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WEIGHT REGULATION IN NORMAL AND HYPOTHALAMIC HYPERPHAGIC RATS[1]

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To study weight regulation in normal and brain-damaged rats, obesity was produced with insulin. Ss surviving insulin injections twice daily for 2 wk. doubled their food intake and gained 58 gm. When treatment stopped, Ss were anorectic until body weight fell to normal. In rats induced to gain up to 210 gm. by 4 mo. of insulin treatment, destruction of the ventromedial hypothalamic "satiety center" caused little overeating and weight gain; hypothalamic obese Ss force-fed to induce "super-obesity" ate less than normal until their weight returned to its "normal" obese level. Some stimulus correlated with obesity acts on the ventromedial hypothalamus to inhibit feeding in normal rats and, at higher weight levels, in hypothalamic hyperphagic rats.

After destruction of tissue in the ventromedial region of the hypothalamus, rats gain weight rapidly until they reach a high, relatively stable weight plateau (Hetherington & Ranson, 1940). Metabolic disturbances do not account for the obesity in these animals; they become obese because they eat too much (Brobeck, Tepperman, & Long, 1943). Hypothalamic rats overeat only until they become obese; when obese, food intake returns almost to normal. If these animals are forced to lose weight by food deprivation, upon return of food they immediately overeat until they reattain their former level of obesity (Brobeck et al., 1943).

The damaged ventromedial hypothalamus fails to inhibit feeding; apparently it does not respond adequately to satiety signals (Anand & Brobeck, 1951). What are the satiety signals? A number have been hypothesized. They fall into two classes: stimuli which influence food intake from day to day, such as blood glucose (Mayer, 1955), body temperature (Brobeck, 1960; Hamilton, 1963), or osmotic factors (Mook, 1963; Smith & Duffy, 1957); and stimuli with a long-term influence, such as body fat (Mayer, 1955), or an unidentified metabolite related to body fat (Hervey, 1957; Kennedy, 1953; Teitelbaum, 1961). Most research has been done on the first class of stimuli, those for which a deficit can be corrected within a meal or a day. As a result, current thought has emphasized possible deficits in day-to-day regulation of food intake that might produce obesity through cumulative errors in daily feeding. It is usually assumed, therefore, that food intake controls body weight.

In the present paper, we reverse the emphasis. We ask: does some correlate of body weight control daily food intake? If so, it should be possible to control food intake by experimentally altering body weight.

METHODS

Short-Term Insulin Treatment

To induce overeating and weight gain in normal rats without brain damage, we used periodic injections of long acting insulin (Mackay, Callaway, & Barnes, 1940). Protamine zinc insulin was injected intraperitoneally twice daily to lower blood sugar and produce overeating.

Measurements of body weight and ad-lib food (powdered Purina chow) and water intake were taken on 23 Sherman female rats, housed at 80 ± 2° F. during a 2-wk. control period, 2 wk. of insulin treatment, and a 2-wk. recovery period. The insulin dose was 8 units per injection for the first 3 days, then 12 units thereafter.

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TABLE 1

EFFECT OF INSULIN INJECTIONS ON FOOD INTAKE AND BODY WEIGHT

Procedure	N	Mean daily food intake (in grams)		Body weight (in grams)					
				Mean daily change		Starting weight		Final weight[b]	
		M	Range	M	Range	M	Range	M	Range
Control: Weeks 0–2	23	16	11–21	1	0–2	253	220–285	266	240–299
Insulin: Weeks 2–4	11	29	23–37	4	2–6	271	250–290	330	309–353
Recovery: Weeks 4–6[a]	11	13	7–15	−3	−(2–6)	330	309–353	284	270–306

[a] To show the severe anorexia which caused weight to fall sharply during first few days, mean values are given for each of the first 7 days after insulin treatment stopped—mean daily food intake: 3, 8, 14, 11, 14, 14, 15; mean daily body weight change: −22, −3, −3, −4, 0, +2.

[b] Ranges of total changes in body weight for control, insulin, and recovery procedures were 5 to 35, 31 to 80, and −60 to −29, respectively.

Long-Term Insulin Treatment

In an attempt to produce as much weight gain as possible with the insulin technique, rats were given insulin every 12 hr. for as long as 4 mo. In this experiment, 33 female Wistar rats, kept at 65 ± 5° F., received 2–4 units of protamine zinc insulin under the skin of the back at each injection.[2] It was difficult to maintain a steady weight gain without causing lethal hypoglycemia. When symptoms of hypoglycemia appeared, such as stuporousness or urine on the undercoat, the injections were abated until *S* recovered.

Hypothalamic Lesions in Prior Obese Rats

In three rats which survived the long-term insulin treatment, bilateral ventromedial hypothalamic lesions were produced by 1 μa. dc passed for 30 sec. through a nichrome anode placed perpendicular to the skull, 1.5 mm. posterior to the bregma, .75 mm. lateral to the midsagittal suture, and .5 mm. above the base of the brain.

