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CHANGES IN PARAMETERS OF THE AFTER-DISCHARGE IN THE RAT SENSOMOTOR CORTEX AFTER CESSATION OF CONDITIONING REPETITIVE ELECTRICAL STIMULATION

G. N. Kryzhanovskii, V. K. Lutsenko, N. N. Khlebnikova, and M. Yu. Karganov

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It was shown previously that repetitive above-threshold electrical stimulation (ES) of the sensomotor cortex, in the form of successive series, induces the formation of generators of pathologically enhanced excitation (GPEE) [1]: primary – in the zone of ES, and secondary – dependent, determined by transcallosal synaptic stimulation – in the homotopic zone of the opposite hemisphere [2]. A characteristic feature of the manifestation of activity of a GPEE in the cerebral cortex, which is an epileptic focus, is the prolonged self-maintained poststimulus after-discharges (AD), consisting of spike-wave complexes, the number, amplitude, and frequency of which increased in the course of repetitive stimulation. These features point to structural transformations and to an increase in predisposition to seizures in the neuron population constituting the GPEE.

It was decided to study whether prolonged ES is necessary in order to preserve the acquired properties of the neuron population of GPEE described above or whether these properties can be continued even after cessation of ES. For this purpose parameters of AD arising in the course of consecutive series of repetitive electrical stimulations (RES), were compared on the 1st day and again 24 h after the last (20th) series of RES.

EXPERIMENTAL METHOD

The operative technique, the parameters of single and repetitive stimulation of the sensomotor cortex, and the arrangement of the electrodes and method of recording the electrocorticogram were all described previously [2]. Threshold values of stimulation to evoke direct (DR) and transcallosal (TCR) responses were determined 20-30 min before the first series of RES and 10 min after the end of AD arising immediately after the last (20th) series of RES. After the end of the experiment, on the 1st day the exposed areas of the sensomotor cortex were flooded with sterile physiological saline and covered with polyethylene film, which was secured to the cranial bones with phosphate cement. The film was removed after

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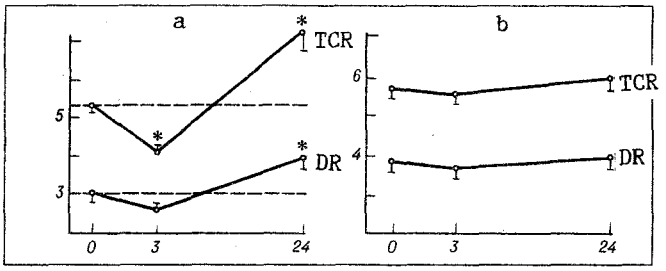

Fig. 1. Changes in threshold values of ES to evoke DR of right sensomotor cortex in zone of stimulation and of synaptically evoked TCR in left hemisphere. a) In group of rats subjected to 20 series of repeated RES (n = 35); b) in control group of animals (n = 23). Abscissa, time: 0) for first determination of thresholds of DR and TCR in all rats studied; 3) 3 h after immobilization of animals of control group in frame and 10 min after end of RES (3 h) in rats of experimental group; 24) repeated measurement of thresholds 24 h after previous determination; ordinate — intensity of stimulus (in V). Asterisk marks data for which $p < 0.05$.

24 h, the animal's head was securely fixed in a frame, and repeated tests were carried out under the same conditions as on the 1st day of the experiment: initially the threshold of evocation of DR and TCR were determined, after which changes in the amplitudes of DR and TCR and the parameters of AD were studied for five consecutive series of RES. The control group consisted of animals undergoing a similar operation and immobilized for 3 h (the time occupied by repeated RES in animals of the experimental group on the 1st day), but were not subjected to electrical stimulation. In the control rats 24 h after the operation and immobilization AD formation was studied in the course of 20 series of RES under the conditions described above, just as in the experimental animals on the 1st day of the investigation. The experimental results were subjected to statistical analysis by Student's t test and Fisher's F test.

EXPERIMENTAL RESULTS

The study of threshold values before and after application of 20 series of RES on the 1st day of the investigation revealed a significant decrease in strength of the threshold stimulus required to evoke TCR, whereas thresholds to evoke DR did not change significantly (Fig. 1a). On the 2nd day, 24 h after the end of the last series of RES the previous day, a significant increase was found in the threshold to evoke both DR and, in particular, TCR in animals of the experimental group (Fig. 1a). Conversely, in the control animals under analogous experimental conditions (excluding the procedure of application of RES) the thresholds to evoke DR and TCR remained unchanged (Fig. 1b). Comparison of the dynamics of AD formation in the course of 20 repeated RES in these animals with the data for the experimental group, which underwent RES on the 1st day, revealed no differences.

Comparison of the number of series of RES required to evoke the first AD, the amplitude of spike-wave complexes, and also the duration of AD on the 1st and 2nd days of stimulation revealed significant differences: on the 2nd day not four or five, but only one or two series of RES were needed to evoke the first AD; moreover, starting with the second series of RES, AD became longer in duration than the corresponding AD the previous day (Fig. 2a). Comparison of amplitudes of spike-wave complexes of AD, which accompanied RES with the same serial number, showed a considerable increase in the value of this parameter on the 2nd day of stimulation (Fig. 2b).

Since the last effect could be connected with the use of stronger stimulation because of an increase of the thresholds required to evoke DR and TCR on the 2nd day, in order to compare DR, TCR, and AD we distinguished a group of animals in which stimulation of equal strength was used on the 1st and 2nd days. Analysis of the change in amplitudes of DR and TCR in the course of a separate series of RES revealed no significant differences in the results of the 1st and 2nd days of tests. On the contrary, after 24 h the amplitude of the spike-wave complexes forming AR was increased by several times compared with the amplitude of the corresponding potentials evoked by series of RES with the same serial number on the 1st day (Fig. 2b).

