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EFFECTS OF ACTH AND POSTURE ON ALDOSTERONE METABOLISM IN ESSENTIAL HYPERTENSION

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SUMMARY

Timed urinary excretions of aldosterone 18-oxo-conjugate (oxo-c, a renal metabolite) and tetrahydroaldosterone glucuronide (THA-g, a hepatic metabolite) in response to posture and an 8-h infusion of ACTH were measured in control subjects and in patients with stable and labile essential hypertension.

In patients with labile and also those with stable hypertension, the mean 4-h excretion of oxo-c, with subjects in the recumbent posture, was significantly greater and that of THA-g slightly less than in controls, while during upright posture the excretion rate of oxo-c declined much more in patients with both types of hypertension than in controls. ACTH infusion caused a greater increase in oxo-c excretion and a lesser increase in THA-g excretion during the subsequent 24 h in those with stable hypertension than in controls. These findings suggest that hepatic metabolism of aldosterone is relatively lower in both stable and labile essential hypertension, as supported by evidence of increased plasma protein binding and a comparatively lower metabolic clearance rate of aldosterone in some subjects. Furthermore, these altered patterns of aldosterone metabolite excretion in both stable and labile essential hypertension suggest that they may be the forerunner of established hypertension.

INTRODUCTION

The mean plasma aldosterone concentration is determined by a balance between two physiologic variables: the adrenal secretory rate of the hormone and its metabolic clearance rate (MCR). The latter, in turn, has two important components: the hepatic fraction which leads to the urinary excretion of tetrahydroaldosterone glucuronide (THA-g)†: the renal fraction leading to excretion of the 18-oxo-conjugate (oxo-c)† of unreduced aldosterone [1]. We have already reported that essential hypertensive (EH) patients, in contrast to normotensive subjects, excrete proportionately more oxo-c than THA-g in their urine during prolonged collections. We have also suggested that an observed lower MCR of aldosterone in EH [2–4], although in part related to a lower hepatic blood flow [5], is also closely correlated with an increased binding of aldosterone to a heat labile plasma globulin fraction (also called ABG for aldosterone binding globulin) [4, 6–10].

Other studies have shown that EH patients have a plasma aldosterone response to ACTH infusions [6, 11] and postural stimuli [6, 14] different from that of normotensive controls [12, 13]. As a follow-up to these studies, we describe in this paper the measurement of timed urinary excretions of oxo-c and THA-g in control subjects and patients with EH in response to ACTH infusion and upright posture and the finding that these two stimuli induced an altered pattern of metabolite excretion in EH patients.

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† Abbreviations, trivial names used: 18-oxo-conjugate of aldosterone (oxo-c) = 11β, 21-dihydroxy-18-oxo-pregn-4-ene-3,20-dione-18-glucuronide; tetrahydroaldosterone glucuronide (THA-g) = 18-oxo-3α,11β,21-trihydroxy-5β-pregnane-20-one-3-glucuronide.

METHODS

Subjects. Healthy volunteers aged 21–62 years with no symptoms of any metabolic, endocrine or cardiovascular disorder were studied together with EH patients aged 26–38 years. According to previously established criteria [15], five of the hypertensive group had unresponsive plasma renin activity (PRA) and the rest had normal PRA. In addition, patients were classified into two subgroups, labile EH and stable EH, as previously described [8, 15]: those with labile [8] hypertension were distinguished from those with the stable form by a decline in their blood pressure without any medication (anti-hypertensive therapy had been withheld for at least 3 weeks prior to the study) to constant normotensive levels during the first 4 days of hospitalisation. Complete clinical examination (including renal angiography) had excluded all known causes of secondary hypertension [8, 15] and all patients and controls were white.

