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Hyperphagia in Rats with Cuts between the Ventromedial and Lateral Hypothalamus

Abstract. *Bilateral cuts between the ventromedial and lateral hypothalamus in female rats consistently produced hyperphagia. Hyperphagia occurred slightly less reliably when one of the cuts entered the ventromedial hypothalamus and only infrequently if one entered the lateral hypothalamus. The results are consistent with other evidence that suggests that fibers originating medially stop eating by inhibiting cells in the lateral hypothalamus.*

The lateral (LHA) and ventromedial (VMH) hypothalamic areas are generally thought to be the important neural regions governing hunger and satiety. The conceptual scheme that has emerged from the evidence is that when an animal is hungry, there is a high level of neural activity in the lateral hypothalamic "feeding center." As the animal becomes satiated, activity in the ventromedial "satiety" region increases and inhibits firing in the feeding center, and eating stops. There is substantial support for this conclusion. The evidence centers on observations that electrical (or chemical) stimulation of the lateral feeding center initiates eating in a sated animal while activation of the ventromedial satiety area arrests eating in a hungry animal (*1*). Conversely, lesions of the lateral area cause aphagia while removal of the medial satiety region gives hyperphagia (*2*).

The most widely accepted neural mechanism that accounts for these results is a direct inhibitory connection between the VMH and LHA. In support of this model, neural connections have been demonstrated histologically, and electrophysiological recordings have been obtained which show reciprocal patterns of neural activity between the VMH and LHA (*3*). However, this model has also been vulnerable to serious criticism. Electrical stimulation of the VMH will stop other ongoing activity as well as eating, and there is some evidence that the hyperphagia following lesions in the VMH may be due to irritation of the LHA by deposited heavy metal ions and scar tissue (*4*).

The present experiment is intended to reexamine the functional interaction between the VMH and LHA. The method is to simply sever direct fiber connections by making a cut between these structures. If the VMH stops eating by inhibiting the LHA through direct fiber connections, cutting these pathways should result in an increase in food intake and a rapid weight gain similar to that occurring with VMH lesions.

Figure 1 shows the device used for making the cuts. The outer guide cannula (21-gauge stainless steel hypodermic tubing) was stereotaxically lowered into the brain of an anesthetized (sodium pentobarbital) female hooded rat (150 to 200 g). When the guide cannula was in place, a 26-gauge insert with a cutting blade made from stainless steel wire [diameter, 0.006 inch (0.015 cm)] was lowered into the cannula. When the cutting blade reached the lower slit, it extended and then cut through the neural tissue as it was lowered further. The cutting blade was removed and the guide cannula raised out of the brain. The size of the cutting blade and the distance the blade was pushed through the tissue were adjusted to give a cut of the desired dimensions (*5*). The cut used extended approximately 1 mm anterior and posterior to either end of the VMH. At the level of the VMH it extended ventrally to the base of the brain and dorsally about 0.0 to 1.0 mm above the fornix.

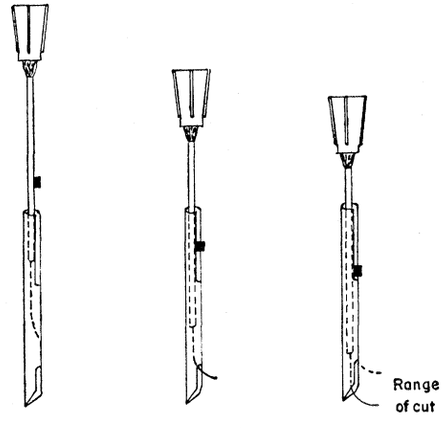

Fig. 1. Guide cannula and cutter used for making brain tissue cuts, showing cutter insert positions. The cutter is inserted into the guide cannula. The area cut begins where the blade emerges from the cannula.

After surgery the animals were housed individually and maintained on a diet of wet mash, Purina lab chow, and water, which were freely available. Each animal was weighed daily for 20 days following the operation. The animals were then killed and their brains examined histologically.

On the basis of the histological examination the operated animals were divided into groups according to the placement of the cuts. For this classification, the hypothalamus was divided into three zones (Fig. 2). A VMH zone included cuts invading the VMH. A middle zone (M) was between the VMH and LHA and included cuts that did not extend medially into the VMH or further than 0.5 mm lateral to the fornix. Cuts entering the region further than 0.5 mm lateral to the fornix were in the LHA zone.

