THE EFFECTS OF VENTROMEDIAL HYPOTHALAMIC LESIONS ON FOOD INTAKE AND ALIMENTARY INSTRUMENTAL CONDITIONED REFLEXES IN DOGS

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There is considerable evidence that the ventromedial part of hypothalamus is an important part of the alimentary system playing the role of the satiety center. Several experiments have shown that bilateral lesions of the ventromedial hypothalamic nucleus produce marked overeating and lead to obesity. Conversely electrical stimulation of this area by means of chronically implanted electrodes inhibits eating (Hoebel and Teitelbaum 1962, Krasne 1962).

Although dogs were the first experimental objects in which the observations concerning the role of the hypothalamus in obesity were made (Bailey and Bremer 1921, Heinbecker et al. 1944, and others), further experiments were carried out almost exclusively on other species such as rats, rabbits, sheep, goats and monkeys. In our previous reports (Rożkowska and Fonberg 1970, Glavcheva et al. 1970) it was demonstrated that the lateral hypothalamus plays the role of a feeding center also in dogs. Besides supporting the studies of other authors on different species, the experiments on dogs furnished some new data. For example, the vomiting symptom, which as a rule accompanied the aphagia or hypophagia syndrom in our experiments, was not described by other authors. We also found various changes in instrumental performances to the conditioned stimuli which were not observed in other species. Therefore, it was interesting to study the role of the ventromedial nucleus of hypothalamus on dogs and to ascertain whether it is really a satiation center. As the dog is a perfect subject for instrumental training, we were also interested in studying the motivational changes following hypothalamic

lesions. Several authors reported that after ventromedial hypothalamic lesions, in spite of hyperphagia the animals showed a lowered motivation as measured by their ability to perform tasks rewarded by food. In our work we were interested in the effect of ventromedial hypothalamic lesions on the alimentary differentiation. We supposed that if the operation affected the instrumental performance to positive stimuli, it could indicate the decrease of motivation. The disinhibition of the instrumental reaction to unrewarded stimuli could indicate either an increase of the alimentary drive, or an impairment of inhibitory mechanisms. The aim of the paper was to elucidate these problems.

MATERIAL AND METHODS

Training. The experiments were performed on 17 naive mongrel dogs, 12 experimental and 5 control, 2–3 years old, weighing 8–12 kg.

Group I (seven dogs) was trained before the operation. The alimentary instrumental CR was established in a sound-proof conditioning chamber according to the Konorski and Miller method (1933). A sound with a frequency of 1000 cycle/sec from a generator was used as a CS. The instrumental response, which consisted in putting the right forepaw on the feeder, was immediately reinforced by offering 12.5 g of food (a piece of bread moistened with broth and sprinkled with boiled minced meat). As soon as the positive instrumental alimentary CR had been established to the criterion of 100% of performance during the last 10 experiments (100 trials), differentiation was trained. A new acoustic stimulus with a frequency of 700 cycle/sec was introduced without reinforcing it with food (a negative CS). Each experimental session consisted of 20 trials (10 positive and 10 negative), applied at random with intertrial intervals of about 1 min. The dogs were trained to a 95% criterion, that is, to 95 correct responses to a negative CS performed in the last 10 experiments.

Group II (five dogs) was trained after the operation.

Group III (five dogs) was used as a control for the Group II. The dogs were not operated and the differentiation training was performed parallely to that in the Group II.

Surgery. The ventromedial nucleus was destroyed by means of electrocoagulation in a stereotaxic apparatus under the Nembutal anesthesia and in aseptic conditions. In all the dogs one point on each side was coagulated with a 4 ma anodic d-c was applied during 1 min by means of either stainless steel or platinum electrodes. For coordinates the atlas of Lim et al. (1960) was used.

Measures of food intake. The amount of food and water ingested ad libitum once a day has been measured for 10 days before and 30 days

after the operation, and for 20 days after a month's interval. Standard food was used as a rule i.e. broth with cereal and boiled meat. The preference test to various kind of food and to food with a small admixture of quinine hydrochloride was tested sporadically.

The dogs were weighed in 4 day intervals: 5 times before the operation, 10 times after the operation and again 5 times after one month's interval.

