STATE OF THE ADRENAL MINERALOCORTICOID FUNCTION IN SODIUM DEFICIENCY ACCOMPANIED BY ADEQUATE OR EXCESSIVE WATER INTAKE

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Sodium deficiency has been shown to stimulate the renin-angiotensin-aldosterone system indirectly through a decrease in the extracellular fluid volume [13]. However, intravenous bulk loading with dextran solution did not inhibit aldosterone production by the adrenals in rats with sodium deficiency [4]. Whether or not drinking a large volume of water in this situation has any modifying effect on the mineralocorticoid function of the adrenals has not yet been studied.

The aim of this investigation was to study aldosterone synthesis in the zona glomerulosa of the adrenal cortex *in vitro* and its level in the peripheral blood plasma in animals on a restricted sodium diet accompanied by an adequate (*ad lib.*) or excessive water intake.

EXPERIMENTAL METHOD

Experiments were carried out on male albino rats weighing 220-260 g. The control group received a normal intake of salt (12 ± 0.6 meq) and water (90 ± 3 ml); the sodium deficiency group has a salt intake of 0.45 ± 0.07 meq and a water intake of 85 ± 5 ml, and the sodium deficiency with excess water intake group received 1050 ± 50 ml water/kg body weight daily for 2 weeks. An excess water intake was achieved by feeding the rats on a liquid diet. The rats were decapitated and the capsular regions of the adrenals, containing cells of the zona glomerulosa [5], from six animals were pooled and incubated for 2 h at 37°C in 5 ml of Krebs—Ringer bicarbonate buffer with 200 mg% glucose, saturated with a mixture of 95% O_2 and 5% CO_2, with the addition of 0.136 μCi [^{3}H]progesterone (53 Ci/mmole, from Amersham, England) to the incubation medium. The [^{3}H]corticosteroids thus formed were identified by thin-layer chromatography and determined quantitatively [2]. Incorporation of the tritium label was estimated on a liquid scintillation spectrograph (Mark II, from Nuclear Chicago, USA). The plasma aldosterone concentration was determined by a radioimmunochemical method, using kits from CEA-Ire-Sorin. The results were subjected to statistical analysis by Student's t test and Wilcoxon's U test.

EXPERIMENTAL RESULTS

As Table 1 shows, under conditions of sodium deficiency with an adequate water intake, aldosterone production by the capsular part of the adrenals was significantly increased, whereas the production of its precursors — deoxycorticosterone (DOC) and corticosterone — was reduced, in agreement with data obtained by other workers [11, 15]. The ratio between production of aldosterone and corticosterone changed sharply, evidence of specific activation for the state of sodium deficiency of the late state of aldosterone biosynthesis [5]. The percentage conversion of [^{3}H]progesterone into [^{3}H]aldosterone increased more then threefold but remained at the control level for ^{3}H-DOC and [^{3}H]corticosterone.

The values of specific activities of the ^{3}H-labeled corticosteroids of animals on a restricted salt diet were significantly increased, evidently due to the lower degree of their dilution with unlabeled endogenous precursors of the pregnenolone pathway of aldosterone biosynthesis [1]. Incidently the increase in specific activity of ^{3}H-DOC could also be due

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TABLE 1. Parameters of Biosynthesis of Aldosterone and Its Precursors in Capsular Part of Adrenal Cortex during Limitation of Sodium Intake under Different Conditions (M ± m)

Experimental conditions	DOC			Corticosterone (B)		
	I	II	III	I	II	III
Control	2,2±0,12	6,4±0,14	8 430±550	3,9±0,32	6,8±0,22	5 034±250
Sodium deficiency	1,54±0,15*	7,1±0,87	13 330±1 170*	1,92±0,17*	6,1±0,52	9 523±1 110*
Sodium deficiency with water loading	1,52±0,02*	6,5±0,5	12 342±828*	2,2±0,17*	4,6±0,32*,†	6 150±386*,†

Experimental conditions	Aldosterone (A)			Production of A/ production of B	SA of B/ SA of DOC×100	SA of A/ SA of B × 100
	I	II	III			
Control	1,65±0,07	1,8±0,08	3165±148	0,42±0,03	60±3,4	64±3,7
Sodium deficiency	2,63±0,12*	7,2±0,8	7860±720*	1,42±0,16*	71±4,3*	85±8,7*
Sodium deficiency with water loading	3,1±0,35*	5,9±0,61*	5532±259*	1,43±0,18*	50±2,5*	91±6,4*

