ACTA NEUROBIOL. EXP. 1971, 31: 19-32

HYPERPHAGIA PRODUCED BY LATERAL AMYGDALAR LESIONS IN DOGS

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In our previous papers (Fonberg 1965, 1967) the assumption was made, that the baso-lateral part of amygdala consists of an inhibitory alimentary center, similar to the "satiety center" in the ventromedial hypothalamus. This assumption was mostly based on the results of our earlier experiments on cats (Fonberg and Delgado 1960, 1961) which showed that stimulation of the baso-lateral portion of the amygdaloid complex inhibits the food intake and performance of instrumental alimentary reactions. These findings were confirmed on dogs (Fonberg 1963), and on rats (Morgane 1962).

Several authors described hyperphagia after amygdalar ablation (Fuller et al. 1957, Morgane and Kosman 1957, 1959, Schwartzbaum 1961, Grossman and Grossman 1963, Koikegami 1964, and others). In most of the studies, however, large amygdalar lesions or total ablation was performed, and strict localization was not the problem under study or yielded controversial results. For example Wood (1958) observed an increase of food intake after lesions situated in the central nucleus. On the other hand, Green et al. (1957) on the basis of reconstruction of amygdalar lesions on cats stated that the junction between lateral and basal nucleus is crucial for the hyperphagia syndrome. Our recent experiments seem to show, that performing a small circumscribed lesion is a good method to localize the specialized functions of the amygdala. It was found that lesions situated in the dorso-medial part of amygdala produce aphagia with subsequent hypophagia (Fonberg 1966, 1968, 1969ab). However, if lesion involved also the lateral nucleus, subsequent

increase of food intake may occur (Fonberg and Sychowa 1968). In this respect it was interesting to study whether lesion purposely directed to lateral part of amygdala will produce hyperphagia in dogs.

METHOD

Experiments were performed on eight naive, male, mongrel dogs 2–3 years old, weighing from 11–14 kg. The animals were housed individually in home cages about 2.5×2 m wide. Daily measurements of food intake were taken twice a day, at about 8 AM, and at 2:30 PM when the dogs were fed at libitum. The food consisted in cooked cereal with broth and meat. Before the operation measurements were taken during a period of 10–15 days. When the food intake showed a stable level, five last days before the operation were compared with five days just after the operation. The measurement of food intake was continued further from the 6th to 10th day after the operation. Then in all dogs the measurements were again made one month later. In five dog's measurements of food intake were, in addition, performed two months after the operation, and in three dogs also after three months. In between these periods the dogs were not fed ad libitum but got standart portion once a day of about 1.5 kg. Body weight was measured once or twice a week.

Operation. The lesions were performed bilaterally under Nembutal anesthesia by electrocoagulation. The electrodes were stainless steel needles, 0.5 mm in diameter, insulated by enemel except for 0.5 mm on the tip. They were placed stereotaxically, according to coordinates based on the Atlas of Lim et al. (1960). Symmetrical openings were made by removing the skull. Dura was left intact, and electrodes were implanted through the dura. In four dogs (A60, A62, A63, A67) three points were coagulated by moving the electrodes in the vertical plan 1.5 mm up from the next point in order to involve both dorsal and ventral part of the lateral nucleus. In four other dogs (A87, A88, A89, A92) two points were coagulated. A direct anodal current 4.0 ma for 1 min was used. The circuit was completed by means of cathod connected to the skin on the head.

Anatomical verification. When the experiments were accomplished, the dogs were anesthetized and perfused by formaline. Their brains were embedded in paraffine and cut frontally at 20 μ. Every tenth section was stained by Klüver or Nissl method alternately.

