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# LIMBIC-MIDBRAIN LESIONS AND ACTH-INDUCED EXCESSIVE GROOMING[1)]

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## SUMMARY

The induction of excessive grooming by intraventricular administration of $ACTH_{1-24}$ was studied in rats with lesions in midbrain-limbic structures. Such areas have been reported to be implicated in mediating ACTH-induced effects on avoidance behavior, sexual excitement or stretching and yawning. Electrolytic lesions in the septal complex, the anterior hypothalamic/preoptic area, the mammillary bodies, the amygdala, the posterior thalamus and dorsal or ventral hippocampus did not interfere with ACTH-induced excessive grooming. Lesioning of the hippocampal complex by aspiration led to an inhibition of excessive grooming depending on the degree of hippocampal damage. Amygdala and hippocampal lesions enhanced the display of stretching and yawning activity after treatment with the peptide. The data indicate differences in the neural substrates mediating the effect of ACTH on extinction of conditioned avoidance behavior, excessive grooming, sexual excitement and stretching and yawning.

It is now well known that ACTH/MSH/LPH peptides influence the activity of the central nervous system. The effects of these hormone fragments are often measured by changes in performance in learning tasks, both during acquisition and extinction (1,2) and lesions in structures related to limbic systems seem to alter some of their effects (3).

Intraventricular administration of peptides derived from ACTH/MSH/LPH induces excessive grooming which in most instances is followed by a stretching and yawning syndrome (SYS) (4,5,6,7,8,9,10). Some authors suggest that in addition to SYS, intraventricular application of these peptides also induces sexual arousal in rabbits (6,11,12,13) and rats (14). This is characterized by recurrent episodes of penile erections accompanied by copulating movements. However, the male does not seek to copulate with either male or receptive female partners (14) and it is therefore questionable whether indeed the elicited penile erections reflect sexual excitement. Damage to the preoptic area suppressed ACTH-induced penile erection leaving SYS activity unaltered (15).

The behavioral significance of the grooming response is not entirely established. Grooming in rodents is sometimes interpreted as representive of "displacement activities" (16,17), but other investigators think of grooming as collateral act, i.e. behavior associated with, but not part of, a goal-directed activity (18,19,20). While feedback from the periphery is usually important for the

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development and maintenance of integrated movement repertoire like grooming (17) there is evidence for a strong internal control of grooming (21).

Since excessive grooming and SYS begin at different times after peptide-injection and there are discrepancies between effectiveness of various peptides in inducing grooming and/or SYS, it is likely that different neural substrates exist for these two behaviors (7,8). In the present paper, the induction of excessive grooming induced by intraventricular administration of $ACTH_{1-24}$ is studied in rats with lesions of brain areas which have been reported to be implicated in mediating peptide-induced effects on avoidance behavior, sexual excitement or SYS.

## Methods

### Animals and surgery

Male rats, weighing 160-180 g, of a Wistar strain were used. One week prior to the observation session, a polyethylene cannula (Ø 0.357 mm) was implanted into the brain ventricular system (foramen interventriculare, A 6360, König and Klippel, 1963) under Hypnorm (Philips Duphar, Amsterdam, The Netherlands) anesthesia (7). Using standard stereotaxic techniques, bilateral RF electrolytic lesions were made in the brain regions given below. The coordinates of the electrode tip for each lesion site are given in the parentheses and are based in the atlas of Albe-Fessard *et al.* (22) except for the total septal lesion which was made following coordinates of the atlas by König and Klippel (23). The target areas were: amygdala (A 6,0; L 4,5; D 2,5), mammillary body (A 4,0; L 0,5; D 1,8), rostral septum (A 9,8; L 0,8; D 0,0), rostral medial septum (A 8,0; L 0,5; D 5,0), large septal lesion (A 7,8; L 0,5; D 6,5), n. parafascicularis (A 4,1; L 1,2; D 4,5), medial preoptic area (A 8,2; L 0,5; D 3,5), lateral preoptic area (A 8,2; L 2,0; D 3,0), anterior hypothalamus (A 7,3; L 0,7; D 2,8), dorsal hippocampus (A 4,8; L 2,0; D 7,5), and ventral hippocampus (A 4,0; L 4,5; D 2,5). In some animals, nearly total or dorsal hippocampectomy was performed by aspiration as described previously (24). In view of the anticipated damage to the ventricular system occurring during aspiration of the hippocampus, four animals had cannulae placed in the fourth ventricle rather than the interventricular foramen as was done in the other animals with hippocampal destruction. The posterior neocortex overlying the hippocampus was removed in six rats to serve as control for the neocortex damaged during removal of the hippocampus (Group CC).

