LIMBIC KINDLING WITH SHORTENED INTERSTIMULUS INTERVAL

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KEY WORDS: kindling; postictal inhibition; short interval.

Kindling is of particular interest as a way of inducing a state of long-lasting high predisposition to convulsions. The classical work of Goddard and co-workers [2, 3] showed that the optimal interval between weak electrical stimulations (ES) of brain structures to induce an increase in predisposition to convulsions is 24-48 h. However, it was later shown that a similar effect can be achieved by ES with shorter or longer intervals between them [4, 6].

The aim of this investigation was to study the possibility of creating a state of increased predisposition to convulsions by ES, the interval between which was shortened to 5 min, and to examine the particular features of development preservation of that state.

EXPERIMENTAL METHOD

Experiments were carried out on 14 adult waking rabbits weighing 2.5-3 kg with electrodes implanted chronically into the brain. The electrodes were located in the sensomotor and occipital regions of the cerebral cortex, bilaterally into the dorsal hippocampus, and into the amygdala and rostral parts of the caudate nuclei. The animals were used in the experiment 2 weeks after the operation. ES were applied to the hippocampus of 11 rabbits and to the amygdala of three. The strength of the stimulating current and the duration of ES were chosen for each animal so that stimulation induced a short after-discharge. The strength of the current varied in different animals from 80 to 500 μA and the duration of the session of ES from 0.5 to 2 sec (60 Hz, square pulses, 1 msec). These sessions of ES were given every 5 min for a period of 2-5 h, to animals lightly secured in a wooden frame. Throughout the experiment the EEG and the character of the motor responses were recorded. A discharge arising not later than 1 min after the end of ES, or a spontaneous discharge arising at later stages, was regarded as an after discharge. The severity of the motor seizure response was estimated in points on the following scale: 1) movement of the facial muscles, 2) turning of the head, 3) turning of the trunk, clonus of the forelimbs, 4) jerks, 5) generalized clonic convulsions, 6) generalized clonicotonic convulsions. The location of the electrodes in the brain structures was verified histologically.

EXPERIMENTAL RESULTS

ES of the limbic structures (amygdala or hippocampus) caused the development of a convulsive kindling syndrome in 10 of the 14 animals: in all three rabbits with ES of the amygdala and in seven with ES of the hippocampus. Formation of the syndrome was manifested as an increase in duration (up to 100 sec or more) of the after discharge, the appearance of spontaneous discharges, and an increase in the duration (up to 50 sec or more) and severity (up to 5-6 points) of the motor seizure responses, and also weakening, slowing, and shortening or even complete disappearance of the periods [5, 7, 8] with which ES did not induce an epileptic response or induced only a weak response (Figs. 1 and 2). This last effect was one of the main distinguishing features of the rapid development of the kindling syndrome. After the first distinct after-discharge, lasting more than 30 sec, and after the first generalized seizures, lasting more than 10 sec, the refractory phase was longest and varied in different animals between 85 and 10 min for the after discharge and between 125 and 25 min for seizures. With lengthening of ES, the periods of inhibition were shortened to 10-5 min, and became weaker. Later short periods of postictal inhibition developed less frequently not after every generalized epileptic fit, but after several (2-5 or more) of the generalized seizures next in turn. Each

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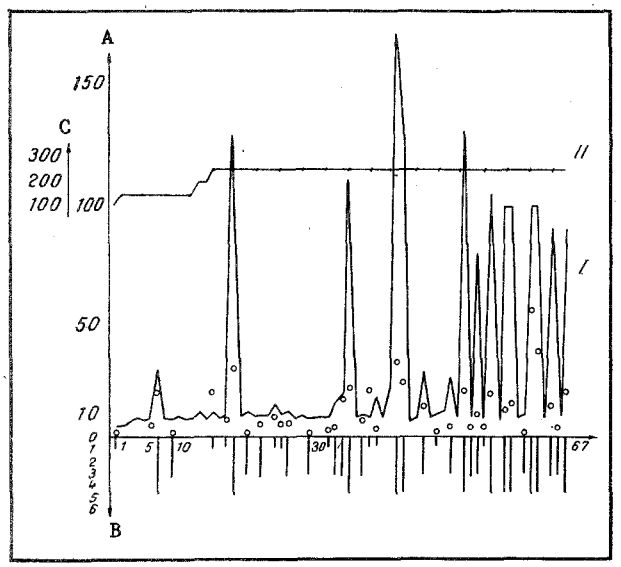

Fig. 1

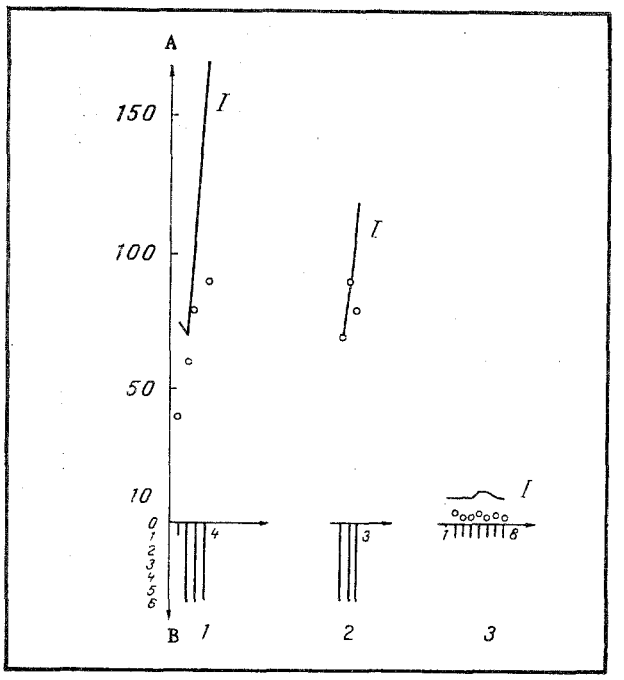

Fig. 2

Fig. 1. Example of rapid development of convulsive kindling syndrome in a rabbit during electrical stimulation of right hippocampus. Abscissa, number of ES. Ordinate: A) time (in sec); B) severity of seizures (in points); C) strength of stimulating current (in μA). I) After discharge, II) strength of stimulating current; circles indicate motor seizures, in seconds; vertical straight lines show motor seizures in points.

