THE ROLE OF HYPOTHALAMUS IN BODY WEIGHT REGULATION*

RICHARD E. KEESER
University of Wisconsin

The talk to follow focuses on the role of central nervous system, in particular the hypothalamus, in the regulation of body weight. Though the observations and conclusions I shall offer are based primarily on research on laboratory animals, notably the rat, there is reason to believe that they apply as well to other mammals such as those with which many of you are concerned. Let me begin then by giving a brief historical account of the observations and research implicating the hypothalamus in the control of food intake and body weight regulation.

The Lateral Hypothalamus and Feeding

Hypothalamic contributions to the control of food intake has been the subject of intensive research for the past several decades. Much of this research has centered on the lateral hypothalamus (LH) following the observations of Brobeck and his coworkers that lesions of this area either in rats (Anand and Brobeck, 1951a), cats (Anand and Brobeck, 1951b) or monkeys (Anand, Dua and Schoenberg, 1955) caused eating to cease even to the point of death by starvation. They interpreted these results as indicating a crucial role for the lateral hypothalamus in feeding behavior, and it is primarily these observations from which the concept of the lateral hypothalamus as a "feeding center" derives.

Work which followed these initial observations emphasized, however, that the aphagia produced by LH damage was not necessarily chronic (Teitelbaum and Stellar, 1954; Morrison and Mayer, 1957). Rather, free-feeding gradually reappeared according to an orderly process that Teitelbaum and Epstein (1962) have carefully detailed. They characterized Stage 1 of this LH syndrome as a period of aphagia and adipsia during which time the lesioned animal's body weight declines at a rapid rate. In Stage 2, described as one of anorexia and adipsia, the animal ingests highly palatable food if hydrated, but not yet in amounts sufficient to maintain body weight. Finally, an animal is judged to be in Stage 3 when it again ingests sufficient food to maintain its body weight on hydrated foods.

Several assumptions are commonly made concerning the physiological factors underlying this LH feeding syndrome. First, it is assumed that the aphagia resulting from lateral hypothalamic lesions reflects the loss of neural control over feeding behavior. A second assumption is

that the successive feeding stages through which the LH-lesioned animal passes are indicative of a process by which neural control over feeding is regained (Teitelbaum and Epstein, 1962). Finally, it follows from the first two assumptions that changes in body weight after lesioning are only secondarily related to lateral hypothalamic damage. That is, since it is assumed that the primary effect of LH lesions is to create an impairment in feeding, the postlesion changes in body weight are presumed to be secondary to the resulting disruption of ingestive behavior.

The Lateral Hypothalamus and Weight Regulation

Our own research over the past several years has caused us to question the above conception of the lateral hypothalamus as a feeding center and to focus instead upon its role in regulating body weight. Indeed, the thesis I should like to develop in this talk is that the lateral hypothalamus plays a critical role in determining the maintenance level or "set-point" for body weight. In the section which follows I shall detail the experiments from which the support for this view is derived.

We were first led to consider a role for the LH in weight regulation following our observation (Powley and Keesey, 1970) that, even after the return of free-feeding, LH-lesioned rats maintain their body weight at a level substantially below that of control animals. That is, even many months following the return of free-feeding and weight maintenance, these animals fail to compensate for the weight lost during the immediate postlesion periods of aphagia and anorexia. Figure 1 nicely illustrates both the permanence of this lesion-produced reduction of body weight and the precision of regulation at this lower level. Shown are the body weights of LH-lesioned and intact rats over a period of 24 weeks following surgery. In the immediate post-operative period, the LH-lesioned animals were aphagic and/or anorexic for approximately three days during which time they lost approximately 75 grams. Food intake then returned approximately to normal levels and these animals displayed the slow but steady weight gain characteristic of adult male rats. Their body weight, however, remained significantly below the control level, and at essentially a fixed percentage of the control level (84 ± 2.3%), for the remainder of the experiment.

