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DAILY PATTERN OF EEG ACTIVITY IN RATS WITH LATERAL HYPOTHALAMIC LESIONS

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The experiment was aimed to further elucidate the phenomenon of sleep suppression observed earlier after electrolytic lesions of the lateral hypothalamus (LH). In male Wistar rats the amounts of waking (W), slow wave sleep (SWS) and paradoxical sleep (PS) were counted in 1h samples of EEG taken from the light and dark parts of the circadian cycle, as well as in the whole 12h diurnal records before lesioning and after electrolytic or sham lesions of LH. Significant increase of W with a simultaneous reduction of SWS and PS was found in 1h and 12h diurnal records; no effect of the lesion on nocturnal EEG was observed. The results suggest that lesion-induced sleep suppression concerns the light part of the day when rats are naturally less active, and that 1h samples of diurnal EEG may be sufficient to diagnose LH insomnia. No correlation was found between the magnitude of waking-sleep disturbances and the intensity of ingestive impairments (aphagia, adipsia, body weight loss) evoked by LH lesions which suggests that LH insomnia may be a result of disruption of a mechanism directly involved in the regulation of waking-sleep cycle rather than a secondary effect of other lesion-induced impairments.

Key words: *EEG, insomnia, lateral hypothalamus, lesions, sleep-waking cycle*

INTRODUCTION

Extensive, bilateral destruction of the lateral hypothalamic area (LH) produces a set of severe behavioral abnormalities called the lateral hypothalamic syndrome. The most prominent symptom of LH damage is the cessation of ingestive activity resulting in aphagia and adipsia (1, 2). Failure to eat and drink is usually accompanied by other deficits (3—5) such as disturbances in sensorimotor integration (sensory neglect), difficulties in initiation of a movement (akinesia and catalepsy) and loss of unspecific behavioral activation (somnolence). Under special care, the animals can gradually regain the lost behaviors (2) and in time the only observable residual deficits are failures to respond to acute homeostatic challenges with rapid behavioral regulatory reactions (6).

Judging from the heterogenous picture of the LH syndrome, the damage to this area seems to disturb several systems subserving various functions (7). In fact, the lateral hypothalamus is not homologous structure. It contains about 50 bundles of axons which interlink the reticular nuclei of the midbrain and lower brainstem with different prosencephalic and diencephalic structures, as well as its own intrahypothalamic neurons scattered among the fibers of the medial forebrain bundle (8—12).

There is evidence (13—17) suggesting that one of the most essential effects of the damage to the lateral hypothalamus is the abolishment of an influx of unspecific, arousing stimuli from the lower brainstem reticular formation to the prosencephalon and diencephalon. Behaviorally it is believed to be reflected by somnolence and akinesia and also to some extent by aphagia and adipsia which may be temporarily reversed by highly activating external stimuli or by stimulant drugs (16, 17). The majority of EEG studies (18—23) performed on animals with massive destructions of the lateral and posterior hypothalamus demonstrated that during the acute stage of the syndrome behavioral sluggishness is accompanied by a pathological cortical EEG dominated by sleep-like pattern which shows no correlation with behavioral symptoms of an actual state of vigilance. However, signs of the sleep-waking cycle can be seen at the subcortical level (24).

In our previous experiments (25, 26) carried out on rats with relatively less extensive LH lesions quite opposite effects on EEG pattern were found. There was an increase in the amount of the desynchronized waking activity (W) accompanied by a simultaneous fall in the amount of large amplitude irregular activity related to slow wave sleep (SWS) and also by a reduction of paradoxical sleep (PS), in spite of behavioral somnolence occurring in some animals. Drastic reduction of the amount of sleep was also described by Danguir and Nicolaidis (18) in rats partially recovered from the effects of large LH destructions. Thus, LH rats may display insomnia or constant sleep-like pattern depending on the size of the lesion and the stage of recovery. As LH lesion-induced waking-sleep disturbances are not well understood, the present experiment was aimed to further elucidate the phenomenon of the lateral hypothalamic insomnia.

