Hypothalamic Lesions by Electrocauterization: Disinhibition of Feeding and Self-Stimulation

Abstract. *Contrary to a recent report, destruction of the medial hypothalamus by electrocauterization with radio-frequency current consistently produced overeating and obesity in rats. This confirms the earlier consensus that destruction in the region of the ventromedial hypothalamus releases feeding from normal inhibition. In addition to augmenting feeding, the same lesions increased the rate of lateral hypothalamic self-stimulation after food satiation had depressed it. Thus the medial hypothalamus, when intact, inhibits both feeding and lateral hypothalamic self-stimulation.*

A recent series of papers (*1*) refutes the traditional view that the hypothalamus contains a mechanism necessary for satiety. The present report investigates this issue.

Twenty-five years ago, Hetherington and Ranson (*2*) found that bilateral electrolytic lesions in the ventromedial hypothalamus of the rat cause excessive feeding (hypothalamic hyperphagia) which leads to obesity. On the assumption that electrolytic lesions augment feeding by destroying neural tissue, it was hypothesized that ventromedial destruction releases feeding from normal inhibition. It follows from this that the ventromedial hypothalamus, when intact, inhibits feeding. Therefore, the ventromedial hypothalamus is commonly viewed as part of a satiety system (*3*). The lateral hypothalamus, on the other hand, is necessary for eliciting feeding (*4*, *5*). The dual nature of the hypothalamic system was confirmed by using procaine anesthetic in place of lesions (*6*). In sum, the lateral hypothalamus elicits feeding and the ventromedial region inhibits it.

Stimulation of the ventromedial hypothalamus stops feeding, as would be expected if an inhibitory system were excited (*7*). However, ventromedial stimulation causes aversion (*8*), which may simply disrupt feeding (*9*). Therefore, the inhibition theory rests largely on the observation of hyperphagia following ventromedial depression.

Reynolds (*1*) found that ventromedial lesions made by electrocauterization with radio-frequency current generally failed to produce hyperphagia and obesity. On the basis of this finding, he suggests that the medial hypothalamus does not inhibit feeding. He proposes, instead, that electrolytic lesions cause hyperphagia as an artifact of irritation to the lateral hypothalamic feeding system, and that by minimizing such irritation, electrocauterization fails to give the effect. The lack of hyperphagia following medial hypothalamic electrocauterization is directly contrary to the earlier results cited above; therefore, the experiment with electrocauterization was repeated in an effort to clarify the issue. This was the first of two questions to be investigated.

Electrical stimulation of the lateral hypothalamus can elicit responses previously learned with food as a reward (*10*). Lateral stimulation is also a reward by itself (*8*). For example, a rat will learn an arbitrarily chosen response, such as pressing a bar, if the response produces the electrical stimulus. The rate of lateral hypothalamic self-stimulation varies with food intake, being greatest when the rat is deprived (*11*) and least when force-fed (*12*). Self-stimulation, again like feeding, is augmented by electrolytic lesions or procaine injections in the ventromedial hypothalamus. This suggests that self-stimulation of the lateral hypothalamus is under inhibitory control of the ventromedial region (*12*). If so, self-stimulation should be increased (disinhibited) by ventromedial electrocauterization with radio-frequency current. This was the second question investigated.

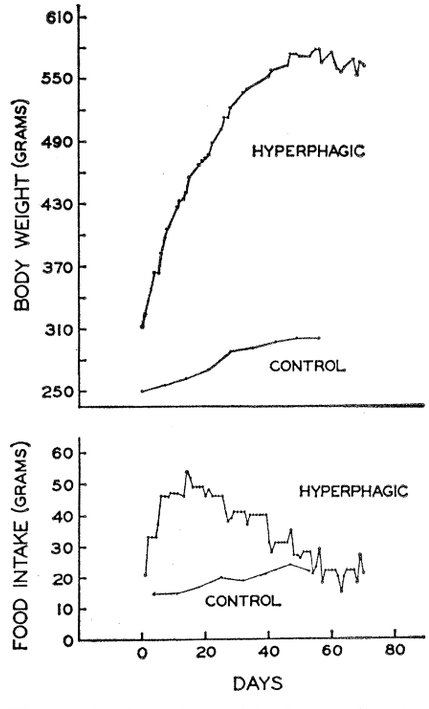

Fig. 1. Food intake and body weight of a normal rat compared with a typical rat made hyperphagic and obese by radio-frequency lesions in the medial hypothalamus.