Protocols. Subjects were studied while on a diet containing 135 mEq of sodium and 90 mEq of potassium. Blood samples for basal aldosterone determinations were drawn between 0800 and 0900 h after overnight recumbency and on the fourth day of hospitalisation. Menstruating female subjects were studied during the early follicular phase of their menstrual

cycles [16]. Immediately after the blood sampling, an 8-h infusion of 25 units of ACTH (Acthar, Armour Pharmaceutical Co.) in 1 l. of 5% dextrose in water was begun and two blood samples were collected 4 and 8 h after the beginning of the infusion. Urinary collection was started at the same time as the infusion and continued over a 24-h period. All subjects were recumbent during the 8 h infusion, upright for the next 6 h and recumbent during the following 10 h.

The 4-h urinary excretions of the oxo-c and THA-g were determined in controls and some EH patients. To avoid the changes in aldosterone levels due to diurnal rhythm or posture, urines were collected between 0800 h and noon with subjects recumbent, since in previous studies with subjects recumbent, plasma aldosterone was found to be highest near 0400 h and again near noon [4, 6, 7].

Additional postural effects on urinary excretion of the oxo-c were studied by collecting urine between 0800 h and noon on two consecutive days with subjects alternately recumbent and upright each day and postural sequence selected at random. Samples for plasma aldosterone were drawn at the end of each four h period.

Techniques. The urinary excretions of the oxo-c and THA-g of aldosterone were determined by a double-isotope dilution procedure with [^{3}H]-labelled oxo-c and [^{3}H]-THA-g as markers [17].

The MCR of aldosterone was determined by continuous infusion of the tritium-labelled hormone [3] in subjects who had been recumbent for at least 10 h before the study. The technique for the constant infusion of tritium labelled aldosterone and ACTH was as previously described [11] except that both aldosterone and ACTH were administered in 5% dextrose. Immediately after the withdrawal of the baseline blood sample, ACTH was infused at the rate of approximately 3 U/h for 8 h and the MCR was determined 6 h after the start of the infusion.

Plasma levels of aldosterone were measured by radioimmunoassay [16] and the heat labile plasma globulin bound fraction of aldosterone was measured as previously described [6, 8].

The PRA was measured by the method of Boucher *et al.* [18] and electrolytes and creatinine by standard techniques. Student's two tailed '*t*' test for unpaired comparisons was used for statistical analysis. A difference was considered statistically significant when $P < 0.05$.

RESULTS

ACTH Infusions

Table 1 and Fig. 1 show the 24-h urinary excretion of the 18-oxo and tetrahydroaldosterone conjugates in controls and patients with stable EH first under baseline conditions and then after the ACTH infusion.

Both control subjects ($n = 15$) and patients with stable EH ($n = 13$) excreted greater amounts of the THA-g than the oxo-c during the control period but the quantity of oxo-c excreted by those with stable EH was greater ($P < 0.05$) and that of THA-g less ($P < 0.01$) than the corresponding amounts excreted by the control group during this same baseline period (Table 1). Twenty-four h urinary excretion of the oxo-c increased to a greater degree ($P < 0.005$) and THA-g increased less ($P < 0.001$) in response to ACTH in the hypertensive patients than in the controls (Fig. 1). Under baseline conditions, the ratio of the oxo-c to THA-g was significantly higher ($P < 0.005$) in EH patients than in control subjects (Table 1), reflecting the greater oxo-c excretion in this group. Following ACTH stimulation, this ratio increased significantly more in patients ($P < 0.005$) than in controls, indicating the relatively greater increase in oxo-c in patients and THA-g in controls in response to this stimulus (Fig. 1).

Mean plasma aldosterone levels after ACTH stimulation were significantly greater in EH patients with

Table 1. Basal 24 h urinary excretion of aldosterone oxo-conjugate (oxo-c) and tetrahydro glucuronide (THA-g)