RESULTS

After the operation the food intake of all dogs increased significantly (Table II). Arithmetical means for five days before and five days after

TABLE I

Maximal amount of food intake in grams

Dogs	Before operation	After operation
A60	2500	4500 (11 day)
A62	1500	2800 (5 day)
A63	1800	3300 (8 day)
A67	1200	2800 (14 day)
A87	2150	3500 (4 day)
A88	1050	2200 (8 day)
A89	950	1900 (10 day)
A92	2900	4800 (16 day)

TABLE II

Postoperative food intake in percent of preoperative level. Mean values from five days in each period

Dogs	Days 1–5	Days 6–10	One month later	Two months later	Three months later
A60	145.5	168.8	92.0	118.6	114.4
A62	212.0	140.4	84.3	45.0	59.9
A63	121.9	181.0	119.2	96.2	53.8
A67	202.3	237.0	249.0	158.2	
A87	156.9	122.6	131.4	171.9	
A88	170.4	252.0	106.4		
A89	119.4	179.5	129.9		
A92	105.7	153.8	113.0		

the lesion were computed and compared. In all dogs the increase of food intake was statistically significant ($p < 0.01$ Wilcoxon matched-pairs signed rank test, two-tailed). This increase was even greater during next five days, because in some dogs just after the operation a decrease of food intake was observed, due probably to the effect of anesthesia or surgery (Fig. 1 and 2). In most of the dogs however hyperphagia was observed immediately after the operation. For example, dogs A60, and A92 just being awaken from anesthesia ate voraciously at once 1800 g of food. And Dog A87 also ate more than 3 kg the first postoperative day. The dogs A89, and A63 ate less during first few days following the operation,

but a greater increase of food intake showed later on, at the end of a ten day period of observation. In most dogs the maximal amount of food intake was observed in 4–16 days after the operation (Table I).

The dogs not only ate more food but they consumed it more voraciously. They approached the food bowl rapidly and ate quickly, swallowing food almost not chewed. Although the dogs ate very voraciously, they never took into the mouth or swallowed inedible objects. Some of the dogs showed food preference. A special test for finickiness was not performed, but it was noted that food intake increased when the diet was very tasty and multiform, and decreased when the dogs had to eat normal diet. This means that the taste of food was not an indifferent factor.