### Injection

Synthetic $ACTH_{1-24}$ or $|D\text{-}Phe^{7}|ACTH_{4-10}$ (Organon Int.b.v.,Oss,The Netherlands) were dissolved in saline, stored at -20°C for 4-6 weeks and thawed 15 min prior to use. Intraventricular injections were made with a microliter syringe (Unimetrics Corp., type 5010R) affixed with a 30 gauge blunt-tipped needle. The needle and the end of the cannula were cut so that, when inserted into the cannula, the end of the needle bisected the 45° level of the cannula tip. Injection volume was 1 µl, containing 1 µg of peptide. Saline (1 µl) was the control solution.

### Behavioral analysis

Behavior was observed every 15 sec by a time sampling procedure (7,8,10). After injection the rats were placed individually in glass boxes (24 x 12.5 x 14 cm) in a low noise room. Behavioral recording began 15 min afterwards. If leg vibration, washing, grooming, scratching or licking body was observed, a positive grooming score was recorded. In a 50 min observation period (15-65 min after injection) a maximum of 200 positive grooming scores can be obtained. The occurrence of stretching (S) and yawning (Y) during the observation period was recorded and the combined number of S and Y for a given rat was taken as a measure

of SYS activity. In the tables the grooming scores are expressed as mean number per treatment group, the data on SYS are given as mean number of S + Y scores per group. The experimental rats were used twice. On post surgical day 8 they received either $ACTH_{1-24}$ or saline solution interventricularly and on day 11 the other solution. Differences between lesions per treatment were assigned to be significant for values of $p < 0.05$ (Student t-test, two-tailed) and differences between treatments per lesion were tested using a paired two-tailed test.

### Histology

After termination of the experiments all rats were anesthesized with Nembutal and their brains were perfused by intracardial perfusion with saline followed by 10% formalin.

For histological examination of size and location of the electrolytic lesions, frozen sections of 100 µm were cut and microscopically examined. If suction lesions were made, the fixed brains were embedded in paraffin and cut coronally at 25 µm. Every 10th section was mounted and stained with thionin. The extent of damage and the localization after lesions was determined as described previously (e.g. 25).

## Results

### Histology

Bilateral lesions in the rostral septal area mainly damaged the n. accumbens septi, the rostral portion of the medial septal nuclei, and various degrees of damage to the septotubercular and septohypothalamic tract was found. Rostral medial lesions of the septal area produced damage to the medial septal nuclei and portions of the lateral septal nuclei, the fornix, and portions of the hippocampal commissures. Preoptic damage was mainly restricted to the medial or lateral preoptic areas. Anterior hypothalamic lesions were localized in the anterior hypothalamic area with partial damage of the caudal portions of the preoptic area and the rostral portion of the paraventricular nucleus. Unilateral damage to the fornix was found in one rat in this group. Lesions in the mammillary bodies also involved the mammillothalamic tract. Bilateral lesions in the posterior thalamus damaged the parafascicular nuclei and the fasciculus retroflexus. Some damage to the centrum medianum was also observed. Electrolytic lesions of the dorsal hippocampus produced partial damage to the hippocampus proper. In only one animal was a complete transection of the hippocampus achieved. Electrolytic ventral hippocampal lesions were also partial and incomplete. The amygdaloid complex was almost completely destroyed by the electrolytic procedure aimed at that area.

After histological examination, one rat of the hippocampectomized group was discarded from further analysis due to evidence of infection surrounding the cannula. The rats of group CC in which only the neocortical tissue overlying the hippocampus was removed, evidenced only slight and superficial damage to the hippocampus. The amount of damage to the neocortex tended to be smaller than that in the other three groups with aspiration lesions. In the groups of rats with hippocampal lesions, only slight damage to the thalamus and/or habenular complex was observed in some animals. Figure 1 shows the extent of damage for each of the brain-damaged groups. However, despite 12 surgical attempts to remove the hippocampus completely, only 4 were successful. Two rats having a cannula in the interventricular foramen and two having a cannula in the fourth ventricle were found to have near total hippocampal resections. In the other rats most of the dorsal hippocampus was removed but the ventral part was damaged to a variable degree and in no case totally removed. Therefore, the following groups were composed for behavioral analysis: CC-neocortex damage; DH-dorsal hippocampus removed; DVH-dorsal hippocampus removed and considerable damage to the ventral part; H-nearly total hippocampus removed (2 with IIIrd ventricle placements and 2 with IVth ventricle placements cannula).

