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EFFECT OF ANTIDIURETIC HORMONE ON THE PLASMA ALDOSTERONE LEVEL IN RATS WITH CHRONIC HIGH WATER AND RESTRICTED SODIUM INTAKE

V. A. Shul'ga

UDC 612.018+616-008.6

KEY WORDS: antidiuretic hormone, high water intake, aldosterone.

The phenomenon of functional mismatching between components of the renin–angiotensin–aldosterone system under conditions of a high water intake has been described. The peripheral blood aldosterone level is disporportionately low relative to the increased level of activity of the renin–angiotensin component of the system in albino rats drinking excessively [4], in homozygous Brattleboro rats [9], and also in patients with untreated diabetes insipidus [8]. The present writer previously demonstrated marked disparity between high aldosterone production by the adrenals and its relatively low blood level in rats on a sodium-deficient diet combined with chronic high water intake [5]. In all the situations mentioned above, functionally or genetically determined inhibition of antidiuretic hormone secretion evidently takes place.

The aim of this investigation was to verify the hypothesis that antidiuretic hormone (ADH) may have a regulatory influence on the blood aldosterone level.

EXPERIMENTAL METHOD

Male rats weighing 250-300 g were kept for 12 days on a fluid diet with low sodium and high water intake (0.5 meq and 900 ± 50 ml/kg body weight/day respectively). Rats of different groups received a subcutaneous injection 1 h before sacrifice of the following substances (per 100 g body weight): 1) 0.2 ml of distilled water; 2) 0.1 mU pituitrin; 3) 0.5 mU pituitrin; 4) 5 U ACTH; 5) 5 U ACTH + 0.5 mU pituitrin. Groups 4 and 5 were included in the experiment because of previous data showing that ADH may affect the glucocorticoid and mineralocorticoid function of the adrenal cortex indirectly through stimulation of ACTH secretion by the pituitary [11], and the fact that the water loading model used in the present investigation has not previously been studied from this standpoint. The rats were decapitated and blood plasma separated by centrifugation, after which its aldosterone concentration was measured by radioimmunoassay (using the appropriate kit from CEA-IRE-Sorin) and the corticosterone level was measured flurometrically. The adrenals were pooled 5 at a time for each test and incubated *in vitro*. The method of incubation and quantitative assay of the hormones was described previously [5]. The results were subjected to statistical analysis by Student's test.

Laboratory of Physiological Genetics, Institute of Cytology and Genetics, Siberian Branch, Academy of Sciences of the USSR, Novosibirsk. (Presented by Academician of the Academy of Medical Sciences of the USSR V. P. Kaznacheev.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 98, No. 8, pp. 137-139, August, 1984. Original article submitted June 8, 1983.

 0007-4888/84/9808-1010$08.50

TABLE 1. Effect of Pituitrin and ACTH on Plasma Levels of Corticosteroid Hormones and Their Production by the Adrenals in Rats (M ± m)

Group No.	Experimental conditions	Aldosterone		Corticosterone	
		In plasma, ng %	Production, μg/100 mg/h	In plasma, ng %	Production, μg/100 mg/h
1	Control	13,8±1,2	1,35±0,12	13,5±2,3	2,9±0,2
2	Pituitrin	34,3±4,6	1,2±0,1	17,5±2,8	2,37±0,2
	P	<0,001	>0,05		
3	Pituitrin 0,5 ME/100 r	38,8±3,6	1,25±0,1	15,0±1,5	2,8±0,18
	P	<0,001	>0,05		
4	ACTH 5 E/100 r	20±2,2	1,71±0,08	54±2,3	4,4±0,4
	P	<0,05	<0,05	<0,001	<0,05
5	ACTH 5U+ 0,5 ME/100 r	27±3,7	1,76±0,15	52±2,4	4,45±0,37
	P	<0,01	>0,05	<0,001	<0,05
	P_{3-5}	<0,05	<0,05		

Legend. In every case the number of separate determinations of hormone concentrations in the blood plasma was 8; the number of separate incubations of adrenals was 4; P — comparison with control, P_{3-5} — comparison of groups 3 and 5.

