DISTURBANCES IN SLEEP-WAKING PATTERN AND CORTICAL DESYNCHRONIZATION AFTER LATERAL HYPOTHALAMIC DAMAGE: EFFECT OF THE SIZE OF THE LESION

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Abstract. The effect of electrolytic lesions of varying size within the anterior part of the lateral hypothalamus (LH) on neocortical activity and quantitative sleep-waking relations was studied in male Wistar rats. It was found that extensive LH lesions caused simultaneously an abolishment of cortical desynchronizing reactions and an electroencephalographic insomnia. More restricted damage left the qualitative pattern of cortical EEG unchanged, but still produced substantial reduction in the amount of sleep. Pronounced EEG disturbances coexisted with relatively mild behavioral deficits. It is concluded that a constellation of the LH syndrome symptoms is critically dependent on the variations of lesion parameters.

In our recent experiment (12) we found that electrolytic lesions of the lateral hypothalamic (LH) area disturb quantitative EEG pattern and shift sleep-waking relations toward insomnia. Contrary to the other authors (2, 3, 5, 7) we did not observe impairments in cortical desynchronization despite severe behavioral depression, including somnolence, occurring in some animals. Seeking for the explanation of this discrepancy, we assumed that only large lesions of the LH region involving substantial parts of adjacent tissue, may significantly depress tonic acti-
vating influx to the neocortex. More limited damage does not abolish cortical desynchronization, but rather disturb sleep-waking relations.

The present experiment was performed to test this assumption. In a group of rats we made electrolytic lesions of varying size within the LH region and then analyzed an amplitude of neocortical EEG activity during waking. Simultaneously, in one hour samples taken from the light part of day, we investigated quantitative EEG pattern before and after LH damage and related possible disturbances to the size of the lesion. In our previous work (12) we explored mainly the intermediate and the posterior parts of the lateral hypothalamic-medial forebrain bundle area finding no difference between the two in their influence on EEG pattern. Now we extended the experiment to the anterior lateral hypothalamus.

The experiment was carried out on 7 male albino rats of the Wistar strain weighing 230-270 g on the day of surgery. The animals were kept in individual home cages with food and water ad lib., in an artificially maintained 12:12 h light/dark cycle.

Each rat was implanted, under Nembutal anesthesia, with chronic electrodes for lesions bilaterally in the region of the anterior part of the lateral hypothalamus and with recording electrodes in the left dorsal hippocampus (CA 1 pyramidal cell layer) and over the right occipital cortex.

Stereotaxic coordinates for lesion electrodes were: 1.2 mm posterior to the bregma, 1.7 mm lateral to the midline and 7.7 mm below the surface of the skull (with the flat skull). Hippocampal recording electrode (concentric, bipolar) was implanted 2.5 mm posterior to the bregma, 2.5 mm lateral to the midline and 3.0-3.5 mm below the skull surface. Neocortical screw electrode was positioned 5 mm posterior to the bregma, 3 mm lateral to the midline at a depth of 1 mm below the skull surface. Construction and implantation of electrodes was described in detail elsewhere (12).

EEG recording began after 10 days of recovery period, during which the rats were adapted to the experimental conditions. The recording was carried out in an illuminated, sound attenuating chamber for 1 hour daily (11.00-12.00 a.m.) with the use of 16 channels Medicor Polygraph (passband 0.53-50 Hz). The animals were continuously observed by the experimenter through a camera connected to a monitoring system and their behavior (waking, rearing, probable sleep etc.) was noted concomitant with EEG records. Normal EEG pattern was recorded for 3 days (baseline). Then the rats were subjected, under light ether anesthesia, to electrolytic lesions made by passing anodal current through previously implanted electrodes. The different size of the lesion in particular
subjects was obtained by varying the intensity of the current from 10.-
1.5 mA. The current duration was always 15 s.

Starting from the day following the brain damage, EEG pattern was
recorded for 8 consecutive days and then on the days 11 and 14, and
in some animals periodically up to 36th postlesion day.

All records were visually analyzed and counted for the amount of
waking, slow wave sleep and paradoxical sleep. Quantitative distribu-
tion of all these types of EEG activity was expressed as a percentage
of the total recording time. The records were inspected in order to de-
fine possible qualitative abnormalities in the neocortical EEG. Three
10 s samples of waking activity were taken randomly from each prele-
sion and from the first three postlesion records and the amplitude of
arousal pattern was measured. If it was changed, neocortical EEG was
sampled on subsequent days up to the recovery of amplitude to preope-
ervative value.

The rats were tested for behavioral disturbances resulting from brain
damage. For a few days prior to and following the lesion, daily food
and water intake and body weight were measured. The animals were
also observed for the occurrence of somnolence.

After completion of the experiment the rats were treated with an
overdose of ether, 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.

Out of 7 investigated rats, in 3 the lesions of the anterior LH were
small to medium sized, and in 2 — large. Two further rats had damage
placed outside the LH, in the periventricular, prosencephalic structures,
and their results served as the control for unspecific effects of the
lesions.

Figures 1-3 show examples of LH damage of increasing size concomi-
tant with sleep-waking distribution in an experimental hour, samples
of polygraph records and amplitude of cortical waking EEG.

The lesions equal to or smaller than that shown in Fig. 1 had no
deleterious effect on cortical desynchronizing activity. Simultaneously
the damage impaired quantitative sleep-waking relations and increased
the amount of waking pattern, sometimes up to complete cessation of
sleep in the first 3-4 days after the lesion.

