# ROLE OF THE HYPOTHALAMUS IN THE FORMATION OF AUDIOGENIC EPILEPSY

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Unit and integral activity of the medial zone of the hypothalamus during an epileptiform response to acoustic stimulation was recorded in rats excited by sound as a result of sensitization with homologous brain antigen and in genetically excitable rats of the Krushinskii-Molodkina line. The appearance of spindle-shaped groups of sharp waves is evidence of an epileptic disposition and is characteristic of both genetically excitable rats and of animals which have been made excitable by sensitization with homologous brain antigen. Neurons of the medial hypothalamus in rats excited by sound respond to an acoustic stimulus mainly by excitation; a decrease in the number of weakly responding and nonresponding neurons also was observed.

Experimental and clinical material now available gives direct or indirect evidence that the hypothalamus certainly participates in the development of many forms of epilepsy, [2, 3, 7, 8, 10]. More recently interest in the hypothalamus, many of whose structures are directly concerned with the central regulation of immunogenesis, has increased still more because of discovery of the role of immunological changes in the formation of epilepsy [9, 11, 12]. It has been shown, in particular, that sensitization of rats with homologous brain antigen causes them to develop an epileptic disposition and lowers the threshold to acoustic stimulation [1]. Nevertheless, very few investigations have been made of the intimate mechanisms of this transformation and electrophysiological data concerning the role of the hypothalamus are virtually absent.

The object of this investigation was to study changes in the functional state of the medial hypothalamus (its ventromedial nucleus), which is known to be a relay structure in afferent-efferent extra- and intrahypothalamic connections [4, 5, 14, 15], in the dynamics of formation of the epileptic state evoked by sensitization with homologous brain antigen. The results were compared with those obtained in experiments on rats of the Krushinskii-Molodkina (K—M) line which are genetically excited by sound.

## EXPERIMENTAL METHOD

The autoimmune brain lesion reproduced by six intraperitoneal injections, each of 0.5 ml of a 20% saline extract of homologous brain, was used as the model for the investigation. Experiments were carried out on eight rats which became excited by sound after sensitization, on seven rats of line K—M genetically predisposed to audiogenic convulsions, and five intact, inexcitable rats which were used as the control. The animals were immobilized by intraperitoneal injection of listhenon and artificial respiration was applied, after which the animals were fixed in a stereotaxic frame and placed in a screened and soundproofed chamber. Unit activity was recorded extracellularly by glass microelectrodes with a tip 0.3-0.6 $\mu$ in diameter, filled with 3 M KCl solution. The microelectrodes were inserted by means of an oil micromanipulator in accordance with coordinates from the atlas of Fifkova and Marsal [13]. The potentials were led through a cathode follower and trigger device to the input of a 4-channel 4 ÉÉG-1 electroencephalograph, which also recorded the integral activity of the hypothalamus, sensomotor cortex, hippocampus, and medial nuclei of the thalamus from unipolar nichrome electrodes inserted a few hours before the experiment.

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TABLE 1. Distribution of Neurons by the Character of Their Evoked Activity Depending on Tonic Firing Rate

| Group of rats | Change in firing rate in response to acoustic stimulation | Spontaneous firing rate (spikes/sec) | | | | | Total number of neurons | |
|---|---|---|---|---|---|---|---|---|
| | | <0,3 | 0,3—0,6 | 0,6—1,0 | 1,0—2,0 | >2,0 | abs. | % |
| Inexcitable, intact | No change | 2 | 1 | | | | 3 | 11,1 |
| | Increase | 7 (3) | 2 (1) | 1 (1) | 1 (1) | | 11 (6) | 40,7 (22,2) |
| | Decrease | 6 (3) | 5 (3) | 2 (1) | | | 13 (7) | 48,2 (26) |
| K—M | No change | 1 | 1 | 1 | 2 | | 5 | 12,5 |
| | Increase | 1 | 9 | 2 | 11 (1) | 4 | 27 (1) | 67,5 (2,5) |
| | Decrease | | 2 | 2 | 4 (1) | | 8(1) | 20 (2,5) |
| Sensitized | No change | | 6 | | 4 | | 6 | 13 |
| | Increase | | 17 (2) | 7 (1) | | 2 (1) | 28 (3) | 60,9 (6,5) |
| | Decrease | | 2 (1) | 6(1) | 2 | | 12 (3) | 26,1 (6,5) |

Note: Number of weakly responding neurons given in parentheses.

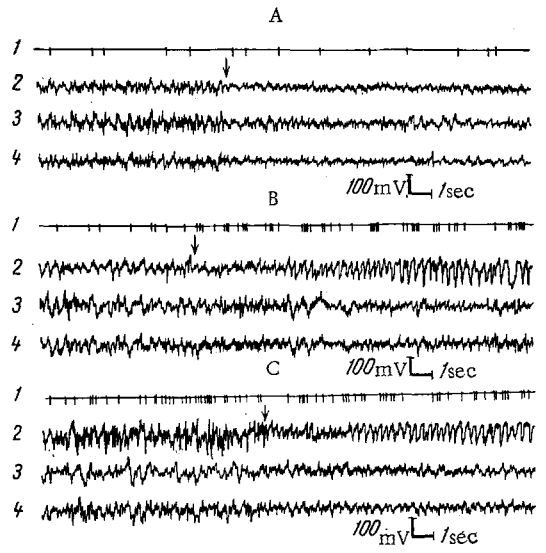


Fig. 1. Unit activity of hypothalamus (1), and integral electrical activity of hypothalamus (2), cortex (3), and thalamus (4) of intact, inexcitable rat (A) and various responses of two hypothalamic neurons of a Krushinskii-Molodkina rat (B, C) to acoustic stimulation (indicated by arrow).

