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VENTROMEDIAL HYPOTHALAMIC HYPERPHAGIA IN THE HYPOPHYSECTOMIZED WEANLING RAT[1]

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Ventromedial hypothalamic (VMH) lesions in weanling rats lead to obesity only after a delay of several weeks. This suggests either that the VMH is (*a*) undeveloped and not yet functioning in weanlings or (*b*) capable of functioning in weanlings, but inoperative for some reason. We demonstrate that hypophysectomized weanling rats, which otherwise eat very little and grow at a markedly reduced rate, show hyperphagia with rapid onset following VMH lesions. We support Kennedy's view that the presence of high levels of growth hormone in the weanling is responsible for VMH inactivity, either by eliminating the usual metabolic satiety signals and/or via a direct effect of the hormone on the VMH. Growth hormone involvement could account for the greater ease in producing hypothalamic hyperphagia in female than in male rats.

In the adult rat, damage to the ventromedial region of the hypothalamus (VMH) results in immediate hyperphagia and the rapid development of obesity (Brobeck, Tepperman, & Long, 1943). In the weanling rat, however, following medial hypothalamic ablation, sustained hyperphagia may appear only after a delay of several weeks, and obesity develops gradually as true growth slows down (Bernardis & Skelton, 1966; Kennedy, 1957). In a previous study (Groome, 1966), these results were verified and it was found that normal and VMH-damaged weanling rats maintained on a liquid diet could compensate for caloric dilution of the diet by increasing the volume consumed. Thus, gastric capacity cannot be the limiting factor on the food consumption of the young VMH-damaged animal.

Two possibilities are suggested, then, concerning the regulatory activity of the hypothalamus in the normal weanling rat. (*a*) The VMH may be undeveloped and inoperative in the infant rat, becoming functional in the regulation of food intake only as the animal matures. (*b*) Alternatively, the infant VMH may be capable of functioning, as suggested by the report by Kennedy (1957) that a few weanling rats, dwarfed due to VMH lesions, showed a more rapid development of obesity. If the VMH were functional, its failure to operate in the weanling could result from (*a*) active suppression or inhibition of the VMH or (*b*) absence of the appropriate metabolic "satiety signals," resulting from the high rate of metabolism and minimal lipogenesis in very young rats. Kennedy (1966, 1967) suggests that the absence of an appropriate signal to the "lipostat" may be a critical factor.

In order to demonstrate a possible immediate release from inhibitory hypothalamic control of feeding in the young, we have studied the effects of ventromedial hypothalamic damage on hypophysectomized weanling rats.[4] If the inhibitory activity of the VMH is not present at weaning, but increases with increasing age due to the later maturational development of its function, there should be a delayed onset of both hyperphagia and obesity in

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[4] While this work was being prepared for publication, Goldman, Schnatz, Bernardis, and Frohman (1970) reported similar experiments. Our observations on food intake and weight gain agree with theirs, and give further detail on the latency of onset of hyperphagia in hypophysectomized weanlings subjected to ventromedial hypothalamic damage.

the hypophysectomized young rat with damaged hypothalamus. If the VMH can function in the weanling rat, and the reduced food intake seen in the hypophysectomized weanling compared to that of the normal young rat is due to its inhibitory action, ablation of the VMH should result in immediate hyperphagia and rapid weight gain in comparison to the hypophysectomized weanling control.

Method

Animals

The subjects were female weanling rats hypophysectomized at the Charles River Breeding Laboratories at the age of 20 days, using the parapharyngeal approach. The rats were then shipped to the University of Pennsylvania. From the age of 21 days, the subjects were housed in individual cages and allowed unlimited access to water and Dutch Chocolate Metrecal.

Procedure

Volume of food intake and body weight were recorded daily. Within 10 days of hypophysectomy the subjects' weights had become fairly stable and medial hypothalamic ablation was performed. The mean age of subjects at surgery was 34 days, ranging 31–44 days.