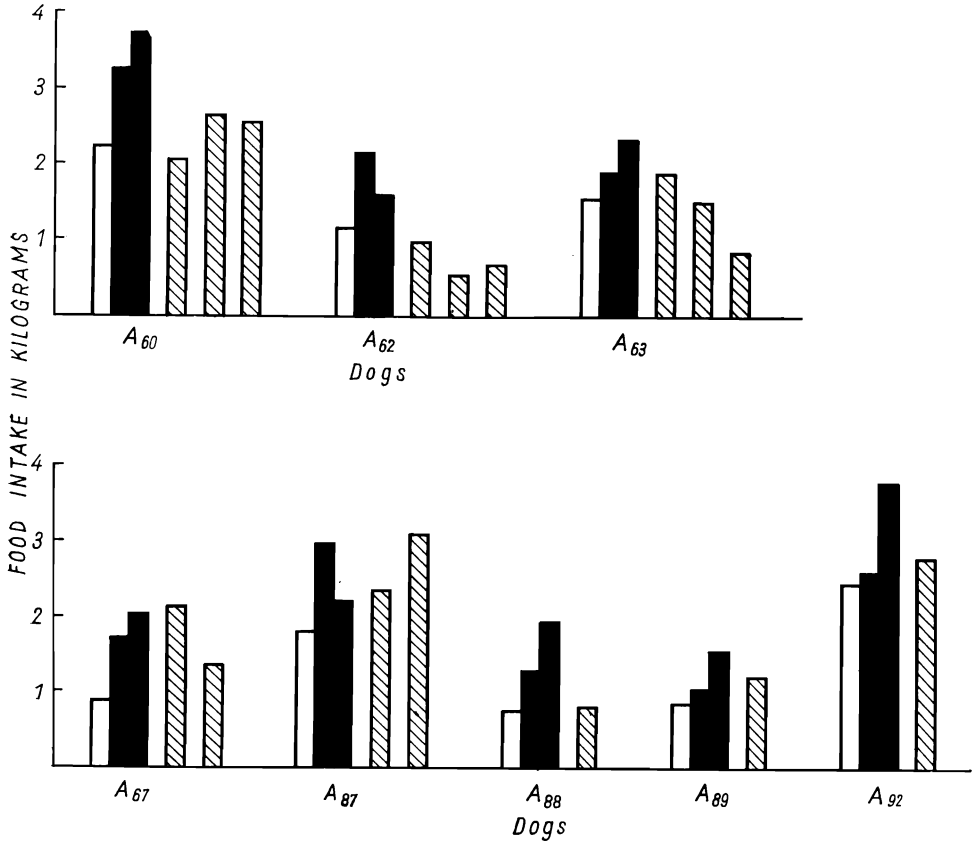

FIG. 1. Increase in food intake after lateral amygdalar lesions in individual dogs. The bars represent the mean food intake in five day periods. White bars, five days immediately prior to operation. Black bars, days 1–5 and days 6–10 after the operation. Striped bars, five day periods one month two and three months later.

Body weight increased also consistently, but the increase was not so great (about 6–21% of preoperative level) (Fig. 3). Following the ten days postoperative period the dogs were not fed at libitum during the whole subsequent period, therefore the gain of weight was beyond the

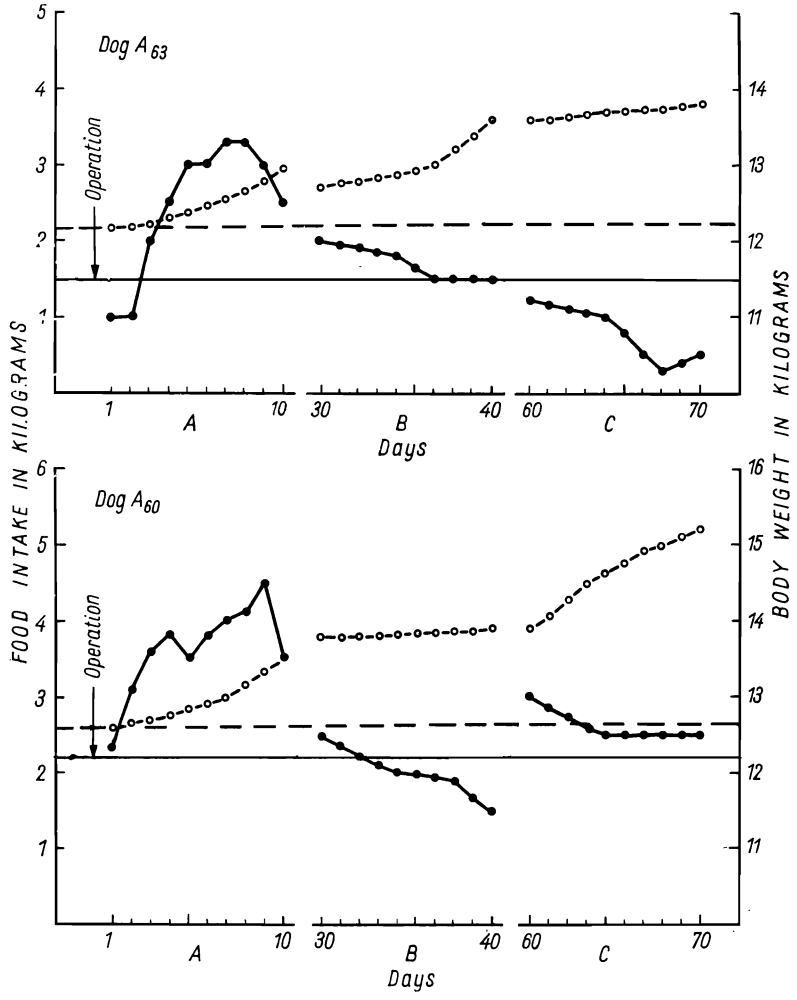

FIG. 2. Comparison of the course of changes in body weight and food intake produced by lateral amygdalar lesions in two representative dogs. Note the discrepancy between these two parameters in the late period after the operation. Solid horizontal line, level of the preoperative food intake. Broken horizontal line, level of the preoperative body weight. Solid line with circles, course of the postoperative food intake. Broken line with open circles, course of the postoperative body weight. *A*, ten day period just after operation; *B*, one month after the operation; *C*, two months after the operation.

subject's own control. The next periods of ad libitum feeding and food intake measurement were performed four weeks and then two months after the operation.

