ROLE OF THE LATERAL AND VENTRO-MEDIAL PORTIONS OF THE HYPOTHALAMUS IN THE REGULATION OF INSULIN SECRETION

B. V. Stul'nikov

UDC 612.349.7.018-06:612.826.4

Electrical stimulation of the lateral hypothalamus in acute experiments on adult cats increased the insulin concentration to an extent which was independent of the accompanying increase in the blood sugar concentration. Stimulation of the ventro-medial hypothalamic nuclei caused a rapid and transient decrease in the insulin concentration and a simultaneous elevation of the blood sugar. Bilateral coagulation of the lateral hypothalamus lowered the blood insulin and sugar concentrations whereas coagulation of the ventro-medial nuclei did not lower the insulin concentration although it sharply lowered the blood sugar. Coagulation of both the lateral hypothalamus and the ventro-medial hypothalamic nuclei disturbed the discharge of insulin and the glucose tolerance curve in response to sugar loading.

The hypothalamic regulation of insulin secretion is still a matter for discussion. The significance of investigations [1, 2, 5, 7, 11, 12, 16] in which insulin secretion was judged from changes in the blood sugar concentration is limited by the fact that there is no strict correlation between changes in the blood sugar and insulin levels in different states of the body [6, 8, 14, 18, 19]. The evidence so far obtained on the effect of the hypothalamus on insulin secretion in recent years by direct determination of the blood hormone concentration [4, 9, 10, 13, 15] is insufficient to explain the role of the various hypothalamic structures in the regulation of insulin secretion.

The object of this investigation was to examine the role of the lateral hypothalamus and the ventro-medial hypothalamic nuclei in the regulation of insulin secretion.

EXPERIMENTAL METHOD

Acute experiments were carried out on adult cats deprived of food for 18-24 h before the experiment. The hypothalamic stimulation experiments were carried out on unanesthetized cats with the use of muscle relaxants. Experiments on adrenalectomized animals or those involving coagulation of the hypothalamic structures were carried out on animals anesthetized with pentobarbital (30-40 mg/kg). The stimulating electrodes were implanted into the lateral hypothalamus and ventro-medial hypothalamic nuclei stereotaxically with reference to coordinates from the atlas of Jasper and Ajmone-Marsan [17]. Electrical stimulation was applied through bipolar electrodes insulated throughout their length except at the tips and with an interpolar distance of 0.5-0.7 mm. The parameters of the stimulating current were: frequency 50 Hz, voltage 4-6 V, pulse duration 5 msec, volley duration 20 sec with intervals of 20 sec between volleys, total duration of stimulation 10 min. Coagulation was produced by passing a direct current (1.5-3.0 mA for 1-2 min) through monopolar electrodes with the insulation removed from the tips for a distance of 1-1.5 mm. In all experiments the insulin and sugar concentrations were determined in blood flowing from the pancreas. Blood samples were taken before and 3, 25, and 60 min after the beginning stimulation. In the coagulation experiments blood samples were taken before and 3.5 h after the procedure. Cannulation of the pancreatic

Laboratory of Nervous Regulation of Endocrine Functions, Institute of Normal and Pathological Physiology, Academy of Medical Science of the USSR, Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR, A. M. Chernukh.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 76, No. 10, pp. 3-7, October, 1973. Original article submitted March 2, 1973.

TABLE 1. Insulin (in mg/g adipose tissue, after incubation for 3 h) and Sugar (in mg%) Concentrations in Blood Draining from Cat Pancreas

