SOME ASPECTS OF COPPER METABOLISM IN HYPOPHYSECTOMIZED ALBINO RATS

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The copper concentration in the organs and tissues and the ceruloplasmin activity in the blood of albino rats were studied 3, 10, 20, 30 and 60 days after hypophysectomy. The copper concentration in the blood, liver, kidneys, and testes was increased, while in the muscles it was reduced, and in the heart and brain it was unchanged. The blood ceruloplasmin activity was more than twice as high a normal in the experimental animals.

Copper plays an important role in biochemical processes [2, 3, 6, 7, 9, 12]. Its metabolism in the body is closely connected with the endocrine organs and it is to some extent controlled by them. On the other hand, a disturbance of the optimal proportions of copper in the tissues of the body plays an important role in the pathogenesis of diseases connected with disturbances of endocrine function. However, the relationship between copper metabolism and pituitary hormones has not been studied, despite reports [16, 17] indicating the important role of the pituitary in the metabolism of copper and other trace elements.

In the investigation described below the dynamics of the copper concentration in the organs and tissue and the level of ceruloplasmin (1.10.3.2) in the blood were studied in hypophysectomized rats.

EXPERIMENTAL METHOD

Experiments were carried out on 150 hypophysectomized, 115 control, and 27 intact male albino rats weighing 150-230 g. The pituitary was removed by Smith's method in the modification of Bagramyan and Sakhatskaya [4]. Complete removal of pituitary was verified initially by the decrease in weight of the animal and later by examination of the sella turcica and by the decrease in weight of the thyroid and adrenal glands and the testes of the sacrificed animals. An operation similar to hypophysectomy, but without actual removal of the gland, was performed on the control animals. The control and experimental animals were sacrificed on the 3rd, 10th, 20th, 30th, and 60th days after the operation. Samples of tissues and organs were taken, dried, and incinerated in a muffle furnace at 450-500°C. The copper concentration in the tissues and ceruloplasmin activity in the blood were determined by Babenko's method [1]. Numerical results were subjected to statistical analysis [12].

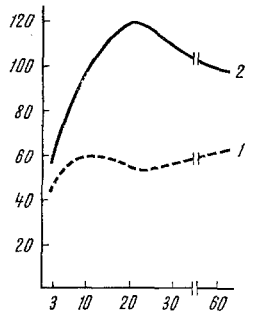

Fig. 1. Blood ceruloplasmin activity of control (1) and hypophysectomized (2) albino rats. Abscissa, days after operation; ordinate, activity of enzyme (in conventional units).

EXPERIMENTAL RESULTS

In the hypophysectomized animals (Table 1) the copper concentration in the blood, liver, kidneys, and testes was significantly increased. The copper concentration in the heart also was increased, but the increase was not statistically significant. The concentration of copper in the skeletal muscles was reduced, and in the brain it was unchanged. The maximal changes in copper metabolism were observed in the early periods after hypophysectomy (in the

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TABLE 1. Dynamics of Copper Concentration (in mg% of ash) in Organs and Tissues of Control and Hypophysectomized Albino Rats (M ± m)

Time after operation (in days)	Animals	Blood	Liver	Skeletal muscle	Kidneys	Brain	Heart	Testes
—	Intact	10,2±2,4	23,0±1,3	10,2±1,1	21,0±1,1	9,0±1,5	24,8±2,0	7,7±1,3
3	Control	9,5±1,3	29,8±1,3	10,2±0,2	17,9±3,0	7,0±1,1	28,2±2,8	7,5±1,4
	Experimental	14,4±0,8	29,5±1,7	9,8±0,6	19,3±2,8	10,0±2,2	25,5±2,4	7,3±0,7
	P	<0,02	>0,5	>0,5	>0,5	>0,5	>0,5	>0,5
10	Control	10,2±0,2	28,4±1,4	9,8±0,4	21,2±1,5	10,0±1,1	27,9±2,5	7,1±0,7
	Experimental	17,7±0,9	34,9±1,1	7,4±0,9	29,6±1,8	9,5±1,6	30,3±3,3	9,9±0,6
	P	<0,01	<0,001	<0,05	<0,01	>0,5	>0,2	<0,02
20	Control	8,6±1,3	21,9±2,4	10,4±0,3	19,4±0,8	8,4±1,2	23,8±3,3	6,7±0,8
	Experimental	16,2±1,3	32,0±1,3	6,7±0,2	24,2±1,1	8,4±1,9	30,3±5,1	11,0±1,3
	P	<0,01	<0,01	<0,001	<0,01	>0,5	>0,2	<0,05
30	Control	12,4±1,1	24,0±1,3	9,8±0,3	20,3±2,2	8,0±1,1	26,2±4,3	8,2±1,0
	Experimental	15,9±0,8	31,8±0,8	8,1±0,5	24,9±2,6	7,8±1,5	28,6±3,6	10,4±1,1
	P	<0,05	<0,01	<0,05	>0,1	>0,5	>0,5	>0,1
60	Control	10,4±0,6	24,1±1,3	10,1±0,8	19,7±1,1	8,8±2,2	28,6±3,6	7,9±0,8
	Experimental	19,0±2,0	30,8±2,4	8,6±0,4	25,9±2,7	7,9±0,5	26,0±3,5	11,5±0,8
	P	<0,01	<0,05	>0,05	>0,05	>0,05	>0,5	<0,02

