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HYPOTHALAMIC OBESITY IN OLD RATS

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Together with atherosclerosis and diabetes, obesity is a widespread disturbance of metabolism in old age. In the development of obesity in general and of obesity during aging in particular, great importance is attached to disturbances of hypothalamic mechanisms of regulation. During aging significant changes take place in the functions of the hypothalamus and, according to some data [3], they are expressed unequally in its different structures. Production of an experimental model of hypothalamic obesity in animals of different ages, through injury to the ventromedial hypothalamic nuclei (VMN), could help, first, to shed light on the special features of development of this form of obesity at different ages and, second, to establish some age differences in hypothalamic regulation of endocrine functions.

In the investigation described below changes in the degree of obesity, the quantity of food and water consumed, the concentrations of insulin, growth hormone (GH), thyroid-stimulating hormone (TSH), corticosterone, sugar, total lipids, cholesterol, and free fatty acids in the blood, and also the concentration of GH in the pituitary gland were compared in relation to the time elapsing after destruction of VMN and the degree of obesity which developed.

EXPERIMENTAL METHOD

Bilateral electrolytic injury to VMN was produced in 12 male albino rats ages 24-26 months (old) and in 41 rats aged 8-10 months (young). Intact animals (15 old and 32 young) and animals undergoing a mock operation (12 old and 29 young) served as the control. The conditions of keeping, determination of body weight, food consumption, sacrifice, and methods of determination of GH in the pituitary, and of total lipids, cholesterol, free fatty acids (FFA), and sugar in the blood were described previously [4]. Immunoreactive insulin (IRI), GH, TSH, and corticosterone levels in the blood plasma were determined by the competitive binding method. To describe the degree of obesity, the percentage of gain in body weight was used (20-29% – degree I, 30-49% – degree II, 50-99% – degree III, over 100% – degree IV). The numerical results were subjected to statistical analysis.

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TABLE 1. Hormonal and Metabolic Disturbances after Injury to VMN in Rats of Different Ages

Group of animals	Time after operation, months	Statistical index	IRI, microunits/ml	Plasma GH, ng/ml	Pituitary GH, μg/g dry tissue	TSH, ng/ml	Corticosterone, ng/ml	Sugar, mg%	Total lipids, mg%	Cholesterol, mg%	FFA, meq%
Old	0 (intact)	*n*	12	11	4	10	5	15	15	15	15
		M	26,0	0,58	31,5	6,13	76,8	85,4	613	94,0	0,53
		±*m*	4,5	0,06	1,4	1,04	16,8	3,2	41	6,0	0,07
	1	*n*	7	7	5	4	5	7	7	7	7
		M	53,1†	0,20†	26,0	1,52†	60,2	106,1†	761*	76,0	0,59
		±*m*	5,3	0,11	4,0	0,37	10,0	11,8	71	12,9	0,11
	3	*n*	3	3	1	1	1	4	4	4	4
		M	63,7‡	0,73	19,3	0,95	42,0	109,0†	625	73,0	0,40
		±*m*	7,8	0,08				7,5	156	23,7	0,08
	10	*n*	1	1	1	1	1	1	1	1	1
		M	70,0	0,55	16,6	6,40	—	131,0	570	50,0	0,50
Young	0 (intact)	*n*	23	25	15	15	11	25	25	25	25
		M	30,6	0,36	20,7	4,61	79,2	104,3	646	93,8	0,55
		±*m*	2,2	0,05	1,4	0,80	6,6	3,1	23	6,1	0,06
	½	*n*	6	6	3	6	7	7	7	7	7
		M	56,8‡	0,44	6,7*	2,46*	78,6	93,0	777	120,0	0,31*
		±*m*	5,6	0,10	1,6	0,60	15,8	7,0	98	14,8	0,03
	1	*n*	6	5	4	6	5	7	7	7	7
		M	53,2	0,44	19,2	2,42*	97,4	131,1*	947	92,9	0,39
		±*m*	20,0	0,08	3,7	0,53	6,5	10,6	178	12,9	0,10
	2	*n*	6	5	3	5	3	6	6	6	6
		M	142,5‡	1,12‡	33,4	2,36*	33,5*	120,0	732	106,0	0,84
		±*m*	23,5	0,22	15,6	0,57	10,1	42,3	58	17,1	0,29
	3	*n*	5	4	1	3	1	6	6	6	6
		M	120,0‡	0,95*	54,6	1,77†	28,0	84,2	678	83,0	0,62
		±*m*	32,0	0,22		0,64		11,4	17	7,5	0,14
	4	*n*	5	5	5	4	3	5	5	5	5
		M	47,0‡	0,40	15,7	2,22*	82,7	122,8	666	100,0	0,68
		±*m*	2,3	0,15	5,4	0,82	16,7	8,8	56	18,2	0,11
	10	*n*	9	11	6	—	—	10	10	10	10
		M	73,2*	0,58	21,8			101,8	517†	60,8‡	0,50
		±*m*	18,5	0,10	4,8			5,4	45	3,9	0,06

