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EFFECT OF HYDROCORTISONE ON FORMATION OF THE OSMOTIC CONCENTRATION FUNCTION IN ALBINO RATS

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During ontogeny physiological systems pass through special "critical" periods of development, the most characteristic features of which are nowadays considered to be the accelerated formation of the developing structure or function and increased sensitivity to controlling factors [11, 14]. During these periods realization of the genetic program may be substantially modified by various factors which exert their action through the endocrine system. A transient disturbance of the steroid hormone balance in prenatal or early postnatal ontogeny leads to changes in behavioral responses, functions of the endocrine system, and responses to hormonal and stressor influences in the adult stage [2, 4], which are evidently based on changes in the activity of certain inducible enzymes [3].

In mammals of species born unable to see, morphological and functional maturation of the kidney takes place in the postnatal period. It was accordingly decided that it would be interesting to study the potential ability of certain hormones to influence the course of ontogeny of the concentrating function of the kidney.

In the investigation described below the modifying effect of a single increase in the blood hydrocortisone level in rats was studied during the first few days after birth.

EXPERIMENTAL METHOD

Experiments were carried out on Wistar albino rats of both sexes aged from 5 to 60 days. On the 5th day after birth, during the period when intensive formation of the structures of the concentrating mechanism of the kidney begins [7], physiological saline was injected into control rats in a volume of 100 µl. The experimental rats received an intraperitoneal injection of a suspension of microcrystalline hydrocortisone (from Gedeon Richter, Hungary) in a dose of 1 µg/g body weight. From the 7th day of life until two months, with different age intervals (Table 1), rats of the various subgroups were tested for manifestation of an antidiuretic response. For this purpose, half of the animals of each age subgroup received an

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TABLE 1. Age Changes in Osmotic Concentration Index $(U/P)_{osm}$ and Papilla-Cortex Urea Concentration Gradient in Kidney of Rate Receiving Injection of Physiological Saline (I) or Hydrocortisone (II) at Age of 5 Days

Parameter tested	Group of animals	Test procedure	Age of rats, days					
			7	10–12	14–16	18–20	30	60
$\left(\frac{U}{P}\right)_{osm}$	I	Inj. of phys. saline	1,03 ± 0,23 (3)	1,55 ± 0,27 (6)	2,37 ± 0,39 (8)	3,21 ± 0,17 (13)	2,57 ± 0,18 (18)	2,91 ± 0,26 (16)
		Inj. of pituitrin	0,91 ± 0,08 (4)	1,69 ± 0,25 (4)	3,02 ± 0,25 (18)	3,94 ± 0,27^{c} (16)	3,86 ± 0,28^{d} (12)	4,13 ± 0,20^{r} (21)
		Water deprivation	—	—	3,33 ± 0,25 (8)	5,00 ± 0,14 (16)	5,48 ± 0,26 (13)	7,17 ± 0,36 (20)
	II	Inj. of phys. saline	0,82 ± 0,06 (4)	1,06 ± 0,27 (6)	2,18 ± 0,21 (14)	1,75 ± 0,09^{b} (28)	2,29 ± 0,22 (18)	2,29 ± 0,27 (9)
		Inj. of pituitrin	1,06 ± 0,10 (4)	1,62 ± 0,10 (5)	1,20 ± 0,09 (9)	2,12 ± 0,09^{b} (35)	3,10 ± 0,10^{a} (18)	3,31 ± 0,30^{a} (10)
		Water deprivation	—	—	3,99 ± 0,15 (9)	4,44 ± 0,23^{a} (27)	6,25 ± 0,27^{a} (14)	5,12 ± 0,36^{b} (11)
Urea gradient	I	Inj. of phys. saline	6,0 ± 2,3 (3)	9,8 ± 1,1 (6)	12,7 ± 1,9 (6)	18,8 ± 1,7 (16)	18,1 ± 1,1 (14)	22,5 ± 3,3 (6)
		Inj. of pituitrin	9,8 ± 1,5 (4)	11,6 ± 2,8 (4)	16,7 ± 1,9 (9)	22,6 ± 1,9 (14)	24,9 ± 3,2^{c} (11)	30,0 ± 2,5 (8)
		Water deprivation	—	—	15,4 ± 0,5 (5)	20,6 ± 1,4 (10)	26,1 ± 2,9 (9)	31,5 ± 2,0 (21)
	II	Inj. of phys. saline	6,4 ± 1,0 (3)	8,7 ± 1,8 (7)	7,0 ± 0,5^{b} (16)	14,1 ± 0,9^{a} (22)	17,7 ± 3,1 (4)	15,3 ± 1,4 (4)
		Inj. of pituitrin	11,5 ± 2,6 (3)	5,6 ± 0,8 (5)	10,5 ± 1,0^{c} (11)	14,1 ± 0,6^{b} (24)	23,4 ± 2,3 (7)	17,3 ± 0,9^{b} (4)
		Water deprivation	—	—	14,9 ± 1,0 (9)	18,0 ± 1,2 (10)	24,1 ± 2,3 (8)	29,0 ± 1,4 (17)

