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THE FUNCTIONAL PROPERTIES
OF HYPOTHALAMUS

ACTA BIOLOGIAE EXPERIMENTALIS

THE FUNCTIONAL PROPERTIES
OF HYPOTHALAMUS

Proceedings of a Symposium held in Lublin
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INTRODUCTION TO THE SYMPOSIUM
"THE FUNCTIONAL PROPERTIES OF HYPOTHALAMUS"

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Opening our symposium on the functional role of the hypothalamus I would like to indicate that the function of this structure, which has been studied with growing energy for several decades, represents one of the most interesting and dramatic chapters of neurophysiological investigations. It started with the routine method frequently used in neurophysiology, of electrical stimulation of this region in anesthetized animals and recording the responses of particular effectors. By this method it was easily discovered that the hypothalamus controls a number of autonomic effects such as heart rate, blood pressure, dilatation or constriction of pupils, sweating, secretion of adrenalin, and many others. It is characteristic that even in the second edition of F u l t o n's famous monograph (F u l t o n 1945) on the physiology of the nervous system, published in early forties, only that side of the hypothalamic function was emphasized.

The realisation of the fact that the hypothalamus controls the integrated emotional activity of the organisms was the achievement of Rudolph H e s s, an achievement awarded by the N o b e l prize in 1949 (H e s s 1957). By electrical stimulation of various points of this region through implanted electrodes, this author obtained such integrated responses as fear, rage, or sleepiness with all their typical autonomic and motor manifestations. As was emphasized be H e s s, these manifestations do not differ in any way from those which are produced by the respective emotions in natural life of the animal.

A further step in this direction was made by enriching the H e s s method with a new factor consisting in the presentation during the hypothalamic stimulation of particular stimulus-objects, such as food, water, the animals of prey, or the animals of opposite sex. By these simple measures it was discovered that stimulation of a given hypothalamic point, which in a „vacuum" environment gives rise only to an anonymous and indefinite restlessness, in the presence of the appropriate stimulus-object produces a quite definite and well directed behavior. Thus, first B r ü - g g e r (1943) and thereafter A n a n d and B r o b e c k (1951) and L a r - s s o n (1954) found that stimulation of the lateral hypothalamus — in the presence of food — elicits the act of eating even in a fully food satiated animal. A n d e r s s o n (1951) discovered that stimulation of the points situated in the anterior hypothalamus evokes, in water satiated goats, drinking behavior when water is presented. W a s m a n and F l y n n (1962) found that if stimulation of particular hypothalamic points — probably those involved in feeding behavior (H u t c h i n s o n and R e n - f r e w 1966) — is applied in a cat in the presence of a rat, this stimulation produces a typical hunting behavior: the cat catches the rat by the neck with his teeth and kills it, unless the stimulation of the hypothalamus is discontinued. When a piece of cotton wool is presented instead of a rat, his response to the hypothalamic stimulation is abortive or nil. Finally, stimulation of the anterior dorsolateral hypothalamus in male rats produces typical sexual responses towards females (V a n g h a n and F i s h e r 1962).

The next stage in the development of the physiology of the hypothalamus was originated by A n d e r s s o n and W y r w i c k a (1957) in respect to drinking behavior, and by M i l l e r (1957) and G r a s t y a n et al. (1956) in respect to feeding behavior. Their crucial findings were as follows. An animal with electrodes implanted in the hypothalamic hunger center, or thirst center, is trained to perform in the experimental situation a certain instrumental movement, for instance, pressing a lever, in order to obtain food or water respectively. Thereafter the animal is given food or water ad libitum so that the instrumental response disappears. Now, when the appropriate hypothalamic point is stimulated the animal immediately starts to perform again the trained movement and stops when stimulation is discontinued. Thus it has been shown that hypothalamic stimulation does not produce a „compulsory" food intake or water intake, as was earlier assumed, but a true hunger drive or thirst drive respectively.

What is the main impact of these discoveries upon our understanding of central nervous processes? First, they have shown that particular „centers" or systems in the brain control definite integrated and biologically meaningful activities of the organism rather than some elementary and

isolated effects. Secondly, it was demonstrated that the phenomena denoted in psychology as *emotions* or *drives,* such as fear, anger, hunger or thirst, are controlled by definite, anatomically delineated regions in the central nervous system which possess a definite functional organization; thus the physiological approach to these phenomena, so far considered purely psychological, became possible. Third, by artificial elicitation of particular drives through stimulation of corresponding points in the hypothalamus, we have obtained a deeper understanding of their mechanisms. And finally, an important general conclusion which can be reached from these investigations is that electrical stimulation of particular nervous structures may only lead to a discovery of their actual function, when it is administered not in a physiological vacuum, but in a meaningful biological environment, that is in the presence of specially selected stimulus--objects or in specially trained animals. This last point becomes now increasingly clear in the study of other parts of the brain, such as the limbic system, or the frontal lobes.

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STUDIES ON THE THIRST MECHANISM

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Any change in the internal environment leading to cellular dehydration generally elicits thirst together with an increased secretion of antidiuretic hormone from the neurohypophysis. Verney's (1947) refined experiments in the dog have revealed that the latter response is mediated by a central "osmoreceptor" mechanism. By intracranial vascular ligations it has been possible to localize these "osmoreceptors" in the anterior hypothalamus (J e w e l l and V e r n e y 1957). Apparently the "osmoreceptors" are not stimulated by a rise in total body fluid osmolarity per se, but rather by changes in the extracellular fluid which reduce their volume, such as an elevated Na^+ concentration in the blood. Thus V e r n e y (1947) has shown that intracarotid infusions of hypertonic Na-salts are much more effective in eliciting a release of antidiuretic hormone than are infusions of hypertonic K-salts, urea or glucose which are transferred much more readily into the cells.

In acute experiments performed in the goat it was found that injections of small amounts of hypertonic NaCl solution into the anterior medial hypothalamus or into the 3rd brain ventricle may elicit excessive drinking (A n d e r s s o n 1953), and it was suggested that the same, or a similar "osmoreceptor" mechanism as that controlling the release of antidiuretic hormone also regulates the urge to drink. In the acute experiments, however, the drinking effect of intrahypothalamic injections of hypertonic NaCl was not very reproducible. Further, it could not be excluded that the drinking effect of these injections was due to nonspecific

stimulation of structures concerned with the development of thirst, and
not the result of a specific stimulation of an "osmoreceptor" mechanism
in V e r n e y's (1947) sense. For this reason the effects of intraventricular
injections of hypertonic solutions have been the subject for further studies
during the last year in goats with permanent cannulas implanted into the
3rd and into the lateral ventricles of the brain (Fig. 1). The use of perma-
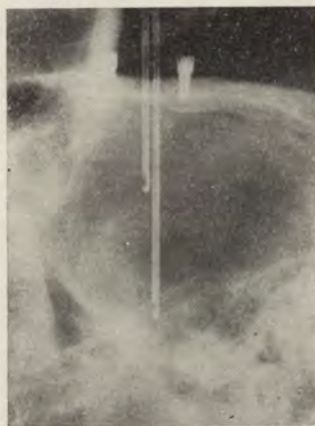nent cannulas have made it possible to make repeated experiments during

Fig. 1. An X-ray picture of
part of the skull of a goat
having two permanent can-
nulas implanted into the
brain ventricles. The shor-
ter cannula is placed in the
right lateral ventricle and
the longer one in the 3rd
ventricle

several (5 to 8) months in each animal, and the effects of intraventricular
injections have been studied in the same animal both during periods when
no supplementary NaCl was added to the diet and during periods when the
animals received extra salt added to the daily food ration.

A preliminary communication and a more complete report of the expe-
riments have been published elsewhere (A n d e r s s o n, el al. 1966 a
and b).

A. THIRST

It was found that an injection of 0.1 ml of 0.85 M NaCl into the 3rd
brain ventricle elicited a strong urge to drink within 30—90 sec. The inje-
ctions of hypertonic NaCl were not seen to have any other behavioral
effects and did not cause any visible irritation to the animals. If no water
was available to the goats after such an injection the urge to drink gra-
dually became weaker and disappeared in about 20 min. On renewed inje-
ctions at this stage the urge to drink reappeared with full strength and
with shorter latency time (10 to 15 sec) than after the first injection.

In experiments in which the goats had free access to water the inje-
ction of 0.1 ml of 0.85 M NaCl into the 3rd ventricle induced the

animals to drink in one sequence 1.5 to 2.0 l of water within few minutes after the injection. When in this manner the goats had been allowed to quench their thirst after a first injection of hypertonic NaCl, a renewed injection performed 20 min after the first gave no, or a very reduced drinking response. This inhibitory effect of hydration was also seen if the goats had been given 4 l of water by stomach tube 1 1/2 hr prior to the intraventricular injection of hypertonic NaCl. Then no drinking at all cccurred as result of the injection, but the diuresis was reduced to one third of the preinjection level within 30 min and then rose again during the following hour. The observed inhibition of water diuresis indicates that the injection of 0.1 ml of 0.85 M NaCl in the hydrated animal still caused the release of significant amounts of antidiuretic hormone, although it was no longer sufficient to elicit thirst.

In an attempt to determine whether the drinking effect might be attributed either to the sodium or the chloride ion, hypertonic solutions of other salts were injected into the 3rd ventricle. The results of injections of sodium salts with other anions than Cl^- were inconclusive, since they caused trembling, exitation and had other disturbing effects. More conclusive results were obtained from injections of 0.1 ml of 0.85 M NH_4Cl and of 1.7 M d-glucose into the 3rd ventricle. These injections did never induce any visible urge to drink in the goats and were not seen to disturb or irritate the animals. Moreover, injections of 0.1 ml of 0.85 M NaCl performed 5 to 15 min later gave the usual thirst effect, indicating that no side effects of NH_4Cl or glucose had been the reason for the negative drinking response to these substances.

Comparisons between the effects of injections of 0.1 ml of 0.85 M NaCl into the lateral ventricle and into the 3rd ventricle were also made. In contrast to the injections into the 3rd brain ventricle, the injections of this amount of hypertonic NaCl into the lateral ventricle did not elicit drinking.

B. URINARY AND SALIVARY SECRETION AND COMPOSITION

The effects on urinary and parotid salivary flow and composition of repeated injections of 0.1 ml of 0.85 M NaCl into the 3rd brain ventricle were also studied.

As a result of the injections the urinary Na^+ and Cl^- excretion rose markedly, showing a 5 to 10-fold increase over pre-injection level towards the end of the injection period. The urinary electrolyte excretion remained at this high level for about 1 hr after the last injection. Then it fell to pre--injection level concomitant with a gradual decrease in urine flow. A second, and more pronounced diuresis (up to 7 times basic flow) usually

occurred about 2hr after the last intraventricular injection of hypertonic NaCl. This second increase in urine flow had the character of a water diuresis (salt excretion remaining at, or below basic level) while urinary electrolyte concentration dropped to very low levels (Fig. 2). A 5 to 10% decrease in hematokrit and plasma protein was usually observed during the period of intraventricular injections especially when the goats received no extra salt with the diet.

In an attempt to find out if the observed increase in urinary Na$^+$ and Cl$^-$ excretion might be the result of an inhibition of aldosterone secretion, repetitive injections of 0.1 ml of 0.85 M NaCl into the 3rd ventricle were made also when exogenous aldosterone (Aldocorten, "Ciba") was given to the animals. Although the basic urinary Na$^+$ excretion was depressed by the aldosterone, the intraventricular injections of hypertonic NaCl still
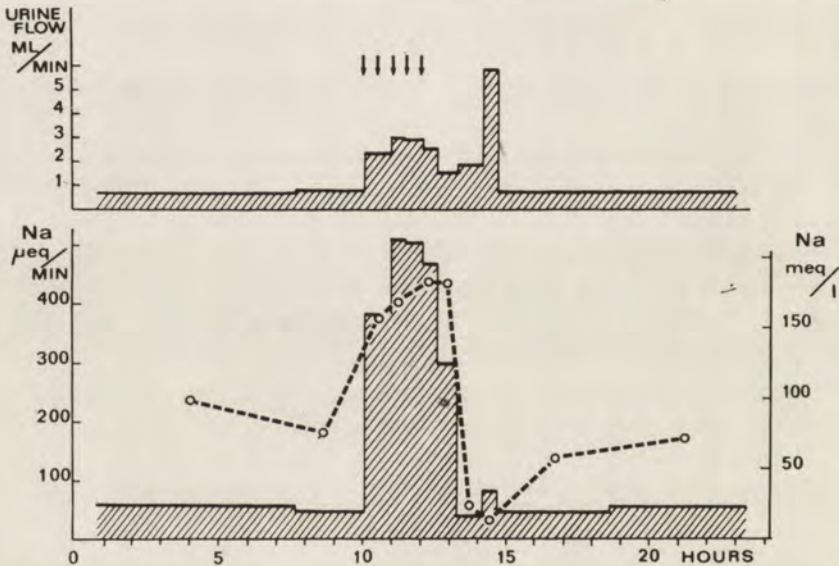

Fig. 2. Effects on urine flow, urinary excretion of sodium and urinary sodium concentration (broken line) of injections of hypertonic NaCl-solution into the 3rd brain ventricle of a goat. Each arrow indicates the intraventricular injection of 0.1 ml of 0.85 M NaCl. (From: *Andersson, Jobin* and *Olsson* 1966a)

caused the usual conspicuous increase in Na$^+$ and Cl$^-$ excretion and a considerable rise in the urinary concentration of these ions.

Urinary flow and composition were also followed in experiments involving repetitive injections of 0.1 ml of 0.85 M NH$_4$Cl and 1.7 M d-glucose into the 3rd ventricle. Such injections, having a negative thirst effect, did

not cause any increase in urinary electrolyte excretion either. A similar negative result was abtained by repeated injections of 0.1 ml of 0.85 M NaCl into the lateral ventricle of the brain (Fig. 3).
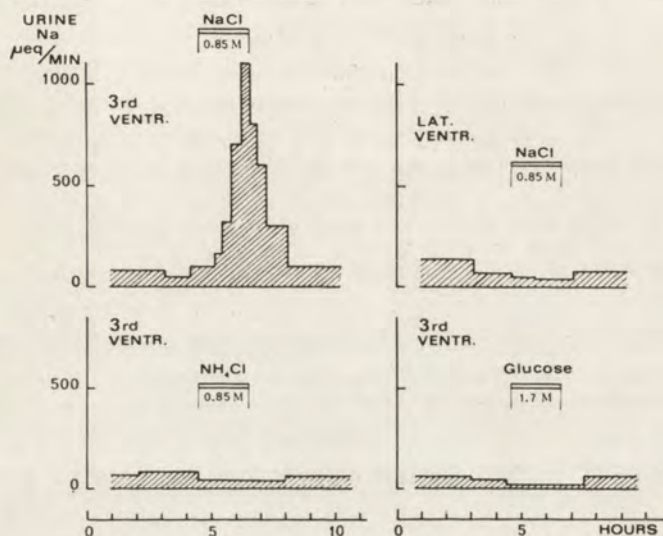

Fig. 3. Urinary Na excretion during repetitive injections of hypertonic solutions into the brain ventricular system. Upper left: Stimulation of Na excretion by a series of 5 injections of 0.1 ml of 0.85 M NaCl at 30 min intervals into the 3rd ventricle. Upper right: Lack of effect of this sequence of 0.85 M NaCl injections into the lateral ventricle of the same goat. Lower left and right: Absence of response to repetitive injections of 0.1 ml of 0.85 M NH_4Cl or 1.7 M d-glucose into the 3rd brain ventricle (5 injections with 30 min intervals). (From: *Andersson, Jobin* and *Olsson* 1966b)

Some preliminary experiments were also recently made in which the effect on parotid salivary flow and composition of repeated injections of 0.1 ml of 0.85 M NaCl into the 3rd ventricle were studied. An effect similar to that on urine secretion was obtained. In the aldosterone treated animal the injections caused a conspicuous increase in salivary flow and Na^+ concentration after a latency time of half to one hour. In the animal not treated with aldosterone the same marked and delayed increase in salivary flow was obtained. However, here the initial salivary Na^+ concentration was well above plasma Na^+ level, and the marked increase in flow obtained after the intraventricular injections of hypertonic NaCl rather caused a slight fall of the Na^+ concentration towards plasma level.

DISCUSSION

The present study provides more direct evidence than earlier acute experiments that hypothalamic "osmoreceptors" in V e r n e y's (1947) sense are concerned not only with the release of antidiuretic hormone, but also with the development of the urge to drink. Of the hypertonia solutions tested, only NaCl elicited thirst, whereas NH_4Cl and glucose, which are likely to move more readily into the cells, were negative. The thirst response to injections of hypertonic NaCl into the 3rd ventricle was very reproducible when water was restricted, but was inhibited or blocked by voluntary overdrinking or forced hydration. This indicates that the state of hydration of the reactive nervous elements determines their responsiveness to the thirst stimulus, and speaks against a non-specific stimulatory effect of the injected NaCl. That the hypothalamus is the responding part of the brain is indicated by the negative results of lateral ventricular injections of hypertonic NaCl.

The present experiments do not afford any definite explanation for the mechanism responsible for the conspicuous increase in urinary Na^+ and Cl^- excretion, and in salivary flow caused by injections of hypertonic NaCl into the 3rd brain ventricle. However, this response and the lack of response to lateral ventricular injections, suggest the existence of some kind feed-back control of the Na^+ concentration of the extracellular fluid which is located near the 3rd brain ventricle. Such a control does not seem to be effected through changes in aldosterone secretion since the effect was also present in the aldosterone treated animal. A fall in hematokrit and plasma protein was observed in most cases during the periods of repetitive injections of hypertonic NaCl into the 3rd ventricle. These changes may have reflected an expansion of the blood volume or the total extracellular fluid volume, which in turn might have been the cause of the increase in urinary salt excretion (increased glomerular filtration rate?) and the rise in salivary secretion rate. It is hoped that future studies of body fluid distribution with more adequate methods will reveal whether such an expansion of the blood or total extracellular fluid really takes place in response to a raised NaCl concentration in the 3rd brain ventricle.

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INVESTIGATIONS ON THE ACTION
OF HYPOTHALAMIC SUBSTANCES IN THE SECRETION
AND RELEASE OF GONADOTROPINS

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The path of centrifugal transmission from the central nervous system
to endocrine organs appears to be organized in the form of a complicated
chain in which secretory effectors alternate with vascular links. The
neurons in this chain are located in the medial region of the hypothala-
mus. These hypothalamic neurons combine characteristic features of nerve
cells and of secretory cells and are thought to elaborate hormonal sub-
stances, some of which are hormones, or their precursors, while others
serve as transmitter substances affecting the secretory mechanisms of
the anterior pituitary gland.

In the control of hypophyseal gonadotropin secretion a dual hypotha-
lamic function is suggested:

1) The first one, the neurosecretory center, is claimed to elaborate
some substances, so-called releasing factors, being able to stimulate the
production and release of gonadotropins by the pituitary gland. This neu-
rosecretory function, as shown by the experiments with lesions (F l e r k ó
and B á r d o s 1959, T a l e i s n i k and M c C a n n 1961, S a w y e r
1962), implantations of solid estradiol (L i s k 1960) and electrical stimu-
lation (C r i t c h l o w 1958), is associated in rats and rabbits with the
arcuate ventromedial region of the hypothalamus. In sheep this function,
according to our experiments, seems to be located in the ventromedial
area of the hypothalamus (not yet published).

2) The second function is assotiated with a "release regulating mechanism" which stimulates or inhibits the function of the above called neurosecretory center; this "release regulating mechanism" in rats seems to be located in the preoptic area of the hypethalamus (S a w y e r 1962, S z e n-t á g o t h a i et al., 1962). The functional relationship between these centers is illustrated by the diagram in Fig. 1.
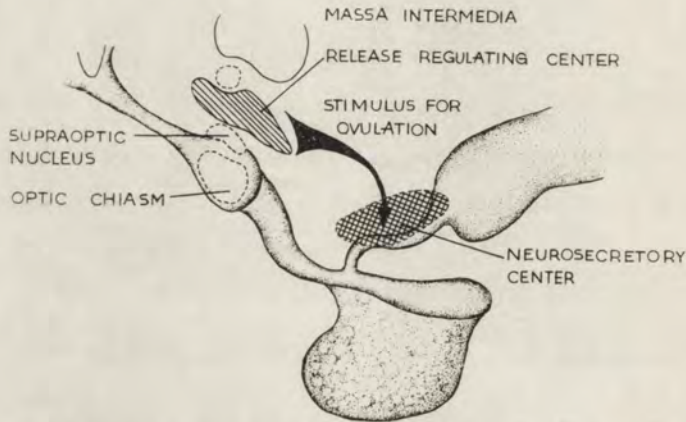

Fig. 1. Diagram showing controlling centers of the hypothalamus over the secretion and release of gonadotropins by the pituitary gland

If this concept of localization of nervous centers and of neurosecretion is right then the substances able to stimulate the secretion and release of FSH as well as LH must exist in the hypothalamic tissue. To date, however, as it is generally accepted, only one substance from the hypothalamic tissue, being able to release gonadotropins, has been isolated, namely — the so-called LH releasing factor (H a r r i s, 1961, M c C a n n, 1962), while the experiments on the existence of FSH releasing factor cannot be looked upon as conclusive (I g a r a s h i and M c C a n n, 1964; D a v i d et al., 1965). Our investigations, therefore, have been concerned with the problem of whether there exists in the hypothalamic tissue only a substance releasing LH or if it would be possible to record there another substance able to release FSH as well.

In experiments on this problem we applied infusions of extracts of median eminence (ME) directly into adenohypophysis of a non-cycling sheep; and after infusions we followed the reaction of ovaries in infused animals. A sheep is very suitable as experimental animal for these purposes, for it is a spontaneously ovulating animal and in its sexual behaviour it shows a long — about half a year lasting non-cycling — quiescent sexual period. At first we used to intraadenohypophyseal infusions non-cycling

ewes in the middle of their quiescent period and having obtained negative results in these animals we used next also non-cycling ewes but in the last weeks of their quiescent sexual period (about 2—3 weeks before the onset of the sexual cycles). The results of these infusions are presented in Table I.

Table I

The response of non-cycling ewes to intraadenohypophyseal infusions of the stalk median eminence (ME) extracts

No. of ewes	Time of the infusion during quiescent sexual period	Serial of the experiment /year/	The dose level of the extract as equiv. to lyophyl. tissue in mg. for one infusion	No. of infus. for one animal	Reaction		
					receptivity to service by the male	character of vaginal smears /v. s./	ovaries 48 hr after the last infusion
6	about in the middle	1/1965/	250	3	no one animal receptive	in all animals anoestrous v. s.	no response in all animals
9	2—3 weeks before onset of sex. cycles	2/1965/	250	3	no one animal receptive	7 ewes, anoestrous v. s.	3 ewes, no response 6 ewes with ripened or ruptured follicles
4	2—3 weeks before onset of sex. cycles	3/1966/	250	2—3	no one animal receptive	3 ewes, anoestrous v. s. 1 ewe, oestrous v. s.	1 ewe, no response 3 ewes with ripened or ruptured follicles

As it is shown in Table 1 there is quite a different reaction of ewes in the middle and in the last weeks of their quiescent period. In order to interpret this discrepancy it will be of a great help to present very shortly our experiments on the seasonal variation in the reactivity of rabbits to LHRF.

