ROLE OF THE HIPPOCAMPUS IN THE GENESIS OF AUDIOGENIC CONVULSIONS OF MYOCLONIC TYPE

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In experiments to study the effect of electrical stimulation of the hippocampus on the audiogenic epileptiform reaction, recognized as one of the best models of epilepsy in man [19], the authors found that in certain conditions it has an inhibitory action, producing the inhibitory phase of the reaction and an increase in the latent period [14]. In this way it was shown that the hippocampus may inhibit not only normal [3, 16, 18], but also pathological reactions of the organism. On the other hand, it was found that if the voltage used to stimulate the hippocampus is high enough, this may itself cause convulsions, outwardly identical with audiogenic and cardiazol myoclonus.

In face of these results, and also of the many clinical and experimental facts showing the high level of preparedness of the hippocampus for convulsive activity and its role in the genesis of epileptic fits in man, the present investigation was undertaken with the object of elucidating the role of the hippocampus in the genesis of audiogenic myoclonic convulsions.

EXPERIMENTAL

Thirty rats of a line highly sensitive to the action of an acoustic stimulus [7], and also four rats of an ordinary population, insensitive to the action of a bell, were used in the experiments. Audiogenic myoclonus was produced in the sensitive rats as follows. The rats were exposed to the action of a strong acoustic stimulus two or three times daily with a break for 2-3 days every 7-8 days [9]. After 15-20 days, besides the ordinary audiogenic fit during its inhibitory phase, tic-like myoclonic convulsions constantly appeared. The brain was stimulated with a sinusoidal current with a frequency of 40 cps and a voltage of 0.5-3 V, through permanently implanted nichrome electrodes. The duration of stimulation was 10 sec and the interval between stimuli was 5-10 min. Functional exclusion of the hippocampus was obtained by injecting a 25% KCl solution into it through permanently implanted nonrusting cannulas (the technique of obtaining spreading depression [15] adapted for chronic conditions). The cannulas and electrodes were fixed to the skull by means of phosphate cement. The appearance and spread of depression were checked by means of a four-channel oscillograph with ink recording. Motion pictures were used to record the motor reactions.

DISCUSSION OF RESULTS

During weak electrical stimulation of the hippocampus (0.5-2 V) of the quietly sitting rat the animal began to sniff. If the voltage was increased (to 2.5-3 V) the sniffing became more intensive and prolonged, and changed into an active orienting reaction, spreading to the intervals between stimuli. A stimulus applied against the background of this orienting reaction led to its inhibition. In the intervals between stimuli a very characteristic picture of alternation of periods of depression and periods of active investigatory activity, accompanied by peculiar shaking movements, could be observed. The appearance of the shaking reaction was taken as a sign of the rapid development of a fit. Twitching of the vibrissae appeared first, spreading to the eyelids and ears, and convulsive contractions gradually extended to all the muscles of the head. A further increase in the voltage led to the spreading of the

convulsions to the forelimbs and, in certain cases, to the hind limbs. Hence the convulsions observed during stimulation of the hippocampus reproduced the picture of audiogenic and cardiazol myoclonus. Since it has been shown that audiogenic [5] and cardiazol [6] myoclonic convulsions develop only with the participation of the motor cortex, a series of experiments was carried out in which the motor cortex was stimulated in order to study the character of the convulsions developing in these conditions. Weak stimulation (0.5-2.5 V) of the motor cortex also led to the appearance of a sniffing reaction, but this was not intensified so clearly when the voltage was increased to 3-4 V as during stimulation of the hippocampus. Depression of the orienting reaction was observed only in individual cases, and the shaking reaction typical of stimulation of the hippocampus was hardly observed at all.

In response to stronger stimulation of the motor cortex, depending on the localization of the electrodes, a tremor of the forelimb or of the hind limb developed. In contrast to this, during stimulation of the hippocampus the reaction was always bilateral immediately, starting with a tremor of the facial muscles, spreading only rarely and last of all to the hind limbs. In addition, any reaction to stimulation of the cortex was accompanied by the rat's adoption of a stooping position towards the floor of the chamber, whereas during stimulation of the hippocampus its body moved in the opposite direction—the rat stretched upward, standing on its hind limbs. Hence it was not possible to reproduce the picture of tic-like myoclonus by stimulation of the motor cortex. These results confirmed the view that the primary focus of myoclonus is not in the cortex, but in the underlying regions [2, 12], and they suggest that the hippocampus is one of these regions. To test this hypothesis, in six rats in which a stable audiogenic myoclonus had been formed, before the beginning of the action of the acoustic stimulus the function of the hippocampus was excluded by means of 25% KCl solution. In 93.7% of cases (15 of 16 experiments) this prevented the development of myoclonus while leaving the main audiogenic convulsion unaffected. It may be noted that in the one case when myoclonus did not disappear the depression in the hippocampus was incomplete. These results show that the development of audiogenic myoclonic convulsions evidently involves the participation of the hippocampus.

