ROLE OF THE HIPPOCAMPUS IN DEVELOPMENT OF THE SEIZURE SYNDROME INDUCED BY KINDLING STIMULATION OF THE CAUDATE NUCLEUS

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KEY WORDS: kindling; hippocampus; caudate nucleus; determinant.

A kindling syndrome is readily formed in animals by electrical stimulation of limbic structures [5-7]. Such a syndrome develops much less successfully as a result of analogous stimulation of the sensomotor pathways, cerebral cortex, and corpus striatum [3, 4, 6, 7]. The hippocampus is known to have the highest degree of predisposition to paroxysmal discharges [2].

The aim of this investigation was to study ways of induction of epileptiform activity in the brain by electrical stimulation (ES) of the caudate nucleus and the degree of involvement of limbic formations and, in particular, the hippocampus and amygdala, in the development of the seizure syndrome.

EXPERIMENTAL METHOD

Experiments were carried out on 12 chinchilla rabbits weighing 2.5-3 kg. Electrodes (nichrome wire 100 μ in diameter) were implanted into the sensomotor and occipital areas of the cerebral cortex, the dorsal regions of the hippocampus bilaterally, the amygdaloid nuclei, and the rostral parts of the caudate nuclei 2 weeks before the beginning of the experiments. The caudate nucleus was stimulated with bipolar square pulses (1 msec) with a frequency of 60 Hz for 12 sec at intervals of 24-48 h. The strength of the stimulating current was chosen individually for each animal: stimulation evoked short (for a few seconds), but distinct changes in the initial EEG. The strength of the current varied from 100 to 350 μA. The EEG and seizure motor responses were recorded in the animals daily for 10 min before and 10 min after ES. The severity of the seizures was determined on a point scale: 1) movement of the facial muscles (sniffing, chewing, and so on), 2) nodding movements, 3) rotation of the trunk to the right or left, thrusting forward of the head, 4) jerking, 5) generalized clonic convulsions, 6) generalized clonicotonic convulsions. The EEG was processed manually. The arrangement of the electrodes in the brain structures was verified histologically.

EXPERIMENTAL RESULTS

Repeated ES of the caudate nucleus induced seizure responses of varied severity in the animals. In six animals, during the time of study (25 ES) stable generalized seizures (5-6 points) were formed, whereas responses of the remaining rabbits to ES developed irregularly and were limited to a set of seizure movements, rated at 1-3 points.

The principal epileptic changes in the EEG were an after-discharge (developing not later than 60 sec after ES), a spontaneous epileptic discharge (developing later), and spikes (paroxysmal high-amplitude hypersynchronized waves with a duration of under 40 msec). Three types of spikes were distinguished: 1) "local," recorded only in one structure, 2) "paired," recorded in two structures at the same time, and 3) "generalized," recorded in three or more structures simultaneously.

A characteristic feature of animals with severe seizures was the development of powerful stable epileptic activity in the hippocampus, both immediately after ES and in the late stages (Fig. 1). The caudate nuclei were much less involved in this process, and the amygdala less still. In the latter structures spontaneous discharges were rare and, if they developed, as a rule they were synchronous with hippocampal discharges. Epileptic discharges began in the hippocampus on both sides and spread later to other formations, indicating that the development of epileptogenic responses in other structures is dependent on hippocampal pathological activity. Spike activity was found only in one animal with a severe

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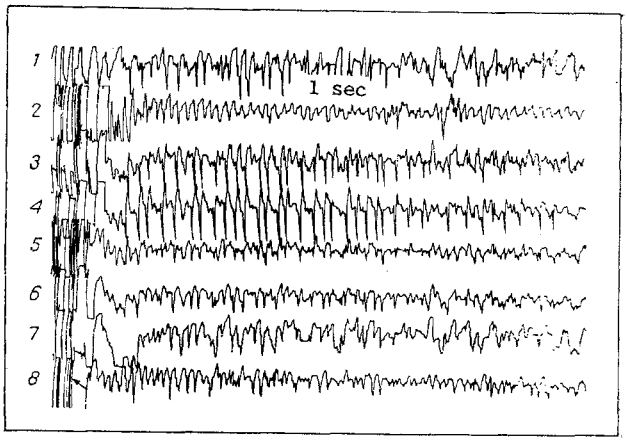

Fig. 1. Spontaneous epileptic discharge in a rabbit in response to ES of left caudate nucleus. 1) Sensomotor cortex; 2) occipital cortex; 3) right hippocampus; 4) left hippocampus; 5) right caudate nucleus; 6) left caudate nucleus; 7) right amygdala; 8) left amygdala.