Legend. Number of animals in parentheses; a) significance of differences between groups I and II at $P < 0.05$ level, b) the same at $P < 0.01$ level, c) significance of differences in $(U/P)_{osm}$ after test injections of pituitrin and physiological saline at $P < 0.05$ level, d) the same at $P < 0.01$ level, e) significance of differences between urea gradients after injection of pituitrin and physiological saline at $P < 0.05$.

intraperitoneal injection of antidiuretic hormone (ADH, pituitrin P, 500 microunits/100 g body weight) whereas the remaining animals of the corresponding subgroups received an injection of the same volume of physiological saline. The rats were decapitated 40 min after the testing injection. The response of the kidneys to elevation of the endogenous ADH level as a result of deprivation of water for 24 h was investigated in corresponding parallel subgroups of control and experimental rats. The concentrating power of the kidney was estimated as the concentration index $(U/P)_{osm}$, the ratio between osmolarities of the urine and plasma. The urea concentration was determined by the method described previously [8] in slices of kidney tissue, separated into papilla and cortex. The corticomedullary urea gradient was determined as the ratio of the concentration of urea in the papilla to that in the cortex. Student's t test was used for statistical analysis of the data.

EXPERIMENTAL RESULTS

The ability of the albino rat kidney to produce urine hypertonic relative to plasma appears toward the end of the second week of life, and a distinct response to ADH can be recorded after the 23rd day of postnatal development [5]. No significant differences were found between osmotic concentrations, after a test injection of physiological saline and of pituitrin P, were found in rats of the control group before the 20th day of life (Table 1). By the 30th day of life a distinct specific response to exogenous ADH appeared and the osmotic concentration of the urine after injection of pituitrin P was significantly greater than that observed after testing with physiological saline. The antidiuretic response to dehydration appeared after the 20th day, and by the end of the second month of life $(U/P)_{osm}$ under water deprivation conditions reached the level observed in adult intact animals under similar conditions (7.4 ± 0.2, according to [1]). A single injection of physiological saline into rats aged 5 days thus evidently does not lead to any significant change in the rates of formation and effectiveness of the osmotic concentration function, although the injection procedure itself may induce a stress effect [6].

A different time course was recorded in rats receiving injections of hydrocortisone at an early age (Table 1). Before the age of 14-16 days no significant differences compared with the control group were observed. An antidiuretic reaction also was absent until the age of 30 days, but starting from 20 days the concentration index after test injections was significantly lower in the experimental animals than in the controls. The response to water deprivation in animals of the experimental group became distinct after the second week of life. Toward the end of the first month $(U/P)_{osm}$ did not differ from the control value, but by the age of 60 days no further increase in osmotic concentration took place in response to dehydration and the concentration index in rats of the experimental group was considerably lower than in the control animals.

The efficiency of osmotic concentrations is determined by the reaction of the epithelial cells of the collecting tubules to ADH, as a result of which permeability to the flow of water from the lumen into the interstitial tissues increases, and also by the level of the intrarenal osmotic gradient, which largely depends on the urea concentration in the tissue of the renal papilla [9]. In the control group the corticomedullary urea gradient gradually increased until the end of the second week of life, after which the urea concentration in the papilla rose rapidly and by the 20th day the papilla-cortex gradient had reached the level characteristically found in adult rats (Table 1). This time course corresponds to the characteristics of formation of the thin segment of the loops of Henle [7]. The corticomedullary gradient observed after the test injection of physiological saline or pituitrin in the group of rats receiving hydrocortisone at the age of 5 days was significantly lower than in the control animals and reached the characteristic level for adult rats only by the end of the first month.

The results of measurement of the urea gradient could be interpreted as evidence of delayed development of structures of the concentrating mechanism, and primarily of the thin segments of the loops of Henle, on which recirculation of urea depends [10], for hydrocortisone is known to inhibit cell growth and division in tissue cultures [13]. However, during the prolonged action of endogenous ADH under conditions of water deprivation the corticomedullary urea gradient was practically identical in the control and experimental animals. The lower values of this index at the age of 14-16 and 18-20 days in the experimental animals after injection of physiological saline and pituitrin P, just like the differences in $(U/P)_{osm}$, may reflect changes in sensitivity of the epithelium of the collecting tubules to ADH in rats exposed at an early age to the action of hydrocortisone (modification of reception of the hormone or a change in activity of enzymes involved in the reaction to ADH). The probability of the validity of this hypothesis is supported by data showing that hydrocortisone can significantly modify cAMP-dependent protein kinase activity in certain tissues [12].

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