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VARIABILITY OF BODY FAT IN HYPERPHAGIC RATS¶

Although hypothalamic hyperphagia was described and named 25 years ago,[1] the nature of this phenomenon is still not clear. Presumably it is brought about by some deficiency in the systems controlling food intake. What this deficiency might be was explicitly considered by Kennedy[3] in the paper where he suggested that the body regulates its fat content. He had confirmed the observation of Brobeck, Tepperman, and Long[1] that one of the characteristics of this hyperphagia is that it tends to disappear as the animal becomes obese. Kennedy decided that the obesity more or less directly antagonizes the hyperphagia, and wrote as follows: "The only invariable index of the loss of hypothalamic function is the level of obesity which develops . . . Once the level of fatness is determined, it is actively maintained . . . The only disturbance of appetite which ever does develop, in fact, is the transient increase incidental to getting fat."[3]

His view of these phenomena has been accepted into the literature as the "lipostatic" hypothesis of control of food intake. According to this hypothesis, the hypothalamus adjusts food intake so as to regulate the size of fat depots. After ventromedial lesions the food intake is increased because the control system is given a new set point that requires a greater amount of fat in the body. When this greater amount has been acquired, the system functions to maintain energy balance as before. In subscribing to this hypothesis, Teitelbaum[4] has written, ". . . then one might say that the hyperphagic rat overeats to get fat. Once it is fat, it no longer overeats" (p. 49).

Some animals with hypothalamic lesions become more obese than other animals, presumably because the effectiveness of ventromedial lesions varies from one animal to another; in any given animal, however, the effective-

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ness is presumed to be constant. Kennedy[8] proposed that it can be measured by the degree of fatness that develops, because fatness is an index of how much the set point has been shifted. If this be true, then each animal with ventromedial lesions (and every other animal, for that matter) should have some one "preferred" degree of fatness, and it should be possible to discover what this level is. In considering this conclusion, however, along with data of Lundbaek and Stevenson,[5] we came to question whether each animal has its own characteristic fatness. Lundbaek and Stevenson found that the rate of weight gain of hyperphagic rats is a function of the composition of the diet; gain is greatest on a high-fat diet, and less on a high-carbohydrate diet. Their data imply a very definite possibility that the final body weight and degree of fatness might also be affected by the composition of the diet, and not alone by effectiveness of the lesions. If the lipostasis idea were correct, any change in composition of the diet would not alter the ultimate obesity but merely the rate of weight gain toward the set point maximum.

Consequently, we decided upon a simple test of the stated conclusion. We fed hyperphagic rats on a conventional, high-carbohydrate diet until they had attained a stable or "static" obesity. We then added fat to the diet and thus induced a higher level of weight and fatness. While our early experiments were in progress, Corbit and Stellar[6] performed a similar experiment using Purina pellets and then a high-fat diet. Our results agree with theirs, but we have in addition determined the fat content of the carcasses of many of our rats so that we are able to specify how much fat was gained during the high-fat feeding. We also have data on food intake that can be expressed in grams, kilocalories, or as bulk in milliliters per day.

METHODS

Two sets of experiments were performed, as follows:

1. In Tapei, Taiwan, 1962-63: Female rats of the Sprague-Dawley strain were used; in October when they weighed something less than 200 gr. they were given bilateral lesions of the ventromedial hypothalamus with an electrolytic current of 2 mA. for 15 sec. These lesions were similar to those described earlier.[1] The rats were fed ad libitum on a commercial animal feed in powdered form and of 60-70% carbohydrate content by weight, until February 6 when one half of the rats with lesions and their controls were shifted to the same diet with peanut oil added, 20% by weight (Fig. 1). Ad libitum feeding was then continued unchanged until autopsy on or just after April 29. Temperature of the animal room was 25-28°C; drinking water was available ad lib.

2. In Coatesville, Pennsylvania: In May, 1965, male rats of the Sprague-Dawley strain weighing between 300 and 350 gr. were given bilateral lesions of the ventromedial hypothalamus with a current of 2 mA. for 15

