Differential Effects of Cuts Through the Posterior Hypothalamus on Food Intake and Body Weight in Male and Female Rats

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GROSSMAN, S. P. AND J. W. HENNESSY. Differential effects of cuts through the posterior hypothalamus on food intake and body weight in male and female rats. PHYSIOL. BEHAV. 17(1) 89–102, 1976. — Large knife cuts in the coronal plane through the posterior hypothalamus which transected the caudal connections of the medial hypothalamus without producing significant direct damage to cellular components of the region resulted in a very marked increase in food intake and rate of weight gain in female rats, but had little or no effect in male rats of the same strain. Water intake was equally elevated in both sexes. A detailed analysis of the effects of smaller cuts in the same region indicated that the pathways that are responsible for the effectiveness of the larger cuts do not course through the region immediately behind the ventromedial nuclei (VMN) but, instead, through the perifornical region lateral and posterior to the VMN. In the female, hyperphagia is not seen after cuts behind the VMH or lateral to the fornix but all cuts that invade the perifornical region to a significant extent result in overeating and obesity. In the male, a very mild hyperphagia (but no obesity) is seen after cuts that are restricted to this perifornical region but larger cuts that involve even minor aspects of the lateral hypothalamus (LH) are entirely ineffective. Analysis of the effects of cuts that involve the medial, perifornical, and lateral hypothalamus to varying extent suggested that the disinhibitory effects of perifornical transections may be counteracted by relatively strong inhibitory effects due to damage to fibers in the lateral hypothalamus in the male, where the influence of the perifornical system appears to be weak, but not in the female, where the influence of the perifornical system appears to be very strong. The marked sex differences which characterize the effects of all cuts on body weight indicate that the perifornical system may be concerned specifically with metabolic functions that contribute to the development and/or maintenance of the organism’s setpoint for body weight.

Hyperphagia Hypothalamic knife cuts Hyperdipsia Satiety Hypothalamus-satiety Ventromedial hypothalamus Food intake Water intake

The precise anatomical localization of the components of the ventromedial hypothalamus (VMH) that are responsible for the overeating and obesity which are seen after large lesions in the area and the pathways that mediate their influence on food and water intake remain uncertain. Many effective lesions are outside the ventromedial nucleus (VMN) and tend to cluster ventral and lateral to the nucleus itself [12,15]. Because some effective lesions are caudal to the region of the VMN itself, Brobeck [3] suggested many years ago that hyperphagia and obesity might be due to an interruption of the caudal connections of the hypothalamus rather than destruction of cellular components of the region.

A number of experimental observations have been reported in recent years which are compatible with such an interpretation. Joseph and Knigge [16] have reported that extensive damage confined to the VMH in guinea pigs did not produce overeating whereas lesions outside the nucleus were quite effective. Gold [10] has recently reexamined the question and suggested that only lesions ventrolateral to the VMN itself produce hyperphagia and obesity in the rat.

That the effects of these lesions may, at least in part, be due to an interruption of fibers is suggested more specifically by reports of overeating and obesity following surgical interventions which selectively affect fibers of passage. Grossman [14] reported that surgical transection of most of the posterior connections of the medial hypothalamus resulted in marked hyperphagia and hyperdipsia in the rat. Gold et al. [11] have reported overeating after a lesion behind and lateral to the region of the ventromedial nucleus of the rat and obtained similar effects when a unilateral lesion in the premammillary area was combined with a parasagittal knife cut that severed the connections between the anterior aspects of the VMH and the adjacent lateral hypothalamus (LH) on the contralateral side of the brain.

Several investigators have reported increases in food or water intake after lesions in more caudal portions of the
behind the region of the VMN. Paxinos and Bindra [21] reported a similar failure to observe hyperphagia after large lesions, however, two reports of experimental observations that are not readily congruent with such interpretations. Sclafani [24] reported a failure to observe significant effects on food or water intake following coronal cuts just behind the region of the VMN. Paxinos and Bindra [21] reported a similar failure to observe hyperphagia after large coronal cuts that severed most of the caudal connections of the mid hypothalamus.

The present experiments were designed to replicate the effects reported by Grossman [14] to delineate the boundary conditions that apply to them.

**EXPERIMENT 1**

The first step in our investigation was an attempt to replicate the observations reported by Grossman [14] using the procedures employed in those experiments.

**METHOD**

**Animals**

Female albino rats of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin), weighing 200–250 g at the beginning of the experiment, were housed singly in an air-conditioned vivarium that was illuminated on a 12-hr light/dark cycle.

**Procedure**

Throughout the experiment, the animals had ad lib access to dry laboratory chow (Teklad Rat and Mouse Pellets, 6% fat content). Food and water intake and body weight were recorded daily.

