SPONTANEOUS INTERICTAL SPIKES IN RABBITS DURING KINDLING STIMULATION OF THE HIPPOCAMPUS

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UDC 616.831.31-02:615.844]-092.9

KEY WORDS: spontaneous interictal spike; kindling; hippocampus; cerebral cortex

The specific character of bioelectrical manifestations of seizure activity enables it to be used to study the character of involvement of efferent connections of brain structures to which the epileptogenic action is directed in the pathological process. A spontaneous interictal spike (SIS) is one of the clearest manifestations of pathological hyperactivity of neurons that is responsible for the existence of epileptic foci in the brain.

The object of this investigation was to describe the character of spread of SIS in the rabbit CNS during formation of the kindling syndrome [6], and to study their relations with the seizure preparedness of the animals.

EXPERIMENTAL METHOD

Experiments were carried out on five adult chinchilla rabbits. Nichrome wire electrodes 100 μ in diameter were implanted into the amygdaloid nuclei, posterior hypothalamic nuclei, sensorimotor and occipital regions of the cerebral cortex, and bilaterally into the dorsal hippocampus. The reference electrode was fixed in the nasal bone.

The rabbits took part in the experiment two weeks after implantation. In four animals bipolar, and in one animal monopolar electrical stimulation (ES) of the hippocampus was applied in the classical manner: a stimulus 12 sec in duration, consisting of square pulses (0.5 msec, 60 Hz), every 24 h. The strength of the stimulating current was chosen individually for each animal depending on its ability to evoke a short (2-5 sec) after-discharge (AD) in the brain structures or a short motor response; it varied from 70 to 250 μA. Throughout the experiment, except for individual cases, the strength of the stimulating current was kept constant. The EEG was recorded for 7 min before ES and 10-15 min after ES in the rabbits which were lightly secured to an ordinary wooden frame. The animals' respiration and, in some cases, the myogram were recorded simultaneously. The location of the electrode tips was verified histologically (rapid photographic method) in all animals. SIS was defined as a hypersynchronized paroxysmal oscillation of spike-wave type. The period of the wave was under 80 msec, and its height was 4 or more times greater than its base.

EXPERIMENTAL RESULTS

SIS appeared (Fig. 1) only in those animals in which a bursting type of AD developed in response to ES of the dorsal hippocampus. Of the 14 rabbits tested, only 5 were of this kind.

In the initial period, i.e., after 5 or 6 stimulations, SIS appeared in the stimulated region. During this period the spikes were single. SIS appeared in response to the 6th or 7th stimulation in the contralateral hippocampus, but on the 7th-9th days they were recorded not only after ES, but also before it. During this period the spikes became more numerous (10-15 spikes in the hippocampus during a 5-min time interval) and they spread to the other test structures in both hemispheres (amygdala, hypothalamus, cerebral cortex). The largest number of spikes was observed in the dorsal hippocampus, and in other structures SIS were less numerous, and as a rule they were synchronous with the hippocampal SIS. By the 20th-25th ES the average number of SIS in the hippocampus was 40-50, counted in a period of 5min (Fig. 2).

The increase in the number of SIS in the brain structures and their generalization were accompanied by an increase in seizure preparedness of the animals. Immediately after ES the

Moscow. (Presented by Academician of the Academy of Medical Sciences of the USSR P. D. Gorizontov.) Translated from Byulleten' Éksperimental'noi Biologii i Meditsiny, Vol. 96, No. 10, pp. 5-8, October, 1983. Original article submitted October 11, 1982.

