EXPERIMENTAL ANALYSIS OF THE EPILEPTIC DISCHARGES ARISING DURING ELECTRICAL STIMULATION OF THE HIPPOCAMPUS

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During our study of cortico-subcortical relationships in conditioned reflex activity, we carried out experiments in which electrodes were implanted for long periods of time in various brain structures, and found that epileptiform discharges developed in some rabbits soon after the operation.

Despite the considerable variety of epileptiform discharges, their commonest form during the first few days after implantation of the electrodes was of synchronous, rhythmic discharges, varying in frequency and duration. They appeared spontaneously, and just as spontaneously disappeared. In some cases they gradually increased or decreased in frequency, and finally subsided, whereas in others their frequency did not alter. As a rule the development of the rhythmic discharge in the early stages after operation began with asynchronous activation and ended with a phase of exhaustion.

Sometimes the epileptiform discharges consisted of series of biphasic waves of high amplitude, more or less prolonged, and repeated several times or alternating with bursts of rhythmic discharges. In the later stages after operation paroxysmal discharges appeared sporadically, mainly in the form of single, and less frequently of multiple peaks or complexes of peaks (forming a wave). During this period they developed whatever the nature of the electrical background activity.

In most cases paroxysmal discharges were recorded only in the subcortical structures, namely, the region of the reticular formation of the brain stem, the zone of the intralaminar nuclei of the thalamus and, less frequently, the hippocampus and the hypothalamus. Although epileptiform discharges arose in any of these structures, characteristically their localization was variable. Most frequently they appeared after implantation of the electrodes into the thalamic structures or into the hippocampus.

Although capable of wide generalization among the various subcortical structures, epileptiform discharges were sometimes very circumscribed in their localization. This was demonstrated by special experiments in which bipolar and unipolar recording of the potentials from a given area were carried out at the same time. In this way the total electrical activity of the nervous structures lying between the two electrodes could be compared with the electrical activity of the local group of neurons surrounding each of these electrodes.

The experiments showed that the epileptiform discharges recorded from the bipolar leads appeared from only one electrode. The electrical activity of the nervous structures in which the second electrode was buried was as a rule unchanged. Only if two different forms of epileptiform discharges were recorded by the bipolar electrodes could they be recorded separately by using unipolar leads.

As a rule paroxysmal discharges appeared in the region of the subcortical formations, i.e., where the deep electrodes were situated. It was suggested that these discharges are an expression of hypersynchronization of the electrical oscillations associated with a reactive state of the numerous neurons injured to some extent by implantation of the electrodes, i.e., with the local reaction of the nerve tissue elements. However, this suggestion was not confirmed by the fact that the epileptiform discharges could also develop in the cortical zones of the cerebral hemispheres, where the possibility of a local reaction to insertion of the electrodes was excluded by the fact that they were actually placed on the inner plate of the cranium. These observations showed that for paroxysmal discharges

to develop it is necessary to have certain additional mechanisms, responsible for the wide generalization of the stimuli arising initially in isolated structures. Researches in P. K. Anokhin's laboratory (the work of V. N. Shelikhov on strychnine discharges, and of Liu Chuan-kuei and others) have shown that the generalization of excitation in the cortex may have a secondary association with the reticular structures of the brain stem and thalamus ("back generalization").

On the basis of these results we set out to analyze the results of electrical stimulation of those subcortical structures in which the deep electrodes were situated. We paid special attention to the possibility of the production of paroxysmal discharges.

EXPERIMENTAL METHOD

Experiments were carried out on rabbits with electrodes permanently implanted in the sensomotor zone of the cerebral cortex, and the temporal and occipital lobes. The subcortical electrodes were buried at a suitable depth in the zone of the reticular formation of the brain stem, the intralaminar nuclei of the thalamus, and in the region of the fimbria of the hippocampus and the fornix. In some experiments the electrodes were also inserted into the hypothalamus or into the lateral nuclei of the thalamus. The electrodes were made from nichrome wire, coated with bakelite varnish and a layer of plexiglas or polystyrene. The diameter of the cortical electrodes was 500 μ and the distance between them 4 mm. The diameter of the subcortical electrodes was 100-200 μ and the distance between