The posterior fiber connections of the medial hypothalamus were transected as follows: a 30 ga stainless steel guide shaft was stereotaxically inserted into the brain at the following coordinates from the deGroot [7] atlas of the rat brain: AP = 4.8; H = -2.0; L = 2.0. A 125 micrometer diameter tungsten wire knife was then extended from the slightly curved tip of the guide cannula so that the wire projected medially for 2.0 mm at an angle of approximately 90° to the guide shaft. The entire knife assembly was then lowered to H = -4.4. The wire was then retracted and the knife assembly withdrawn. The procedure was repeated contralaterally. The bilateral transections were intended to produce a continuous cut from L = 2.0 on one side of the brain to L = 2.0 on the other, and from the base of the brain to the level of the mammillothalamic tracts.

Following completion of the experiment, the animals were killed by an overdose of Nembutal and perfused transcardially with a 10% formal saline solution. The brain was removed from the calvarium and frozen after storage in Formalin to permit the cutting of 25 micrometer frontal sections through the area of the knife cuts. The sections were stained with Cresyl violet and examined with the aid of a light microscope. The descriptions of the anatomical observations were made without knowledge of the behavioral results.

**RESULTS AND DISCUSSION**

**Anatomical**

Seven rats sustained bilaterally symmetric coronal cuts between AP = 4.6 and 5.0 (see Fig. 1). The cuts traversed the region immediately behind the tip of the ventromedial nucleus in 5 animals and passed through the caudal-most section of the VMN in the remaining 2 rats. The food and water intakes of these 2 animals could not be distinguished from those of animals which sustained cuts not involving the VMN. All cuts included a region that extended laterally approximately halfway into the lateral hypothalamus (L = 1.6–2.0), and extended upward from the base of the brain to an imaginary horizontal line approximately halfway between the fornix and the mammillothalamic tract (H = -2.5). The location and extent of the cuts of these 7 animals were all but identical. Two additional rats sustained cuts of comparable mediolateral and vertical dimensions at AP = 3.8. The cuts differed from those used in the experiment reported by Grossman [14] in being narrower (the present cuts did not extend as far laterally and shallower (they did not extend as far dorsally) and succeeded in transecting the fornix, thus involving the region ventral to it. The cuts made in the present experiment appeared to differ from those used by Sclafani [24] and Paxinos and Bindra [21] mainly by extending further laterally and thus involving the region ventral and ventrolateral to the fornix.

**Behavioral**

All of our experimental animals which sustained cuts at AP = 4.8–5.0 overate after surgery (p<0.001) and continued to do so throughout the 30-day observation period (see Fig. 2). If one discounts the first few days after surgery where some animals appeared to suffer from general surgical trauma and overate only slightly, the smallest effect observed represents a 119% increase over preoperative baseline, the largest an increase of 193%. (Both comparisons use a baseline established during the last 5 days before surgery and Days 6–10 postoperative.)

All of these animals also consumed very large quantities of water after surgery. This effect was attenuated toward the end of our 30-day observation period but intake remained significantly (p<0.01) above the preoperative baseline during the last 5 days of this period (see Fig. 2). An analysis of the water/food ratio of these animals indicated that the increase in water intake did not merely compensate for the added dry food consumption (see Fig. 3). Many animals drank more than 300% of their preoperative intake during the first weeks after surgery and continued to drink more than 200% at the end of the 30-day observation period. The average water/food ratio was consequently significantly (p<0.02) elevated through-
FIG. 1. Schematic representations, based on the de Groot [7] atlas of the rat brain, of knife cuts just behind the region of the ventromedial hypothalamus. Female rats which sustained cuts at AP 4.6 or 5.0 as shown in the left and middle section of the top row displayed pronounced hyperphagia and hyperdipsia. Rats which sustained cuts at AP 3.8 as shown in the right portion of the top row showed much smaller increases in food and water intake. The approximate position of the cuts in parasagittal sections is shown in the bottom half of the illustration. The behavioral effects of these cuts are summarized in Figs. 2 and 3.

out the postoperative observation period. The increased water/food ratio suggests that the effects of our cuts on food and water intake may be independent. Inspection of the data from individual animals confirms this interpretation. Although all of our rats consumed very large quantities of water, some showed little or no postoperative change in the water/food ratio. One example of such an apparently pure hyperphagia is shown in Fig. 3. This animal overate by an average 123% throughout the 30-day postoperative test period but drank only enough additional water to keep the water/food ratio roughly constant. Figure 3 also shows data from an animal which consumed huge quantities of water that were disproportionately greater than its elevated food intake. This animal overate about as much as the one just discussed (111% over the 30-day postoperative period) but drank 243% of its preoperative baseline during this time. A primary disturbance of mechanisms that are specifically related to the regulation of body water is clearly indicated in the second case but not in the first.

All animals with coronal cuts at AP = 4.6–5.0 gained significant amounts of body weight during the 30-day test period, and clearly outgained the control animals by a wide margin (see Fig. 2). Over the entire 30-day test period, 7 female control rats gained an average of 28.3 g (or 0.94 g/day). The 7 experimental animals gained an average of 121.3 g (or 4.03 g/day) during the same time. There was no overlap in the distributions of weight gains for the 2 groups.