Control subjects				Stable essential hypertension			
Age and sex	oxo-c	THA-g	oxo-c: THA-g	Age and sex	oxo-c	THA-g	oxo-c: THA-g
42M‡	2.5	67.6	0.037	29M‡	13.8	39.6	0.348
35M‡	4.9	48.8	0.100	41M‡	8.2	37.5	0.219
30M‡	8.1	53.3	0.152	54F†‡	7.5	42.1	0.178
62M‡	3.0	24.0	0.125	48M†‡	7.2	41.0	0.176
23M‡	7.1	58.6	0.121	54F†‡	9.8	25.7	0.381
28M‡	3.0	42.5	0.071	45M‡	16.1	19.0	0.847
30F‡	5.8	61.1	0.095	42F‡	17.1	28.9	0.592
31M	7.1	37.0	0.191	58M†‡	10.2	20.1	0.507
31M	15.1	48.2	0.313	47M†‡	17.5	25.2	0.694
26M	6.1	37.4	0.163	40M‡	14.1	25.9	0.544
23M	8.4	20.1	0.417	26F	9.8	28.0	0.350
22M	11.2	39.3	0.284	52F	3.6	27.5	0.130
24F	7.6	22.6	0.336	40M	5.9	19.0	0.31
22F	10.5	25.6	0.410				
24F	12.4	47.8	0.259				
N	15.0	15.0	15.0	*N*	13.0	13.0	13.0
Mean	7.5	42.3	0.20	Mean	10.8	29.2	0.41
S.E. ±	0.9	3.8	0.03	S.E. ±	1.2	2.3	0.06
					$P < 0.05$*	$P < 0.01$	$P < 0.005$

* *P* vs controls. † Unresponsive PRA. ‡ Subsequently given ACTH.

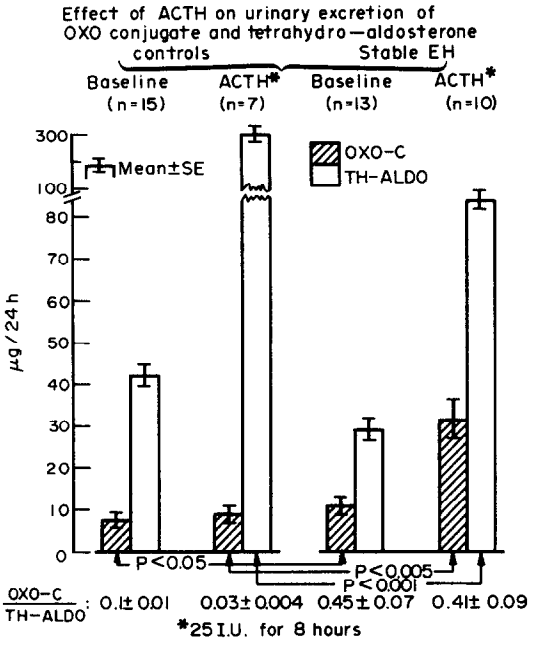

Fig. 1. The mean 24-h urinary excretions of the aldosterone 18-oxo-conjugate (oxo-c, hatched bars) and tetrahydroaldosterone glucuronide (THA-g, open bars) before and after an 8-h intravenous infusion of ACTH in subjects with stable essential hypertension and in controls. The baseline and post-ACTH oxo-c excretion was significantly higher for the hypertensive patients, and the post-ACTH THA-g excretion significantly lower, than for the controls. The higher oxo:THA-g ratios for the hypertensive patients reflect these responses.

normal and low PRA than in controls after 4 ($P < 0.005$) and 8 h ($P < 0.001$) of infusion (Table 2).

A concurrent decrease in the mean percentage of the plasma aldosterone bound to the heat labile plasma protein fraction was more pronounced in the control subjects than in EH patients with both normal and low PRA (Table 2).

The increase in the MCR of aldosterone after 6 h of ACTH infusion was less in six EH patients than in three control subjects.

Concomitantly determined hepatic blood flow as estimated in all subjects once before and once after ACTH by fractional clearance of indocyanine green remained unchanged (K values 0.196 ± 0.09 S.E.M. and 0.209 ± 0.09 at 60 and 320 min after the start of the infusion of labelled aldosterone).

