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Aldosterone Response to Prolonged ACTH Infusion in Juvenile Hypertension

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Summary

The effects of a continuous 5-day ACTH infusion (40 units/24 hr) on plasma aldosterone (aldo) concentration and urinary excretion of aldosterone pH 1 conjugate, tetrahydroaldosterone and free aldo were investigated in 6 normotensive children, and 7 children with hypertension of unknown origin. In both groups, an initial rise of plasma aldo and all urinary aldo metabolites and a subsequent fall were observed during the ACTH test. The decline in plasma aldo correlated significantly with a decrease in plasma renin activity and serum K^+. There was, however, evidence for another regulatory factor of aldo secretion during ACTH infusion because on a low salt diet, ACTH produced a similar aldo pattern which could not be attributed to the changes in plasma renin activity or serum K^+. Urinary excretion of both free aldo and tetrahydroaldosterone, a metabolite formed in the liver, showed a slower decrease during ACTH infusion than aldosterone pH 1 conjugate, which is of renal origin. The change in pattern of urinary aldo metabolites may be caused by a relative increase of the free, nonprotein bound plasma fraction of aldo and an enhanced metabolism of aldo in the liver during ACTH infusion. Neither in the baseline state nor during the ACTH test was there a difference between the normotensive and the hypertensive group in any of the aldo parameters.

Speculation

ACTH stimulation produces a transient increase in plasma aldosterone secretion and a change in the pattern of urinary aldosterone metabolites. Thus, measurement of a single metabolite during stress or any high ACTH state may be misleading.

The role of ACTH in the regulation of aldosterone has been the subject of many studies. At physiologic concentrations, ACTH appears to influence aldosterone secretion in normal adults, in patients with essential hypertension and in subjects with an aldosterone producing adenoma (5, 7, 10, 11, 25). Prolonged administration of pharmacological doses of ACTH in adults has been found to produce a transient rise in aldosterone and a subsequent fall (3, 14, 19, 27). The aim of the present study was to assess the aldosterone response to prolonged ACTH administration in normotensive children and in patients with juvenile hypertension. The evaluation of the ACTH effect has been facilitated by the development of sensitive and specific radioimmunoassays for plasma aldosterone and various urinary metabolites of aldosterone. The measurements of the different urinary metabolites provided information about alteration in the pattern of aldosterone metabolites during ACTH infusion. Furthermore, the ACTH induced changes in electrolytes and plasma renin activity and their interaction with aldosterone secretion were investigated. This report provides reference standards for aldosterone metabolites in normotensive and hypertensive children. Such data have not been available for children.

MATERIALS AND METHODS

All patients were studied under metabolic balance conditions at the Pediatric Clinical Research Center of The New York Hospital-Cornell Medical Center. The investigations were carried out under protocols approved by the Committee on Human Rights in Research. Informed consent was obtained from all parents and from children who could understand the procedure. Unless otherwise stated, the patients received a diet calculated for sodium (87 mEq/m^2/24 hr) and potassium (40 to 60 mEq/m^2/24 hr). The effect of a 5-day continuous ACTH infusion (Acthar, 40 units in 500 ml 5% glucose per 24 hr) was investigated in the following groups of patients.

NORMOTENSIVE

Six children (age 7½ to 18 years) with normal blood pressure underwent an endocrine evaluation for various disorders (*e.g.*, ambiguous genitalia, micropenis, and short stature). In these patients, no adrenal or renal abnormality was detected.

HYPERTENSIVE

Seven patients (ages 9 to 19 years) had chronically elevated blood pressure [above 90th percentile for age (16)] in whom extensive clinical and laboratory evaluation did not reveal the cause of their hypertension.

Blood was drawn every morning at 8 AM after 2 hr ambulation for determination of serum electrolytes, plasma cortisol, plasma renin activity (PRA), and plasma aldosterone (aldo).

Urine was collected before and after ACTH administration in 24-hr periods. Urinary excretion of sodium, potassium, aldosterone pH 1-metabolite (pH 1 aldo), tetrahydroaldosterone (TH aldo), and free aldosterone (free aldo) were measured daily.