It is interesting to note that the rate of weight gain was significantly (p<0.05) larger in our experimental females than in a group of 6 male controls that weighed 36% more at the start of the experiment. These males gained 86 g (2.8 g/day) over the 30-day test. When weight gain is expressed in terms of a percentage of preoperative body weight (see Fig. 2), the experimental females gained an average of 51% of their preoperative weight, whereas the control males gained only 28%. There was no overlap in the two distributions. The control females, by comparison, gained only 12% of their preoperative weight during the 30-day test period, a value that was reliably different (p<0.01) from the rate of gain of both control males and experimental females.

The two rats with coronal cuts at AP = 3.8 were hyperphagic but the effect was smaller (49 and 79% increase over baseline during Days 6–10 after surgery) and appeared less persistent (only a 30% increase over preoperative baseline remained during the last 5 days of the experiment) than the changes seen in rats with more anterior cuts (see Fig. 2). Although the postoperative increase in food intake was substantial, the 2 animals with more posterior cuts did not gain weight significantly faster than unoperated controls (0.97 and 1.3 g/day) (p>0.05) compared to 0.94 for controls, an interesting contrast to animals with slightly more anterior cuts which gained an average of 4.0 g/day. It thus appears possible to produce significant increases in food intake which are not reflected
FIG. 2. Daily food and water intake and body weight of female rats during a 30 day observation period immediately following the surgical transection of the posterior connections of the medial hypothalamus at AP 4.6–5.0 or AP 3.8. The size and location of these cuts is shown schematically in Fig. 1. The data are expressed as a percentage of each animal's baseline as recorded during a 10 day observation period immediately preceding the day of surgery.

FIG. 3. The ratio of daily water intake (in ml) to daily food intake (in g) in 7 female experimental rats with coronal cuts behind the ventromedial hypothalamus (AP 4.5–5.0) compared to that of 7 control animals of comparable age and preoperative body weight. The data for the 2 experimental animals which showed the largest (No. 649) and smallest (No. 590) change in the water/food ratio are shown separately. Each point on the illustration represents a mean of 5 days before or after surgery (op.).

in the animals' body weights, a fact which may have confounded the results of investigators who have relied mainly on body weight as a measure of lesion effects. Both rats with posterior cuts were hyperdipsic (102 and 117 ml during the second 5-day period after surgery) and showed a significantly ($p<0.05$) elevated water/food ratio throughout the observation period.

The results of this experiment replicate in detail the observations reported by Grossman [14]. In both cases, coronal cuts immediately behind the region of the ventromedial nucleus increased food intake by approximately 150% in the first few weeks after surgery and produced an apparently persistent increase of about 100% over preoperative baseline. In both experiments, water intake increased even more dramatically shortly after surgery and remained elevated by an average of about 150% toward the end of the test period. The disproportionate increase in water intake resulted in a significant increase in the water/food ratio, the final value of approximately 2.0 being almost identical in the two experiments.

EXPERIMENT 2

The results of our first experiment demonstrate unambiguously that coronal cuts immediately behind the region of the VMN can produce hyperphagia. They also result in hyperdipsia which appears to be independent of the hyperphagia, at least in some cases. Since the phenomenon is readily obtainable and robust, it remains to be established why Sclafani [24] and Paxinos and Bindra
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failed to obtain comparable results. Closer inspection of Sclafani's histological data and discussion indicates that his cuts were considerably narrower than the ones used by Grossman [14] and were probably also narrower than the cuts used in the preceding experiment. It is thus possible that the overeating and obesity may not reflect an interruption of fibers which course through the area immediately behind the VMN itself but which traverse the region postero-lateral to the nucleus. Such an interpretation is congruent with earlier lesion data [10,12]. The cuts made by Paxinos and Bindra [21] appear to have been larger but do not appear to be bilaterally symmetric because only a single cut across the midline was made. Many of these cuts unilaterally invade the lateral hypothalamus but spare significant portions of the contralateral medial hypothalamus. They may thus have involved pathways in the lateral hypothalamus which may be essential to food and water intake (transient aphagia was reported in some of their animals) and not interrupted pathways in the contralateral perifornical region that may be important for satiety.

The following experiment was undertaken to test the effects of narrow medial perifornical and lateral cuts in order to test the validity of these conclusions.

METHOD

Animals

Female albino rats, of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin) weighing 200–250 g at the beginning of the experiment, were used. The animals were maintained as described in Experiment 1.

Procedure

The surgical and histological procedures were identical to those described in Experiment 1 except that the location and extent of the cuts was changed. Three types of cuts were attempted, each 1 mm wide and 2.5 mm long. In all cases, the guide cannula was inserted at AP = 4.8; the knife extended in a medial direction for 1 mm, and the entire knife assembly raised from the bottom of the brain to H = -2.5 (approximately halfway between the fornix and the mammillothalamic tracts). The lateral coordinates for the three types of cuts were 1.0, 1.5 and 2.0.

RESULTS

Anatomical

Six animals sustained bilaterally symmetric or nearly symmetric coronal cuts between AP = 4.4 and 5.0 in the region immediately behind the VMN (see Fig. 4). In 4 of the animals the cut passed through the caudal-most portion of the nucleus; in the remaining 2 animals, the cut was behind the VMN. The cuts extended from L = 0.8 medially to L = 0.8 on the contralateral side; and from the bottom of the brain to H = -2.0 to -2.5.

