SENSORY CONTROL OF HYPOTHALAMIC HYPERPHAGIA[1]

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A number of recent experiments have focused attention on the hyperphagia (overeating) and the obesity produced by hypothalamic lesions. As a result, several important points are now firmly established. (*a*) The obesity is not due to damage to the pituitary (7, 16). (*b*) The effective lesions are bilateral, in the vicinity of the ventromedial nuclei of the hypothalamus (4, 8). (*c*) These lesions result in extremely voracious eating and an increase in food intake to about two to three times the normal food intake (4). (*d*) There seems to be no major impairment of metabolic processes as a direct result of the lesions (4, 6, 20, 21), and the obesity which develops is due primarily to the increased food intake (4, 5).

The problem which remains is: What is the mechanism underlying this increase in food intake? The overeating which results from ventromedial hypothalamic lesions may be considered a release phenomenon. Release phenomena have been explained in terms of an increased level of neural activity in an area which has been released from the inhibitory influence of a different area that has been damaged (19). Thus, the exaggerated eating behavior in hypothalamic hyperphagia may be considered to be due to the destruction of an area of the nervous system which normally acts to inhibit eating behavior.

Is it possible to specify this release in more concrete terms? One possible way of doing this is to think of the heightened activity in the nervous system as resulting from a heightened reactivity to certain stimulus aspects of the environment. According to this hypothesis, it would be predicted that in hypothalamic hyperphagia there is a heightened reactivity to certain stimuli provided by the diet, such as its taste and texture.

An alternative way of explaining the exaggerated food intake may be to postulate a derangement of the mechanism for maintaining caloric intake appropriate to energy expenditures, such that the caloric intake far exceeds the energy needs of the animal and it becomes very obese.

It will be the purpose of the present experiment, then, to investigate these two possibilities: (*a*) that hyperphagic rats are hyperreactive to sensory stimuli provided by the diet, and (*b*) that their ability to regulate the intake of calories is deranged.

METHOD

Animals

The 40 animals used in these experiments were adult female rats, 9 to 12 months old, descendants of the Lashley strain, ranging in preoperative weight from 230 to 270 gm. The animals were housed individually in small living cages with wire-mesh flooring.

Measurements

Daily measurements of weight, water intake, and food intake were taken. In each experiment, the intake of a standard powdered diet (Purina Laboratory Chow Meal) was measured for a five-day control period and compared with the intake of the experimental diet over a five-day period. Except in the first experiment, the rats were allowed a two-day acclimatization period on each diet before the five-day testing period.

Hypothalamic Lesions

Bilateral electrolytic lesions were made in the vicinity of the ventromedial nuclei of the hypothalamus with the aid of a modified version of the Horsley-Clarke stereotaxic instrument. To facilitate fixing the animals into the ear bars of the instrument, the ears were slit and the meatus exposed under Nembutal anesthetic. With the skull exposed and the animal fixed, the bregma, the intersection of the longitudinal and the frontal-parietal sutures, was located in terms of the stereotaxic coordinates, and was used as a reference point to determine the site of the lesion. All lesions were made at a depth of 9 mm. below the cortex,

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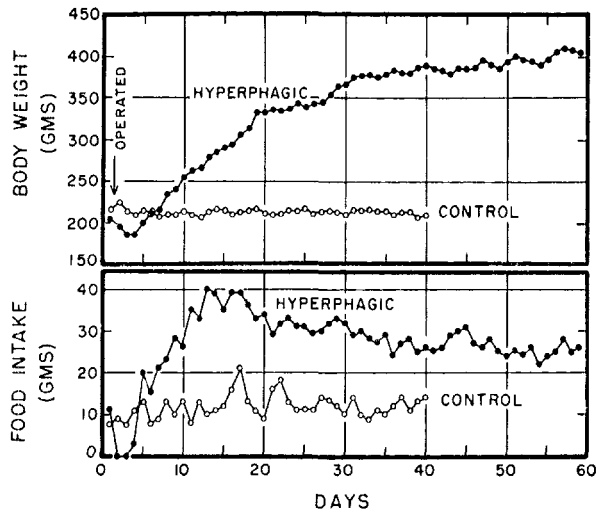

FIG. 1. Postoperative body weight and daily food intake of a typical operated animal compared to that of a normal unoperated control animal.