Postural responses

Table 3 shows the 4-h urinary excretions in the recumbent posture of the oxo-c, THA-g and also the oxo-c/THA-g ratios in controls and patients with stable EH and labile EH. The control subjects consistently excreted more THA-g than the oxo-c, whereas the labile EH group excreted significantly higher amounts of the oxo-c than controls ($P < 0.01$), and this exceeded the quantity of THA-g excreted in 6 out of the 10. In the stable EH group, the ratio of oxo-c to THA-g was slightly but not significantly greater than the ratio in the control subjects, whereas this ratio was significantly greater in labile EH subjects compared to controls ($P < 0.005$) (reflecting the greater oxo-c excretion in this group).

Following the assumption of upright posture in different groups of subjects, the 4-h excretion of the oxo-c increased consistently in controls from a mean of 1.5 μg/4 h to 4.5 μg/4 h (Table 4). Patients with labile EH had a higher mean recumbent value of 5.0 μg/4 h and a decrease on assuming upright posture to 3.3 μg/4 h. The group with stable EH, similarly to the control group, had an increase from a mean recumbent value of 3.8 μg/4 h to a mean upright value of 4.5 μg/4 h. The mean ratios of 4-h aldosterone oxo-c urinary excretion in the recumbent and upright postures were significantly greater in both stable ($P < 0.05$) and labile ($P < 0.05$) EH (Table 4, Fig. 2).

When the results were expressed as a percentage increase or decrease of the urinary oxo-c during upright posture relative to supine values, or per gram of creatinine, changes comparable to uncorrected levels were observed indicating that the observed modifications are most probably not due to different renal hemodynamics in EH patients. The postural changes in PRA in the labile and stable hypertensive patients were not significantly different from those of controls (Table 4).

Table 2. Effect of ACTH on plasma aldosterone (total and bound) and aldosterone metabolic clearance rate in control subjects and patients with essential hypertension

	Mean ± S.E. Plasma aldosterone (ng/dl)			Mean ± S.E. % ABG Bound aldosterone			Mean MCR‡ ± S.E. of aldosterone L plasma (24 h/m²)	
	0	4 h*	8 h*	0	4 h	8 h	Baseline	After 6 h of ACTH
Control Subjects	$n = 8$† 6.3 ± 1.3	13.3 ± 2.7	10.9 ± 1.1	$n = 5$ 6.5 ± 1.0	1.0 ± 0.1	0.2 ± 0.01	$n = 3$ 906 ± 80 (58%, range 44–74%)	1445 ± 110
EH Patients with normal PRA	$n = 6$ 10.3 ± 1.8	21.2§ ± 1.0	19.6¶ ± 1.8	$n = 4$ 18.4 ± 1.7	5.2¶ ± 1.1	3.2¶ ± 0.5	$n = 4$ 763 ± 72 (27%, range 17–49%)	963 ± 86
EH Patients with low PRA	$n = 4$ 9.0 ± 2.0	19.4§ ± 2.8	22.2¶ ± 3.0	$n = 5$ 19.1 ± 1.6	5.5¶ ± 1.2	4.8¶ ± 0.6	$n = 2$ 584 ± 38 (41%, range 31–51%)	814 ± 70

* After 4 h and 8 h of ACTH Infusion. † n = Number of experiments. ‡ MCR before and after 6 h of ACTH infusion (% increase and range). § P vs controls <0.05. ¶ P vs controls <0.01.

Table 3. Four h recumbent urinary excretion* of aldosterone oxo-conjugate (oxo-c) and tetrahydro aldosterone glucuronide (THA-g) in essential hypertension