Experiments were resumed on the third postoperative day. Observations were carried on during 4–5 months.

Histology. The brains were perfused with 10⁰/₀ formalin. Four brains were embedded in paraffin and 20 μ thick slices were stained alternately by means of the Klüver and Nissl methods. The remaining brains were frozen and 40 μ thick slices were stained by means of the Klüver method.

<div align="center">RESULTS</div>

<div align="center">*Food intake*</div>

After the operation a two or threefold increase of food intake was observed from 8 to 32 days (Fig. 1 and 2). During the first postoperative period, a sudden increase in food intake was observed, which reached
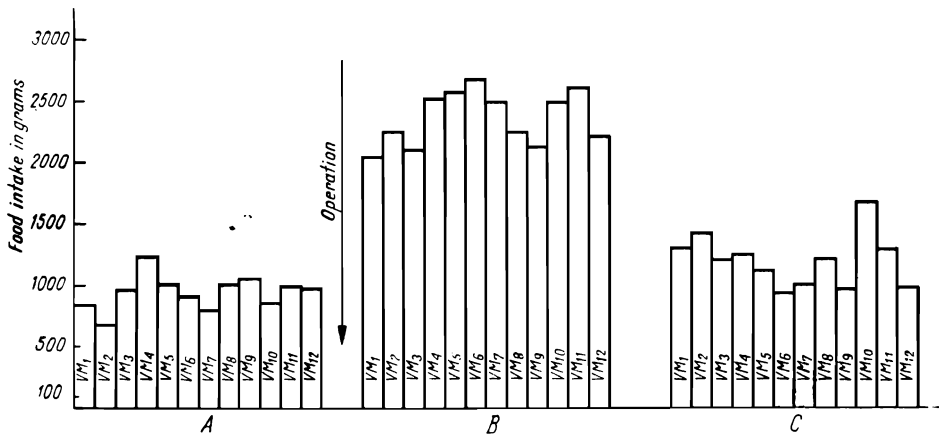

Fig. 1. Mean food intake for each dog during 10 day's periods: *A*, before the operation; *B*, after operation; *C*, 2 months after the operation.

its peak on 18th day, and was accompanied by a rapid increase in body weight (Fig. 3). The dogs ate voraciously great amounts of various kind of food and devoured even meatless or tastless food and also food with small admixtures of quinine. During the second period (within 2–4 weeks after surgery) they gradually ate less and less, but nevertheless no de-

crease was observed in their body weight. In this period they
showed the preference to the palatable and high-caloric food, and refused
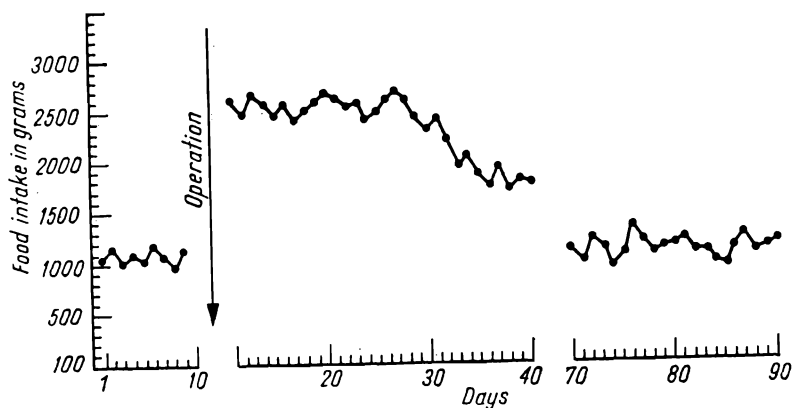to eat food spoiled by quinine. After 2 months the amount of food ingest-

Fig. 2. Daily food intake in the representative dog (VM₄).