HORMONE DETERMINATIONS

All hormone determinations were performed by specific radioimmunoassays. PRA and plasma cortisol were measured by previously described methods (24, 28). Plasma aldo, urinary pH 1 aldo, and urinary free aldo were determined after Celite column chromatography with ethylene glycol:water (80:20) as a stationary phase (1, 4). Ethyl ether was used for the extraction of plasma aldo. For the measurement of pH 1 aldo, urine was pre-extracted with dichloromethane to remove free steroids. Subsequently, pH 1 hydrolysis (24 hr), dichloromethane extraction, Celite chromatography, and radioimmunologic determination of aldosterone were performed. Urinary free aldo was measured in separate aliquots of urine after dichloromethane extraction and Celite chromatography. Urinary TH aldo was determined using a highly specific antibody against TH aldo (12), which was kindly provided by Dr. Vecsei, University of Heidelberg. TH aldo was generously supplied by Dr. Ulick, Veterans Administration Hospital, Bronx, NY. One ml of urine was incubated with 2000 units of bovine liver β-glucuronidase for 24 hr at pH 5.0 and 37°C. For recovery

estimation, 10,000 dpm of [1,2,-^{3}H]TH aldo (54 Ci/mmole; New England Nuclear) were added. After extraction with 10 ml of dichloromethane and evaporation, the extract was taken up in 1 ml of 20% ethylacetate in isooctane and transferred to a Celite microcolumn. Celite column chromatography was performed using a modification of the method described by Abraham *et al.* (1). Ethylene glycol:water (60:40) was used as the stationary phase. Elution was carried out stepwise using 5 ml each of 30, 40 and 50% ethylacetate in isooctane. The 50% fraction containing TH aldo was collected and dried under filter air.

Following the chromatography, radioimmunological determination of TH aldo was performed using standard techniques (incubation in 0.05 M phosphate buffer containing 0.6% human gamma globulin for 4 to 24 hr at 4°C; separation of free and antibody-bound hormone by dextran-coated charcoal). The use of Celite column chromatography greatly facilitated processing large numbers of samples. Further, Celite column chromatography yielded a higher recovery of [1,2-^{3}H]TH aldo (64 ± 6%; mean ± S.D.) than paper chromatography (12).

The results of the measurements of plasma aldo and all urinary aldosterone metabolites were corrected for the recovery of added tritiated hormone. The specificity of the determinations was assured by chromatographic separation and the use of highly specific antibodies. Sufficient purification by the Celite column chromatography was documented by rechromatography in a second system (paper, system, benzene:methanol:water, 4:2:1) and radioimmunological analysis of the chromatogram which demonstrated the absence of interfering immunoactive substances.

The sensitivity of the determination for urinary pH 1 aldo and free aldo was 2 to 3 ng/100 ml of urine and 5 to 10 ng/100 ml of urine for urinary TH aldo. Thus, even extremely low metabolite levels could be measured accurately.

RESULTS

All values given represent mean ± S.E. The data concerning electrolyte balance and urinary excretion of hormone metabolites were corrected for surface area (m^2). Two-way analysis of variance (31) and Scheffé test were used for statistical analysis.

SERUM Na^+ AND K^+ (TABLE 1)

Serum K^+ decreased significantly ($P < 0.05$) in both groups on the second day of ACTH administration, whereas only minor changes in serum Na^+ were found.

Na^+ AND K^+ BALANCE (TABLE 1)

In normotensive and hypertensive children, a positive Na^+ balance was observed after ACTH administration. The sodium retention was most pronounced in the first 3 days of ACTH administration whereas in some patients a natriuresis occurred on day 4 or 5 of the ACTH test. On the first day of ACTH, K^+ balance was negative in both groups. On the following days, K^+ balance became slightly positive or urinary K^+ output approximately equalled the dietary intake.

PLASMA CORTISOL (TABLE 1)

Plasma cortisol rose progressively throughout the ACTH test. No significant difference was found between the two groups.

PRA (FIG. 1)

Prior to ACTH infusion, PRA was 6.3 ± 1.3 ng AI/ml/hr in the normotensive children, and 5.1 ± 0.8 ng AI/ml/hr in the hypertensive children. During ACTH infusion, PRA decreased significantly ($P < 0.01$) in the normotensive and the hypertensive group. No significant difference between the groups was found.

PLASMA ALDO (FIG. 1)

In the normotensive children, plasma aldo rose from 11.8 ± 2.3 to 17.2 ± 3.4 ng/dl ($P < 0.01$) after one day of ACTH and subsequently decreased to below baseline levels. A similar pattern of plasma aldo response to ACTH was observed in the hypertensive patients.