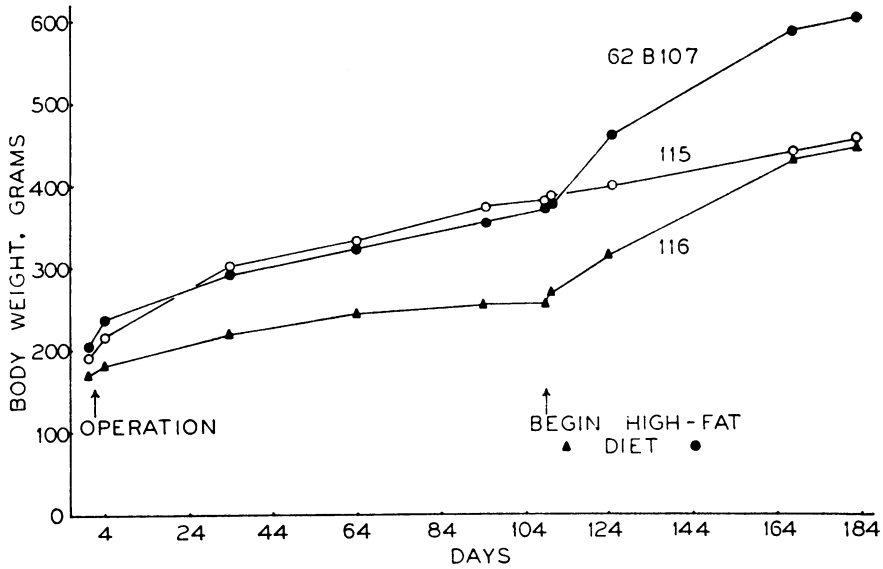

FIG. 1. Weight gain of rats with ventromedial hypothalamic lesions, rats 107 and 116, before and after a high fat diet was given. Rat 115 was given commercial, high-carbohydrate diet continuously. (Taipei experiments.)

sec. They were fed on a variety of schedules incident to psychological testing until July 21, when they were placed continuously on a powdered commercial chow with daily recording of food intake (Fig. 2). On November 3 they were shifted to a chow-lard diet containing added lard, 30% by weight, and on January 29, 1966, they were returned to the powdered chow. Room temperature was 25°C.; drinking water was ad lib.

Autopsy data. Only the animals used in Taipei were analyzed after autopsy. Each gastrointestinal tract was opened, emptied, and returned to the carcass. The entire carcass was then dried at 95°C. to a constant weight, and extracted with petroleum ether according to the technique used by Han, *et al.*[7] Weight of fat in the body was calculated for each rat.

We tried to estimate the gain in fat content in the following way: On Figure 3 are plotted the body weight and the weight of body fat of all rats of the Taipei series, as determined by carcass analysis. The solid lines are drawn so as to include all data; the line of dashes is the regression of the data of Montemurro and Stevenson.[8] The relationship shown on this graph was used to estimate the fat content of each rat's body at the time it was shifted from the commercial to the high-fat diet. That is to say, the autopsy data from all rats were used for estimation of the fat content of living rats by interpolation among the data of Figure 3. The resulting values are shown in Figure 4, where the open triangle is the estimated relationship in the living animal, and the solid triangle is the actual relationship found later by carcass analysis.

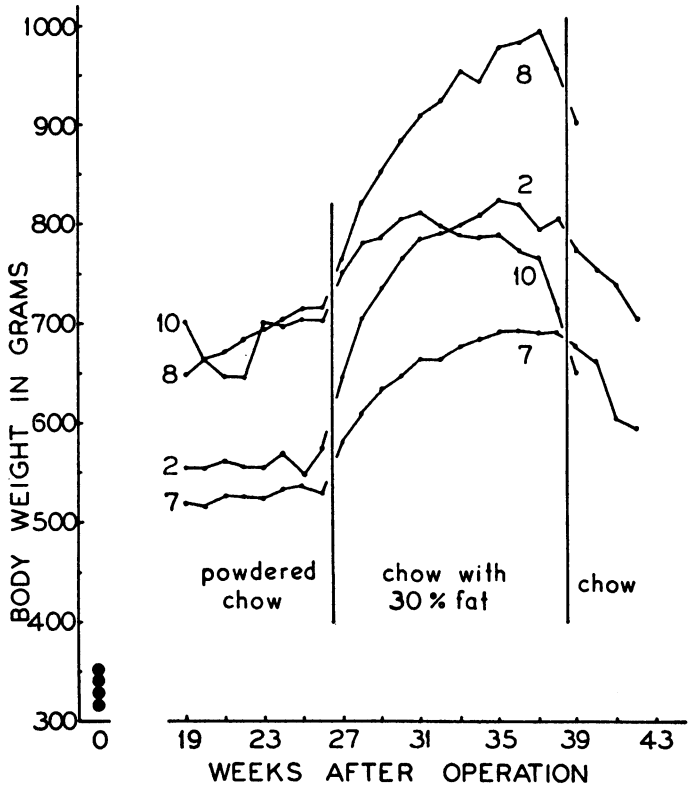

FIG. 2. Body weight of four animals with ventromedial lesions when high-fat diet was substituted for powdered chow. (Coatesville experiments.)

