TWO TYPES OF CHRONIC EPILEPTOGENESIS IN RABBITS DURING KINDLING STIMULATION OF THE HIPPOCAMPUS

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KEY WORDS: kindling, electrical stimulation; hippocampus; epileptiform activity.

Kindling electrical stimulation (ES) of the hippocampus is accompanied by the formation of two types of after-discharges (AD) in different rabbits and, correspondingly, by two types of epileptic states. In animals of one group, in the period between attacks marked generalized epileptiform changes were observed on the EEG although the motor fit, induced by ES, was short and was accompanied by chronic convulsions. Meanwhile in animals of the other group the motor fit was longer (prolonged tonic and clonicotonic convulsions), despite the fact that their EEG was almost normal in the period between attacks.

The kindling syndrome [4] is a convenient model with which to study the plastic properties of the brain, its compensatory powers, and central—peripheral relations. However, dependence of the clinical manifestations of chronic epileptogenesis on the degree of central disturbances has not been adequately studied.

The object of this investigation was to study the character of the relationship between central and peripheral manifestations of predisposition to convulsions in rabbits during kindling stimulation of the hippocampus.

EXPERIMENTAL METHOD

Experiments were carried out on 14 adult Chinchilla rabbits. A stimulating electrode was inserted into the dorsal region of the hippocampus on right or left sides. Recording electrodes were located in both gyri of the hippocampus, in the amygdaloid nuclei, posterior hypothalamic nuclei, and sensomotor and occipital areas of the cortex ipsilaterally or contralaterally to the side of stimulation. Electrodes were made from nichrome wire 100 μ in diameter. The reference electrode was fixed in the nasal bone. The animals were used in the experiments 2 weeks after the operation. Bipolar ES of the hippocampus was carried out on eight animals, monopolar on six, by the following program: Every 24 h a burst of square pulses (0.5 msec, 50 Hz), 12 sec in duration, was applied. The strength of the stimulating current was chosen for each animal individually by its ability to evoke short (2-5 sec) AD in brain structures or a short motor response. This strength varied from 70 to 250 μA for different animals. The EEG was recorded on an encephalograph (Nihon Kohden, Japan) for 7 min before and 10-15 min after ES. Respiratory movements and the myogram were recorded at the same time. The location of the electrode tip in the brain was determined histologically (by a rapid photographic method, staining by Nissl's method).

EXPERIMENTAL RESULTS

Kindling stimulation of the dorsal hippocampus was accompanied by the formation of two types of AD in different rabbits and, correspondingly, of two forms of epileptogenic states. One type of AD was called bursting, the other type hypersynchronous. Bursting AD were characterized by the appearance of a short period of desynchronization (2-3 sec) on the EEG followed by high-amplitude and high-frequency oscillations, periodically alternating with slow waves (2-6 Hz) and changing into bursts of high-frequency discharges (Fig. 1). After the bursts, as a rule, a period of desynchronization was again observed, varying in duration in different animals and at different times of stimulation from 50 to 300 sec. The bursting discharge occurred as early as 1-3 sec after stimulation.