URINARY PH 1 ALDO (FIG. 1)

Prior to ACTH, urinary pH 1 aldo was 7.2 ± 1.6 $\mu g/m^2/24$ hr in the normotensive group and 7.5 ± 1.6 $\mu g/m^2/24$ hr in the hypertensive group. There was a 4-fold rise on the first day of ACTH in the normotensive and the hypertensive groups ($P < 0.01$). Subsequently, a sharp decline in urinary pH 1 aldo was observed in both groups. On day 5 of ACTH, urinary pH 1 aldo was significantly lower ($P < 0.01$) than under baseline conditions in the normotensive and hypertensive children.

URINARY TH ALDO (FIG. 1)

Under baseline conditions, urinary excretion of TH aldo was 22.2 ± 4.3 $\mu g/m^2/24$ hr in the normotensive group and 24.1 ± 8.9 $\mu g/m^2/24$ hr in the hypertensive group. In the normotensive and hypertensive children, TH aldo increased 4-fold on day 1 of ACTH ($P < 0.01$). On the following days, there was a gradual decline to baseline levels. In both groups, TH aldo on the fifth day of ACTH infusion did not differ significantly from pre-ACTH values.

URINARY FREE ALDO (FIG. 1)

Pre-ACTH urinary free aldo was 0.18 ± 0.05 $\mu g/m^2/24$ hr in the normotensive group and 0.18 ± 0.05 $\mu g/m^2/24$ hr in the hypertensive group. During ACTH infusion, a 4- to 5-fold rise ($P < 0.01$) and a subsequent fall was observed in all patients. On the last day of ACTH administration, free aldo excretion was still above baseline (ns) in both groups.

When the relationship beteen plasma cortisol and the relative magnitude of free aldo excretion during ACTH was examined, a significant correlation between plasma cortisol and the ratio of urinary free aldo:urinary pH 1 plus TH aldo ($r = 0.33$; $P < 0.001$) was found.

CORRELATION BETWEEN SERUM K^+, PRA, AND PLASMA ALDO

From days 1 to 5 of the ACTH infusion, a progressive decrease of serum K^+, PRA, and plasma aldo was observed in the normotensive and the hypertensive patients.

There was a significant correlation between PRA and plasma aldo during ACTH infusion (days 1 to 5) in the normotensive ($r = 0.62$; $P < 0.001$) and the hypertensive group ($r = 0.82$; $P < 0.001$) (Fig. 2). There was also a significant correlation between serum K^+ and plasma aldo during ACTH administration in the normotensive group ($r = 0.65$; $P < 0.001$). In the hypertensive children, a lower correlation coefficient was found ($r = 0.4$; $P < 0.06$).

ACTH ON LOW-SALT DIET (TABLE 2)

In 3 hypertensive children, the ACTH test was carried out on a low salt diet (Na^+, 10 mEq/24 hr) following a 5-day period on a low salt intake. The means of the PRA and aldo response to ACTH are summarized in Table 2. Because of the limited number of patients in this group, no detailed statistical analysis was performed. PRA and aldo were stimulated by the low-salt diet prior to ACTH administration. Mean serum K^+ did not change after ACTH. PRA decreased at the end of the 5-day ACTH test. Plasma aldo showed an increase on the first day of ACTH from elevated levels. Subsequently, a decrease to below pre-ACTH values was found.

The urinary aldo metabolites showed an initial rise and a subsequent fall on a low-salt diet similar to that observed on a normal salt intake.

DISCUSSION

In the present study, the normotensive and the hypertensive children showed a biphasic response of plasma aldo and urinary

Table 1. *Serum Na^+ and K^+, Na^+ and K^+ balance, and plasma cortisol during 5-day ACTH test in 6 normotensive and 7 hypertensive children*