3 mm. posterior to the bregma, and 1 mm. on each side of the mid-line. A platinum-iridium anode, completely insulated by glass except for ½ mm. at the tip, was used to pass a direct current of 2 milliamperes for 20 sec. The circuit was completed by means of a rectal cathode.

Experimental Groups

In each experiment, three groups of animals were used: a normal, unoperated control group, an obese hyperphagic group, and a dynamic (nonobese) hyperphagic group. The obese hyperphagics were allowed to eat ad libitum until they reached their asymptote of weight, usually above 400 gm. The dynamic hyperphagics were allowed to go through a minimum period of ten days of ad libitum feeding postoperatively to show they were hyperphagic by eating large quantities of food and gaining weight rapidly and steadily. After this, they were brought back to their preoperative weight levels by a restriction of their food intake. Before each intake-measurement period, the dynamic hyperphagics were returned to preoperative weight and the obese animals were allowed to regain their asymptotic weight levels. A partial hyperphagic group was also used in the first experiment. These animals had been operated upon but showed only slight increases in food intake and weight.

EXPERIMENT I. CALORIC DILUTION

One way of checking on the ability of hyperphagic rats to regulate caloric intake is to test their response to diets containing varying amounts of calories per gram. If they have a greater-than-normal need for calories, they should eat even greater amounts of diets in which the calories have been diluted. On the other hand, if they are unable to regulate intake according to the caloric content of diets, they should fail to make the adjustments of intake expected of normal animals.

Method

To manipulate the calories available in the food, the standard powdered diet was thoroughly mixed with varying amounts of nonnutritive cellulose (Fisher's Ruffex). Thus, dilutions of 0, 5, 15, 25, 50, and 75 per cent were achieved. Six animals were studied in each of the four groups, the unoperated normals, the dynamic (nonobese), the static (obese), and the partial (slightly obese) hyperphagics.

Results

When rats with hypothalamic lesions are fed the standard, undiluted diet, it is quite clear that they fail to make normal caloric adjustments, for they eat far more than normals and store excessive amounts of energy as fat. This contrast between normal rats and hyperphagic rats is shown in Figure 1, which compares the weight and food intake of one typical hyperphagic animal with that of one typical unoperated control animal. It can readily be seen that hypothalamic hyperphagia consists of two phases: (*a*) a dynamic phase, in which the hyperphagic rat eats great quantities of food and shows concomitantly a very rapid and steady weight gain; (*b*) a static phase, after a period of about thirty days, in which the animal's weight levels off at a relatively high plateau, and its food intake

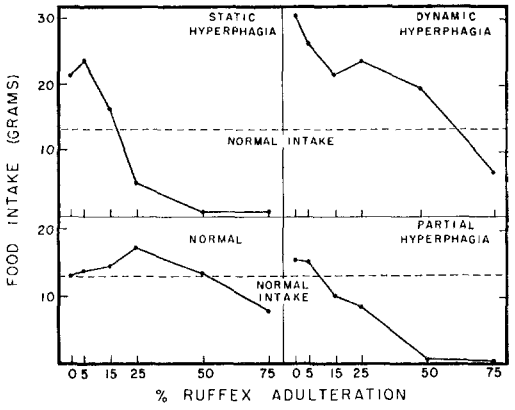

FIG. 2. Mean food intake of normal, static (obese) hyperphagic, partial hyperphagic, and dynamic (nonobese) hyperphagic animals as a function of percentage of cellulose (Ruffex) adulteration. The dotted lines represent the normal intake of rats fed the standard diet.

decreases somewhat. It has been reported elsewhere (9) that the food intake returns to normal in the static phase, but although the hyperphagic animals in this experiment showed a decrease in food intake in the static phase, they still ate almost twice as much as normal animals.