As seen in Fig. 1 and 2 the hyperphagia persisted or even increased in some dogs in this late period after the operation. In some others dogs the food intake dropped to the preooperative level, or even below it. The comparison of the amount of food intake and body weight reveals interesting facts. In the first weeks after the operation the food intake increased and the body weight increased in consequence. Later, the

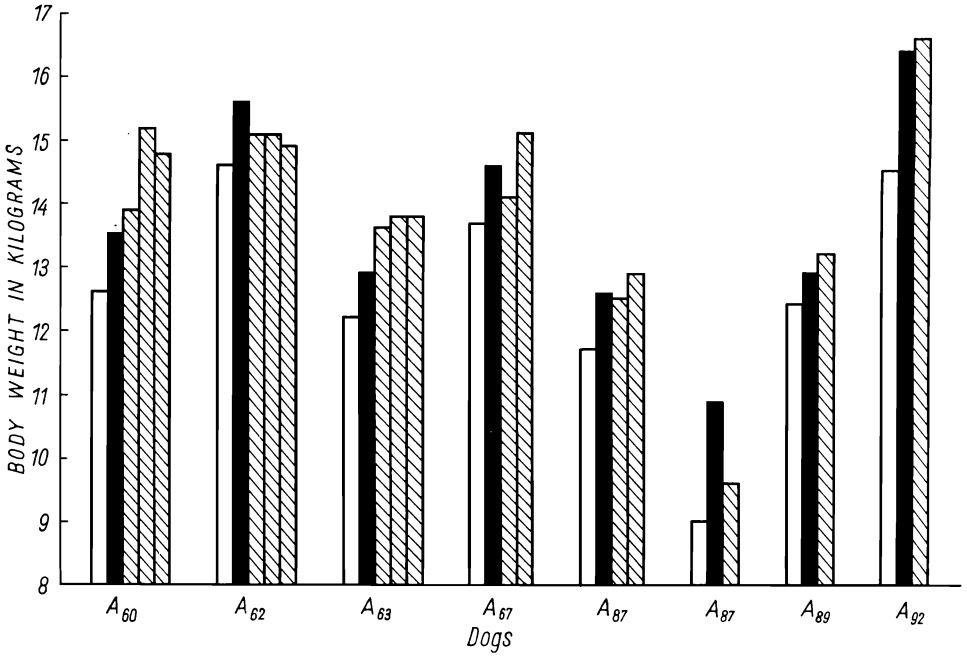

FIG. 3. Increase of body weight after lateral amygdala lesions in individual dogs. Bars represent the body weight before the operation (white bars), on 10th day after the operation (black bars), and one, two and three months later (stripped bars).

amount of food consumed had, in most of the dogs, the tendency to drop to the preoperative level or even below it. In spite of this fact the increase of body weight progressed (dogs A60, A63, A67, A89), or at least maintained a stable level (dogs A62 and A92). The dog A87 was an exception. In this dog food intake increased in parallel with an increase in body weight. Another exception was dog A88, in which body weight after one month decreased to the preoperative level with a similar decrease of food intake. This dog, however, before the operation usually ate very little, much less than the other dogs.

The general behavior of the dogs was not greatly changed. They were more lively, gay and friendly, they jumped, rolled or played like puppies. They greeted affectionally the experimenter and asked for petting. They were also rather friendly toward other dogs, and if exposed to the agressivenes of these last they responded with a kind of orienting reaction and slow withdrawal. The dogs which were normally fastidious and shy lost these habits and became voracious and brave after the operation (Fig. 4 and 5).