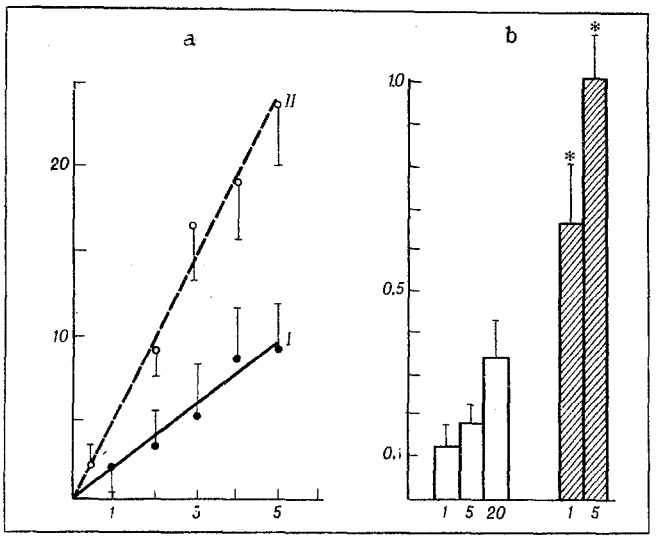

Fig. 2. Changes in duration of AD and amplitude of spike-wave complexes in the course of consecutive series of RES of rat sensomotor cortex. a) Dependence of duration of AD on number of series of RES for animals of the same group (n = 38) on 1st day of investigation (I) and on testing 24 h later (II). Differences significant, starting with second series of RES ($p < 0.01$, paired t test); b) change in mean amplitude of spike-wave complexes of AD depending on number of RES on 1st day (unshaded columns) and after 24 h (shaded columns). Abscissa, serial No. of series of RES (a) and number of RES (b); ordinate, duration of AD (in sec for a) and amplitude of AD measured from spike to spike of largest spike-wave complex (in mV for b). Asterisk marks data for which $p < 0.01$. Data given for AR recorded in left hemisphere. Changes in parameters of AD in right sensomotor cortex are similar in character.

The mean duration of AD 24 h after the fifth series of RES (24.5 ± 3.4 sec) was almost the same as after the 20th series of RES on the 1st day of the experiment (28.6 ± 5.6 sec). However, to understand changes in predisposition of the neuron population of GPEE to seizures, this fact alone is not sufficient. Analysis showed that the average numbers given above conceal the multidirectional changes in the duration of AD in animals within the experimental group. In rats with a long duration of AD, on the 2nd day shortening of AD took place (from 67.4 ± 9.0 to 18.5 ± 5.1 sec), whereas in animals with a short AD, it lengthened after 24 h (from 8.5 ± 2.6 to 1.5 ± 4.3 sec). As a result, with respect to the distribution of duration of AD the group became more homogeneous ($p < 0.05$ by Fisher's F test).

The data described above indicate that a long series of repeated RES, leading to the appearance of long poststimulus AD, evokes long-term (at least 1 day) plastic changes in the neuron population of GPEE, affecting both excitation and inhibition. Actually, the fact that to evoke the first AD next day required fewer series of RES than the previous day, and that a larger number of neurons was involved in the generation of AD (the amplitude of the spike-wave complexes was increased) indicates an increase in predisposition to seizures of the neuron population of GPEE involved, and an increase in power of the latter. On the other hand, elevation of the thresholds for evoking DR and TCR indicates strengthening of inhibition. These multidirectional changes in neuronal excitability and in excitation and inhibition of processes are also observed during kindling [4]. The study of kindling of neurons in the limbic system, for instance, showed that 20-24 h after routine stimulation, in order to evoke a focal excitatory postsynaptic potential (EPSP) stronger stimulation of the perforant path was needed, whereas the focal EPSP which appeared had an amplitude greater than the unpotentiated response of the granular neurons [3]. Since strong seizure discharges activate more powerful inhibition of AD [5], we can begin to understand data showing that long AD 24 h after the first series of RES become shorter, whereas short AD become longer in duration (Fig. 3).

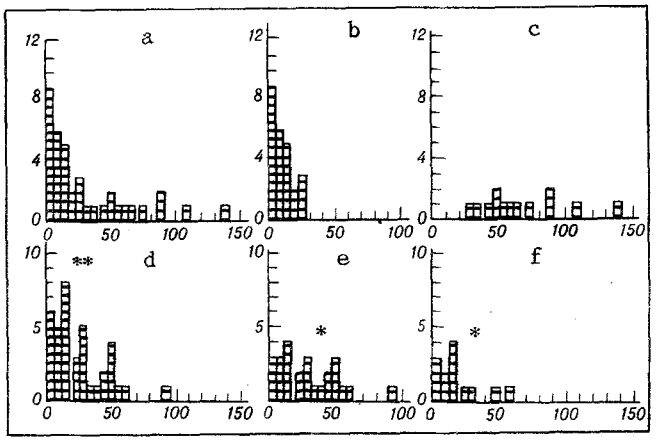

Fig. 3. Histograms of distribution of maximal durations of AD on 1st day after 20th series of RES (a, b, and c) and 24 h after fifth testing series of RES (d, e, and f). a, d) In all groups tested (n = 38); b, e) in subgroup of animals with short (under 10 sec) AD on 1st day (n = 13); c, f) in subgroup of rats with long (over 30 sec) AD on 1st day of RES (n = 25). Abscissa, duration of AD (in sec); ordinate, number of animals with that particular duration of AD. Asterisk indicates significant ($p < 0.01$) increase (e compared with b) and decrease (f compared with c) of duration of poststimulus AD 24 h after first session of repeated RES; two asterisks indicate decrease ($p < 0.01$) in total sample (d compared with a).

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