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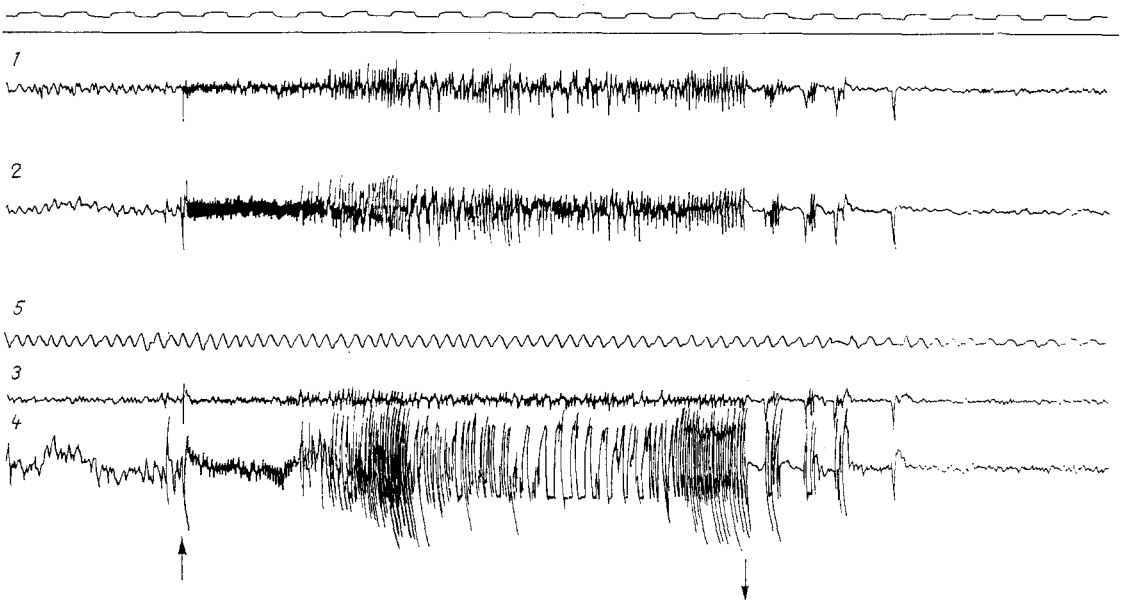

Fig. 1. EEG of rabbit during and immediately after ES of left hippocampus (bursting AD). 1) Sensomotor cortex, 2) occipital cortex, 3) amygdala, 4) right hippocampus, 5) respiratory movements. Arrows indicate beginning and end of ES. Calibration: 12.5 μV, 1 sec.

The hypersynchronous AD developed much later than the bursting type, either at the end of ES or a few seconds after its termination, and it was characterized by the appearance of high-amplitude spikes against the background of the normal EEG, changing into a high-frequency hypersynchronous paroxysm. Later the frequency of this discharge either decreased or increased (Fig. 2). The duration of the bursting AD varied from 8 to 30 sec and of the hypersynchronous AD from 50 to 120 sec.

Of 14 experimental animals five had a bursting AD, five had a hypersynchronous AD, and four rabbits had a mixed type of AD.

At a certain stage of development of this phenomenon the AD began to be accompanied by motor fits.

In animals with a bursting type of AD this took place on average at the 22nd ES (with variation from 18 to 30 ES), but in rabbits with hypersynchronous AD it occurred at the 15th ES (with variation from 13 to 17 ES).

In the first case the muscular paroxysm developed suddenly, in most cases immediately in the fifth stage [5], whereas in the case of the hypersynchronous AD the fit formed gradually. In the first case the attack was characterized mainly by general muscular clonic spasms and was short in duration (10-30 sec). In the second type of AD the attack was more severe and the paroxysms had a marked tonic component and lasted between 50 and 90 sec. Muscular spasms in the animals of the first group occurred almost simultaneously with the appearance of AD, but in animals of the second group they developed much later, namely 20-30 sec after the beginning of the epileptiform electrophysiological changes. An important distinguishing feature of the EEG of animals with bursting AD was the appearance of spontaneous interictal spikes (IIS) — hypersynchronous paroxysmal oscillations with an amplitude of 200-600 μV and a period of under 80 msec (Fig. 3). IIS appeared after 5-6 ES, at first in the stimulated hippocampus and later in the contralateral hippocampus, but on the 8th-10th day they appeared in all structures tested (amygdaloid nuclei, posterior hypothalamic nuclei, sensomotor and occipital cortex). IIS were recorded both before and after ES and their number increased during development of the kindling syndrome from single to 30-50 counted over a period of 5 min. After the end of stimulation the spikes did not disappear for a long time. IIS in the amygdaloid nuclei, hypothalamus, and cortex in most cases were synchronized with the hippocampal IIS, but often independent spikes were found in these structures, and isolated paroxysmal discharges also occurred in the cortex and hippocampus.

In rabbits with hypersynchronous AD changes in the EEG between episodes were mild and were manifested as episodic amygdalar or hippocampal epileptiform paroxysms.