0007-4888/83/9610-1345$07.50

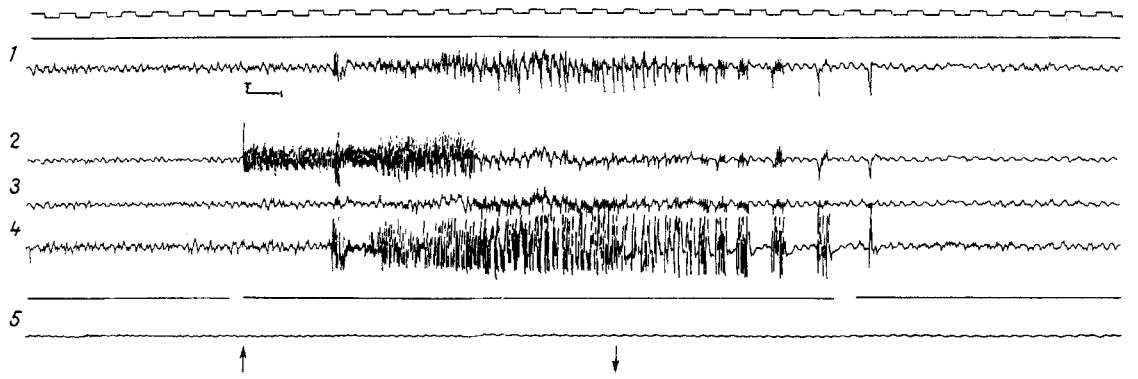

Fig. 1. EEG of rabbit during and immediately after ES of left hippocampus (bursting type of AD). Here and in Figs. 2 and 3: 1) sensorimotor cortex, 2) occipital cortex, 3) amygdala, 4) right hippocampus, 5) respiration. Arrows point to start and finish of ES, 12.5 mV, 1 sec.

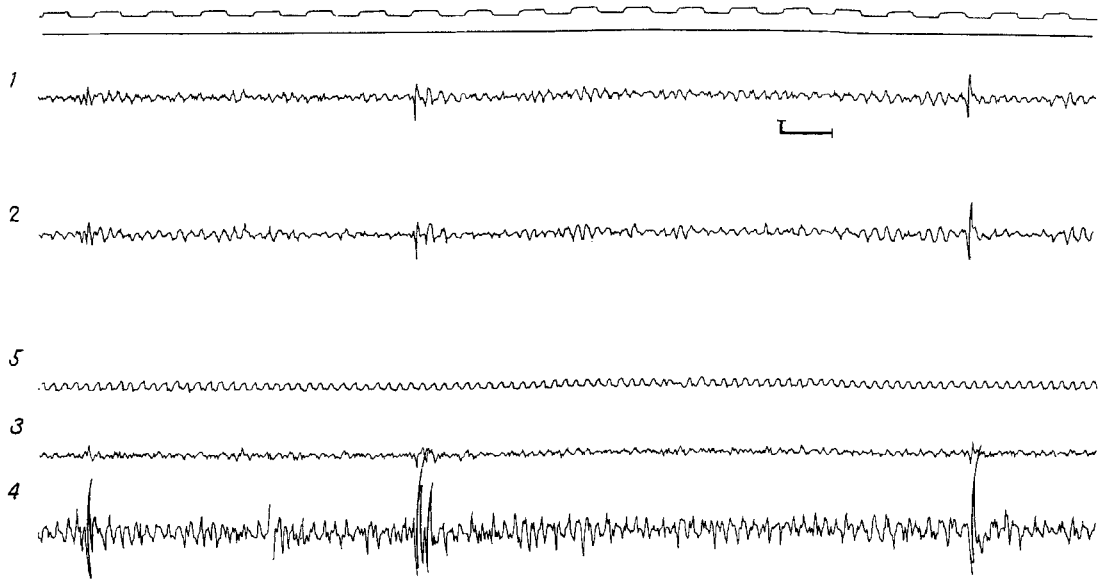

Fig. 2. EEG of rabbit No. 2 after 18 ES.