Namely, in our experiments on the purification and evaluation of LHRF we were able to observe that the extracts containing this factor, infused into adenohypophysis of rabbits in the spring and summer, induced ovulation in 90% of animals, while they failed to do so during late autumn and the first months of winter.

This observation on the seasonal variation in the reactivity of rabbits

2*

to hypothalamic extracts was supported by additional experiments carried out on two groups of rabbits (40 animals in each group) kept under quite different environmental conditions during the whole year. Thus the phenomenon of the lack of reactivity of rabbits to intrahypophyseal infusions of LHRF during some seasonal periods may be accepted as consistent. It is suggested that this lack of reaction to LHRF of rabbits is associated with some kind of seasonal insensitivity of adenohypophysis to neurogenic factor (Domański et al. 1966). It is worth to note that this phenomenon of seasonal variation in the response of rabbits to LHRF was confirmed by Campbell (unpubl.).

In the light of this seasonal variation in the sensitivity of rabbits to LHRF it is possible to suggest the existence of an analogous phenomenon in sheep and that this phenomenon may be the cause of the lack of positive responses in these animals to hypothalamic extracts during their "deep" quiescent period.

On the other hand, the rupture of follicles and the development of corpora lutea after intraadenohypophyseal infusions of these extracts during the last weeks of quiescent period in sheep — spontaneously ovulating animal — seem to indicate that these infusions evoked as well a release of FSH; in other words the extracts of ME appeared to contain substance being able to release both LH and FSH. It is worthwhile to note that the ewes which ovulated after intrahypophyseal infusions of ME extracts mostly did not show symptoms of heat and their vaginal smears were anoestrous or slightly expressed this character only. This behaviour seems to be interpreted by the fact that analogous phenomena are mostly observed in the first natural oestrus in sheep occured after quiescent sexual period.

An attempt to answer the question whether the LH releasing factor and the FSH releasing factor are one and the same substance or quite different ones was made by separation, purification and chemical characterization of active substances in extracts. To date on the basis of gel filtration by using Sephadex G 50, Sephadex G 25 and CM chromatography we were able to separate LHRF from proteins, oxytocin and vasopressin (fig. 2 and 3).

Purified LHRF was subjected to several tests to determine its character and mode of its action.

Boiling in 0.1 N HCl for 15 min was without any effect, while trypsine completely destroyed its biological activity. Reduction with 1 M cysteine only slightly decreased its activity; disulphide bridge, therefore, is absent in its molecule or is unimportant for its biological activity. On the basis of these experiments it is suggested that the LHRF is a polypeptide with molecular weight 1400—2500.
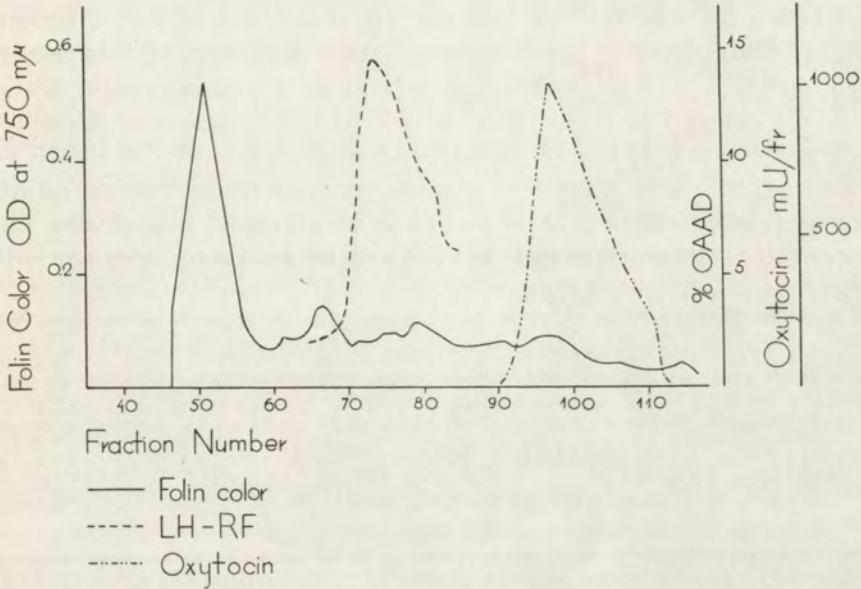
Fig. 2. Separation of LHRF on a column of Sephadex G 25 (2×210 cm) in 0.1 M ammonium acetate, pH 5.0. Fraction size 6.0 ml; 0.1 ml. aliquots taken for Folin-Lowry analyses. LHRF tested by elevation of plasma LH — 1 ml.; oxytocin tested using horn of uterus the rat against Pitocin (Parke, Davis) standard

Fig. 3. Separation of LHRF from vasopressin on CM cellulose column (2.8×70 cm) equilibrated with 0.005 M ammonium acetate, pH 4.5 buffer. Fraction size 10 ml.; 0.2 ml. taken for Folin-Lowry analyses. LHRF tested by elevation of plasma LH-1 ml., antidiuretic estimation of fraction were performered on rat against Pitressin (Parke, Davis) standard

In order to obtain some information about the mode of action of LHRF in the process of hormone release, the influence of this factor on the selubilization of tropic hormones from pituit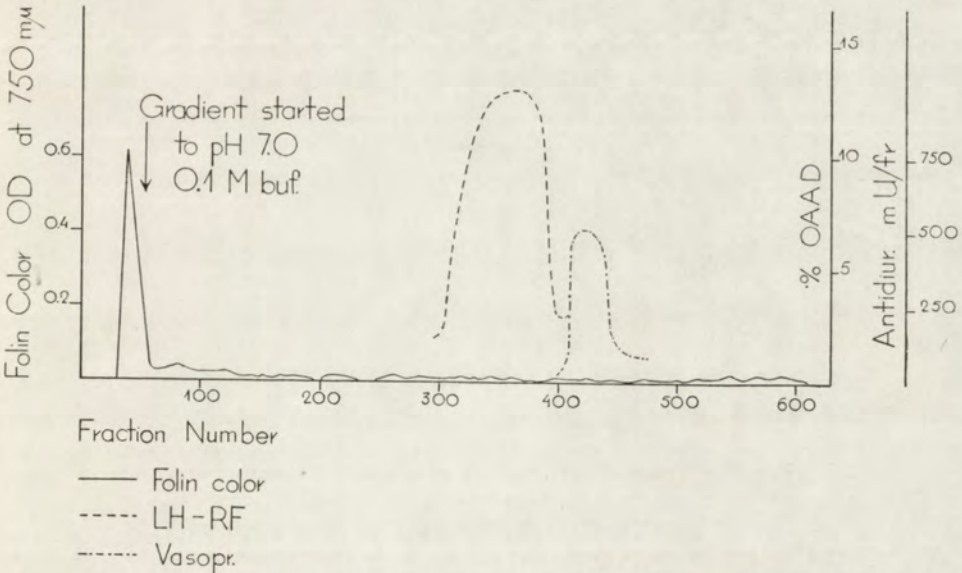ary hormonal granules was investigated. The incubations of whole homogenates of adenohypophysis and of granule fractions, with and without addition of LHRF were carried out. The preparation of granule fraction from anterior pituitary cells was made according to H a r t l e y et al. (1960) introducing Celite 545 separation (H y m e r and M c S h a n 1963). This procedure is illustrated by the scheme (Fig. 4).

ANT. PIT.

Homogenate in sucrose 0.25 M − 7.3 % PVP

pH 7.4

275 × g 10 min

NF S_1

4,400 × g 20 min

LG S_2

20,400 × g 1 hr

SG S_3

Column of 545 Celite
1.5 × 12.8 cm

Granule Fraction

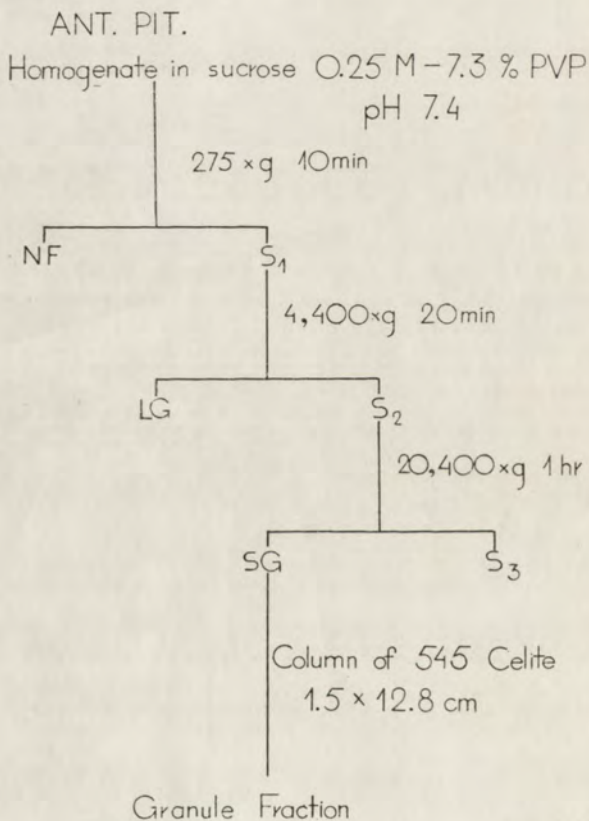Fig. 4. Scheme of preparation of granule fraction from anterior pituitary homogenate. PVP — polyvinylpyrolidone; NF — nuclear fraction; LG — large granules; SG — small granules; S_1, S_2, S_3 — supernatants

The effect of the action of LHRF on anterior pituitary homogenate and granule fraction was checked by the ovarian ascorbic acid depletion test of Parlow (OAAD). The effect of this action is presented in Table II.

Table II

The effect of LHRF on AP homogenate and on granule fraction

	LH-RF added	Pellet* % OAAD ± SE	Supernatant* % OAAD ± ES
Saline	—	−0.5±0.3	
A. P. Homogenate in 0.25 M sucrose	2µg	−41.5±4.2	
A. P. Homogenate in 0.25 M sucrose	—	−24.1±2.8	−15.0±2.2
A. P. Homogenate in 0.25 M sucrose	2µg	−10.3−1.5	−29.6±3.2
Granule fraction whole	2µg	−40.2±3.9	
Granule fraction in saline	—	−31.1±3.0	−9.3±1.9
Granule fraction in saline	2µg	−27.2±2.9	−13.4±1.5
Granule fraction in 0.25 M sucrose	—	−32.0±2.5	−8.2±1.1
Granule fraction in 0.25 M sucrose	2µg	−30.2±3.1	−8.0±1.5

* — centrif 20,400 — hr

It is evident that the values expressed in percentage of OAAD for whole incubates of A.P. homogenates and these for granule fraction are nearly the same, while the values for supernatants of A.P. homogenate are much higher than these of granule fraction. It means that in A.P. homogenates an increase of solubilization of LH after incubation was obtained, while no increase was observed after incubation of granule fraction. It is suggested, therefore, that LHRF acts rather on the cells and on their enzymatic activity than directly on granules.

Further experiments on the character of LHRF and on the separation and identification of FSHRF are now being carried out.

SUMMARY

1. To date all experiments support the idea that the endocrine functions of adenohypophysis are controlled by neurogenic substances elaborated in hypothalamic centers.

2. There is some evidence that these substances are specific for particular trophic functions of the pituitary gland.

3. The mechanisms, however, of production and release of these substances are as yet not known.

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THE CONTROL OF RELEASING
THE HUMORAL FACTORS FROM HYPOTHALAMUS

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The neurosecretory cells in the hypothalamus are the final common
pathway for the neural impulses controlling the pituitary gland. All
known factors released from hypothalamus, are polypeptides and their
chemical composition is related. They are present within the same
chromatographic fractions of hypothalamic extracts (S c h a l l y, et
al. 1962; G u i l l e m i n, et al. 1963). These compounds may be either
stored in the neurohypophysis and from here liberated into the blood
(vasopressin, oxytocin) or may penetrate, within the tuberal region,
into the capillaries of the hypophyseal portal system (corticotropin,
thyrpotropin and luteinizing hormone releasing factors). Direct stimu-
lation of the neurosecretory neurons causes the release of vasopressin
and oxytocin (H a r r i s, 1947; F a n g, et al. 1962; T r a c z y k and
J a k u b o w s k a, 1966), as well as the appearance of several symp-
toms indicating augmentation of ACTH, TSH and LH Secretion (H a r r i s
1937 and 1948; H a t e r i u s and D e r b y s k i r e, 1937; M a r k e e
et al. 1946; H a r r i s and W o o d s, 1958; G o l d f i e n and G a n o n g,
1962; S n y d e r and d'A n g e l o, 1963; d'A n g e l o, et al. 1964; S h i -
z u m e and O k i n a k a, 1964; T r a c z y k, et al. 1966).

The function of the hypothalamic secretory neurons has been investi-
gated, as yet, in an indirect way only. Nevertheless, in the release of
the factors, such as CRF, TRF and LRF, a three-link chain occurs:
the first link in the hypothalamus, the second in the adenohypophysis
and the third in the adrenal cortex, thyroid or gonads. Similarly, the

estimation of vasopressin in the blood, even taken from the jugular vein, is not an index for the functional state of hypothalamic neurons, but only for the vasopressin liberation from the neurohypophysis. The vasopressin content of the neurohypophysis remains much greater than that of the hypothalamus both during hydration and dehydration. Under different water balance conditions the ratio of the antidiuretic activity of whole neurohypophysis to the antidiuretic activity of whole hypothalamus has been found about 100 : 1,5—3,8 (G u z e k, 1966).

The study of factors which influence the function of the hypothalamic neurosecretory neurons is therefore seriously restrained, when indirect methods are used. The hypothalamic neurons receive information from peripheral receptors (F e l d m a n, et al. 1959) and central detectors (K o i z u m i, et al. 1964), as well as from the limbic system-midbrain circuit (N a u t a, 1963). Stimulation of the pathways in the limbic system-midbrain circuit brings about vasopressin liberation from the neurohypophysis. Such an effect also has been observed after stimulation of the corpus amygdaloideum and septum (D i g m a n and G a i t o n, 1959) and after stimulation of certain regions more distant to the hypothalamus — hippocampus and brain stem (H a y w a r d and S m i t h, 1963) or the prepyriform area (Yoshida, et al. 1965). This neurohumoral reaction evoked by stimulation of many limbic structures, might be explained by free passage of impulses through the pathways in the limbic system-midbrain circuit.

A close examination of the relationship between the limbic system-midbrain circuit and the function of secretory hypothalamic neurons may be possible, when neurohumors are obtained directly from the hypothalamus. During the last year a method was developed which allowed vasopressin to be obtained directly from chronically implanted cannulae in the hypothalamus of unanaesthetized dogs by means of permanent perfusion of a small hypothalamic area between the paraventricular and supraoptic nuclei. In the outflow perfusion fluid an vasopressin is detectable by the method of H e l l e r and Š t u l c (1959) as modified by C z a c z k e s and co-workers (1964). During the hypothalamic perfusion, the midbrain and /or the hippocampus were stimulated, 5 cycle/sec pulses were used with the stimulus intensity lower than the threshold of distinct somatic manifestations.

The perfusion was performed successfully in 10 animals. The amount of effluent perfusion fluid from the cannula ranged in the experiments from 0.35 to 1.15 ml/hr, mean 0.56 ml/hr. The concentration of vasopressin in perfusion fluid collected in the course of 2 hr varied from 0.021 to 0.195 microunits of synthetic arginine-vasopressin („S a n d o z")

in different experiments. Midbrain and/or hippocampal stimulation decreased or increased the vasopressin outflow from the hypothalamus, but — as yet — no constant relation has been observed among vaso-pressin contents in the outflow fluid during control the period, midbrain stimulation and hippocampus stimulation.

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THE PARTICIPATION OF THE HYPOTHALAMUS
IN FOOD-REINFORCED PERFORMANCE AND INHIBITION

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This investigation, which has been carried out on rabbits, is an evalu-
ation of the roles of the lateral and medial hypothalamus in retention
of differentiation and extinction problems.

Experiments on rabbits, like experiments on other animal species,
have shown that lesions in the medial hypothalamus which is considered
to be the "satiation center", produce hyperphagia, enhancement of reac-
tivity, and somatomotor inhibitory deficit (as revealed by testing the
animals still in the dynamic phase of hyperphagia), whereas lesions of
the lateral hypothalamus which is considered to be the "feeding center"
produce aphagia associated with a loss of the previously learned instru-
mental response. More recent work has demonstrated that aphagia and
impairment of reactivity resulting from a damage to the rabbit's lateral
hypothalamus disappear when isotonic saline with glucose is injected
subcutaneously within a few days after surgery. As a result of this type
of treatment, animals with lateral hypothalamic lesions begin to accept
food, and eventually, return to the preoperative level of feeding behavior
and instrumental performance, and may even become hyperphagic and
hyperreactive (B a l i ń s k a 1963a, b, B a l i ń s k a et al. 1961). The fin-
ding of the lateral hypothalamic lesions producing loss of reactivity
followed by augmented reactivity suggests that the effects of lateral
hypothalamic lesions on instrumental performance must be considered
in terms of time after surgery. The unresolved issue is whether the incre-
ased reactivity at the later postoperative period would interfere with the
suppression of an instrumental response on an inhibitory (that is, unre-
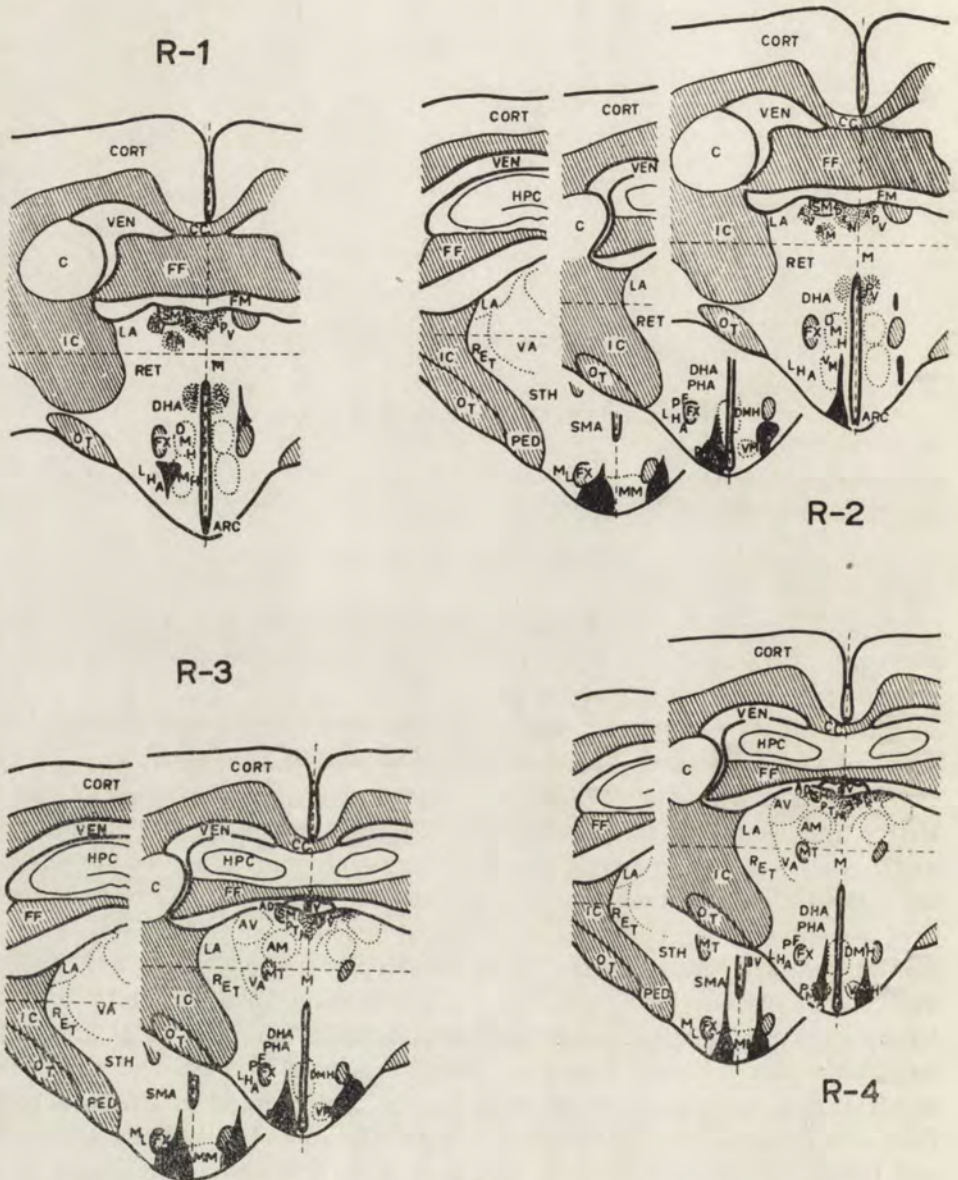
Fig. 1. Reconstructions of medial hypothalamic lesions described in the text

inforced) trial. It therefore seemed desirable to use the differentiation and extinction situations in an effort to find a set of conditions that would include inhibition of response. Animals with medial hypothalamic lesions were added for comparison.

