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ROLE OF THE INCRETORY FUNCTION OF THE PANCREATIC ISLETS IN THE MECHANISMS OF DEVELOPMENT OF HYPOTHALAMIC OBESITY

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Administration of alloxan, which injures the β cells and depresses insulin secretion, to animals with experimental hypothalamic obesity prevented any further increase in body weight despite an excessive food intake by the animals. It is concluded that the most important mechanism of development of obesity following injury to the ventromedial hypothalamic nuclei is the hypersecretion of insulin caused by such injury.

KEY WORDS: hypothalamic obesity; insulin; pancreatic islets; alloxan diabetes.

Destruction of the ventromedial hypothalamic nuclei (VMHN) or deafferentation of that region in rats is accompanied by hyperphagia, obesity [2, 4], and a raised blood insulin level [1, 4, 9]. Changes developing under these circumstances in the pancreatic islets have been attributed to hyperstimulation of the β cells as a result of overeating [2, 3]. However, the increased secretion of insulin after injury to VMHN could be the cause of the hyperphagia and obesity, and not its effect [9]. If this hypothesis is true, weakening of the insulin-producing function of the pancreatic islets ought to stop the increase in weight of animals after destruction of VMHN.

To study this problem the development of hypothalamic obesity after injury to the pancreatic β cells by alloxan was investigated.

EXPERIMENTAL METHOD

Symmetrical bilateral destruction of VMHN in sexually mature female rats was carried out by means of a stereotaxic apparatus with a direct current of 2 mA for 15 sec [3]. Two weeks after the operation diabetes was produced in the animals by subcutaneous injection of 100 mg/kg alloxan in buffer solution, pH 4.0, into each animal after starvation for 16-18 h. The controls were intact rats, animals with alloxan diabetes but without destruction of VMHN, and animals with destruction of VMHN but without alloxan diabetes. For 2 months, during which all the rats were kept on the same balanced diet ad libitum, regular determinations were made of their body weight, their blood sugar (by the method of Hagedorn and Jensen), and sugar in their urine (by Benedict's method). At the end of the experiments the concentration of immunoreactive insulin (IRI) in the plasma was determined [8]. The presence of obesity was established from the index:

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TABLE 1. Changes in IRI, Blood Sugar, Food Intake, Body Weight, and Lee's Index in Rats (M ± m)

Animals	Time of investigation	Plasma IRI, microunits/ml	Blood sugar, mg %	Daily caloric value of diet, cal	Body weight, g	Lee's index
Intact (n = 23)	Before experiment				177,0±4,8	
	Two weeks later		107,5±4,9	75,0±3,8	193,1±8,6	293,0±4,6
	End of experiment	17,6±2,5			>0,1	
Intact + alloxan (n = 8)	Before experiment				180,2±8,3	
	Two weeks later		545,7±24,6	91,8±5,2		
			<0,001	<0,02		
	End of experiment	5,8±1,2			176,2±7,5	284,2±3,1
		<0,001			>0,5	
Injury to VMHN (n = 12)	Before experiment				186,3±5,5	
	Two weeks later		93,4±2,5	134,5±5,7	274,3±7,4	
			<0,05	<0,001	<0,001	
	End of experiment	55,9±4,0			382,9±14,2	345,8±7,0
		<0,001			<0,001	<0,001
Injury to VMHN + alloxan (n = 11)	Before experiment				189,0±4,3	
	Two weeks after injury to VMHN	38,1±3,6	89,7±4,7	100,5±6,5*	267,5±7,0	
		<0,001	<0,02	<0,05	<0,001	
	End of experiment	9,7±2,3	557,3±21,0		190,5±7,6	294,9±2,3
		<0,02	<0,001			

*Two weeks after development of diabetes

$$\frac{\sqrt[3]{\text{body weight, in g}}}{\text{length from nose to anus, cm}} \times 1000,$$

which in this case must exceed 300 units [5]. The brain and part of the pancreas were fixed in Bouin's fluid. The location of the injury was established by reference to De Grott's atlas in sections through the hypothalamus stained with azure II. Sections through the pancreas were stained with aldehyde-fuchsin, and to reveal insulin in the β cells by pseudoisocyanin [6].