		ACTH (40 units/24 hr)					
		Pre-ACTH	Day 1	Day 2	Day 3	Day 4	Day 5
Serum Na^+ (mEq/liter)	Normotensive	140.5 ± 0.9[1]	140.5 ± 1.5	141.2 ± 0.9	139.0 ± 1.5	138.0 ± 1.6	137.5 ± 0.8
	Hypertensive	140.9 ± 0.8	136.3 ± 1.0	139.7 ± 1.9	138.0 ± 1.1	140.0 ± 1.7	140.8 ± 2.3
Serum K^+ (mEq/liter)	Normotensive	4.1 ± 0.1	3.9 ± 0.1	3.6 ± 0.1[2]	3.4 ± 0.1[2]	3.5 ± 0.2[2]	3.4 ± 0.2[2]
	Hypertensive	4.5 ± 0.2	3.9 ± 0.1	4.0 ± 0.1[2]	3.8 ± 0.1[2]	3.7 ± 0.1[2]	3.6 ± 0.2[2]
Na^+ balance[3] ($mEq/m^2/24$ hr)	Normotensive	15.4 ± 4.2	51.8 ± 8.4[2]	58.0 ± 7.8[2]	52.1 ± 6.3[2]	13.7 ± 10.9	20.3 ± 11.8
	Hypertensive	3.9 ± 3.3	24.4 ± 5.1[2]	46.2 ± 13.5[2]	38.3 ± 10.4[2]	20.9 ± 10.6	30.4 ± 11.3
K^+ balance[3] ($mEq/m^2/24$ hr)	Normotensive	17.0 ± 2.7	−9.4 ± 6.0[2]	10.7 ± 7.3	12.3 ± 4.7	0.9 ± 4.1	7.0 ± 3.2
	Hypertensive	6.5 ± 4.0	−16.2 ± 7.1[2]	6.8 ± 5.2	0.4 ± 4.1	−2.8 ± 3.3	1.8 ± 2.0
Plasma cortisol (μg/dl)	Normotensive	13.9 ± 2.2	42.2 ± 2.3[2]	50.3 ± 1.7[2]	56.6 ± 2.2[2]	62.7 ± 4.7[2]	66.7 ± 1.3[2]
	Hypertensive	11.7 ± 1.4	38.9 ± 5.0[2]	53.1 ± 4.9[2]	74.4 ± 12.1[2]	56.3 ± 6.3[2]	89.5 ± 20.5[2]

[1] Mean ± S.D.
[2] Significantly different from pre-ACTH value ($P < 0.05$). No significant differences between the two groups were found.
[3] Na^+ and K^+ balance represent daily dietary intake minus urinary output corrected for surface area (m^2).

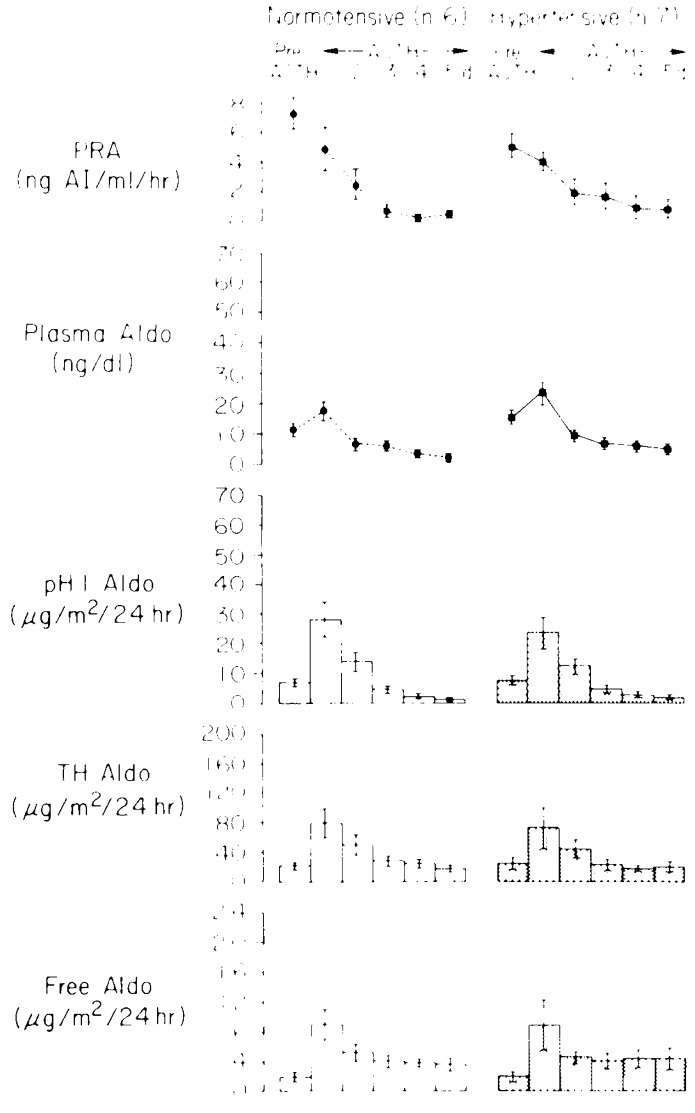

Fig. 1. PRA, plasma aldo, urinary pH 1 aldo, TH aldo, and free aldo in 6 normotensive children and 7 hypertensive patients before and during a 5-day ACTH infusion Mean ± S.E.