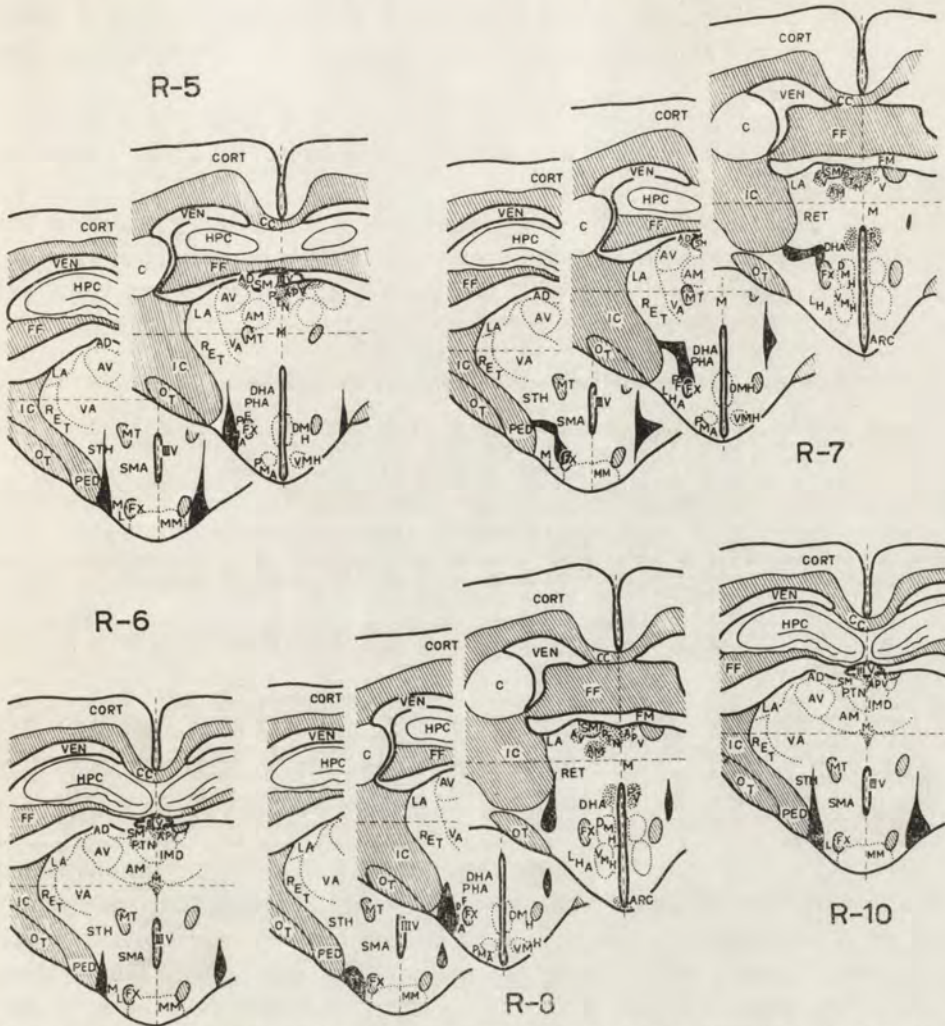The experiments to be reported are of two types. They both were

Fig. 2. Reconstructions of the lateral hypothalamic lesions described in the text

simple in design. Prior to hypothalamic lesions, the animals were trained to a fairly high criterion on either a buzzer 1-buzzer 2 differentiation or an extinction task. Postoperatively, they were retested on their original tasks until they failed or reattained the criterion.

In experiment 1, the task required the rabbit to place the right fore-paw on the feeder on the positive trial and to withold this response on the inhibitory trial. On positive trials, the animals were reinforced with a piece of carrot, whereas on inhibitory trials the reinforcement was omitted.

At the conclusion of the preoperative training, the animals were

subjected to either medial or lateral hypothalamic lesions. Figs. 1 and 2 show the outcomes of the reconstructions of the brain of animals that sustained an operation.

Animals with lateral hypothalamic lesions were injected 100 cc of 4% glucose with saline daily for 3—7 days at which time they recovered their voluntary eating behavior.

Table I presents the distribution of errors on positive trials in the postoperative period for individual animals of both hypothalamic groups. It is clear that the animals with medial hypothalamic lesions were not

Table I

Distribution of errors on positive trials in the postoperative period

Rabbit No.	50-trial blocks					
	1	2	3	4	5	6
Medial hypothalamic lesions, group HM						
R—1	0	0	0	0	0	0
R—2	0	0	0	0	0	
R—3	0	0	0			
R—4	2	0	0			
Lateral hypothalamic lesions, group HL						
R—5	50	44	18	12	2	1
R—6	41	13	5	4	2	1
R—7	40	38	15	5	1	

affected. Two out of five animals with lateral hypothalamic lesions failed to learn the instrumental response once again, although there were presented 2 to 3 times as many trials as needed by normal rabbits to reach criterion. These animals were not included in the figure. Three other lateral hypothalamic animals could relearn the instrumental response. Moreover, as seen from Table II these animals, after having relearned the response, exhibited an excessive intertrial interval responding as it was shown by animals that underwent the medial hypothalamic lesion.

Table III presents the postoperative distribution of errors on inhibitory trials for individual animals of both groups. It is apparent that animals with medial hypothalamic lesions displayed a very severe impairment of inhibition. Although animals with lateral hypothalamic lesions were not impaired in the immediate postoperative period, it is clear that after having relearned the instrumental response, they exhibited a long-lasting impairment.

In experiment 2, the animals were trained in a free-choice situation to select either of two kinds of food reinforcements with one of two

instrumental response. The placing of the right forepaw on the feeder was followed by the presentation of grains of oats or purée-type potatoes from feeder No. 1, whereas grasping and pulling with the teeth a bakelite ring was followed by a carrot reinforcement from feeder No. 2. There were also opposite associations between the instrumental response and the food reinforcement.

Table II

Distribution of CR performances during
intertrial intervals in the postoperative period

Rabbit No.	100-intertrial blocks					
	1	2	3	4	5	6
Medial hypothalamic lesions, group HM						
R—1	80	84	50	26	23	23
R—2	121	79	67	57	13	
R—3	57	67	16			
R—4	64	71	20			
Lateral hypothalamic lesions, group HL						
R—5	0	0	30	44	54	78
R—6	24	70	78	62	57	41
R—7	0	22	16	15	10	

Table III

Distribution of errors on inhibitory trials
in the postoperative period

Rabbit No.	50-trial blocks					
	1	2	3	4	5	6
Medial hypothalamic lesions, group HM						
R—1	45	21	11	8	14	1
R—2	43	30	16	12	7	
R—3	45	19	6			
R—4	40	24	·1			
Lateral hypothalamic lesions, group HL						
R—5	0	0	23	6	6	2
R—6	4	23	8	14	12	4
R—7	4	14	3	0	0	

In the preoperative training, after the two instrumental responses had been well established an extinction session was carried out for both responses simultaneously. The extinction followed a 5-min. conditioning session, and was terminated when no response occurred for 5 min.

Table IV

Extinction of CR's associated with the presentation of carrots or oats in rabbits before (pre-op) and after (post-op) lesions in the medial hypothalamus

Rabbit No.	Extinction time in min.		Number of responses during extinction session			
			carrots		oats	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
11	10	7	26	5	11	15
12	8	8	18	4	4	13
13	4	3	23	8	4	9

Extinction of CR's associated with the presentation of carrots or potatoes in rabbits before (pre-op) and after (post-op) lesions of the medial hypothalamus

Rabbit No.	Extinction time in min.		Number of responses during extinction session			
			carrots		potatoes	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
16	6	5	16	7	8	7
17	6	5	19	7	12	2

Table V

Extinction of CR's associated with the presentation of carrots or oats in rabbits before (pre-op) and after (post-op) lesions of the lateral hypothalamus

Rabbit No.	Extinction time in min.		Number of responses during extinction session			
			carrots		oats	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
19	8	25	28	93	5	17
20	20	30	34	105	13	13
21	6	14	15	58	5	12

Extinction of CR's associated with the presentation of carrots or potatoes in rabbits before (pre-op) and after (post-op) lesions of the lateral hypothalamus

Rabbit No.	Extinction time in min.		Number of responses during extinction session			
			carrots		potatoes	
	pre-op	post-op	pre-op	post-op	pre-op	post-op
24	3	12	12	43	0	23
25	5	14	9	40	11	15
26	9	26	27	75	7	25

Testing the animals with medial hypothalamic lesions was resumed 3—5 days after surgery, that is when the animals were still in the dynamic phase of hyperphagia, whereas the tests of animals with the lateral hypothalamic lesions started a few days later, that is after the recovery of voluntary eating due to subcutaneous injections of saline and glucose in the immediate postoperative period.

In animals with medial lesions, the extinction session was carried out at the early postoperative stage. On the other hand, animals with lateral lesions were retested on extinction after a complete recovery of both instrumental responses. This occurred a few weeks after surgery.

Unexpectedly, the animals with lesions of the lateral hypothalamus following recovery of the performance extinguished a food-reinforced response much slower than did the animals with medial hypothalamic lesions still in the dynamic phase of hyperphagia. These data are shown in Table IV and V.

Thus, the findings that animals with lateral hypothalamic lesions after recovery of feeding behavior and performance exhibit a profound inhibition impairment in a differentiation task and much slower extinction of a food-reinforced response than animals with medial hypothalamic lesions still in the dynamic phase of hyperphagia suggest that lesions of the lateral hypothalamus produce behavioral effects which cannot be explained in terms of the "feeding center" disturbances.

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VENTROMEDIAL HYPOTHALAMUS:
PARTICIPATION IN CONTROL OF FOOD INTAKE
AND FUNCTIONAL CONNECTIONS WITH VENTRAL AMYGDALA

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As a result of investigations which were made over the last quarter
of a century the ventromedial nucleus of the hypothalamus (NHvm) is
generally acknowledged as a "satiety center". The main criterion confir-
ming this view is that stimulation of NHvm inhibits food intake and
lesions lead to hyperphagia and obesity. Animals which became hyper-
phagic by NHvm ablation differ in behavioral picture from intact hungry
animals. As they do not show increased food motivation (M i l l e r et al.
1950, L e w i ń s k a 1964), the reason for hyperphagia is regarded as an
inability to stop eating. Recently some new data have been found which
throw strong doubt upon previously accepted views (K r a s n e 1962,
R o b i n s o n 1964, R e y n o l d s 1965, G r o s s m a n 1966), however the
results obtained on hyperphagia in rats are in general not refuted.

It should be emphasized that the majority of the experiments con-
cerning hypothalamic "satiety center" were carried out on rats. On the
other hand, the analogous experiments performed on cats show a surpri-
singly small number of successful results, and the exact localization of
lesions responsible for hyperphagia is still poorly understood. Therefore,
an attempt was made to find in cats localization of critical area in ven-
tromedial hypothalamus. Furthermore the reciprocal functional relation
between the NHvm and the ventral part of the amygdalar complex known
as an inhibitor of food intake was investigated.

MATERIAL AND METHOD

The cats were nourished ad libitum with milk and cereal mixed with cooked horse meat. In addition they received 30 g of raw horse meat daily. It was expected that this diet would reflect changes both in hunger and in thirst because cats, which receive milk, refuse to take water. Cats were trained in an instrumental conditioned reflex (CR) consisting in placing the right foreleg on the foodtray in response to a bell. Small bits of raw meat were used as reinforcement. After the CR had been established in one group of 45 cats particular points in the ventromedial hypothalamus and in the ventral amygdala were coagulated for 40 sec with a 3 mA anodal DC. In the other group composed of 40 cats electrodes were implanted in 50 points of the NHvm and adjacent region and in 100 points of the nucleus amyglaloideus basalis. During 6—8 weeks the experiments with stimulation were performed. An unipolar stimulation with rectangular impulses of a frequency of 50 cycle/sec, a duration of 1.0 to 10.0 msec and amplitude of 0.05 to 2.0 mA was used. Thereafter the coagulation was carried out.

RESULTS AND CONCLUSIONS

The first perceptible symptom of light stimulation of the dorsolateral part of the NHvm was the increase of the speed of eating. More intensive stimulation resulted in the reaction of fear and flight followed by the inhibition of feeding reaction which lasted for several minutes. The threshold stimulation of the ventromedial part of the nucleus usually produced a brief inhibition of both the food CRs and URs and was accompanied by a tense posture, pupil dilatation and immobility. A more intensive stimulation led to an aggressive reaction which, when stimulation was switched off, was followed by the immediate response to both conditioned and unconditioned stimuli (L e w i ń s k a et al. 1966). It was observed that animals, which had the electrodes in central or dorsal part of the NHvm, very soon stopped responding to the CS and refused to eat meat from the foodtray when they were often stimulated. But when meat was offered by hand in another part of the experimental compartment, they accepted it readily. A complete refusal to eat during the experimental session was certainly due to repeated or strong hypothalamic stimulation.

The negative effect of stimulation upon the daily intake of cereal and milk was not prominent. When electrodes were implanted in the central part of the NHvm, the intake of both milk and cereal was somewhat decreased, particularly in days of stimulation. The effect of stimulation
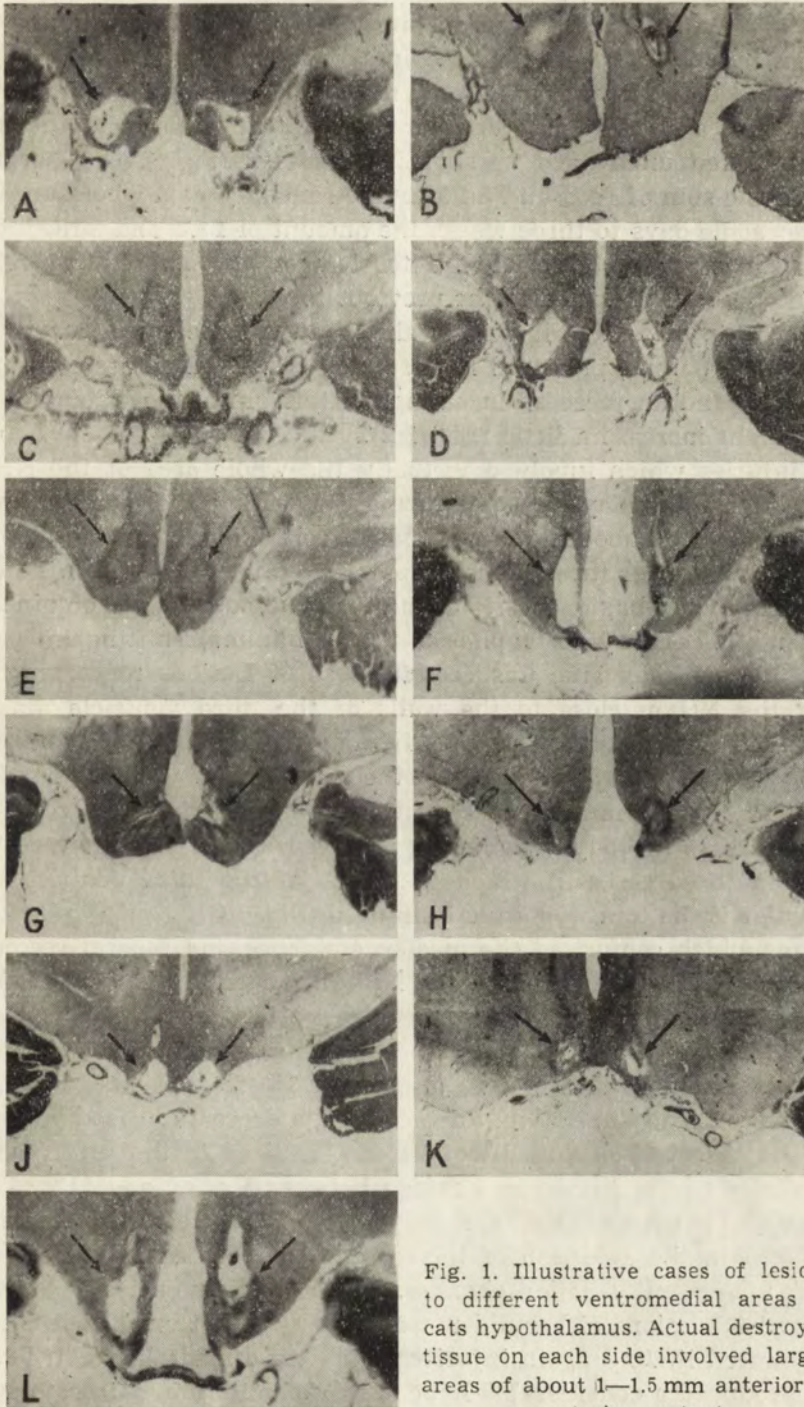
Fig. 1. Illustrative cases of lesions to different ventromedial areas of cats hypothalamus. Actual destroyed tissue on each side involved larger areas of about 1—1.5 mm anterior — posterior extent

of the ventral part of NHvm was manifested by reduced milk intake and sometimes by slight increase of food intake.

The damage of ventral part of the medial hypothalamus usually produced at first a decrease in cereal intake. At the same time the milk intake remained unchanged or slightly increased (Fig. 1 A). Therefore in general the sum of food and milk intake remained as a whole unchanged. After some days to three weeks the amount of food and milk intake returned to its preoperative level. After temporary decrease the weight of the animals also returned to the previous level.

The small injuries, which were localized in the more dorsal part of the medial hypothalamus, produced reverse results: first a decrease in drinking of milk and an increase in eating. In this group the weight of the animals might increase a little (Fig. 1 B).

The injuries which involved virtually the whole area of the NHvm resulted after a few days in some increase of eating and drinking; milk intake increased by about 25% and that of cereal by 40%. The maximal weight gain was after three month about 20% (Fig. 1 C, D, E). In no case considerable hyperphagia, obesity or increase in food CR were obtained.

It seems neccessary to emphasize that a minimal shifting in localization of lesions may give unsuccessful results. Lesions concerning the parts of the NHvm close to the walls of the third ventricle did not produce any hyperphagia (Fig. 1 F). In some animals poliuria and polidipsia were obtained; in these cases the milk intake was increased by 150 to 400%, but simultaneously eating dropped almost to zero and a sharp decrease in body weight was observed. Such results were often obtained in those cases in which the walls of the third ventricle and in particular its bottom was directly injured (Fig. 1 G).

Lesions which comprised the median eminence and tuberal region in the immediate neighbourhood of the NHvm and the third ventricle did not result in hyperphagia but, on the contrary, they produced hypophagia and hypodipsia (Fig. 1 H).

Hypophagia and aphagia were also obtained after lesions of an area situated laterally to the NHvm. Furthermore, a decrease in food and milk intake was observed as a result of lesions localized in the ventromedial area caudally to the NHvm in a region between Fr. 9.0 and 11.0 (J a s - p e r and A j m o n e - M a r s a n 1954), (Fig. 1 J). The more the lesions were placed in the direction of the mammillary bodies, the eating and drinking underwent smaller changes. In the region enclosed between Fr. 7.0 and 9.5 lesions either did not evoke any effect on food intake or even increased it. And again injuries which were made between Fr. 5.0 and 7.5 produced a considerable hyperdipsia of milk amounting to 500% (Fig. 1K). The cereal intake first diminished by 30% but after about

10 days returned to the previous level and than began to increase. More-
over a notable augmentation of drinking (by 200%) and eating (by 40%)
was observed after lesions, localized rostrally and dorsally to the NHvm,
in an area containing the paraventricular nucleus.

Concerning ventral nuclei of the amygdala and particularly the pos-
terior part of nucleus basalis parvocellularis, stimulation of these struc-
tures produced clear-cut inhibition of the food intake. The decrease of
drinking was strongly manifested. Even the irritation of the tissue by
implantation of electrodes already decreased the milk intake more than
by half.

On the contrary, lesions in this region led regularly to hyperphagia
and hyperdipsia by about 200%. Even a partial damage of nucleus was
effective.

When in amygdalar hyperphagic cats the hypothalamic injuries were
made, hyperphagia was never increased. On the other hand ventromedial
lesions of the hypothalamus, comprising the larger part of the NHvm,
not only abolished amygdalar hyperphagia but also could produce a tem-
porary decrease of cereal intake, even below the preoperative level. In
two cats aggression evoked by the amygdalar lesions also disappeared
(Fig. 1 L).

Tuberal injuries of the hypothalamus beyond the NHvm produced in
amygdalar hyperphagic cats the same effect as in intact animals, i.e.
hypophagia and hypodipsia. Amygdalar hyperphagia was also abolished
after hypothalamic injuries giving poliuria and polidipsia. These effects
of ventromedial hypothalamic lesions were always predominant and inde-
pendent of the succession of lesions.

On the other hand, if hypothalamic ventromedial lesions were fol-
lowed by hyperphagia, it was increased as a result of amygdalar lesions.

The results presented here indicate that the area of the NHvm shows
a great functional complexity in regard to alimentary reactions. In con-
sequence, small differences in the localization of lesions may easily lead
to great variety of symptoms. The functional relationship between the
NHvm and the ventral amygdala is at present not clearly understood. On
the basis of our results it may be assumed that the ventral part of the
NHvm which shows rather a facilitating effect on the food intake is inhi-
bited by the ventral part of amygdala. On the other, hand, the dorsola-
teral part of the NHvm seems to be in functional alliance with this struc-
ture. This problem requires further investigations.

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THE MOTIVATIONAL ROLE
OF THE HYPOTHALAMUS IN ANIMAL BEHAVIOUR *

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The importance of the hypothalamus in motivation has been shown by numerous investigators. Nevertheless the neural mechanisms underlying drives, emotions and related patterns of animal behaviour are still far from being fully elucidated. According to some authors, activation of the hypothalamus produces unspecific arousal of motivation, the direction of the performance being determined by the external stimuli. A number of investigators, beginning with Hess (1928), have however demonstrated that stimulation of different points of the hypothalamus evokes different or even opposite patterns of behaviour, under the same stimulus conditions. Furthermore, these reactions could be evoked stably from the same loci.

To investigate this problem further we performed several series of experiments in which we examined the effect of the stimulation of several points within the hypothalamus on various complex forms of behaviour, emotional expression and also their role in conditioning of instrumental reactions.

Experiments were performed on 21 male, mongrel dogs, weigthing 11—14 kg. Electrodes consisted of stainless steel needles, 0.6 mm in diameter, insulated by enemal except for 1 mm at the tip. They were implanted stereotaxically and cemented to the skull together with a plastic ring box. The needles were cut off a few milimeters above the cement,

and provided the bare ends which during experiments were attached by miniature connectors to the leads running from a stimulator (Fig 1 A). Outside the experimental room the ring was covered by a plastic cover to prevent the electrodes from touching or being scratched out by the dog (Fig. 1 B).
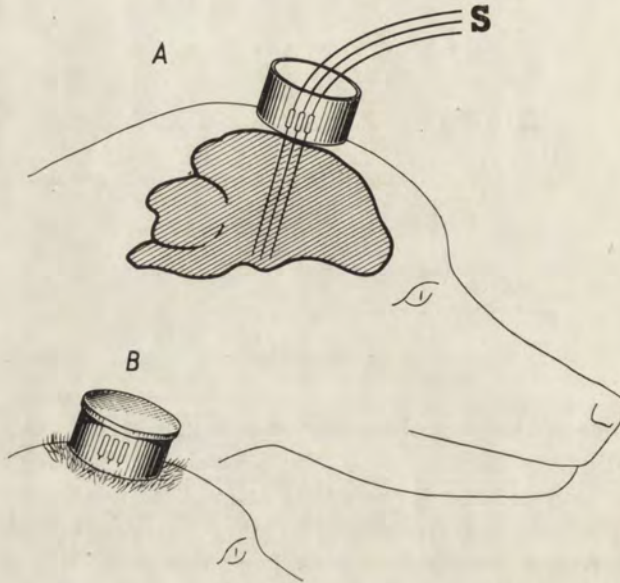
Fig 1. Schematic diagram of the method of electrode implantation used for the dogs. A. During the experiments, leads are connected with the stimulator (S). B. During intervals between experiments the ring, containing ends of the electrodes, is covered by plastic cover

After one week of postoperative recovery the dogs were tested in a conditioned reflex-chamber. The animals were placed in a stand and fastened by harness which permitted movement but prevented them from jumping out. Parameters for brain stimulation were rectangular biphasic waves 50—100 c/sec with a pulse duration 0,5 to 1,0 msec. Intensities (monitored on an oscilloscope) varied from 0,1 to 1,0 mA. In the first exploratory trials, the intensities started from 0,1 mA then gradually were increased to the level for threshold, optimal or maximal behavioral effect. In later trials, intensities for optimal reactions were used. In each dog several points were investigated.