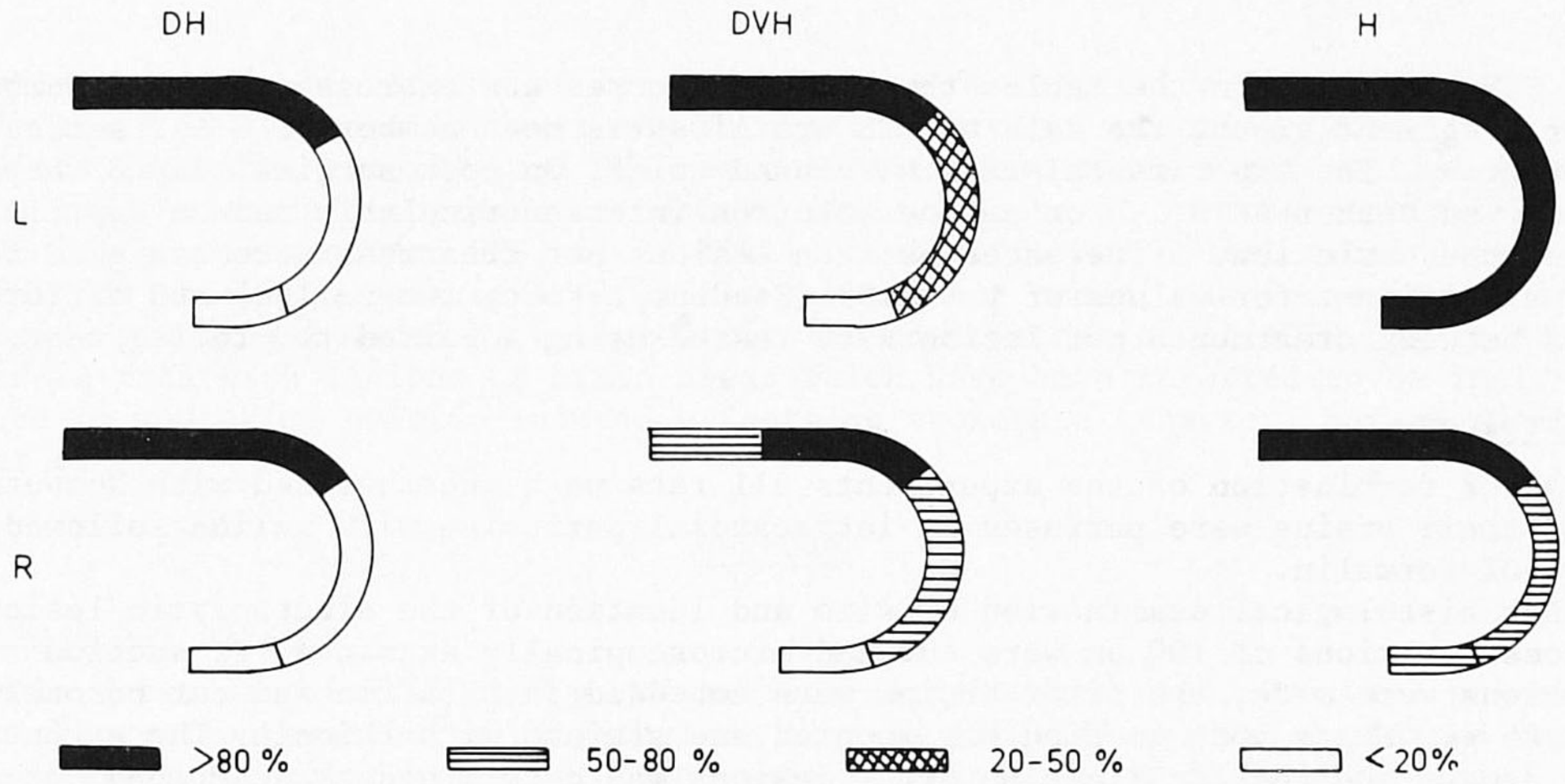


FIG. 1

The extent of hippocampal damage in the dorsal group (DH), the dorsal-ventral group (DHV) and in the group with near total hippocampectomy (H). The left (L) and right (R) hippocampi are presented as sagittal projections in one plane.
DH n = 7; DVH n = 8; H n = 4.