Bilateral electrolytic lesions were placed in the region of the ventromedial hypothalamus with the aid of a stereotaxic instrument while subjects were under Nembutal anesthesia. Lesions were made .5 mm. lateral and 1.1 mm. posterior to bregma at a depth of .5 mm. from the base of the brain by passing a direct current of 2 mA for 20 sec.

Seven of 14 animals survived this operation. The food intake and body weight of these 7 experimental subjects and 10 hypophysectomized

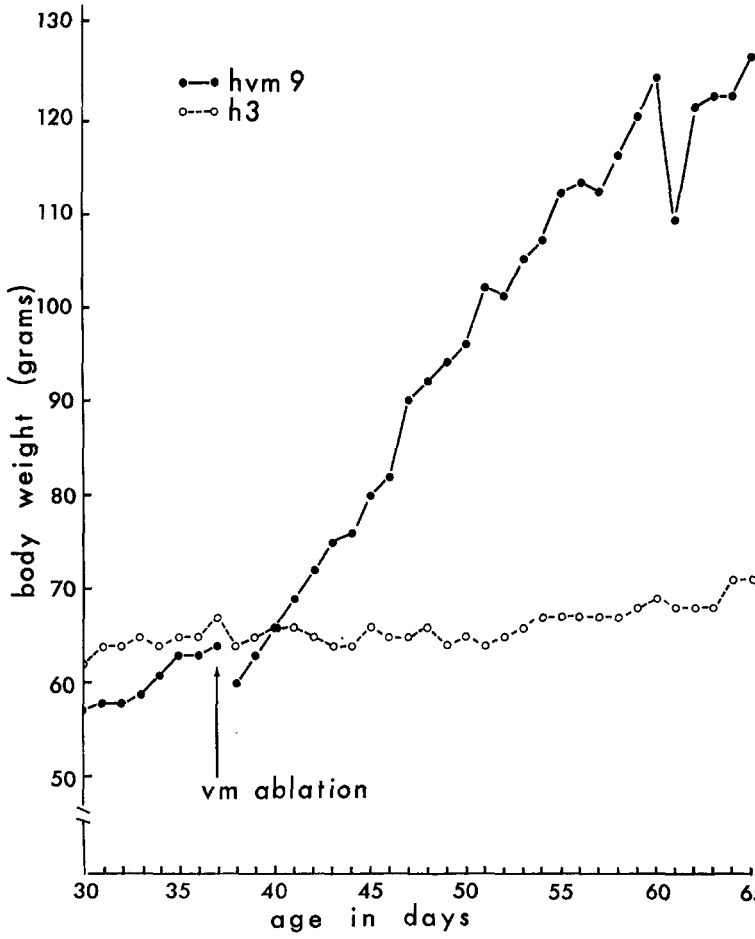

Fig. 1. Rapid body weight gain after ventromedial hypothalamic damage in a 37-day-old female hypophysectomized rat (Animal hvm 9) compared to its hypophysectomized control (Animal h 3). (The initial drop in weight is due to the 24-hr. food deprivation following surgery.)

control subjects were recorded daily. In a pilot study, all experimental animals had died within a day following surgery, many having eaten very large meals in this time. Food was therefore withheld from five of the seven experimental subjects in the first 24 hr. following surgery to prevent any possible deaths by choking. Two animals were given access to food following surgery in an attempt to replicate the phenomenon of immediate hyperphagia.

The brains of all subjects with hypothalamic lesions were embedded in Parlodion, cut at 40 μ, stained with thionin, and examined to determine the extent of the lesions.

Results

Figure 1 shows the body weight of the rat in which the effect of hypothalamic damage was most marked (Animal hvm 9). The other curve indicates the weight of a typical hypophysectomized control animal (Animal h 3). A dramatic increase in daily weight gain is seen following ventromedial ablation in comparison to the subject's own preoperative rate of weight gain and in comparison to the weight curve of the hypophysectomized control rat. The initial drop in weight is due to the 24-hr. food deprivation following surgery.