Force-Feeding Hypothalamic Obese Rats

In the final experiment, ventromedial hypothalamic lesions were made in six Sherman female rats of normal weight; in three, a nichrome anode was used, and in the other three, platinum. After the operation, all *S*s were allowed to reach a stable obese weight plateau (defined as 1 wk. without a net weight gain). Then they were force-fed to cause additional obesity. The diet (Cohn & Joseph, 1959) was mixed to the consistency of honey and mechanically pressed through a French 8 catheter inserted into the rat's stomach. Force-feedings occurred at 10 A.M. and 5 P.M. on weekdays, and were gradually increased from 5 cc at the beginning to 15 cc by the second week.

[2] The long-term insulin experiment was carried out in the winter of 1956–57 in the laboratories of the Harvard University Psychology Department; the short-term experiment was performed in the summer of 1962 at the University of Pennsylvania. The room temperature represents that prevailing in the available quarters. Room temperature, site of drug injection, and strain of rat probably combine to affect the dose of insulin necessary to produce overeating.

RESULTS AND DISCUSSION

Obesity Induced with Insulin

All rats given protamine zinc insulin increased their food intake, presumably in response to hypoglycemia. In the short-term experiment, 11 of the 23 rats survived by consuming nearly twice their normal daily food intake. Their average weight gain was 58 gm. during the 2 wk. of insulin treatment, as compared to 13 gm. during the previous 2 wk. In the long-term experiment, three animals survived. Their median weight gain was 169 gm., with a maximum gain of 210 gm. in 4 mo. The median weight gain for all 33 animals, including those that died, was 95 gm.

This confirms the original observations of Mackay et al. (1940) and extends their results to indicate that marked obesity as well as overeating can be produced with insulin.

Feeding Inhibited during Obesity

Every rat taken off the insulin regime after 2 wk. ate subnormal amounts of food and lost weight precipitously. On the average they were anorectic for 4 days and lost 46 gm., which was 79% of the weight previously gained under the influence of insulin (Table 1).

In Figure 1 are shown the data for one

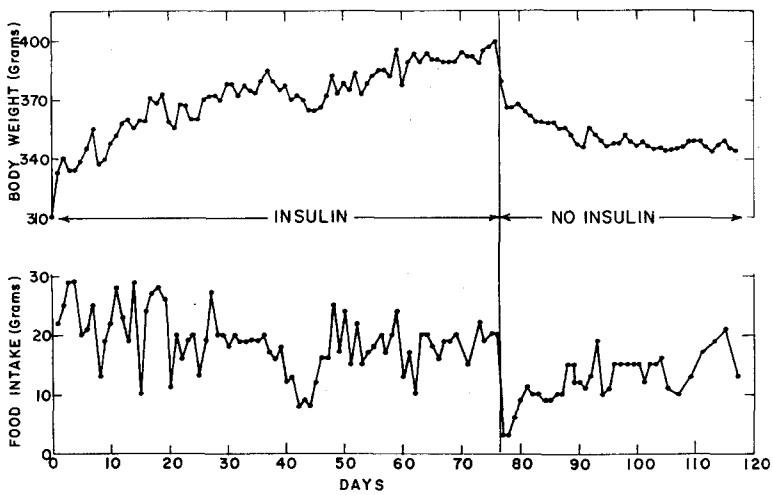

FIG. 1. Effect of insulin injections on daily food intake and body weight.

rat which was abruptly taken off the long-term insulin regime after gaining 90 gm. in 2½ mo. It voluntarily diminished food intake for 11 days. On each of the first 2 days it ate only 3 gm. of food; then, as its body weight fell to normal, its feeding gradually increased to normal (Figure 1).

A related experiment has been reported by Cohn and Joseph (1962). They caused rats to gain weight by 3 mo. of force-feeding, then found that ad-lib food intakes were subsequently inhibited until weight returned to nearly normal levels. Recently, Steinbaum and Miller (1965) reported a similar phenomenon in rats induced to overeat and become obese by lateral hypothalamic stimulation. Our results agree and suggest that some factor correlated with body weight can exert a regulatory control over food intake in animals with an intact central nervous system.

Hypothalamic Hyperphagia Inhibited by Prior Obesity

The previous experiment demonstrated that, in the normal rat, obesity curbs food intake until excess weight is lost. Does obesity also affect hypothalamic hyperphagia? Figure 2 shows the day-to-day postoperative record of the rat which was