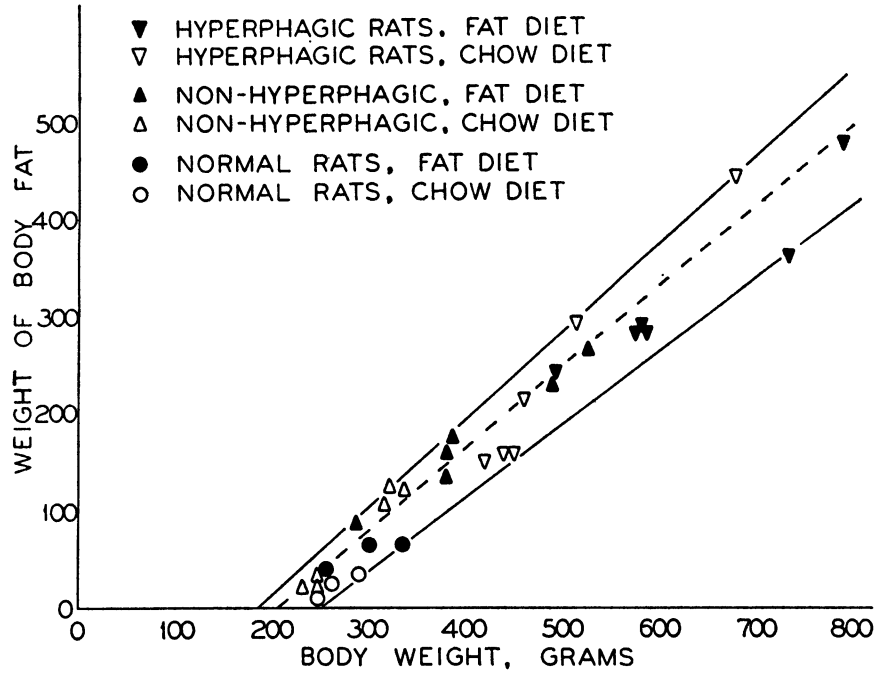

FIG. 3. Weight of fat in body of all animals of Taipei series as determined by analysis of carcass, plotted against body weight.

RESULTS

The graph in Figure 4 indicates that body-fat content increased by about 100% in many of the rats as a result of the fat feeding. Some of the "non-hyperphagic" rats showed an even greater percentage change in fat content.

There was no important difference in the results of the two experiments; in both of them the animals became obese on the commercial, high-carbohydrate diet, and then attained a second stage of obesity when shifted to the high-fat diet (Figs. 1 and 2). Because time was limited for the Taipei experiment, some of the animals had not reached a completely stable weight on the high-carbohydrate diet by the time it was necessary to transfer them to the high-fat diet (Fig. 1). On this point the Coatesville experiments are more conclusive, since there is little question that three of the four rats had been stabilized in weight and fat content. They had showed no significant changes in a period lasting 42 days just prior to the shift to the high-fat diet (Fig. 2). With this stability as a background, their rapid gain in weight during the fat feeding was all the more impressive.

An equally impressive result, however, was obtained with one set of rats in the Taipei experiments: those animals that had lesions but no obvious hyperphagia when fed the commercial diet. Their data are given in Table 1