One of the experimental subjects was unaffected by the operation, exhibiting no hyperphagia or change in weight gain. Since histological examination indicated no hypothalamic damage in this animal, the data for this rat are not included in calculating averages for the experimental subjects. The other experimental subjects sustained hypothalamic damage in at least one ventromedial nucleus, with bilateral involvement in four of the animals.

These remaining six experimental animals were noticeably different from their controls, gaining 10–40 gm. more within 25 days of surgery than did the control hypophysectomized rats. Figure 2 illustrates the

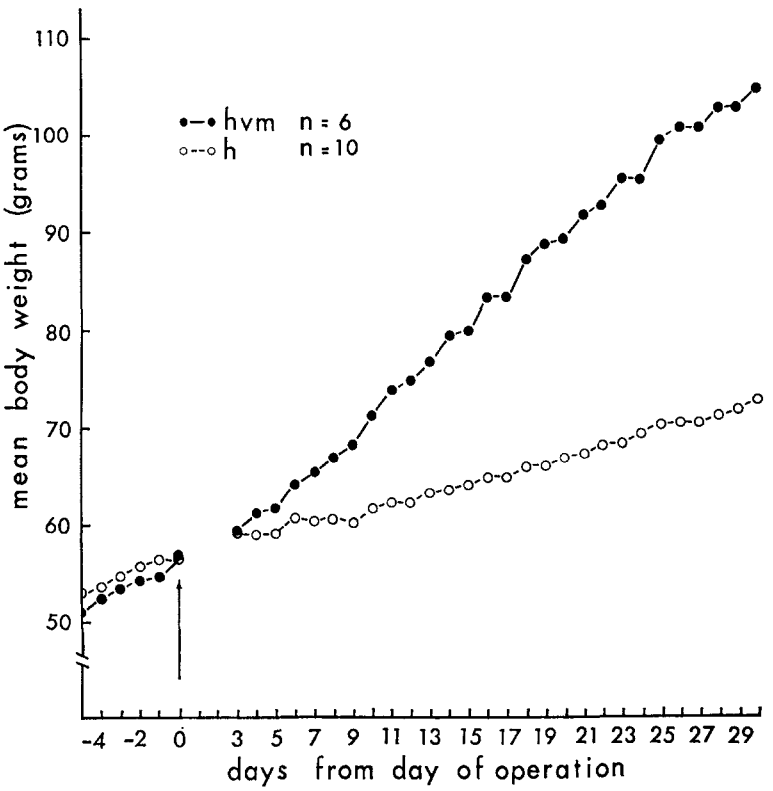

Fig. 2. Mean change in body weight of six VHM-damaged hypophysectomized weanling rats (filled circles). (The control value [open circles] is the change in mean body weight of 10 hypophysectomized control animals from their weight at 34 days [which is the average age at VMH operation of the experimental subjects].)