A lower body weight, even if precisely and persistently maintained, is not, of course, evidence in itself of an altered regulation level or "set-point." Either general insult or impairments in specific systems controlling food intake could also lead to a chronically lower level of body weight. For these reasons, we next conducted a series of experiments in which the LH animal's lowered level of maintained body weight was challenged in various ways. The aim of this work was to determine whether or not LH animals could and would defend this reduced weight level.
In one experiment (Powley and Keesey, 1970), we observed the weight maintained by LH-lesioned and control animals while systematically varying the caloric density and palatability of their diet. The LH-lesioned animals at the beginning of these manipulations were maintaining their body weight at 85.1% of the control level (see Figure 2). When highly palatable eggnog diet was introduced, both the LH-lesioned and control groups displayed some gain in weight before stabilizing at a higher maintenance level. When the eggnog diet was then subjected to a series of progressive caloric dilutions, both groups compensated by increasing their intake by an amount sufficient to maintain this higher body weight. Finally, when both groups were placed again on a less palatable diet of wet mash, the weight of both groups declined. The important observation, however, is that the mean body weight of the LH-lesioned animals remained at essentially a constant percentage (86.3 ± 1.2%) of the control level during the entire 50-day period of dietary manipulations.
Similar results have been obtained by subsequent experiments involving other types of dietary manipulations. In one (Keesey and Boyle, 1973), animals receiving lateral hypothalamic lesions first reduced and then maintained their body weight at 90% of the control level. When their normal laboratory diet was diluted with quinine, a non-nutritive, bitter-tasting substance, they further reduced their maintained level of body weight by 12.8%. This quinine-induced reduction in the level of weight maintenance was essentially identical to the decrease (12.3%) observed in normal animals when their diet was adulterated in the same manner. In another experiment (Boyle and Keesey, 1975), it was demonstrated that neither high-fat diets nor highly palatable drinking solutions caused the body weight maintained by LH-lesioned
animals to deviate from these reduced levels. Thus, to each type of
dietary manipulation we have so far employed, the response of the LH-
lesioned animal has been quite the same as that of the normal. However,
the LH-lesioned animals make their adjustments in body weight around a
markedly lower maintenance level.

In a second series of experiments, we attempted to assess the LH-
animal's ability to defend its lower weight level by observing the
response to experimental manipulations of its body weight. In one
(Powley and Keesey, 1970), two groups of male rats received either
moderate or small LH lesions while at normal weight levels. After
lesioning, both groups displayed aphagia and anorexia (3.2 days and 1.0
days, respectively) and anorexia (an additional 2.1 days and 1.3 days)
before regulating their body weight at a reduced level (see Figure 3).

Fig. 3. Body weight functions of lateral hypothalamically-lesioned and
control animals. The body weight of the starved groups was
reduced by partial starvation prior to the time of lesioning.
Ad lib groups were allowed to feed ad lib until the time of
Two other groups, given equivalent lesions, but only after having been starved to 80% of their normal body weight, exhibited a markedly different postlesion feeding pattern. Those receiving the moderate-sized lesions displayed an average of only 0.2 days of aphagia and then only 1.3 days of anorexia. They then resumed a pattern of food intake which served to maintain their body weights at the same level (88%) that the animals receiving the lesion at a normal weight level achieved only after 5.3 days of aphagia and/or anorexia. Premeasure starvation of the animals receiving the smaller 4-sec. lesion produced an even more dramatic effect. These animals not only failed to display aphagia and anorexia but were actually hyperphagic for the first week postlesion. During this time they gained an average of 50 grams, thereby bringing their body weight to the same maintenance level (93%) as the group that had been lesioned at a normal body weight. It thus appears that the postlesion feeding behavior of the LH-lesioned animals is appropriate to the achievement of a reduced level of weight maintenance. If lesioned at a normal body weight, LH animals are aphagic and anorexic, and achieve this new maintenance level by a loss of body weight. But, if lesioned below this new level of weight maintenance, they are hyperphagic and rapidly gain weight to reach their new level. In both cases, the primary effect of the LH lesion appears to be that of setting a new weight maintenance level, while adjustments of food intake appear to be secondary to the achievement of this level.