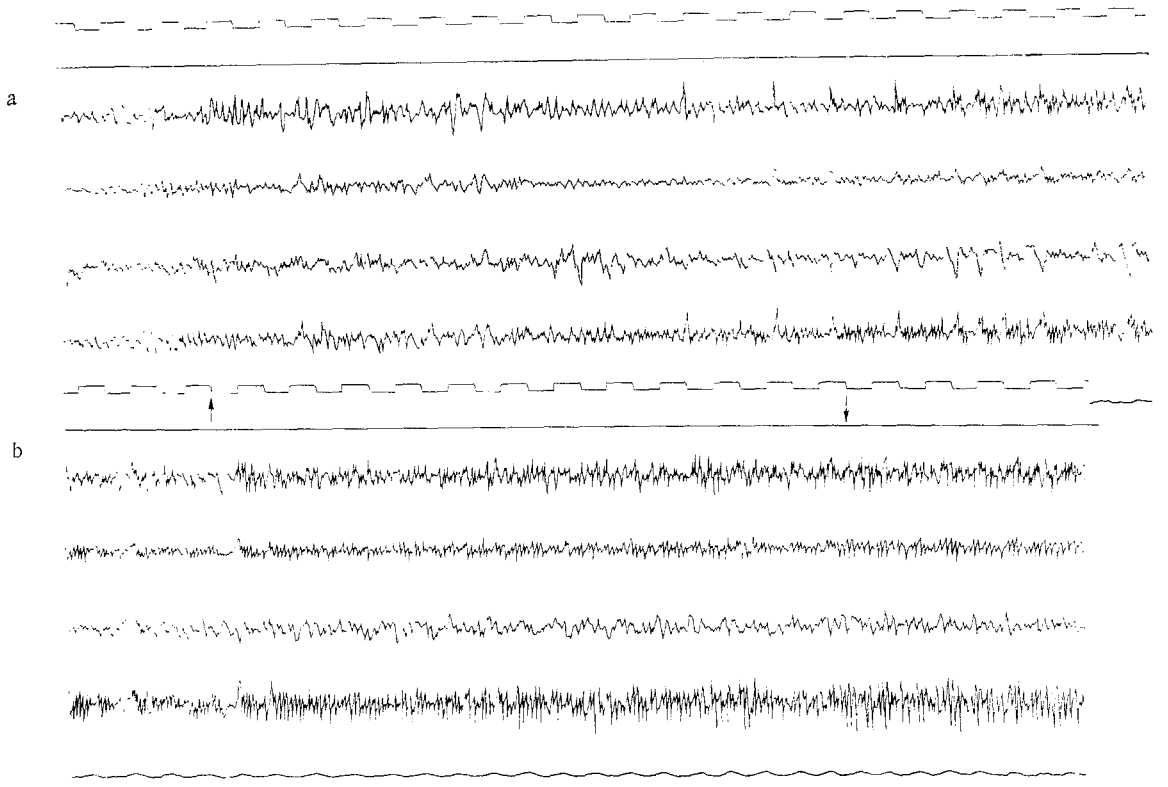

Fig. 2. EEG of rabbit during and immediately after ES of left hippocampus (hypersynchronous AD). a) Beginning, b) continuation of trace. Remainder of legend as to Fig. 1.