ed by dogs VM₁, VM₃, VM₅, VM ₁₀ and VM₁₁ again increased slightly and
their body weight all the time remained on a level somewhat higher
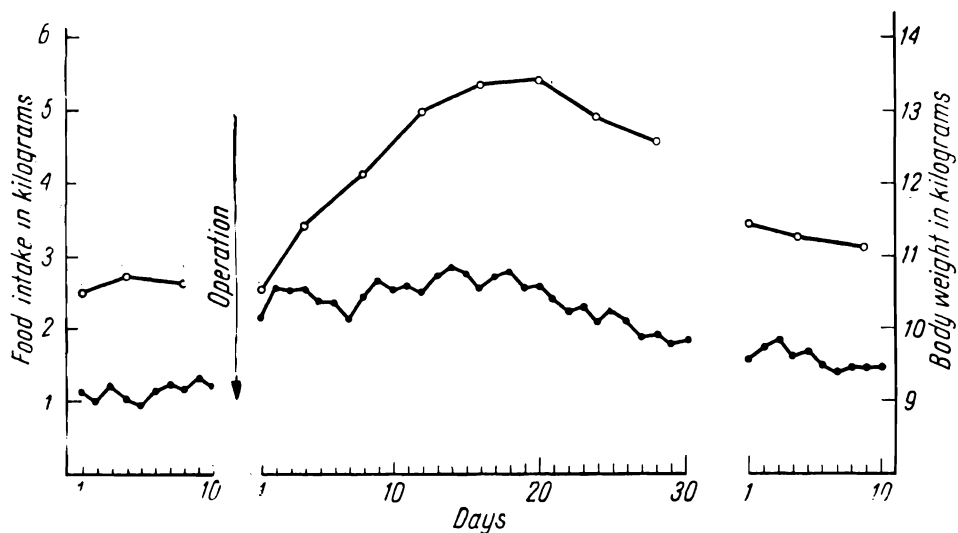than prior to surgery. No changes have been recorded in the water intake.

Fig. 3. Comparison between the mean food intake and mean body weight before
and after operation in all dogs. Line with circles, food intake; line with open
circles, body weight.

General behavior

During a few postoperative days, the dogs displayed an increased nervousness and excessive excitation when the time of feeding was closing in. They ran around, barked, reared and tried to climb the walls of their cage. When they were offered food, they jumped at it and ate voraciously, often choking with the morsels swallowed and immediately demanding new helpings. After having eaten too much, they became inert, torpid and apathetic (Fig. 4). Some of them were so insisting that
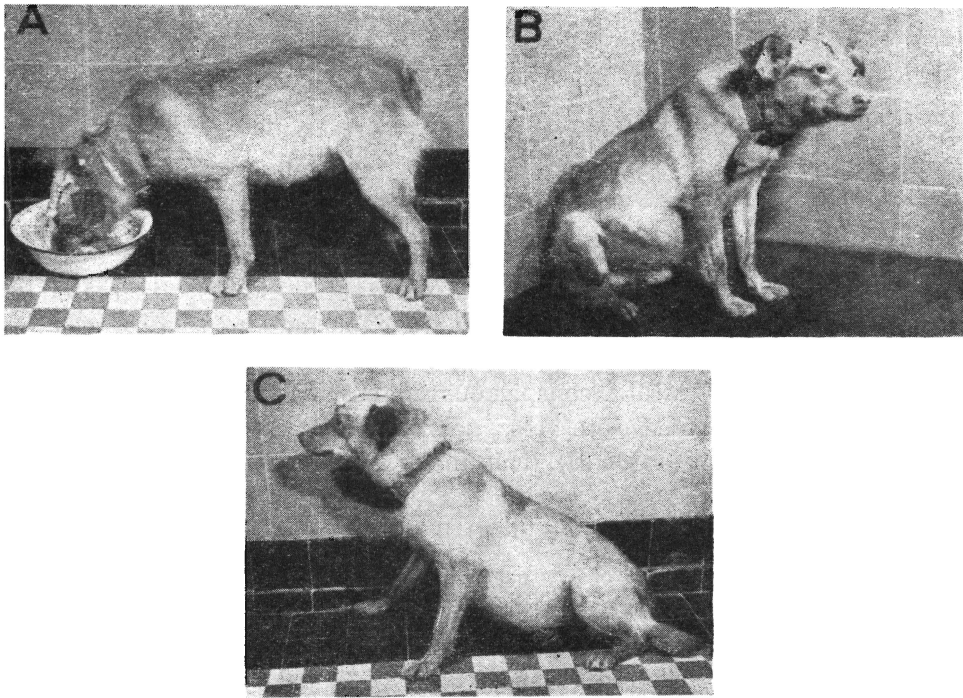

Fig. 4. Hyperphagic dog (VM₁₁). *A*, voracious eating; *B* and *C*, positions after overeating. Note the overloaded abdomen.

they had to be fed three times a day, while before the operation they were fed only once a day. Within 2 to 3 weeks they became calmer and ate less voraciously. They were friendly towards humans, except for dogs VM₆ and VM₁₁ who growled when approached, but even these dogs never attacked people or other dogs.

