EFFECT OF INJURY TO THE MEDIAL FOREBRAIN BUNDLE AND PREOPTIC REGION ON ACTIVITY OF A STRYCHNINE-INDUCED EPILEPTIFORM FOCUS (ON THE PHENOMENON OF THE HYPERACTIVE DETERMINANT DISPATCH STATION)

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Experiments on cats showed that injury to the medial forebrain bundle (MFB) and to some extent of the preoptic region (PR) also on the side of application of strychnine to the cerebral cortex (middle suprasylvian gyrus) causes depression of seizure activity (spike potentials) in the "strychnine" focus and also in a secondary "mirror" focus in the symmetrical zone of the cortex of the opposite hemisphere. The same effect could be obtained in some cases after injury to MFB only. Injury to MFB and to part of PR on the side of the "mirror" focus causes depression of spike potentials in that focus only and does not affect activity in the primary epileptiform focus. The effects described above are examined from the standpoint of the role of the determinant dispatch station (DDS) in CNS activity: The primary epileptiform focus is a hyperactive DDS which induces the appearance of secondary foci and maintains and determines the character of their activity. It can be concluded from these experimental results that MFB participates in the modulation of cortical epileptiform activity. KEY WORDS: cerebral cortex; strychnine; determinant dispatch station; medial forebrain bundle; preoptic region; epileptiform focus.

The epileptiform focus arising after application of strychnine to the cerebral cortex is a good example of a hyperactive determinant dispatch station (DDS). The DDS is a structure of the CNS which forms an intensified volley and consequently determines the character of activity of subsequent parts of the CNS to which this volley is addressed, and, consequently, determines the behavior of the systems which it activates [1-4, 6]. From this standpoint the "mirror" focus arising in the cortex of the opposite hemisphere after organization of a primary epileptiform focus can be regarded as a "destination station" (DS), induced by the DDS and manifesting its influence. The elucidation of correlation between the two functional structures is an important step in the understanding of the principles and mechanisms of CNS activity. One possible method of experimental analysis of these relations is to study the combined effects of separate depression of activity of DDS and DS, in the present case depression of activity of primary and secondary epileptiform foci. The system of the medial forebrain bundle (MFB) plays an important role in the mechanism of brain activity [10, 14, 16], for injury to MFB causes inhibition of seizure activity [11, 12].

The object of this investigation was to study the effect of injury to MFB on the hyperactive DDS created by local strychnine poisoning of the cerebral cortex on the secondary DS ("mirror" focus) and on relations between these two structures. The study of this problem is also interesting in connection with investigation of the pathogenesis of epilepsy and, in particular, to discover the role of MFB in the formation of epileptiform activity.

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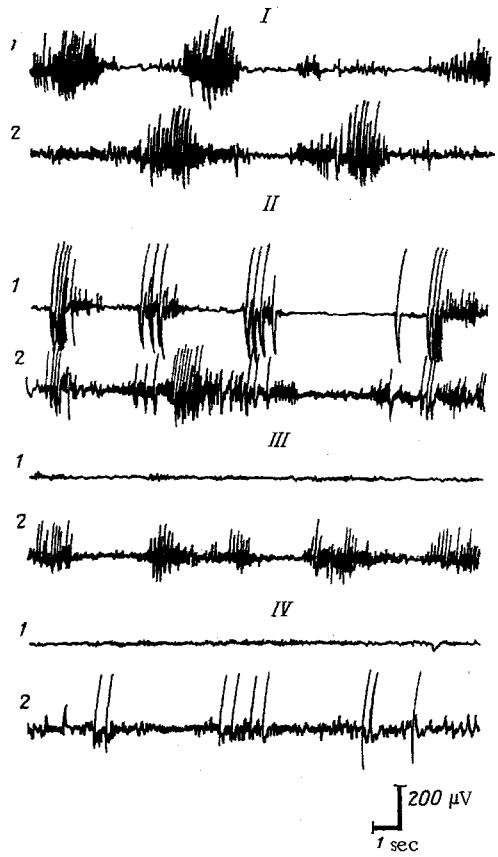