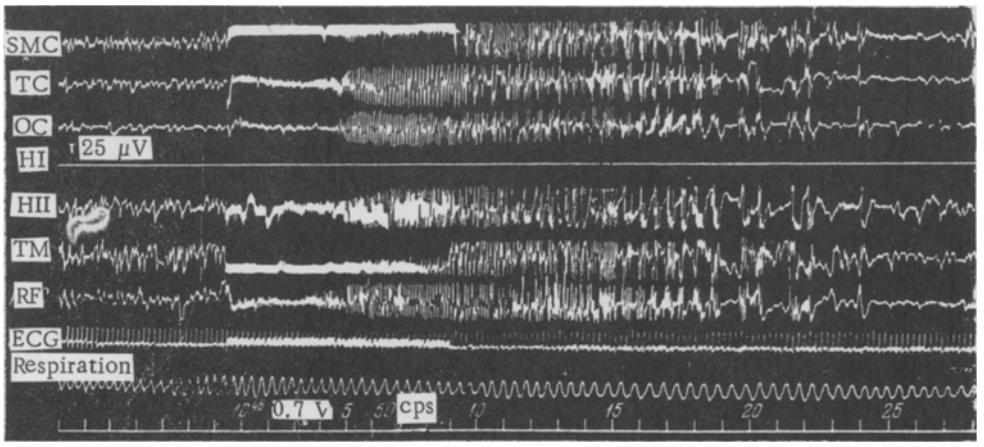

Fig. 1. Reaction of the electrical activity of the cortex and subcortical formations to stimulation of the fimbria of the hippocampus. Paroxysmal discharges appeared in all the structures from which recordings were made. The respiratory movements of the chest changed appreciably in amplitude, although they remained regular. SMC—sensomotor cortex; TC—temporal cortex; OC—occipital cortex; H I—fimbria of hippocampus; H II—fornix of hippocampus; TM—region of the intralaminar nuclei of the thalamus; RF—reticular formation of the brain stem.

them about 1 mm. The electrodes were fixed with phosphate cement. The subcortical structures were stimulated by efferent electrodes, a suitable pair being connected to a "Myostim" stimulator (manufactured by the firm Disa) supplying rectangular impulses of current. The duration of each impulse was 1 msec, their frequency from 20 to 150 cps, and voltage from 0.5 to 5 V. Electrical potentials from bipolar electrodes were recorded by a 10-channel ink-writing encephalograph (Alvar). At the same time as the electrical potentials were recorded from the various structures of the brain, tracings were made of the respiratory movements of the chest and the ECG. Stimuli were applied to all the subcortical structures in which the electrodes were implanted, i.e., the reticular formation of the brain stem, the intralaminar nuclei of the thalamus, the fimbria of the hippocampus, and the fornix.

EXPERIMENTAL RESULTS

The experiments showed that of all the subcortical structures in which we were interested only the anterior division of the hippocampus, when stimulated, gave rise to a generalized burst of paroxysmal discharges in both the cortex and the subcortical structures. The characteristic feature of this burst was that, despite their wide generalization, the paroxysmal discharges did not always emerge to the muscular system—the animals lay quietly and their

respiratory cycles were not deformed (Fig. 1). Only if the electric current were increased in strength were the bursts of paroxysmal discharges accompanied by means of the head, trunk, and limbs, but these ceased long (10-30 sec) before the paroxysmal discharges. The latent period of the epileptiform discharges varied depending on the voltages of the stimulating current, the individual peculiarities of the experimental animal, the functional state of the central nervous system, and other factors from 3.5 to 8 sec. Particularly attention should be paid to the fact that at a threshold strength of the electric current the paroxysmal discharges did not appear in all the structures at the same time. They began first in the structures of the fornix and occipital cortex, followed by the temporal cortex and the reticular formation of the brain stem, and appeared finally in the medial nucleus of the thalamus and the sensomotor zone of the cortex (Fig. 2). If a subthreshold strength of current was used, the paroxysmal discharges arose simultane-