Instrumental differentation: Group I (VM₁–VM₇)

After operation all dogs displayed only slight impairment of instru-
mental differentiation and all of them reached the criterion within 5–9
successive sessions (Table I).

TABLE I

Number of errors in negative trials in Group I

Dog	Before lesion (last 10 sessions)	After lesion (first 10 sessions)
VM_1	1	4
VM_2	2	7
VM_3	0	0
VM_4	2	8
VM_5	2	3
VM_6	3	9
VM_7	1	2

As follows from Table I the number of erroneous responses to a ne-
gative CS during 10 successive experiments after surgery increased as
compared with the period of the last 10 experiments prior to electro-
coagulation. This difference is statistically significant at a level of
$p < 0.05$ (Wilcoxon test). A conspicuous increase in the number of move-
ments during intertrial intervals, persisting for 10 to 28 days, was
observed in all dogs (Table II). This difference is statistically significant

TABLE II

Number of intertrial movements in Group I

Dog	Before lesion (last 10 sessions)	After lesion (first 10 sessions)
VM_1	0	138
VM_2	3	49
VM_3	6	79
VM_4	1	124
VM_5	1	162
VM_6	2	104
VM_7	0	96

at a level of $p < 0.001$ (Mann–Whitney test). At the end of observation
period (after 5 months), only dogs VM_4 and VM_5 performed some inter-
trial movements.

Instrumental differentiation: Group II (VM_8-VM_{12}) and Group III

The training of the dogs has been started on the third postoperative day and consisted in establishing an instrumental alimentary CR to a positive CS. It was noticed that the dogs adapted themselves unusually fast to the experimental conditions (within 1–2 days). Even on the first experimental day they put their forepaws on the feeder and instrumentalization of these movements was very easy (Table III). They reached

TABLE III

Duration of instrumental training to the positive CS

Group II (operated)		Group III (control)	
Dog	Days	Dog	Days
VM_8	3	C_1	9
VM_9	7	C_2	14
VM_{10}	4	C_3	11
VM_{11}	6	C_4	13
VM_{12}	8	C_5	17

the criterion of 100% of performance to the positive stimulus within 3–8 days. A statistical analysis of the Group II of dogs VM_8-VM_{12} was compared to a control group (five non-operated dogs). The difference between these groups was statistically significant at a level of $p < 0.01$.

After the dogs had learned the positive instrumental reaction, a negative CS was introduced and the establishment of differentiation was started. During 11–22 experiments, the dogs reached a 95% criterion (Table IV).

TABLE IV

Duration of differentiation training

Group II (postoperative training)		Group III (control)	
Dog	Days	Dog	Days
VM_8	22	C_1	21
VM_9	20	C_2	18
VM_{10}	18	C_3	24
VM_{11}	11	C_4	26
VM_{12}	14	C_5	17

The dogs of the Group III (control) reached the some criterion within 17–26 experimental sessions. The difference in the rapidity of differentiation training between Group II and III is statistically insignificant. In

all the dogs from Group II a much higher number of the intertrial move-
ments than in the control dogs has been observed ($p < 0.001$, Mann–
Whitney test). At the end of the observation period (4–5 months), this
number considerably decreased.

Anatomical verification of the lesions

In all dogs the lesions included bilaterally the ventromedial hypotha-
lamic nucleus. In addition in dogs VM_8 and VM_9 the dorsomedial nucleus,
part of the dorsal nucleus, lower part of the periventrical area and part
of the ventrolateral nucleus were damaged. In dogs VM_1, VM_3, VM_5 and
VM_{11} the medial part of the fornix was damaged (Fig. 5).