blood, liver, and kidneys on the 10th day and in the muscles on the 20th day after the operation). Later (30th and 60th days) there was a tendency toward restoration of the normal copper concentration in the tissues (except of the testes).

Changes in ceruloplasmin activity in the blood followed a similar course to the changes in the copper concentration (Fig. 1). The activity of this metaloenzyme in the blood increased sharply in the hypophysectomized rats to reach a maximum on the 20th day after the operation.

The disturbances thus revealed in copper metabolism in the organs and tissues of the hypophysectomized rats must be considered in connection with the biological role of this trace element in various aspects of metabolism.

Hypophysectomy sharply inhibits tissue respiration in the liver, kidneys, muscles, and spleen [5] and lowers the activity of the copper-containing enzyme cytochrome oxidase [14] and of other oxidative enzymes. Copper stimulates tissue respiration [6] and increases activity of oxidases [2] and, in particular, of cytochrome oxidase [7].

Hypophysectomy is followed by inhibition of erythropoiesis, by the development of anemia [13], and by characteristic disturbances of protein metabolism with a negative balance of nitrogen, phosphorus, and calcium [10]. Copper has a well-marked antianemic action, it stimulates hemoglobin synthesis [7], improves the absorption and utilization of iron by the organism [19], promotes assimilation of proteins, increases the gain in weight of experimental animals [3], and increases the uptake of calcium and phosphorus salts by the body [8]. In addition, there is evidence that copper has a direct relationship with pituitary physiology. Voinar [7], for instance, emphasizes that in mammals the action of copper salts is similar to that of gonadotropic hormones. Copper acetate induces ovulation in rabbits through direct stimulation of the hormonal activity of the anterior lobe of the pituitary. According to Pavlova [11] copper salts increase the activity of pituitary hormones which are unstable and rapidly inactivated in the blood stream.

The increase in the copper concentration in the blood, liver, kidneys, and testes of the hypophysectomized albino rats must probably be regarded as a protective measure by the animal. The increased blood ceruloplasmin activity in the experimental animals must be regarded in the same light. This enzyme oxidizes adrenalin, noradrenalin, serotonin, and other biogenic amines. Synthesis of some of them, notably noradrenalin, in the tissues of hypophysectomized rats is sharply increased [18], with a consequent increase in ceruloplasmin activity.

However, compensatory changes in the copper concentration in the tissues of hypophysectomized animals are evidently reflected to a certain degree in the metabolism of other substances, especially carbohydrate metabolism.

Administration of biological doses of copper induces a hypoglycemic effect, facilitates glycogen formation in the liver, reduces diabetic hyperglycemia and glucosuria, reduces alimentary and adrenal hyperglycemia, and increases insulin hypoglycemia. These facts served as the basis for the treatment of diabetes mellitus with microdoses of copper [3].

Disturbances of carbohydrate metabolism arising after hypophysectomy (hypoglycemia, a decrease in alimentary and adrenal hyperglycemia, a decrease in the glycogen content in the liver and an increase in its content in the muscles [10, 18, 19] are analogous to those following administration of microdoses of copper and they are probably due to the accumulation of this trace element in the tissue and organs of hypophysectomized rats.

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