Fig. 1

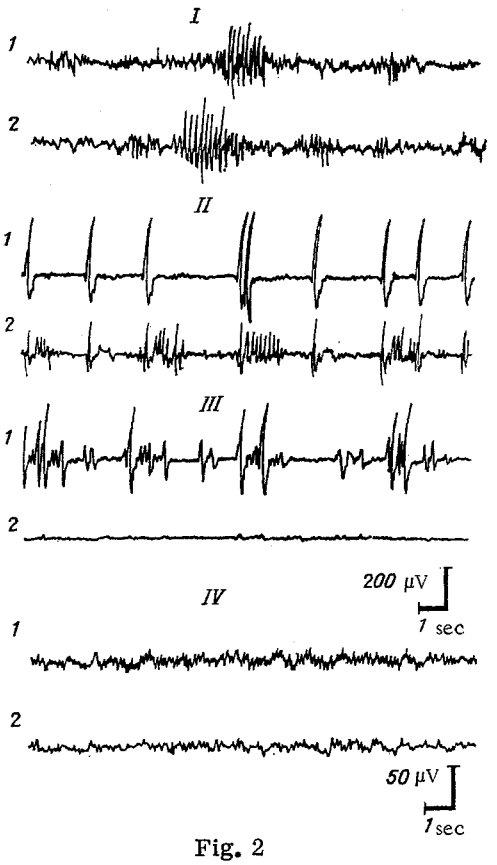

Fig. 2

Fig. 1. Formation of primary and secondary foci of excitation during local strychnine poisoning of cerebral cortex and effect of injury to MFB on side of primary focus on them. Primary strychnine focus created in right hemisphere. In all records: 1) ECoG of right, 2) ECoG of left hemisphere. I) ECoG before application of strychnine; II) seizure spike activity after application of strychnine; III) disappearance of seizure spike activity after injury to MFB on side of primary strychnine focus; IV) appearance of seizure spike activity after application of strychnine to cortex of left hemisphere (on side of previous secondary strychnine focus).

Fig. 2. Formation of primary and secondary foci of excitation during local strychnine poisoning of cerebral cortex and effect of injury to MFB on side of secondary focus on them. Primary strychnine focus created in right hemisphere. In all records: 1) ECoG of right, 2) ECoG of left hemisphere. I) ECoG before application of strychnine; II) seizure spike activity after application of strychnine; III) disappearance of seizure spike activity in secondary strychnine focus after ipsilateral injury to MFB; IV) disappearance of seizure spike activity in primary strychnine focus after injury to MFB on side of primary strychnine focus.

EXPERIMENTAL METHOD

Experiments were carried out on 23 cats under pentobarbital anesthesia (25 mg/kg, intraperitoneally). The preliminary operation consisted of exposing the hemispheres and opening the dura. Potentials were recorded on an ink-writing electroencephalograph. Monopolar derivation of potentials was used and the reference electrode was secured to the nasal bones. The hyperactive DDS was created in the cortex of one hemisphere (middle suprasylvian gyrus) by application of a 1-3% solution of strychnine nitrate, in which a piece of filter paper measuring 2 × 2 mm was soaked. The region of MFB was injured under visual control from the basal surface of the brain by galvanocautery. In some experiments coagulation was carried out by a stereotaxic technique in the zone of MFB (Fr 10.5, L 3, H−5) and in the zone of the preoptic region (PR) (Fr 13-14, L 3, H−4.5) in accordance with the coordinates in the atlas [15]. At the end of the experiment the animal's brain

was fixed in 10% neutral formalin and sections were cut to a thickness of 50 μ on a freezing microtome and stained with hematoxylin and eosin. A stereotaxic atlas [15] was used to identify lesions in the hypothalamus.

EXPERIMENTAL RESULTS

Application of strychnine to the cortical association area depressed bursts of spindles and caused the appearance of characteristic strychnine spikes (Fig. 1, II), the maximal amplitude of which in some cases reached 1.5 mV. Some time later, depending on the strychnine concentration, a "mirror" focus appeared in the symmetrical region of the opposite hemisphere (Fig. 1, II). The behavior of the latter focus reflected the behavior of the primary focus (coupled changes in amplitude and frequency of spike generation, coupled changes in activity with time, etc.).