				Stable				Labile			
Age and sex	oxo-c	TH-Aldo	oxo/THA	Age and sex	oxo-c	TH-Aldo	oxo/THA	Age and sex	oxo-c	TH-Aldo	oxo/THA
30M	6.2	8.9	0.7	31M	5.8	7.3	0.80	24M	7.4	3.9	1.89
25M	1.3	7.7	0.17	64F	0.6	3.1	0.19	31F	12.8	5.4	2.37
42M	0.7	4.0	0.18	46F	5.0	10.2	0.49	29F	15.2	12.2	1.25
24F	2.8	18.0	0.16	47M	6.6	11.4	0.58	45F	9.5	4.7	2.02
24F	1.6	5.4	0.30	55M	6.7	14.9	0.45	40F	2.8	3.7	0.76
22F	1.7	6.8	0.25	61M	3.4	11.6	0.29	30M	4.5	5.8	0.77
38M	6.6	15.9	0.42	40M	3.4	10.2	0.33	26F	10.0	11.2	0.89
24F	2.6	10.3	0.25	22F	1.5	3.8	0.39	33M	9.1	4.6	1.98
				33F	2.3	5.1	0.45	22M	15.5	4.4	3.52
				50F	10.2	8.0	1.21	27M	0.8	12.3	0.06
MEAN	2.9	9.6	0.30		4.6	8.6	0.52		8.8	6.8	1.55
S.D. ±	2.2	5.0	0.18		2.9	3.8	0.30		5.0	3.6	1.00
S.E. ±	0.8	1.6	0.06		0.9	1.2	0.09		1.6	1.1	0.32
		$n = 8$				$n = 10$				$n = 10$	
							$P < 0.005$				
						$P < 0.01$					

* Recumbent posture 0800 h–1200 h

DISCUSSION

These results which show a reversal from normal in basal excretion pattern of 18-oxo-conjugate and tetrahydroaldosterone glucuronide in both 4 and 24-h urinary collections (more pronounced in the labile than in the stable hypertensive group) are consistent with the hypothesis that the decreased MCR of aldosterone in hypertension is due to the decreased formation of THA-g in the liver and a concomitant increase in oxo-c production by the kidney. The hepatic metabolism of aldosterone in EH is probably affected by two factors, both of which would be expected to contribute to its significant reduction: (a) increased binding of aldosterone to a plasma binding globulin (ABG) [4, 6–10] and (b) reduced hepatic blood flow, noted to be decreased from normal by 20% by Wollheim [19] and recently by about 10% by Messerli *et al.* [5]. Such a formulation is in agreement with the evidence provided by Tait and Burstein[20] that that fraction of the steroid which is specifically bound to circulating proteins has a negligible hepatic extraction. The significant negative correlation between the aldosterone fraction bound to plasma ABG and the MCR suggests a regulatory role of this binding in the metabolism of aldosterone [8, 11].

Although some of the above values for the 4-h urinary excretion of oxo-c may seem high compared to other reported 24-h excretion rates, the explanation may be that the circadian cycle of aldosterone reaches a peak between 0300 and 0800 h [6, 7] and because our method, unlike others, allows correction for procedural losses, including hydrolysis, by the use of [^{3}H]-labelled conjugates of both urinary metabolites [17]. The increase in the urinary oxo-c may not reflect an enhanced secretion of aldosterone but rather be merely a consequence of the modified hepatic metabolism [4, 6] which would be in agreement with previous studies indicating a moderately increased excretion of the oxo-c [21, 22] and a slightly lower secretion rate of aldosterone [2, 3, 23–25] in EH.

The postural effects on urinary aldosterone metabolites were studied because in control subjects [26, 27] the MCR of aldosterone is affected by

Table 4. Effect of posture on plasma renin activity (PRA) and 4 h aldosterone urinary oxo-conjugate excretion