Fig. 2. Epileptic syndrome in same animal after cessation of ES. 1) 16 days after end of ES; 2) after 17 days of stimulus-free period; 3) after 23 days of stimulus-free period. Remainder of legend as to Fig. 1.

subsequent seizure response arising immediately after postictal inhibition was either weaker than the predecessor, or unchanged, or stronger. All three types of responses could be observed in the same animal. Considerable strengthening of the seizure responses after postictal inhibition was commonest.

During the formation of the kindling syndrome in the animals, the threshold of ES inducing generalized seizures fell. Two periods can be distinguished in the formation of this syndrome: the 1st – a period of unstable generalized seizure with long and marked postictal inhibitions, and the 2nd – a period of stable, severe epileptic seizures with deep inhibition of the refractory period. In the 2nd period the seizures were distinguished by their greater severity and longer duration.

The state of high predisposition to seizures formed in this manner lasted a long time. It was observed 1 week after the end of ES, without any sign of weakening in eight of the nine rabbits, after 3 weeks in five of five, after 4 weeks in four of six, and after 7 weeks in one of four rabbits. In two animals, epileptic responses were actually much stronger after 2-4 weeks (Fig. 2), whereas in three animals, predisposition to convulsions was even lower after 1.5 months than before the beginning of ES. Our observations showed that predisposition to convulsions formed by the method indicated may subsequently become intensified or inhibited without any additional external procedures in the same animal.

The rate of development of the kindling syndrome described above and its character did not depend essentially on which structure – hippocampus or amygdala, was subjected to ES. However, epileptic activity was greatest in the hippocampus whatever zone was stimulated. This is in agreement with data on the leading role of the hippocampus in the development of the epileptic syndrome during kindling induced by systemic administration of subconvulsive doses of metrazol [1].

The strength of the stimulating current applied to these animals varied from 150 to 500 μA ($M \pm m = 267 \pm 92$ μA), and the duration of ES was 2 sec. The tip of the stimulating

electrode in these animals was located either in area CA1 of the dorsal hippocampus or in the amygdala (area anterior).

In four rabbits which did not develop the syndrome of increased predisposition to seizures, the stimulating electrode likewise was located in area CA1 of the dorsal hippocampus. The strength of the stimulating current applied to these animals was small (80 μA) and the duration of ES was only 0.5 sec. Despite the fact that stimulation of this kind was sufficient to induce a short after-discharge, it did not induce progressive predisposition to seizures. The parameters of ES must evidently have an important role in the development of this syndrome. As the investigation showed, ES applied to the limbic structures (amygdala or hippocampus) by a current of moderate strength (about 267 μA), repeated regularly for 2 sec every 5 min, induce the development of a stable and severe epileptic syndrome in the course of 2-4 h in conscious rabbits, an important feature of which is the long-term suppression of postictal inhibition.

LITERATURE CITED

1. G. N. Kryzhanovskii, A. A. Shandra, R. F. Makul'kin, and L. S. Godlevskii, Byull. Eksp. Biol. Med., No. 5, 527 (1985).
2. G. V. Goddard, D. C. McIntyre, and G. K. Leech, Exp,. Neurol., 25, 295 (1969).
3. G. V. Goddard, The Kindling Model of Limbic Epilepsy, Sydney (1980), pp. 107-116.
4. J. G. Fitz and J. O. McNamara, Electroenceph. Clin. Neurophysiol., 47, 592 (1979).
5. Mitsumoto Sato and Takashi Moriwake, Epilepsia, 25, 545 (1984).
6. S. Puckprink and A. Stuart, Epilepsia, 25, 471 (1972).
7. T. Ulrich, A. Paananen, and J. Tuomisto, Eur. J. Pharmacol., 85 (1974).
8. G. Stock, L. Klimpel, V. Sturm, and K. H. Schlor, Exp. Neurol., 69, 239 (1980).

STRUCTURAL SPECIFICITY OF FACTORS INVOLVED IN CHEMICAL REGULATION OF MUSCLE TONE AT THE SPINAL LEVEL

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Oligopeptide factors found in the CNS, known as postural asymmetry factors (PAF), have a selective activating action on flexor motor centers in the lumbar enlargement of spinalized recipients, located to the right or left of the median sagittal plane [2-4, 7, 10]. The presence of focal lesions of the CNS, the specific features of the action of PAF on either side are determined by anatomical connections of the damaged structure with the segmental apparatus. For instance, trauma to structures with direct (uncrossed) connections with the spinal cord is accompanied by activation of PAF, inducing increased muscle tone in the ipsilateral limb relative to the focus of injury [3, 10]. Conversely, destruction of the higher motor centers, whose spinal projections are crossed, leads to activation of PAF inducing an increase in flexor tone on the contralateral side [2, 7]. This is evidence of differences in the chemical regulation of the symmetrically opposite lumbar centers for the right and left limbs in unilateral brain injury. At the same time, it is well known that in certain local lesions of the human brain, motor disturbances are formed and are accompanied by increased muscle tone only in one of the four limbs [11], reflecting the somatotrophic organization of higher motor centers.

These clinical data and also the experimental results described above suggested the existence of specific chemical regulation of muscle tone of each of the four limbs. The dis-

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