Total, bilateral dissection of the medial forebrain bundle in the ante-
rior LH region with partial involvement of neighbouring structures
(Figs. 2, 3 and 5) impaired both sleep-waking relations and cortical
arousal activity. In such rats the cortical EEG during waking took
a form of large amplitude slow activity (synchronization) which was ho-
Fig. 1. Effect of medium-sized damage to the anterior LH (rat no 44). A, anatomical verification of the lesion placement (shaded areas) superimposed on sections taken from the atlas by König and Klippel (8); B, percentage distribution of waking, slow wave sleep, and paradoxical sleep; C, example polygraph records of neocortical (CO) and hippocampal (HI) EEG during immobile waking (1) and during movement (2); D, amplitude of neocortical activity during immobile waking.

wewer relatively easy to distinguish from slow wave sleep both on the basis of EEG and animals' behavior. The comparison shown of rats in Fig. 2 and Fig. 3 indicates that the amplitude of cortical EEG was proportional to the size of the lesion. In the early postlesion period high amplitude neocortical activity accompanied immobile waking as well as movements.

The ability of the neocortex to desynchronizing reactions although se-
A severely depressed, was not completely eliminated. Several (11-14) bursts of low amplitude irregular activity similar to the prelesion arousal pattern were observed even in severely disturbed animals. These desynchronizing reactions were short (mean duration: 9.7-10.2 s) and were not associated with any particular behavior. In the first 3 days after the lesion they took about 4% of the total time of waking. The recovery of the neocortical EEG was relatively fast. On the 6th postlesion day normal desynchronization occupied about 70%, and on the 14th day —
Fig. 3. Effect of large damage to the anterior LH with marked invasion of the neighbouring structures (rat no 48). Explanations as in Figs. 1 and 2.

100% of the total time of waking. A comparable time-course of recovery of cortical activity after LH lesions was found by Danguir and Nicolaidis (2).

Although aberrant, the waking pattern dominated in the records of the animals with large LH damage. In the case presented in Figs. 2 and 5, except the 3rd day, there was a marked reduction of slow wave sleep with a complete suppression of paradoxical sleep on the eight first days after the lesion (because of displacement of recording electrode this rat was not investigated on further days). In the other subject (Fig. 3) in-
creased amount of waking was observed up to the 11th postlesion day.

Fig. 4 shows an example of the control rat in which the lesion was misplaced. The electrodes passed through the lateral ventricles and as a result the current spreaded preferentially in the cerebrospinal fluid damaging mainly periventricular structures. The lesions although relatively large gave neither quantitative nor qualitative changes of EEG. This proves that the observed effects are specific for the hypothalamic damage.

LH rats showed also abnormalities in hippocampal theta rhythm, which are described in details in a separate paper (6).
Fig. 5. Photograph of LH lesion shown schematically in Fig. 2 (rat no 45).
As was expected, the rats showed disturbances in food and water intake typical for the lateral hypothalamic damage (1, 11). Similarly to earlier observations (9) concerning the anterior part of LH they were short (2-5 days) and not severe. One day of aphagia and hypodipsia followed by 2 days of strong hypophagia and 6 days of hyperdipsia were observed in the rat with the largest lesion (shown in Fig. 3). The remaining LH animals were mildly hypophagic and hypodipsic. No ingestive impairments were found in rats with lesions of the forebrain paraventricular structures. Strong, 4 day somnolence occurred in rat no 48 (Fig. 3). Two other LH animals were aggressive for the first two days after the lesion.

The results obtained seem to demonstrate that indeed only large lesions of the LH region are able to impair cortical desynchronizing activity. Similarly to the previous reports (2, 3, 5, 7) cortical EEG was dominated by high voltage slow activity, but in our experiment only in the animals in which the lesions caused total dissection of the lateral hypothalamic-medial forebrain bundle area with simultaneous partial involvement of the adjacent tissue. In agreement with our previous results (12) partial lesions of LH area did not abolish cortical arousal activity. Thus, the size of the lesions seems to be critical for qualitative characteristic of cortical EEG after LH damage. Observed effects were specific to the hypothalamus because even relatively extensive damage to the prosencephalic periventricular structures did not influence cortical activity.

Whether disturbances in desynchronization appeared or not, in all LH rats there was a significant suppression of both slow wave and paradoxical sleep with a simultaneous increase of the amount of waking. The duration of these abnormalities corresponded with the size of the LH damage. This finding supports our results (12) obtained with lesions of the more caudal parts of LH. Enhanced waking might have taken a form of typical desynchronization in the case of animals with more limited lesions, or synchronous, high amplitude activity in rats with a substantial damage of the same region.

Previously (12) we found a dissociation of electroencephalographic and behavioral indices in the level of arousal in LH rats. Behavioral somnolence might have been accompanied by almost constant desynchronization. The same EEG pattern was also seen in animals with no obvious behavioral depression. We concluded therefore that anatomical substratum for both aspects of activation must be separated, although they are neighbouring within the LH region.

The data obtained by other authors as well as those from our experiments indicate that damage to the same LH region may give different
constellation of symptoms, depending on the size of the lesion and slight variations in its localization. Thus we may obtain behavioral somnolence accompanied by constant synchronization of cortical EEG (2, 3, 7) or, oppositely with constant desynchronization when the lesion is a little less extensive (12). Moreover both types of cortical EEG may not be accompanied by a marked behavioral depression (12, present results). Our experience with LH rats shows that also other symptoms of the classical LH syndrome, such as disturbances in food and water intake, regulatory deficits, catalepsy etc., may be dissociated from one another by varying the parameters of the lesion. Whereas behavioral deficits seem to be dependent on the rostro-caudal level of the lesion (4, 9, 10), EEG changes, at least quantitative, are the same with the localization of the brain damage within the posterior, intermediate (12) or anterior (present results) parts of LH. This suggests an involvement of fiber system passing through LH rather than a specialized group of hypothalamic neurons.

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