As was shown in behavioral studies (27—29) recovered LH rats display exaggerated circadian rhythms of ingestive behavior with a shift to the nocturnal phase of the cycle. In the recovered rats food and water intake is almost completely nocturnal and they are able to respond to acute homeostatic challenges such as cellular dehydration only in the dark part of the day (28). In the present experiment we were interested whether these exaggerated circadian rhythms are reflected in the EEG pattern and whether they are also present in the acute stage of the syndrome. We took 1 hour samples of EEG from the light and the dark portions of the day and counted the amount of the

desynchronized pattern (waking state), slow wave sleep and paradoxical sleep before and after LH lesions. For comparison, 12-h light-part records were also analyzed.

Mechanism of LH insomnia is obscure. Sleep disturbances may result from destruction of neuronal elements directly involved in the regulation of waking-sleep cycle or they may be secondary to other symptoms of the LH syndrome. For example Danguir and Nicolaidis (18) related LH insomnia to ingestive disturbances evoked by the lesions. In our recent studies (30) we tested a hypothesis that increased waking is a secondary effect of motor restlessness which LH rats display when properly observed (31, 32). In the present experiment we addressed the question whether indeed there is a correlation between increased waking and LH ingestive impairments as earlier suggested (18), because our preliminary observations of LH rats did not support such suggestion.

MATERIAL AND METHODS

Animals

The experiment was done on 28 male Wistar rats weighing 250—350 g at the day of surgery. The animals were kept in individual home cages with laboratory pellets and tap water *ad libitum*, in an artificially maintained 12 : 12 hour light/dark cycle. The rats which developed aphagia and adipsia after LH damage were additionally fed and watered by means of a gastric tube, once or twice a day just after completion of EEG recordings.

The experiment was performed on 4 groups of rats: 3 experimental LH-lesioned groups, and 1 control sham-operated group.

Surgical procedure

Each rat was implanted under Nembutal anesthesia with chronic electrodes for bilateral electrolytic lesions aimed at the region of the lateral hypothalamus, bilateral recording electrodes in the dorsal hippocampus and over the occipital cortex, earth screw electrode and the reference electrode. All rats were also implanted with a silver wire EMG electrode in the neck muscles. Detailed description of construction and implantation of electrodes was presented elsewhere (25).

Stereotaxic coordinates for LH electrodes were following: 1.5—1.7 mm posterior to the bregma, 1.7—2.0 mm lateral to the midline and 8.4—9.0 mm below the surface of the skull. Recording electrodes in the dorsal hippocampus were implanted 2.5—2.8 mm posterior to the bregma, 2.5 mm lateral to the midline and 2.5—4.0 mm below the skull surface. Neocortical recording electrodes were screwed 10 mm posterior to the bregma and 3 mm lateral to the midline at a depth of 1 mm below the skull surface.

Electrolytic lesions in the experimental animals were performed under light ether anesthesia after completion of baseline EEG recordings, i.e. about 10 days after implantation of electrodes. Lesions were produced by passing 1.5—2.0 mA anodal current for 15—20 s. Sham operated groups were treated in the same way except that no current was passed through LH electrodes.

EEG recording

After implantation of electrodes the animals were allowed about a week recovery period from the surgery, during which they were adapted to the experimental conditions. The rats were put into the recording chamber for the same hours of the day as those of the actual experiment.

After completion of adaptation procedure EEG recording began. The recordings were carried out in glass cages measuring 260 × 260 × 400 mm placed in a sound attenuating chamber twice a day for 1 hour from 11.00 to 12.00 a.m. (groups LH-light; n = 13 and LH-sham; n = 11) and from 9.00 to 10.00 p.m. (group LH-dark; n = 4) or once a day for 12 hours from 6.00 a.m. to 6.00 p.m. (group LH-12h; n = 4). Diurnal recording started 5 hours after the onset of light in the artificial 12 : 12 hour light/dark cycle, and evening recording — 3 hours after offset of light. The recording chamber was illuminated during 1h and 12h diurnal experiments and kept dark during nocturnal recordings. The rats were put into the chamber 1 hour before the beginning of the EEG recording to avoid possible arousing effects of moving the animal from the home cage to the recording cage.