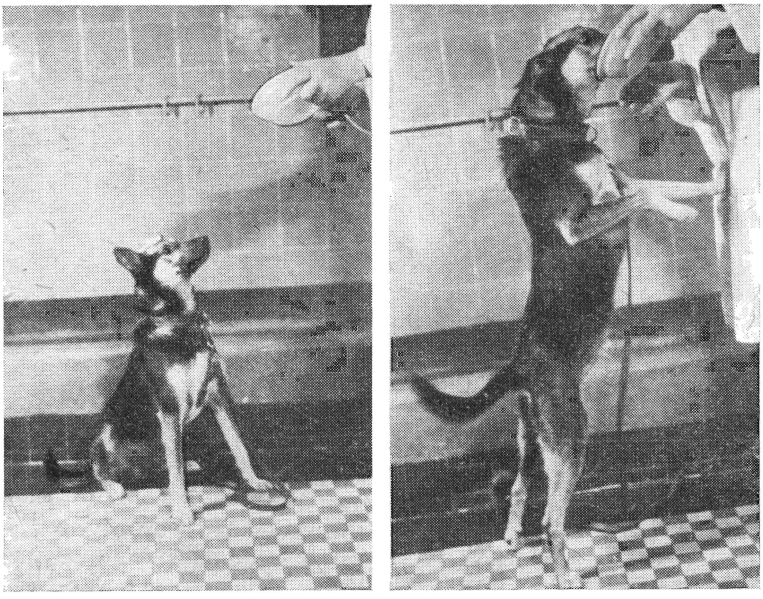

FIG 4. Dog A87 on 5th day after the operation. Note lively behavior and attitude toward food bowl.

Anatomical verification. In all the dogs the lateral nucleus of the amygdaloid complex was damaged bilaterally, in some dogs only on its ventral posterior part. Only on dog A88 lateral nucleus was damaged only unilaterally on its lower left posterior part, and besides that right hippocampus was touched. A larger lesion was found in dog A63. It involved on the right side almost the whole lateral nucleus and part of the central, and on the left side, beside damaging the lateral nucleus, the lesion reached also the basal nucleus (magnocellular part, and upper edge of the parvocellular part), and part of medial and central nuclei. In dog A 60 on the left side a part of basal and central nuclei, and lower edge of putamen were also damaged.

The capsula externa and the neighbouring part of the temporal lobe was damaged unilaterally on the right side on most of the dogs: (A60, A62, A67, A87, A88, A89, A92).

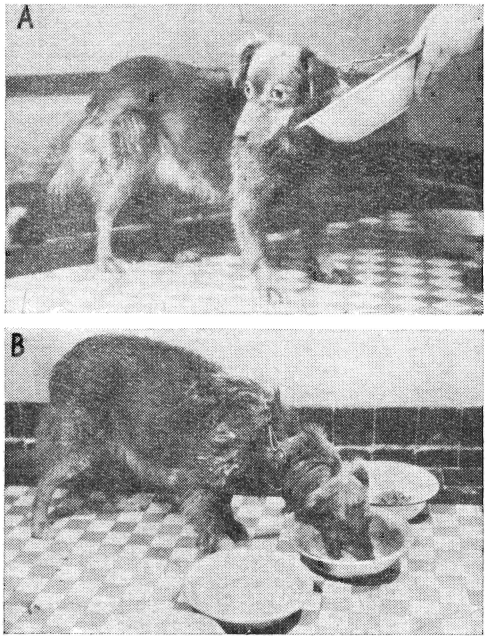

FIG. 5. Voracious eating in a dog A88 (*B*) which before the operation was shy and fastidious (*A*).

In two dogs the electrode tract cut unilaterally the fibers of capsula interna on its lateral portion, on the left (A92) or right side (A87). Figure 6 shows the representative photographs of the typical lesions of four dogs, with larger lesions (A60, A63) and small lesions (A89, A92) limited to the ventral posterior part of lateral nucleus and the neighbouring part of the pyriform lobe.

