

# OBESITY IN RATS AFTER ISOLATION OF THE VENTROMEDIAL HYPOTHALAMUS

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Hyperphagia and obesity arise in rats not only after electrolytic injury to the ventromedial hypothalamic nuclei but also after circumferential operative isolation of this region without damage to it. The development of obesity is accompanied by an increase in size of the pancreatic islets and elevation of the blood insulin level.

KEY WORDS: obesity; hypothalamus; pancreatic islets; insulin.

Hyperphagia and obesity have been obtained in rats after injury to the ventromedial hypothalamus [11]. In recent years a similar effect has been observed after division of the nervous connections anteriorly, posteriorly, and laterally to the ventromedial nuclei without their destruction [4, 12, 14, 16, 17]. Additional injury to these nuclei did not alter the degree of hyperphagia and obesity [4]. Destruction of the lateral region led to temporary aphagia. The suggestion has been made that blocking the function of the ventromedial nuclei liberates the food center from inhibitory influences [5]. Meanwhile, in some animals, after destruction of the ventromedial hypothalamus, not only hyperphagia and obesity were seen to develop, but also diabetes [2, 6, 10]. However, the state of the pancreatic islets after this operation has received little study [1, 2, 7, 13], and it has not been studied at all after isolation of the ventromedial nuclei.

The object of the present investigation was to study the dynamics of development of hyperphagia and obesity induced by destruction of the nervous connections of the ventromedial hypothalamus and by electrolytic damage to this region, and to examine the state of the pancreatic islets during the development of obesity.

## EXPERIMENTAL METHOD

Experiments were carried out on 30 female albino rats weighing 190-240 g, of which 19 animals took part in the main series of experiments. The control consisted of 5 rats undergoing a mock operation and 6 animals in which the ventromedial hypothalamic nuclei were destroyed electrolytically. The nervous connections of these nuclei were divided in a stereotaxic apparatus by means of a special knife [14] made of thin steel wire (Fig. 1). The axis of rotation of the knife, designed in consideration of the position of the bregma according to the atlas [8], lay in the plane X-5.8. During rotation of the blade through 360° all nervous connections were divided along the circumference of a circle 3 mm in diameter, surrounding the two ventromedial nuclei. In the mock operation, the knife was inserted into the brain in the same position but was not rotated. Bilateral electrolytic destruction of these same nuclei was produced by the action of a direct current of 2 mA for 15 sec [2].

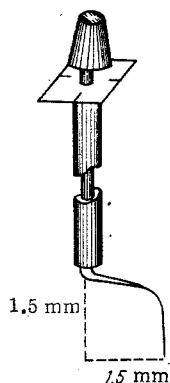


Fig. 1. Diagram of knife for dividing nervous connection of the ventromedial hypothalamus.

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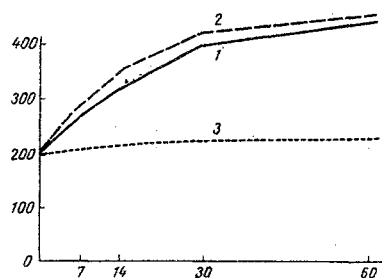


Fig. 2. Changes in body weight of rats after division of nervous connections of ventromedial hypothalamus (1), electrolytic destruction of ventromedial nuclei (2), and the mock operation (3). Abscissa, days of investigation; ordinate, weight (in g).

After the operation, the experimental and control animals were kept in separate cages and given food and water ad lib. The rats were regularly weighed, the blood sugar determined by the Hagedorn-Jensen method, and sugar in the urine by Benedict's method. The pancreas and brain were fixed in Bouin's fluid and embedded in paraffin wax. Sections through the gland to study the insulin content in the B-cells of the islets were stained with aldehyde-fuchsin and pseudoisocyanin [3, 15]. Serial brain sections 10-12  $\mu$  in thickness were stained with azure II and examined under the microscope. Parallel unstained sections were photographed with the aid of a photographic enlarger to verify the site of injury of the nuclei and the completeness of division of their connections. In some animals the plasma insulin concentration was estimated by a radioimmunochemical method [9].

## EXPERIMENTAL RESULTS

After the mock operation no visible change took place in the animal's condition. Of the 19 rats, 3 died during the 1st-3rd days after circumferential division of the nervous connections of the ventromedial hypothalamus. Seven of the 16 surviving rats, as well as all 6 animals with injured ventromedial nuclei, devoured their food greedily and ate much more of it than the rats after the mock operation. The weight of these seven rats rose in 1 week from  $205 \pm 7.4$  to  $259 \pm 6.6$  g and it continued to increase rapidly for a further 30-40 days (the dynamic phase of obesity), after which it increased more slowly and became similar to the weight of the control animals (static phase). Similar changes took place in the weight of the rats with electrolytic injury to the ventromedial nuclei (Fig. 2). The mean blood sugar of the rats after division of the nervous connections of the hypothalamus, as in the other animals, was within normal limits ( $109 \pm 4.2$  mg%); no sugar was found in the urine.

Examination of the brain sections showed that in all cases in which the rats developed hyperphagia and obesity, division of the nervous connections of the ventromedial nuclei was sufficiently complete (Fig. 3a) or the nuclei themselves were destroyed by the current (Fig. 3b).

The pancreas of the seven obese rats of the principal series, like that in the rats with electrolytic destruction of the ventromedial hypothalamus, had the usual structure. The dimensions of the islets were slightly increased. The B-cells obtained the usual number of aldehyde-fuchsin granules. On staining with pseudoisocyanin the granules luminesced a bright orange color, further evidence of the high insulin concentration in them. The concentration of immunoreactive insulin in the plasma, studied in 4 of the 7 rats which developed obesity after isolation of the ventromedial nuclei, was increased in all cases.

The writers observed previously [2] signs of exhaustion of the insulinogenic function of the B-cells (their complete degranulation) in the pancreas of rats with diabetes arising as a result of destruction of the ventromedial hypothalamic nuclei, even in animals without diabetes but during prolonged "hypothalamic" obesity, and the glucose tolerance of these animals was lowered. Meanwhile, many obese rats

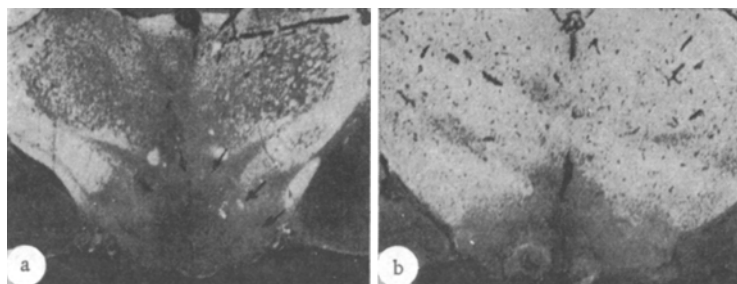


Fig. 3. Section through hypothalamus of rat after division (line of division shown by arrows) of nervous connections of ventromedial hypothalamus (a) and after electrolytic destruction of ventromedial nuclei (b).

showed evidence of increased activity of the islets (an increase in their size, the presence of intermediate B-cells). Taken in conjunction with the results of the present investigation, this very strongly suggests that "hypothalamic" obesity is the result of primary stimulation of the pancreatic B-cells, whereas the accompanying disturbance of carbohydrate metabolism is the result of exhaustion of their insulinogenic function. The development of "hypothalamic" obesity can take place not only during destruction of the hypothalamic ventro-medial nuclei, but also after division of the nervous connections of this region while maintaining the integrity of the nuclei.

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