The cortical and hippocampal EEG recordings were made using a 16-channel Medicor electroencephalograph (bandpass 0.5—50 Hz). The animals were continuously observed through a camera connected to a monitoring system and their behavior (walking, rearing, probable sleep etc.) was noted concomitantly with EEG recording. The EEG pattern was recorded for 3 days before the brain damage (baseline), for 5—8 consecutive days after the lesion and then on days 11 and 14 postlesion.

All EEG records were visually analyzed and counted for the amount of low voltage fast activity in the neocortex and the hippocampus (waking without theta), low voltage fast activity in the neocortex accompanied by theta rhythm in the hippocampus (waking with theta), large amplitude irregular activity in the neocortex and hippocampus (slow wave sleep) and generalized theta rhythm in the neocortex and hippocampus accompanied by neck muscle atonia (paradoxical sleep). The amount of the particular types of EEG activity is presented as a percentage of the total recording time.

Behavioral observations

After the lesion rats were observed for somnolence and disturbances in food and water intake. Daily consumption of standard laboratory pellets and tap water, as well as body weight were measured during the first 10 postlesion days i.e. in the acute stage of the syndrome. The intensity of ingestive disturbances was evaluated on the basis of duration of aphagia and adipsia (in days) and on the basis of the maximal body weight loss expressed as a percentage of weight on the day of the lesion.

Somnolence was assessed by the experimenter observing animals behavior in a new environment according to the procedure described elsewhere (25).

Histology

After completion of the experiment rats were treated with an overdose of anesthetic and then intracardially perfused with 0.9% saline followed by 10% solution of formalin. The brains were removed from the skull and placed in 10% formalin. After fixation brain sections 30 μm thick were cut using a frozen tissue technique. The sections were stained with cresyl violet for cell bodies.

Statistics

Separate one-way repeated measures ANOVAs were conducted on the percentage amounts of waking (both with and without theta rhythm), SWS and PS in the tested EEG samples with factors: lesion, group and time postlesion. Findings from the ANOVA were further analyzed using Student's t-test (two-tailed).

RESULTS

Effect of LH lesions on waking-sleep pattern

Analysis of variance performed on the prelesion and the postlesion daily data revealed significant effect of the lesion on waking-sleep distribution in the LH-light and LH-12h group. In both groups total waking time was significantly increased postlesion (LH-light: $p < 0.0001$; LH-12h: $p < 0.001$), slow wave sleep (LH-light: $p < 0.0001$; LH-12h: $p < 0.001$) and paradoxical sleep (LH-light: $p < 0.002$; LH-12h: $p < 0.0001$) were reduced. Waking and sleep time was not significantly changed in the LH-dark and the LH-sham groups. Although total amount of W was similarly affected by the lesion in the LH-light and LH-12h groups, there were differences in distribution of waking time between W with and W without hippocampal theta rhythm. In LH-light group waking time increased at the expense of W with theta ($p < 0.0001$) whereas in the LH-12h group at the expense of W without theta ($p < 0.0001$). *Fig. 1* presents percentage distribution of W, SWS and PS in all tested groups before lesioning and in the first and the second postlesion week.

In the control conditions analysis of variance revealed significant group effect on the amount of W ($p < 0.001$), SWS ($p < 0.001$) and PS ($p < 0.05$). Thus, time at which recordings were performed significantly affected waking-sleep distribution in the neurologically intact rats. Total amount of waking (mean $\pm$ SE calculated for all prelesion records) in the LH-light group ($50.77 \pm 2.76\%$) of the total recording time) was shorter than in the LH-12h group ($63.07 \pm 2.73\%$) ($p < 0.01$) and then in the LH-dark group ($71.68 \pm 2.30\%$) ($p < 0.0001$). Groups LH-12h and LH-dark differed at the level of $p < 0.05$. Thus, as expected rats were more active in the dark than in the light part of the circadian cycle. Accordingly, SWS was longer in the LH-light group ($40.72 \pm 2.23\%$) than in the LH-dark group ($23.53 \pm 1.87\%$) ($p < 0.0001$) and also longer than in the LH-12h group ($30.22 \pm 2.42\%$) ($p < 0.01$). Groups LH-12h and LH-dark differed at the level of $p < 0.02$. PS took $8.51 \pm 0.83\%$ in the LH-light group, $6.71 \pm 0.51\%$ in the LH-12h group and $4.78 \pm 0.83\%$ in the LH-dark group. Groups LH-light/LH-12h and LH-12h/LH-dark did not differ significantly; groups LH-light and LH-dark differed at the level of $p < 0.01$.