	Control subjects				Labile essential hypertension					Stable essential hypertension				
Age and sex	PRA (ng/ml/h)		oxo-c (μg)		Age and sex	PRA (ng/ml/h)		oxo-c (μg)		Age and sex	PRA (ng/ml/h)		oxo-c (μg)	
	*(R)	(U)	(R)	(U)		(R)	(U)	(R)	(U)		(R)	(U)	(R)	(U)
21M	0.57	0.32	0.76	2.22	21M	1.33	1.81	1.89	7.38	22F	0.31	0.41	1.49	2.17
22F	0.35	0.62	1.68	7.70	24M	0.42	0.99	7.44	2.41	33F	0.41	0.19	2.31	6.03
22M	0.73	1.31	1.72	5.23	26M	0.42	1.10	5.63	3.68	40M	0.33	0.66	3.38	4.17
22F	0.37	0.84	1.47	6.88	27M	0.41	1.39	4.72	0.42	46F	0	0	5.02	2.18
23M	0.83	1.33	1.44	2.73	28F	0	0	4.48	2.43	48F	0	0	10.22	4.65
23M	0.66	0.99	1.50	2.80	30M	0.65	0.87	3.57	6.08	52F	0.33	0	2.42	5.18
23M	0.33	0.83	0.86	1.55	33M	0.52	1.10	9.10	4.02	54F	0.69	0.83	1.42	7.38
24F	0.49	0.54	0.71	2.19	41M	0.82	0.62	3.75	1.66					
24M	0.66	1.66	2.83	6.62	45F	0.21	0.20	9.52	2.65					
25F	0	0.21	2.64	9.62	45F	0.21	0	0.55	2.07					
31M	0.33	0.33	0.84	1.94										
Mean	0.48	0.81	1.49	4.49		0.50	0.81	5.07	3.28		0.29	0.29	3.75	4.53
S.D.	0.24	0.47	0.72	2.81		0.37	0.60	2.92	2.10		0.24	0.34	3.11	1.91
S.E.	0.07	0.14	0.22	0.85		0.12	0.19	0.92	0.66		0.09	0.13	1.17	0.72
					$P < 0.001$									
					$P < 0.05$									

* (R): Recumbent. (U): Upright

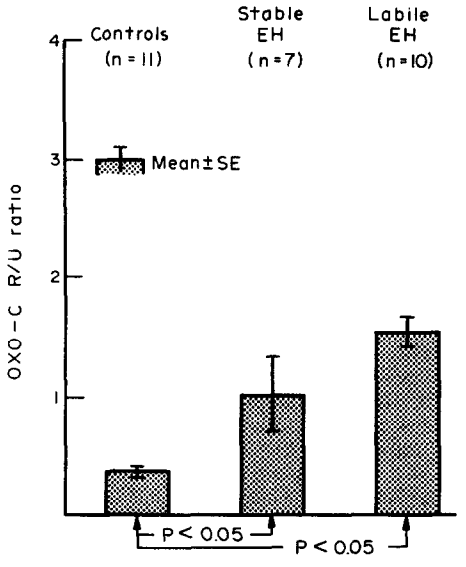

Fig. 2. Mean ratios of 4-h aldosterone 18-oxo-conjugate excretions in the recumbent (R) to upright (U) postures in control subjects and patients with stable and labile essential hypertension. The R/U ratio was significantly higher than normal in both subtypes of hypertension.

posture and is significantly reduced in EH [2–4, 6, 8] although Brown[28] has recently failed to confirm this latter observation, primarily owing to lower basal MCR values in his controls. The majority of his subjects were, however, black and it is known that among blacks there is a higher incidence of hypertension [29] and in particular low renin hypertension [30], apparently because of genetic factors. Our data indicate that patients with labile hypertension have a significantly lower 4-h excretion of the urinary oxo-c than control subjects during upright posture. Conversely, this excretion is higher in supine patients than in supine controls. In patients with stable EH, there is also decreased excretion of the oxo-c during upright posture as compared to the supine position but this is less pronounced. Similar postural changes in PRA exclude the effects of renin as the cause of these differences. Although postural changes in hepatic blood flow in patients with stable essential hypertension are reported to be comparable with those in normal subjects [31], such measurements have not been performed in those with labile hypertension. An abnormal redistribution of the cardiac output from the renal to the splanchnic bed could in part account for the lower urinary oxo-c excretion in the labile hypertensive subgroup.

Thus, the number of h the patient has been recumbent or ambulatory greatly affects the 24-h measurement of the oxo-c excretion. These observations certainly explain some of the conflicting data in the literature on urinary oxo-c excretion since at the time of these latter studies [21], the influence of posture on the metabolism of aldosterone was not fully recognised. Our data probably also explain the greater than expected day-to-day fluctuations recorded in this parameter, especially in patients with early or mild EH [32, 33]. Since these changes in oxo-c excretion do not change substantially when expressed relative to the urinary creatinine excretion, modifications in renal clearance of the metabolite induced by a change in posture are not responsible.