The ventromedial hypothalamic region was bilaterally cauterized in 16 adult, Sherman, female rats weighing 245 to 325 g. Ten of these rats, with temporary brain and rectal electrodes, were anesthetized at the time lesions were made. The other six animals were fully awake; they had electrodes implanted in the ventromedial and lateral hypothalamus with an indifferent electrode under the scalp. Twelve normal rats formed a control group for a 2-week test of normal daily food intake and weight gain; for two rats, measurements were continued weekly for 5 months. The method of constructing platinum-iridium electrodes and implanting multiple electrode assemblies was described previously (*13*); stereotaxic coordinates and self-stimulation parameters have also been reported (*12*). In brief, the coordinates were A-6, L-0.7, D-8.5 for the ventromedial hypothalamus, and A-6, L-2, D-7.5 for the lateral hypothalamus; electrode depth was measured from the cortical surface and perpendicular to the skull. Lesions were made with a Grass LM-3, 2-Mcy/sec (radio frequency) sine wave generator such as Reynolds used. For three rats with temporary electrodes, the current was adjusted to pass 25 ma (r.m.s.) for 10 seconds per lesion; all other rats received 50 ma for 10 seconds per lesion. A 50-ma current was slightly less than sufficient to cause the audible pop of a steam bubble which can be generated by heat at the electrode tip (*14*). The animals were given free access to Purina rat chow and water for 2 to 4 months to assess changes in body weight.

As a result, all rats with lesions overate and became obese. Every rat with lesions ate more food and gained more weight in a 2-week period than any control rat. The results are contrary to Reynolds' negative findings.

The control rats ate an average of 16 g of powdered meal per day (range, 11 to 21) and their body weight in-

creased an average of 1 g per day (range, 0 to 2) during 2 weeks. In the same length of time, the rats with brain lesions made by temporary electrodes ate an average of 33 g of meal per day (range, 26 to 43) with a mean weight gain of 6 g per day (range, 3 to 9). The animals in this group reached a weight plateau in an average of 48 days (range, 10 to 133) with a mean increase in body weight of 154 g (range, 40 to 414). Lesions made with the smaller current, 25 ma, caused the largest weight gains; an illustrative record for one of these animals is shown in Fig. 1 to indicate the correlation between food intake and weight gain.