When the calories per gram of standard diet are diluted with nonnutritive cellulose, several noteworthy differences appear between the normal and operated groups. Figure 2 shows that the normal control group increases its intake of the adulterated diet up to 25 per cent dilution. Beyond this point, the normal group fails to maintain a normal caloric intake, although it continues to eat an appreciable quantity of food even at 75 per cent adulteration.

The static (obese) hyperphagic group, on the other hand, presents a striking contrast. With increasing adulteration it shows a very sharp decrease in food intake, which, at 50 per cent and 75 per cent adulteration, amounts practically to a complete rejection of the adulterated diet. This result confirms and extends previous findings with obese hyperphagics by Kennedy (9), who diluted the diet with 50 per cent kaolin, and by Strominger, Brobeck, and Cort (18), who used dilutions of 25 per cent cellulose.

The partial hyperphagic group, which overate and gained weight in a much less marked fashion, presents much the same picture as the static obese group, except that the slope of the curve is much less. This fits in well with the hypothesis that these animals possess the same characteristics as the obese animals, but to a much less marked degree. For this reason, they were not used in subsequent experiments.

The dynamic (nonobese) hyperphagic group resembles the obese hyperphagics in that they decrease their intake as a function of caloric dilution. But they also resemble the normal animals, for they continue to eat appreciable quantities of the adulterated diet, even at 50 per cent and 75 per cent dilution.

These results may be understood if we consider that the animal eating the cellulose-diluted diets is faced with the problem of maintaining an adequate caloric intake despite negative qualities of the cellulose such as its texture, taste, bulk, etc (1). The normal animal apparently can satisfy its caloric requirements by increasing its food intake up to 25 per cent dilution, and thus has some ability to ignore the negative qualities of the diet. But at higher degrees of adulteration, it is forced to decrease its intake below that necessary to provide normal caloric intake. The obese, static hyperphagics, and the partial hyperphagics, on the other hand, seem to have an exaggerated sensitivity to the negative stimulus qualities of the cellulose, for they reject it at concentrations which are not sufficient to disturb the normal animal. The dynamic hyperphagic animals, which differ from the static obese animals only in their weight levels, also seem to be sensitive to the negative stimulus aspects of the diet. But they are not nearly as sensitive as the obese animals, for they are able to maintain their intake of the highly adulterated food easily as well as the normal animals.

Taken together, the results of the caloric-dilution experiment show that the hyperphagic animals were not able to respond to the caloric dilution like the normal animals. They seemed to be much more sensitive than the normals to certain negative qualities of the cellulose-adulterated diet. Since the cellulose makes the diet quite powdery, one of the obvious characteristics which had been changed by the adulteration was the texture of

the diet. The second experiment was therefore set up to test the effect of the texture of the diet on food intake.

EXPERIMENT II. TEXTURE EXPERIMENT

It had been noted in preliminary experiments that obese hyperphagics leveled off at higher weights when they were fed Laboratory Chow pellets than when they were fed the same food in powdered form. This observation, together with the results of Experiment I, led to the hypothesis that powdery texture would cause hyperphagic animals to eat less food than would pellet texture.

Method

Six normal animals, 5 dynamic hyperphagic animals and 13 obese hyperphagic animals, were used. Since rats break up the large Purina pellets when they eat and let half-eaten pellets fall through the mesh flooring in such great quantities, accurate measurement of food intake was almost impossible. Therefore, because of their small size, Gaines Dog Meal pellets were used, and the same pellets were then ground to a fine powder to test the effect of a powdery texture.

Results

Table 1 shows the mean food intake of normal, obese hyperphagic, and dynamic hyperphagic groups on two diets, Gaines pellets and Gaines powder. The intake of the normal group was unaffected by the change in texture from pellets to powder ($F = 1.11$, $df = 1$ and 48), whereas the obese hyperphagic group showed a drop in food intake which was highly significant ($F = 77.03$, $df = 1$ and 104, $p < .01$). The dynamic hyperphagics showed a slight increase in their intake when they switched from pellets to powder. The difference was barely significant at the 5 per cent level ($F = 4.38$, $df = 1$ and 40), but it was not nearly as large as the decrease which was shown by the obese animals, and is therefore felt to be of little practical significance.

