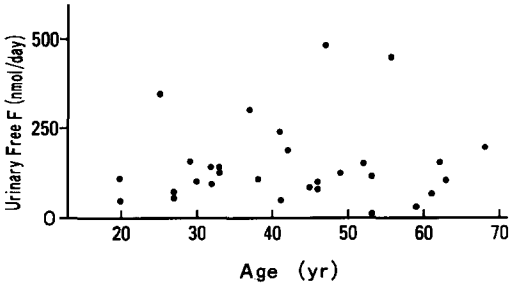

Fig. 2. Correlation between age and urinary excretion of free cortisol (free F) in the normal subjects. No significant correlation was observed.

Conn's syndrome [9] and was reported to be elevated in the urine of patients with either Conn's adenoma [10] or the rare glucocorticoid-remediable hyperaldosteronism [11]. We reported that urinary 18-OH-F is a good marker to distinguish aldosterone-producing adenoma from idiopathic hyperaldosteronism [12]. Hegstad *et al.* [4] suggested that aldosterone secretion declines with advancing age and that the effect of age on aldosterone secretion is an important consideration when one evaluates older hypertensive patients for primary aldosteronism. In this study, urinary excretion of 18-OH-F decreased with aging. The effect of age on 18-OH-F secretion is as important a consideration as the effect on aldosterone secretion. PRA declines with advancing age in normotensive persons [5]. Hegstad *et al.* [4] suggests that this decrease in PRA with increasing age is likely to be the primary cause of the lower plasma aldosterone levels. 18-Hydroxycortisol is transformed from cortisol by cytochrome $P450_{aldo}$, which synthesizes aldosterone from corticosterone and 18-hydroxycorticosterone [2]. Shibata *et al.* reported that cytochrome $P450_{aldo}$ is regulated by angiotensin II and potassium in rats [3]. In humans, urinary excretion of 18-OH-F is increased by sodium restriction [6], which suggests 18-OH-F is partly under the control of the renin–angiotensin system. The decrease in angiotensin levels with aging may contribute to the fall in 18-OH-F levels. Yamakita *et al.* reported that 18-OH-F and 18-oxo-F levels increased by being in an upright position for 2 h and that this increase disappeared with treatment of dexamethasone [13]. They concluded that 18-oxo-F and 18-OH-F were more dependent on ACTH regulation in an acute phase. Our results suggest that angiotensin may contribute to chronic regulation of 18-OH-F.

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