Insulin hypoglycemia and hypothalamic hyperphagia*

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Adult female rats were subjected to bilateral lesions of varying extent in the ventromedial nuclei of the hypothalamus. On reaching asymptote, Ss were given subcutaneous injections of protamine zinc insulin, daily, for 10 days. Obesity asymptote attained by brain damage was positively correlated with judged extent of lesions, while insulin-induced superobesity was negatively correlated with hypothalamic obesity asymptote. No relationship was found between the time taken to reach hypothalamic obesity asymptote and the asymptotic weight.

The dominant mechanism in the regulation of food intake appears to be neural activity in the lateral hypothalamus, which promotes eating, while activity of the ventromedial nuclei (VMN) acts as an inhibitor of the lateral area. Releasing the inhibitory influence by lesioning the VMN bilaterally results in an organism's increasing its food intake and hence its rate of weight gain (the dynamic phase) until an obesity asymptote is reached (the static phase), when the organism eats little more than a normal animal (Brobeck, 1960).

The glucostatic theory of the regulation of food intake (Mayer, 1955) proposes that glucoreceptors in the VMN monitor the difference between arterial and venous blood-glucose levels, and that decreasing differences, indicating decreased cell utilization of glucose, constitute the adequate stimulus for activation of VMN neural elements. Recording from the VMN under conditions of food deprivation, satiation, and intravenous injection of glucose lends support to this theory (Anand, Chhina, & Singh, 1962). However, because there is still some control of food intake and weight gain in hypothalamic hyperphagics during the static phase, albeit at an obese level, it has been suggested that other factors also contribute to a regulatory influence, e.g., metabolites related to body fat deposits circulating in the blood, with receptors located elsewhere (Mayer, 1955; Teitelbaum, 1961).

It is conceivable that in the foregoing studies there may have been some elements of the VMN remaining after lesioning, and that with complete destruction of the VMN the animals would have overeaten and gained weight indefinitely. While there are data to show a positive correlation between the extent of lateral hypothalamic destruction and degree of aphagia (Morgane, 1961), there do not appear to have been any systematic studies to ascertain if there is a direct correlation between the extent of VMN lesions and obesity levels reached, but there are scattered reports indicating that this may be the case. For example, Brobeck (1946) reports, "There are certain animals, however, which never enter a true static phase because they continue to over-eat and gain weight almost indefinitely." The writer has observed the same thing.

Hoebel & Teitelbaum (1966) studied weight regulation in normal and hypothalamic hyperphagic rats with a degree of obesity previously induced by insulin. Unoperated Ss surviving injections twice daily for 2 weeks doubled their food intake and gained on the average 58 g. With cessation of insulin treatment they became anorectic until body weight dropped to normal levels. Other rats that gained 210 g in 4 months with insulin treatment and were then subjected to VMN lesions gained very little additional weight. Hypothalamic obese Ss force-fed to super obesity ate less than normal animals until their weight returned to the former hypothalamic obesity levels. The investigators concluded that some correlate of body weight controlled daily food intake and that obesity resulting from VMN lesions depended upon initial weight level.

The purpose of the present study was to test the hypothesis that in hypothalamic hyperphagics that have reached the static phase, any further weight gain induced by insulin treatment would be inversely proportional to the hypothalamic obesity asymptote and, as a corollary, to the extent of the lesions.

SUBJECTS

Forty-five female Long-Evans hooded rats, varying in weight from 220 to 350 g at the commencement of the study, were divided into three groups, equated for weight.

LESIONING

Under pentobarbital sodium anesthesia, bilateral lesions were created stereotaxically in the ventromedial nuclei of the hypothalamus (DeGroot coordinates A 5.8, L 0.7, V −2.5) as follows: Group 1, 1.0 m A, 20 sec; Group 2, 1.5 mA, 20 sec; and Group 3, 2.0 mA, 20 sec.

PROCEDURES

Ss were weighed daily. The normal rate of weight gain for this colony is from 1 to 2 g per day; Ss which did not show a weight gain of at least 2.5 g per day were discarded. The remainder, on reaching an obesity asymptote (defined as no weight gain over a period of 10 days) were then subjected to subcutaneous injections of protamine zinc insulin over a 10-day period. S was given two units the first day,