During stimulation of the hypothalamus, various patterns of complex behaviour and correlated emotional symptoms were evoked. The following syndroms were observed: fear-flight, fear-defense, rage-attack and appe-

tite-food intake. All these reactions appeared to be similar or even identical in all their features to the normal behaviour of the animals in natural situations.

Stimulation of each particular point gave regularly in all successive trials the same form of behaviour even on different experimental days. This lasted, without change, for weeks or even months. Therefore it seems justified to say that various forms of behaviour were mediated by different anatomical loci.

The question arises as to whether stimulation of particular loci, which evokes a certain kind of behavioral pattern, can be used as positive and negative reinforcement.

With regard to motivation, the hypothalamus may be roughly divided into two systems: aversive and positive.

The first classification was made by H e s s (1947, 1954). He devided all reactions evoked by stimulation of the hypothalamus into ergotropic, to which belong the defensive reactions and trophotropic. It was later suggested by O l d s (1958, 1962) and O l d s et al. (1960) that stimulation of the ergotropic system is aversive and of the trophotropic rewarding. His line of division between these two antagonistic systems in based on the speed of respectively escape or avoidance and positive instrumental performance (selfstimulation). The speed of acquisition of instrumental reactions was then used by many authors as the basis for evaluation of the motivational level and motivational (positive or negative) meaning of the stimulation of particular structures.

In our experiments we used a similar criterion. For the sake of clarity the results obtained by stimulation of the aversive-defensive system and the alimentary system will be described separately.

AVERSIVE — DEFENSIVE SYSTEM

As already mentioned, three different patterns of aversive-defensive behaviour were noticed: flight, defense and attack.

Fear-flight reactions were evoked in 15 dogs. During, stimulation the dog screamed, whined, stood with legs bent, tail under, or moved in all directions, tried to escape in panic, often defecated and urinated. Heart rate was accelerated, respiration was fast and superficial. Sometimes, the fear reactions were accompanied by various motor effects, different in each case (F o n b e r g 1963a). All emotional, autonomic and motor effects could be easily conditioned first to a sporadic stimulus, preceeding hypothalamic stimulation and thereafter to the whole experimental situation.

Fear-defense reactions were observed on 17 dogs. In this group the attack was mixed with flight attempts. During stimulation the dogs bit

the lines but very rarely barked or growled. In addition, they showed obvious signs of fear such as acceleration of heart rate and respiration, yelping, whining and attempt to escape. The biting and other signs of attack were directed only towards those objects which prevented flight, such as the harness, lines attached to the legs, etc. Therefore, the form of attack differed from trial to trial and was more multiform than in the pure rage-attack syndrome. Defecation and urination was very rarely observed. The defense reactions usually outlasted the stimulation, and after several experimental sessions became conditioned to the CS and experimental situation and appeared spontaneously in the intervals between stimulation trials.
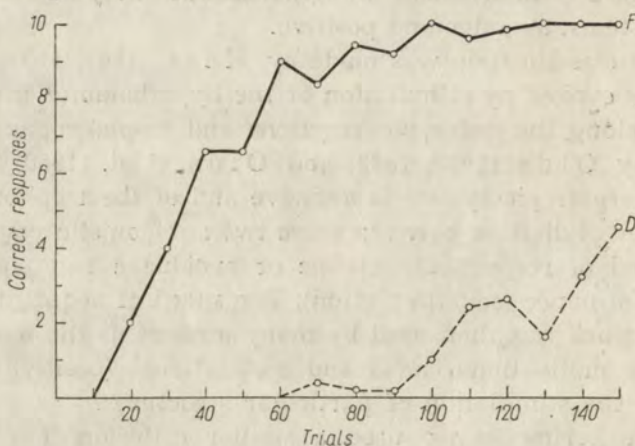
Fig 2. Comparison between the acquisition of avoidance reaction to the stimulation of "fear" and "defense" points. Each curve represents mean responses for one group, containing 5 dogs each. Avoidance acquisition is much slower in the "defense" than in the "fear" group, and does not reach hundred percent performance within 150 trials. Ordinate: mean number of correct responses. Abscissa: successive trials. Solid line: "fear" group. Broken line: "defense" group

Rage-attack reactions were observed in six dogs. The picture of the rage syndrome was as follows: immediately (1—5 sec) after the onset of the stimulation the dog bared his teeth, rolled his eyes, snarled with increasing violence, growled or barked, and then started to attack the objects in the vicinity, such as harness, lines, bars etc. Occassionally he also tried to bite the experimenter's hand, if exposed. If threatened with a stick, he tried to grasp it with his teeth. On the whole the attack was well directed.

Almost immediately after the offset of the stimulation the dog retur-
ned to his previous calm and friendly state, and if touched showed no
aggressiveness. Only in two dogs did the intense barking sometimes
outlast the stimulation for 1—5 min. Other symptoms usually evoked
simultaneously with the rage-attack reactions were: deep breathing, pupil-
lary dilatation, exophtalmus, sometimes salivation and turning to right
or left. Motor symptoms and defecation or urination were observed when
the intensity of the stimulation was above that for optimal rage reactions.
Attempts at flight, whining or other signs of fear were not observed in
the pure rage-attack syndrom.

After selection of the points, which gave the most typical reactions,
avoidance training was started. The conditioned stimulus was a tone,
while the unconditioned stimulus was stimulation of the particular
system through implanted electrodes. The instrumental reaction consisted
in leg flexion. The avoidance reactions were trained on five dogs from
the fear-flight group, five from the fear-defense group and four from
the rage-attack group.

The results presented on Table I and Figs 2 and 3 show that the most
efficient negative reinforcement in avoidance training was the stimulation
of the fear-flight points. Most of the animals started to avoid brain stimu-
lation of the fear-flight points within 20 trials. After 120 trials all of
them showed a hundred percent performance, which thereafter was
mantained on a stable level (Table I).

The avoidance training in the fear-defense group progressed much
more slowly than in the previous one. After 60 trials none of the animals
had even started to perform the avoidance reactions, and only one dog
learnt to avoid after 130 trials. In the others, even after 150 or more trials,
the avoidance reaction had not reached the hundred percent level. Later
it was not stable having a tendency to drop during some experimental
sessions. The difference in avoidance training between the fear-flight and
fear-defense groups are highy significant statistically ($P < 0,01$). These
results support the distinction made in our previous paper (Fonberg
1963a) between the fear-flight and fear-defense syndroms in spite of the
fact that the emotional and some autonomic expression of fear were
similar in both cases.

We were not able however, to show a strict anatomical division
between the two systems. The fear-flight and fear-defense points were
somehow intersperced. It was nevertheless possible to detect the loci of
the greatest accumulation of points belonging to a particular system.
And so, most of the fear-flight points were found in the posterior
hypothalamus near the mamillothalamic tract (Fig. 4A) and the fear-
defense points were assembled in the perifornical area (Fig. 4B).

Table I

Acquisition of the avoidance reaction to the stimulation of the hypothalamic "fear", "defense" and "rage" points

No. of dog	FEAR														
	10	20	30	40	50	60	70	80	90	100	110	120	130	140	trials 150
F—10	0	3	9	10	10	10	10	10	10	10	10	10	10	10	10
F—13A	0	2	9	10	7	10	7	9	9	10	10	10	10	10	10
F—13	0	4	2	6	8	7	7	10	8	10	8	10	10	10	10
F—14A	0	0	0	7	4	9	9	10	9	10	10	10	10	10	10
F—14	0	1	0	0	4	9	9	8	10	10	10	9	10	10	10
DEFENSE															
D—12	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
D— 6	0	0	0	0	0	0	0	0	0	1	0	0	0	0	0
D— 1	0	0	0	0	0	0	2	0	0	0	1	4	4	5	9
D—21	0	0	0	0	0	0	0	0	0	0	1	1	1	10	10
D—18	0	0	0	0	0	0	0	1	1	4	10	8	3	1	4
RAGE															
R—20	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R—16	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
R—13	0	0	0	0	0	0	0	0	0	0	0	0	3	7	8
R—15	6	7	9	10	10	10	10	10	10	10	10	10	10	10	10

In the body of the table there are given numbes of correct responses within each ten trials.

Avoidance reactions to the Rage-attack points were trained in four dogs. This group was not uniform in its performance (Table I and Fig. 3). In one dog, R-20 even after three hundred trials, the avoidance reactions could not be established. It should be mentioned that in this dog the rage reactions were the most typical and stable, i.e. stimulation did not produce, even on the high level (np to 1,0 mA), any other symptoms, such as motor reactions or signs of fear or attemps at flight. Furthermore the pattern of behaviour did not change for 3 months, i.e. to the end of experiments.

In two other dogs, the avoidance reactions were still not present after more than a hundred trials. At the same time as the acquisition of the avoidance reaction started some new symptoms such as signs of fear, whining and restlessness also began to appear. This fact suggests that the stimulation overpassed the rage-attack system and might have involved the fear system, probably because of the dislocation of the electrodes.

Only in one dog (R-15) did the avoidance training progress quickly.

In this dog, although the behavioural symptoms were identical with the other dogs, the location of the electrode tip was different. Whereas in the remaining dogs it was located in the medial hypothalamus near the
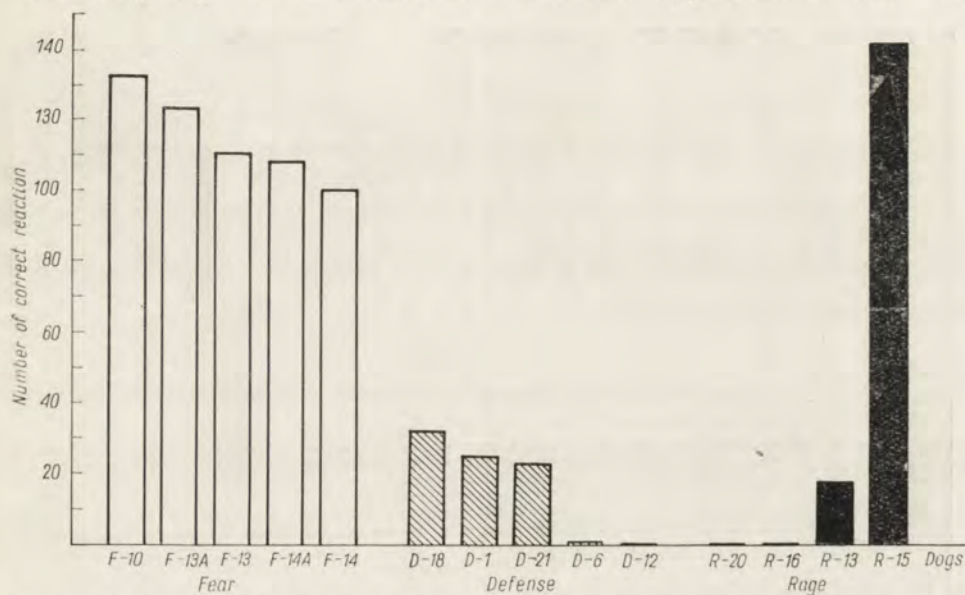

Fig 3. The number of correct avoidance responses in 150 trials for individual dogs in "fear" "defense" and "rage" groups. White blocks, "fear" group. Stripped blocks, "defense" group. Dark blocks, "rage" group

ventro-medial nucleus, in the vicinity of the third ventricle (Fig. 4C); in this particular dog the tip of the electrode was situated in the midbrain, lateral to the central grey (Fig. 4D), in the region of the colliculus inferior.

This shows that, although the behavioral syndroms of rage-attack were similar in all cases, the level of anatomical location is important in respect with the motivational role. It is possible that the particular points of aversive-defensive system, which are separate at the hypothalamic level, collect at the level of the midbrain. In the dog D-15, in spite of the fact, that the rage-attack reactions were predominant, nevertheless the fear or pain system might also have been stimulated. This last could have accounted for the quick avoidance training.

None of the dogs in the rage-attack group showed any signs of the classical conditioning of the rage symptoms to the conditioned stimulus, or experimental situation.

Our results are in agreement with the group of authors who found that within the aversive system there exists several subsystems mediating particular forms of behaviour and correlated emotional symptoms.

Most of the authors agree that flight and attack syndroms are separate and have a distinctive behavioral pattern and different anatomical location (H u n s p e r g e r 1956, N a k a o 1958, Y a s u k o c h i 1960,
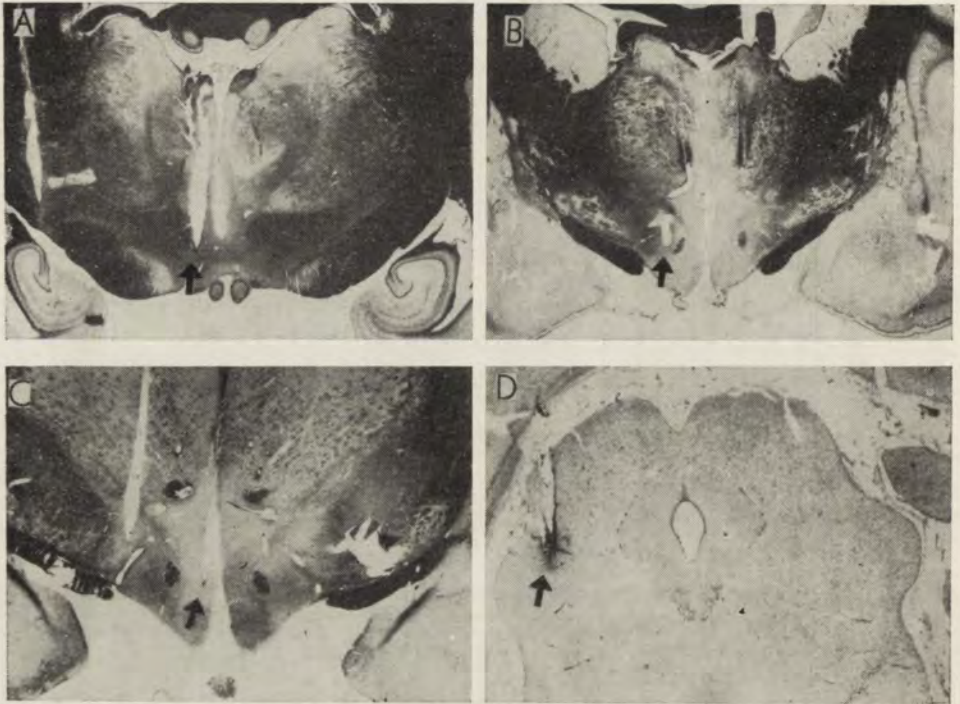

Fig. 4. Brain sections showing typical sites of the electrodes for "fear" (A) "defense" (B) and "rage" (C and D) groups. Tip of the electrode, which when stimulated produced fear-flight responses, lay near the mammillary bodies in the posterior hypothalamus (A) and the tip of the electrode, which when stimulated evoked the fear-defense syndrom, is situated in the perifornical region (B). Section C shows the location of the electrode, which produced a typical rage syndrom (dog 20). As indicated by arrow it was found in the ventromedial hypothalamus near the third ventricle. Section D shows the location of the electrode in dog D-15. In this case the electrode was situated in the midbrain, in the region of the colliculus inferior. Note: the brain was perfused and put into formalin together with the electrode assembly. Therefore during shrinkage of the brain tissue the electrode tracts were artificially enlarged

F o n b e r g and F l y n n 1963, K o z l o v s k a i a and V a l d m a n 1963, K o z l o v s k a i a 1964, R o m a n i u k 1965, and others). Several authors found the further divisions within fear-flight and rage-attack syndroms. For example, W a s m a n and F l y n n (1962) described three different forms of rage-attack behaviour: affective arousal, affective attack and stalking attack. Roberts (1958) distinguished two kinds of fear-flight

behaviour i.e. "alarm" and "flight", and found that stimulation of "alarm" points serves as a good negative reinforcement for avoidance training while, to the stimulation of "flight" points he was not able to establish the avoidance reaction. His results are controversial with those of other authors, who showed that acquisition of avoidance is very fast if stimulation of "fear-flight" points is used as negative reinforcement (D e l g a d o et al. 1954, N a k a o 1958, L i l l y 1960, F o n b e r g 1963b, 1966a, 1966b, R o m a n i u k 1964, and others).

There is also some controversy as to whether it is possible to elicit by brain stimulation pure behavioral syndroms. Hunsperger found that the flight and defense reactions can easily transfer from one to the other during stimulation, and that both syndroms can be elicited from one point. He described also, that combined stimulation of attack and flight areas intensified the attack response (Brown and Hunsperger 1963, Hunsperger et al. 1964).

In recent years however, several authors were able to evoke the pure rage syndrom, which was stably elicited from the same electrode points and did not transfer to flight (N a k a o 1958, Y a s u k o c h i 1960, W a s - m a n and F l y n n 1962, E g g e r and F l y n n 1963, F o n b e r g 1963a, 1966a, 1966b, L e v i s o n and F l y n n 1965, R o m a n i u k 1965). From the experiments of F o n b e r g and F l y n n (1963, 1967 in preperation) it results that flight and attack reactions are somehow opposed to each other and that — simultaneous stimulation of both "flight" and "attack" areas did not facilitate either reaction but, on the contrary, produced complete interference of both, or changes in the behavioral patterns. The discrepancy of the results obtained by particular authors may be due to the methodological differences, like stimulus parameters, stimulation time and so on, and may not reflect significant basic differences.

Some doubts also exist as to whether the rage-attack reactions, should be classified, at least in their predatory form, as belonging to the aversive-defensive system. For example, R o b e r t s and K i e s s 1964) found that attack reactions with the presence of prey are rewarding. And H u t c h i n s o n and R e n f r e w (1966) showed that the same points may mediate the attack and alimentary reactions. On the other hand, R o b e r t s and K i e s s (1964) and W a s m a n and F l y n n (1962) showed that if stimulation of attack points started during eating a cat left the bowl with food and went to attack a rat. This seems to show that, although in carnivores the predatory attack and food intake are probably synergetic, they are mediated by separate systems. According to most authors and in agreement with our own results the alimentary system is quite distinct and does possess specific properties.

4*

THE ALIMENTARY SYSTEM

In exploratory experiments, we found that in 13 dogs stimulation of several points produced food intake in previously satiated animals (Fig. 5). During stimulation of these points the dogs looked around them, licked their lips or neighbouring objects and if food was available, ate voraciously. The food intake started a few seconds after the onset of stimulation and in some dogs overlasted stimulation by a few minutes. The dogs were overeating to such an extend that even after vomiting the food they immediately started to eat again if the stimulation was still on. In some dogs a high level of stimulation produced also chewing. No signs of fear, defense, and attack reactions were observed.

Fig. 5. Brain section showing typical location of the electrode's tip, which during stimulation evoked both food intake in satiated animals and "reward" effect

Starting with the hypothesis that hunger is aversive we tried to establish an avoidance reaction to the stimulation of these points in hungry or satiated animals. We did not succeed. On the other hand it was very easy to establish under the same conditions positive instrumental reactions.

The results, of the experiment performed on 3 dogs, (Fig. 6) indicate clearly that it was possible to establish an instrumental reaction to an acoustic stimulus reinforced only by brain stimulation of an "hunger" point without food being given (Fig. 6A). When the conditioned stimulus + instrumental reaction was no longer reinforced by brain stimulation the reaction became extinguished (Fig. 6B). However, it was easily restored when the conditioned stimulus was again followed by brain

stimulation (Fig. 6C). These facts seem to indicate that, in instrumental training, stimulation of the feeding system possesses properties of reward similar to food intake.

The same conclusion seems to follow from the next experiment, performed on two dogs. These animals were previously trained to perform to the conditioned stimulus (tone) an instrumental reaction (bar pressing) reinforced by food. When, in the crucial experiments, brain stimulation of an alimentary point was substituted for food reinforcement, full transfer occurred. When these two reinforcements were given alternately in blocks of five trials each, the dog performed the instrumental reaction in 100% of trials i.e. equal to the condioned stimulus reinforced by food intake or brain stimulation (Fig. 7).
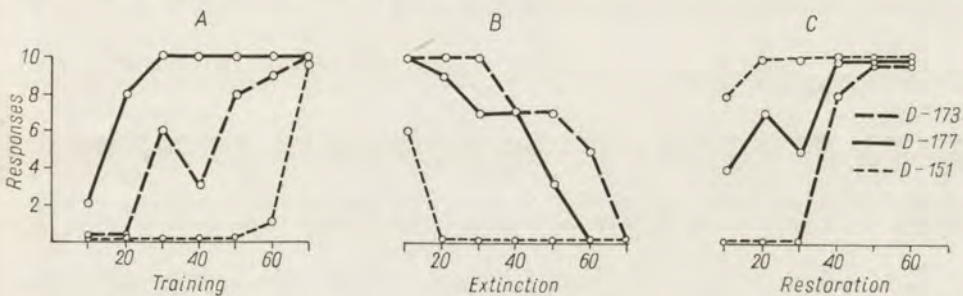

Fig 6. Instrumental training reinforced by brain stimulation of "food" points. Ordinate: number of instrumental responses during each block of ten trials. Abscissa: number of successive trials. A, Training, B, Extinction, C, Restoration of the instrumental response. We see that within 70 trials all dogs learnt perfectly to perform to the conditioned stimulus an instrumental reaction reinforced only by the cerebral stimulation of "food intake" points (A). When the instrumental reaction was no longer reinforced by brain stimulation, it became extinguished (B) but was quickly restored (20—50 trials) when the conditioned stimulus was again reinforced by stimulation of "alimentary" points (C)

Also differentiation of two conditioned stimuli, trained to food reinforcement, was fully preserved when food was substituted by cerebral stimulation.

These facts are consistent with the results obtained by M a r g u l e s and O l d s (1962) and H o e b e l and T e i t e l b a u m (1962) by the method of selfrewarding. In their method however, because of the short trains of stimulation ($1/_2$—1 sec after each press), the offset of stimulation almost immediately followed it's onset. Therefore the adherents of the drive-reduction theory may claim that this is the offset of stimulation, i.e. — decrease of hunger drive which is rewarding. In our experiments the long time of on-stimulation (10—20 sec, and in special series of experiments even 60 sec or more) excludes this criticism.

It is interesting to note that the same results were obtained both on satiated and hungry animals (24 hr of deprivation).