DISCUSSION

These results clearly indicate that bilateral lesions of the ventromedial
hypothalmus involving the ventral part of the dorsomedial nucleus prod-
uce a marked increase of food intake which is two or even three times
larger than before the operation and which persists during about 3–4
weeks. During this period, the dogs ate voraciously and put on weight
(on the average of 3 kg). Gradually they ate less and less, but their body
weight remained at a high level for a long time. Our results are in agree-
ment with those of other authors obtained after ventromedial lesions of
the hypothalamus mainly on rats and also on various other species (Hein-
becker et al. 1944, Brobeck 1946, Ruch and Patton 1946, Anand and
Brobeck 1951, Romaniuk 1962, Balińska 1963, Hamilton and Brobeck
1964, and many others) and indicate that the ventromedial nucleus of
the hypothalamus plays a role of the satiation center in alimentary me-
chanisms.

There exist, however, a different group of authors who believe that
hyperphagia produced by hypothalamic ventromedial lesions is an arte-
fact produced by prolonged irritation of the "alimentary center" in the
lateral hypothalamus, caused by the deposition of iron ions in its vicinity
following electrocoagulation accomplished by means of steel electrodes
(Reynolds 1965, Rabin and Smith 1968, and others).

On the other hand, it was demonstrated that hyperphagia may be
evoked without the use of electrolytic lesions. Sclafani and Grossman
(1969), and Gold (1970) observed an increase of food intake in rats in
which a small incision was made between the ventromedial and lateral
nucleus of the hypothalamus. Hoebel (1965) obtained hyperphagia by
means of lesions caused by a radio-frequency current. To avoid the
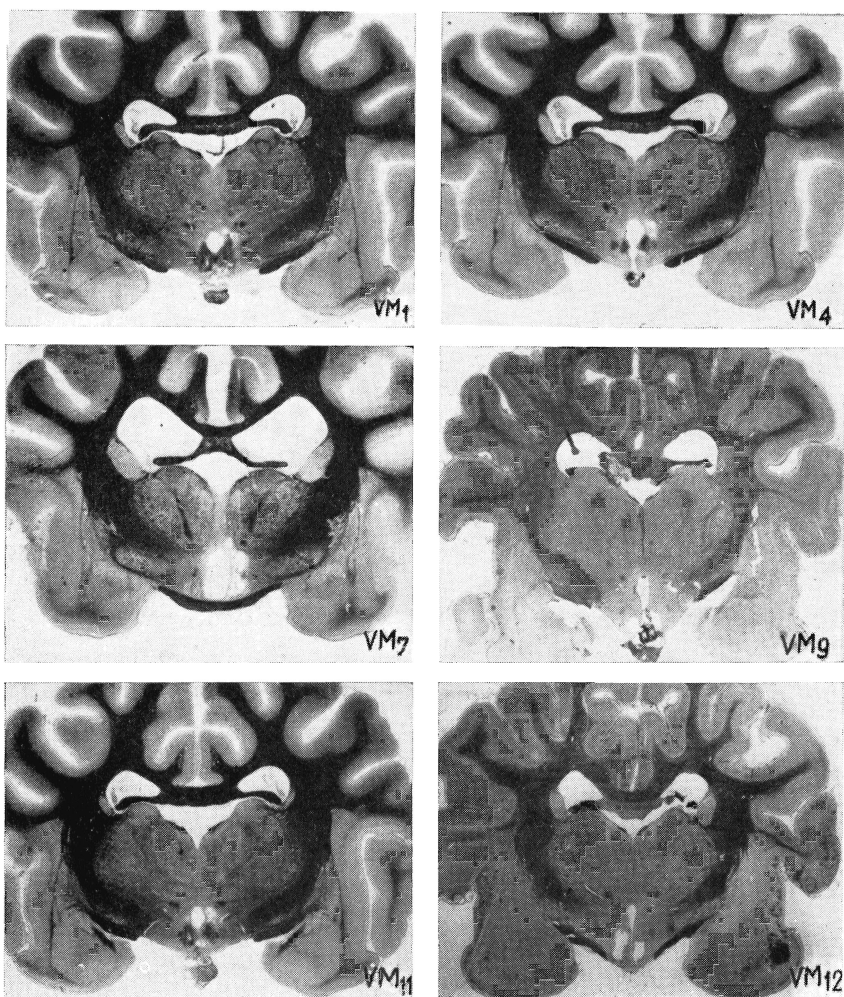deposition of metal ions, in some dogs iridium platinum electrodes were

Fig. 5. Frontal sections of the representative brains with ventromedial hypothalamic bilateral lesions.

used, but we observed hyperphagia and increase in body weight, similar to that in dogs lesioned by means of stainless steel electrodes.