DISCUSSION

The results of the present experiment show that lesions of the lateral part of the amygdala on dogs result in hyperphagia. These findings are consistent with those of Green et al. (1957) which showed that lesions of the baso-lateral part of amygdala caused hyperphagia on cats. They fit also with our previous work on the effect of stimulation of the baso-lateral part of amygdala on cats (Fonberg and Delgado 1961) and dogs (Fonberg 1963, 1966), and with the preliminary report on the effect of lateral amygdalar lesions (Fonberg 1969 c). In the experiment performed on dogs, the most efficient localization of the electrodes points, (i.e. those

in which stimulation resulted in the inhibition of food intake), were in the ventral part of the lateral nucleus. In the present experiments the lesions involved in most dogs also the lower part of lateral nucleus, and touched basal nucleus unilaterally on two dogs. Therefore it may be suggested that lateral nucleus in its ventral part is the most responsible for the inhibitory alimentary mechanisms.

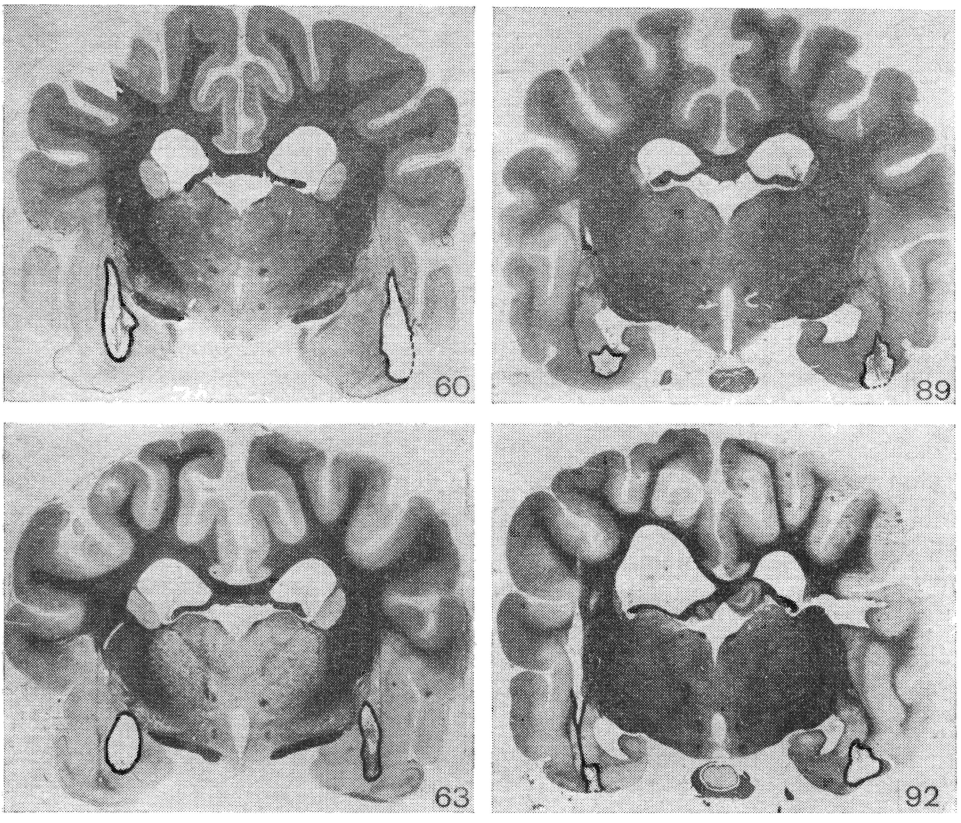

FIG. 6. Typical lesions of four representative dogs. Borders of the lesions are outlined.

Anand and Brobeck (1952) also found hyperphagia on cats as a result of lateral amygdala lesions. They stated however, that the increase in food intake was only in these cases when the neighbouring part of temporal lobe, lateral to the amygdala was damaged. In most of our dogs this area was also damaged although only unilaterally. So, the hypothesis cannot be excluded, that the part of temporal lobe lateral to amygdala, or the fibers of capsula externa which were also damaged by our lesions, are important for the hyperphagia syndrome.

