BLOOD INSULIN LEVEL IN RATS AFTER INJURY TO THE VENTROMEDIAL HYPOTHALAMUS

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Experiments on rats showed that injury to the ventromedial portion of the hypothalamus or interruption of its nervous connections is followed by hyperinsulinemia; in conjunction with the hyperphagia, this could be the direct cause of the adiposity.

KEY WORDS: adiposity; hypothalamus; insulin.

In adiposity in man [3, 5, 7, 14, 16] and also in hereditary adiposity in mice [6, 15] hyperinsulinemia is observed. Destruction of the ventromedial region of the hypothalamus in rats is followed by hyperphagia, adiposity [1, 2], and a raised blood insulin level [4, 9, 12, 13, 17]. The mechanism of development of hyperinsulinemia and its connection with hyperphagia and adiposity remain unexplained.

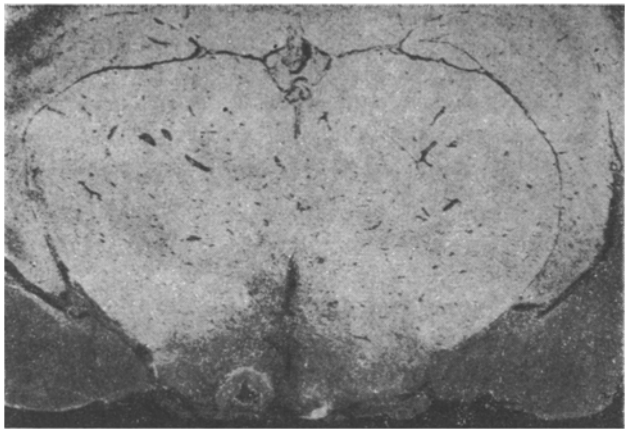

Fig. 1. Section through rat hypothalamus after electrolytic destruction of ventromedial hypothalamic nuclei.

To investigate this problem the relationship between hyperinsulinemia and hyperphagia was studied in the early stages after injury to the ventromedial portion of the hypothalamus, and changes in the internal secretory function of the pancreatic islets were studied after division of the nervous connections of the hypothalamus, subdiaphragmatic division of the vagus nerves, and removal of the splenic portion of the pancreas with simultaneous electrolytic destruction of the ventromedial portion of the hypothalamus.

TABLE 1. Content of Immunoreactive Insulin in Plasma at Various Times after Injury to VMNH

Concentration of IRI (in microunits/ml)	Group of animals				
	control (13)	after injury to VMNH			
		1 day (5)	4 days (5)	7 days (5)	14 days (6)
Limits of variation	14—24	20—53	39—62,5	31—64	32,5—45
$M \pm m$	18,3±3,6	34,4±2,23	40,0±4,3	46,0±5,6	38,1±3,6
P		<0,01	<0,01	<0,001	<0,01

Legend: Number of animals in parentheses.

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TABLE 2. Plasma IRI Concentration after Injury to the Hypothalamus, Vagotomy, and Partial Pancreatectomy

Series of experiments	Number of rats	IRI concentration (in microunits/ml) (M ± m)	P
I. Intact rats (control)	13	18,3±3,6	
II. Injury to VMNH	6	38,1±3,6	I and II<0,01
III. Division of nervous connections of hypothalamus	4	34,2±10,0	IIandIII>0,1
IV. Subdiaphragmatic vagotomy	19	17,2±2,23	IandIV>0,1
V. Subdiaphragmatic vagotomy + injury to VMNH	5	26,5±4,4	IIand V>0,05
VI. Removal of splenic part of pancreas + injury to VMNH	9	42,0±6,6	IIandVI>0,1

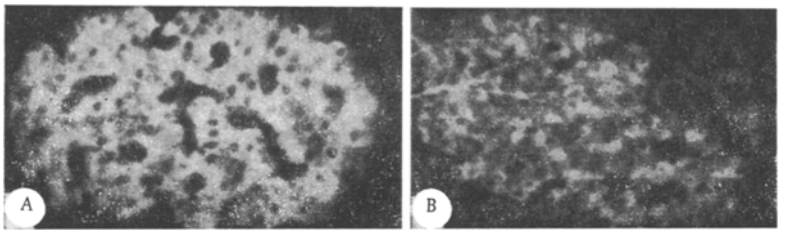

Fig. 2. Insulin content in pancreatic islet. Metachromatic staining with pseudoisocyanin, 120 ×. Insulin content in pancreatic islet: A) normal; B) reduced.