The bioelectrical activity of the hippocampus during myoclonia is characterized by the same high-voltage epileptoid discharges as are associated with other parts of the brain, and it is indistinguishable from the latter [1]. The epileptoid changes on the EEG during the main audiogenic convulsion appeared in the hippocampus only after several fits, but they were just as clearly defined as in the medulla, which is considered to be the primary focus of excitation in audiogenic epilepsy [2]. The formation of an intensive pathological focus of excitation in the hippocampus undoubtedly disturbs the normal functions of this structure [10]. Comprehensive studies during recent years of the functions of the hippocampus have confirmed the previous hypothesis that it plays an important role in the regulation of the general level of excitability of the brain [11, 17] and have shown that the effect of the hippocampus is principally, but not entirely, inhibitory [3, 16, 18]. Since during repeated reproduction of audiogenic convulsions in rats an epileptoid focus develops in the hippocampus [1] and the process of inhibition is greatly weakened, facilitating the development of myoclonus [8], it may be suggested that the disturbance of the regulatory function of the hippocampus plays a definite role in this weakening of inhibition.

Electroencephalographic investigations have led to the conclusion that a focus of excitation in tic-like myoclonus is formed in the auditory subcortex, for epileptoid discharges are found in the medial geniculate bodies sooner than in other parts of the brain [12]. The motor cortex, which is evidently the efferent part of the reflex arc of myoclonic convulsions [4], also takes part in the reaction.

The spread of impulses of excitation from the auditory subcortex to the cortex is facilitated by the marked weakening of the inhibitory process which, as described above, may be the result of the disturbance of the regulatory functions of the hippocampus when a pathological focus of excitation is formed in the structure. On the other hand, since the audiogenic myoclonic convulsions were found in the present investigation to disappear if the function of the hippocampus was excluded, and the myoclonic convulsions arising during stimulation of the hippocampus are similar to the audiogenic convulsions, we consider that the pathological focus of excitation formed in the hippocampus plays an active (and perhaps dominant) role in the genesis of audiogenic myoclonic convulsions.

It is thus possible to speak of the dual role of the hippocampus in convulsive reactions of different genesis and localization. The hippocampus is not directly concerned in the audiogenic convulsion localized in the subcortex and and brain stem, but it may exert an inhibitory influence upon it [14]. On the other hand, the hippocampus plays a direct part in myoclonic convulsions whose appearance is associated with the motor cortex. As the epileptoid focus develops in the hippocampus that structure loses its protective function and itself becomes the focus of a pathological process.

LITERATURE CITED

1. K. G. Gusel'nikova, In the book: The Problem of Epilepsy [in Russian], Moscow (1959), p. 270.
2. K. G. Gusel'nikova, Nauchn. dokl. vyssh. shkoly. Biol. nauki, 1 (1959), p. 69.
3. N. N. Zislina, In the book: Electrophysiology of the Nervous System [in Russian], Rostov-on-Don (1963), p. 156.
4. B. I. Kotlyar, Nauchn. dokl. vyssh. shkoly. Biol. nauki, 4 (1958), p. 73.
5. B. I. Kotlyar, Nauchn. dokl. vyssh. shkoly. Biol. nauki, 2 (1959), p. 98.
6. B. I. Kotlyar and D. A. Fless, Nauchn. dokl. vyssh. shkoly. Biol. nauki 2 (1962), p. 98.
7. L. V. Krushinskii, Byull. Moskovsk. obshch. ispytatelei prirody. Otdel biol., 64 (1959), p. 105.
8. L. V. Krushinskii and L. N. Molodkina, Zh. vyssh. nervn. deyat., 10, 5 (1960), p. 779.
9. L. N. Molodkina, In the book: Proceedings of an All-Russian Conference on the Problem of Epilepsy [in Russian], Moscow (1964), p. 112.
10. W. Penfield and H. Jasper, Epilepsy and the Functional Anatomy of the Human Brain [Russian translation], Moscow (1958).
11. N. A. Rozhanskii, Fiziol. zh. SSSR, 5 (1953), p. 549.
12. A. F. Semiokhina, Zh. vyssh. nervn. deyat., 8, 2 (1958), p. 278.
13. A. F. Semiokhina, In the book: The Problem of Epilepsy [in Russian], Moscow (1959), p. 259.
14. D. A. Fless, N. A. Tushmalova, and Z. A. Zorina, In the book: Proceedings of the Tenth Congress of the I. P. Pavlov All-Union Physiological Society [in Russian], Moscow–Leningrad (1964), p. 362.
15. I. Bures, O. Buresova, and T. Weiss, Physiol. Bohemosl., 9 (1960), p. 219.
16. E. Grastyan, In the book: The Central Nervous System and Behavior, Transactions of the Second Conference Washington (1959), p. 119.
17. C. Herrick, Proc. Nat. Acad. Sci. (Wash.), 19 (1933), p. 118.
18. K. Lissak, et al., Acta physiol. pharmacol. neerl., 6 (1957), p. 451.
19. Psychophysiologie, neuropharmocologie et biochimie de la crise audiogene. Paris (1963).

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