## Excessive grooming and SYS

Table 1 gives the mean grooming and SYS scores for each treatment group. Data on sham lesioned septal rats and on rats with damage to the neocortex also are presented.

The injection of 1 µl $ACTH_{1-24}$ induced significantly more grooming and SYS activity than after saline treatment in all groups except those with total hippocampal destruction. Rats with large lesions in the septal complex groomed as vigorously as non-lesioned rats. Electrolytic lesions confined to the preoptic and anterior hypothalamus, mammillary bodies, amygdala, n. parafascicularis of the posterior thalamus, dorsal and ventral hippocampus, did not interfere with $ACTH_{1-24}$-induced excessive grooming.

Rats with electrolytic lesions in the ventral hippocampus were notably different from control rats when being handled. When touched, they were aggressive and difficult to restrain for injection.

In rats with bilateral lesions in the thalamic parafascicular area, $|D\text{-}Phe^{7}|$ $ACTH_{4-10}$ was also tested and the grooming activity elicited was similar in magnitude to that observed in intact rats (7,10). Rats from which the dorsal hippocampal complex was removed by suction showed slightly less grooming activity than those with only neocortical damage ($0.05 < 2p < 0.10$). If, however, the damage was extended to the ventral part of the hippocampus as well, a severe interference with ACTH-induced grooming occurred (DVH vs CC $0.01 < 2p < 0.02$, H vs CC $p < 0.01$).

In general, saline-treated rats evidenced little SYS activity and there were no differences among groups. As with grooming activity, all ACTH-treated rats displayed significantly more stretching and yawning during the observation period than saline-treated rats, except for those with the most extensive hippocampal lesions. Electrolytic lesions of the amygdala enhanced display of SYS ($0.02 < 2p < 0.025$). All rats which had hippocampal damage but from which the hippocampus was not totally removed, showed increased SYS activity. The difference was significant between DH and CC ($0.02 < 2p < 0.025$) and DVH and CC ($0.025 < 2p < 0.05$). This effect was not found in animals with total hippocampal destruction.

## Discussion

The present paper aimed to study the effects of brain lesions on the induction of the excessive grooming produced by intraventricular injection of $ACTH_{1-24}$. The lesions were made in brain regions that have been implicated in mediating other behavioral effects of ACTH by previous reports.

Extinction of a conditioned avoidance response in rats is delayed by peripheral or intraventricular administration of peptides derived from the N-terminus of ACTH (1,26). Implantation studies as well as lesion experiments, revealed that the posterior thalamic area (including the n. parafascicularis) and the rostral septal region are involved in the expression of these peptide-induced behavioral changes (3,27,28,29). In addition, after intraventricular administration of a radioactively labeled $ACTH_{4-9}$-analog, high uptake of the peptide was restricted to various dorsal-medial septal nuclei (30). In this study no suppression of excessive grooming or SYS was found after the septal lesion. In fact, tendency towards enhanced grooming was noted. Although little signs of the so-called septal syndrome (viciousness, rage-like behavior, over-reactivity to stimuli; 31) was noted, a tendency to display enhanced grooming activity when compared to sham lesioned groups may be related to their known increased reactivity to stimulation (e.g. 32,33). Furthermore, both $ACTH_{1-24}$ and $|D\text{-}Phe^{7}|$ $ACTH_{4-10}$ induced excessive grooming and SYS in rats bearing lesions in the posterior thalamic area including the n. parafascicularis. These data indicate differences in the neural substrates of ACTH-induced excessive grooming and ACTH-induced delays in the extinction of avoidance responses.

Micro-injections of $ACTH_{1-24}$ (20 µg/5 µl) into different regions of the cat brain have shown that SYS can be most easily elicited from the hypothalamic areas lining the third ventricle (34). It is of interest that in the squirrel monkey, injecting ACTH in the medial preoptic region or MSH into the septal area results in episodes of SYS, scratching, and penile erection. Such injections were ineffective when placed in the ventromedial hypothalamus or premammillary region (35). In cats, injection of $ACTH_{1-24}$ into the mammillary bodies induced SYS within 7 min. This was the shortest latency found in all brain locations studied (34). In this study rats with lesions in the mammillary bodies displayed more SYS. Therefore in rats the mammillary region can not be the site of SYS inducing activity of $ACTH_{1-24}$.