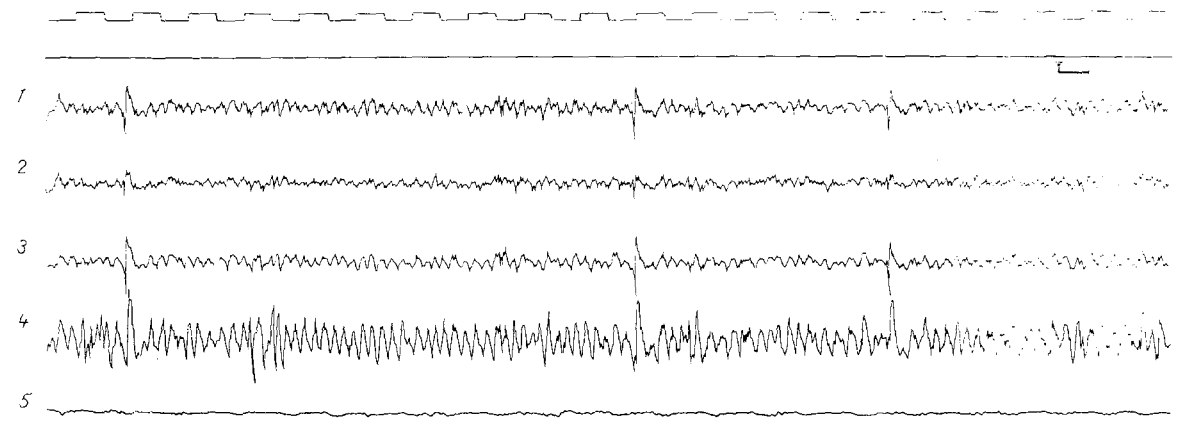

Fig. 3. EEG of rabbit after 15 ES of hippocampus. Legend as to Fig. 1.

The data described above indicate greater epileptization of the brain in animals with the bursting type of AD. However, despite the marked epileptiform changes on the EEG in the interictal period, the fit evoked by ES in these animals followed a much milder course (short clonic convulsions) than in rabbits with the hypersynchronous AD (convulsions of tonicoclonic type), in which the EEG remained sufficiently normal in the interictal period. ES is known to bring to light latent excitation in the "pretriggering integration" system [1]. Consequently, the formation of multiple hyperactive foci in central structures is not itself evidence of intensification of the peripheral epileptic process. It may be that independent generators of enhanced excitation [2, 3] are formed in the complex mechanism of intercentral relationships, and because of their biological significance or other reasons, they have an inhibitory effect on the basic pathological process and limit the epileptic process as a whole and, in particular, the outflow of excitation to the effector path. The development of the two patterns of AD described above during kindling stimulation of the hippocampus suggests the presence of two groups of neuronal ensembles in this structure, which can function in accordance with different paroxysmal programs. Neuronal ensembles of this kind can evidently be activated not only independently, but also simultaneously, forming AD of a third (mixed) type.

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STRUCTURAL AND FUNCTIONAL PROPERTIES OF PLATELETS IN ISCHEMIC HEART DISEASE

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One stage in the pathogenesis of atherosclerosis is an increase in coagulability of the blood as a result of a disturbance of equilibrium between the clotting and anticlotting systems of hemostasis, in which platelets are the principal key component. Atherosclerosis is accompanied by increased platelet activity, manifested as a decrease in the platelet circulation time, increased sensitivity to aggregation inducers, and a decrease in the thrombus formation time [6, 7, 11, 12]. However, investigations of this kind have been conducted on platelet-rich plasma, and it is not known whether hyperreactivity was the result of certain changes in the properties of the cells themselves or of the humoral action of clotting factors. Another debatable problem is whether the cholesterol (Ch) fraction in the platelet membranes of patients with ischemic heart disease (IHD) and, in particular, in hyperlipidemia, is increased. Whereas investigations (experimental and clinical) have revealed an increase in the molar ratio cholesterol/phospholipids (Ch/PL) in the erythrocyte membranes in atherosclerosis, inducing an increase in microviscosity and inhibiting membrane Na^+, K^+-ATPase [1], the few data relating to platelets are highly contradictory [10-12].

This paper describes the first attempt to study microviscosity of platelet membranes and aggregation of isolated platelets of patients with IHD and to compare them with the results of determination of the Ch fraction in them.

EXPERIMENTAL METHOD

Experiments were carried out on platelets isolated from blood of patients with IHD aged from 30 to 60 years. The diagnosis was based on clinical manifestations of angina, ECG changes, and the results of graded physical exercise tests. Blood from healthy blood donors of the same age was used as the control. Blood was taken from the cubital vein into a siliconized tube with 3.8% sodium citrate in the ratio 9:1 by volume. Platelets were isolated from platelet-rich plasma by gel-filtration on sepharose 2B. The state of platelet function was judged by the ADP-induced aggregation time. The rate of platelet aggregation was measured by the method [4], by recording the decrease in scattering of light by a cell suspension in buffer (134 mM NaCl, 15 mM Tris-HCl, 1 mM EDTA, 5 mM glucose; pH 7.35) after addition of 10^{-4} M ADP and $3 \cdot 10^{-3}$ M $CaCl_2$ per 10^7 cells in 1 ml; the time of reaching maximal translucency was estimated at a wavelength of 620 nm and at 37°C. The Ch content in the plate-

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