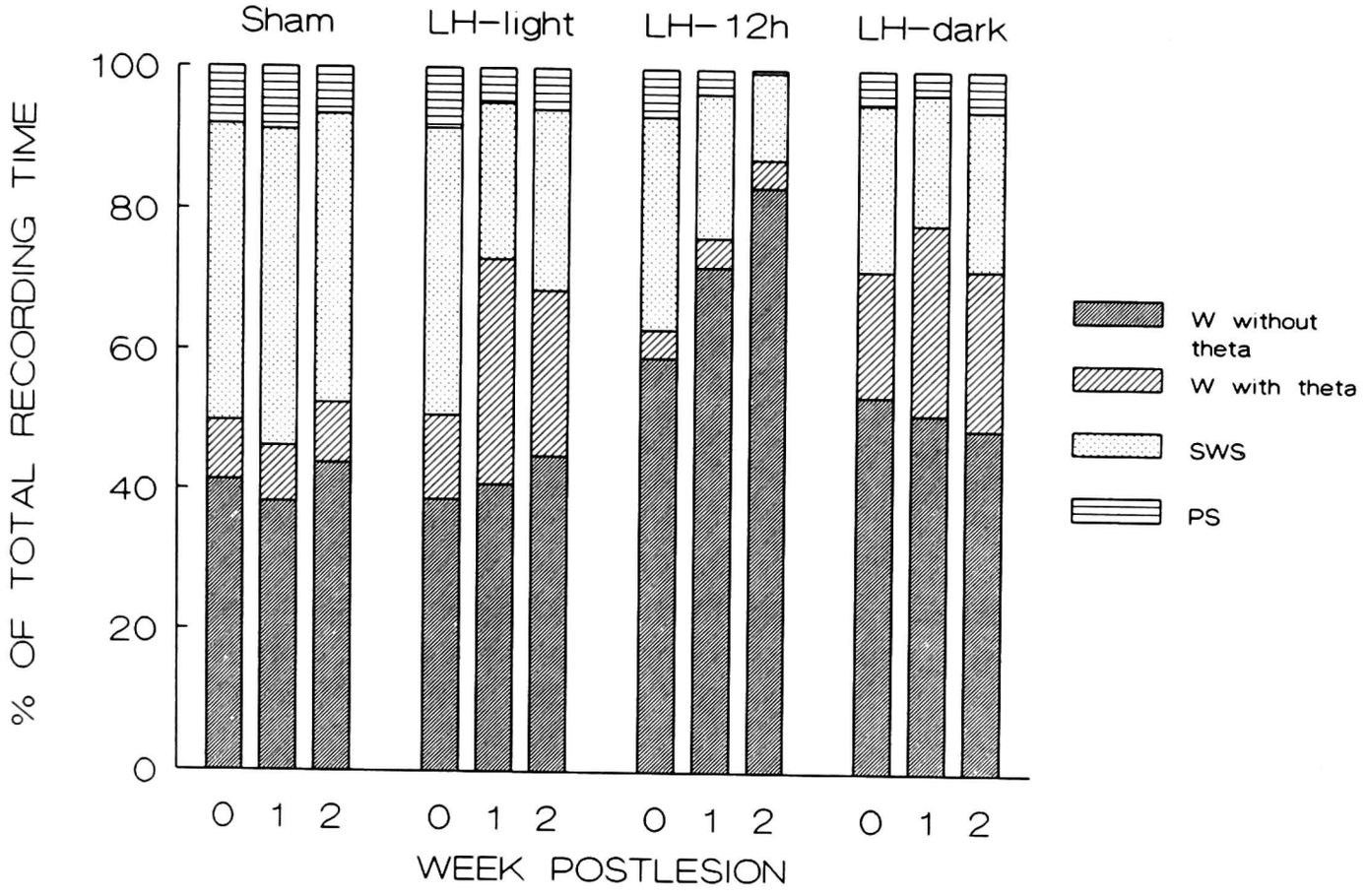

Fig. 1. Effect of LH lesions and the time of EEG recording on the percentage distribution of W, SWS and PS. Daily data were averaged across weeks of testing.