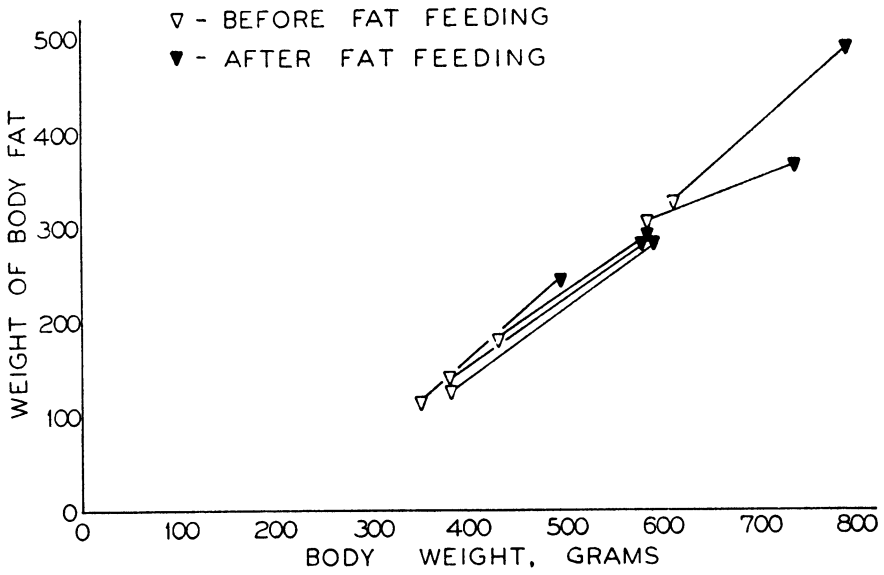

FIG. 4. Estimated gain in fat content for six animals when they were shifted from high-carbohydrate to high-fat diet. Open triangles are points taken by interpolation from Fig. 3; filled triangles are autopsy data.

TABLE 1. WEIGHT GAIN OF NONHYPERPHAGIC RATS

Rat no.	*Op. 1962*	*Body wt. (grams)*				*Fat content (grams)*			*Wt. gain (grams)*	
		Op.	*Feb. 5*	*Mar. 22*	*Apr. 29*	*Feb. 5*	*Mar. 22*	*Apr. 29*	*12/22-2/5 (45 days)*	*2/6-3/22 (45 days)*
102	Oct. 9	184	262	339	380	40	100	161	12	77
104	Oct. 9	173	304	459	490	70	200	232	7	155
116	Oct. 18	180	259	353	383	35	115	174	19	94
123	Oct. 23	180	218	280	287	(?) 0	50	87	11	62
130	Oct. 26	226	271	351	382	45	110	137	13	80

and illustrated by the record of rat 116 in Figure 1. These five animals had gained only about 100 gr. during the four months of feeding on the commercial diet, and in the 45 days prior to the dietary change their maximal gain was 19 gr. (rat 116). During the first 45 days on the high-fat diet their gains were 62, 77, 80, 94 and 155 gr. respectively. Subsequent analysis of carcass fat, together with data of Hetherington and Weil[9] and those of Montemurro and Stevenson,[8] suggest that all of this gain was fat.

DISCUSSION

These data show that there is no one "degree of obesity" for any given set of lesions of the ventromedial hypothalamus, nor is there any one "preferred" weight or fat content. Rather, there must be a set of preferred weights, one for each diet on which an animal is able to live. For nonpalatable diets the weight at which stability occurs is relatively low,[10,11] whereas for diets containing increasing concentrations of fat or oil it is progressively greater.[6] Contrary to the conclusion of Kennedy[2] that food intake of these rats is controlled by body-fat content, the data seem to show rather that body-fat content is controlled by food intake, and that the body can store whatever amount of energy it is able to eat. Animals with ventromedial lesions seem to have little concern about how much fat they have stored, and may either double their fat content or cut it in half as the composition of the diet is varied.

Although the food intake expressed as calories, for both hyperphagic and nonhyperphagic animals with lesions, increased by about 50% when the animals were shifted to the high-fat diet (Table 2), the intake in grams or by bulk in milliliters showed no significant change. These data suggest that the animals were indifferent to the caloric value of the food, and that they ate a constant weight or volume independently of whether or not fat was present.

The data do not seem to be complicated by any question of either palatability or "finickiness."[12] Our experience with animals with ventromedial lesions, and also with animals with lateral hypothalamic lesions, suggests that finickiness is a sign of injury to the lateral feeding system rather than a part of the medial syndrome. A maximal finickiness is shown by animals with the lateral lesions; these animals are so finicky that for a time no food is acceptable to them. As they begin to recover from the operation, they first of all eat highly palatable foods including moistened, chocolate chip cookies,[13] yet even after recovery of spontaneous feeding they are notably finicky. By contrast, Graff and Stellar[12] found that animals with ventromedial lesions do not necessarily show this phenomenon. We would like to add, however, that some rats with ventromedial lesions in their immedi-