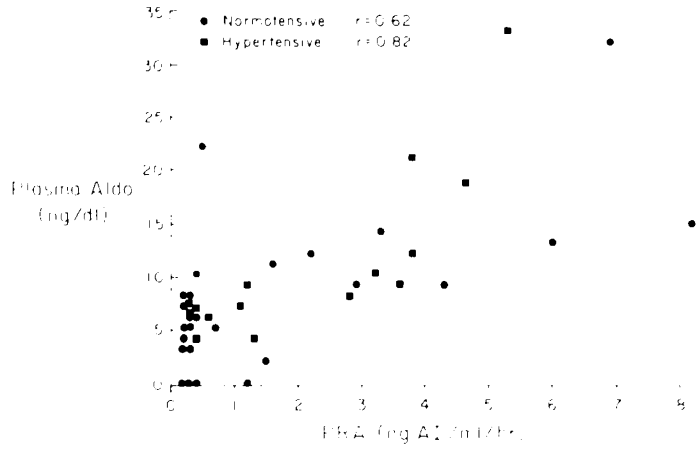

Fig. 2. Relationship between PRA and plasma aldo in 6 normotensive and 7 hypertensive children during a 5-day ACTH infusion.

pH 1 aldo to prolonged ACTH administration. The initial rise and subsequent fall are similar to the findings in normotensive and hypertensive adults (3, 14, 19, 27). The elevation of urinary aldosterone metabolites on the first day of ACTH, which reflects a stimulation of aldosterone over a 24-hr period, was more pronounced than the increase in plasma aldo seen 24 hr after the start of the ACTH infusion (Fig. 1). The cause of the decline of aldosterone after prolonged ACTH has been the subject of much debate. One possibility is that the initial increase of aldosterone and the sustained elevation of other steroids such as cortisol, deoxycorticosterone, and 18-hydroxydeoxycorticosterone lead to sodium retention and to fluid shifts into the vascular space. The consequent blood volume expansion may result in an inhibition of renin and subsequent decrease of aldosterone secretion. Indeed, a marked rise in deoxycorticosterone and 18-hydroxydeoxycorticosterone after ACTH has been documented in adults and in children (3, 23). In this report, a sodium retention was observed during the 5-day ACTH test, which may have resulted from an increased production of salt-retaining hormones. Furthermore, because glucocorticoids may induce fluid shifts into the vascular space (13, 30), the rise in plasma cortisol observed may have contributed to the expansion of plasma volume and the progressive decline of PRA during ACTH infusion. The described fall in PRA is in contrast with the report of Newton and Laragh (19) who found no consistent changes in renin after prolonged ACTH

Table 2. *Serum K⁺, PRA, plasma aldo, urinary pH 1 aldo, TH aldo, and free aldo in 3 hypertensive children on regular salt, low salt, and during ACTH on low salt*

	Regular salt	Low salt	ACTH on low salt[1]				
			Day 1	Day 2	Day 3	Day 4	Day 5
Serum K⁺ (mEq/liter)	4.2	4.4	4.2	4.3	4.3	4.3	4.3
PRA (ng AI/ml/hr)	5.3	8.2	9.9	9.0	11.7	6.0	5.0
Plasma aldo (ng/dl)	16.7	43.5	63.2	31.5	25.4	15.6	11.3
pH 1 aldo ($\mu g/m^2$/24 hr)	4.4	12.1	56.4	34.0	26.1	14.8	12.7
TH aldo ($\mu g/m^2$/24 hr)	18.5	53.1	221.1	131.4	116.3	77.6	72.8
Free aldo ($\mu g/m^2$/24 hr)	0.14	0.22	1.62	0.92	0.75	0.70	0.61

[1] Values, mean.

administration. Our results agree with those of Benraad and Kloppenborg (2) in humans and with those of Ganong (6) in animals. The significant correlation between PRA and plasma aldo during ACTH infusion suggests that the suppression of PRA is at least in part responsible for the decrease in aldosterone.

There is, however, evidence that even though renin may play a role, other regulatory mechanisms are operative in response to ACTH. It has been shown that the pattern of aldosterone response is similar in normal subjects with normal PRA and in patients with an aldosterone-producing adenoma with constantly suppressed renin levels (3, 19). Furthermore, during ACTH on a low-salt diet, a biphasic response of aldo excretion without significant changes in renin has been reported (19). In the present study, a fall in plasma aldo and urinary aldosterone metabolites was observed before the PRA fell in three patients on a low-salt diet with constant ACTH infusion. Thus, our data support those of others suggesting the presence of an aldosterone-regulating factor other than renin during prolonged ACTH administration.