Other data favoring this conclusion come from an experiment only recently completed (Mitchel and Keesey, unpublished observations). In this work male rats were first given LH lesions and then observed for one month postlesion. At the end of this month they were maintaining their body weight at 86% of the control level. Half the LH-lesioned animals were then placed upon a restricted feeding schedule until they reached a weight level that was 80% that of the LH animals remaining on an ad lib feeding regimen. The same procedure was followed with half the animals in the non-lesioned control group. Both the lesioned and the non-lesioned deprived groups were then returned to ad lib feeding conditions. When again permitted to feed ad lib, both deprived groups, whether lesioned or not, quickly returned to the weight levels of their nondeprived controls (see Figure 4). Of special significance, however, is how closely the pattern of weight recovery of the LH group paralleled that of the non-lesioned animals. Both recovered nearly identical percentages of the lost weight each day and took nearly an identical number of days to reach the level of their non-deprived controls. In fact, the only difference to emerge between the LH-lesioned and normal animals in this experiment is in the level of body weight each was prepared to defend.

It may be useful at this point to review what I think can be concluded from the preceding experiments. First, it appears that lesions of the lateral hypothalamus have the effect of reducing the regulated level or "set-point" for body weight. Second, the LH-lesioned animal strives to defend its reduced level and is remarkably effective in doing so. Finally, many feeding effects of LH lesions are
Fig. 4. Body weight of lateral hypothalami-cally-lesioned and control animals. See text for details of the dietary manipulations (Mitchel and Keesey, unpublished observations).

evidently secondary to the animal's efforts to reduce its body weight to this lowered maintenance level. If an animal is lesioned at a normal body weight, the subsequent aphagia and anorexia facilitate its achievement of the new level of weight maintenance. The usual pattern of aphagia and anorexia can, however, be altered by experimentally manipulating body weight. An animal whose weight has been reduced to a level below its new weight maintenance level prior to lesioning will not only fail to display aphagia and anorexia after lesioning but will actually be hyperphagic. Thus, in defending its body weight, the LH animal adjusts its food intake in essentially the same manner as a normal. The only significant difference seems to be that the LH-lesioned animal seeks to defend a level of body weight substantially below that of its nonlesioned control.
A Hypothalamic Model of Weight Regulation

While I have focused thus far upon the lateral hypothalamic contributions to feeding and weight regulation, another area, the ventromedial hypothalamus (VMH), is widely recognized for its role in these functions. In fact, reports describing a syndrome of hyperphagia and obesity associated with tumors at the base of the hypothalamus can be found in the clinical literature long before the turn of the present century. It was originally thought that this syndrome resulted from a pituitary dysfunction, but the investigations of Hetherington (1943) using stereotaxically-placed lesions in rat brain indicated clearly that the critical factor was damage to the ventromedial area of the hypothalamus. In a series of experiments following closely upon this work, many components of the new familiar VMH syndrome were first described. Both Tepperman, Brobeck, and Long (1943) and Brooks and Lambert (1946) noted that the hyperphagia following VMH lesions was not chronic. Rather, within several months postlesion, food intake returned to near-normal levels and body weight was subsequently maintained at a stable, though elevated, level. Figure 5 shows the weight function of a group of VMH-lesioned rats extending from the immediate postlesion period of hyperphagia and rapid weight gain to the later stage of stable weight maintenance.

It is not the case, however, that the hyperphagia is simply a postlesion effect from which the animal subsequently recovers. Starving the obese animal until its weight returns to the preoperative level simply reinstates the syndrome of hyperphagia and weight gain (Tepperman, Brobeck, and Long, 1943). It is also the case that, if the obese VMH rat's weight is experimentally elevated to a still higher body weight, daily caloric intake is reduced until body weight declines to the former level of obesity (Hoebel and Teitelbaum, 1966).