Seven animals sustained bilaterally symmetric or nearly symmetric coronal cuts between AP = 4.8 and 5.0 just posterior and lateral to the caudal portion of the VMN. The cuts extended from L = 0.8 to L = 1.6 and from the bottom of the brain to H = -2.5. In 4 of the animals the fornix was transected bilaterally; in 1 rat the fornix was cut unilaterally. In the remaining 2 animals there was no discernible damage to this tract. The region immediately caudal to the VMN was not involved in any animal.

Five animals sustained bilaterally symmetric or nearly symmetric coronal cuts between AP = 4.6 and 5.2 through the lateral hypothalamus, extending from the internal capsule to the region just lateral to the fornix (intact in all animals) and from the base of the brain to H = -2.0. The ventrolateral portion of the lateral hypothalamus was partly
had a postoperative (Days 5-10) water/food ratio of 1.98: based on a 5-day preoperative baseline and Days 5-10 after intake rose from 168% to 256%. (Both comparisons are compared to a preoperative baseline of 1.47, one animal significant amounts of body weight after surgery and gained another reached 4.65 during the same period.

portion of the hypothalamus, including the ventromedial, interruption of the caudal connections of the medial-most weight significantly faster than 6 female controls of comparable age and preoperative body weight. All animals showed an elevated water/food ratio although comparable age and body weight. Some animals with such cuts showed a significant increase in food intake and water intake even though pathways which ascend to or descend from the region of the lateral hypothalamic feeding center were undoubtedly disrupted. This finding is in good agreement with the observation that lesions [4,19] or knife cuts [22] posterior or anterior to the feeding center have little or no effects on food and water intake. Our observation that cuts which invaded the internal capsule produced the most severe depression of intake is compatible with the suggestion that the effects of more anterior LH lesions on food and water intake may be due to an interruption of nigro-striatal projections [27] and/or pallidofugal pathways [19].

Our observations do not contradict the report by Albert et al. [2] that much larger corona cuts which extend into larger cuts at the same rostro-caudal plane (see Experiment 1). Sclafani [24] reported an average increase in water intake of 32% (terminal level against preoperative baseline) which was not statistically reliable, presumably because of wide inter-animal variance. This pattern of results is not incompatible with that seen in the present experiments. Paxinos and Bindra observed very large increases in some animals and none in others, a pattern which is all but identical to that observed in our experiments.

Coronal cuts through the lateral-most region of the hypothalamus produced only transient decreases in food and water intake even though pathways which ascend to or descend from the region of the lateral hypothalamic feeding center were undoubtedly disrupted. This finding is in good agreement with the observation that lesions [4,19] or knife cuts [22] posterior or anterior to the feeding center have little or no effects on food and water intake. Our observation that cuts which invaded the internal capsule produced the most severe depression of intake is compatible with the suggestion that the effects of more anterior LH lesions on food and water intake may be due to an interruption of nigro-striatal projections [27] and/or pallidofugal pathways [19].

Our observations do not contradict the report by Albert et al. [2] that much larger corona cuts which extend into
the internal capsule laterally and the zona incerta and subthalamus dorsally, produced long-lasting aphagia and adipia. It appears likely that the pathways which may be responsible for the aphagia and adipia that is seen after lateral hypothalamic lesions do not course through the medial forebrain bundle as defined anatomically but, instead, through more dorsal and lateral portions of the diencephalon.

The ventral portion of the perifornical cuts that produced sustained increases in food and water intake is just posterior to the region ventral and lateral to the VMN that has been identified as the site of the most effective electrolytic lesions [10,12], and just anterior to the premammillary region which Gold et al. [11] destroyed to produce overeating and obesity. It thus seems likely that both lesions as well as cut knife cuts interrupt a satiety-related neural pathway that may or may not synapse in the ventromedial hypothalamus.

EXPERIMENT 3

The results of the preceding experiments provide a ready explanation for the apparent discrepancy between the observations reported by Sclafani [24] and Grossman [14]. Sclafani (personal communication) has more recently also observed hyperphagia and obesity after wider cuts which extended into the area implicated by the results of our experiments.

Our observations do not provide an equally satisfying explanation for Paxinos and Bindra's failure to observe overeating and obesity after coronal cuts in the posterior hypothalamus which appear to be large enough to involve the perifornical region. It is possible that their failure to observe hyperphagia may be due to the fact that some portion of the apparently critical subfornical region appears to have been spared unilaterally in all of their animals with posterior knife cuts. This is not, however, an entirely satisfying interpretation since unilateral VMH lesions [8] as well as unilateral mammillary region damage and unilateral parasagittal knife cuts [11] produce some overeating and accelerated weight gain. Matters may be confounded by the fact that Paxinos and Bindra used male animals and a standard, dry laboratory chow, whereas we used females in this as well as earlier [14] investigations. It is well known that male rats do not overeat nearly as much as females after VMH lesions when maintained on a standard dry food diet [6]. Males do overeat substantially and become obese when a palatable high-fat diet is offered [9] but this was not the case in Paxinos and Bindra's experiments.