All these facts reveal the existance of another aspect of the function of the hypothalamic food system, which cannot be accounted for by the increase of the hunger drive activity. If stimulation increases hunger it is difficult to explain why it acts as reward. Why would deprived animals perform a reaction which resulted in increasing their hunger and repeat it for hundreds of trials? One rather would expect the opposite i.e. that an increase of hunger should serve as punishment.
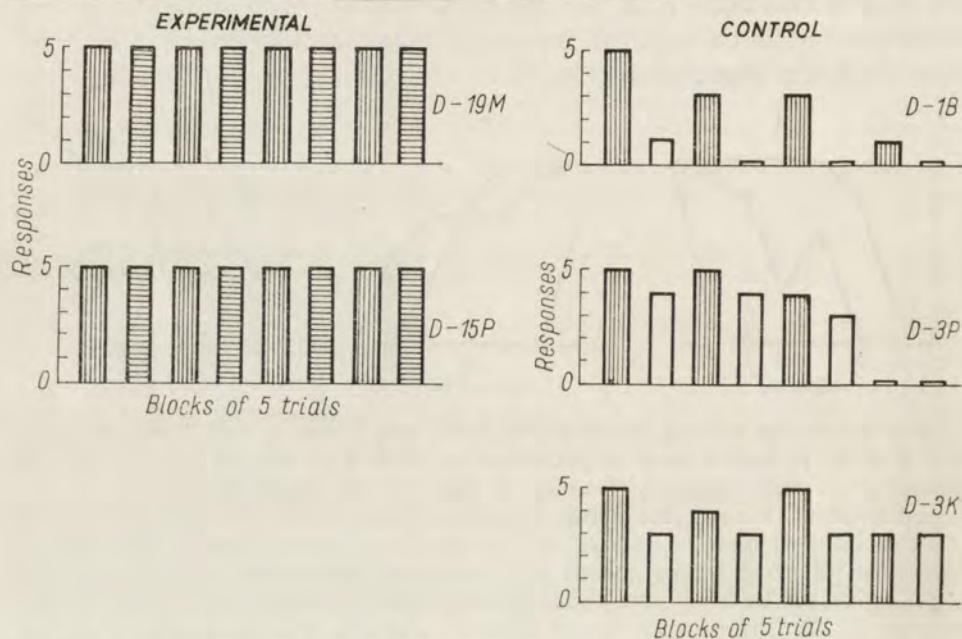

Fig 7. Schematic diagram of the experiments with different reinforcements of the instrumental reaction. Ordinate, Number of correct responses within each block. Abscissa, Successive blocks of 5 trials each. E x p e r i m e n t a l: the instrumental reaction is reinforced either by the stimulation of "alimentary" points (horizontal stripes) or by food (perpendicular stripes). The performance of the dog, in spite of the shifts in reinforcement, keeps to the maximal level of performance. C o n - t r o l: — the instrumental reaction is either reinforced by food (perpendicular stripes) or nonreinforced (white). In these conditions the instrumental reactions show a tendency to partial extinction

In fact, it seems that our results can be understand by assuming that stimulation of the hypothalamic food system does not produce augmentation of hunger but rather a state equivalent to food reward. This is in agreement with the formulation of H o e b e l and T e i t e l b a u m (1962) that stimulation of alimentary system is similar to the gratification

obtained by eating. Developing furter this idea we may hipothetize that hypothalamic stimulation produces some sensations similar to those caused by food intake i.e. smell and taste of food (W y r w i c k a 1966a). The behaviour of our animals seems to favor this assumption: often during stimulation the dogs sniffed and licked their lips or neigbouring objects with signs of "satisfaction". The great importance of taste and smell in the act of eating was proved by T e i t e l b a u m (1962) and P f a f f m a n (1960). The hypothesis of "sensory reward" may explain, why stimulation alone serves as reinforcement. It may be considered as a sort of "hallucination" of a good meal. If food is available this stimulation drives the animal to eat voraciously, a fact which was the main basis for the "hunger theory" of hypothalamic stimulation (M i l l e r 1957, W y r w i c k a 1960). How explain it by the "sensory reward" hypothesis? Why does the animal eat during stimulation, if he is satiated and has refused to eat before stimulation, if the stimulation does not produce hunger? Although, we cannot say that stimulation of the alimentary system produces only sensory sensations we may assume that stimulation augments the taste, smell and all the pleasurable values associated with food, and it is these values and not hunger that would cause the animal to eat during stimulation. As we know from our own experience we often eat not because we are hungry but because the food tastes good. The same reason i.e. gourmandies not hunger may drive the animal to eat during stimulation. In a situation where stimulation is applied alone he may indefinitely profit from the pleasures of eating without the discomfort of oversatiation.

Another explanation of this dual effect of hypothalamic stimulation was that proposed recently by K o n o r s k i (1967). This author assumes that the lateral hypothalamus is composed of two kinds of hunger units, which may be denoted as on-units and off-units. Excitation of the first is responsible for hunger drive state and the excitation of the second ones for the satisfaction of drive, equivalent of food intake. Electrical stimulation of the food system may excite both kinds of neurons and thus produce both food intake and reward effect.

M o r g a n e (1962) put forward another hypothesis i.e. that the alimentary and rewarding systems are separate but they are intersperced with each other at the level of the lateral hypothalamus, and that simultaneous stimulation of both system is responsible for compound effect i.t. food intake and reward.

There exist also some other evidence that the alimentary system is not uniform but composed of different parts, and that by lesions of different structures within the alimentary system the particular functions of the alimentary behaviour can be separated. For example W y r w i c k a

(1966b) in her last work showed that, while the lateral hypothalamic lesions abolished both the instrumental responses and food intake, the anterior hypothalamic lesions produced only aphagia, leaving intact performance of the instrumental alimentary reactions.

The final conclusion, following from the experiments of other authors and our own data is not yet possible to be formulated. It is justified to say only, that the motivational role of the hypothalamus, cannot be regarded as uniform. Both the aversive-defensive and consumatory systems are complex and consist of different subsystems with a different motivational role. At the hypothalamic level all these specific systems are interconnected, intersperced and related in various ways. Moreover, they extend beyond the hypothalamus. The influences of the cortex, thalamus, limbic system, reticular formation, and humoral balance add further factors to this complexity. The fact that, in spite of these multiform influences, it is possible to evoke by electrical stimulation of certain points, the particular, global, unmixed forms of behaviour, prove however the specificity and relative independance of the various hypothalamic systems.

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THE MAMMILLARY BODIES:
THEIR FUNCTION AND ANATOMICAL CONNECTIONS [1]

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Knowledge concerning the anatomical connections of the mammillary
bodies is unquestionably greater than knowledge concerning their func-
tion, a situation typical of limbic structures but atypical of hypothalamic
structures. Although the mammillary bodies are by definition hypotha-
lamic nuclei, we shall see later that by virtue of both their connections
and function they might be more profitably considered as limbic struc-
tures. This issue is, however, perhaps best resolved by adopting the
current notion of considering the hypothalamus and limbic system as
functionally and anatomically inseparable.

The following discussion of the mammillary bodies will consist of four
sections: a) a description of their anatomical connections; b) a conside-
ration of their phylogenetic development; c) a discussion of data relevant
to their function, which will include a brief presentation of two recent
experiments conducted in our laboratory with the assistance of R. L o -
r e n z, E. E. C o o n s, J. W e i s s and T. G r e e n s p o n, and, d) specu-
lations on the function of the mammillary bodies which have been
presented in a summary fashion elsewhere (K r i e c k h a u s, 1966b).

Anatomical Connections. Before presenting a simplified outline of the
connections of the mammillary bodies in the cat, it should be pointed out
that the degeneration techniques on which most of the following studies

are based are far from perfect (R a i s m a n, 1966). Furthermore, the
evidence of P o w e l l et al. 1957) that the Nauta silver technique can stain
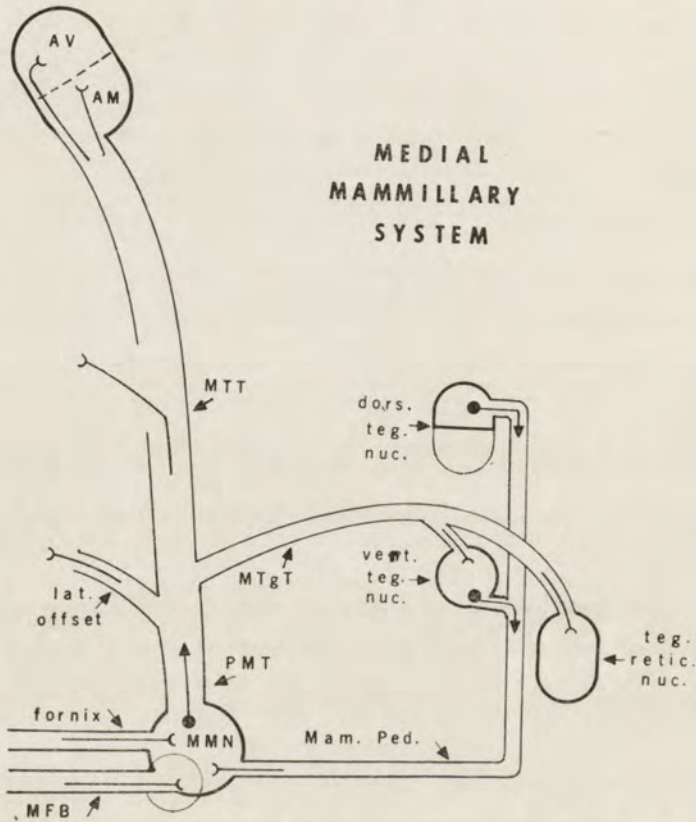retrograde as well as antrograde fiber degeneration in the anterior tha-

Fig. 1. Schematic representation of the medial mammillary system in cat. The two
descending afferents to the medial mammillary nucleus (MMN), which are the
fornix and the median forebrain bundle (MFB), are shown in the lower left hand
corner of the figure approaching MMN from rostrally located forebrain areas. The
ascending MMN afferent, the mammillary peduncle (Mam. Ped.), is shown in the
lower right hand part of the figure approaching MMN from the caudally located
tegmentum, more specifically from the dorsal portion of Gudden's dorsal tegmental
nucleus (dors. teg. nuc.) and from Gudden's ventral tegmental nucleus (vent. teg.
nuc.). The MMN efferents which leave the MBs all course through the principal
mammillary tract (PMT), which gives rise to three efferent bundles: The descending
mammillotegmental tract (MTgT) is seen to terminate in ven. teg. nuc. and in the
tegmental reticular nucleus of Bechterev (teg. rectic. nuc.). The fibers of the
mammillothalamic tract (MTT) which terminate diffusely in the ventromedial
nucleus of the thalamus are represented by the rostrally directed projection seen
leaving the MTT midway in its course. More dorsally the MTT is seen to terminate
in the anteroventral (AV) and anteromedial (AM) thalamic nuclei. The lateral
offset of the PMT (lat. offset) terminates diffusely, probably in the subthalamus.

lamus, and the evidence of Fry et al. (1964) for transneuronal cell degeneration in the cat mammillary bodies suggest that it may often be difficult to establish with certainty the direction of conduction of mammillary connections. It would be hoped that concomitant electrophysiological analyses of these connections would be of value in future investigations.

In all mammalian species thus far studied the mammillary bodies (MBs) can be divided into two parts, the large medial mammillary nucleus (MMN), and the smaller lateral mammillary nucleus (LMN), which lies on the lateral edge of MMN. The connections of MMN, which are simpler than those of LMN, are presented schematically in Fig. 1. Fibers ascending to MMN via the mammillary peduncle (Man. Ped.), which may be thicker than those terminating in LMN (C a j a l, and R a m o n 1955; F o x, 1941), originate, in part, in G u d d e n's ventral (deep) tegmental nucleus (F o x, 1941; F r y et al., 1964) and terminate largely in the anterior part of MMN (F o x, 1941). N a u t a and K u y p e r s (1958) and A k e r t and A n d y (1955) found in cat that Mam. Ped. fibers also arise from G u d d e n's dorsal tegmental nucleus. However, F r y et al., (1964) indicated that those fibers which terminate in MMN originate exclusively in the dorsal portion of this nucleus. C o w a n, et al. (1964) in rat and M o r e s t (1961) in rabbit found a similar restricted origin of the MMN afferents in the central part of this nucleus. Mammillary afferents in Mam. Ped. originating in the medial leminicus as first suggested by C a j a l (1955) are improbable; those originating from the interpeduncular nucleus as first suggested by P a p e z (1932), have not been specifically identified in cat.

The chief descending afferents to both MMN and to LMN arise in hippocampus and travel via the post commissural fornix (N a u t a, 1958; V a l e n s t e i n and N a u t a, 1959; F r y et al., 1964; J o h n s o n, 1965). Differential sites of origin within the subdivisions of the hippocampus for those fornix fibers which terminate in the MBs, recently worked out by R a i s m a n, et al. (1966) for rat, have yet to be rigorously demonstrated in cat. It has been shown by N a u t a (1958) and F r y et al., (1964), that MMN as well as LMN receives additional descending afferents via the median forebrain bundle (MFB). More recently, J o h n s o n (1965) and P o w e l l (1966) have indicated that at least some of these afferents arise in the septum. This suggests that the origin of MFB fibers which show terminal degeneration in MBs following lesions which interrupt MFB between septum and MBs, such as those of N a u t a (1958) in cat and W o l f and S u t i n (1966) in rat, would be difficult to interpret. The extent to which fornix and MFB in cat also carry fibers from the neocortex and from the cingulate cortex is still open to question.

It appears that the axons of all MMN cells which do not terminate within the MBs, leave the MBs in the principal mammillary tract (PMT) and have only unilateral projections (F r y, et al. 1963; F r y et al., 1964;
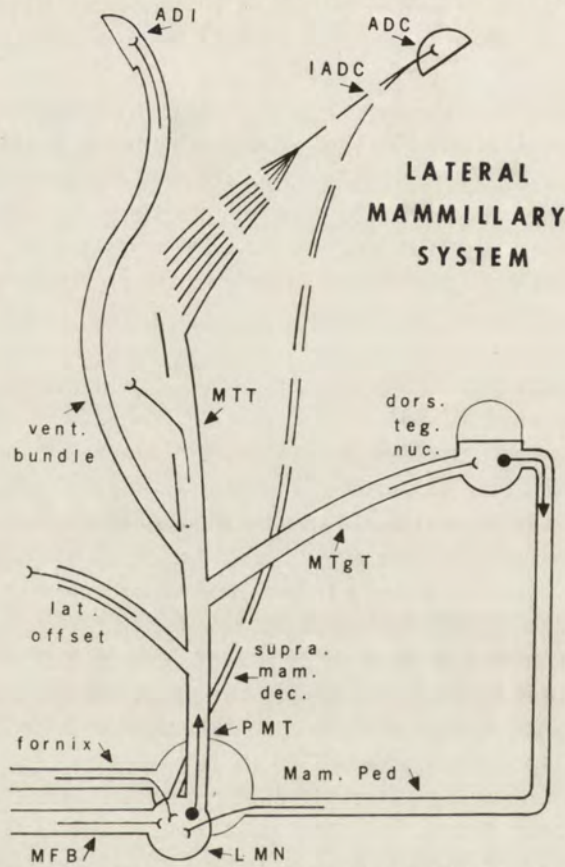

Fig. 2. Schematic representation of the lateral mammillary system in cat. The descending and ascending mammillary afferents are similar to those of the medial system. Note, however, that LMN affferents in Mam. Ped. are shown to originate exclusively in the ventral portion of dors. teg. nuc. In addition to LMN efferents which course through PMT, there may be others (represented by the thin dashed pathway leaving LMN dorsally) which cross the midline in the suprammillary decussations (supra. mam. dec.) to run to the contralateral anterodorsal thalamic nucleus (ADC). The lat. offset of PMT is not known to differ from that of the medial system. Note that MTgT fibers from LMN are shown to terminate exclusively in the ventral portion of dors. teg. nuc. Fibers which terminate in ipsilateral anterodorsal nucleus (ADI) course in the ventral portion of PMT and MTT and are shown to leave MTT in the ventral bundle (vent. bundle). MTT fibers terminating in ADC which cross the midline diffusely are represented by the converging dashed lines seen leaving the head of MTT. These fibers then gather together again in the fairly compact inter-antero-dorsal commissure (IADC) to terminate in ADC

G u i l l e r y, 1961). Leaving aside the longstanding question of the origins of the bifurcating fibers in PMT, which is adequately discussed by G u i l l e r y (1955, 1961), it is well established that MMN efferents in PMT give rise to three distinct bundles. The most prominent of these, the Vicq d'Azyr's bundle or mammillothalamic tract (MTT), has diffuse projections in the ventral medial nucleus of the thalamus (F r y et al., 1963) and extensive terminations in the anteroventral and anteromedial thalamic nuclei (F r y et al., 1963, 1964; G u i l l e r y, 1961). G u i l l e r y (1956) reported that in rat MTT fibers which terminate in the anteroventral nucleus arise from the well deliniated pars posterior of the rat MMN. Although clear subdivisions of MMN have not been rigorously identified in cat, it does appear that the posterior MMN in cat projects to the anteroventral nucleus (G u i l l e r y, 1961). This suggests that feline homologues of the subdivisions of rat MMN may be fruitfully explored in cat on the basis of homologous connections as well as on the basis of cytoarchtectonic similarities. The second most prominent bundle, the mammillotegmental tract (MTgT), with thinner fibers than those in MTT (G u i l l e r y, 1961), terminates in G u d d e n's ventral tegmental nucleus (G u i l l e r y, 1961; F r y et al., 1964) and in the tegmental reticular nucleus of B e c h t e r e v (G u i l l e r y, 1961). The third bundle, the lateral offset of MTT, appears to project diffusely in the subthalamus, perhaps to the fields of F o r e l l and zona incerta (N a u t a, 1958; F r y et al., 1964).

The connections of LMN, presented in Fig. 2, differ from those of MMN in many important respects. In fact, the only connections of LMN which have not been demonstrated to differ from those of MMN are those which are as yet poorly understood. Since the origin of MB afferents coursing in MFB is unclear, it is not known if the MFB fibers terminating in LMN and MMN have different origins. The origin within MBs and the exact locus of termination of both the diffuse MTT connections to the ventral medial nucleus of the thalamus and of the lateral offset are still unknown. Thus, a clear distinction between MMN and LMN in the origin of these projections also can not be made. The lateral system, while similar to the medial in its intimate tegmental connections, differs from the medial in the precise locus of these connections. As seen in Fig. 2, the tegmental afferents in Mam. Ped. to LMN arise exclusively from the ventral portion of G u d d e n's dorsal tegmental nucleus, which is also the exclusive projection area for LMN efferents via MTgT (F r y et al., (1964); G u i l l e r y, 1961). There is presumptive evidence (V a l e n s t e i n and N a u t a, 1959; G u i l l e r y, 1961; J o h n s o n, 1965) that the cat is similar to the rat (C o w a n et al., 1964) in that LMN afferents arise almost exclusively from Mam.

Ped., i.e., fornix afferents are few or nonexistent. However, this has not been rigorously confirmed in cat.

The greatest difference between the lateral and medial system in cat is their completely different locus of termination in the anterior thalamic nuclei. Whereas MTT fibers originating in MMN terminate unilaterally in the anteromedial and anteroventral thalamic nuclei, LMN fibers terminate bilaterally in the anterodorsal thalamic nuclei (G u i l - l e r y, 1961; F r y et al., 1963, 1964). This difference in the thalamic projections of the lateral and medial systems is maintained further rostrad as well. Whereas the anteroventral and anteromedial nuclei receive additional afferents from both hippocampus and from septum the anterodorsal nucleus appears to receive projections exclusively from septum (N a u t a, 1958; P o w e l l, 1966). Furthermore, the anterodorsal nucleus efferents terminate in the retrosplenial cortex while those of the anteromedial and anteroventral nuclei terminate in the anterior limbic and cingulate cortex respectively.

A final differentiation of the lateral and medial systems is suggested by the findings of F r y et al. (1963) that the ipsilateral LMN projection to the anterodorsal nucleus courses through the ventral part of PMT and MTT, and leaves MTT as a distinct group of fibers, the ventral bundle.

It has long been known in rabbit (Y a m a g a t a, 1927) and in an insectivore (C l a r k, 1929) that many of the fibers coursing in MTT cross the midline diffusely throughout the midportion of the course of the MTT and then gather together in the compact inter-antero-dorsal commissure to terminate in the contralateral anterodorsal nucleus. Although F r y et al., (1963) identified at least some of these fibers in cat as the contralateral LMN efferents, it was suggested later (F r y et al., 1964) that other fibers from LMN may cross the midline just dorsal to the MBs in the supramammillary decussations. Whether these fibers might be those described by R a m o n y C a j a l (1955) and other investigators as the decussating post mammillary fornix fibers remains to be seen. Thus it is still not clear from a quantitative point of view where the contralateral LMN fibers cross the midline.

Phylogenetic Aspects. Although it appears that homologues of the well developed mammalian MBs may exist in inframammals, the rostral mammillary projections to the anterior thalamic nuclei and the corresponding thalamo-cortical projections to the cingulate cortex, all of which are so prominent in mammals, appear to be absent or poorly developed in inframammals. This generalization concerning the mammillothalamic system appears to be borne out by recent investigations in our laboratory on the chicken brain; however, for more thorough discussion of infra-

mammalian homologous of the mammillothalamic system see C l a r k
(1938), B e r g q u i s t (1954a, 1954b) and K a p p e r s, et al. (1960). Also,
it has long been known in man (H i s, 1904), as well as in infrahumans
(C o g g e s h a l l, 1964), that the recent phylogenetic appearance of the
mammillothalamic system is paralleled ontogenetically by a very late
myelination of MTT. This is in marked contrast to the caudal mammillary
efferent, the mammillotegmental tract, which is one of the first fiber
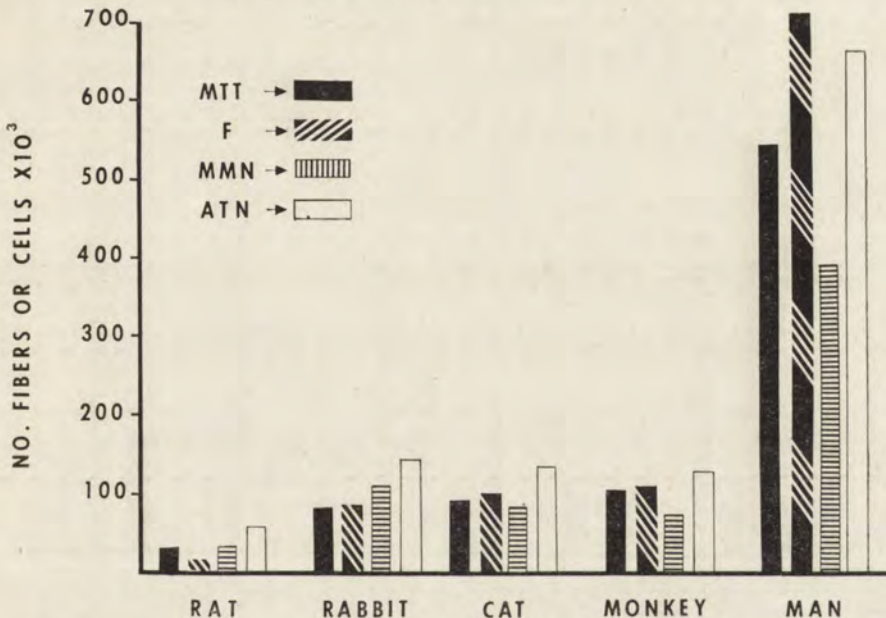tracts to become myeliniated during ontogeny.