* $P < 0.05$, † $P < 0.02$, ‡ $P < 0.001$.

EXPERIMENTAL RESULTS

The increase in body weight after injury to VMN was much less marked in the old than in the young animals (Fig. 1). No age difference was found in the dynamics of the changes or in the absolute value of food consumption (Fig. 2). Considering the possible role of the higher initial body weight in the old rats and the less effective assimilation of the food they consumed, it should be noted that in a group of specially selected animals of different ages with identical initial body weight the degree of obesity was somewhat higher in the young rats. The development of obesity after injury to VMN is associated with considerable hormonal-metabolic disturbances, and special importance is attached to activation of the insular apparatus [1]. Analysis of the data on dependence of these disturbances on the duration (Table 1) and degree of obesity (Fig. 3) indicates that the insulinemia was less marked in the old rats, that there is direct correlation between the increase in IRI and the degree of obesity, that the fall in the TSH level was not dependent on the degree of obesity, and that opposite changes in the plasma GH concentration occurred in animals of different ages.

The mechanisms of the increase in insulin secretion after injury to VMN include nervous and humoral—hormonal components. The food consumption is increased, the load on the insular apparatus rises, and insulin secretion is activated. Injury to VMN frees the lateral hypothalamus from inhibitory influences of VMN, and the lateral hypothalamus activates the liberation of insulin by direct nervous, primarily including the vagus nerves [11, 15], and humoral pathways [9]. Inhibition of the somatostatin mechanism arising after injury to the basal hypothalamus may play a definite role, for somatostatin inhibits the secretion of GH by the pituitary and of insulin by the pancreas [5, 7, 14]. Direct data on the concentrations of somatostatin in the hypothalamus and blood during aging are not available. In our experiments on young rats a parallel increase was observed in the IRI and GH levels, whereas in the old animals, elevation of the IRI level was accompanied by a fall in the GH concentration. It can be tentatively suggested that under normal conditions the somatostatin mechanism of the hypothalamus is weakened in old animals, so that its blocking in old animals by destruction of VMN has no activating effect on the GH level or that its action is much weaker.