TABLE 1

Effect of Texture of Diet on Mean Food Intake (in Grams) of Normal, Obese Hyperphagic, and Dynamic Hyperphagic Animals

Group	Pellets	Powder	F	p
Normal	15.23	15.97	1.11	
Obese	27.57	23.42	77.03	<.01
Dynamic	30.04	31.48	4.38	.05

It is obvious, therefore, that the obese hyperphagics are very sensitive to the texture of the diets, whereas normals, and, for some reason, dynamic hyperphagics are not.

EXPERIMENT III. TASTE EXPERIMENT

If hyperphagia really is a release phenomenon in which the animals are hyperreactive to certain stimulus aspects of the diet, then the hyperreactivity ought to be double-edged. That is to say, hyperphagic rats ought to show exaggerated positive responses to certain "positive" stimulus aspects of the diet and therefore overeat (e.g., standard diet). But they should also show exaggerated negative responses to "negative" stimulus aspects of the diet and thus reduce their food intake or refuse to eat (e.g., adulterated diets). Therefore, the effect on food intake of "positive" and "negative" taste qualities added to the diet was investigated.

Method

"Negative" taste. The intake of a diet homogeneously blended with 0.125 per cent by weight of quinine sulphate was compared with the intake of the standard powdered diet. There were seven animals in the normal control group, seven in the obese hyperphagic group, and five in the dynamic hyperphagic group.

"Positive" taste. Fifty per cent dextrose by weight was mixed with the standard diet, and, again, the intake of this flavored diet was compared with that of the standard diet. There were seven animals in the normal control group, five in the obese hyperphagic group, and five in the dynamic hyperphagic group.

Results

Table 2 shows the results of adding 0.125 per cent by weight of quinine to the diet. The normal group shows no significant decrease in its intake of the 0.125 per cent quinine diet ($F = 0.54$, $df = 1$ and 56). The obese hyperphagic group, however, shows a marked de-

TABLE 2

Effect of Negative Taste (Quinine) on Mean Food Intake (in Grams) of Normal, Obese Hyperphagic, and Dynamic Hyperphagic Animals

Group	Standard Diet	0.125% Quinine	F	p
Normal	16.09	15.80	0.54	
Obese	19.51	2.14	1156	<.01
Dynamic	25.40	24.36	1.40	

TABLE 3

Effect of Positive Taste (Dextrose) on Mean Food Intake (in Grams) of Normal, Obese Hyperphagic, and Dynamic Hyperphagic Animals

Group	Standard Diet	50% Dextrose	F	p
Normal	16.86	14.20	20.67	$<.01$
Obese	22.20	29.28	55.24	$<.01$
Dynamic	26.52	26.52	no diff.	

crease in its response to the same quinine diet, amounting to practically complete rejection ($F = 1156$, $df = 1$ and 56, $p < .01$). The dynamic hyperphagic group, on the other hand, was similar to the normal group in that it showed no significant decrease in its intake of the quinine diet ($F = 1.40$, $df = 1$ and 40).

Miller, Bailey, and Stevenson (14) reported essentially the same results on obese hyperphagic rats and were led to the general interpretation that hypothalamic lesions increase eating but, paradoxically, decrease hunger motivation. The results reported here on dynamic hyperphagics, however, suggest that it is not the hypothalamic lesions, but rather the obesity, which reduces hunger motivation.

From the results of the present experiment, therefore, it appears once more that obese hyperphagic animals react in an exaggerated way to the stimulus aspects of the diet, in marked contrast with the normal and dynamic hyperphagic animals.

Table 3 shows the effect of 50 per cent dextrose diet. Since sugar is a more concentrated source of calories than is the standard Purina powder,[3] it was predicted that normal animals, which seem to regulate their eating in terms of caloric intake, should eat less of 50 per cent dextrose diet.