Acoustic stimulation with an intensity of 105 dB was applied by means of a bell placed in the chamber. At the end of each experiment the localization of the electrodes was verified morphologically.

## EXPERIMENTAL RESULTS

The initial integral activity of the hypothalamus of the intact rats consisted of a polyrhythmic curve composed of $\beta$-, $\theta$-, and $\alpha$-waves. It corresponded to the firing rate of most of the 27 neurons constituting the control group, which did not exceed 1/sec. By the action of the bell, desynchronization was found in the electrohypothalamogram (EHG) of some animals (Fig. 1A), while in others there were no significant changes. Against the background of these two types of EHG response to acoustic stimulation, neurons which potentiated and others which weakened the activity were found. Most of the neurons (48%) belonged to the weakly reacting group (Table 1).

The integral EEG of the hypothalamus and also of the cortex, thalamus, and hippocampus of K-M rats in the original state was characterized by the periodic appearance of spindle-shaped groups of sharp waves (Fig. 2C), which in most cases arose synchronously. The isolated appearance of sharp waves of their complexes was recorded much less frequently in the hypothalamus. The response of these animals to the bell was expressed by an increase in the frequency and duration of the spindles and, in some cases, by the appearance of epileptic spike activity. In some animals well-marked and regular $\theta$-waves appeared (Fig. 1B, C). The original firing rate in the animals of this group varied from 0.3 to 3.5/sec. In response to acoustic stimulation the overwhelming majority of neurons increased their firing rate independently of the great variability of the EHG-response, which could take the form of desynchronization, the appearance of $\theta$-waves, of periodic sharp waves, or of high-amplitude spike potentials. The changes in unit activity in some cases preceded the EHG response while in others the changes appeared concurrently, especially in the presence of well-marked epiwaves (Fig. 2D) and, finally, the integral electrical activity could be reorganized without any response at the unit level (Fig. 1C). A sharp decrease in the number of weakly responding neurons (2 of the 40 neurons recorded in this group) by comparison with the first group will be noted.

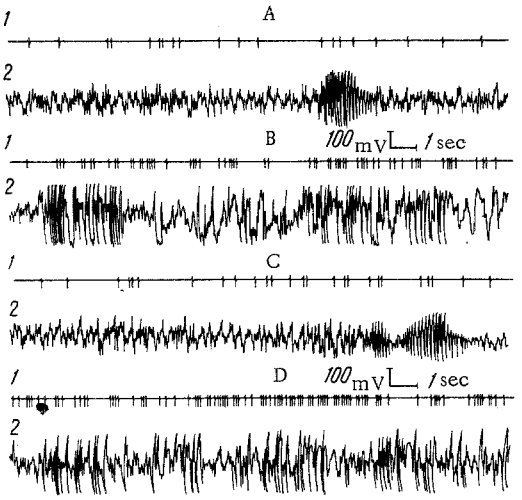


Fig. 2. Unit activity of hypothalamus (1) and integral electrohypothalamogram (2) of sensitized rat at rest (A) and during acoustic stimulation (B); D) neuron of Krushinskii-Molodkina rat at rest; C) the same neuron during acoustic stimulation.

After sensitization 10% of the hitherto inexcitable rats began to respond by convulsions assessed at 2-4 points on Krushinskii's 4-point scale [6] to acoustic stimulation. The character of the EHG of these animals corresponded exactly to the EHG of the K-M rats both in the initial state and during the action of the bell. Altogether 46 neurons, whose initial firing rate (Fig. 2A) was higher than that of the intact rats (Fig. 1A) but slightly lower than that of the genetically excitable rats (Fig. 2C), were tested in this group. The number of weakly responding neurons (13%) was much lower than in the intact rats.

In line K-M rats and in the sensitized animals the firing rate against the background of marked epileptic discharges reached 6-8/sec; the spikes were grouped into volleys (Fig. 2B, D).

Results showing the distribution of the neurons by their response to acoustic stimulation and depending on the level of tonic activity are given in Table 1.

Analysis of these results showed that a change in immunological reactivity organ-specific relative to the brain forms a state of predisposition to epilepsy in structures of the central nervous system and, in particular, in the medial hypothalamus which is comparable with that in rats genetically excitable by sound and characterized by an increase in excitability of the cells and in the degree of their response to acoustic stimulation.

These results indicate that the immunological factor may participate not only in the pathogenesis, but also in the etiology of epilepsy and also that active involvement of neurons of the medial hypothalamus in the process is closely connected with the appearance of the epileptic response.

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