EXPERIMENTAL METHOD

Experiments were carried out on 71 female albino rats weighing 180-240 g. Bilateral symmetrical injury to the ventromedial nuclei of the hypothalamus (VMNH) was inflicted on 21 of them by means of a stereotaxic apparatus (steady current of 2 mA for 15 sec; 37 animals were used in additional experiments described below, and 13 intact rats served as the control. The animals received a balanced diet and water ad lib. They were weighed regularly and their blood sugar determined by the method of Hagedorn and Jensen. The plasma insulin concentration was investigated at the end of the experiment by a radioimmunochemical method [11] using a specially marketed kit. The animals were killed 1, 4, 7, and 14 days after the operation after preliminary starvation for 16-18 h. The plasma was quickly frozen and kept at −30°C.

The pancreas and brain were fixed in Bouin's fluid. Sections through the gland were stained with pseudoisocyanin [8] to reveal the insulin content in the pancreatic islets. The location of the injury was determined from De Groot's atlas [10].

EXPERIMENTAL RESULTS AND DISCUSSION

Complete bilateral destruction of VMNH was revealed in the animals undergoing the stereotaxic operation (Fig. 1).

The concentration of immunoreactive insulin (IRI) was increased 24 h after injury to VMNH (Table 1). Despite considerable individual variations in IRI, at all times of investigation its concentration exceeded the control by a statistically significant degree.

Histological examination of the pancreas by the metachromatic reaction with pseudoisocyanin revealed a sufficient quantity of insulin in the β-cells in most of the rats (Fig. 2A), and less than in the intact animals in only a few cases (Fig. 2B).

The blood IRI level in the rats was thus increased 24 h after electrolytic injury to VMNH. The most acceptable explanation of this fact was considered to be that hyperphagia induced by destruction of this part of the brain leads to an increased entry of carbohydrates into the blood stream, stimulating the internal secretory function of the β-cells [17]. This explanation, however, was not confirmed by the present experiments, which indicate that hyperinsulinemia preceded the development of hyperphagia. Another interesting

fact is that excessive gain in weight of young rats after this operation can also take place in the absence of hyperphagia [9].

Hypersecretion of insulin, hyperphagia, and adiposity may be the general consequence of the primary stimulant action of the injured hypothalamus on the insular β-cells. Injury to the ventromedial hypothalamus is considered to be followed by an increased flow of impulses to the pancreas from the lateral portion of the hypothalamus.

The object of the subsequent experiments was to study the mechanism of development of hyperinsulinemia after injury to the ventromedial hypothalamus (Table 2). By means of a specially designed knife this region was isolated from the rest of the hypothalamus in four rats (series III) in a stereotaxic apparatus, and this was followed by the rapid development of adiposity and of hyperinsulinemia, just as after destruction of VMNH.

In other animals the vagus nerve, which stimulates insulin secretion, was first divided below the diaphragm and a few weeks later VMNH was injured. Vagotomy itself did not alter the blood insulin concentration in the intact rats (series IV), but in the vagotomized animals with injury to VMNH, hyperinsulinemia was found (series V).

Removal of not less than half of the pancreas (its splenic part) did not prevent the development of hyperinsulinemia after destruction of VMNH (series VI).

The results of this investigation indicate that injury to the ventromedial part of the hypothalamus and division of its nervous connections are followed by rapid development of hyperinsulinemia, and this is responsible for the development of hyperphagia and the subsequent adiposity.

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