Fig. 3. Prominence of the mammillothalamic system within mammals. Numbers
of cells in the medial mammillary nucleus (MMN), anterior thalamic nucleus (ATN),
and numbers of fibers in the mammillothalamic tract (MTT) and in the fornix (F)
are presented for five mammallian species, including man. The quantitative data
for this and the following figure were compiled from P o w e l l, et al., 1957;
B r u e s c h and A r e y, 1942; L a s s e k and R a s m u s s e n, 1940; and L a s s e k
1941

When the mammillothalamic system is evaluated within mammals
(Fig. 3) it can be seen that in man as compared to rat, rabbit, cat and
monkey (Macaca mulatta) there is an approximate five-fold increase
in the number of cells in the MBs and anterior thalamic nuclei, and in
the number of fibers in the MTT and fornix. In an effort to evaluate
this phylogenetic development of the mammillothalamic system relative
to a general, nonspecific development of other brain structures, the data
of Fig. 4 are presented. The solid bars and open bars in Fig. 4 represent

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a ratio of the number of fibers in MTT to those in the optic tract and
pyramidal tract respectively. The dashed bars, a ratio of the number
of cells in the anteroventral and anteromedial thalamic nuclei to the
number of cells in the medial mammillary nucleus, are a measure of
the relative prominence of the rostral termination site of the MTT.
These findings, based on fiber and cell counts, are similar to those of
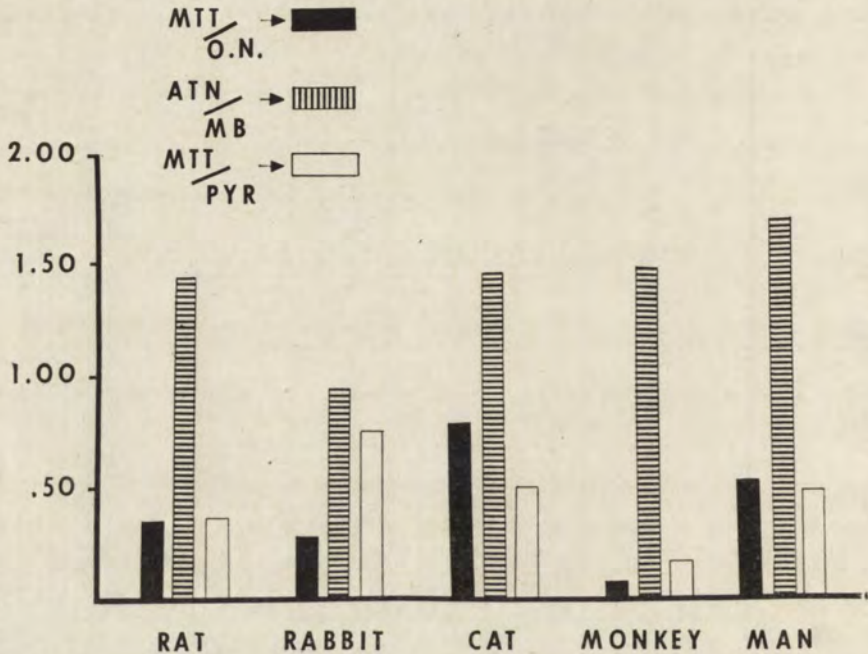

Fig. 4. Relative prominence of the mammillothalamic system within mammals. The
solid bars (MTT/O.N.) and open bars (MTT/PYR) represent a ratio of the number
of fibers in the mammillothalamic tract (MTT) to those in the optic nerve (O.N.)
and pyramidal tract (PYR) respectively. The dashed bars (ATN/MB) represent
a ratio of the number of cells in the anteroventral (AV) and anteromedial (AM)
thalamic nuclei to the number of cells in the medial mammillary nucleus (MMN)

R o s e (1939), based on a comparison of the volumes of the MBs to
those of the hypothalamus and thalamus in a variety of species.
Furthermore, H o p f (1965) in a comparative volumetric study of the
prominent anteroventral thalamic nucleus in primates reported that,
whereas the thalamus as a whole doubles in volume from orangutan to
man, the anteroventral nucleus triples in volume. Although far-reaching
conclusions should not be drawn from the above data, it certainly
appears that there is no relative decrease in man in the prominence
of the MTT or in the thalamic terminations of MTT.

Function. Although the MBs have long been implicated in functions as diverse as anterograde amnesia (K o r s a k o f f's syndrome) and autonomic and endocrine regulation, none of the many studies are convincing in localizing the dysfunction to the mammillary bodies. (For a discussion of this problem see: K r i e c k h a u s, 1962; B a r b i z e t, 1963; V i c t o r, 1964, T a l l a n d, 1965). Experimental work deliberately focusing on the mammillothalamic system, which has been largely behavioral in emphasis, suggests that this system is important in the performance of conditioned defensive behavior (escape and avoidance behavior).

Before discussing the behavioral effects of mammillothalamic tractotomy, brief mention should be made of the problem of localization of these effects specifically to the mammillothalamic system. Utilizing small, ultrasonic lesions, many of which were confined entirely within the limits of the MTT, it was shown in cats (K r i e c k h a u s, 1964a, 1964b) that in the near vicinity of the MTT, lesions of the MTT were the necessary and sufficient conditions for the observed changes in behavior. All subsequent work in our laboratory with cat (K r i e c k - h a u s, 1966a; K r i e c k h a u s and C h i, 1966) and with rat (K r i e c k - h a u s, 1964a) has been based on comparisons of lesions which interrupted the MTT with those which missed the MTT but were in the near vicinity of the MTT. Nonetheless, recent studies with rat (S a n t a c a n a and D e l a c o u r, 1966; V a n A t t a, et al., unpublished and preliminary results in our laboratory on the effect of MTT lesions on the effectiveness of punishment) strongly suggest that other areas, probably lateral and posterior to the MTT, play a nonspecific role in defensive behavior. Thus, an essential aspect of future investigations of the role of the mammillothalamic system in defensive behavior will be the accurate deliniation of the critical areas.

In the first of the two experiments to be reported here, three groups of rats were taught the same difficult contingent discrimination in a T maze. The first group was motivated by hunger, i.e., the correct choice was rewarded by food, and the second group by escape from shock, i.e., the rat was continuously shocked until it made the correct choice; in the third group the rats could avoid as well as escape the shock, i.e., the rat was given 10 sec to initiate the correct response before the shock came on. In all the groups the rats had to learn to go to the right arm of the maze if both arms were illuminated and to the left if both arms were dark. Following surgery in which it was attempted to interrupt the MTT bilaterally with DC lesions, the animals were tested for their ability to retain the discrimination under the same conditions as employed preoperatively. It can be seen from Fig. 5 that rats with MTT lesions did not differ from rats in which the lesions

5*

missed the MTT in their ability to make the correct choice, whether
motivated by fear, pain or hunger. However, if the ability of MTT
lesioned animals to initiate the response is evaluated, the situation is
quite different. Whereas there was no change following mammillotha-
lamic tractotomy in the animal's latency in initiating the response with
pain or hunger motivation, MTT lesioned animals were much slower in
their initiation of the response in order to avoid the impending shock
than rats in which the MTT was missed; and more importantly it can
be seen from the dashed line in Fig. 5 that in most cases the MTT
lesioned rats did not avoid at all, i.e., they did not initiate the response
until after the shock came on. Thus, although MTT lesions have no
observable effect on the animal's making the correct response, they
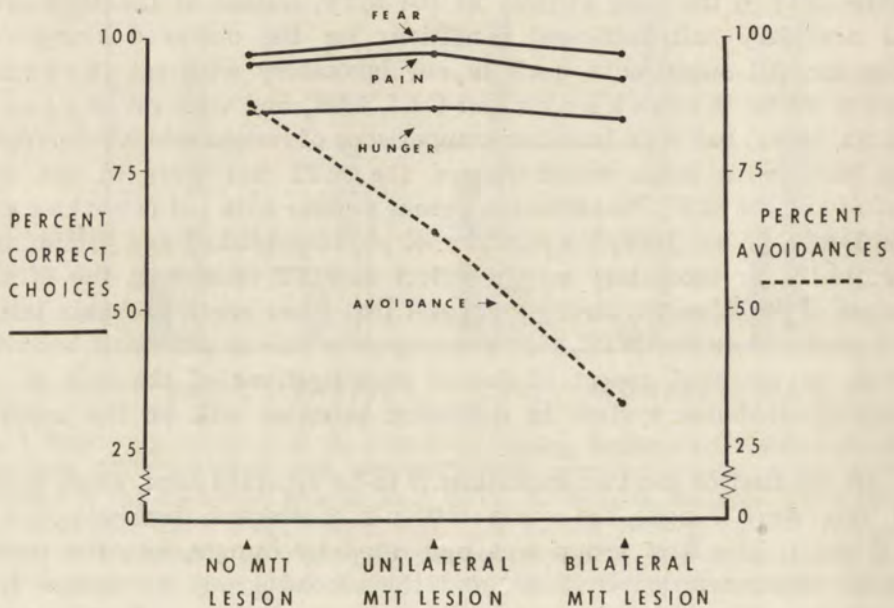have a great effect on the rat's ability to initiate the response in order
to avoid pain.

Fig. 5. Postoperative performance in T maze. Percent correct choices, postopera-
tively, in the visual discrimination for each of the three motivational states-fear,
pain and hunger are represented by the three solid lines. The percentage of the
trials on which the rat initiated the response before shock, onset, i.e. avoided
shock, are represented by the dashed line

In the second experiment, cats were taught to press a lever in order
to get milk (conditioned alimentary behavior). Later they were taught
to press the lever to avoid shock when an auditory stimulus was
presented (conditioned defensive response). The apparatus in shown in

Fig. 6 and 7. Following surgery the cats were tested for 3 days for their retention of the conditioned defensive response under extinction conditions (no shock was given for a failure to avoid). They were then tested for their retention of the conditioned alimentary behavior, and finally they were retrained in the conditioned defensive behavior. The cats with complete bilateral lesions of the MTT showed a complete loss of avoidance behavior, whereas cats in which the MTT was spared showed no loss of the avoidance response. Cats with partial MTT damage showed graded decrements roughly proportional to the extent of MTT
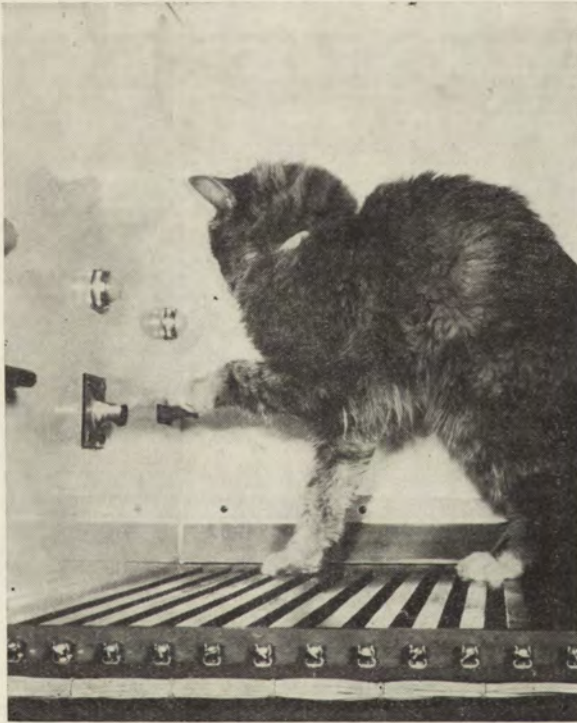

Fig. 6. Cat pressing lever to obtain milk

damage. When shock was reintroduced the MTT lesioned cats not only showed a profound decrement in the reacquisition of avoidance behavior but also had to be retrained to press the lever to escape from the shock. Finally, in marked contrast to these decrements in defensive behavior, there was no decrement in the retention of the conditioned alimentary behavior.

Taking these two experiments together with earlier work, the following general conclusions seem warranted. First, of the several kinds

of behavior that have been assessed following mammillothalamic trac-
totomy, only conditioned defensive behavior has been found unequivo-
cally to be affected. Second, these decrements in conditioned defensive
behavior are not attributable to changes in the animal's basic sensory
mechanisms, relevant motor systems, or ability to retain complex and

Fig. 7. Cat drinking milk from dispenser

difficult discriminations. For a more complete discussion of these first
two conclusions see T h o m a s et al., (1963), K r i e c k h a u s (1964a,
1965, 1966a) and K r i e c k h a u s and C h i (1966). Third, although
increases in freezing behavior are strongly implicated in these decre-
ments in conditioned defensive behavior, there is no measurable increase
in freezing behavior following MTT lesions when freezing is measured
independently of avoidance behavior (K r i e c k h a u s, 1966a).

If we dichotomize conditioned defensive behavior into that involving
escape from pain and that involving avoidance of pain, several other
conclusions emerge. First, decrements in escape behavior following
mammillothalamic tractotomy are greater when the escape response is
more difficult or unnatural for the animal to execute. Thus, a cat's
ability to run or jump as a means of escaping a painful stimulus is well

retained following MTT lesions (K r i e c k h a u s, 1964a). On the other hand, the cat's ability to escape shock by pressing a lever which, at least for the cat, is an unnatural response to pain, is very difficult for the cat to learn initially and is severely reduced following MTT lesions, as is shown in the results of the second experiment. The next conclusion, which concerns avoidance behavior, also involves the notion of difficulty or unnaturalness, but now these terms are applied to the overall task confronting the animal rather than to the movement or response itself. Thus, in the simple one-way avoidance task in which the cat easily learns to leave a particular compartment in which it always gets shocked (K r i e c k h a u s, 1964a) or to move away from a localized conditioned stimulus signaling shock (I r w i n and M c A d a m, 1966), there is little or no decrement in the cat's avoidance behavior following lesions in the mammillothalamic system. On the other hand, in the two-way or shuttle task, in which the cat is not allowed to leave the apparatus, the cat has great difficulty preoperatively in learning to move back and forth between the two compartments in order to avoid pain, and shows substantial decrements in the retention of the avoidance behavior following mammillothalamic tractotomy (K r i e c k h a u s, 1964). Finally, as we have seen in experiment two, in the case in which the cat must learn an unnatural response (lever pressing) and also has no opportunity to get out of the dangerous situation, the loss of avoidance behavior is complete and the cats show great difficulty in relearning to avoid.

The last and perhaps most important point is that the behavior of animals following mammillothalamic tractotomy has never been observed to differ in any way from that observed in most animals during their initial acquisition of the avoidance behavior. For example, during initial training in the T maze experiment reported here, after the rats had quickly mastered the discrimination problem, most of them still did not initiate the running response in order to avoid shock, but usually remained motionless and frozen until and shock came on. The post operative behavior of the few rats which had preoperatively learned to avoid, and then suffered mammillothalamic tractotomy, was identical to the behavior of the many rats which initially did not learn to avoid.

Speculations. That the difficulty or unnaturalness of the task confronting a rat or cat determines the severity of the decrement in avoidance behavior following MTT lesions immediately suggests that the lesions may disrupt the sensory or cognitive functions necessary for the animal to perform such difficult tasks. However, as we have seen, there is no decrement following MTT lesions in the rat's ability to make the correct response in a difficult T maze discrimination once

the rat initiated the response. Thus, sensory and cognitive processes do not appear to be affected. Why then do MTT lesions affect the initiation of avoidance behavior only for difficult tasks, yet have no affect on the performance of these tasks once the animal initiates the behavior? This raises the more general question of why initiation of avoidance behavior is closely related to the unnaturalness or difficulty of the task in unlesioned animals.

The answer to both these questions may lie in an analysis of animals' primitive, unlearned, species-specific responses to danger. We shall assume that in dangerous situations the unlearned response patterns highest in the animal's response hierarchy are freezing, fleeing or fighting. Since in the procedures we have been using, stimuli adequate to elicit fighting behavior have not been employed, the problem reduces to one of explaining why an animal freezes in one circumstance and flees in another. If we assume that the survival value of freezing lies, at least in part, in its minimizing the probability of the animal being detected by predators, while that of fleeing lies in its removing the animal from the dangerous situation, then freezing rather than flight would be adaptive when flight behavior would probably not remove the animal from danger and when the danger is not immediate. If we apply this reasoning to laboratory experimentation, then the simple one-way avoidance situation presumably will be perceived by the rat and cat as being such that flight behavior will have a high probability of leading to safety since jumping out of the compartment removes the animal from danger. Thus freezing will not successfully compete with the flight response and the avoidance response is readily initiated. However, situations such as the difficult two-way situation are presumably perceived as ones in which flight will probably not lead to safety since ultimately there is no exit from the dangerous situation; thus freezing predominates and we observe that the avoidance response is not initiated. It is thus suggested that the more difficult is the task confronting an animal in a dangerous situation, the smaller will be the animal's subjective probability that flight behavior will lead to safety, and thus the more the balance between flight and freezing will be tipped in favor of freezing, a situation which will be manifested in an absence of the avoidance response.

Although it admittedly can be misleading to apply conclusions based on natural selection to laboratory experiments, there is evidence to support the application in this case. We have shown by using d-amphetamine, which reduces freezing behavior independently of changes in avoidance behavior (K r i e c k h a u s, et al. 1965) and by manipulating the circumstances surrounding the acquisition of the avoidance responses,

that the conflict between flight and freezing is an extremely important variable in the acquisition of the two-way avoidance response, yet appears to play only a minimal role in the acquisition of the one-way avoidance response (K r i e c k h a u s, et al., 1964; K e n y o n and K r i e c k h a u s, 1965; W e i s s et al., unpublished).

It should be pointed out that freezing in the highly artificial two-way avoidance situation is unquestionably maladaptive for the organism. However, when the phenotype which we now observe in rat and cat underwent selection, it was presumably of advantage to these species to freeze in these many kinds of circumstances in which pain is not imminent and in which flight would probably not lead to safety. This of course assumes that in a time of danger, animals tend to react in a stereotyped nondiscriminitive manner, which appears to be the case (E a s t e r b r o o k, 1959).

Whereas this formulation in terms of a balance between freezing and fleeing provides an answer to the earlier question of why the unnaturalness or difficulty of an avoidance task is related to the animal's initiation of avoidance behavior, the other question as to why mammillothalamic tractotomy affects only these difficult tasks remains to be answered. Although in circumstances such as the two-way situation the response highest in the animal's hierarchy is freezing, some rats and almost all cats do, in time, stop freezing to the warning signal and do initiate adaptive flight behavior. Because animals with MTT destruction closely resemble those animals which preoperatively persist in freezing, and do not flee, it is hypothesized that in difficult and unnatural danger situations the mammillothalamic system normally plays a role in this shift in the response hierarchy from freezing to flight. (This characterization of the role of the mammillothalamic system does not imply that this system is the only part of the central nervous system which plays a role in this function nor is it implied that the function of the mammillothalamic system is limited to this role.)

Since the lever press avoidance response is similar to the two-way response in that the cats are also not allowed to escape from the dangerous situation, the post mammillothalamic tractotomy decrements in avoidance behavior in this situation would be explained like those in the two-way situation. However, as we have seen earlier, the affect of mammillothalamic tractotomy on the lever press response is very different from its affect on the two-way response. Whereas in the two-way situation the behavioral deficit was largely confined to the animals ability to avoid shock, in the lever press situation the animal was not only deficient in avoiding shock but was also unable to execute the lever press response to escape from the shock. If the role of the

mammillothalamic system were confined to that of tipping the balance from freezing behavior to flight behavior, then these decrements in escape behavior following mammillothalamic tractotomy in the lever press situation would be inexplicable since cats show no sign of freezing to the shock itself. However, from watching cats in this situation it is apparent that pressing a lever to escape from shock is very unnatural for the cat and that before it can learn this response more natural, unlearned flight responses, such as running, jumping and clawing, which are high in the animal's response hierarchy to pain must be suppressed.

Thus it would seem fruitful to think of the mammillothalamic system more generally as playing an important role in a system which tips a balance away from primitive and stereotyped response patterns which are innately high in the animal's response hierachy to danger. In cases in which the pain is not yet present, but imminent, i.e., the avoidance situation, the balance is tipped from freezing to the initiation of motor activity; in the situations in which pain is actually present, i.e., the escape situation, the balance is tipped from primitive and stereotyped flight behavior to novel, trial and error behavior.

The importance of this hypothesized role of the mammillothalamic system in mediating the balance between stereotyped and novel behavior can best be understood from a phylogenetic point of view. Whereas inframammals have exploited their particular ecological niches with stereotyped response patterns, mammals, particularly primates, have been successful because of their ability to initiate novel, nonstereotyped responses and to appreciate the outcome of this behavior. This plasticity of higher animals has been attributed to the development of the neocortex and its associated subcortical mechanisms. However, at least in the case of dangerous situations, it appears that the animal's ability to initiate novel forms of behavior is also critically dependent on the suppression of innate, primitive response patterns which are high in the animal's response hierarchy — a function which we suggest is dependent on the integrity of the mammillothalamic system.

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THE ROLE OF THE HYPOTHALAMUS
IN DEFFENSIVE BEHAVIOR

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A number of investigators has shown that the diencephalon is associated with defensive behavior (H e s s a n d B r ü g g e r 1943, H e s s 1949, B r a d y et al. 1954, M a c L e a n 1955, D e l g a d o 1955, H u n s p e r g e r 1956, 1959, K l i n g and H u t t 1958, N a k a o 1958, A b r a h a m s et al. 1959, 1962, R o m a n i u k 1962, 1963, 1965, F o n b e r g 1963, K o z l o v s k a i a 1964). All these investigations show that a variety of defensive patterns have their central representation in the hypothalamus. In addition many workers have demonstrated that the motor and autonomic symptoms related to the defensive reactions are integrated by the hypothalamus (C a n n o n and B r i t t o n 1925, B a r d 1928, P a p e z 1937, H e s s and B r ü g g e r 1943, M a c L e a n 1955, A b r a h a m s, et al. 1960).

Electrical stimulation of the hypothalamus in awake, freely moving animals elicites a typical defensive behavior, noted in intact animals, resembling those observed when an animal attacks or is attacked. It is also well known that stimulation of many points of the hypothalamic region can elicit defensive responses in the form of aggression and flight reactions. The reaction of aggression is characterized by pupil dilation, pilo-erection, back arching, growling and snorting, salivation, baring teeth, pushing out claws, locomotor reaction and violent rushing on all objects within the animal's reach. The reaction of flight is characterized by pupil dilation, increase in the respiratory rate, acoustic effects in the form of shrill mewing, urination, defecation and violent locomotor activity.

It appears reasonable to believe that both the reaction of aggression

and the reaction of flight with their characteristic autonomic and motor symptoms are components of the defense type of behavior. The flight reaction might be considered a passive defensive behavior in a sense that an animal defends itself avoiding a harmful situation, while the aggression reaction might be considered an active defensive behavior in a sense, that an animal defends itself by attacking.

Despite numerous investigations, the topographical organization of the diencephalic regions associated with defensive behavior is not clearly established.