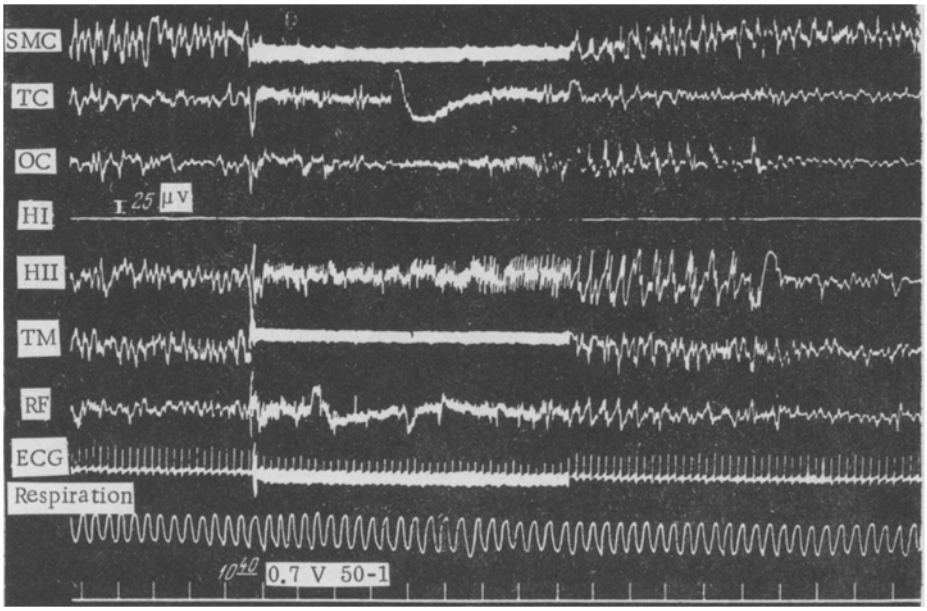

Fig. 2. Stimulation of the fimbria of the hippocampus with an electric current of threshold strength. Paroxysmal discharges appear first in the optic cortex and the hippocampus. Legend as in Fig. 1.

ously in the fornix of the hippocampus, the optic and temporal zones of the cortex, and the reticular formation of the brain stem, and subsequently in the medial nucleus of the thalamus and the sensomotor cortex. If a stronger current was used, the burst of paroxysmal discharges began simultaneously in all the structures. Extinction of the epileptiform discharges also took place at different times. They were extinguished last of all in the hippocampal fornix and in the optic cortex. These results showing the difference between the latent periods confirmed the existence of a close functional link between the hippocampal structures themselves and also between the fimbria of the hippocampus and the optic zone of the cerebral cortex.

When the current was of threshold strength the burst of paroxysmal discharges lasted 15-25 sec, and if the strength was increased the epileptiform discharges were prolonged to about 1 min, sometimes as a continuous series of bursts, sometimes as groups. Although they appeared as a result of a common, generalized influence, in their form they nevertheless reflected the background activity of the electrical oscillations in the particular structure concerned. Each burst of paroxysmal discharges terminated in a phase of exhaustion, characterized by flattening of the ECG and the absence of high-amplitude oscillations.

Since the convulsions appeared in response to stimulation of the sensomotor region of the cerebral cortex, it could be suggested that the paroxysmal discharges arising during stimulation of the fimbria of the hippocampus were the usual reaction of the brain tissue to electrical stimulation. This, however, was contrary to the results of stimulation of the other subcortical structures. None of these structures—neither the reticular formation of the brain stem nor the intralaminar nuclei of the thalamus, nor the hippocampal fornix—gave rise to generalized epileptiform discharges even if the current used to stimulate them was 4-5 times stronger than that producing paroxysmal discharges during stimulation of the fimbria of the hippocampus (Fig. 3).