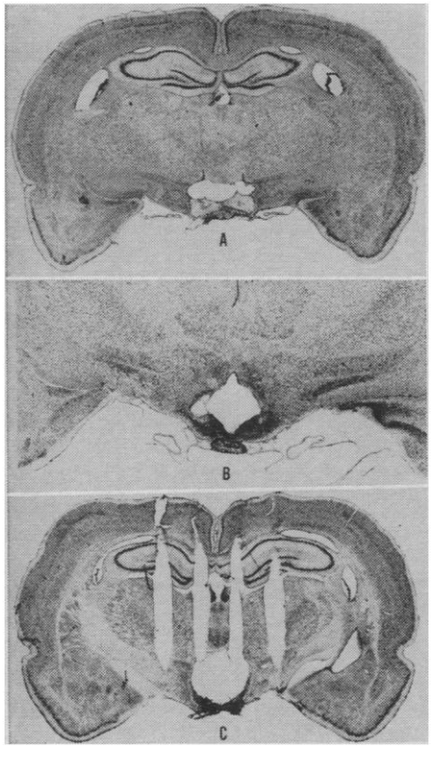

Fig. 2 (*A*) Frontal section of the brain of the hyperphagic rat shown in Fig. 1. This is a 30-μ section of Parlodion-embedded, thionine-stained tissue cut at the level of the medial hypothalamus. Tracks from temporary electrodes are seen as thin, dark lines leading down to the hole caused by electrocauterization (bottom center). When the electrodes were withdrawn they pulled the floor of the brain up into the hole; therefore, the area of destruction includes the light-gray patches of frayed tissue under the hole. (*B*) The same lesion as in section *A*, but shown at the level of the posterior hypothalamus. The dark areas under the hole are the arcuate nuclei, ventral premammillary nuclei, and a small remainder of the ventromedial hypothalamic nuclei. The animal gained 267 g. (*C*) The four vertical holes were made by four implanted electrodes which were in place when the animal was perfused. (This is a 50-μ, thionine-stained, frozen section.) The lesion is the round hole, including the dark mass of coagulated tissue under it. This lesion, made with the medial electrodes, augmented electrical self-stimulation through the left lateral electrode and caused an increase in body weight of 163 g.

The six rats with implanted electrodes did not appear disturbed by thermocoagulation of the ventromedial hypothalamus during wakefulness. One of these rats had food available at the time lesions were made; it did not eat in the 10 minutes before lesions, but started eating 1.5 minutes afterwards and continued for 5 minutes without pause. The other five animals of the group were trained to press a lever to trigger lateral hypothalamic stimulation. After 1 day of food deprivation, when the self-stimulation rate was at least 330 responses per 10 minutes, the animals were allowed to eat a sweet liquid diet, or, if necessary, were force-fed the diet, until the response rate decreased 20 percent or more. Then lesions were made. As a result, every animal increased its self-stimulation rate at least 40 percent; the mean response rate nearly tripled, from 205 responses (range, 0 to 480) per 10 minutes, before the lesions were made, to 593 responses (range, 308 to 790) per 10 minutes, afterwards.

The same lesions which augmented lateral hypothalamic self-stimulation also caused hyperphagia and marked obesity. On a diet of food pellets the six rats in this group gained an average of 6 g per day (range, 4 to 9) during the first 2 weeks, and required 52 to 110 days before a week passed without a net gain in body weight. At that time their mean weight gain was 259 g (range, 165 to 347).

Histological examination of the brains of eight rats revealed medial and ventromedial hypothalamic destruction. Symmetrically placed lesions destroyed the walls of the third ventricle and adjacent structures, leaving an enlarged ventricle extending laterally as far as the fornix. Figure 2*C* shows a large lesion and its relation to the self-stimulation site. The large lesions, however, did not cause the greatest weight gains; neither did very small lesions. The rat which gained the least weight had small, asymmetric lesions which destroyed less than half the ventromedial nucleus on each side. Therefore, lesion size and position were critical; symmetrical lesions which destroyed tissue in and around the ventromedial nuclei were most effective; see, for example, Fig. 2, *A* and *B*.

These findings demonstrate that electrocauterization in the general region of the ventromedial hypothalamus can consistently increase food intake and lateral hypothalamic self-stimulation. In contrast to Reynolds' results, there was no evidence that lateral hypothalamic irritation is essential to produce hypothalamic hyperphagia; to the contrary, electrocauterization, which was selected to deactivate neural tissue with a minimum of irritation to surrounding tissue, augmented both feeding and self-stimulation. This confirms the results obtained following ventromedial anesthetization with procaine and electrolytic lesions made with a platinum electrode (*12*). Therefore, it is concluded that hyperphagia is, at least in part, a result of neural deactivation in an area that inhibits feeding. This supports the traditional view that the medial hypothalamus is necessary for normal satiety. In addition, the observation that feeding and self-stimulation of the lateral hypothalamus covaried provides new evidence for Anand and Brobeck's hypothesis (*4*) that the medial satiety system curbs feeding by inhibiting neural activity stemming from the lateral hypothalamus.

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References and Notes

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