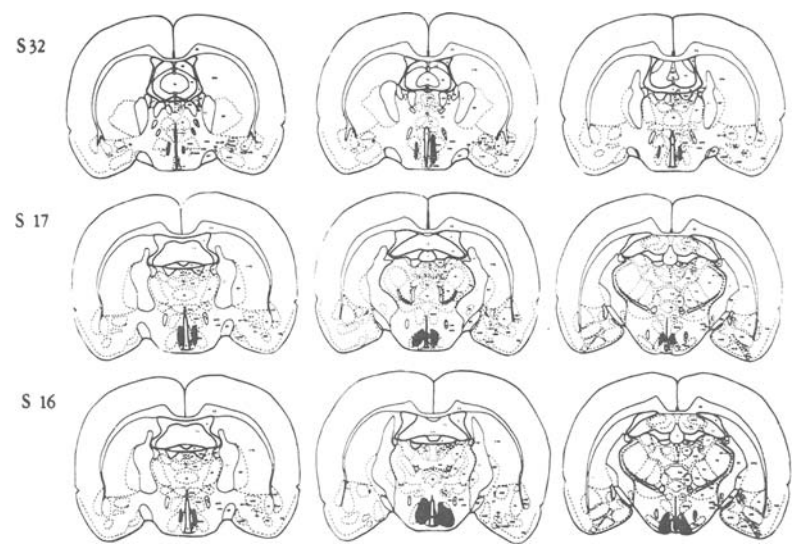

Fig. 1. Representative lesions showing farthest extent anterior (left), greatest extent (middle), and farthest extent posterior (right).

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Table 1
Weight Gain Under Insulin Treatment Following Hypothalamic Hyperphagia

Subject Number (1)	Weight at Operation (2)	Bilateral Lesions, 20 Sec (3)	Days to Asymptote (4)	Mean Daily Weight Gain Grams (5)	Obesity Asymptote Grams (6)	Rank Order Judged Size of Lesions (7)	Weight Gain Under Insulin (8)
12	280	2.0 mA	77	5.06	670	5	13
44	252	2.0 mA	77	5.21	653	6	10
29	232	2.0 mA	70	5.80	638	9	11
16	270	2.0 mA	63	5.68	628	2	8
41	351	1.0 mA	93	2.74	605	8	13
26	302	2.0 mA	70	4.26	600	1	10
28	285	2.0 mA	70	4.49	598	3	11
39	320	1.5 mA	77	3.38	580	14	12
13	230	2.0 mA	56	6.13	573	11	12
43	242	2.0 mA	61	5.19	560	18	10
7	282	1.5 mA	63	3.81	522	16	14
17	310	1.0 mA	82	2.50	515	10	14
35	265	1.0 mA	84	2.98	515	7	14
24	208	1.5 mA	88	3.33	498	4	18
9	208	1.5 mA	87	3.23	488	12	12
22	238	1.5 mA	56	3.96	460	19	16
3	265	1.0 mA	62	2.51	420	13	20
34	223	1.0 mA	74	2.65	420	20	22
32	242	1.0 mA	68	2.60	418	15	22
5	210	1.0 mA	70	2.64	395	17	18

and the dosage was increased by two units daily until S was receiving 12 units per day, with this dosage maintained for 5 days, i.e., a total of 90 units over 10 days. After insulin treatment Ss were left for 3 to 4 weeks before being sacrificed.

HISTOLOGY

Ss were perfused through the heart with isotonic saline, followed by 5% formalin. Brains were then frozen and sectioned at 40 microns, every 10th section being stained with luxol-fast blue and neutral red. The sections were inspected and brains ranked in order of extent of lesions.

RESULTS AND DISCUSSION

Of the 45 animals lesioned, 36 met the criterion for hyperphagia. Of these, three died of unknown causes and 13 died of insulin shock. This is a smaller loss than that experienced by Hoebel and Teitelbaum and is probably due to the gradual increase in dosage and the shorter period of insulin treatment, i.e., 10 vs 14 days.

The data for the remaining 20 animals are shown in Table 1.

The correlation between obesity asymptote (Table 1, Column 6) and weight gain under insulin treatment (Column 8) was $-.84$ ($p < .01$), while the correlation between daily weight gain (Column 5) and gain under insulin treatment (Column 8) was $-.67$ ($p < .01$). Both correlations are given as, of course, Ss varied in the number of days taken to reach a weight plateau. There was, in fact, no relationship between the number of days to obesity asymptote and asymptotic weight ($r = .12$, n.s.).

Judged extent of lesions and obesity asymptote correlated .66 ($p < .01$). Representative lesions are illustrated in Fig. 1.

Granted that Ss in this study received a somewhat shorter period of insulin treatment than Hoebel and Teitelbaum's Ss, nevertheless it may be seen from Table 1, Column 8, that, on reaching obesity asymptote, weight gain under insulin is considerably less than could be expected (Hoebel & Teitelbaum, 1966) if obesity level, and thus extent of VMN lesions, were not a critical factor.

The data indicate that the amount of superobesity that can be induced by insulin hypoglycemia in the static phase is inversely proportional to hyperphagic weight asymptote and proportional to the extent of VMN tissue destroyed. Similarly, the obesity plateau reached is proportional to the extent of VMN tissue destruction. This strongly suggests that with total destruction of the VMN an organism would continue to gain weight throughout its life span. A study is currently in progress to ascertain this. If so, it would point to the VMN as the ultimate determinant of weight level and not some other system located elsewhere.

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