# LONG-TERM FLUCTUATION OF CEREBRAL ELECTRICAL ACTIVITY AS RELATED TO COAGULATION OF THE CONNECTIONS BETWEEN HYPOTHALAMUS AND HYPOPHYSIS

N. A. Aladzhalova and A. V. Kol'tsova

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By "long-term fluctuations of electrical activity" we mean its periodic increase in certain regions of the brain, occurring at intervals of a few tens of minutes, which arises when a powerful stimulus is given to one of the cerebral centers of the waking animal [3]. These fluctuations occur after a long latent period of several tens of minutes, and typically show several waves of enhanced electrical activity (Fig. 1). These cycles of excitation may fade away in 1-2 hr, but in certain cases they again arise in the second or third hour of the experiment and do not die away until 3-5 hr after presentation of the powerful stimulus. Here we may distinguish two stages of fluctuation.

In the first stage, which develops 25-30 min after the initial shock and lasts for 1-2 hr, three to seven waves of fluctuation of activity are observed, and for each wave of the electrogram high-amplitude and high-frequency fluctuations characteristic of excitation develop.

In the second stage, which in most cases occurs 130 min after the excitation, again several fluctuations occur, but in many of the cerebral structures at this time the electrical activity takes the form of spindles. In both first and second stages of fluctuation there is an increase of the very slow potentials having a frequency of eight per min [1, 2].

We interpret most of the fluctuations and the very slow waves as a manifestation of the slow controlling system of the brain. One of the characteristics of this system is that it does not respond to change, external excitations having little significance for the animal. The mechanisms are caused to operate when a factor in the environment acquires the characteristic of an excessive load or of a more or less systematically acting stimulus; in this case regulation is directed not only to overcoming the alterations induced in the internal medium (homeostasis) but also to active reorganization of the level of activity of the brain for the work of foreseeing the future action of the new factor. The effect is that at the start of the experiment, in response to the first excitation applied to animals, no long-term fluctuations arise, and the very slow waves are not increased. The effects do not occur until the third or fourth experiment when the stimulus becomes a systematic factor; then at first only the first stage of fluctuation occurs (after two or three experiments) but by the fourth experiment, the second phase is included also. After a long interruption the effect disappears.

Previously it has been pointed out [3] that long-term fluctuations in the rabbit brain were observed to continue longest after stimulation of the hypothalamic and neurosecretory regions.

For example, stimulation of the dorsal region of the hypothalamus caused eight waves of fluctuation of activity in the dorsal region itself to occur after a latent period of 14 min. In the thalamus the fluctuations developed after 28 min, and there were seven waves in the dorso-medial and five in the reticular nucleus of the thalamus. At the 143rd minute the second stage of long-term fluctuations occurred.

The occurrence of reactions so late raises the question of whether hormonal factors are concerned in the long-term fluctuations. It is of the first importance to destroy the connection between the hypothalamus and hypophysis in order to determine its significance.

## EXPERIMENTAL METHOD

Ten days before the start of the experiments, bipolar nichrome electrodes of diameter 100 $\mu$ and 250 $\mu$ separation were implanted stereotactically into the rabbit brain. Three bipolar electrodes were implanted in the hypothalamus and thalamus. As a control over the electrocorticogram, one pair of plastic electrodes of diameter 4 mm and at