Analogous analysis performed on the postlesion data did not show significant group effect on waking-sleep distribution. Total amounts of W, SWS and PS calculated for the whole postlesion period were as follows: W: LH-light — $71.83 \pm 2.34\%$, LH-12h — $79.92 \pm 2.17\%$, LH-dark — $77.13 \pm 2.86\%$; SWS: LH-light — $23.06 \pm 1.88\%$, LH-12h — $17.63 \pm 1.79\%$, LH-dark — $19.1 \pm 2.24\%$; PS: LH-light — $5.1 \pm 0.56\%$, LH-12h — 2.46 ± 0.54, LH-dark — $3.77 \pm 0.79\%$. Thus, LH lesions resulted in a disappearance of natural day-night differences in waking-sleep time. As LH lesions did not affect waking-sleep distribution in EEG samples taken in the dark period, an increase of waking and a decrease of sleep in the 1h and 12h light samples is responsible for a disappearance of group differences in the postlesion period.

Analysis of the time postlesion factor in the LH-light and the LH-12h groups did not show significant effect of day postlesion. When data were averaged across weeks of postlesion testing significant effect was found in the LH-12h group on total amount of W ($p < 0.01$), SWS ($p < 0.05$) and PS ($p < 0.001$). In this group deleterious effect of LH damage was more pronounced in the 2nd than in the 1st postlesion week (*Fig. 1*). Thus, no significant recovery from the effect of LH damage on waking-sleep pattern occurred in the disturbed rats during the experimental period.

Behavioral observations

Damage to the lateral hypothalamus evoked disturbances in food and water intake of different intensity. Although all rats were observed for behavioral abnormalities after LH lesion detailed analysis of ingestive impairments and their correlation with a percentage increase in waking time was performed for LH-light group. The results are presented on *Table I.*

Tab. 1. Disturbances in food and water intake, body weigh loss and percentage increase of waking time in the LH-light group

RAT	aphagia	adipsia	decrease of body weight (%)	increase of waking time (%)
1	5	4	29.4	41.0
2	8	8	34.3	47.4
3	5	4	26.4	17.5
4	5	8	31.2	3.0
5	1	1	8.3	3.9
6	0	0	2.6	19.1
7	0	0	3.4	20.6
8	0	0	8.8	25.2
9	1	0	6.6	33.0
10	4	5	36.6	36.3
11	2	3	18.4	29.9
12	2	2	23.4	9.6
13	0	0	14.4	52.5

0—8 day complete aphagia and adipsia was observed. Rats which were not aphagic and adipsic usually showed decrease in daily food and water intake. Loss of body weight paralleled ingestive impairments despite artificial feeding of the aphagic rats. No correlation was found between percentage increase of waking time and a number of days of aphagia ($r = 0.14$) and adipsia ($r = 0.04$), and maximal body weight loss expressed as a percentage of weight on the day of the lesion ($r = 0.11$).

Four to five days somnolence was found in the most disturbed animals. The other rats were either not changed or showed signs of abnormally increased motor activity similar to that described by Campbell and Baez (33) and Jurkowlaniec et al (31). No ingestive and behavioral abnormalities were found in the sham operated rats.

Histological verification

Lesions were situated in the lateral hypothalamus from the level of the anterior hypothalamic nucleus to the posterior hypothalamus. Damage basically involved the medial forebrain bundle but it frequently invaded also

the medial border of the internal capsule, zona incerta, fields of Forel and occasionally the ventral thalamic nuclei. *Figure 2* shows example lesions in a representative rat.

DISCUSSION

The results obtained can be summarized as follows: 1. LH lesions caused an increase in waking time and a decrease in SWS and PS time in diurnal part of the circadian cycle. No influence of the lesions on nocturnal quantitative waking-sleep pattern was found; 2. Total amounts of W, SWS, and PS in the 1h samples of EEG taken in the middle of the light recording period and in the records of the whole 12h diurnal EEG were comparable. In 1h samples prevailed waking with theta whereas in the 12h period waking without theta rhythm; 3. There was no correlation between the intensity of ingestive impairments evoked by LH damage and a magnitude of an increase in waking time.