Damage to the ventromedial hypothalamus may affect food intake in at least 2, possibly unrelated, ways. It may increase responsiveness to taste (i.e., increase affective reactivity to taste sensations as Grossman [13] has suggested). This effect of the lesion appears to be responsible for the hyperphagia that is seen in males and females when palatable diets are offered. In the female, there are also hormonal consequences of VMH damage which may affect food intake and body weight much like ovariectomy [17]. This mechanism is of little consequence in the male but may play an important role in body weight regulation in the female. The present experiments were designed to investigate the possibility that the hyperphagia and obesity that is seen after transection of some of the posterior connections of the hypothalamus may specifically be related to an interference with this second, hormone-related mechanism. To test this hypothesis, cuts of various sizes were made in several locations behind the ventromedial hypothalamus in male rats.

METHOD

Animals

Male albino rats of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin), weighing 250–375 g at the beginning of the experiment, were housed singly in an air-conditioned vivarium that was illuminated on a 12-hr light/dark cycle.

Procedure

Throughout the experiment, the animals had ad lib access to dry laboratory chow (Teklad Rat and Mouse Pellets, 6% fat content) identical to that used in Experiments 1 and 2. Daily food and water intake and body weight were recorded for 10 days prior to surgery and for at least 10 days afterwards.

Using surgical procedures identical to those employed in the previous experiments, attempts were made to transect the posterior connections of the hypothalamus. The rostro-caudal plane of the cuts varied from AP = 4.0 to AP = 5.0; their width from 1.4 mm to 1.8 mm; and their height from −2.0 to −2.5 mm terminating at the bottom of the brain.

RESULTS AND DISCUSSION

Anatomical

Seven animals sustained bilaterally symmetric or nearly symmetric cuts in the coronal plane at AP = 4.6–4.8 which extended from the midlateral hypothalamus (L = 1.6–1.8) on one side of the brain to the midlateral hypothalamus on the contralateral side and from the base of the brain to an imaginary horizontal line just below the mammillothalamic tracts. The fornix was transected bilaterally in all animals. These cuts were similar in location and extent to those made in females in Experiment 1 (see Fig. 1). Three of the 7 males which sustained these cuts were small and thus had preoperative body weights (X = 292 g) that were similar to those of the female rats used in the first experiment. The remaining 4 males were larger (X = 357 g). There were no discernible differences in the histological or behavioral effects of our cuts in these 2 groups of male rats.

Nine additional male rats sustained cuts in the coronal plane at AP = 3.8–4.0 that were similar in their lateral (L = 1.4–1.6) and horizontal (base of brain to H = −2.5) extent to those described above.

Three animals sustained cuts in coronal planes at AP = 5.6–6.6 that were similar in their lateral (AP = 1.4–1.8) and horizontal (base of brain to H = −2.5) extent to those of the preceding groups.

Behavioral

Large coronal cuts immediately behind the ventromedial nucleus failed to produce a reliable, sustained effect on food intake in 7 male rats. One animal ate considerably more food during the first 5 days after surgery than he had before (a 62% increase from baseline) but his intake returned to baseline during the second 5-day period. A second animal of this group ate less food during the 5-day period immediately after surgery than he had before (a 53% decrease from baseline). This effect also disappeared during
FIG. 6. Daily food and water intake and body weight of 7 male rats (filled circles) with large cuts in the coronal plane immediately behind the region of the ventromedial nucleus (AP 4.6–4.8). The results are compared with data from 7 female rats (open circles) with comparable cuts (see Fig. 1) obtained in experiment 1. Each point on the illustration represents the mean of 5 days before or after surgery (op.).

the second 5-day period of postoperative observation. The remaining 5 rats of this group did not display reliable changes in food intake, and the group mean for all 7 animals did not differ reliably ($p>0.05$) from preoperative baseline (see Fig. 6). Attempts to correlate the behavioral and anatomical data failed to disclose possible reasons for the transient hyperphagia that was seen in one animal. The rat which displayed a transient hypophagia had cuts that were slightly wider than those made in the rest of the animals of this group. Figure 6 includes comparison data from 7 female rats with similar cuts (Experiment 1) which emphasizes the marked sex differences that are seen in this preparation.

The average body weight of the 7 animals in this group did not change ($p>0.05$) during the 10 day period after surgery (see Fig. 6). The animal which was transiently hypophagic gained 53 g during this time, the transiently hypophagic rat lost 43 g. This is in marked contrast to the substantial weight gain seen in female rats with comparable cuts.

All 7 of the animals in this group drank enormous quantities of water after surgery (see Fig. 6). The animal which was hypophagic during the first 5 days after surgery drank somewhat less than before (38 ml versus a preoperative baseline of 48 ml) during this time but increased its water consumption to 202% of baseline during the second 5 day period postoperatively when its food intake returned to normal. The effect on water intake was not only universal but quite robust. A comparison of the intake on Days 6–10 postoperatively with the preoperative baseline showed increases ranging from 100–373%. The magnitude of the effect of the cut did not appear to be related to the animal’s preoperative body weight. The second smallest rat recorded the largest increase and the smallest rat showed the second smallest increase. Comparison data from 7 females with similar cuts (Experiment 1) indicate that their effects on water intake are comparable.