According to several authors electrical lesions or excitation of the ventromedial hypothalamic nucleus cause chiefly changes in the emotional state of the animals (Wheatley 1944, Wyrwicka and Dobrzecka 1960, Krasne 1962, Romaniuk 1962, Grossman 1966, Lewińska and Romaniuk 1966, Fonberg 1967, and others). In our experiments, an increased timidity after the operation was observed only in two dogs. It has been shown by an anatomical verification that in these dogs the lesions were more extensive than in other dogs and included, in addition to the ventromedial nucleus, also a considerable part of the dorsomedial nucleus and a part of the periventricular area. Our observations, clearly indicate that after ventromedial hypothalamic lesions changes in the emotionality of the dogs were rather small, and that the main effect of these lesions concerned the alimentary functions, i. e. increased food intake and body weight. Probably in the ventral medial part of the hypothalamus there exists a separate group of neurons mediating defensive and alimentary mechanisms. Wyrwicka and Dobrzecka (1960) were able to divide these two effects by electrical stimulation of different points in goats. They found that separate points exist, ones the stimulation of which evoked a cessation of eating with obvious emotional-defensive signs, others the stimulation of which had a purely inhibitory influence on food intake. Only these last points revealed the rebound-effect i. e. voracious eating after stimulation cessation. In our two exceptionally timid dogs besides the satiation center also the defensive centers might have been also reached by the lesions. The main effect of the ventromedial lesion concerns, however, as it was shown, the alimentary functions.

The occurrence of hyperphagia is probably evoked by disorders in the satiety controlling mechanism. Sharma et al. (1961), Anand and Pillari (1967) observed that under normal conditions the ventromedial nucleus receives impulses from contractions of the stomach's wall and, therefore, in the case of lesion, information from the receptors of the stomach does not reach the hypothalamus and consequently, hyperphagia develops. As a result of a lesion of the ventromedial nucleus, which according to Anand (1961), Mayer (1955), and many others is the main chemical analizer of the content of nourishing blood components, humoral stimuli do not exert as strong an influence on the control of food intake as previously, while the main role is played by such stimuli as, food taste and smell, as well as memory traces of the sensations connected with food ingestion. Consequently, the animals eat very much if supplied with, tasty food and put on weight.

Many physiologists, such as Teitelbaum (1957, 1964), Balińska (1963),

Corbit and Stellar (1964), Mook and Blass (1968), and others, emphasize that the animals with lesions of the ventromedial hypothalamic nucleus become very fastidicus despite their voracity. They are sensitive to both positive and negative gustatory qualities of their diet and refuse eating food mixed with neutral substances, while normal animals in such cases usually increase their food intake to meet the caloric demand. According to these authors, hyperphagic subjects also refuse food with admixtures of small doses of quinine, which are still accepted by normal animals. An increase in gustatory and nourishing values of the diet increases hyperphagia in ventromedial rats, whereas normal animals eat less, because of the raised caloricity of the food (Teitelbaum 1955). In the experiments, in which the taste was omitted by using a technique of intrastomach feeding, the hyperphagic animals refused to perform their task (pushing the lever), which consequently led to starvation (McGinty et al. 1965). These authors believe that taste plays a great role in the occurrence of hyperphagia and obesity and that it is a very strong motivational stimulus.

The dogs we observed during the first postoperative weeks did not display any distinct preference for food with increased gustatory values. They ate voraciously large quantities of meatless food, as well as food with a small admixture of quinine. Later, that is, after 3–4 weeks, when the amount of food ingested gradually decreased, the dogs refused food without meat, while they continued to eat willingly and in large amount food containing meat. Thus, the alimentary preference occurs in dogs only in the "static phase" (called so by Teitelbaum) of the development of obesity. Therefore, it may be suggested that in this period methabolic factors already exert an obvious influence in overeating inhibition. This may be overcome by the motivational values of tastefull food.