As may be seen in Table 3, normal animals do show a significant decrease in their food intake of the dextrose diet ($F = 20.67$, $df = 1$ and 56, $p < .01$). The obese hyperphagic group, however, showed a marked increase in its intake of 50 per cent dextrose diet ($F = 55.24$, $df = 1$ and 40, $p < .01$). This supports the idea that they respond in an exaggerated way to positive taste stimuli, and also fail to respond to the increased caloric energy supplied by the diet. The dynamic group, also shown in Table 3, eats no more of the dextrose diet than it does of the standard diet. This finding suggests the possibility that dynamic hyperphagic animals eat as much as possible all the time, and thus cannot increase their intake in response to "positive" qualities of the diet.

[3] Purina Chow Meal powder, as computed by the author and verified by the Purina Company, yields 3.61 kcal per gram. Sugar yields 4.1 kcal per gram (see J. F. Fulton, *Textbook of physiology*. Philadelphia: Saunders, 1950, p. 1002).

GENERAL DISCUSSION

There are two salient features of hypothalamic hyperphagia which emerge from the data presented above and which must be accounted for by any theory. (*a*) There is inability to regulate caloric intake, indicated, on the one hand, by the extreme overeating of hyperphagic rats, and, on the other hand, by their failure to make any compensation for caloric dilutions. (*b*) There is the striking difference in the effect of sensory qualities of the diet on the food intake of obese hyperphagic animals as contrasted with the effect on the food intake of normal and dynamic hyperphagic animals.

From the present experiments alone, it is quite clear that changes in the reactivity of hyperphagic rats to the stimulus aspects of the diet may account for both their failure to regulate caloric intake and their extreme dependence on sensory qualities of the diet. However, it is quite unlikely that such changes in reactivity to stimuli are solely responsible, because the obese hyperphagics are always much more reactive to changes in sensory qualities of the diet than dynamics. The fact that the obese animals differ from the dynamics only in the level of fat deposits suggests that, very likely, some change in the internal environment operates in combination with the change in reactivity to the stimuli provided by food. In fact, the importance of internal factors is stressed, quite properly, by several current theories of hyperphagia.

Brobeck (2), for example, has formulated the problem in terms of an impairment to the energy regulation mechanism of the organism. In a review of the problem in 1946, he suggested that there must be some quantitative regulation and integration of the variable factors upon which the equilibrium between

energy intake and energy output rests; i.e., of food intake, work output, and heat loss. He postulates that the hypothalamus may achieve control of food intake by sensitivity to the heat released during the metabolism of food (17, 18). He bases this hypothesis upon the fact that thermosensitive areas are known to exist in the hypothalamus (15), and that factors such as environmental temperature and the specific dynamic action of food (SDA) seem to have important effects upon food intake (3, 18).

Mayer and his co-workers (11, 12, 13) have formulated a "glucostatic" theory of hunger. The variations of blood sugar would be taken as the physiological stimulus for specialized chemoreceptors found, for example, in the hypothalamus. Nervous messages sent from the hypothalamus to the cortical centers would thus initiate the quest for food and control the amount eaten (11).

Kennedy (10) agrees with Mayer that the evidence seems to indicate that the hypothalamic centers involved in hunger and satiety seem to be sensitive to metabolites in the blood stream, rather than changes in body temperature, but he feels that the control of intake is dependent on the whole complex of metabolites in the blood stream, rather than on glucose alone.

It is not possible to specify, in any exact way, how changes in the internal environment operate together with changes in reactivity to sensory qualities of the diet in hyperphagia. On the other hand, some sense can be made of the facts of hyperphagia by considering how these two types of change interact, and some worth-while experiments become apparent.

The following is the organization of facts that looks best at present. After ventromedial lesions, all rats give positive exaggerated reactions to positive sensory stimuli and hence overeat. Before they get fat, it appears that they are also somewhat sensitive in a negative way to negative stimulus aspects of diets, for they steadily decrease their intake of diets adulterated more and more with cellulose. But the positive reactions are still quite powerful, since the dynamics continue to eat more of the adulterated diet than normal rats.