Considering the general failure of our cuts to significantly increase food intake it is not surprising to find a significant ($p<0.01$) increase in the water/food ratio during the 10-day postoperative observation period. Since water intake increased gradually after surgery in some of our animals, the change in the water/food ratio was greater during the second 5-day observation period than immediately after surgery.

Large cuts in the coronal plane at AP = 3.8–4.0, approximately 1 mm posterior to those made in the animals of the first group, produced generally similar effects on food and water intake (see Fig. 7). Seven animals which sustained such cuts showed no reliable increase ($p>0.05$) in food intake within 10 days after surgery; the range of individual change being $-24\%$ to $+23\%$. The body weights of these rats also did not change reliably ($p>0.05$) after surgery. Two female rats with comparable cuts showed a significant increase in food intake but also no reliable increase in body weight in Experiment 1 (see Fig. 7). Two additional male rats with large cuts at this posterior level that were not readily distinguishable from the remaining 7 on histological grounds, increased their food intake by 60 and 61% respectively during 10 days after surgery. One of these animals actually lost 20 g of body weight during this
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FIG. 7. Daily food and water intake and body weight of 9 male rats (filled circles) with large cuts in the coronal plane approximately 1.0 mm behind the region of the ventromedial nucleus (AP 3.8–4.0). The results are compared with data from 2 female rats (open circles) with comparable cuts (see Fig. 1) obtained in Experiment 1. Each point on the illustration represents the mean of 5 days before or after surgery (op.).

The results of the preceding experiments indicate that a transection of the posterior connections of the medial hypothalamus results in significant hyperphagia and obesity.
in the female but not in the male rat. This apparent sex difference may, entirely or in part, be responsible for Paxinos and Bindra's [21] failure to replicate our earlier findings of hyperphagia after coronal cuts in the posterior hypothalamus [14]. The lack of lateral symmetry in Paxinos and Bindra's cuts may have contributed to the negative outcome.

We were, however, concerned that other factors may play a role in the apparent sex difference because 2 male rats with large cuts posterior to the region of the VMN showed significant and persisting hyperphagia in Experiment 3 and other males with similar cuts displayed transient increases in food intake. Our large cuts involve much of the lateral hypothalamus which is thought to be traversed by pathways that may carry excitatory influences on feeding and it is possible that most of our cuts may have little net effect on food intake because they concurrently remove both excitatory and inhibitory influences.

Such an interpretation receives support from our observation (Experiment 2) that cuts restricted to the lateral hypothalamus produced transient inhibitory effects on food intake which were followed, in some instances, by small but apparently persistent facilitatory effects. The significant increase in food intake seen after coronal cuts through more rostral aspects of the medial hypothalamus of male rats (Experiment 3) is also congruent with such an interpretation if the feeding-related pathways in the lateral hypothalamus are located more laterally and/or dorsally in the anterior sections of the hypothalamus. Such a distribution is typical of the nigro-striatal projections which have been implicated in the regulation of food and water intake by numerous recent investigations (e.g., [18, 26, 27]).

It thus appeared important to investigate in the male the effects of smaller cuts which interfere selectively with pathways that course through the perifornical region and adjacent portions of the medial and lateral hypothalamus which appear to play an important role in satiety in the female (see Experiment 2).

METHOD

Animals

Male adult rats of the Sprague-Dawley strain (Holtzman, Madison, Wisconsin), weighing 300–325 g at the beginning of the experiment, were housed singly in a vivarium that was illuminated on a 12 hr light/dark cycle. Standard pellet rat chow (Teklad Rat and Mouse Pellets, 6% fat) and tap water were available ad lib throughout the experiment. Food and water intake as well as body weight were monitored daily.

Procedure

Using surgical procedures described in more detail in Experiment 1, knife cuts were made in the coronal plane at AP = 4.2–4.8 which were 1.0 mm in width and extended upward from the bottom of the brain to an imaginary horizontal plane 1.5–2.5 mm dorsal to it. Histological verification of the intended placements, based on microscopic examination of cresyl violet stained sections, was performed on all animals as described in Experiment 1.

RESULTS AND DISCUSSION

Anatomical

Five animals sustained coronal cuts at AP = 4.6–4.8 of approximately 1 mm width through the perifornical region which extended only a short and nearly equal distance (0.4–0.6 mm) into the medial and lateral hypothalamus respectively. The cuts extended from the base of the brain to an imaginary horizontal line approximately 2.0 mm above the base of the brain.
FIG. 9. Schematic representations, based on the de Groot [7] atlas of the rat brain, of knife cuts just behind the region of the ventromedial nucleus (AP 4.6), which severed the caudal connections of the perifornical region (top left); medial region (bottom left); and intermediate areas (top and bottom right). The behavioral consequences of these cuts are summarized in Fig. 10.