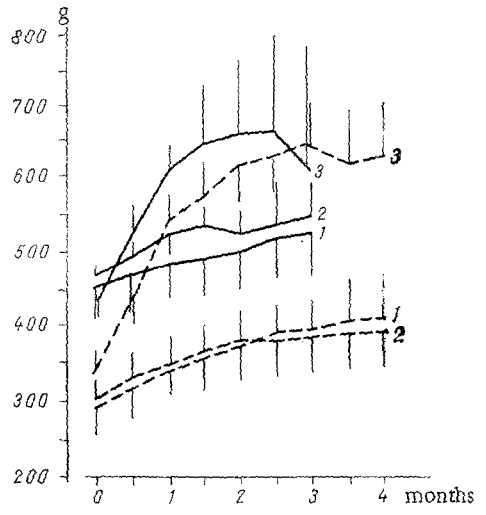

Fig. 1

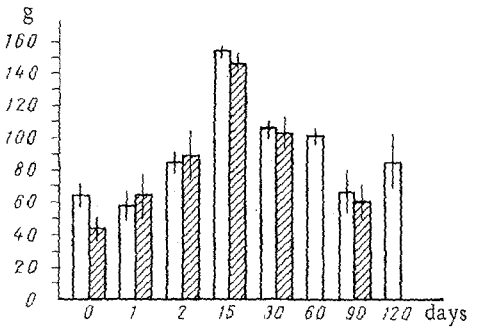

Fig. 2

Fig. 1. Changes in body weight in old (continuous line) and young (broken line) rats at different times after operation. Abscissa, time after operation (in months); ordinate, body weight (in g). 1) Intact animals, 2) rats undergoing mock operation, 3) rats with injury to VMN.

Fig. 2. Changes in daily food consumption by old (shaded columns) and young (unshaded columns) rats at different times after injury to VMN. Abscissa, time after operation (in days); ordinate, quantity of food consumed by one animal per diem (in g).

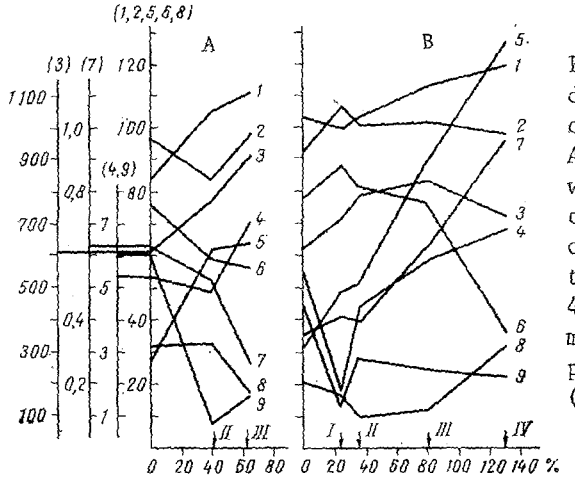

Fig. 3. Dependence of hormonal-metabolic disturbances on degree of hypothalamic obesity in old (A) and young (B) rats. Abscissa, percent increase in body weight with indication of degree of obesity for corresponding points; ordinate, biochemical indices. 1) Sugar (in mg%), 2) cholesterol (in mg%), 3) total lipids (in mg%), 4) FFA (in meq%), 5) IRI (in microunits/ml), 6) corticosterone (in ng/ml), 7) plasma GH (in ng/ml), 8) pituitary GH (in μg/mg dry tissue), 9) TSH (in ng/ml).

In old age a decrease in excitability and weakening of the influences of the lateral hypothalamus and vagus nerves on several vegetative indices are observed [2, 3]. Consequently, the weaker insulin-stimulating effect of destruction of VMN may be attributed both to weakening of influences of the lateral hypothalamus on insulin secretion, transmitted through the vagus nerves, and to weakening of reciprocal relations between VMN and the lateral hypothalamus. The less marked insulinemia and obesity observed in the old rats and the equal change in food intake of the old and young rats after injury to VMN may be evidence that the influences of different regions of the hypothalamus on different functions changed differently with age. Changes in other mechanisms of development of hypothalamic obesity, expressed differently at different age periods, likewise cannot be ruled out [10]. These results agree to some extent also with evidence of the different roles of afferent and efferent fibers of the vagus nerves in the mechanism of food behavior, insulinemia, and obesity, caused by stimulation of the lateral hypothalamus and injury to VMN [12, 13]. Age changes in hypothalamic feedback mechanisms and also in the pancreas itself may also play a definite role in the lower level of insulinemia in old animals.

The age differences revealed in this investigation in the development of hypothalamic obesity and the hormonal and metabolic disturbances developing under these conditions, revealed by this investigation, thus showed that disturbance of the functions of the hypothalamic centers in old animals leads to less marked changes in one of the trigger mechanisms of obesity, namely the blood insulin level. These differences, it may be considered, are largely determined by essential changes in the state of the hypothalamic centers and pathways of realization of their influences during aging.

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