Another factor known to participate in aldosterone regulation is potassium. We observed a continuous decrease in serum K⁺ after prolonged ACTH. The positive correlation for serum K⁺ and plasma aldo during ACTH infusion in the normotensive group suggests that the fall in serum K⁺ contributes to the decrease in aldosterone. In the three patients on a low-salt diet, however, aldosterone also showed a biphasic response to ACTH whereas serum K⁺ remained unchanged.

It has been suggested that the ACTH stimulatory effect on aldosterone secretion is not as transient as generally assumed (21) and that an increased metabolic clearance rate of aldosterone after ACTH (18, 21, 32) may contribute to the fall of plasma aldo. After ACTH, a prolonged increase of urinary TH aldo was reported, but using a more specific method of determination, the same authors found only a transient rise of TH aldo after ACTH (22). Using a radioimmunologic determination with a highly specific antibody against TH aldo after Celite column chromatography, we found a transient increase of TH aldo excretion followed by a gradual decrease to baseline levels during prolonged ACTH. It is of interest that the decrease of TH aldo after ACTH is not as rapid as the fall of pH 1 aldo. TH aldo, the major metabolite of aldo, is formed in the liver, unlike the more commonly measured metabolite of aldosterone, the aldosterone 18-oxoglucuronide (pH 1 aldo), which is primarily of renal origin (15). A possible explanation for the slower fall of TH aldo is a relative increase of reductive metabolism of aldosterone by the liver during ACTH administration.

Urinary free aldo showed an initial 4- to 5-fold rise followed by a gradual decrease during the 5-day ACTH test. The decline of urinary free aldo was slower than the fall of urinary pH 1 aldo and TH aldo. Similar to other steroids, the excretion of free aldo is presumably a function of the amount of the circulating nonprotein bound aldosterone fraction in the plasma (26). Plasma aldo, as measured in this study, reflects the total plasma aldosterone concentration which consists of a free and a protein bound fraction. Administration of ACTH or cortisol has been shown to displace aldosterone from plasma binding sites and to increase the free fraction of plasma aldo (18, 31). Towards the end of the 5-day ACTH test, the relatively increased proportion of urinary free aldo, as compared to pH 1 aldo or TH aldo, may therefore reflect the increase of the free, nonprotein-bound plasma fraction of aldosterone. The relative increase in urinary free aldo may be consequent to the high plasma cortisol observed during the ACTH stimulation. The significant correlation between the increase of plasma cortisol and the ratio of urinary free aldo:urinary pH 1 aldo plus TH aldo during the ACTH test supports this concept. Salivary aldo, a reflection of the unbound plasma aldo fraction, rises with ACTH infusion, corroborating these findings (17).

In summary, in response to prolonged ACTH administration in normotensive and hypertensive children, we found changes in the pattern of urinary aldosterone metabolites with a relative increase of TH aldo and free aldo as compared to pH 1 aldo. Furthermore, our findings of an initial rise and subsequent fall in metabolites corroborate the reported effects on aldosterone secretion in adults (27). Tucci *et al.* (27) described a 5-fold rise of aldo secretion rate on the first day, compared to a 2-fold increase on the second day of a continuous ACTH infusion. Although the decline in PRA and serum K⁺ may participate in the decrease of aldosterone secretion during prolonged ACTH infusion, other factors must play a role. Prolonged ACTH administration on a low-salt diet produced a biphasic response with an initial rise and a subsequent fall of all aldosterone parameters, before any change in PRA or serum K⁺ occurred. *In vitro* studies indicate that ACTH can actually decrease aldosterone production (9, 29), and it has been proposed that the decline in aldosterone secretion during prolonged ACTH administration is the result of an intra-adrenal inhibition of aldosterone production (3).

Previous investigators described differences in aldosterone profiles between normal subjects and patients with essential hypertension. Nowaczynski *et al.* (20) reported a relative decrease in TH aldo excretion in patients with essential hypertension under baseline conditions. Furthermore, a more pronounced rise of plasma aldo was found in patients with essential hypertension in an 8-hr ACTH stimulation test (8). In the present study, however, there was no difference in plasma aldo, urinary pH 1 aldo, TH aldo, and free aldo between normotensive children and children with hypertension of unknown origin either in the baseline state or during prolonged ACTH infusion. Further studies are necessary to determine whether graded doses of ACTH or changes in sodium intake will reveal differences in aldosterone response between normotensive and hypertensive children.

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