The present experiment confirmed our previous observations (25, 26) made on the basis of 1h samples of diurnal EEG that LH damage shifts quantitative waking-sleep relations towards insomnia. Similar waking-sleep disturbances were found by Danguir and Nicolaidis (18) in the 24h EEG recordings of partially recovered LH rats. Thus, it appeared that waking-sleep distribution in the 1h diurnal EEG was similar to that of the whole 24h daily period. In the present study we found that waking enhancing effect of LH damage concerned the light part of the circadian cycle i.e. the period when rats are naturally less active. No increase of waking time was found in the 1h samples of nocturnal EEG. Although it is disputable whether 1h sample can represent the whole dark part of the day, we believe that any major effect of the lesion on nocturnal EEG should have emerged in our sample similarly as it did in the diurnal EEG. The best way to study waking-sleep disturbances is of course recording the whole 24h daily period. However, in certain experimental conditions it may be desirable having the method of reliable EEG sampling basing on shorter periods. LH rats are severely impaired in various physiological and behavioral functions, they frequently do not survive the acute stage of the syndrome, and they are difficult to handle in conditions of the chronic experiment thus, a possibility of limiting disturbing such animals during the experiment is undoubtedly advantageous. We suggest that sampling the EEG in the light part of the day may be sufficient to diagnose the presence of insomnia after LH damage.

We did not find evidence of exaggeration of circadian rhythmicity of EEG activity in LH rats which would parallel the sharpening of feeding rhythms described by other authors (27—29). Instead, LH damage resulted in a disappearance of natural day-night difference in waking-sleep time.