Four rats sustained coronal cuts of comparable width and vertical extent which involved the perifornical region at AP = 4.4–5.0 and the area medial to it, but did not invade the lateral hypothalamus. All of these cuts extended from the base of the brain to an imaginary line 1.5–2.0 mm above it.

Two rats sustained coronal cuts of comparable width and vertical extent which involved the perifornical region at AP = 4.6 and the area lateral to it without invading the area medial to the fornix.

Eight animals sustained coronal cuts through the medial hypothalamus of comparable width and vertical extent at AP = 4.6–5.0 which extended from the midline to an imaginary vertical line just medial to the area of the fornix.

In general, all cuts were similar in location and extent to those made in female rats in Experiment 2.

Behavioral

The 5 animals with coronal cuts that were clearly restricted to the perifornical region just posterior to the rostro-caudal level of the posterior VMN consistently increased their food intake after surgery and continued to overeat throughout the 30 day observation period (see Fig. 10). Most animals displayed the largest intake during the second or third week. If one considers the animals' intake over the entire 30 day postoperative observation period, the smallest increase over preoperative baseline was 27%, the
FIG. 10. Daily food and water intake and body weight of male rats with cuts in the coronal plane (AP 4.6) that selectively destroyed the caudal connections of (a) the perifornical region (peri, n = 5); (b) the medial hypothalamus (med n = 7); (c) the perifornical region and tissues just medial to it (peri-med n = 4); and (d) the perifornical region and tissues just lateral to it (peri-lat n = 2). Data from 7 operated controls of comparable preoperative food and water intake and body weight are also shown. The data are presented as a percentage of a baseline established during the last 5 days prior to surgery (there were no reliable differences between any of the preoperative baselines X). Each point on the illustration represents the mean of 5 days after surgery except that body weights are averaged over 10 day periods.

largest 63%. With reference to our hypothesis that larger cuts may be ineffective because they involve inhibitory pathways in the lateral hypothalamus, it is interesting to note that the 2 animals which showed the smallest average increases in food intake (X = 30%) in the present experiment both had cuts which extended significantly farther into the LH than those of the remaining rats which consistently displayed much larger increments in food intake (X = 59%).

All 5 rats in this group gained weight during the 30 day observation period but their average rate of gain (2.1 g/day) was significantly (p<0.05) smaller than that recorded concurrently for 6 operated controls of similar age and body weight (2.8 g/day). This is particularly interesting in view of the fact that the experimental animals ate significantly (p<0.01) more than the controls during this period. These observations are consistent with the pattern of results seen in Experiment 3 where the 2 male rats which overate consistently gained weight slower than the controls.

Water intake was not reliably affected by the cut in any of the 5 animals of this group, the average postoperative change ranging from -10% to +27% (see Fig. 10). The average water/food ratio was consequently lowered in all animals (p<0.05). It is interesting to note that female rats with comparable cuts showed similar increases in food intake but also a marked elevation of water consumption (see Experiment 2, Fig. 5).

Knife cuts of similar size which involved the lateral hypothalamus in addition to the perifornical region produced small but consistent increases in food intake that became more pronounced toward the end of the 30 day observation period. Water intake was unchanged (X = -1% and 16%) and the water/food ratio consequently showed a small but statistically reliable decrease (p<0.05). The animals gained weight postoperatively at a rate (2.4 g/day) which was slightly lower than that of control animals of comparable preoperative weight. The magnitude of the cut's effects on food intake is similar to that seen in the 2 animals of the preceding group which sustained coronal cuts through the perifornical area that also involved significant aspects of the lateral hypothalamus and is consistently smaller than the increase seen in rats with cuts that were confined to the perifornical region itself (p<0.01).

These observations suggest that an interruption of some of the fibers that course through the lateral hypothalamus may produce inhibitory influences on feeding that counteract the effects of lesions in the perifornical area. This conclusion is further supported by our observation that 3 of the 4 animals with coronal cuts that involved the perifornical region and portions of the hypothalamus medial (but not lateral) to it, resulted in significant overeating (an average increase of 45%) over preoperative baseline. The fourth animal with a very large cut that met
than the remaining rats of this group and this may have been a factor in the weight loss. However, the results of Experiment 1 as well as earlier observations [14] indicate signs of ill health. Both animals drank larger quantities respectively) in food intake and in the absence of any overt period. It is worth emphasizing that this loss of body experimental animals gained as fast as the slowest control and 2 actually showed a net loss for the 30 day observation period. It is interesting to note that the three animals which were hyperphagic after surgery gained weight at a considerably slower rate (0.9 g/day) than controls that were monitored concurrently. The animal which failed to increase its food intake after the cut lost 0.3 g/day on the average in the course of the 30 day postoperative observation period.

Our present observations of the feeding behavior of female rats with coronal cuts just behind the ventromedial hypothalamus (Experiment 2), as well as Sclafani's [24] and Paxinos and Bindra's [21] earlier reports, suggest that the caudal connections of the medial-most portion of the hypothalamus may not be critical for the regulation of food intake. The results of the present experiment confirm this interpretation.