W h e a t l e y (1964) found that electrolytic lesions of the medial hypothalamus in cats evoked aggressive behavior and irritation or produced a decrease of reactions to nociceptive stimuli. These reactions occurred as a result of bilateral lesions of the ventromedial nucleus of the hypothalamus or of the areas situated somewhat dorsally to this nucleus. More recently, R o m a n i u k (1962) showed that after small lesions of the medial hypothalamus in the rabbit a marked impairment on defensive CR occured, i.e. the latency was lenghtened, the CRs was often abolished, and the number of intertrial responses decreased. Also R o m a n i u k (1962) has shown that the destruction of the dorsal portion of the medial hypothalamus produces reaction of aggression, and the destruction of the ventral part of the medial hypothalamus produces an increase in defensive CR, and in the general emotionality. On the other hand, B a l i ń s k a and W y r w i c k a (1961), B a l i ń s k a, R o m a n i u k and W y r w i c k a (1964) have shown that limited lesions of the lateral hypothalamic regions in rabbits produced a decrease or complete abolition of conditioned as well as unconditioned defense reaction. These disturbances in the defensive behavior occured as a result of lesions in the anterior and posterior regions of the lateral hypothalamus. These investigations would indicate that the lateral hypothalamus is also associated with defensive behavior, and plays an important role in the performance of defensive CR.

Discrepancies as to localization of aggression and flight reactions in the hypothalamus are related to the experiments in which the electrical stimulation of the brains in awake, unanesthetized animals was used. H e s s (1949) elicited the reaction of aggression by stimulation of the anterolateral areas of the diencephalon, including the basal septal nuclei, the preoptic area and the basal part of the central thalamus, while an increased restlessness and flight responses was produced by stimulation of the posterior hypothalamus and the adjacent subthalamic regions. H u n s p e r g e r (1956) confirmed H e s s' results, and in addition, found that the aggression and flight reactions can be also evoked by the stimulation of the central gray matter of the mesencephalon. H u n s p e r - g e r (1956) concluded that the substrate concerned with the various pat-

terns of defensive behavior constitutes an unbroken field, comprising portions of the preoptic area, the hypothalamus posterior, and the central gray matter of the mesencephalon. Within the responsive field, two central regions can be located from which the active defence reaction was obtained. The first region is situated in the rostral hypothalamus, and the second in the central gray matter of the mesencephalon. These two central regions lie embedded in a common peripheral region of which passive defence reaction can be elicited. Furthermore, H u n s p e r g e r (1956) noticed that, depending on the parameters applied and on the time of stimulation, in some cases, the reaction of aggression and, in other cases, the reaction of flight, or even passing one into the other, can be evoked by stimulating always the same point. Recently, a different and even opposite localization of the reaction of aggression and flight to that of H e s s (1949) and H u n s p e r g e r (1956) was indicated. N a - k a o (1958) obtained the reaction of flight by stimulating the anterior hypothalamus and the preoptic area from points, situated somewhat laterally to ventricle III and, the reaction of aggression by stimulating middle and ventral parts of the central hypothalamus. The reaction of fear and flight caused by the stimulation of the anterior hypothalamus and the reaction of aggression as a response to the stimulation of the central hypothalamus were also observed by Y a s u k o c h i (1960). W a s - m a n and F l y n n (1962) evoked the reaction of both the aggression and flight by the stimulation of lateral regions of an area, stretching from the anterior to the posterior hypothalamus. In experiment on rabbits (K o z l o v s k a i a 1964), the reaction of aggression was produced by the stimulation of the medial areas of the posterior hypothalamus. R o m a - n i u k (1963, 1965) has shown that the reaction of aggression can be evoked by stimulation of the points located in the ventral part of the anterior, central and posterior portions of the medial hypothalamus, distributed from the preoptic area up to corpora mamillaria, instead the reaction of flight can be produced by stimulation of the points located in the dorsal part of the anterior, central and posterior subdivisions of the medial hypothalamus.

On the basis of the results of electrolytic lesions of the hypothalamus in rabbits and investigations during which an electrical stimulation was applied to this structure in cats (R o m a n i u k 1962, 1963, 1965), a hypothesis was put forward that the "aggression center" is located in the ventral part of the medial hypothalamus, while the "flight center" is located in the dorsal part of the medial hypothalamus. Both "centers" are situated in the area, including the anterior, central and posterior subdivisions of the medial hypothalamus, contained in the frontal planes 10.0 to 13.0 and situated 1 to 2 mm laterally to ventricle III.

Our experiments suggest that the discrepancies met with in the literature may be due to the fact that in earlier investigations on the relationship between the hypothalamus and emotional behavior, the location of the points associated with defensive reactions, was considered basically in anteroposterior and not in dorsoventral aspect. Thus, from the illustrations presented in the papers by H e s s (1949) and H u n s p e r g e r (1956), it becomes evident that the reaction of flight was produced by stimulating the dorsal portion of the posterior hypothalamus, while the ventral portion of the posterior hypothalamus was not explored at all. From the illustrations represented in the papers by N a k a o (1958) and Y a s u k o c h i (1960) it is clear that the reaction of aggression was produced basically by stimulating the ventral and central portions of the posterior hypothalamus. On the other hand, the dorsal portion of the posterior hypothalamus appears less explored. It is also possible that some of these discrepancies result from the application of different techniques and parameters of electrical stimulation.

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SPREADING DEPRESSION
AND RECOVERY OF SUBCORTICAL FUNCTIONS [1]

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The recovery of function after damage to various subcortical struc-
tures is the problem that actually attracts much attention. Among those,
the recovery of feeding and drinking that occurs after damage to the la-
teral hypothalamus is probably the most convenient for experimental
investigation. In 1951, A n a n d and B r o b e c k reported that bilateral
damage in the areas of the lateral hypothalamus produces a syndrome
of aphagia that leads to death from starvation. This finding was verified
in 1954 by T e i t e l b a u m and S t e l l a r, who stated two things:

1) Not only do the animals stop eating but they also do not drink
water.

2) If they are kept alive by forced feeding they will usually recover
feeding and drinking again.

In 1962, the recovery through a sequence of regular stages has been
described by T e i t e l b a u m and E p s t e i n. In the first stage, of apha-
gia and adipsia, animals do not eat or drink and will die unless kept
alive by intragastric tube-feeding. Then they progress to the second stage,
of anorexia and adipsia, in which they eat wet and palatable foods but
not enough to maintain their weight and they still refuse to drink water.
Thus the tube-feeding must be continued. In the third stage, preceding
recovery, they regain ability to regulate their caloric intake and main-
tain their weight, but they remain adipsic — they still refuse to drink
water. Eventually, however, they drink water, eat dry food, and appear
recovered.

In this paper we turn our attention to another aspect of the problem

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of recovery. That is, how does the recovery process occur? There are three major facts which are pertinent for the present paper:

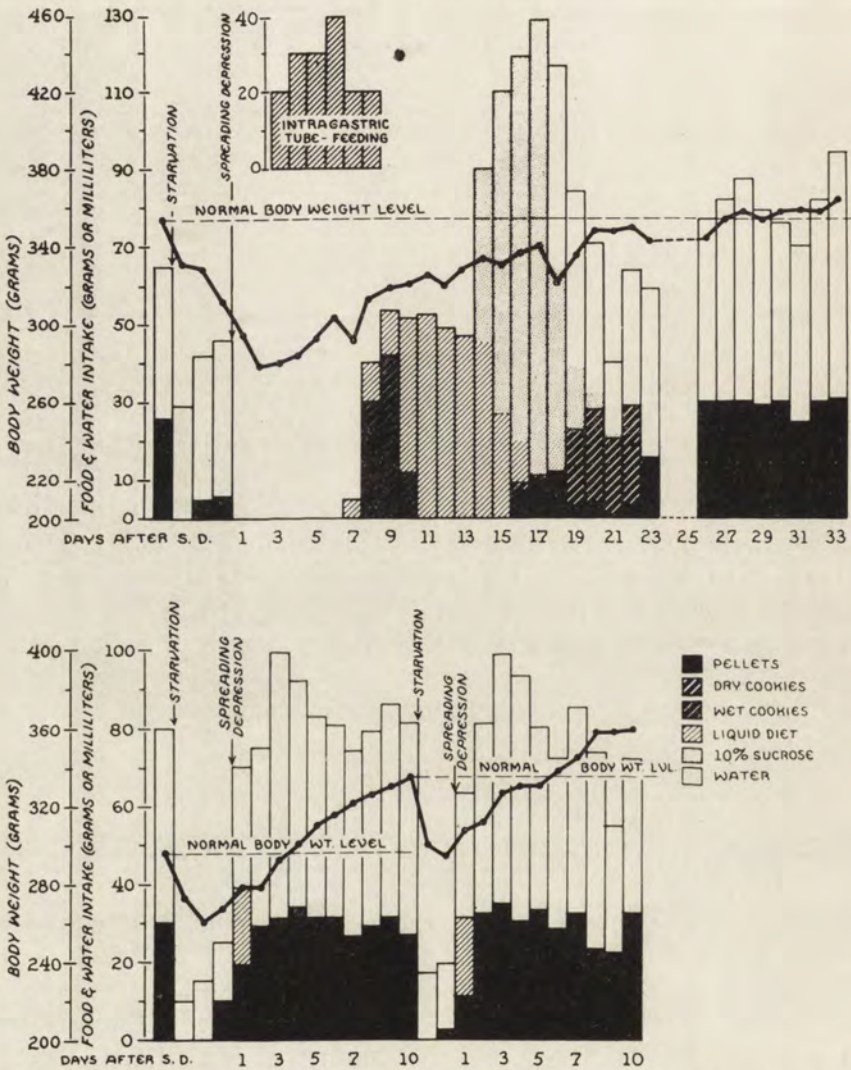1) In 1962 T e i t e l b a u m and E p s t e i n stated that the tissue im-

Fig. 1. Daily body weight and food and water intake after the onset of spreading depression. The height of each bar on any day represents the cumulative intake of all substances on that day (e. g. 30 g of food plus 50 ml of water equals a total height of 80).Top: Prolonged aphagia and adipsia reinstated in a rat recovered from lateral hypothalamic lesions. During recovery, the rat was weaned from wet cookies to a liquid diet, and from a liquid diet to pellets and water. Bottom: In a control rat, on two occasions, spreading depression had little effect on the food and water intake

mediately around the original lesion is important in the recovery from
lateral hypothalamic damage. If after an animal has fully recovered
from the effects of lateral hypothalamic lesions, additional damage is
made in the areas adjacent to the original lesion, the animal will starve
all over again and recover once more. The recovery is slower and not
as complete. Destroying more tissue will cause starvation to again result
with incomplete recovery and so on.

2) Also in 1962, H o e b e l and T e i t e l b a u m showed that the self-
stimulation system described by O l d s (1958) runs through the lateral
hypothalamus completely overlapping the area that controls feeding.

3) In recent papers, B u r e š et al. (1961) and O l d s (1962) have shown
that spreading cortical depression depresses lateral hypothalamic acti-
vity so that animals will not stimulate themeselves in this region during
cortical depression. From these facts it follows that spreading cortical
depression should decrease the activity of the tissue immediately adja-
cent to the original lateral hypothalamic lesions and should, therefore,
reinstate the syndrome of lateral hypothalamic aphagia and adipsia in
animals previously recovered from lateral hypothalamic damage.

In our paper of 1965, we have proved that this prediction is correct.
As shown in Fig. 1. a normal animal subjected to spreading depression
after period of food deprivation will, for two or three hours, eat and
drink nothing at all. Then it will begin to take a liquid diet, but will
refuse ordinary food and water until about six hours have elapsed. From
that time on, it will eat and drink normally and will usually regain its
weigh within two or three days. Recovered lateral hypothalamic ani-
mals, however, are much more affected by spreading depression. As
can be seen in the Fig. 1, one animal did not eat or drink anything for
six days following spreading depression. On the seventh and eighth day,
it accepted a liquid diet and wet cookies but still had to be tube fed
throughout the eight day period. Thus, it went through stages 1 (aphagia
and adipsia) and 2 (anorexia and adipsia) of the lateral hypothalamic
syndrome. On the nineth day it recovered its ability to regulate caloric
intake, but would only eat palatable foods and would still not drink
water. It was weaned to water through a sequence of sweet fluids and
began to drink water on the 22nd day. It did not regain its weight until
the 27th day. Other animals have shown essentially the same phemenon
although in lesser degree except one, which was not tube fed, and which
did not eat or drink for 4 days following depression and died without
recovering. Therefore, it is clear that spreading cortical depression rein-
states the lateral hypothalamic syndrome in recovered animals. It is
done presumably by depressing the tissue immediately adjacent to the
original lesion.

In one lateral hypothalamic animal spreading depression not only reinstated aphagia and adipsia but also produced a tremendous enhancement of emotionality similar to that seen when septal lesions are produced in rats. This suggested to us that septal fibres concerned with the control of emotionality run through the lateral hypothalamus and are destroyed by lateral hypothalamic damage. However, the destruction is not sufficient to be seen in lateral hypothalamic animals, but is revealed by spreading depression. It also suggested that a system of structures involved in spreading cortical depression runs along the self-stimulation system, through the septal area and lateral hypothalamus. As it is known, the medial forebrain bundle has connections from and makes connections to structures in the septal area, anterior hypothalamus, lateral hypothalamus and posterior hypothalamus. All of these structures lie along the self-stimulation system. It is also interesting that lesions in each of these areas produce discrete syndromes from which recovery occurs. Thus, septal lesions produce hyperemotionality, anterior hypothalamic lesions produce temperature impairment, lateral hypothalamic lesions cause aphagia and adipsia, and posterior hypothalamic lesions produce somnolence — with subsequent recovery from each syndrome. It follows, therefore, that spreading depression instituted after recovery should reinstate each syndrome.

Bilateral septal lesions were produced stereotaxically in seven rats. As shown in Fig. 2 the typical syndrome of heightened emotionality and aggressiveness as described by B r a d y and N a u t a (1953, 1955) is produced. We rated these animals on an emotionality rating scale
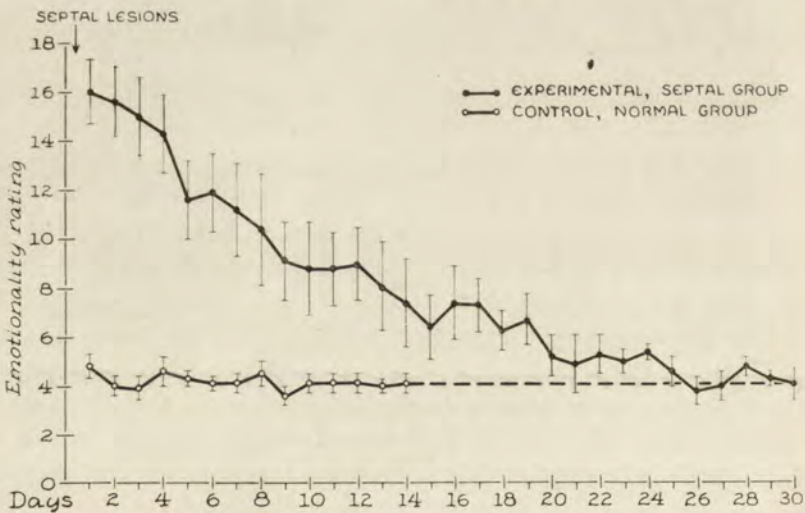

Fig. 2. Changes in emotional reactivity following septal lesions

everyday, and, as was reported by B r a d y and N a u t a and is seen in the Fig. 2, the animals recovered steadily so that their emotionality decreased to approximately normal in about two to three weeks. Spreading depression by means of potassium chloride applied directly to the dura was then instituted in both normal and recovered animals. As shown in Fig. 3, during the first ten hours after spreading depression, emotionality steadily increases in recovered septal animals and reaches a degree of emotionality quite comparable to that produced by septal lesions.
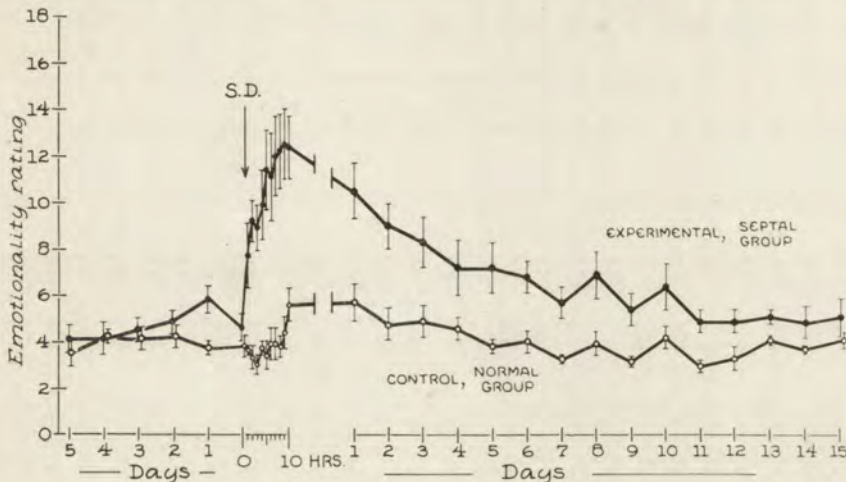
Fig. 3. Effect of first spreading depression due to application of 25 per cent KCL on emotional reactivity of rats recovered from septal lesions and control rats

Normal animals show a very slight heightening of emotionality. Again similar to the effect of septal lesions, the emotionality induced by spreading depression steadily decreases day after day until it is approximately normal sometime between one and two weeks after spreading depression. As shown in Fig. 4, after recovery had occured, spreading depression was produced a second time by means of crystaline potassium chloride applied directly to the dura. As before, tremendous emotionality was produced quite comparable to that produced by large lesions in the septal area. Recovery steadily occured during the next week. The normal animals were much more affected by the second application of potassium chloride and showed increased emotionality, although, never as extreme as animals recovered from septal damage. As shown in Fig. 5, in animals recovered from septal lesions, spreading depression has no enhanced effect on food and water intake. They bahave exactly as do normal animals. Therefore, in animals recovered from septal lesions,

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spreading cortical depression reinstates the original syndrome of hyper-emotionality, but not the syndrome of aphagia and adipsia as was seen in experiments with rats recovered from lateral hypothalamic damage.

Six animals were subjected to anterior hypothalamic lesions. All of them showed an impairment in the ability to keep warm in the cold. When placed in a refrigerator kept at 0° centigrade, all anterior hypothalamic animals were unable to maintain their normal body temperature. Within half an hour their temperature dropped down to about 32 degress centi-grade, and, to avoid death, they had to be removed from the refrigerator
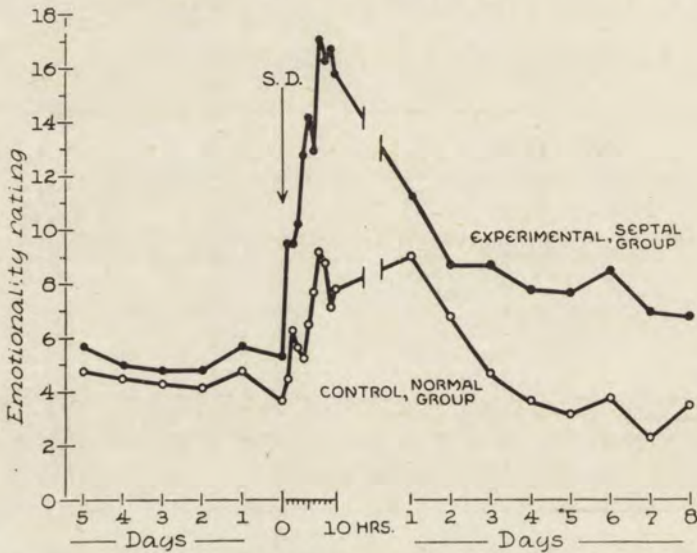
Fig. 4. Effect of second application of spreading depression by means of crystalline KCL on emotionality of septal and control rats

before usual testing time of two hours elapsed. Normal animals maintain their temperature perfectly in this situation. The anterior hypothalamic animals were tested every day postoperatively and were found to recover the ability to maintain their temperature in the cold after periods ranging from 3 weeks to 7 monthes. After having recovered, spreading depression was produced in the normal control and in each anterior hypothalamic animal. Fig. 6 shows a typical effect. On the day before spreading depression, when placed at 0° centigrade for two hours, the anterior hypothalamic animal maintains its temperature as well as normal. On the next day, during spreading depression, it can be seen that temperature regulation is drastically affected in the recovered anterior hypothalamic animal while only slightly affected in the normal. The anterior hypothalamic animal's temperature drops from 37.6° down to 30.7°. On the
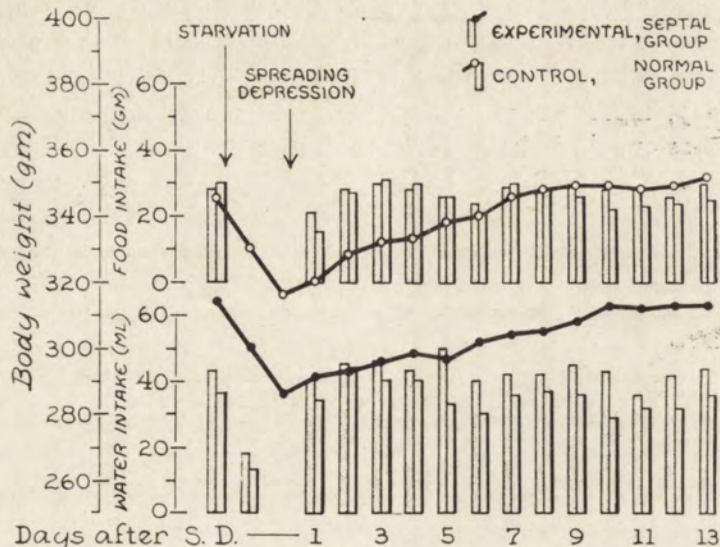
Fig. 5. Daily body weight and food and water intake after the onset of spreading depression. In both septal and control groups, spreading depression had practically no effect on the food and water intake
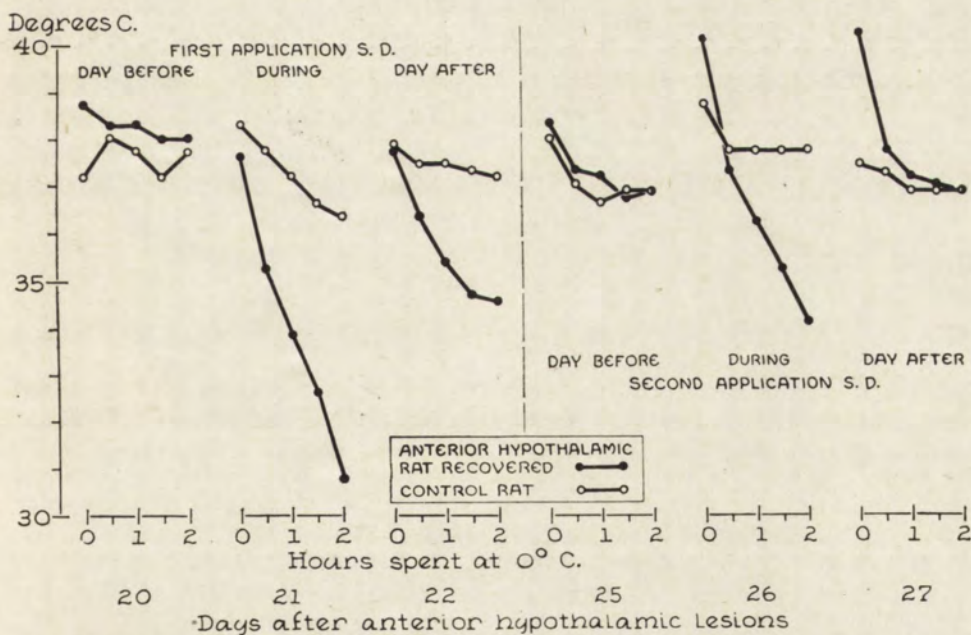

Fig. 6. Effect of spreading depression upon temperature regulation in rat recovered from anterior hypothalamic lesion and control rat

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following day, it is still relatevely unable to maintain its temperature, dropping from 37.8° to 34.4° in 2 hr. Three days later, it is found to have recovered its ability to regulate temperature normally in the cold. On the next day, therefore, it was subjected to second application of spreading depression. As before, its temperature drops drastically while the normal is able to maintain body temperature. On the following day, recovery has once again occured. These effects were seen in all animals recovered from anterior hypothalamic lesions. The histological examination done after animals were sacrified showed that the lesions were large, producing great destruction in the anterior and preoptic areas of the hypothalamus.