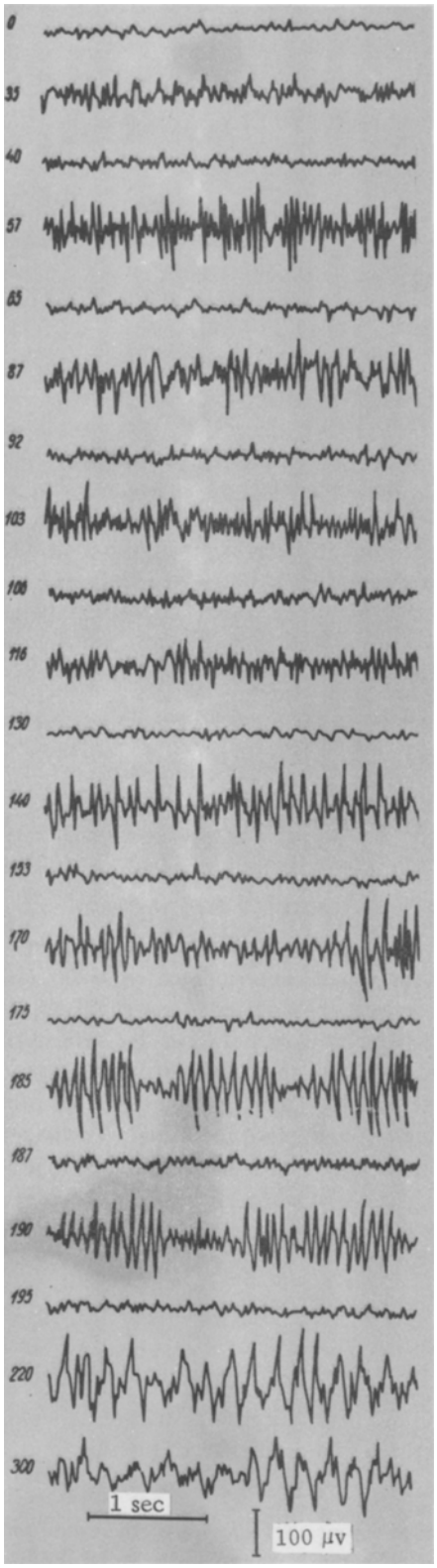


Fig. 1. Long-term fluctuations of electrical activity in the lateral hypothalamic region after stimulation applied to it at zero time. The figures indicate the time in minutes after stimulation. The second stage of fluctuation begins after 140 min. After 300 min the following activity begins.

a separation of 6 mm were implanted in the surface of the sensory-motor cortical area. During the experiment electrical impulses of amplitude 4 v, duration 10 msec and frequency 100 cycles were applied for 15 sec to one of the electrodes implanted in the hypothalamus. Before stimulation and for five hours afterwards, electrical recordings were made from all the electrodes; a capacitor-coupled amplifier and ink writer were used. Two weeks after the performance of several experiments whose long-term effect had been to induce fluctuation in animals with intact hypothalamo-hypophysial connections, coagulation was applied to various parts of this region. For this purpose an electrical current of 3 ma was passed through bipolar glass-insulated electrodes of diameter 100 $\mu$ for 2.5 min. After coagulation the electrodes were removed; then the area of coagulation and position of the lead-off electrodes were determined histologically. The experiments were repeated one week after coagulation, and continued for two weeks.

## EXPERIMENTAL RESULTS

One week after combined coagulation of the infundibulum and hypophysis, in response to stimulation of the lateral pre-optic region fluctuations developed both in the region itself and in the ventro-medial hypothalamic nucleus and in the supramamillary region (Fig. 2). The fluctuations occurred after a latent period of 33 min and consisted of 5-6 cycles of excitation. They terminated 3.5 hr after the occurrence of a change to the other activity of the impulsive type. It is important to emphasize that electrical records from the nuclei during the fluctuation and after coagulation are more intense. For example before coagulation, in response to stimulation of the lateral pre-optic region in the third experiment, after 102 min and at the height of the fluctuation, oscillations of 7 cycles occurred with an amplitude 200 $\mu$v. After coagulation the wave of one fluctuation consisted of a transition from low activity to high amplitude oscillations whose frequency rose from 14 to 28 cycles. In other words after damage to the connection between the hypothalamus and hypophysis long-term fluctuations of activity were more marked, and took on a wider variety of forms.

In another set of experiments we tried to avoid such extensive coagulation, which in itself seriously interferes with the regulatory function of the organism, and we therefore caused only a very restricted arc-shaped coagulation of the paraventricular nucleus on the left side. In this way we interrupted the pathway between the supra-optic region and the hypophysis on one side.

Before coagulation the response to stimulation of the lateral region of the hypophysis consisted of two stages of long-term fluctuations (see Fig. 1 on the 4th day of presentation of the stimulus); however, in the