Seven animals which sustained narrow cuts in the coronal plane just behind the ventromedial hypothalamus which did not invade the perifornical region, did not become hyperphagic (see Fig. 10). Food intake averaged 15% above the preoperative baseline (with a range of 8-26%), an increase that was not reliably (p>0.05) greater than that seen in control animals of comparable preoperative weight. One rat which sustained cuts of similar size at a slightly more anterior level (AP = 5.6) overate by 41% after surgery. These results are consonant with those seen in female rats (see Experiment 2, Fig. 5). Cuts in the coronal plane which do not involve anterior sections of the medial hypothalamus apparently do not produce overeating in male or female rats.

Although food intake appeared unchanged or even slightly increased in this group of animals, body weight increased much slower (0.9 g/day) than in controls of comparable age and initial body weight. None of the experimental animals gained as fast as the slowest control and 2 actually showed a net loss for the 30 day observation period. It is worth emphasizing that this loss of body weight occurred in spite of small increases (8% and 9% respectively) in food intake and in the absence of any overt signs of ill health. Both animals drank larger quantities of water after surgery (an average of 157 ml and 223 ml/day) than the remaining rats of this group and this may have been a factor in the weight loss. However, the results of Experiment 1 as well as earlier observations [14] indicate that female rats are capable of gaining weight very rapidly in spite of similarly elevated water consumption.

Cononal cuts immediately behind the ventromedial region of the hypothalamus produced variable effects on water intake. All animals increased their intake after surgery (see Fig. 10) but the magnitude of this effect varied from 23 and 24% of the preoperative baseline (not reliably different from control levels) to 564% (5 of the 8 animals of this group increased their water intake by more than 200%). Inspection of the histological materials failed to provide unambiguous explanations for the differential effects of our cuts on water intake, although it appeared possible that the median eminence may have been involved in the 5 animals which showed the most dramatic increase in water intake. Female rats with similar cuts just behind the VMN displayed only a quite moderate and transient hyperdipsia (Experiment 2, Fig. 5).

GENERAL DISCUSSION

The results of the present series of experiments should lay to rest the recent controversy concerning the effectiveness of knife cuts posterior to the VMN in producing hyperphagia. It is clear from our observations that the effect is readily obtained in female rats when the cut invades the perifornical region and appears to be due to an interruption of fibers which course lateral to the VMN itself. Even on a standard pellet diet which is not particularly palatable to laboratory rats, our cuts produced increases in food intake and accelerations in body weight gain that were as large or larger than any seen after massive lesions in the ventromedial hypothalamus. Cuts through the lateral hypothalamus produced surprisingly small and short-lived inhibitory effects on food and water intake and cuts restricted to the medial hypothalamus immediately posterior to the VMN did not result in reliable changes in either food intake or body weight.

Our data also show quite clearly that the effects of our cuts are significantly different in male rats of the same strain. Large cuts which clearly involve the perifornical region do not result in overeating or obesity. Smaller cuts that are restricted to the perifornical area (as well as coronal cuts through the anterior VMN itself) produced some degree of hyperphagia, but the effects were very small when compared to those seen in the female, and appeared to be capricious (i.e., many rats with substantial damage to the perifornical region did not show a reliable increase in food intake). Moreover, males which did overeat reliably gained weight more slowly than controls of comparable age and initial weight, in contrast to females with similar cuts that quadrupled or even quintupled their preoperative rate of weight gain.

There has been a lively controversy in the literature concerning sex differences in the efficacy of VMH lesions and the issue is not yet entirely settled. A review of the older literature [28] indicated that overeating and obesity are much more readily obtained and much more pronounced in the female than in the male and experimental support for this conclusion is not lacking (e.g., [61]). The issue is, however, complicated by reports that males with VMH lesions or parasagittal cuts lateral to the VMN get just as fat as females with comparable cuts when highly palatable high fat diets are used [9]. Attempts to show that female rats also do not gain weight faster than males on a less preferred powdered food diet [23] have produced less
convincing results, since males with VMH lesions gained little faster than controls during the first 30 days after the lesion whereas females clearly outgained their controls by a wide margin. Although our data may be relevant to this controversy, we believe that the sex differences seen, particularly in Experiments 1 and 2, are of a different magnitude than those previously investigated. Female rats with large knife cuts through the posterior hypothalamus doubled and even tripled their food intake and quadrupled or quintupled their rate of weight gain, whereas males with knife cuts that were as similar as we could make them, showed no reliable increase in food intake and no reliable increase in rate of weight gain. Clearly, this is not merely a matter of degree but a sex difference which suggests a possibly fundamental difference in the organization of neural mechanisms related to body weight setpoint and/or satiety. Matters are less clear when we consider the effects of smaller cuts in the perifornical region which produced a significant increase in food intake in males as well as females. The obvious differences in the magnitude of the effect and its persistence indicate that this too may be a genuine sex difference that may reflect a differential involvement of hormonal mechanisms in the regulation of body weight and food intake but further experiments will be required to strengthen this conclusion.

REFERENCES