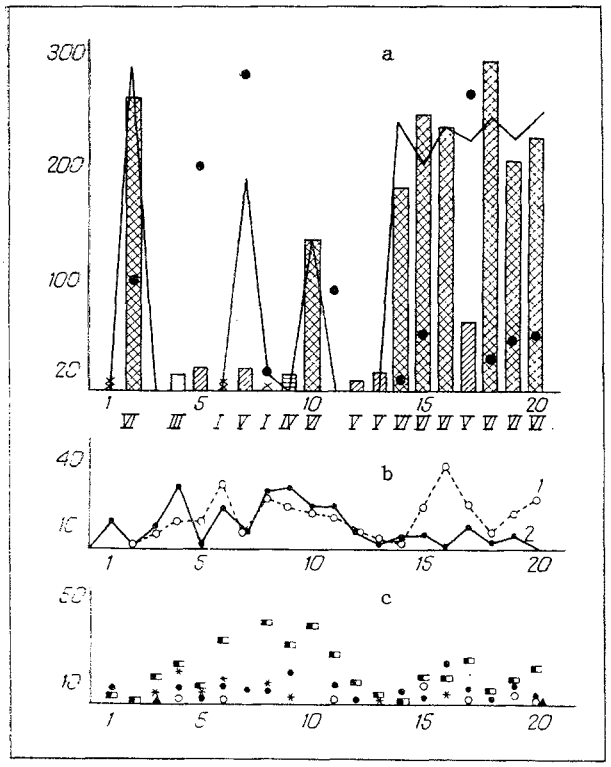

Fig. 2. Example of rapid development of seizure syndrome in rabbit in response to ES of left caudate nucleus. a: Abscissa, number of ES, ordinate, time (in sec); Roman numerals denote severity of seizures (in points), continuous line — duration of after-discharge (in sec); filled circles — duration of spontaneous discharge (in sec); 1 cross) seizures rated at 1 point, 2 crosses — 2 points; unshaded column — 3 points; column with horizontal shading — 4 points, oblique shading — 5 points, cross-hatching 6 points. b: abscissa, number of ES; ordinate, number of spikes in 10 min, 1) before ES, 2) after ES; c: abscissa, number of ES; ordinate, number of spikes in 10 min; black and white rectangles denote generalized spikes with maximal amplitude in both hippocampi; filled circles — local left hippocampal spikes; empty circles — local right hippocampal spikes; asterisks — paired hippocampal spikes.

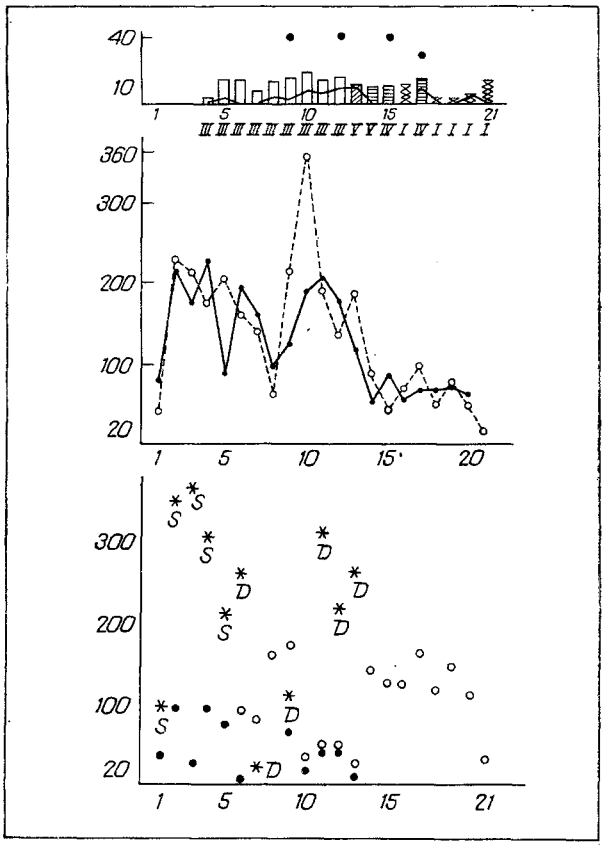

Fig. 3. Example of development of weak seizure syndrome in rabbit in response to ES of left caudate nucleus. Legend as to Figs. 1 and 2.

seizure syndrome (Fig. 2). In this case the amplitude and number of the spikes were constantly greater in the hippocampus than in other structures. A strictly definite set of structures with maximal amplitude in the hippocampus was involved in the "generalized" spike. All these data suggest that a pathological determinant, producing generalized epileptogenesis, was formed in the hippocampus structures of these animals. The experimental results also show that the more stable and powerful the epileptic activity in the hippocampus, the faster the seizure syntdrome develops and the severer its manifestations.

