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CHANGES IN BLOOD URIC ACID LEVELS IN PATIENTS WITH RETINITIS PIGMENTOSA AND RATS WITH HEREDITARY DEGENERATION OF THE RETINA

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The writers showed previously that in the early stages of postnatal life of rats with hereditary degeneration of the retina (HDR) (a model of retinitis pigmentosa — RP) in man the 5'-nucleotidase activity of this tissue is modified [4]. The mechanism of development of HDR, according to one hypothesis, is linked with a disturbance of nucleotide metabolism [1], and 5'-nucleotidase is known to be one of the enzymes of purine nucleotide metabolism. The results of biochemical investigation of patients with RP [6] suggest that this disease is accompanied by a raised blood level of uric acid, the end product of purine metabolism in man.

In the view of these data [1, 4, 6], it was decided to attempt to determine whether the blood uric acid level is raised in human subjects with HDR and also to undertake a corresponding investigation on affected rats in order to compare possible changes in metabolism in animal models and in man.

EXPERIMENTAL METHOD

Campbell rats with HDR were used as experimental rats and healthy Wistar rats served as the control group. Animals at different stages of postnatal development were used. The blood uric acid concentration was determined in the patients (27 persons) at the Clinic of the Helmholtz Moscow Research Institute of Eye Diseases. The diagnosis and stage of the disease were determined by the usual clinical tests [2]. Corresponding determinations on healthy subjects (37 persons) served as the control.

TABLE 1. Uric Acid Concentration in Human Serum

Group of subjects	Uric acid concentration, mg%	
	men	women
Healthy	5,8±0,2 (8)	4,6±0,1 (29)
Patients:		
with HDR	8,3±0,6 (14)	7,0±0,7 (13)
with stage II and III of the disease	7,6±0,6 (11)	5,9±0,3 (8)
with stage IV of the disease	9,6±0,5 (3)	8,6±0,4 (5)

Legend. Figures in parenthesis in Table 1 show number of persons, in Tables 2 and 3 number of experiments.

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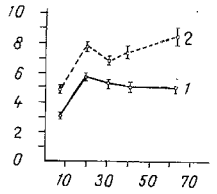

Fig. 1. Serum uric acid levels in Wistar (1) and Campbell (2) rats during postnatal development. Abscissa, animals' age (in days); ordinate, uric acid concentration (in mg%).

TABLE 2. Uric Acid Concentration in 24-Hourly Urine of Healthy and Affected Rats during Postnatal Development

Age of animal, days	Uric acid concentration, mg%	
	healthy rats	affected rats
24 (6)	31±8	44±8
31 (7)	29±6	39±7
44 (13)	36±5	60±10
65 (11)	35±6	57±5

TABLE 3. Uric Acid Concentration in Retina, Brain, and Liver of Healthy and Affected Rats during Postnatal Development

Tissue	Animal's age, days	Uric acid concentration			
		μg/g wet weight of tissue		μg per retina	
		healthy	affected	healthy	affected
Retina	8 (23)	600±35	628±25	6,1±0,4	6,3±0,2
	20 (13)	386±38	329±27	5,7±0,6	5,0±0,5
	31 (8)	144±13	173±15	2,9±0,2	2,9±0,2
	43 (17)	160±15	235±28	3,0±0,2	3,0±0,3
	63 (8)	140±13	224±22	3,5±0,3	2,9±0,4
Brain	10 (8)	811±26	736±28		
	22 (7)	757±27	680±31		
	41 (22)	570±33	545±35		
Liver	10 (8)	415±29	365±28		
	22 (7)	546±50	550±17		
	41 (25)	441±25	426±32		

In the experimental series the animals received no food for 20 h before blood was taken. The rats were than decapitated under ether anesthesia and the blood obtained from them was kept for 24 h in a refrigerator. Before the lactic acid concentration was determined the blood serum was centrifuged for 10 min at 3000-5000g. To investigate the uric acid concentration in the tissues, one retina, 20 mg of brain tissue (cerebral cortex), and 20 mg of liver tissue were homogenized in 1.0 ml distilled water, after which the homogenate was centrifuged for 20 min at 12,000g and the uric acid concentration in the supernatant was determined. When uric acid was determined in the urine, the latter was diluted with water tenfold. In all cases the uric acid concentration was determined by the method in [3].

EXPERIMENTAL RESULTS

It will be clear from Table 1 that the uric acid concentration in blood serum from patients with RP was higher (on average by 50%) than in healthy subjects. The uric acid concentration did not change significantly in the course of development of the disease, but the number of patients studied at each stage of the disease was small, so that this conclusion requires further confirmation.

A raised serum uric acid level also was found in the affected rats (Fig. 1). These changes, incidentally, were definitely detectable as early as on the 8th day after birth, i.e., they developed before the animals could see (no tests were carried out earlier in life), and they were manifested independently of the character of the diet (milk in the case of 8-day-old rats, later during determination of uric acid levels the animals received exogenous purines with their diet). The rise in the blood uric acid concentration in rats at different stages of the disease also was approximately the same, namely 150% compared with the normal level.

Changes in the uric acid level also were found in the urine of affected animals (Table 2); in rats aged 1 month they were on the borderline of statistical significance and they were clearly manifested in animals aged 1.5-2 months. This phenomenon may reflect the increased uric acid concentration in the blood or it may be the result of changes in renal function.

The uric acid concentration in different tissues of healthy animals changed in different ways during the first 2 months after birth: in the liver it was unchanged from the 19th through the 40th day of life, whereas in tissues of the brain and retina the uric acid concentration was initially higher than in the liver, but later it decreased during development (Table 3). It can be postulated that these differences are connected with differences in the degree of differentiation of the liver tissue, on the one hand, and of the brain and retina on the other hand, until birth of the animals. So far as the retina is concerned, formation of the layer of outer segments of the photoreceptors, taking place during the first month of life [5], was not accompanied by any increase in the uric acid concentration in the tissue as a whole, evidence that the content of this purine in the photoreceptor layer is very small compared with its total content in the retina.

In rats with HDR the uric acid concentration in the liver and brain tissues at all periods of life studied was about the same as in healthy animals (Table 3).

When calculated per gram wet weight of retina the uric acid concentration in the affected animals after the 40th day of life was higher than in healthy rats at the same time. During this period destruction of the retina begins in affected rats, the outer segments degenerate, and RNA is broken down [7]. It is difficult to explain the increase in the uric acid concentration per gram wet weight of retina by RNA breakdown, for no increase was found in the total content of this purine in the tissue as a whole (its content in the retina when the results were expressed per retina was the same in affected and healthy animals, see Table 3). It can accordingly be postulated that the increase in the uric acid content per gram wet weight of retina was due to a decrease in its mass on account of disappearance of the photoreceptor layer.

No significant changes in the formation and breakdown of uric acid thus took place in the tissues studied.

The fact that changes in the blood uric acid concentration were in the same direction in affected humans and rats indicates that the experimental disease of the animals is similar to the disease found in man. The increase in the blood uric acid concentration in affected Campbell rats in the early stages of postnatal development, when no abnormality can be found either electrophysiologically or morphologically, makes this a test which can be recommended for the detection of potential patients with RP in familes afflicted with this disease.

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