The subsequent analysis was to elucidate the relationship between the reticular formation of the brain stem and the hippocampus in the mechanism of the appearance of these generalized epileptiform discharges. For this purpose we stimulated the hippocampus after administering chlorpromazine, which blocks the adrenergic structures of the reticular formation of the brain stem. These experiments showed that electrical stimulation of the hippocampus, 10-20 min after the intravenous injection of chlorpromazine (1.0-1.5 mg/kg body weight), i.e., at a time

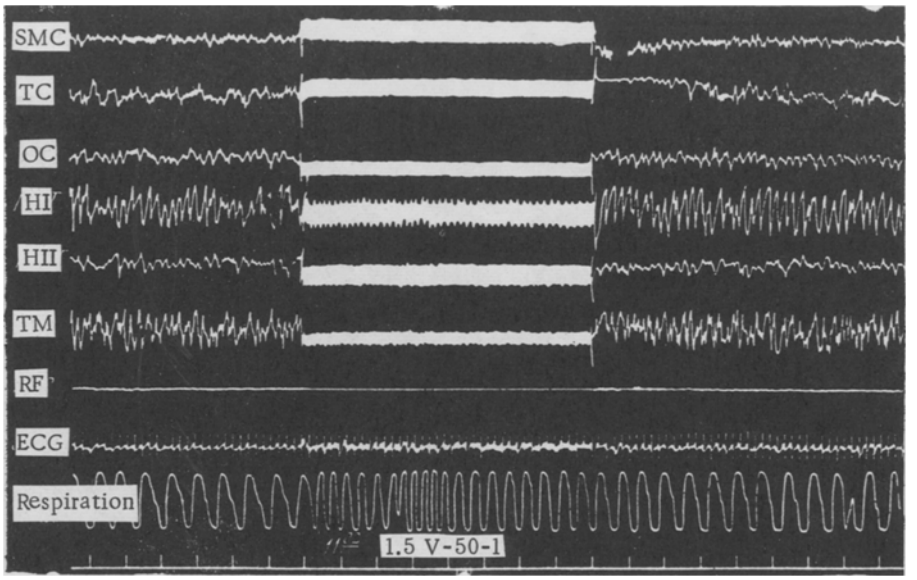

Fig. 3. Stimulation of the reticular formation of the brain stem. A slow, regular rhythm develops in the reticular structures of the subcortical formations. No paroxysmal discharges appear. The respiration rate is increased. Legend as in Fig. 1.

when the electrical activity of the structures from which the recordings were taken was characteristic of a resting state, using a current of the same strength and frequency caused a prolonged (4-5 min) burst of epileptiform discharges, changing after 15-30 sec into a strong convulsion with clonic spasms, salivation, etc. If the electrical stimulation of the hippocampus was applied during desynchronization, or activation, caused by a powerful sound stimulus (a rattle), a stronger current was required as electrical stimulus to produce a burst of paroxysmal discharges.

Identical results regarding the role of the reticular formation and the hippocampus in the production of generalized paroxysmal discharges were obtained in experiments with adrenalin. From 1.5-2 min after the intravenous injection of adrenalin (0.3 ml, 1 : 1000), when the EEG had become characteristic of a state of "stress," electrical stimulation of the hippocampus did not cause epileptiform discharges. In the second phase of the action of adrenalin, however, characterized by a resting electrical activity with bursts of spikes, stimulation of the hippocampus with a current of the same strength again caused a prolonged burst of paroxysmal discharges.

Hence, the experiments with adrenalin and chlorpromazine showed that active excitation of the adrenergic structures of the reticular formation of the brain stem had some form of inhibiting action on the hippocampal structures.

The results of the experiments described above, in which the hippocampus was stimulated, are in agreement with those obtained by Shimamoto and Green, who showed in different variants of experiments (cerveau isolé) involving destruction and aspiration of various parts of the brain and division of various tracts, that only by stimulation of certain hippocampal structures, notably the fimbria, could generalized bursts of epileptiform discharges be produced.

SUMMARY

Experiments were conducted on rabbits with chronically implanted electrodes in the area of the reticular structure of the brain stem and thalamus, in various portions of hippocampus, in the sensomotor, temporal and occipital area of the cortex of large hemispheres. A study was made of the reaction of the electric activity to electric stimulation of subcortical formations. As revealed, only with stimulation of the fimbria hippocampi there occur paroxys-

mal electric discharges, generalized along the whole cortex and subcortical structures. The use of adrenalin and aminazine demonstrated that active excitation of adrenergic structures of the reticular formation had some inhibitory effect on the appearance of paroxysmal discharges.

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