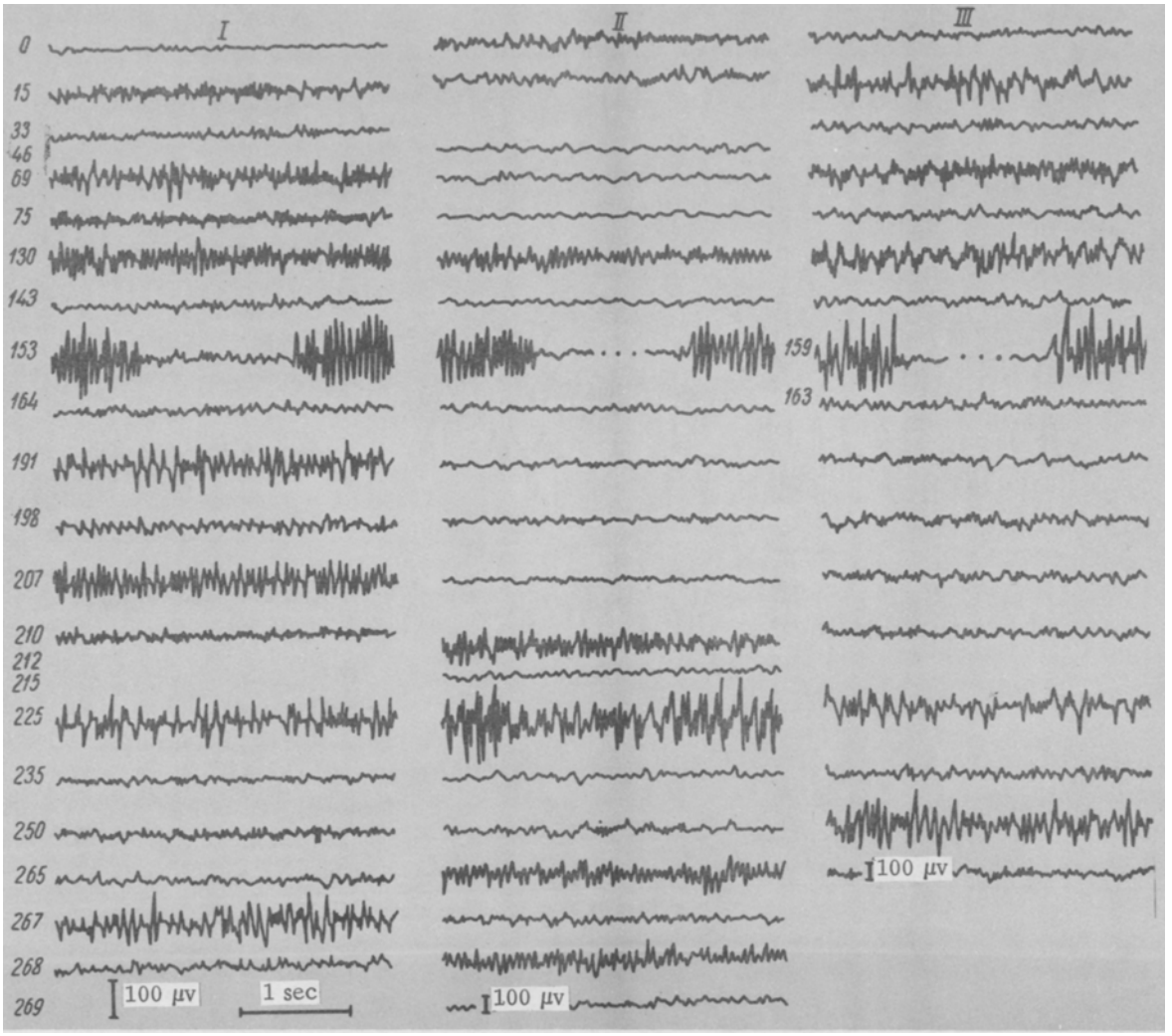


Fig. 2. Long-term fluctuations of electrical activity in the brain of an animal in which the hypophysis was coagulated after stimulation had been applied to the lateral pre-optic region. I) Bipolar lead from lateral pre-optic region, II) ventro-medial hypothalamic nucleus, III) supramamillary region. The figures indicate the time in minutes after stimulation. Before coagulation the fluctuation occurred only in the lateral pre-optic region.

thalamic nuclei (in the postero-lateral and dorso-medial nuclei there were no fluctuations and the electrical activity of these nuclei remained at a low level. Ten days after coagulation of the arc-shaped paraventricular nucleus the background activity was increased: in the electrogram of the cortex and of the lateral and medial thalamic nuclei higher frequency components appeared. During this condition we applied a stimulus to the lateral hypothalamic region on the coagulated side. The response consisted of two strongly-shown stages of long-term fluctuation in the hypothalamic region itself, and there was a well marked second stage of oscillations in the thalamic nuclei (Fig. 3). The effect reappeared in an experiment carried out after four days.