In conclusion, therefore, it is quite clear that in the normal animal spreading depression produces in miniature the effects of lesions along the self-stimulation pathway. As has been shown earlier by B u r e š o v á, spreading depression impairs the ability to maintain body temperature in the cold (1957) and depresses food intake during the two to three hour period of spreading depression (1956). In addition, we show here a heightened emotionality in normal animals by spreading cortical depression. These effects are greatly exaggerated in animals with prior lesions. The effects of spreading depression on animals recovered from prior lesions along the self-stimulation pathway are much more exaggerated. In each case, the effect is to reinstate the original syndrome. We therefore conclude the following:

1) Spreading cortical depression exerts its effect by depressing the activity of subcortical structures within the entire self-stimulation system.

2) We feel that this system is important in promoting and maintaining recovery from damage to these subcortical structures because their depression reinstates the original syndrome.

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THE INFLUENCE OF CORTICAL
AND THALAMIC SPREADING DEPRESSION
ON FEEDING BEHAVIOR OF RATS
WITH LATERAL HYPOTHALAMIC LESIONS

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of Physiology, Czechoslovak Academy of Sciences, Prague

During the last years much attention was devoted to the problems of localization of feeding centers. There is no doubt that elimination of medial hypothalamus in rats causes hyperphagia and obesity (B r o b e c k 1960) while lesions of lateral hypothalamus produce aphagia (A n a n d and B r o b e c k 1951, T e i t e l b a u m and S t e l l a r 1954, T e i t e l b a u m and E p s t e i n 1964). By electrical stimulation of these areas the above results were confirmed and the lateral hypothalamus was shown to be the center of hunger motivation (M i l l e r 1960, S p i e s 1965, C o o n s et al. 1965, M e n d e l s o n and C h o r o v e r 1965). R o d g e r s et al. (1965) demonstrated that the lateral hypothalamic aphagia is not due to a motor impairment of feeding but to a pure motivational deficit. However even extensive lateral hypothalamic lesions can be compensated, provided that the animal is artificially fed during the acute phase of aphagia (T e i t e l b a u m and S̄ t e l l a r 1954, T e i t e l b a u m and E p s t e i n 1962, 1963). Mechanism of the gradual recovery of feeding in the operated animals is obscure. Recently T e i t e l b a u m and C y t a w a (1965) reported that reversible functional decortication induced by cortical spreading depression (CSD) elicits a striking and prolonged decompensation of feeding in rats recovered from the lateral hypothalamic damage. After a single application of 25% KCl onto the exposed cortical surface their animals became completely aphagic for at least 24 hours. The authors sug-

gest that cerebral cortex may facilitate and maintain recovery of feeding by enhancing activity of functionally depressed but otherwise intact tissue, adjacent to the lesion.

Since compensation of a lost function can be regarded as a special kind of learning, the long-lasting decompensation may be due to the effects of CSD disturbing memory by disorganizing the rearranged neural connections (B u r e š and B u r e š o v a 1963). The purpose of the present paper was to test this hypothesis by repeating the experiments of T e i - t e l b a u m and C y t a w a (1965) using two different periods of recovery and different durations of the functional decortication. The specificity of the deficit was tested by comparing the impairment of feeding behavior with that of other functions.

All experiments were performed on hooded rats (D r u c k r a y strain) aged 3 months and weighing 180—200g before the operation. The animals were housed six in each cage and had free access to food (pellets of L a r s e n diet) and water. Rats in which alimentary conditioned re- flexes were established were maintained on 24 hours deprivation schedule. Weight curves were daily plotted for all animals during the whole course of the experiment. After one week observation period (during which conditioned reflexes were elaborated in one group of animals) bilateral hypothalamic lesions were made in the area characterized by stereotaxic coordinates A 2; L 2; V 8 (according to the atlas of F i f k o v á and M a r š a l a, 1960).

Anodal current 1—2 mA was passed for 20 seconds through a steel electrode 0.5 mm in diameter which was insulated except on the tip, a large alligator clip on the skin flap serving as the neutral electrode. The placement of lesions was checked after termination of the experiment in the N i s s l stained serial sections. During the acute aphagia after the lesion the animals received each day intraperitoneal injections of 10 ml of 40⁰/₀ glucose in R i n g e r' s solution. Recovery of the feeding function was tested by placing different kinds of food (wet cookies, milk, wet L a r s e n diet, L a r s e n pellets, water) close to the mouth of the animal. The animals had also free access to food in their cages during the observation period. A similar procedure was used when estimating the duration of aphagia elicited by the CSD both in the operated and in nor- mal rats.

In a group of ten rats magazine feeding was trained before the ope- ration in another 32 rats after recovery from the post-operative aphagia. On the sound of the motor the animal had to take from the feeder a piece of wet L a r s e n food available there for 10 seconds. A simple avoidance reaction was established in the same animals. The rat was placed on the start platform of a 10×40 cm runway and required to reach the insu-

lated goal platform within 5 seconds, otherwise electric shocks were applied through the grid floor.

CSD was elicited by application of filter paper soaked with 25% KCl into the fronto-parietal cortex exposed by trephine openings 5 mm in diameter. The cortex was protected by a polythene well sutured to the skin, which could be closed by a rubber cover stopper. Duration of impairment of cortical functions was estimated by examining at regular intervals the cortical postural reflexes (placing reactions). Thalamic SD was evoked by injecting 1 μl 25% KCl into anterior thalamus. A guiding needle was implanted one day before the proper experiment and closed with a mandrine. Through this guide the injection cannula was inserted to a point characterized by stereotaxic coordinates A 2—2.5; L 0.5—1; V 5.

Out of 61 operated animals histology revealed correctly placed symmetrical lesions in 23 rats. Fig. 1 summarizes the average duration of the complete and partial aphagia of these animals. Similar values were also found in the animals with asymmetric lesions. Data for all 61 animals
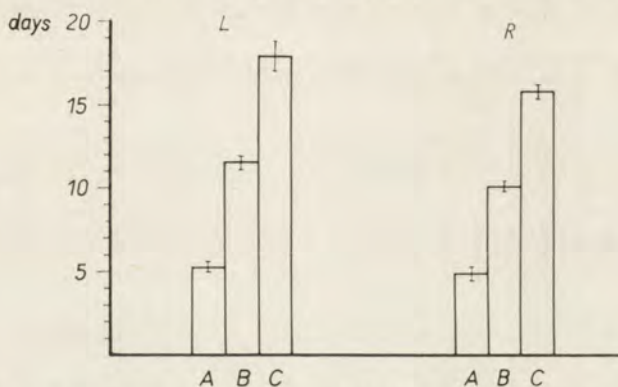
Fig. 1. Recovery of different alimentary functions after hypothalamic lesions. L — animals with symmetrical lesions, R — animals with unsymmetrical lesions, A — onset of spontaneous feeding of milk and wet cookies, B — onset of spontaneous feeding of dry pellets, C — full recovery of feeding

are practically identical (Fig. 1R). Complete aphagia lasted for about 5 days on the average. Spontaneous feeding reappeared for milk and wet cookies then, while the intake of dry pellets and water started 12 days after operation and was fully normalized after another week. As soon as full recovery was reached, the animals were divided into the short and long recovery groups. While in the first group CSD was elicited immediately the second group of animals were allowed further three weeks recovery.

Results obtained after application of 25⁰/o KCl in the long recovery group (corresponding more or less to the conditions of the experiments by Teitelbaum and Cytawa 1965) and in unoperated control animals are summarized in Fig. 2. Impairment of food intake was slightly longer in the operated animals than in the controls, but the difference was much less expressed than in the experiments of Teitelbaum and Cytawa. Also impairment of alimentary and avoidance conditioned reactions was similar in both experimental and control groups, the avoidance reactions recovering earlier than the alimentary ones. No difference in CSD effects was found between animals who learned the conditioned reactions before and after the hypothalamic lesions (Fig. 2B,C). While the duration of most behavioral deficits coincided well with the suppression of cortical postural reactions, the avoidance reactions reappeared earlier evidently because the performance of the simple task did not require a complete recovery of cortical functions. Goal directed escape reactions reappeared at a still faster rate.

Rather different results were obtained in the short recovery group in which CSD evoked by the same amount of KCl caused a much deeper impairment of feeding as well as certain cortical functions (Fig. 3). The animals were completely aphagic for about 24 hours and ate only wet cookies and milk for further three days. Normal feeding resumed only four days after CSD. This is in better agreement with the data of T e i - t e l b a u m and C y t a w a who reported that aphagia elicited by CSD lasted for 24 hours in four rats and for several days in two other animals. As they had obtained these results after long recovery period, however, the difference was probably due to a different placement of lesions and or longer lasting CSD in their experiments. The effect on feeding cannot be regarded as strictly specific, however, since the suppression of cortical postural reflexes was also significantly prolonged (from 4 hours in the control group to more than 24 hours in the experimental group).

It seems that the brain of animals who recovered from the lateral hypothalamic damage was still affected by the lesion and by its consequences (starvation leading to an exhaustion of metabolic supplies). When using cortical postural reactions as a standard indicator of cortical function an interesting dissociation of the CSD effects has to be pointed out. Consumption of palatable food started before complete recovery of cortical functions, but normalization of feeding occured much later.

While CSD evoked by 25⁰/o KCl did not reveal any significant difference between the long recovery group and control animals' a rathei striking difference between these groups was observed when eliciting CSD by 1⁰/o KCl (Fig. 4). Conditioned alimentary reactions and feeding were impaired for 30—50 min in controls but for 3—4 hours in the ex-
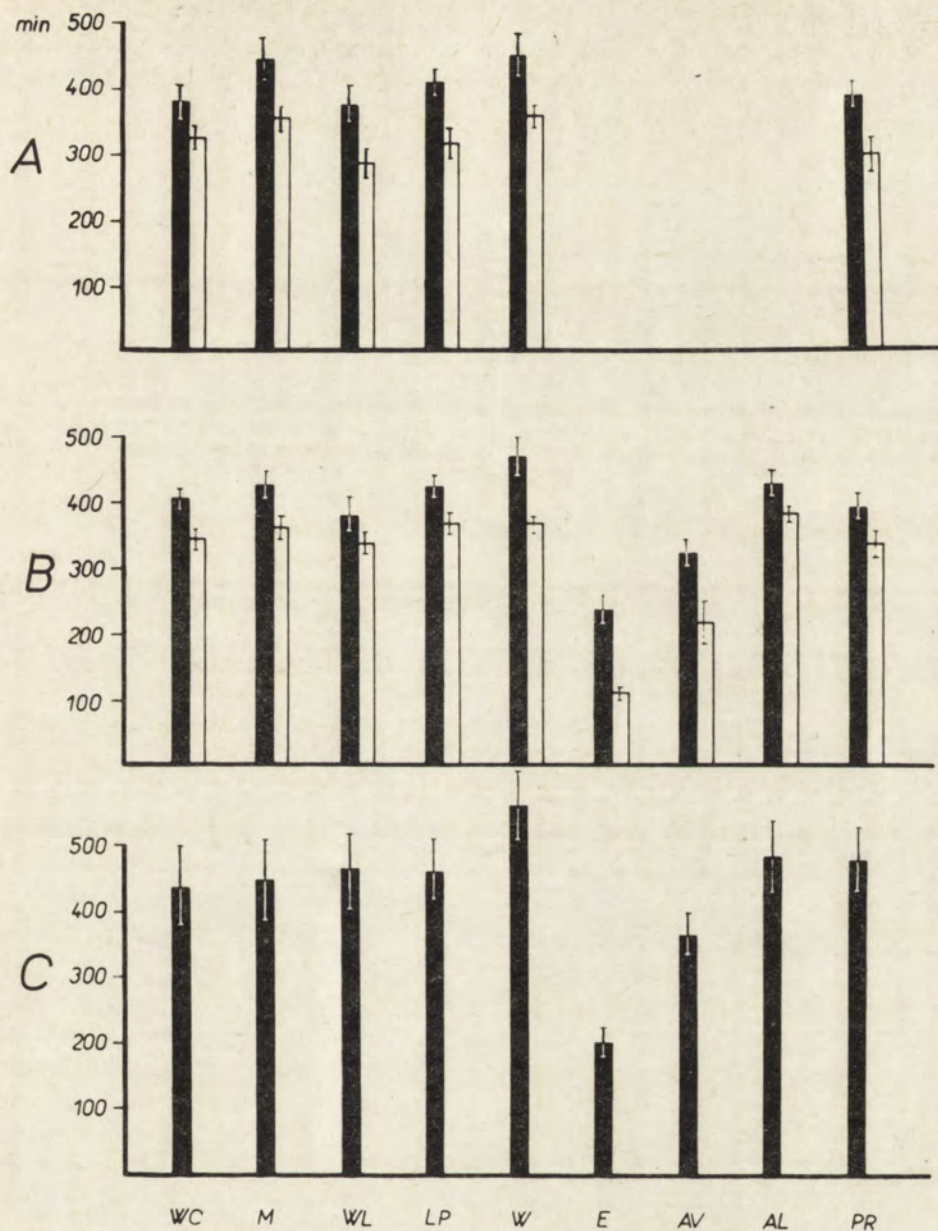
Fig. 2. The duration of impaired intake of different foods (wet cookies-WC, milk-M, wet Larsen-WL, Larsen pellets-LP, water-W) and of depression of conditioned alimentary (AL), avoidance (AV) and escape (E) reactions and cortical postural reflexes (PR) induced by bilateral CSD (25% KCl) in rats recovered from bilateral hypothalamic lesions (long recovery). A: No conditioned reflexes were elaborated. B: Conditioned reflexes elaborated before and retrained after hypothalamic lesions. C: Conditioned reflexes elaborated after hypothalamic lesions. Black columns: Experimental animals. White columns: Unoperated controls

perimental group. For escape and avoidance behavior the difference between control and experimental animals was much less expressed.
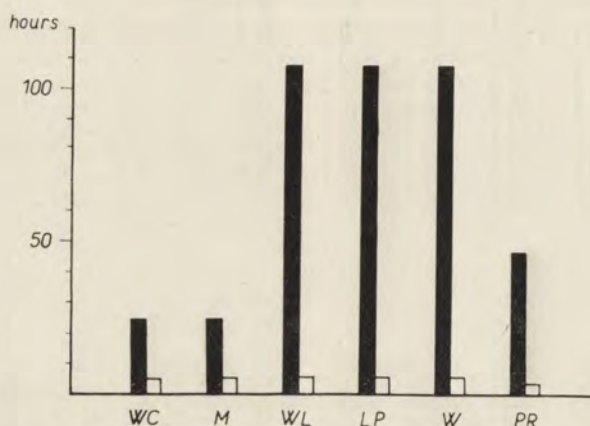
Fig. 3. The duration of impaired intake of different food and depression of conditioned alimentary, avoidance, escape and cortical postural reflexes induced by bilateral CSD (25% KCl) in rats who just recovered from bilateral hypothalamic lesions (short recovery). Other description as in Fig. 2

Similar results were obtained in another group of 10 control and 11 experimental animals (after long recovery period) in whom thalamic SD was elicited. Both avoidance and alimentary conditioned reflexes were impaired by thalamic SD for longer period in the experimental than in the control rats but the alimentary reactions were not more severely depressed than the avoidance behavior (Fig. 5).

Thus in the operated animals 1% KCl causes a suppression of alimentary conditioned reactions which considerably outlasts the impairment of cortical postural reflexes while no such difference was observed with 25% KCl. This may indicate that CSD effect on feeding behavior depends on two different mechanisms: interference with the cortical links of the habit and the transitory impairment of compensatory mechanisms probably localized at the subcortical level. The latter effect lasts for several hours and decays independently of the continuing CSD. With 25% KCl this component disappears before the cortical function has recovered and suppression of feeding coincides then well with the impairment of other cortical functions. On the contrary, with 1% KCl the subcortical impairment outlasts the releasing cortical depression and so does the duration of aphagia.

Lateral hypothalamic lesions induce severe pathological conditions characterized not only by aphagia but also by impairment of other behavioral functions. Avoidance reactions are depressed after the lesion for nearly the same period as the alimentary functions. It is not quite
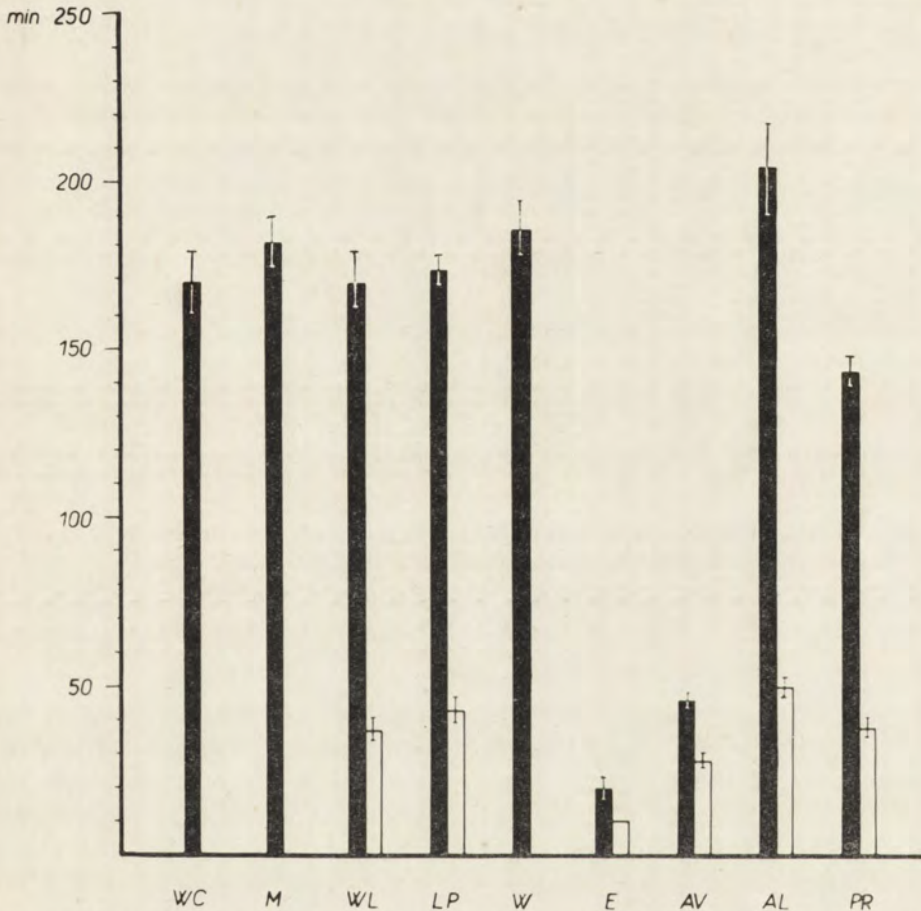

Fig. 4. The duration of impaired intake of different food and depression of conditioned alimentary, avoidance, escape and cortical postural reflexes induced by bilateral CSD (1% KCl) in rats who recovered from bilateral hypothalamic lesions (long recovery). Other description as in Fig. 2

clear whether these changes are a direct consequence of the hypothalamic lesions or a result of starvation. The prolonged depression of cortical postural reactions by CSD in the short recovery group also reflects the non-specific consequences of the lesion. The specific impairment of feeding can only be assesed in relation to the above non-specific manifestation. During recovery both the specific and non-specific consequen-

ces of the lesion gradually subside. At the time when feeding is seemingly normal again the compensation is not yet complete as can be revealed by the CSD. Several weeks later the compensatory mechanisms are already more or less resistant to the CSD. These findings are, in general, well compatible with the consolidation of the reorganized neural connections, substituting the destroyed nerve centers. Owing to the limited
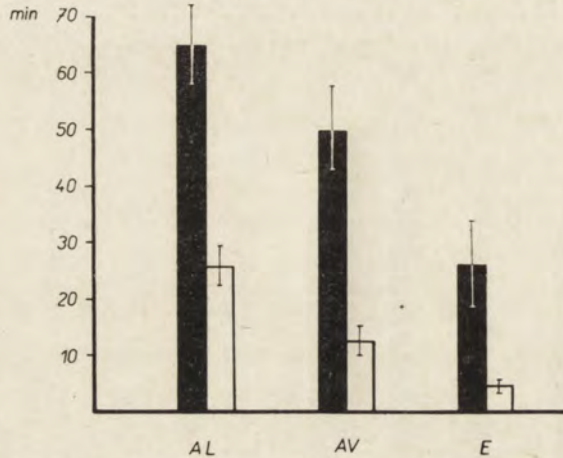

Fig. 5. The duration of impairment of conditioned alimentary (AL), avoidance (AV) and escape (E) reactions after thalamic spreading depression. White columns — control animals. Black columns — operated animals

number of undamaged neurons the formation of new connections and their fixation takes a long time. CSD may block the fragile functional components of the compensation process which, however, become less and less important in the course of the consolidation. Further experiments using other memory disturbing procedure are needed to test the above hypothesis.

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XXIV INTERNATIONAL CONGRESS
OF PHYSIOLOGICAL SCIENCES

The XXIV International Congress of Physiological Sciences will be held in Washington, D.C., U.S.A., August 25—30, 1968. The Congress is sponsored by the International Union of Physiological Sciences (IUPS).

Preliminary notices will be mailed in January 1967, and final notices in October 1967. Plans are already being made for special symposia and invited speakers. Specific suggestions for symposium topics or special lectures should be submitted as early as possible to the President of the Congress, Professor Wallace O. Fenn, University of Rochester Medical Center, Rochester, N.Y. 14620, U.S.A.

In selecting topics for symposia it is expected that the Program Committee will give preference to subjects of a somewhat controversial nature, but of broad general interest, and not recently covered in an international symposium. For speakers, special consideration should be given to promising young physiologists with active research programs as well as to older men of established reputation.

All inquiries concerning the Congress may be addressed to:

Mrs. Helena B. Lemp
Congress Manager
XXIV International Congress of Physiological Sciences
9650 Rockville Pike
Bethesda, Maryland 20014
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