One curious finding is that this elevated level of body weight is apparently not defended with the same vigor that a nonlesioned animal defends a normal weight level. The VMH-lesioned animal is seemingly deficient in its motivation to work for food and is also a "finicky" eater (Miller, Bailey and Stevenson, 1950). The usual hyperphagia and weight gain following VMH lesions can be attenuated or even blocked if the animal is presented with an unpalatable diet (Corbit and Stellar, 1964).

Still, if provided with a palatable diet, the VMH-lesioned rat is characterized by a pattern of stable weight maintenance at an elevated level. With this in mind, we have considered the possibility that, by their opposing or reciprocal influences upon body weight, the VMH and LH jointly determine the weight maintenance level or "set-point." Thus, lesions of both the VMH and LH can alter the weight level normally maintained and thus cause it either to be elevated or reduced. Such an analysis also implies that LH aphagia is functionally the converse of the hyperphagia which follows VMH lesions. That is, both LH aphagia and VMH hyperphagia may be viewed as an attempt by the animal to equilibrate its actual body weight with the new set point level established by the hypothalamic lesion.
What is the Factor Regulated by Hypothalamus?

We have found some support for this hypothalamic model of weight regulation in the course of our efforts to determine how the proportions of fat, non-fat solids, and water are altered by the adjustments in body weight which follow LH or VMH lesions. Though I have thus far treated body weight as if it were the factor regulated by the VMH and LH, it seems unlikely that weight per se if physiologically regulated. More likely, body weight is just a convenient index or correlate of an actively regulated factor. In fact, there is good evidence that the adjustments in body weight made by VMH and LH-lesioned animals are achieved by changes in the same bodily constituents. Kennedy (1950) for example, observed that the weight gained by a VMH-lesioned animal in reaching its higher maintenance level could be accounted for largely in terms of additional body fat. In a similar vein, evidence we have collected suggests that LH lesions exert their influence upon body weight via an adjustment in the maintained level of body fat (Mitchel...
and Keesey, 1974). Fractionating the carcasses of LH-lesioned rats into fat, non-fat solids and water compartments, we found that body fat underwent by far the greatest percentage change in the shift by these animals to a lower maintained level of body weight.

We have continued to add to these initial observations on LH-lesioned animals, as well as to perform similar carcass analyses upon VMH-lesioned animals following their achievement of a stable elevated level of weight maintenance. The results of the fat analyses to date are shown in Figure 6. Each animal's total body fat, expressed as a

Fig. 6. Body fat levels of 115 lateral hypothalamically-lesioned, ventro-medial hypothalamically-lesioned, and control rats. Each animal's body fat, expressed as a percentage of the normal level, is represented as a function of its weight maintenance level, also expressed as a percentage of normal level. The correlation between the level of body weight and body fat is +.90.
percentage of the control level, is represented as a function of its weight maintenance level (also expressed as a percentage of the normal level). Contributing to this function are the data from 115 LH-lesioned, control, and VMH-lesioned animals. The correlation (r) between the weight maintenance level and the level of body fat is +.90. This indicates that the amount of body fat accounts for approximately 81% of the variance in body weight seen among these 115 LH, control, and VMH animals.

No similar relationship was seen between lean body mass and body weight. Shown in Figure 7 is the relation between nonfat solids (expressed

Fig. 7. Level of non-fat solids of 115 lateral hypothalamically-lesioned, ventromedial hypothalamically-lesioned, and control rats. The level of each animal's non-fat solids, expressed as a percentage of the normal level, is represented as a function of its weight maintenance level, also expressed as a percentage of normal level. The correlation between the level of body weight and body non-fat solids is +.02.
as a percentage of control) and the weight maintenance level for each of these same LH, control and VMH animals. The overall linear correlation (r) between these two factors is only +.02. It is worth noting in this regard that we have not found any central nervous manipulation that causes lean tissue to increase to any significant extent. A significant correlation can be found between body water and the level of maintained body weight, but this factor still does not account for a very large proportion of the body weight variance (r = +.41).