Despite the importance of the anterior hypothalamic and preoptic regions for sexual behavior, the present results raise questions about the importance of these areas for grooming and SYS. In female rabbits, intraventricularly injected $ACTH_{1-24}$ increased multiple unit activity in the area of the lateral diagonal band of Broca and the periventricular preoptic area (6). There is a rise in serum LH as a result of ACTH infusion (6,13), but sexual behavior seemed not to depend on this raised LH level (6). Lesions of the preoptic/hypothalamic areas are ineffective in suppressing ACTH-induced excessive grooming and SYS. Bertolini had previously reported that a lesion in the preoptic area suppressed ACTH-induced penile erection but not SYS (15). Furthermore, castration of rabbits and rats suppresses ACTH-induced penile erection leaving SYS activity unaltered (14) and does not interfere with ACTH-induced excessive grooming (7). Only occasionally is penile erection seen during grooming of the genital area and a detailed analysis of the ACTH-induced behavior revealed no difference at all between male and female rats (Gispen *et al.*, in preparation). Therefore, it seems that excessive grooming and SYS are independent of penile erection in the rat.

Hippocampal lesions do not affect grooming in the rat when observed in the familiar environments like the home cages (36,37). However, observations by Oades and Isaacson (38) indicate that hippocampal lesions almost completely eliminated grooming in a relatively unfamiliar open field. The hippocampus also seems to be an important structure for ACTH effects on the CNS. Damage to the dorsal hippocampus has been found to interfere with the effect of ACTH on the extinction of an avoidance response (39). In freely moving dogs, peripheral treatment with $ACTH_{4-10}$ shifted the hippocampal theta activity to lower frequencies (40).

In rats, the peripheral administration of $ACTH_{4-10}$ produced a shift to higher frequencies when hippocampal theta was induced by stimulation of the reticular formation (41). Administration of ACTH increased unit activity in the dorsal hippocampus (42). Segal (43) has reported that iontophoretically applied ACTH inhibited unit firing in the hippocampus and also antagonized the inhibitory effects of norepinephrine in about 50% of the hippocampal neurons tested. In this study, extensive damage to the dorsal hippocampus reduced ACTH-induced grooming activity and extending of the lesions to the posterior-ventral site further decreased this response. In both instances a markedly display of SYS activity was observed. The decrease in grooming can not be accounted for by increased amounts of SYS. Smaller electrolytic lesions in the posterior dorsal part of the hippocampus did not interfere with grooming activity but small lesions of the ventral hippocampus did. The near total hippocampectomized rats had greatly reduced grooming but little SYS activity was observed in these animals. It would appear that damage to the ventral hippocampus or total hippocampectomy suppressed ACTH-induced grooming. Lesions of these regions produce enhanced locomotor activity in the open field while lesions of the dorsal hippocampus do not (25).

The low level of grooming in the total hippocampal lesion group is not likely due to interference with the ventricular system since in two rats with cannulae in the fourth ventricle, grooming was still eliminated. The fourth ventricle is at some distance from the area of brain damage. Injection of the peptides in the fourth ventricle can produce the same amount of grooming as injection into the interventricular foramen (Brakkee, Weyman and Gispen, in preparation). It is unlikely that a general debilitation of condition would have caused the absence of grooming and SYS in ACTH-injected hippocampally lesioned rats since all lesioned rats were gaining weight at the time of testing.

From the dissociation of the effect of $ACTH_{1-24}$ treatment on grooming and SYS in rats with lesions in the mammillary bodies, the amygdala or the dorsal/ventral hippocampus, it is likely that the peptide-induced effects on grooming and SYS depends on different neural substrates. This is further supported by (a) the difference in onset latencies between grooming and SYS (immediately vs 30-40 min), (b) the induction of grooming but absence of SYS by $LPH_{61-91}$ (8) and (c) the elicitation of grooming by injection of $ACTH_{1-24}$ into substantia nigra without the induction of SYS (44; Gispen, Colbern and Cools, unpublished).

The mechanism by which ACTH induces excessive grooming and SYS is unclear. In regard to excessive grooming, there is presumptive evidence for involvement of dopaminergic pathways since $ACTH_{1-24}$ injections into substantia nigra can induce excessive grooming. Haloperidol injections into the caudate can block this response (44).