TABLE 2. AVERAGE FOOD INTAKE PER DAY

	HYPERPHAGIC		*NONHYPERPHAGIC*		*CONTROL*	
	Group A	*Group B*	*Group C*	*Group D*	*Group E*	*Group F*
Period I (Jan. 21-Feb. 5)						
Grams	22.3 ± 4.1	21.3 ± 1.8	15.3 ± 2.3	15.8 ± 0.9	16.3 ± 2.2	16.9 ± 2.9
Vol. (ml.)	18.7	18.0	12.9	13.3	13.7	14.2
Kcal	89.4	85.5	61.3	63.0	65.2	67.7
Period II (Feb. 6-Feb. 21)						
Fat						
Grams	24.9 ± 3.4		18.2 ± 3.1		14.5 ± 1.6	
Vol. (ml.)	19.3		14.5		11.6	
Kcal	124.6		90.8		72.5	
Nonfat						
Grams		20.1 ± 3.5		18.3 ± 2.0		17.0 ± 0.6
Vol. (ml.)		16.9		15.4		14.5
Kcal		80.1		73.3		68.0
Period III (April 4-April 19)						
Fat						
Grams	18.0 ± 2.4		15.1 ± 1.7		12.9 ± 2.0	
Vol. (ml.)	14.4		12.0		10.4	
Kcal	90.1		75.3		64.5	
Nonfat						
Grams		19.1 ± 3.4		18.3 ± 2.3		15.1 ± 0.5
Vol. (ml.)		16.0		15.4		12.7
Kcal		76.4		73.2		60.4

ately postoperative period behave something like animals with lateral lesions. We have observed rats with ventromedial lesions that did not eat for a few days after operation, and where hyperphagia became evident only at a later time. Kennedy noted[10] that there is no invariant correlation between hyperphagia seen immediately after operation and the ultimate degree of obesity (cf. Fig. 5). Our interpretation of these data is that the initial lesion is larger than the permanent one. Consequently, certain animals show greater hyperphagia initially than later because in the beginning the medial or satiety system is incapacitated by an injury from which it later recovers. In the same way, certain animals with ventromedial operations fail to eat at first because the lesions are large enough to involve temporarily the lateral system. It may be that the lateral system is not confined to a lateral position, but is spread more widely through the hypothalamus than is generally recognized. We believe that most lateral lesions do not completely destroy the lateral system; and we propose also that most medial lesions partially injure the lateral system, at least temporarily, and thus may or may not lead to the phenomenon known as finickiness.

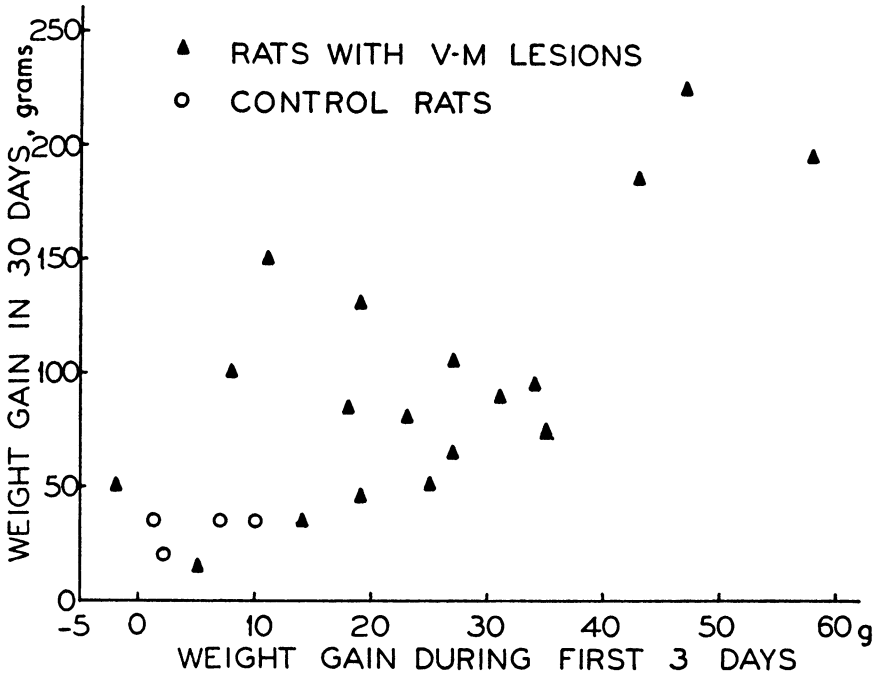

FIG. 5. Weight gain in 30 days plotted against gain in first three days after operation, showing general correlation with exceptions both above and below the average values.

In conclusion, if there is in normal animals a mechanism for regulation of fat content of the body, our data suggest to us that in animals with ventromedial lesions this mechanism no longer functions. The animals seem incapable of preserving any one fat content. The original observation that hyperphagia tends to decrease as the animals gain weight remains a mystery. It is not correlated in any quantitative sense with total body weight, total weight gain, or bodily fat content.

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