EXPERIMENTAL RESULTS

It will be clear from Table 1 that the aldosterone concentration in the peripheral blood plasma of rats 1 h after injection of pituitrin (a preparation of ADH) was significantly higher than in the control. An increase in the dose of pituitrin injected from 0.1 to 0.5 mU made this increase even greater, but even the smaller dose was sufficient to induce virtually maximal development of the effect. No dose of the ADH preparation had any effect on the corticosterone level in the peripheral blood, nor did it change aldostreone and corticosterone production by the adrenals. On the other hand, ACTH stimulated corticosterone secretion by the adrenals and sharply increased its concentration in the blood. Aldosterone secretion by the adrenals also was potentiated by ACTH and the blood aldosterone level rose, but by a lesser degree than in response to pituitrin. Simultaneous injection of ACTH and pituitrin led to the development of a partial total effect of the two hormonal preparations.

Comparison of the effects of exogenous pituitrin and ACTH on the mineralocorticoid function of the adrenals and the blood aldosterone concentration showed that they differed in principle. Elevation of the blood aldostreone level under the influence of ACTH was accompanied by an increase in its secretion by the adrenals, whereas the more marked increase in aldosterone concentration under the influence of pituitrin was unaccompanied by any increase in secretion of the hormone by the adrenals. These results rule out the possibility that the rise in the blood aldosterone level after injection of pituitrin is due to stimulation of endogenous ACTH secretion followed by activation of adrenal mineralocorticoid function. In the doses used, pituitrin thus had no effect whatever on the secretory function of the adrenal cortex of sodium-deficient rats with a chronic high water intake.

Consequently, it can be tentatively suggested that the significant increase in the blood aldosterone concentration of these rats was connected with the inhibitory action of the preparation on the metabolic clearance of the hormone, increased under high water intake conditions ₁5%. The metabolic clearance of aldosterone is known to be highly dependent on the velocity of the blood flow in the liver, a decrease in which leads to an increase in the aldosterone concentration in the peripheral blood [13]. Exogenous vasopressin can reduce the hepatic blood flow, but only if given in much greater doses than those used in the present investigation [3]. However, the possibility cannot be ruled out that the sensitivity of the vessels to vasopressin may be increased by a high water intake combined with sodium deficiency.

Another possible explanation of the effect of vasopressin on metabolic aldosterone clearance is connected with its antidiuretic action. There is evidence in the literature on

excessive urinary excretion of aldosterone [12] and 17-hydroxycorticosteroids [7] in man on a high water intake. In the latter case injection of pituitrin prevented loss of the hormones with the urine. It is suggested that reabsorption of free corticosteroids takes place in the distal part of the nephron [2]. In diabetes insipidus aldosteronuria has been shown to be combined with lowering of the bood aldosterone level and increased plasma renin activity. After administration of arginine-vasopressin the plasma renin activity of these patients fell to normal [8]. The authors cited give no explanation of this effect which, besides the direct inhibitory action of vasopressin on renin secretion [14], may also be the result of increased tubular reabsorption of aldosterone followed by activation of the aldosterone → renin negative feedback. The rise in the blood aldosterone level and the fall in plasma renin activity discovered after injection of pituitrin into homozygous Brattleboro rats [9] are in agreement with this suggestion. The possibility of an increase in reabsorption of aldosterone in the kidney coupled with the antidiuretic action of pituitrin also is confirmed indirectly by the experiment discussed above. For instance, incomplete summation of the effects of the rise of the plasma aldosterone concentration in response to combined injection of ACTH and pituitrin, is evidently connected with the considerable rise in the corticosterone level in the rats' blood. Glucocorticoids, however, have been shown to increase the diuresis both in control rats and in rats on a high water intake, by reducing the tubular reabsorption of water [1]. It must be pointed out that, unlike other investigators, we used low, physiological doses of pituitrin [7], so that the isolated increase in the blood aldosterone concentration, which did not extend to the corticosterone concentration, would appear to be sufficiently specific.

The authors of [10], while emphasizing the role of the kidney in the general aldosterone clearance, consider that the factors determining the renal excretion of this hormone are not yet known. On the basis of data in the literature and our own observations it can be postulated that endogenous antidiuretic hormone is one such factor.

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