In animals with weak seizure responses epileptic changes in the hippocampus on both sides were weak and unstable. Spontaneous epileptic activity was frequently observed in these rabbits in the caudate nuclei. Powerful spike activity also was found in one animal (Fig. 3). However, unlike the animal with severe seizures, the appearance of spikes in the right hippocampus of this rabbit was accompanied by a decrease in the amplitude and number of spikes in the left hippocampus, or even their complete disappearance. This was accompanied by weakening of all other epileptic symptoms and, in particular, of motor seizure responses. The dynamics of spike activity and of the seizure syndrome on the whole indicates that antagonistic inhibitory influences between the right and left hippocampal epileptic foci were present in this animal. Consequently, for a stable pathological determinant to develop in the hippocampus it is not enough for powerful hyperactive foci to appear in them. It is essential that excitation in the structures did not have an inhibitory effect of one on the other.

Since the stimulating electrode was located in the same zone of the caudate nucleus in all the animals the unequal development of the kindling syndrome in them was evidently due to individual differences, determining the possibility of formation of a pathological determinant in the hippocampus.

The seizure syndrome during electrical stimulation of the caudate nucleus can thus be successfully formed if a stable and powerful determinant, organizing epileptogenesis, develops in the hippocampal region on one or both sides.

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EFFECT OF DELTA-SLEEP PEPTIDE ON INTERCENTRAL INTEGRATION IN EXPERIMENTAL EPILEPSY

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Peptides, among them delta-sleep peptide (DSP), possess a broad spectrum of action [11]. The therapeutic effect of DSP has been proved, especially under conditions of stress and in neuroses [3, 7], and this correlates with its ability to modify the convergent properties of brain structures [2] and mediator metabolism [2, 7], and to exert a modulating effect on pineal α_1-adrenergic receptors and on their responses to adrenergic agonists [8, 9]. The effect of DSP on epileptiform activity in the sensomotor cortex, induced by application of strychine and penicillin, has been demonstrated [5]. Meanwhile in epilepsy, the effect of DSP on processes developing in deep brain formations has not been explained, and the investigation described below was undertaken for this purpose.

EXPERIMENTAL METHOD

Experiments were carried out on cats with electrodes implanted into various brain formations: the auditory, visual, and motor areas of the cortex, caudate nucleus, centrum medianum of the thalamus, and the hippocampus of both hemispheres. The animals received an intramuscular injection of crystalline benzylpenicillin (Yugoslavia) in a dose of 400,000 U/kg, which induced epileptiform cyclic discharges, recorded simultaneously in all the brain structures tested, as well as myoclonic contractions of the muscles. Either before the appearance of epileptiform activity or when fully developed, these animals were given an intraperitoneal injection of DSP in doses of 25, 50, 75, and 100 μg/kg. The first three doses of DSP were given with intervals of 1-1.5 h between them, and with continuous monitoring of the EEG and evoked potentials (EP) of each brain structure. The largest dose of DSP was injected 2 days after injection of the smaller doses.

The recording electrodes were connected to a biopotentials amplifier ("Riz," Yugoslavia) with time constant of 0.05 sec and upper limit of the transmission band of 150 Hz. Evoked potentials (EP) were led from the output of the biopotentials amplifier to an analog-to-digital converter (ADC) of a type PDP P/40 computer, where they were averaged and the standard deviations were calculated in real time. The sampling interval was 2 msec and the epoch of analysis 200 msec. The results were displayed as print-outs of characteristics of EP in terms of assigned time limits (peak amplitudes, times until peaks), and also on a "Hewlett-Packard" graph plotter.

Evoked potentials were averaged to five flashes applied with time intervals varying from 2 to 3.5 sec. In this way the characteristics of EP were established for each brain structure before and during the action of penicillin, and again at different times after injection of DSP.

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