On the other hand, as pointed out by several authors, taste plays a prominent role in the alimentary functions and the pleasure of tastefull food may be the strongest motivational factor in alimentary behavior of normal animals (Pfaffmann 1960, Teitelbaum 1964, Fonberg 1967, and others).

According to Konorski's (1967) theory, the effect of the "satiety center" on the "hunger center" consists in controlling a general excitability of hungers units of the latter. After a lesion of the ventromedial nucleus "satiety center", the hunger center in the lateral hypothalamus is primarily controlled by gustatory protopathic sensations which stimulate the switching-on units of hunger when the food is in the oral cavity and the switching-off units of hunger when the food has already been swallowed.

The problem whether, as result of lesions of the ventromedial nucleus, we have to do with an increase in the hunger drive caused by releasing

the "hunger center" from an inhibitory influence of the "satiety center", or whether the animals with such lesions may not display increased hunger but instead a damage of a mechanism controlling satiety occurs is widely discussed in literature (Miller et al. 1950, Teitelbaum 1957, Grossman 1966), who did not observe an increase in the alimentary motivation in hyperphagic animals, maintains that these animals performed reluctantly only the tasks rewarded with food. There exist, however, a number of quite opposite observations as, for instance, that of Balińska (1963), who recorded an increase in positive instrumental alimentary CRs and a partial disinhibition of inhibitory reactions in rabbits with lesions of the ventromedial region of the hypothalamus. Likewise, an increase in alimentary motivation was observed by Hamilton and Brobeck (1964) in monkeys.

In the dogs under study, after lesions of the ventromedial nucleus, we did not observe a drop in the general motility, which according to Hetherington and Ranson (1942) is a symptom characteristic of lesions of this type, but on the contrary, a transitory but distinct increase in the motoric activity occurred and, strictly speaking, a motoric restlessness, connected with the demand for food. In the experiments involving differentiation, a brief disinhibition of alimentary inhibitory reactions occurred together with a considerable increase in the number of intertrial movements which persisted during a few weeks. In the group of dogs in which training of instrumental alimentary CR was undertaken after the electrocoagulation of the ventromedial nucleus, it has been observed that the period of establishing such a CR was somewhat shorter than that in nonoperated animals. Our observations confirm Balińska's and Brutkowski's (1967) results from which it follows that in rabbits with lesions of the ventromedial region of the hypothalamus the period of establishing an instrumental reaction is short. The fast elaboration of positive instrumental alimentary reactions in operated dogs as compared to controls and lack of postoperative deficit in the positive reaction retention may suggest that the alimentary drive is not lowered but to the contrary it is higher than in normal animals. The transient disinhibition of differentiation may also point to the same phenomenon as well as indicate the impairment of inhibitory mechanisms. The fast differentiation restoration indicates that the discriminatory mechanisms are not impaired.

The marked postoperative increase of the intertrial movements is an interesting fact. It may reflect both the increased hunger drive, and the lack of inhibitory impulses which in a normal state are sent by the ventromedial hypothalamus to the lateral hypothalamic feeding center. These results indicate that alimentary motivation is not lowered but to the contrary it is increased after ventromedial hypothalamic lesions.

The fact that the number of intertrial reactions gradually decreased and restoration of normal food intake took place already in about 2–3 weeks after the operation may be accounted for by the compensatory functions of the lateral amygdala. As recently shown by Fonberg (1971) lesions of the lateral part of the amygdaloid nucleus produce an effect similar in some aspects to lesions of the ventromedial hypothalamus i. e. hyperphagia and an increase in body weight. It was suggested that both these structures interplay in regulating the inhibitory functions. The results of the present work seem to confirm the classic point of view of Anand and Brobeck (1951) that the ventromedial hypothalamic nucleus plays a role of the "satiety center" in the control of food intake.

SUMMARY

Lesions of the ventromedial hypothalamic nucleus produced: the increase of food intake and body weight, transient impairment of instrumental differentiation, and a longlasting increase of intertrial responses. It is concluded that this nucleus is the inhibitory alimentary center.

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