According to Wood (1958) lesions of central nucleus produced hyperphagia in cats. As it is known that fibers from lateral nucleus pass through this area, it may be suggested that in this case hyperphagia was caused by cutting of the pathways conducting inhibitory impulses to the hypothalamic feeding centres, from lateral amygdala. With such an explanation the discerepancy between our and Wood's results might be overcome.

It was suggested previously that the baso-lateral part of the amygdala acts as an additional inhibitory or "satiation" center, similar to the ventromedial hypothalamic center (Morgane and Kosman 1959, Fonberg 1965).

The most reasonable assumption seemed to be that lateral amygdalar nucleus acts on the hypothalamus, either by sending inhibitory impulses through the ventromedial "satiation" center, or acting directly upon the lateral hypothalamus. The longitudinal association bundle (Hall 1963), or diffuse ventral system (Nauta 1962, Valverde 1965) could be the pathways for the conduction of such impulses. Oomura et al. (1967) found that there exist negative reciprocal correlation between the spontaneous electrical activity of lateral hypothalamus and lateral amygdala. Moreover, stimulation of the lateral amygdala inhibits the spontaneous activity of the neurons in lateral hypothalamus, and produces an increase in the electrical activity of the ventromedial hypothalamus. Ooniani et al. (1968) found that evoked potentials during stimulation of lateral amygdala have lower threshold in lateral than in ventromedial hypothalamus. These finding prove the close functional relation between the lateral amygdala and lateral hypothalamus. Therefore, after the lesions of lateral amygdaloid nucleus, the lateral hypothalamus liberated from the inhibitory influence may become activated and this activation may cause enhanced appetite or increase of food-intake. On the other hand, there exist some evidence that the lateral hypothalamus is not indispensible in developing the syndrome of hyperphagia. In a dog in which lateral hypothalamus was destroyed, and thereafter aphagia and later hypophagia and apathy was observed, the subsequent lesions of lateral amygdala caused immediate hyperphagia, restoration of energy and increase of weight. The effect of lateral amygdalar lesions were much more spectacular if the operation was performed on a previously aphagic dog (Fonberg 1969b).

The inhibitory influences from the amygdala may therefore act not through hypothalamus but directly on the midbrain feeding centers or lower structures. As shown by Skultety (1968) in mesencephalic central gray and also in the ventrolateral part of midbrain there exist areas which destruction causes an increase of food intake. In addition, Larsson (1954) found that stimulation of the medulla oblongata, in the vicinity of

the vagal nucleus produced food intake. Skultety (1958) showed that midbrain lesions also reverse the aphagia syndrome produced by damage of lateral hypothalamus. Therefore, he concluded that lateral hypothalamic region does not constitute a "primary feeding center".

As hypothesized in our previous work (Fonberg 1969a,b), the hypothalamic "feeding center" is doubled in the dorso-medial amygdala. Could we assume also that the hypothalamic ventromedial "satiation" center is doubled in the lateral amygdala?

If we make the comparison between the hyperphagia produced in dogs by ventromedial hypothalamic lesions (Rożkowska 1970) and lateral amygdalar lesions, we can point out at least two differences. At first although both groups of dogs are voracious, the amygdala dogs, in spite of the fact that they ardently strive for food, when fed ad libitum stop eating after consuming about 50–150% more than before the operation. On the contrary, the ventromedial dogs, at least some of them during the first days after operation, even if overfed, did not stop eating at all, to the point where they were not able to walk. Therefore, they could not be fed ad libitum, in danger of stomach rupture.