Once hyperphagic rats get fat, changes in the internal environment arise (10) which increase their negative reactions to negative stimuli to the point where they practically reject certain diets completely, for example, cellulose-adulterated diets and the quinine diet. However, the obese hyperphagics are still quite affected by the positive qualities of the diet, for they increase their overeating in response to the taste of sugar. This combination of exaggerated reactions to the positive and negative qualities of the diet yields a picture of finickiness in the obese hyperphagic animals which may be attributed to changes in the internal environment produced by their obesity.

The nonobese dynamics, however, show little of this finickiness but rather appear to be eating heedlessly, since they do not seem to be affected by adding either quinine or dextrose to the diet. However, it still remains to be determined whether the less sensitive dynamic hyperphagic rats might still be more sensitive to stimulus aspects of the diet than are normals.

It is clear from the foregoing that changes in the internal environment produced by obesity may be extremely important in the contrasting eating behavior of obese and dynamic hyperphagics. As a matter of fact, Mayer has some data to support this hypothesis. His experiments indicate that obese hyperphagics have higher blood-sugar levels than do dynamic hyperphagics (12).

Sensory denervation studies should be crucial in clarifying the relative contributions of the internal environment and sensory qualities of the diet to hypothalamic hyperphagia. If they actually are responding to "positive" qualities of the diet, all hyperphagic animals should cease overeating following denervation. Obese hyperphagics, in addition, should cease being finicky in their response to the taste and texture of the diets. Furthermore, if the ability to make caloric adjustments is also impaired by hypothalamic lesions, then sensory denervation should cause both dynamic and obese animals to behave in the same way: (*a*) to starve to death if the ability to maintain adequate caloric intake is actually destroyed, or (*b*) to continue to overeat regardless of the taste, texture, or caloric content of diets, and regardless of weight level, if only

the ability to limit their caloric intake is impaired.

SUMMARY

A series of four experiments was performed to investigate the role of stimulus factors in the diet in regulating the food intake of normal rats and of rats made hyperphagic by hypothalamic lesions. Two groups of hyperphagics were used: an obese hyperphagic group, and a dynamic hyperphagic group which was prevented from becoming obese by restricted feeding. The experiments tested the effects on these animals of caloric dilution, texture, and positive and negative qualities of the diet.

The results were as follows:

1. On the powdered Purina diet, hyperphagic animals eat two to three times as much as normals.

2. When the standard diet is adulterated with nonnutritive cellulose we find that (*a*) normal animals increase their intake up to 25 per cent dilution, (*b*) obese and dynamic (nonobese) hyperphagics steadily decrease their intake as a function of added cellulose, and (*c*) obese hyperphagics cease eating at 25 per cent dilution and beyond, whereas normal and dynamic hyperphagic animals maintain appreciable intake up to 75 per cent dilution.

3. Stimulus variation of the standard diet shows that: (*a*) change in texture (grinding pellets to powder) causes obese animals to decrease their food intake, but does not affect normal animals and dynamic hyperphagics, (*b*) negative taste (0.125 per cent quinine) yields exaggerated negative response in obese animals, making them quit eating, but does not affect normal or dynamic animals, and (*c*) positive taste (50 per cent dextrose) yields exaggerated positive responses in obese animals, making them increase their food intake. Normal animals decrease their intake of the dextrose diet, thus appearing to respond to the caloric value of the diet. Dynamic hyperphagic animals eat the same amount of dextrose diet as of the standard Purina diet.

CONCLUSIONS

1. Normal animals seem to eat for calories and tend to ignore stimulus characteristics of the diet over a wide range.

2. Hyperphagic animals fail to adjust intake to caloric needs.

3. Obese hyperphagics show release from inhibition in that they are hyperreactive to positive and negative stimulus qualities of the diet.

4. Dynamic hyperphagics differ from obese animals because they overeat heedlessly. This difference may be attributed to changes in the internal environment of the obese hyperphagics produced by their excessive fat deposits.

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