EXPERIMENTAL RESULTS

During the first days after injury to VMHN the animals developed considerable hyperphagia, their body weight after 2 weeks was increased by 70–90 g, and their blood sugar level was lowered (Table 1). In six animals killed in this stage of the experiment the IRI content was more than twice as high as in healthy animals.

Injection of alloxan into rats both with and without injury to VMHN caused the blood sugar to rise after 24 h to more than 500 mg %, and this was followed by the development of lasting diabetes. The water intake and diuresis increased and glucosuria developed. The body weight, which in the rats with injury to VMHN had increased by 40% by the time of injection of alloxan, began to decline after the development of diabetes, and 1.5 months later it was indistinguishable from its initial value, and Lee's index was normal (confirming the absence of obesity). The IRI level fell sharply and was almost the same as that in rats with alloxan diabetes but without injury to VMHN. In the rats which did not receive alloxan after injury to VMHN, considerable obesity developed over the same period of time and the IRI level was increased threefold. The food intake by the animals with damaged VMHN fell appreciably after their development of alloxan diabetes, but just as in the alloxan-diabetic animals with intact VMHN, it was greater than in the intact rats.

Histological investigation confirmed the sharp decrease in the insulin-producing capacity of the pancreatic islets after injection of alloxan, for they consisted mainly of α cells. The few β cells which remained contained only traces of dust-like aldehyde-fuchsin granularity or of a substance giving a metachromatic reaction with pseudoisocyanin (insulin).

Hence, in rats developing hypothalamic obesity, injection of alloxan, which damages β cells and reduces insulin secretion, arrested the development of obesity and restored the normal body weight even though the food intake by the animals was in excess of normal. The results confirm the view that the most important mechanism in the development of hypothalamic obesity is increased secretion of insulin, caused by direct action on VMNH, which can be found as early as on the first day after the operation [1]. The results described above are in agreement with other published data indicating that the preceding development of alloxan [7] or streptozotocin diabetes [10] prevents the subsequent development of hypothalamic obesity after injury to VMHN.

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EFFECT OF THYROTOXICOSIS ON SKELETAL MUSCLE PROPRIOCEPTOR ACTIVITY

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The effect of prolonged administration of thyroid hormones on the discharges from muscle spindles of the cat soleus was investigated. In animals with thyrotoxicosis the response of the primary spindle endings to a constantly acting and to a sudden rapid stretching increased considerably in both the dynamic and the static phase. The discharge frequency of the secondary endings remained substantially unchanged. It is postulated that the observed changes in activity of the primary endings are connected with disturbances of metabolism in the muscle and also with its atrophy.

KEY WORDS: thyroid hormones; muscle receptors; motor disturbances.

Among the most characteristic symptoms of thyrotoxicosis are motor disturbances, expressed as muscular weakness, rapid fatigue, tremor of the limbs and trunk, etc. [6, 7].

In the analysis of these motor disturbances the study of the state of receptor function of the muscles is particularly important, for afferent impulses from the muscles and joints play an important role in the process of movement control.

It was therefore decided to study the function of muscle spindles in experimental thyrotoxicosis.

EXPERIMENTAL METHOD

Discharges from receptors of the soleus muscle were studied in normal cats and in cats receiving thyroid extract with the diet in accordance with a special scheme [3]. By the end of the second week of the experiment the animals showed tachycardia, a loss of weight of 10-15%, and an increase in the serum protein-bound iodine concentration from 4-5 to 18-20 $\mu\text{g} \%$. Under urethane-chloralose anesthesia (500 and 50 $\mu\text{g}/\text{kg}$ respectively) both limbs of the animals were denervated except the muscle branch to the soleus muscle on the test side. After laminectomy the anterior and posterior roots were divided from L_5 to S_1 inclusive. Throughout the experiment the temperature of the body and of the operation wound, which was flooded with mineral oil, was maintained

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