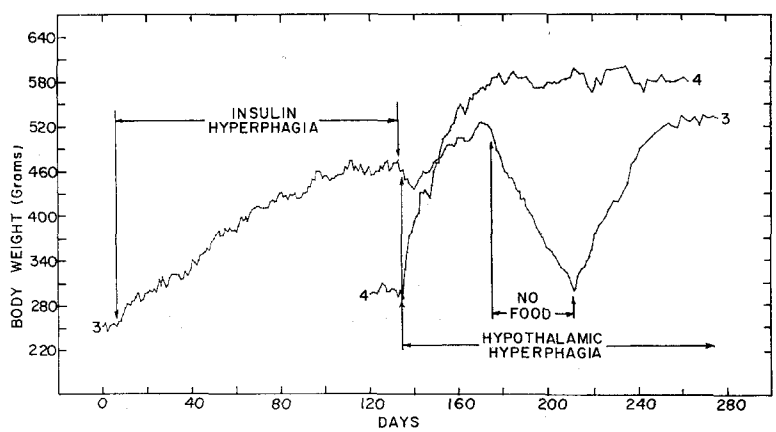

FIG. 2. Gradual, slight gain in weight following destruction of the ventromedial hypothalamus in a preoperatively obese rat is contrasted with the rapid, large weight gain in the same animal (3) or another (4) when they start at a normal body weight.

TABLE 2

INSULIN-INDUCED OBESITY AND ITS EFFECT ON WEIGHT GAIN (IN GRAMS) FOLLOWING VENTROMEDIAL HYPOTHALAMIC LESIONS

S	Starting weight	Insulin hyperphagia		Weight when operated	Hypothalamic hyperphagia			Obese plateau (in grams)
		Days on insulin	Weight gain		Days ad lib	Weight gain	Mean rate of gain	
3	250	128	210	460	41	57	1.4	517
1	256	122	174	430	48	58	1.2	488
2	233	122	122	355	68	270	4.0	625
7	312	34	53	365	53	257	4.8	622
4				301	50	291	5.8	592

most obese due to insulin, compared with the record of one which received no insulin treatment at all. Note that although these two rats received lesions at the same time, the preoperative obese rat (No. 3) gained relatively little weight (57 gm.) before reaching a weight plateau. Rat No. 4, on the other hand, nearly doubled its normal (300 gm.) body weight. In addition, the preoperatively obese rat later served as its own control. From its obese plateau, it was starved to a normal weight level; when given food again, the animal rapidly reattained its obese level, gaining 230 gm. Therefore, the lesion had been fully effective, but preoperative obesity had limited the animal's weight gain.

Table 2 summarizes the measurements taken from all rats in this experiment. In general, the more a rat weighed before operation, the less it gained afterwards. The less it gained, the slower was its rate of gain. Obese animals, weighing over 400 gm. before operation, gained only 1 gm. per day afterwards; animals which were normal or only slightly obese to start with gained 4–6 gm. per day. Therefore, the effect of ventromedial hypothalamic lesions depended on the weight level. This suggests that the obese plateau is normal for the hyperphagic rat. If a rat were made superobese the animal with ventromedial damage, like the normal rat, should actually restrict its food intake and lose weight to return to its normal obese weight level.

Weight Control in Hypothalamic Obese Rats

When six rats had gained at least 200 gm. following ventromedial lesions and

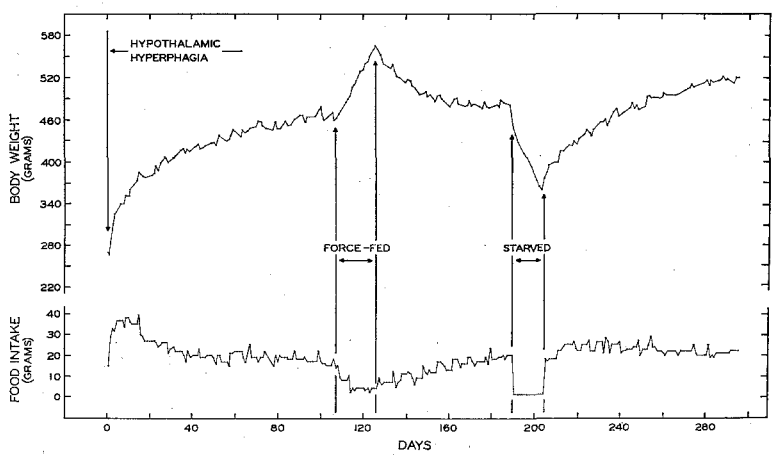

FIG. 3. Effects of force-feeding and starvation on food intake and body weight of a rat with ventromedial hypothalamic lesions.

reached their weight plateaus, they were tube-fed daily until they gained an additional 100 gm. Three died by choking during force-feeding. The other three all behaved as illustrated by the data for one of them, shown in Figure 3. Note that voluntary food intake was inhibited, not only during the period of forced feeding, but for many days afterward. Like normal rats made obese, they ate less until their weight returned approximately to normal. For them, however, normal represented their obese weight plateau. Also, when their food was withheld and they lost weight, they subsequently overate and regained that weight.

We conclude, therefore, that some stimulus correlated with obesity controls food intake, probably by activating cells in the ventromedial hypothalamus. When a number of these cells are destroyed, a higher weight level is required to inhibit food intake, and the animal overeats until it reaches that level. Like normals, hyperphagic animals regulate their body weight, but at an obese level.

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