The observation that VMH-lesioned, normal, and LH-lesioned animals fall along a single function relating the level of maintained body weight to the level of maintained body fat suggests a common mechanism of control. It is tempting in this regard to propose that the VMH and LH reciprocally determine the maintenance level or set point for body fat. While we are partial to such an interpretation, there is at least one observation which causes some concern. That is, while the amount of fat in the adult rat is ordinarily less than 20% of its total weight, we can, by the use of large LH lesions, produce rats which will regulate their body weight as much as 30 to 40 percent below normal. It is evident, therefore, that more than a shift in the level of regulated body fat has occurred in such animals. Indeed, carcass analyses in such animals reveal substantial water and non-fat solid losses. Still, the selective loss of body fat in LH animals from normal body weights to approximately 85% of normal, and the increase of body fat in VMH-lesioned animals over the full range of observed body weights, certainly suggests a reciprocal influence of these two hypothalamic areas upon the adipose tissue stores.

Through what mechanism(s) the LH and VMH exert their influence upon the level of maintained body fat can at this time be only a matter for speculation. The hypothalamus does, of course, via the autonomic nervous system, influence the release of certain metabolic hormones. It may be possible, therefore, to produce such shifts in body fat by altering the levels of these hormones. In this respect it may be instrumental to look to the VMH preparation where data concerning the hormonal consequences of such lesions are already available. It is known, for example, that the increased adiposity of the VMH-lesioned animal is closely associated with a chronically elevated level of insulin. Furthermore, since destruction of the pancreatic beta cells that produce insulin can block the development of VMH obesity (York and Bray, 1972), it appears that hyperinsulinemia is a necessary condition for the obesity of the VMH animal. These observations suggest the hypothesis that the VMH influence upon body fat is achieved by way of its control over pancreatic insulin release (Powley and Opsahl, 1974). Results consistent with such a view are found in the recent report that subdiaphragmatic vagotomy (the vagus provides parasympathetic innervation of the pancreatic beta cells) eliminates VMH obesity (Powley and Opsahl, 1974). Whether or not the effects of LH lesions upon maintained body weight may be mediated by way of this same mechanism is not presently known.
What Factors are Controlled in Regulating Body Fat?

Both the clinical and research literature stress the crucial role played by food intake in successfully regulating body weight. Indeed it is taken almost for granted that the primary, if not the sole, factor leading to obesity in humans is excessive intake. Research on laboratory animals generally supports the view that the maintenance of a stable body weight depends upon the ability to make rather precise adjustments in our daily level of consumption. For example, an animal whose body weight has been elevated by force feeding, or reduced by partial starvation, appropriately decreases or increases its food intake until its former weight level has been again achieved. Or, an animal provided with diets of varying caloric density alters the daily volume of food it ingests so as to achieve a constant daily caloric intake. Likewise, the weight gained by the VMH rat can be largely accounted for by the hyperphagia it displays after lesioning.

Still, there are indications too numerous to overlook that energy utilization and/or expenditure does change according to physiological state or need. Both the VMH-lesioned (Brooks and Lambert, 1946; Han and Young, 1964) and the genetically-obese (Bray and York, 1971) rat become obese even if fed only control amounts of food. Similarly, rates of basal metabolism are known to change with nutritive state in both rats (Quimby, 1948) and man (Apfelbaum, Boutsarron and Lacatis, 1971), thereby altering the efficiency with which ingested food is utilized.