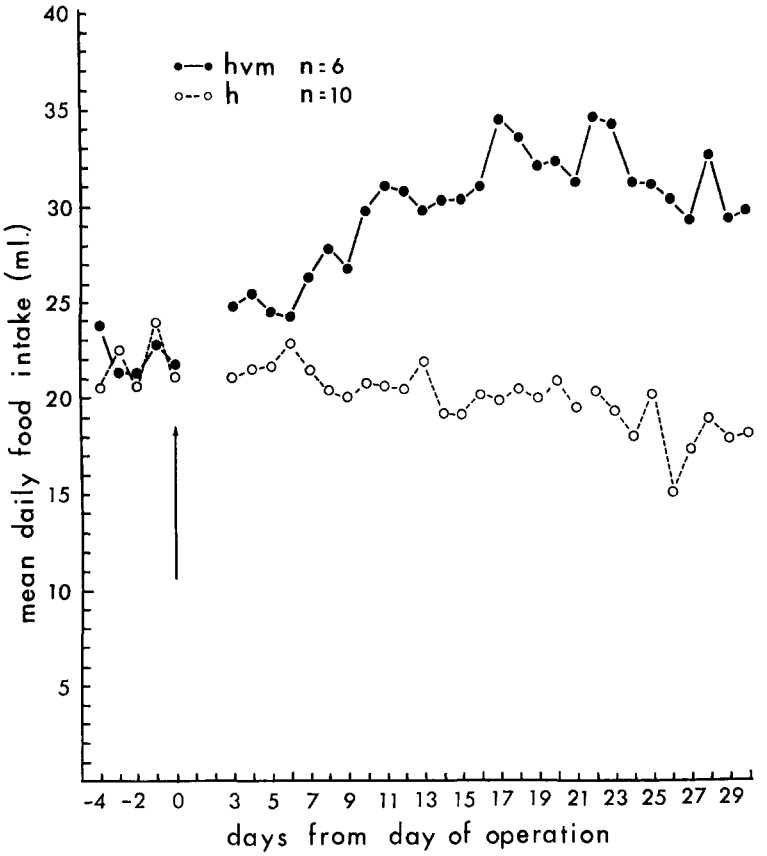

FIG. 3. Marked overeating after medial hypothalamic damage in hypophysectomized weanlings (filled circles) compared to the food intake of non-brain-damaged hypophysectomized controls (open circles). (The averaged data for the first 2 days following surgery are omitted because of the varied access to food given the operated subjects.)

mean change in body weight of the six experimental subjects from weight at surgery. The control value is the change in mean body weight of the 10 hypophysectomized control animals from their weight at 34 days, which is the mean and median age at operation of the experimental subjects. There is an obvious increase in rate of weight gain following ventromedial hypothalamic damage in comparison to the preoperative weight gains and in comparison to the weights of the hypophysectomized controls.

The average daily food intake of the experimental and control animals, both preoperatively and from the third day after surgery, is indicated in Figure 3. It can be seen that there is essentially no difference in food intake betwen the two groups prior to surgery. There is a marked hyperphagia postoperatively in the hypophysectomized weanlings with medial hypothalamic damage. The averaged data for the first 2 days following surgery are omitted because of the varied access to food given the operated subjects.

Immediate hyperphagia was observed in the two subjects allowed access to food immediately after surgery. Although these rats were not yet fully recovered from anesthesia and had been without food for less than 2 hr. in daytime, when they normally eat very little, each of them consumed 4 ml. of Metrecal and one of them an additional 8 ml. of water within 45 min. One of them gained 8 gm. in the first 12 postopera-

tive hr. in contrast to the usual 1–2 gm. daily weight gain in the hypophysectomized controls.

Discussion

The present results show that VMH ablation leads to immediate hyperphagia and the rapid development of obesity in the hypophysectomized weanling rat. Thus, from the release of food intake after lesion, we can be certain that the inhibitory action of the VMH is well developed by 34 days of age. Judging from the restricted food intake seen in 21-day-old hypophysectomized animals, the VMH is probably quite adequately developed at the age of weaning. Because the ventromedial inhibitory system can function at weaning or shortly thereafter, some concomitant of growth must act in the normally growing rat to neutralize the action of the ventromedial hypothalamic inhibitory feeding system, thereby allowing high food intake to provide for the nutritional demands of growth. Our conclusion here agrees with the earlier findings of Kennedy (1957) that obesity develops rapidly in dwarfed weanling rats.

