EFFECT OF HYPOTHIAZIDE* ON THE HYPOTHALAMIC NEUROSECRETION

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The state of the hypothalamic neurosecretion was studied in rats during oral administration of hypothiazide* in a dose of 2 mg/kg daily for 10 and 30 days. The functional activity of the supraoptic neurons was reduced in the experimental rats as shown by a decrease in the area of cross section of the neurosecretory cells and in the volumes of their nuclei and also by the accumulation of Gomori-positive substance in the bodies of the neurons. At the same time the liberation of antidiuretic hormone into the blood stream was inhibited. The diuretic action of hypothiazide is evidently brought about through the participation of central neuroendocrine mechanisms, i.e., inhibition of the neurosecretory activity of the supraoptic neurons.

The supraoptic nuclei of the hypothalamus have been shown to participate in the regulation of water and salt balance. In dehydration the synthesis and liberation of Gomori-positive material from supraoptic neurons are activated [5, 8, 13, 16, 17]. Hydration leads to the opposite changes – to the deposition of neurosecretion in the bodies of the neurons [5, 6, 12].

Evidence of the participation of the hypothalamic neurosecretion in the regulation of blood pressure has recently been published [1-4, 10]. In clinical practice to restore the normal arterial pressure and water and salt metabolism various diuretics are used, although their effects on the hypothalamic neurosecretion have not yet been adequately investigated [14, 15].

This paper describes an investigation into the state of the supraoptic neurons and the neurohypophysis of rats under the influence of hypothiazide.

*The Soviet equivalent of hydrochlorothiazide – Translator.

TABLE 1. Relative Proportions (in %) of Cells with Different Neurosecretion Content in Supraoptic Nuclei of Rat Hypothalamus

Type of cells	Neurons	Normal	Days after adminstration of hypothiazide	
			10	30
I	With high content of neurosecretion	10,6±1,1	16,5±2,7	31,0±2,9
	P		<0,001	<0,001
II	With average content of neurosecretion	60,9±1,0	64,6±3,3	47,3±3,0
	P		<0,05	<0,001
III	Poor in neurosecretion	21,1±1,4	11,7±1,8	11,8±1,3
	P		<0,001	<0,001
IV	Degenerating	7,4±1,0	5,2±1,0	9,9±1,3
	P		<0,01	>0,1

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TABLE 2. Results of Planimetry and Karyometry of Supraoptic Neurons in Rats

Index	Normal	Days after administration of hypothiazide	
		10	30
Mean area of cross-section of cells (in μ^2)	262,6±9,3	206,0±10,1	195,6±6,2
P		<0,01	<0,001
Volume of cell nuclei (in μ^3)	338,5±12,2	294,7±13,5	279,8±14,0
P		<0,05	<0,01

TABLE 3. Antidiuretic Activity of Plasma in Rats

Permeability of frog urinary bladder (in mg)	Plasma of rats	
	control	hypothiazide for 30 days
In control period	4,41	5,84
30 min after addition of plasma	6,61	7,04
Increase in permeability (in %)	150	120

EXPERIMENTAL METHOD

Experiments were carried out on 70 female albino rats weighing 120-160 g. Hypothiazide was given internally through a tube in a dose of 2 mg/kg daily. On the 10th and 30th days of the experiment animals were decapitated and pieces from the base of the brain with the hypothalamus and pituitary were fixed in Bouin's fluid. Celloidin-paraffin sections through the hypothalamus were stained with chrome alum-hematoxylin by Gomori's method in A. L. Polenov's modification and sections through the pituitary were stained with paraldehyde-fuchsin. The functional state of the neurosecretory cells of the supraoptic nuclei was assessed from their content of Gomori-positive material and also from the results of planimetric measurement of the areas of the neurons and the volume of their nuclei. The antidiuretic activity of the rats' blood plasma also was determined [7].

Diuresis was measured (for 4 h) in the animals of a separate group under the influence of hypothiazide for a period of 30 days. Before measurement of the diuresis the rats were deprived of food for 18 h and given hypothiazide simultaneously with water loading (physiological saline in a dose of 2.5% of the body weight). Control rats received physiological saline only.

The blood pressure was measured by a bloodless method using a piezocrystal detector [9].

EXPERIMENTAL RESULTS

In the dose used, hypothiazide induced a marked diuretic effect: the mean excretion by the control rats during the first day was 42% of the fluid intake compared with 120% for the experimental rats. On the 10th and 30th days of the experiment the diuresis of the experimental animals remained increased by 2-3 times. Meanwhile hypothiazide did not change the arterial pressure of those rats in whom initially it was normal, in agreement with observations by other workers [11].