Systemically administered haloperidol at a low, but behaviorally effective dose, fails to affect grooming and may even facilitate peptide-induced grooming (Colbern, Isaacson and Gispen, in preparation) while large doses will attinuate the grooming response (44). A presumptive relationship between forebrain DA systems and hippocampal activity has been established by Fish (45) who found that animals with near total hippocampal destruction seemed to be more resistant to dopaminergic blocking agents than control animals in several behavioral situations. Other behavioral changes usually found after hippocampal destruction are compatible with the idea that the lesion enhances the effectiveness of the ascending DA system. The present results would suggest that the ventral hippocampus is most important to these effects and that fibers may pass through the fimbria-fornix system to other brain regions. This would explain the progressively smaller behavioral effects after aspiration lesions of middle and dorsal portions of the structure. The smaller electrolytic lesions of the dorsal and ventral hippocampus that did not transect the structure would be presumed to have interrupted too few of these fibers to produce an effect on the peptide-induced behavior.

Projections to the hippocampus from the medial septal nuclei do not seem to be necessary for the ACTH-induced grooming since none of the septal lesions,

including those specifically directed at the medial septal area, influenced grooming or SYS.

The analysis of neural systems related to SYS seems more complicated and, at the moment, difficult to interpret. Projections from amygdala and ventral hippocampus reach area of the ventromedial nucleus of the hypothalamus and it would be tempting to consider this nucleus as part of a neural system related to SYS. However, the elimination of SYS by total destruction of the hippocampus and the effects produced by lesions of the mammillary bodies are not explicable on this basis. Further research is needed to clarify the nature of the peptide-sensitive systems related to SYS.

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TABLE I

ACTH-induced excessive grooming and SYS in rats bearing lesions in midbrain limbic structures

| Lesion area | | n* | $ACTH_{1-24}$ grooming | SYS | n* | Saline grooming | SYS |
|---|---|---|---|---|---|---|---|
| None (intact Ss) | | 8 | 173 ± 10** | 4.8 ± 1.2** | 8 | 30 ± 5 | 0 |
| Septum lesion | sham operates | 7 | 154 ± 15 | 4.6 ± 1.9 | 7 | 32 ± 5 | 1.1 ± 0.6 |
| | rostral | 7 | 167 ± 15 | 4.3 ± 2.0 | 7 | 40 ± 6 | 1.9 ± 0.7 |
| | rostral medial | 8 | 161 ± 11 | 4.6 ± 1.6 | | | |
| | large | 9 | 182 ± 5+ | 8.6 ± 1.9 | 4 | 28 ± 5 | 0 ± |
| Preoptic area (medial) | | 8 | 158 ± 13 | 4.6 ± 1.8 | 8 | 35 ± 7 | 0.4 ± 0.1 |
| Preoptic area (lateral) | | 8 | 140 ± 19 | 5.9 ± 1.9 | 8 | 37 ± 5 | 0 |
| Hypothalamus anterior | | 4 | 174 ± 9 | 2.8 ± 0.6 | 4 | 41 ± 5 | 0.7 ± 0.3 |
| Mammillary bodies | | 6 | 149 ± 13 | 11.5 ± 3+ | 8 | 40 ± 8 | 1.0 ± 0.5 |
| Amygdala | | 5 | 157 ± 13 | 10.6 ± 2.0+++ | 5 | 42 ± 6 | 1.4 ± 0.5 |
| n. parafascicularis 4-10 D | | 4 | 108 ± 13 | 3.3 ± 1.0 | – | – | – |
| | 1-24 | 4 | 174 ± 10 | 6.5 ± 2.4 | 5 | 43 ± 5 | 0.4 ± 0.3 |
| Cortex (CC) | | 6 | 176 ± 12 | 3.3 ± 1.3 | 6 | 50 ± 11 | 0.7 ± 0.3 |
| Hippocampus | dorsal (DH) | 7 | 154 ± 4+ | 12.9 ± 3.3+++ | 7 | 38 ± 7 | 1.7 ± 0.9 |
| | dorsal/ventral (DHV) | 8 | 129 ± 16++++ | 10.1 ± 2.4++ | 6 | 22 ± 6 | 1.7 ± 0.7 |
| | near total (H) | 4 | 40 ± 15+++++ | 1.8 ± 0.8 | 4 | 28 ± 5 | 0.8 ± 0.5 |
| | dorsal(electrolytic) | 5 | 169 ± 14 | 7.0 ± 2.1 | 5 | 35 ± 6 | 0.7 ± 0.4 |
| | ventral(electrolytic) | 4 | 152 ± 6 | 8.5 ± 1.6 | 4 | 43 ± 4 | 0.3 ± 0.2 |

* n = number of rats
** = mean ± SEM
\+ = 5% < 2p < 10%
++ = 2.5% < 2p < 5%
+++ = 2.0% < 2p < 2.5%
++++ = 1% < 2p < 2%
+++++ = 2p < 1%