Thus when there is a limited destruction of the connections with the hypophysis, fluctuations are increased. Possibly however the effect is due to coagulation as constituting a form of stress. Disturbance (or mobilization) of the regulatory mechanisms might facilitate the appearance of more intense long-term fluctuations of activity playing some part in regulation. Therefore to control the effect of coagulation itself we also coagulated another region having practically no relationship to the connections between hypothalamus and hypophysis; the region we selected was the thin lamina terminalis, whose upper end is in contact with the anterior commissure and whose lower end reaches the upper edge of the optic chiasma.

Ten days after coagulation there were no noticeable changes in the background activity, and the first stimulation of the dorsal hypothalamus caused no fluctuations. The second stimulation applied one day after the first elicited

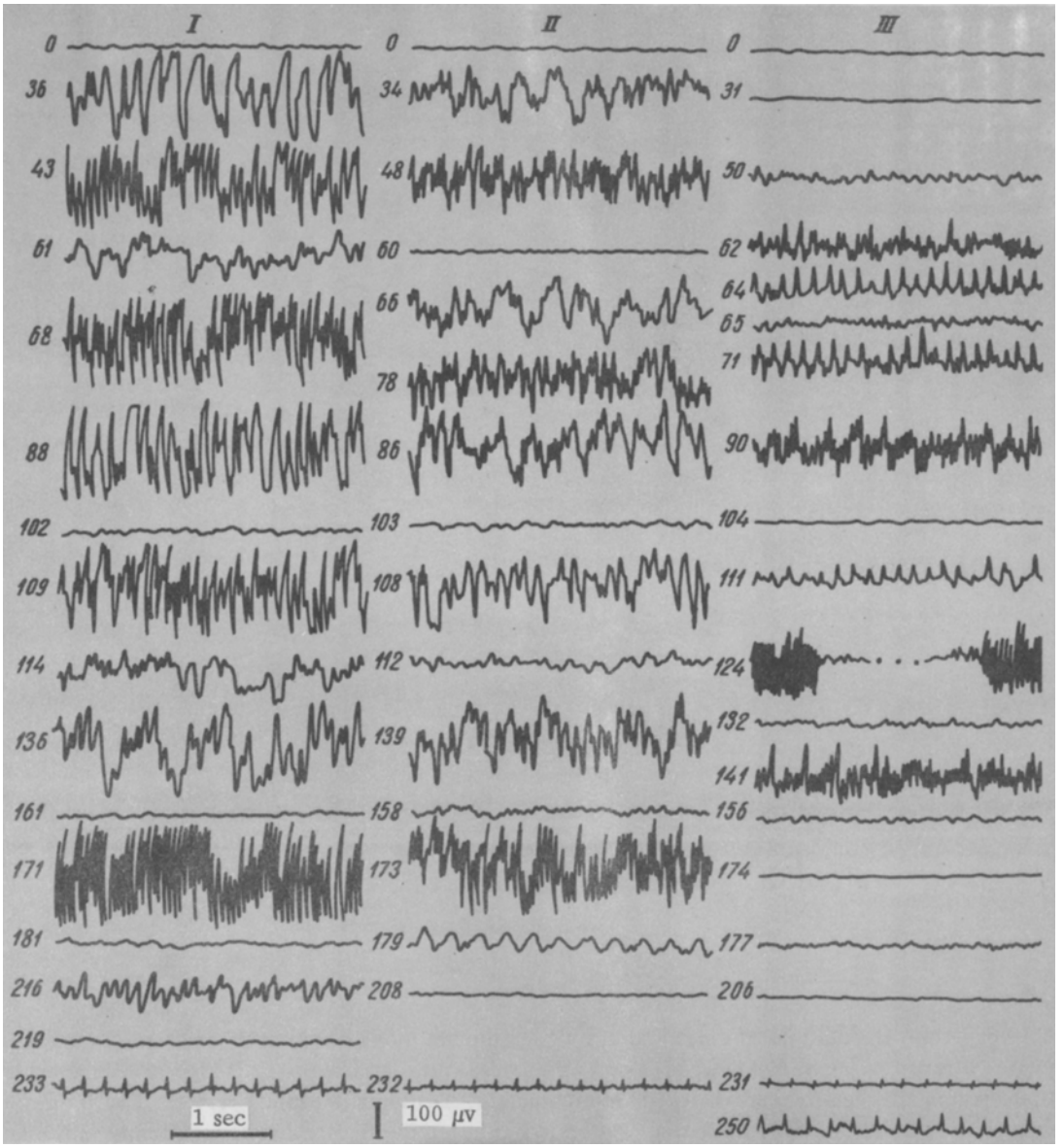


Fig. 3. Long-term fluctuations of electrical activity after coagulation of the hypothalamo-hypophysial tract on one side in response to stimulation of the lateral hypothalamic region at zero minutes. (I) Leads from lateral hypothalamic region, (II) from dorso-medial thalamic nucleus, and (III) from the antero-lateral thalamic nucleus. The figures indicate time in minutes after stimulation. The experiments shown in Figs. 1 and 3 were performed on the same animal.