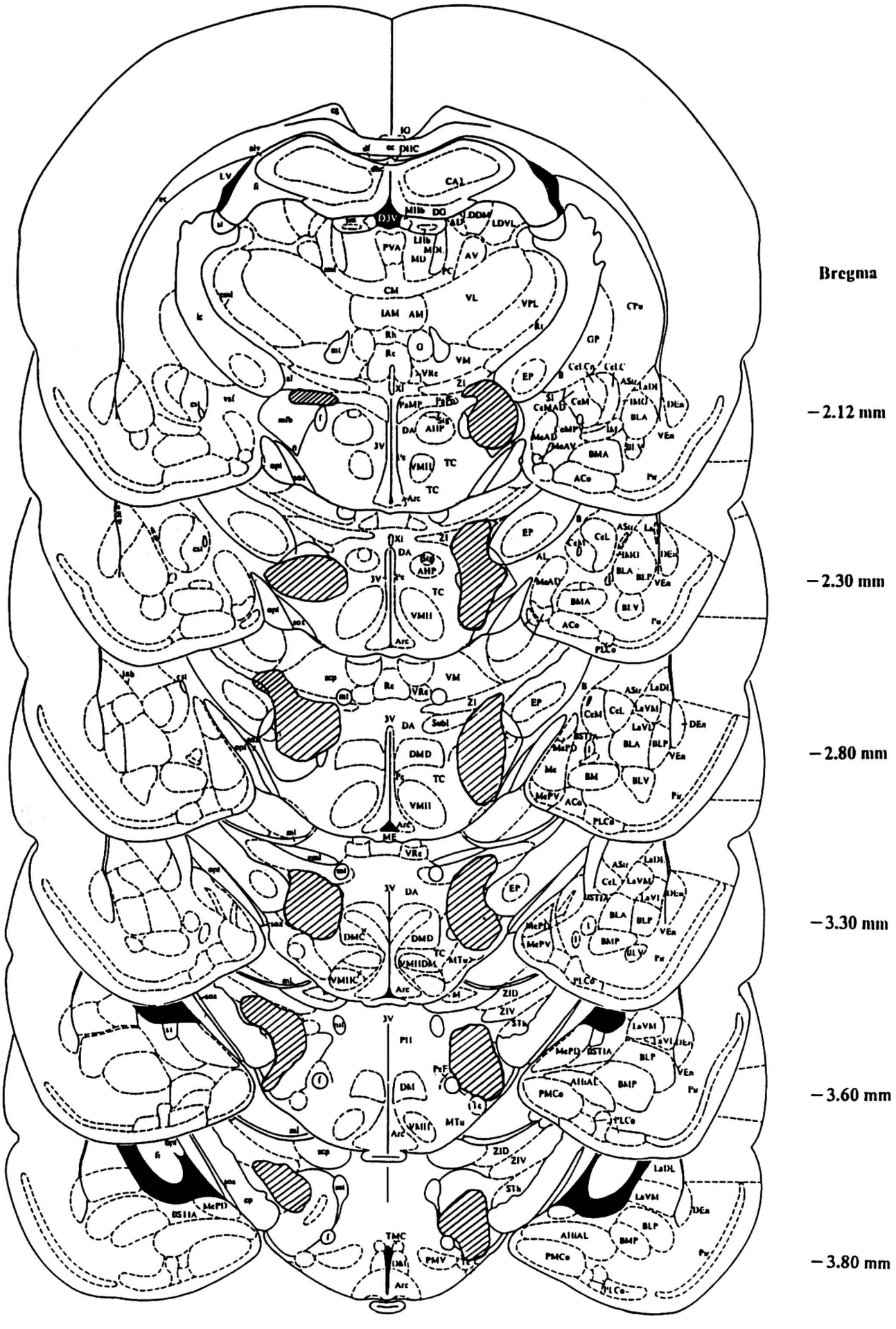

Fig. 2. Histological verification of the lesion (shaded areas) in a representative rat superimposed on plates taken from atlas by Paxinos and Watson (44).

The existence of LH insomnia seems to be proved. There are however doubts as to its mechanism and neurophysiological substrate. The main question is whether sleeplessness of LH rats is secondary to other lesion-induced deficits such as ingestive (18) and motor (30, 31) impairments or it is caused by damage to some sleep-promoting neuronal elements anatomically linked to LH.

Our data do not support earlier suggestions (18) that there is a causative relationship between LH insomnia and feeding deficits. Virtually no correlation was found between duration of aphagia and adipsia, resulting body weight loss and the intensity of waking-sleep disturbances. In our recent experiment (30) we also found no evidence that motor restlessness of LH rats which seems to be a manifestation of some sort of dyskinetic activity is responsible for increased waking in these animals. We would rather think that LH lesion disrupts some basic neuronal mechanism related to regulation of waking-sleep cycle.

Sleep promoting neurons have been identified in the preoptic/anterior hypothalamus and the surrounding ventral basal forebrain. Their destruction produces long-lasting insomnia. (34—38). On the other hand selective inactivation of the LH neurons by means of local injections of muscimol (GABA-agonist) at the tuberal and posterior hypothalamic levels resulted in marked increase in SWS accompanied by hypersynchronization of neocortical and hippocampal EEG (34). Thus, there is little chance that decrease of sleep observed by us after electrolytic lesions of LH can be attributed to destruction of the intrahypothalamic cell bodies. It rather seems that disruption of certain fibers of passage may be responsible for this effect. Such a possibility is strengthened by the fact that insomnia can be produced by destruction of LH at every level (anterior, tuberal and posterior) of its rostro-caudal axis (25, 26).

The question which one out of approximately 50 axonal systems of LH (11) is responsible for waking-sleep regulation can not be answered at present. There are several possibilities. One is suggested by Sallanon et al (39) who found evidence of reciprocal communication between the sleep-inducing anterior/preoptic hypothalamus and the sleep suppressing posterior hypothalamus. This communication can realize through the LH area. Another possibility concerns the serotonergic pathways which ascend through LH and which synchronizing and sleep-promoting action (direct or indirect) has been proved in many experiments (40—43). As insomnia accompanies various neurological syndromes its anatomical basis is worth further studying. Topographical (instead of cellular or neurochemical) approach adopted by us in the present experiment seems to be a suitable model of focal brain injury such as this following stroke, local trauma, tumor, and other kinds of structural damage.

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