Statistical index	Before stimulation		After stimulation					
			3 min		25 min		60 min	
	insulin	sugar	insulin	sugar	insulin	sugar	insulin	sugar
Of lateral hypothalamus								
$n=17$ $M \pm m$ P	3,25±0,34	232±9	4,17±0,33 <0,001	242±9 <0,05	4,16±0,38 <0,01	240±10 >0,1	3,35±0,38 >0,2	252±12 >0,2
Of lateral hypothalamus in adrenalectomized cats								
$n=7$ $M \pm m$ P	3,61±0,43	167±6	5,37±0,89 <0,05	169±7 >0,5	4,77±0,67 <0,05	159±8 <0,05	3,80±0,41 >0,5	143±9 <0,02
Of ventro-medial hypothalamic nuclei								
$n=10$ $M \pm m$ P	3,38±0,46	239±12	2,42±0,30 <0,1	246±13 >0,1	3,68±0,46 >0,1	246±17 >0,1	2,43±0,32 >0,05	243±15 >0,5
Without hypothalamic stimulation								
$n=6$	I test		II test		III test		IV test	
$M \pm m$	3,58±0,24	227±11	3,50±0,24	228±12	3,63±0,25	228±12	3,66±0,25	288±12
P			>0,2	>0,5	>0,5	>0,5	>0,5	>0,5

TABLE 2. Insulin (in mg/g adipose tissue, after incubation for 3 h) and Sugar (in mg%) Concentrations in Cats' Blood after Electrical Coagulation of Lateral Hypothalamus and Ventro-Medial Hypothalamic Nuclei

Statistical index	Before coagulation		3.5 h after coagulation	
	insulin	sugar	insulin	sugar
Of lateral hypothalamus				
$n=10$ $M \pm m$ P	4,71±0,54	207±22	3,59±0,47 <0,01	158±23 <0,01
Of ventro-medial hypothalamic nuclei				
$n=6$ $M \pm m$ P	3,95±0,56	225±17	4,05±0,36 >0,5	185±13 <0,01

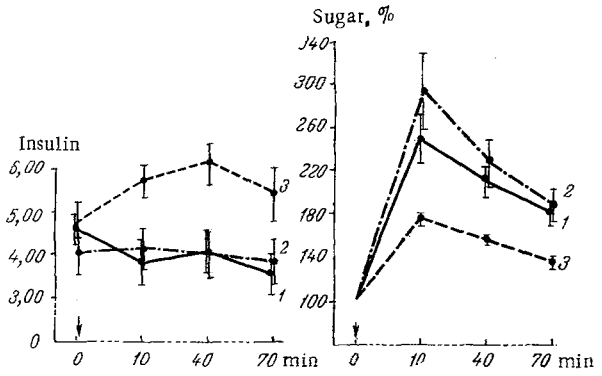

Fig. 1. Insulin and sugar concentrations in blood after glucose loading in control experiments and in experiments with coagulation of lateral hypothalamus and ventro-medial hypothalamic nuclei. Values of $M \pm \sigma$ given: 1) animals with coagulation of ventro-medial hypothalamic nuclei; 2) animals with coagulation of lateral hypothalamus; 3) animals with intact hypothalamus. Abscissa, time of taking blood samples after sugar loading (marked by arrow); ordinate: on left – insulin concentration (in mg/g adipose tissue after incubation for 3 h), on right – blood sugar concentration (in % of initial level).

vein and adrenalectomy were performed by an abdominal approach with complete local anesthesia of the operative field with trimethocaine. The glucose tolerance test was carried out by injecting 40% glucose solution (0.35 g/kg) into the femoral vein. Blood for testing was taken before and 10, 40, and 70 min after the injection of glucose. The insulin activity in the blood was determined on adipose tissue of Wistar rats [3]. The blood sugar concentration also was determined [20]. The location of the electrodes was confirmed histologically. The experimental results were subjected to statistical analysis by the difference method.

EXPERIMENTAL RESULTS

An increase in the blood insulin concentration was observed 3 and 25 min after the beginning of stimulation of the lateral hypothalamus; by 60 min the normal level of the hormone was restored (Table 1). The blood sugar was raised 3 min after the beginning of stimulation only, and any subsequent increase in the sugar concentration was not statistically significant. In samples taken at the same times from individual animals an increase in the insulin concentration could be found in conjunction with either an increase or decrease in the blood sugar concentration.

To determine whether the increase in the insulin concentration was connected with stimulation itself or with the elevation of the sugar concentration a series of experiments was carried out on adrenalectomized animals. Under these conditions stimulation of the lateral hypothalamus also led to an increase in the blood insulin concentration, although the blood sugar level was not raised but was actually lowered.