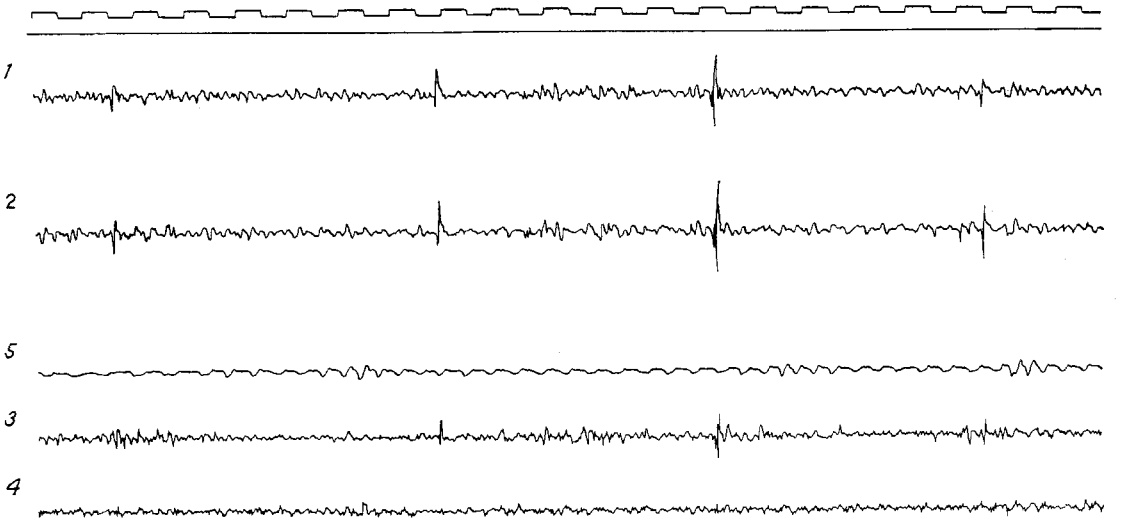

Fig. 3. EEG of rabbit No. 2 after 22 ES.

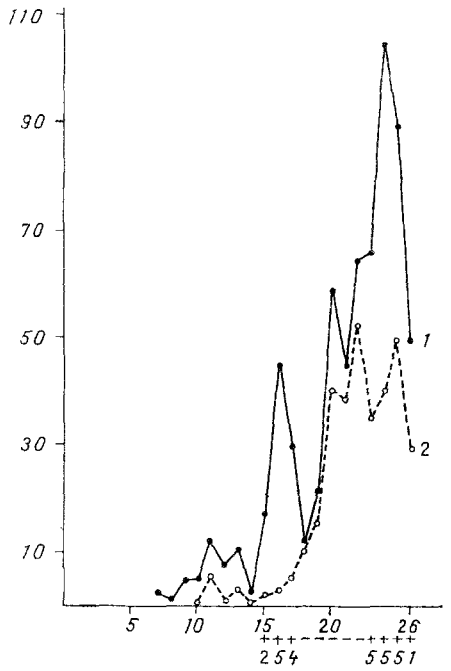

Fig. 4. Dependence of motor fit in rabbit no. 4 on ratio between numbers of SIS in hippocampus (1) and neocortex (2). Abscissa, number of ES; ordinate, number of SIS. + and —) presence or absence of motor fit, respectively. Numbers below symbols indicate stages of motor fit.

SIS disappeared and reappeared only after 100-300 sec. The earlier appearance of SIS inhibited the development of convulsions. Disappearance of the SIS immediately after ES evidently pointed to an emergency change in the conditions of brain function [1, 2], and a disturbance of its new steady state established at that moment of time. Discontinuation of ES in the 2nd-3rd week, when the kindling syndrome had been formed, did not lead to disappearance of the SIS but was accompanied only by some reduction (on average by 30%) of their number. This indicates that in response to hippocampal stimulation long-term generators of pathological excitation were formed in the central structures [3, 4]. By contrast with these observations, it has been shown [5] that during kindling stimulation of the rat amygdala such hyperactive foci are not formed: The SIS disappeared very quickly after the end of stimulation. As was pointed out above, in the present experiments SIS appeared not only in the deep brain structures but also in the cortex. Independent, isolated cortical SIS, not synchronized with hippocampal, were often found under these circumstances. During stimulation of the rat amygdala, on the other hand, the appearance of SIS in the neocortex was not observed [5]; the authors cited emphasize that SIS spread mainly in the deep brain structures.