both stages of fluctuation, which were somewhat more intense than they had been initially. The fluctuations were recorded in the dorsal region of the hypothalamus in the reticular and dorso-medial thalamic nuclei. On the following days the response to stimulation was reduced, but after a two-day interval the two stages of fluctuation in the thalamic and hypothalamic regions were again well marked. A comparison with coagulation of the hypophysial tract showed that the latter causes a much greater difference in the intensity of the long-term fluctuations. However, coagulation of the lamina terminalis also exerted some facilitating influence on the development of the two stages of fluctuation, probably operating as a stress stimulus and eliciting some hormonal response.

The first conclusion from the experiment is that the phenomenon of long-term fluctuations of electrical activity may be observed even after damage to the connections between the hypothalamus and hypophysis. Therefore fluctuations developing several hours after presentation of the stimulus are not the result of a direct interaction between the hypothalamus and hypophysis.

The second conclusion is that electrical activity of the hypothalamic and thalamic nuclei is enhanced after division of the hypothalamo-hypophysial tract.

It has been proposed [9] that the direct connection is brought about by the passage of granules of neurosecretion along axons proceeding to the hypophysis. Interruption of these pathways might cause an accumulation of the secretory granules in the hypothalamus [8, 10]. Possibly the increase of electrical activity in the hypothalamus and thalamus after division is due to the local influence of the accumulated neurosecretion of the excitability of these structures. Possibly too, in this case the increase of thalamic activity (particularly in the dorso-medial nucleus) might result from the transfer of secretory material in the ascending pathways along the wall of the third ventricle. This would be in agreement with cases which have been described of the transfer of neurosecretion along axons of the secretory cells in the third and in the lateral ventricles [5]. Also, neurosecretory fibers of the hypothalamus may terminate in other parts of the nervous system as well [7].

It is therefore not improbable that hormones which play a part in the development of the long-term fluctuations arise in the hypothalamus. However, this does not mean that such hormones as for example oxytocin or the antidiuretic hormone play no part in the phenomenon. It has been shown [6] that these hormones are secreted after the application of epinephrine to the fronto-parietal region of the cortex even after hypophysectomy. Furthermore there is considerable evidence [4] that an adenocorticotropic hormone appears in the blood in response to a "tension" factor even after division of the connection between hypophysis and hypothalamus. We cannot therefore dismiss the possibility of an influence from this hormone in our experiments.

Recently a report has appeared from Hayashi [11] that the injection of certain specific convulsive substances into the cerebral ventricles of a dog caused generalized convulsions to occur not after 20 sec, as for example after metrazol, but after 40 min. The long latent period corresponds to that of the long-term fluctuations of activity in the hypothalamus which we observed in our experiments. The long latent period may be the result of an indirect action of the convulsive agent, because it has three effects: 1) it inhibits the formation of true chemical excitatory transmitters in the paraventricular nuclei, 2) it inhibits the formation of the antagonist transmitter, or 3) it alters its chemical structure so as to become transformed into an excitatory transmitter. Hayashi supports the proposal that the substance which serves as an excitatory transmitter arises by the third mechanism, and is formed from $\gamma$-amino-butyric acid with the involvement of folic acid and vitamins $B_1$ and $B_{12}$. The cases we have described probably belong to the first or second mechanism, because a 40 min latent period might occur after electrical stimulation alone.

## SUMMARY

Daily electrical stimulation of one of the regions of the hypothalamus caused fluctuations of electrical activity, i.e., rhythmic changes of high-amplitude oscillations of augmented frequency and low-amplitude oscillations of a lower frequency to develop in the stimulated center and in some other regions of the brain. Each period lasted for several tens of minutes. The waves were found to continue for several hours after stimulation, and could be subdivided into two stages. Coagulation of the hypophysis and infundibulum not only failed to prevent the development of the fluctuations but even augmented them. A restricted coagulation of the tract between the supra-optic region and the hypophysis on one side caused an increase in the fluctuations in the dorso-medial thalamic nucleus. Chemical transmitters appearing in the hypothalamus may therefore be associated with the phenomenon.

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