Animals with electrodes implanted into the hypothalamus but without the passage of an electric current were used as a control to these experiments. No changes were found in the blood insulin and sugar concentrations throughout the time studied.

Whereas stimulation of the lateral hypothalamus was accompanied by an increase in the insulin concentration, bilateral coagulation of this structure led after 3.5 h to a decrease in the blood insulin concentration and a simultaneous increase in the blood sugar (Table 2).

Stimulation of the ventro-medial hypothalamic nuclei (Table 1) was accompanied by a transient fall of the blood insulin level (only at the third minute). The initial insulin concentration was restored after 25 min. In these animals there was absolutely no correlation whatever between the changes in the insulin and sugar concentrations in the blood at all times studied.

Meanwhile bilateral coagulation of the ventro-medial nuclei (Table 2) caused no significant changes in the blood insulin concentration despite a marked fall of the blood sugar.

The important role of the lateral hypothalamus and ventro-medial hypothalamic nuclei was even more clearly apparent during glucose loading (Fig. 1). Injection of glucose after electrical coagulation both of the lateral hypothalamus and of the ventro-medial nuclei did not produce the discharge of insulin into the blood characteristic of intact animals. The glucose tolerance curve in animals with destructive lesions of the hypothalamus showed a sharper rise and a more protracted course than in the control animals.

These results indicate the important role of the lateral hypothalamus and the ventro-medial hypothalamic nuclei in the regulation of insulin secretion. The lateral hypothalamus stimulates, while the ventro-medial hypothalamic nuclei inhibit, insulin secretion. Several investigators [4, 9, 10, 13-15] have found that bilateral coagulation of the ventro-medial hypothalamic nuclei leads after a few days to a marked increase in the blood insulin concentration. Together with the present results these observations suggest that the effect of the lateral hypothalamus and of the ventro-medial hypothalamic nuclei on insulin secretion is reciprocal in character.

LITERATURE CITED

1. V. P. Glagolev and L. I. Tomilina, Fiziol. Zh. SSSR, No. 11, 1311 (1966).
2. B. K. Anand and S. Dua, Indian J. Med. Res., 43, 1 (1955).
3. P. M. Beigelman, Diabetes, 8, 29 (1959).
4. L. L. Bernardis and L. A. Frohman, J. Comp. Neurol., 141, 107 (1971).
5. M. C. D'Amour and A. D. Keller, Proc. Soc. Exp. Biol. (New York), 30, 1175 (1933).
6. P. M. Daniel and J. R. Henderson, J. Physiol. (London), 192, 317 (1967).
7. J. Feldman and E. Gellhorn, Endocrinology, 29, 141 (1941).
8. L. A. Frohman and L. L. Bernardis, Endocrinology, 82, 1125 (1968).
9. L. A. Frohman, L. L. Bernardis, J. I. Schnatz, et al., Am. J. Physiol., 216, 1496 (1969).
10. L. A. Frohman and L. L. Bernardis, Am. J. Physiol., 221, 1956 (1971).
11. E. Gellhorn, Acta Neuroveg. (Vienna), 9, 74 (1954).
12. E. Gellhorn, R. Cortell, and L. Feldman, Am. J. Physiol., 133, 532 (1941).
13. J. K. Goldman, J. D. Schnatz, L. L. Bernardis, et al., Metabolism, 21, 132 (1972).
14. P. W. Han and L. A. Frohman, Am. J. Physiol., 219, 1632 (1970).
15. B. B. Hustvedt and A. Lovo, Acta Physiol. Scand., 84, 29 (1972).
16. W. R. Ingram and R. W. Barris, Am. J. Physiol., 114, 555 (1936).
17. H. H. Jasper and C. A. Ajmone-Marsan, A Stereotaxic Atlas of the Diencephalon of the Cat, Ottawa (1954).
18. A. Kaneto, K. Kosaka, and R. Nakao, Endocrinology, 80, 530 (1967).
19. T. Kuzuya, J. Jap. Soc. Intern. Med., 51, 65 (1962).
20. N. Nelson, J. Biol. Chem., 153, 378 (1944).