Many EH patients also respond to upright posture with a greater than normal increase in plasma aldosterone concentration [6, 14]. Our group [4, 6] and also Pratt *et al.* [34] recently reported an ACTH-induced increase in the MCR of aldosterone in control subjects [4, 34] and patients with EH [4, 6] on high [34] and normal dietary sodium intake [4, 6] respectively. We also found that ACTH decreased the plasma ABG bound fraction of aldosterone [4, 6], an observation since confirmed by Zager *et al.*[12].

Simultaneously determined 24-h urinary excretions of the oxo-c and THA-g in control subjects indicate that ACTH stimulates the output of the hepatic metabolite more than of the renal metabolite [4, 6, 7]. The evidence from the present study is in agreement with previous preliminary data and also indicates that urinary oxo-c increases more than the THA-g in response to ACTH in EH patients than in controls. The MCR of aldosterone showed a greater increase after 6 h of ACTH infusion in 3 controls than in 6 EH patients. The changes in MCR and the hepatic metabolism caused by ACTH occurred without alteration of the hepatic blood flow as measured by fractional clearance of indocyanine green in both control subjects and EH patients.

In other studies [35], angiotensin II infusions, in contrast to ACTH, induced an increase in aldosterone plasma concentrations in control subjects with a concurrent decrease in hepatic blood flow. This study indicates that ACTH induces an increase in the hepatic metabolism of aldosterone, and that this occurs to a greater extent in control subjects than in EH patients. These findings are in agreement with some degree of impairment of aldosterone metabolism in EH patients and a reduced MCR of aldosterone [6, 8]. A decreased mean basal hepatic blood flow [5] and an increased binding of aldosterone to a heat labile plasma protein fraction, although each alone is probably not sufficient to account for this impairment, together they may contribute to an appreciable reduction in the hepatic extraction of aldosterone in EH. This may also account for the greater ACTH-induced increase in plasma aldosterone concentration after 4 and 8 h of infusion in EH patients than in controls [36] and the significant inverse correlation between the MCR of aldosterone and the ABG bound percentage during ACTH infusion in control subjects [11].

Another possible mechanism involved in the lowered excretions of the hepatic aldosterone metabolite in hypertensive patients is suggested by Kornel *et al.* who observed that they have lower amounts of

plasma [37] and urinary [38] 4-ene reduced cortisol metabolites in the basal state, presumably as a result of decreased activity of hepatic 4-ene reductases. An altered hepatic metabolism of dehydroepiandrosterone and its sulfate has also been recently reported in EH [39].

It has been previously suggested that ACTH induces a greater increase in urinary oxo-c of aldosterone during acute but not chronic ACTH stimulation [40], but recent data indicate that this effect is not necessarily transient [34] and can also be produced by prolonged ACTH stimulation.

CONCLUSIONS

First, a relatively greater 4 and 24-h excretion of oxo-c than THA-g in hypertensive subjects compared to controls supports the concept of a relatively lower rate of hepatic metabolism of aldosterone in both types of EH. Second, lying down increases and standing decreases the excretion of the urinary oxo-c to a greater extent in EH patients than in controls. Third, acute ACTH stimulation induces a greater hepatic metabolism of aldosterone concomitant with the increase in MCR and decreased in ABG binding of aldosterone, with no change in hepatic blood flow. Fourth, the oxo-c excretion rate increased more and THA-g excretion less in response to ACTH in EH patients than in controls. A hyperresponsiveness of plasma aldosterone may result from a small increase in response to ACTH in the aldosterone MCR associated with a relatively limited decrease in ABG binding. Fifth, the results of this study are consistent with an important regulatory role of ABG binding in the metabolism of aldosterone. Furthermore, since similar abnormalities are seen in both stable and labile EH, the alterations in aldosterone metabolism may precede established EH and thus, by implication, be involved in its pathogenesis.

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