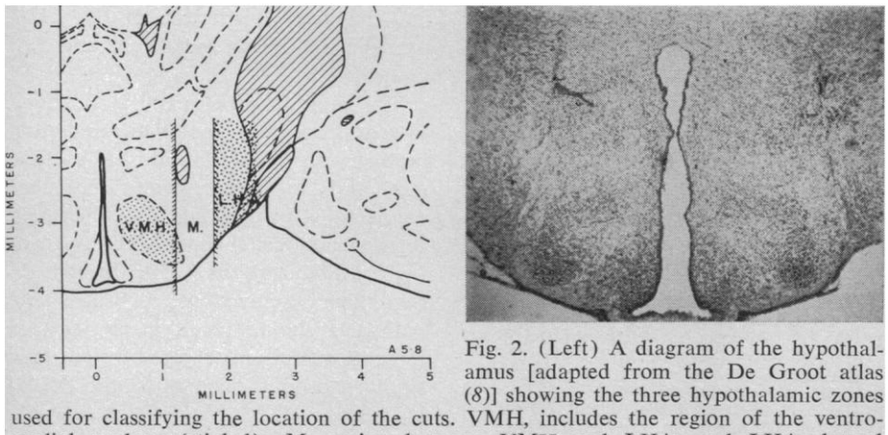

Fig. 2. (Left) A diagram of the hypothalamus [adapted from the De Groot atlas (*8*)] showing the three hypothalamic zones used for classifying the location of the cuts. VMH, includes the region of the ventromedial nucleus (stipled); M, region between VMH and LHA; and LHA, lateral hypothalamic area. (Right) A photomicrograph showing bilateral cuts in the M zone.

The results are shown in Fig. 3. Animals with both cuts in the middle zone (group M-M; $N = 12$) gained an average of 105 g (S.D. = 21.7) over 20 days (mean = 5.2 g/day). Animals with one cut in the middle zone and one in the VMH zone (group M-VMH; $N = 10$) gained an average of 99 g (S.D. = 33.4; mean = 5.0 g/day). The total weight increases of these groups did not differ from each other ($P > .20$) (*6*) but both gained significantly more ($P < .001$) than the unoperated control group ($N = 6$) which gained an average of 28 g (S.D. = 10.5) over the 20-day period (mean = 1.4 g/day). Two other groups that had one cut in the LHA did not differ significantly ($P > .20$) from the control animals. One group (VMH-LHA) that had one cut in the VMH and the other in the LHA zone ($N = 8$) gained an average of 24 g (S.D. = 16.0; mean = 1.2 g/day); the other (M-LHA) had one cut in the middle zone and one in the LHA ($N = 4$) and gained an average of 38 g (S.D. = 44.9; mean = 1.9 g/day).

To summarize, the results indicate that cuts between the VMH and LHA (group M-M) give a clear and consistent hyperphagia. There is no overlap between the weight gains of these animals and controls, and 10 out of 12 of these animals gained 90 g or more. If one cut is placed through the VMH but the other between the VMH and LHA (group M-VMH), hyperphagia also typically occurs but the weight gains are more variable. When one cut enters the lateral hypothalamus (groups M-LHA and VMH-LHA), there is generally a short initial period of aphagia which is not followed by hyperphagia.

The animals that became hyperphagic (groups M-M and M-VMH) seemed to show features characteristic of animals with VMH lesions. Many of these animals began eating as soon as they recovered from the anesthesia and some displayed the increased emotionality and viciousness emphasized by Grossman (*7*). When examined at autopsy, there was a clear accumulation of abdominal fat as well as a slight tendency toward a light speckling of the liver, presumably due to fat infiltration.

These results support the position that connections between regions of the VMH and LHA are critically involved in the regulation of food intake. They are also consistent with other evidence that suggests that fibers originating medially tend to stop eating by inhibiting the LHA, but they do not require that either the VMH or the LHA specifically be the origin or termination of these fibers. The results do not support the suggestion that ion deposits are necessary to obtain hypothalamic hyperphagia since cuts presumably do not leave such deposits. However, the possibility still remains that some form of abnormal activity is induced in the LHA by the cuts.

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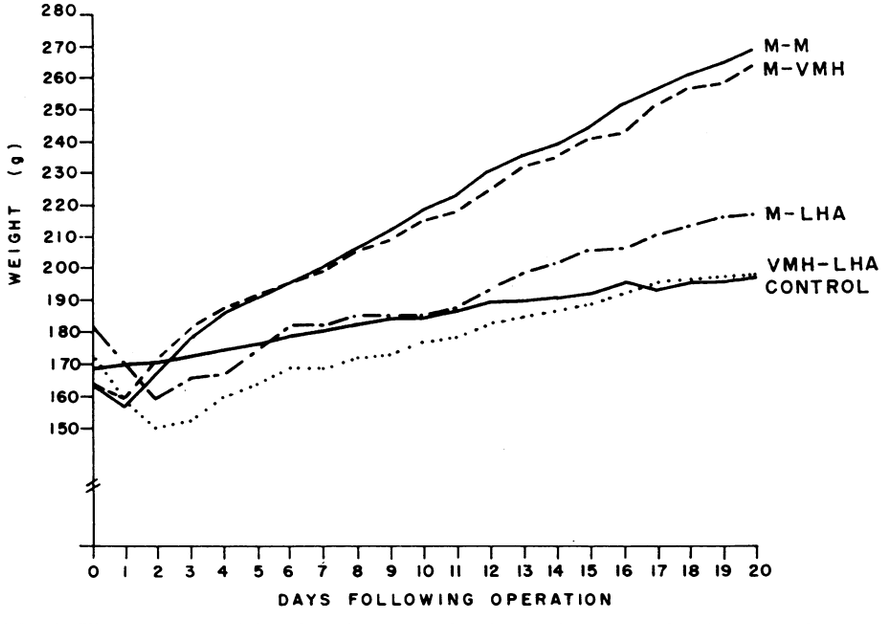

Fig. 3. The average weight of each group of animals (in grams) for 20 days after the cuts were made. Groups are described in text.

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