Relationship of the middle hypothalamus to amygdalar hyperphagia

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MORGANE, P. J. AND A. J. KOSMAN. Relationship of the middle hypothalamus to amygdalar hyperphagia. Am. J. Physiol. 198(6): 1315-1318. 1960.—Stereoaxic lesions in the lateral hypothalamus of the cat at the level of the tuberal region were found not to alter food intake or body weight from preoperative control levels whereas lesions restricted to the ventromedial nuclei produced hyperphagia and obesity. Cats with combined lateral and ventromedial lesions showed no changes in food intake or body weight. Cats with combined amygdalar, lateral and ventromedial lesions developed hyperphagia and obesity but the rates of weight gain were about three times faster than occurred with amygdalectomy alone. Food intake in this group after operation more than doubled preoperative levels and the gain in weight of the group during the dynamic phase of obesity amounted to 23.6% as compared to 2.3% for normal and sham-operated controls. It is concluded that the lateral hypothalamus does not function as a 'feeding' center in the cat but that the ventromedial nucleus is probably a 'satiety' center. Furthermore it is probable that inhibitory amygdalar effects on food intake do not operate through the middle hypothalamus since hyperphagia and obesity result from destruction of the entire middle hypothalamus and amygdalae.

In previous papers (1, 2) we presented evidence that the amygdaloid complex in the cat functions normally as an inhibitory center in the regulation of food intake, i.e. as a 'satiety' center in the terminology of Brobeck (3). We have shown that open removal of the amygdaloid complex invariably resulted in hyperphagia and significantly increased rates of weight gain. However, the manner by which this hyperphagia is mediated has been the subject of speculation. It seemed possible on the basis of anatomical and electrophysiological evidence that the amygdalar effects were mediated via middle hypothalamic centers shown to influence food intake in certain animal species (4). Accordingly, this experiment was designed to determine if these amygdalar effects operate through middle hypothalamic centers. As an integral part of this study an evaluation of the middle hypothalamus in the regulation of food intake in the cat was made.

METHODS

Thirty-three adult male and female cats were used of which twenty-four were experimental animals, the remainder serving as unoperated and sham-operated controls. All animals were maintained on an ad libitum diet of fresh horse meat for the entire duration of the experiment. After the initial adjustment to caged laboratory conditions, food intakes (gm/day, dry weight, over 3-day study periods) as well as body weights were determined at approximately weekly intervals.

When measurements of food intake and body weight had been obtained for a minimum period of 8 weeks the experimental animals were divided into four operative groups. Operations were carried out under intraperitoneal Nembutal anesthesia (30 mg/kg). The lesions were produced by means of a modified Horsley-Clarke stereotaxic machine and a d.c. lesion-maker. In the present experiments reference was made to the stereotaxic atlas of the cat's brain by Jasper and Ajmone-Marsan (5) and to the anatomical slides of Ranson kept in the Anatomy Department of the Northwestern University School of Medicine. The operating planes for the middle hypothalamus and amygdala were obtained from these two sources. Before placing lesions in the experimental animals, however, the machine was calibrated from the standard zero points. These anatomical controls indicated that the planes used were in agreement with the atlas and slides of Ranson for producing satisfactory lesions in the desired structures. Duration and intensity of the test currents approximated those reported in the literature (6-8). Group I, nine animals, sustained bilateral lesions in the lateral hypothalamic area described as a 'feeding' center by Brobeck (3); group II, four animals, sustained bilateral lesions in the ventromedial nuclei of the hypothalamus, a satiety center in Brobeck's terminology (3); group III, three animals, sustained bilateral, combined, simultaneously placed lesions in the lateral hypothalamic area and ventromedial nuclei; group IV, eight animals,
sustained bilateral, combined, simultaneously placed lesions in the lateral hypothalamic area, ventromedial nuclei and amygdalae. Postoperatively, body weights and food intakes of all animals were recorded at nearly weekly intervals in a manner similar to the preoperative measurements.

When this study was completed the animals were anesthetized, and the brains were perfused in situ with 10% formalin, and removed. Frozen sections were made at 40-μ intervals and each section in the immediate area of the needle tracts was mounted and stained with a modified Nissl method. Each brain was carefully studied anatomically in order to determine the exact extent of the lesions and this was correlated precisely with the alterations in food intake and body weight seen in the postoperative period.

**RESULTS**

*Group I.* In the nine animals sustaining bilateral lesions in the lateral hypothalamic area none showed...
significant changes in the food intake or body weight postoperatively. The mean postoperative food intake of this group was 60.3 gm/day (7 studies) compared to a preoperative mean of 61.1 gm/day (12 studies). The mean postoperative body weight of this group was 4.48 kg as compared to a preoperative mean of 4.43 kg.

A histological study of the brains of the animals of this group revealed well placed lesions bilaterally in the lateral hypothalamic area in every instance. Figure 1 is a photomicrograph of the brain of a typical animal of this group showing several sections through the middle hypothalamic area with bilateral lesions placed in the lateral hypothalamic area.