After the character of electrical activity had become stabilized, MFB was injured in the same hemisphere. Histological investigations showed that injury to MFB affected PR. From now on the expression injury to MFB and PR will therefore be used. Injury to MFB and PR on the side of the primary focus reduced the amplitude of the strychnine spikes by 30-50 times or caused them to disappear virtually completely (recording with the same amplification) (Fig. 1, III). This effect was unambiguous and was reproduced to some degree in all tests in which MFB and PR were injured (12 experiments). The depth of reduction of the potentials and the decrease in the frequency of their appearance were seen to depend on the degree of injury to MFB and PR. In the case of a sufficiently complete injury the potentials disappeared throughout the experimental (observation for 4 h). In those cases the potentials did not appear during repeated (sometimes frequently) strychninization of the region of the primary focus. With high amplification infrequent spike potentials with an amplitude of up to 20-30 μV, and also β and γ-activity, could be recorded. Besides depression of spike potentials in the primary, "strychnine" focus, spike potentials also disappeared in the secondary, "mirror" focus (DS); bursts of spindles in the region of the "mirror" focus still persisted under these circumstances (Fig. 1, III) or they were actually strengthened. Meanwhile application of strychnine to the region of the disappearing "mirror" focus led to the appearance of the characteristic spikes in it (Fig. 1, IV).

In the next series of experiments (eight experiments) MFB and PR were injured on the side of the "mirror" focus (DS). In this case deep depression of the potentials of this focus developed, although the potentials in the primary focus (DDS) were substantially unchanged (Fig. 2, III). Only additional injury to MFB and PR on the side of the primary focus led to reduction of its potentials (Fig. 2, IV).

The first conclusion which arises from the results described above is that the effect of injury of MFB and PR is strictly ipsilateral. This suggests, first, that the observed effect was not the result of a generalized lowering of the tone of the cortex following its injury or as a result of a disturbance of its blood supply through coagulation of MFB and PR. This conclusion is also supported by the results of the three experiments in which, as the histological control showed, only the neighboring zones, not MFB, were injured: Under these conditions no depression was observed in either the primary or the secondary focus. The presence of β and γ-activity, observable if high amplification was used, indicates the preservation of intrinsic cortical activity and was thus evidence of a satisfactory state of the cerebral cortex. If only PR and not MFB was injured, no depression of seizure activity was observed. Coagulation of MFB only, without affecting PR, caused depression of the seizure discharges. It can accordingly be concluded that the observed effect of depression of spike discharges after injury to MFB and PR is mainly due to injury to MFB. The fact that injury to MFB on the side of the primary focus caused depression of activity not only in the same, but also in the secondary, "mirror" focus, deserves particular attention; meanwhile injury to MFB on the side of the secondary focus led to depression of spike activity in that focus only. It is remarkable that after injury to MFB on the side of the primary focus the only activity to be depressed in the opposite hemisphere was spike activity, i.e., activity induced by the primary focus; burst activity, intrinsic to the opposite hemisphere, was retained.

The results described above suggest that the primary focus is a controlling functional structure which determines both the appearance of the secondary focus and the character of its activity. The secondary focus has no determinant effect on the primary focus.

The primary focus is thus a true DDS or "determinant" which generates and determines the behavior of the secondary focus as a DS. In that case a situation arises in which the DDS is a generating and controlling structure, whereas the secondary focus, or DS, is a completely dependent structure, which simply carries out the functional instruction from DDS and reproduces its activity.

Under pathological conditions, when inhibitory mechanisms in the neuron population of the DDS are disturbed, the DDS becomes hyperactive and functions as a generator of pathologically increased excitation,

which has a number of characteristic properties and can be depressed by the corresponding inhibitory mediators [5, 8, 9]. Such generators of pathologically increased excitation lie at the basis of epileptiform foci. Depression of the primary hyperactive strychnine-induced DDS may be connected with the blocking of facilitatory influences spreading along MFB. At the same time, considering the generator nature of epileptiform activity, it can be assumed that the phenomenon as described above is also determined by the activation of inhibitory mechanisms capable of depressing the activity of the generator, for weakening the inflow of excitatory stimulation by itself does not lead to the abolition of the generator [7].

The results of these investigations emphasize the importance of establishment of true DDS (determinant foci) in the presence of several hyperactive epileptiform foci. The investigations suggest that the system of the medial forebrain bundle participates in the modulation of epileptogenic activity. This hypothesis is supported by clinical data [13] on the provocation of epileptic fits during stimulation of the frontal cortex, with which the mediator forebrain bundle is connected, and on the role of this cortical region in epileptic activity [17].

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