The second striking difference is that ventromedial hypothalamic dogs are more quiet and apathetic than before the operation, while lateral amygdalar dogs are much more lively, gay and interested in the environment. This may mean that the inhibitory effect of ventro-lateral amygdala is more general, and that ventromedial hypothalamic mechanisms are more specifically connected with alimentary functions. On the other hand, the close vinicity of the upper part of reticular formation may also acount for the lack of energy in hypothalamic dogs. There exist however some striking resemblances of the effects of ventromedial hypothalamic and lateral amygdalar lesions. Brobeck et al. (1943) and Teitelbaum and Campbell (1958) described several stages of ventromedial hyperphagia on rats. The first stage which he named "dynamic hyperphagia" was characterized by increased food intake (two or three times of preoperation level) and increase of body weight. In the second stage the food intake reached a stable level but body weight increased. This stage he called "static phase". Dogs with lesions in ventromedial hypothalamus showed similar stages (Rożkowska 1970).

In our amygdalar dogs these two stages can be also distinguished. The first period was characterized by increased food intake although this increase was never as great as after ventromedial hypothalamic lesions and usually consisted in about 50–150% of preoperative level. It was followed by an increase of body weight. In the second period, which can be compared with Teitelbaum's static phase — the food intake in most of the dogs dropped to the preoperative level, or even lower but body

weight increased further, or kept a high stable level. This shows that by a decrease in their food intake dogs have a tendency to regulate the increase of weight. Even a prominent decrease of food intake below the preoperative level (Fig. 2) was not able to produce a significant drop in body weight. If, however the dog eats as much as before the operation the body weight increases greatly. The exception is dog A87 in which food intake and body weight increased together with time. Another exception is dog A88 in which with a decrease of intake body weight decreased too. In this last dog the lateral nucleus was damaged only unilaterally.

These last facts seem to show that the impairment caused by lateral amygdalar lesion does not only concern the hunger drive or appetite but also consist of changes in metabolic regulation. The resemblance between the ventromedial satiation center and lateral amygdalar inhibitory center extends therefore also in this respect. This suggests that not only is the positive alimentary center "doubled" in hypothalamus and amygdala, but also the "satiation center" has double representation it these two structures. This does not say, however, that the alimentary system is limited to the hypothalamus and amygdala. Several experiments show that the alimentary "centers" are widespread on different levels of the central nervous system and that the complicated interplay of inhibition and excitation of different "centers", or "crucial points", accounts for changes in alimentary behavior. The anatomical studies (Gloor 1955, Guillery 1957, Nauta 1962 and others) support the idea that this system consists of multiples circuits with collateral branches, and therefore it is not possible to localize strictly particular alimentary functions. Several points within the alimentary system seem to yield similar effects and double each other, although not totally but with some specific features. The doubling or even multiplying of "feeding centers" does not mean that all of them are equivalent. The problem of specific function of each of link of alimentary system needs however further investigation.

Although the balance between the excitatory and inhibitory influences within the whole alimentary system seems to be of basic importance, it is difficult to accept Morgane's recent statement (1969), that there is one general energizing or drive state dependent on activity of extensions of the reticular core.

On the contrary, it seems evident that in amygdaloid complex, hypothalamus and mesencephalon there are specific neurons dealing with different drive functions (alimentary, defensive, sexual, etc.). Morever, although within a given system the particular structures may in some extent replace each other (especially in the case of compensation of lesion), in the same time they maintain their specificity.

SUMMARY

Lateral amygdalar lesions were performed on eight dogs. After operation the dogs were more friendly and lively, and showed an increase of food intake (about 50–150% of preoperative intake) and an increase in weight (6–21%). Two "phases" could be distinguished. During the first postoperative period the body weight increased paralelly with the increase of food intake. Later, the increase of weight progressed in spite of the reduction of intake. The possible mechanisms of the doubling and interaction of "inhibitory alimentary centers" were disscussed.

This investigation was partially supported by Foreign Research Agreement no. 287 707 of U.S. Department of the Health Education and Welfare under PL 480. The author is greatly indebted to Drs K. Zieliński and T. Górska for valuable remarks and to Mrs H. Kurzaj and Mrs. M. Raurowicz for technical assistance.

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Received 5 May 1970