The work of Apfelbaum is particularly interesting in this respect. He reports that, when an individual's body weight falls below the level normally maintained, the basal rate of metabolism is lowered and the energy expended in completing a given task is substantially reduced. Conversely, an individual who has his body weight elevated by an increase in daily caloric intake experiences both an increase in rate of basal metabolism and in the energy expended in completing the same task. A negative relationship between body weight and the efficiency of energy utilization is clearly indicated by these observations. They also raise the possibility that individuals may reach a given or "normal" level of energy utilization at different body weight. If this were so, one might expect to find wide individual variation in maintained body weights even with very similar daily levels of caloric intake.

Our own interest in these results was stimulated by the observation that, once our LH-lesioned rats lowered body weight to its new maintenance level, their food intake returned to the level of nonlesioned control animals (Powley and Keesey, 1970). That is, in LH animals regulating their weight at, for example, 80% of control apparently require as many calories per day to maintain this reduced level as a nonlesioned animal needs to maintain a normal body weight. This is clearly suggestive of an altered efficiency of food utilization since, if one reduced the weight of a non-lesioned animal to 80% of normal by food deprivation, it would, when then given the number of daily calories it normally ingests, gain weight rapidly.
Fig. 8. Body weights of lateral hypothalamic-lesioned and control rats. One control (C-C) group and one group of lateral hypothalamic-lesioned (LH-C) animals were fed ad lib over the two-week period represented. Another control (C-E) and another lateral hypothalamic-lesioned (LH-E) group were fed only 50% of their average daily caloric intake for this two-week period (Paciotti and Keesey, unpublished observations).

Subsequent observation has revealed that LH-lesioned animals not only remain at a reduced weight level on a normal intake level, but respond with similar weight changes to restrictions in their daily caloric intake. The group of LH-lesioned animals whose weight function is seen in figure 8 were, in the week prior to the caloric restrictions to be described, ingesting essentially the same amount of laboratory food per day as their nonlesioned controls (23.9 grams versus 24.4 grams, respectively). They were, on this amount of food, maintaining their body weight at 84% of the control level. Half the nonlesioned
and half the LH-lesioned animals were then fed only 50% of their normal daily caloric intake. It can be seen from the figure that both the control and lesioned animals lost weight on the restricted diet. Furthermore, both groups lost equivalent percentages of their initial body weight per day.

We would like to view these data as further evidence of a shift in the set-point for body weight in LH-lesioned rats. These animals require the same daily caloric intake to maintain their body weight as control animals need to maintain a normal weight. Furthermore, restricting the LH animal's daily caloric intake leads to the same shift in body weight as seen in the control following similar restriction. Thus, the LH animal's efficiency of food utilization appears to be the same as that of a control. Furthermore, the LH animal also appears to display the normal increase in efficiency when its body weight falls below the level it normally maintains. However, it is the observation that these adjustments in the LH animal occur at a substantially reduced body weight that indicates an altered set-point.

What underlies the altered levels of maintained body weight we see in the LH-lesioned animal is the question to which much of our current research work is directed. In collaboration with others, we are presently studying the pattern of endocrine change accompanying the shift by LH-lesioned animals to a lower weight regulation level. We are also attempting to assess the changes in metabolic rate and efficiency in such animals. It is our hope that these observations will not only provide an explanation for the altered weight regulation level of the LH rat, but also a better understanding of the crucial neural and endocrine factors that normally determine the maintained level of body weight, both in rat and man.

REFERENCES


* * *

Dave Anderson: Thank you. Our last speaker before the recess will be Dr. Earle Klosterman, Professor of Animal Science, Ohio Agriculture Research and Development Center, Wooster, Ohio. Dr. Klosterman is a South Dakota native. He obtained his Doctorate at Cornell, after which he was on the staff at South Dakota State and later North Dakota State. He finally joined Ohio State University staff. Dr. Klosterman is a highly regarded nutritionist and management expert. He will share with us some of his recent work on the relationship of body size and production efficiency. Dr. Klosterman.

Earle Klosterman: Thank you very much. I consider it an honor to be invited to speak to this group and a pleasure to be here. Without further adieu, I'll get into the talk.