Furthermore, analysis of the results of the present experiments showed that development of the kindling syndrome depended on the ratio between the numbers of SIS in the neocortex and hippocampus and the degree of their synchronization. For instance, in four rabbits during ES the number of SIS in the hippocampus and cortex increased equally (although their absolute number was always greater in the hippocampus); cortical SIS were always synchronized with hippocampal. In these animals buildup symptoms progressed rapidly until complete development of the kindling syndrome. In two other rabbits, at individual periods of time, independent spikes not synchronized with hippocampal spikes developed in the cerebral cortex, but their total number either exceeded that in the hippocampus or came close to it. At these times the epileptogenic manifestations in the rabbits were sharply reduced or disappeared. For instance, in one rabbit, against the background of a sufficiently well developed state of seizure preparedness, the number of SIS in the hippocampus fell sharply (Fig. 3), whereas in the cerebral cortex they were numerous. Simultaneously with this, the animal's epileptic fits induced previously by ES ceased. It must be pointed out that during this period cortical seizure discharges, but not hippocampal, appeared on the rabbit's EEG. To evoke fits in this case the strength of the stimulating current had to be more than doubled, and this was accompanied by an increase in the number of SIS in the hippocampus and by restoration of the kind-

ling syndrome. In the other rabbits, the most marked state of seizure preparedness was at times of maximal excess of the number of SIS in the hippocampus over their number in the cortex. With a decrease in this gap the fits became shorter in duration, with no more than one or two stages [7], or they ceased completely (Fig. 4). The number and duration of the seizure discharges also diminished or they disappeared. In this case also, to restore the kindling syndrome it was necessary to increase the strength of the stimulating current, and this led to an increase in the number of SIS in the hippocampus and to synchronization of cortical spikes with them.

The results thus provide conclusive evidence that an independent and powerful focus of hyperactivity can be formed in response to kindling stimulation of the rabbit hippocampus, not only in the zone of stimulation and in other deep brain formations, but in the cerebral cortex also. If the secondary cortical focus of hyperactivity remains dependent on the primary hippocampal focus and "obeys" it, development of the kindling syndrome is undisturbed. If, however, such a focus acquires the properties of an autonomous focus, independent of the hippocampal focus, it may depress activity of the primary focus and inhibit the formation of the kindling syndrome. Data on the development of intracentral and central-peripheral relations obtained in the course of kindling stimulation will enable the neurophysiological responses under the influence of ionizing radiation on the CNS to be studied more deeply in future research.

LITERATURE CITED

1. N. P. Bekhtereva, D. K. Kambarova, and V. K. Pozdeev, The Steady Pathological State in Brain Diseases [in Russian], Leningrad (1978).
2. N. P. Bekhtereva and V. M. Smirnov, Vestn. Akad. Med. Nauk SSSR, No. 8, 8 (1975).
3. G. N. Kryzhanovskii, Zh. Nevropatol. Psikhiat., No. 11, 1730 (1976).
4. G. N. Kryzhanovskii, Determinant Structures in the Pathology of the Nervous System [in Russian], Moscow (1980).
5. J. C. Fitz and J. O. McNamara, Electroencephalogr. Clin. Neurophysiol., 47, 592 (1979).
6. G. V. Goddard and C. K. Zeech, Exp. Neurol., 25, 295 (1969).
7. R. J. Racine, Electroencephalogr. Clin. Neurophysiol., 32, 269 (1972).

ROLE OF MONOAMINE SYSTEMS IN MECHANISMS OF REGULATION OF ANALGESIA IN SOME TYPES OF REFLEX STIMULATION

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UDC 612.884-06:612.822.1.018:577.175.82

KEY WORDS: monoamines; analgesia; stress; auricular electroacupuncture.

Investigations of analgesia during the action of opiates [2-7, 9, 10, 12, 13] or electrical stimulation of different regions of the brain [2, 5, 8] have demonstrated the important role of monoamine systems. Depression of synthesis of noradrenalin (NA), dopamine, or serotonin (5-HT) by means of various pharmacologic inhibitors modifies sensitivity to pain under these influences, and restoration of the amine level by administration of their precursors causes recovery of the analgesic effect.

It can be postulated that monoamine systems also play an important role in the regulation of pain during the action of auricular electroacupuncture (AEA) or stress. It was accordingly decided to carry out a series of experiments to study the role of monoaminergic systems in the mechanisms of regulation of pain sensitivity during the action of these stimuli.

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(Presented by Academician of the Academy of Medical Sciences of the USSR, A. V. Val'dman.) Translated from Byulleten' Éksperimental Biologii i Meditsiny, Vol. 96, No. 10, pp. 9-12, October, 1983. Original article submitted January 31, 1983.

0007-4888/83/9610-1348$07.50