**Group II.** Of the four animals with lesions placed in the area of the ventromedial nuclei of the hypothalamus, only one showed hyperphagia and marked weight gain. The mean postoperative food intake of this animal was 137.3 gm/day (9 studies) during the dynamic phase of obesity, i.e., during the period of markedly increased food intake and dramatically increased rate of body weight gain. The preoperative mean food intake was 82.2 gm/day (12 studies). The mean postoperative body weight of this animal was 3.66 kg. Subsequent destruction of the amygdala and lateral hypothalamic area in this animal when it was in the static phase of obesity induced a second phase of hyperphagia and rapid weight gain. The remaining three cats of this group showed no significant changes in the food intake or body weight postoperatively. The mean preoperative food intake of this group was 75.5 gm/day (6 studies) as compared to a preoperative mean food intake of 79.7 gm/day (11 studies). The mean postoperative body weight of this group was 3.92 kg as compared to a preoperative mean of 3.86 kg.

Histological study of the brains of this group showed that the one animal which developed marked elevations of the food intake and body weight in the postoperative period sustained lesions bilaterally in the ventromedial nuclei of the hypothalamus (fig. 2), while the other three animals that showed no changes in the postoperative period had lesions located in two instances 1.0 mm posterior to the ventromedial nuclei and in one instance 1.5 mm anterior to the ventromedial nuclei.

**Group III.** In the three cats sustaining simultaneously placed bilateral stereotaxic lesions in the lateral hypothalamus and ventromedial nuclei there were no significant changes in the food intake or body weight postoperatively as compared to the preoperative period. The mean postoperative food intake of this group was 62.7 gm/day (13 studies) as compared to a mean preoperative food intake of 58.9 gm/day (10 studies). The mean postoperative body weight of this group was 4.32 kg as compared to a preoperative mean of 4.30 kg.

A histological study of the brains of the animals of this group (fig. 3) showed bilaterally placed lesions involving both the lateral hypothalamic area and the ventromedial nuclei.

**DISCUSSION**

Numerous reports in the literature have pointed out the existence of centers in the middle hypothalamus important in controlling food intake in some animal species. The evidence is fairly conclusive that the ventromedial nuclei function as satiety centers (8) in such
species as the rat (9, 12), cat (6, 11, 13), monkey (6, 14, 15), mouse (16) and dog (17, 18). Removal of these nuclei bilaterally in these species has resulted in consistently reproducible hyperphagia and obesity. But clear-cut evidence for the existence of a more lateral feeding center in the cat, removal of which results in aphagia in other species (6, 11), is lacking (13). Since several anatomical and electrophysiological studies have indicated strong connections between the amygdaloid complex and the middle hypothalamic areas (19-21) it seemed possible that amygdalar inhibitory effects on food intake are mediated via these hypothalamic centers. Although the present experiments do not furnish any basis for the regulatory function of the lateral hypothalamus as a feeding center, the observations of Morrison et al. (22) may explain our negative findings. These data indicate that, in the rat, the median forebrain bundle may be as important as the lateral hypothalamic area proper in the control of food intake. A careful histological study of our lateral hypothalamic lesions indicates only partial destruction of this area as described by Krieg (23) in the rat. In all instances, except for the more medial components, the median forebrain bundle is essentially intact. Since the lateral hypothalamus is the bed nucleus of the median forebrain bundle it is possible that lateral lesions must be more extensive for the production of aphagia. On the other hand, Anand and Brobeck (11) in the rat have defined the feeding center as being fairly discrete and always in the same anterior-posterior plane in front or behind the ventromedial nuclei. Moreover, the ventromedial nuclei never produced permanent aphagia. Although hypothalamic hyperphagia occurred in only 1 of our ventromedial animals, it is significant that it was the only animal in which the lesion was perfectly placed. These results in no way refute the satiety function of the ventromedial nuclei but rather imply the existence of this center in the cat.

Regardless of the actuality of hypothalamic feeding centers in the cat, the production of amygdaloid hyperphagia in the absence of much of the middle hypothalamus strongly suggests that amygdalar effects upon food intake are not mediated through this part of the brain stem. The marked acceleration of rate of weight gain of group IV animals as compared to amygdalar lesions alone may be due in part to the less traumatic surgery of the stereotaxic procedure used only in the former group. Another possibility is that the ventromedial nucleus operates as an inhibitory area on food intake in parallel with the amygdaloid nucleus and, thus, removal of both of these structures may result in a faster rate of weight gain than removal of either alone.

Krieg (24) states that the periventricular tract and its continuation, the dorsal longitudinal fasciculus of Schütz, mediate impulses important for the intactness of the feeding reflexes. Amygdalar influences on food intake may pass via this system onto the lower brain stem reflex arcs concerned with feeding behavior. In this regard Larsson (25) has reported hyperphagia in sheep and goats following stimulation of the dorsal motor nucleus of the vagus which is where most descending fibers of the dorsal longitudinal fasciculus seem to terminate. The periventricular system and its continuation would not necessarily be damaged in lesions destroying the ventromedial nuclei and lateral hypothalamic areas in the tuberal region and it is thus possible that amygdalar inhibitory effects on food intake descend via this system.

REFERENCES