Most neurons in the supraoptic nuclei of the intact rats contained an average number of granules of Gomori-positive material, distributed in the cytoplasm in the form of dust (Fig. 1a; Table 1). Some neurons contained many neurosecretory granules which filled the whole of their cytoplasm, sometimes masking the nucleus. These cells characteristically were dark in color and smaller in size; normally they accounted for 10.6% of the total. Some neurons contained very little Gomori-positive material and were poor in neurosecretion. Their cytoplasm was pale, and a rim of Nissl's substance could be clearly distinguished. The nuclei were large and pale. At the periphery of the supraoptic nucleus some neurons showed degenerative changes. The cells were shrunken, and their outlines appeared angular; their nuclei were pycnotic or completely invisible.

On the 10th day after the beginning of hypothiazide administration changes were found in the relative proportions of these types of cells. The number of dark cells with abundant neurosecretion was increased, and the number of cells poor in neurosecretion was reduced. On the 30th day these changes were more clearly defined. Stasis and accumulation of neurosecretory material evidently took place in the neurons. The dimensions of the neurons were reduced below normal; the volumes of the cell nuclei also were reduced (Fig. 1c; Table 2), suggesting a decrease in the intensity of functional activity of the supraoptic neurons.

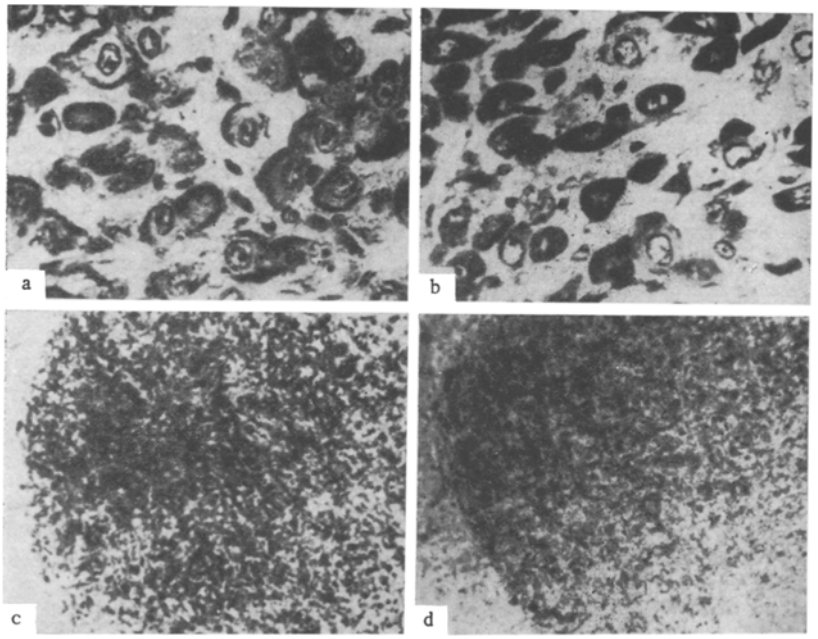

Fig. 1. Neurosecretory cells of supraoptic nucleus (a, c) and posterior lobe of pituitary (b, d) of normal rats (a, b) and after administration of hypothiazide (c, d). Fixation in Bouin's fluid; a, c) stained with chrome alum-hematoxylin, 400×; b, d) stained with paraldehyde-fuchsin, 100×.

This process was also reflected in the state of the posterior lobe of the pituitary of the experimental rats, in which Gomori-positive granules were deposited (Fig. 1d). Since the neurosecretion is the carrier of adiuretin-vasopressin, the liberation of this hormone was evidently reduced.

This conclusion was confirmed by the results of the experiments to determine the antidiuretic activity of the rats' plasma on the basis of the quantity of water passing through the wall of the isolated frog urinary bladder in 30 min (Table 3). Plasma of the experimental animals increased the permeability of the frog urinary bladder by a lesser degree than plasma from the control rats.

If the action of hypothiazide were limited to the kidney, a compensatory increase in activity would be expected in the hypothalamus, with an increase in the secretion of antidiuretic hormone. Since the opposite reaction in fact took place, it can be concluded that the diuretic action of hypothiazide is brought about through the participation of central neuroendocrine mechanisms, i.e., through inhibition of the neurosecretory activity of the supraoptic neurons.

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