Since hypophysectomy releases VMH control over food intake, it is reasonable to assume that pituitary secretions are critically involved in VMH inactivity. Growth hormone is likely to be the critical element, since it is directly tied to the increase in growth and presumably the concomitant increase in food intake during the juvenile period. Furthermore, growth hormone secretion is reduced at about the same time that VMH inhibitory function appears (Daughaday, Peake, Birge, & Mariz, 1968).[5]

We have no certain information on the way in which growth hormone might affect food intake. Two not mutually exclusive possibilities suggested earlier by Kennedy (1966, 1967) are: (*a*) Growth hormone directly inhibits activity of the VMH; (*b*) growth hormone, through its known lipolytic or other metabolic effects, eliminates or greatly reduces the level of those chemicals in the blood which excite VMH activity. In other words, growth hormone, in high levels, eliminates some blood satiety signals. Both possibilities can account, separately or together, for the data available.

The VMH has long been closely linked with the hormonal control of growth. The VMH damage typically leads to stunting of growth in immature animals (Bernardis & Skelton, 1966; Goldman, Schnatz, Bernardis, & Frohman, 1970; Han, 1967; Kennedy, 1957). In VMH-damaged young rats, replacement therapy with hormones other than growth hormone does not restore growth, nor does it affect body weight (Reichlin, 1960), whereas replacement of growth hormone alone does (Goldman et al., 1970; Han, 1968a, 1968b). Other work has directly shown that the hypothalamus influences the secretion of growth hormone (Pecile, Muller, Falconi, & Martini, 1965).

However, to our knowledge there is as yet no direct evidence indicating that growth hormone acts directly on the hypothalamic systems controlling food intake. There is, however, evidence that the female sex hormone, estradiol benzoate, can act directly on the ventromedial hypothalamus (Wade & Zucker, 1970a, 1970b).

Cox, Kakolewski, and Valenstein (1969) have reported that it is easier to produce hypothalamic hyperphagia in adult females than adult males. In this respect, an adult male could be considered similar to a weanling, both showing little or no effect of ventromedial hypothalamic damage. Our explanation of the weanling effect in terms of the effects of growth hormone raises the possibility of a parallel explanation of the male–female difference in adults. Male rats continue to grow throughout much of their adult life, whereas female rats do not. From the age of 56 days on, up to 360 days of age (the upper limit studied), the skeleton of the male albino rat grows more regularly than that of the female. From about 200 days of age on, the female skeleton grows very little, whereas the male skeleton continues to grow at an appreciable rate

[5] Wade and Zucker (1970a) also reached the conclusion that prepubertal pituitary secretions eliminate VMH restraint over food intake. They report that the inhibitory effect of estrogen on food intake, which is exerted via the VMH (Wade & Zucker, 1970b), does not appear in rats below 40 days of age, unless they are hypophysectomized.

throughout the rest of the year (Donaldson & Conrow, 1919). Pituitary growth hormone rises following birth in both male and female rats, and is indistinguishable during the first 8 wk. of life (Daughaday et al., 1968). At about 8 wk. of age, male rats have a greater pituitary growth hormone content (and concentration) than do female rats. After 8 wk. of life, growth hormone content does not increase in the pituitary of female rats, but the pituitary growth hormone content and concentration of males increases up to 160 days of age (the upper limit studied). Thus, with respect to growth hormone secretion, adult male rats are more like weanling rats than are adult females. Direct or indirect inactivation of the VMH by growth hormone, the mechanism we suggest in this paper for failure to demonstrate hypothalamic hyperphagia in weanlings, could also account for the male–female difference in adults.

Pfaff (1969) has offered a different but related explanation of the sex differences in adult response to VMH damage. He reports that injection of growth hormone into hypophysectomized adults increases male food intake, but not female. Conversely, prolactin injection increases food intake of females, but not males. Pfaff suggests, on the basis of some evidence on humoral effects of the ventromedial area on the pituitary, that VMH lesions would increase prolactin levels (increasing female intake, with no effect on males) and decrease growth hormone levels (no effect on females, decreasing males' food intake). The net result would be relative facilitation of female intake. Pfaff's view is complementary to ours. The two views are consistent with one another if we assume that weanling females are sensitive to growth hormone. In any event, both views suggest an involvement of growth hormone in control of food intake, and further investigations into its mode of action seem warranted.

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