Legend. I) Hormone production in μg/100 mg tissue/h; II) incorporation of tritium level in percent of quantity added to incubation medium/100 mg tissue/h; III) specific activity (SA), cpm/μg hormone. Number of separate incubations in each group five; *) comparison with control, †) comparison with group of animals with "sodium deficiency" — $P < 0.05$ in all cases; ratios of specific activities compared by Wilcoxon's U test, in all other cases Student's t test was used.

to the lower degree of dilution of exogenous [^{3}H]progesterone by endogenous progesterone. Evidence of a decrease in the contribution of precursors on the pregnenolone pathway at the DOC — corticosterone and corticosterone — aldosterone stages of biosynthesis is given by the increase in the ratios of the specific activities: ^{3}H-B/^{3}H-DOC and ^{3}H-A/^{3}H-B (Table 1).

Angiotensin II, whose action is realized through activation of the early stage: cholesterol → pregnenolone [10], is known to be a specific stimulator of aldosterone biosynthesis in the presence of sodium deficiency. However, our knowledge of the fall in the level of endogenous precursors of the pregnenolone pathway suggests that under conditions of prolonged restriction of salt intake stimulation of the early state by angiotensin II is replaced by its trophic action, forming a system of "economic" synthesis of aldosterone: With an overall decrease in corticosteroid production by the capsular part of the adrenal cortex, aldosterone formation is increased. Data in the literature on the short duration of the period of activation of the early stage during chronic administration of angiotensin II to rats [7] and, at the same time, of the profound morphological and physiological changes in the zona glomerulosa [8, 9] are in agreement with this view. Under conditions when restriction of sodium intake was combined with loading with drinking water, the parameters of aldosterone synthesis that were studied on the whole remained the same as during sodium deficiency with an adequate water intake. Only a decrease in the percentage of incorporation of label into [^{3}H]corticosterone and a not so marked increase in its specific activity were observed, indicating a certain shift in the system for biosynthesis in favor of the pregnenolone pathway.

Absence of the expected inhibition of aldosterone production suggests that chronic excessive water intake does not make good the loss of the extracellular volume during sodium deficiency. Another possibility is that stimulation of the renin-angiotensin—aldosterone system also is maintained in this situation by an intrarenal mechanism, with the participation of cells of the macula densa.

The aldosterone concentration in the peripheral blood plasma of rats with restricted sodium intake coupled with an adequate water intake was considerably increased (Fig. 1), as was shown previously [3]. When sodium intake was restricted, and this was combined with drinking water loading, the blood aldosterone concentration in the rats was indistinguishable

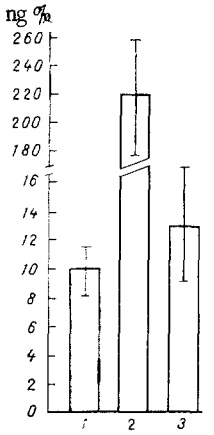

Fig. 1. Aldosterone concentration (M ± m) in peripheral blood plasma of rats with restricted sodium intake under different conditions: 1) control; 2) sodium deficiency; 3) sodium deficiency with excessive water intake. Number of individual determinations in each group was eight; $P_{1-2} < 0.01$; $P_{2-3} < 0.01$; $P_{1-3} > 0.5$.

from the control level and was significantly lower than in sodium deficiency combined with an adequate water intake. Since aldosterone production rose equally in both forms of sodium restriction, its relatively low level in the blood in sodium deficiency with drinking water loading was evidently due to a significant increase in the metabolic clearance of the hormone. Incidentally, an increase in the metabolic clearance of aldosterone was found when the velocity of the hepatic blood flow was increased [14] and when urine formation was increased both in experiments on the isolated kidney [12] and in patients with diabetes insipidus [6], i.e., under the conditions found during water loading.

Chronic drinking water loading combined with restriction of sodium intake thus did not lower the high level of aldosterone production by the adrenals, but led to the establishment of an inappropriately low concentration of the hormone in the peripheral blood, which could be linked with an increase in the rate of its metabolic clearance.

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