EFFECT OF MEBICAR ON FOCAL EPILEPTIC ACTIVITY

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The choice of an adequate experimental model is an essential condition for the correct assessment of mechanisms of action of pharmacological agents. The use of experimental models of neuropathological syndromes with known pathogenetic mechanisms of development, which can be obtained by creating generators of pathologically enhanced excitation (GPEE) in different parts of the CNS [4], enables the action of pharmacological agents on different stages of the pathological process to be evaluated. The model of an epileptic focus in the cerebral cortex, formed by application of penicillin, is a special case of a GPEE in the CNS [5]. In particular, new and hitherto unknown mechanisms of action of a widely used tranquilizer such as diazepam have been obtained previously on a model of primary generalized photogenic epilepsy [6] produced by the formation of a GPEE in the lateral geniculate body and on a model of focal cortical epilepsy [7-9].

In the present investigation the anticonvulsant effect of the new Soviet preparation mebicar, whose action on the CNS is being intensively studied [2, 10], was investigated by an experimental model of focal cortical epilepsy. In the course of clinical trials of mebicar it became clear that it is effective in various forms of neurotic and psychotic states [1]. Mebicar has a tranquilizing action and is comparable with diazepam in its efficacy [2, 3]. However, mebicar [10] has advantages over diazepam. Structurally mebicar is a bicyclic urea, it is closely related to normal body metabolites, harmless and nontoxic, and does not give rise to side effects, including muscular relaxation, loss of attention, and slowing of intellectual processes. Considering these advantages of mebicar over diazepam, which is known not only as a tranquilizer but also as an anticonvulsant, it was deemed useful to obtain experimental data in order to broaden the spectrum of clinical application of mebicar and, in particular, as an anticonvulsant.

EXPERIMENTAL METHOD

Experiments were carried out on 30 noninbred male albino rats weighing 180-200 g. The operation to insert cortical electrodes to record the electrocorticogram (ECoG) in the zone of the epileptic focus and to insert subcortical stimulating electrodes into the region of the ventroposterolateral thalamic nucleus (VPL) was performed the day before the experiment. Glazed nichrome (100 μ) bipolar electrodes with tips uninsulated for 0.5 mm were inserted into VPL on the left side. An excitation generator (epileptic focus) was created by application of a piece of filter paper measuring 1.5 × 3.5 mm soaked in a solution of penicillin-Na (30,000 i.u./ml) to the surface of the pia mater of the left sensomotor cortex of the rats. Experiments were carried out on waking animals kept in a special hammock which did not restrict movements of the animals' limbs, head, and tail. The momentary frequency of interictal discharges (IID) and epileptic fits (EF) was calculated on an ATAK-501-20 computer (Japan). Full details of the method were given in [7]. Mebicar — 2,4,6,8-tetramethyl-2,4,6,8-tetraazobicyclo-(3,3,0)-octadione-3,7 — was synthesized in the Department of Organic Synthesis, N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, and was injected intraperitoneally into the animals as a 10% solution in doses of 300 to 1000 mg/kg.

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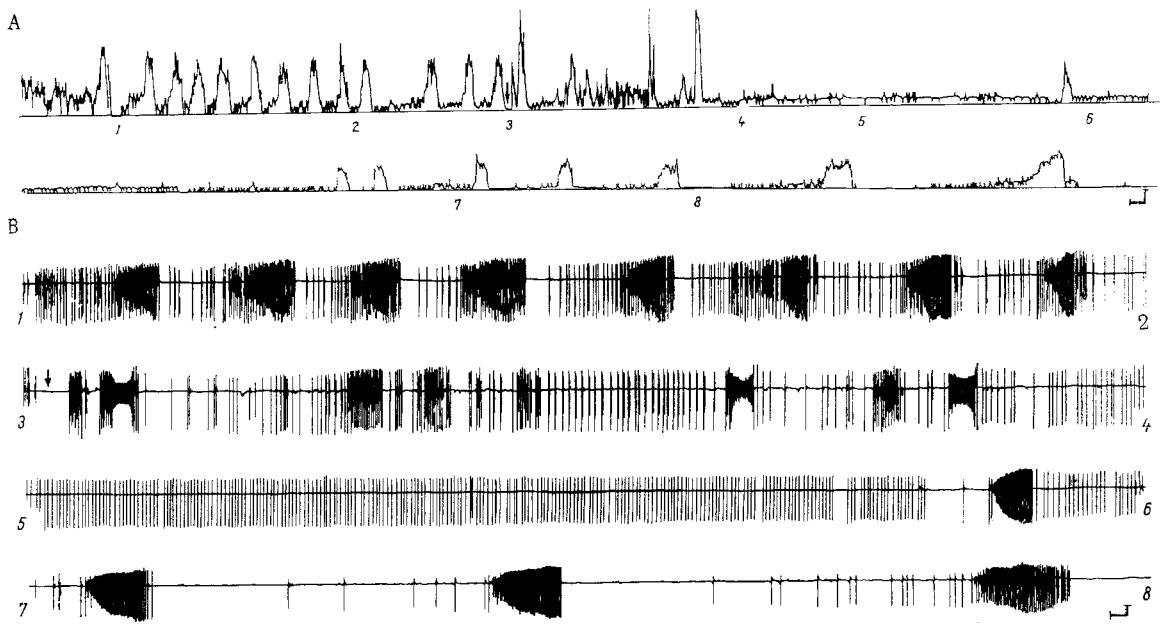

Fig. 1. Effect of mebicar (300 mg/kg) on development of EF and IID in epileptic focus formed by penicillin application. Mebicar injected intraperitoneally 30-50 min after application of penicillin to cerebral cortex during regular EF. A) Successive cuts of record of momentary frequency of EF and IID; cuts designated by numbers illustrated in the form of an ECoG. Arrow shows time of injection of mebicar. Recording began 30 min after application of penicillin. Calibration: For A 1 Hz, for B 200 mV.

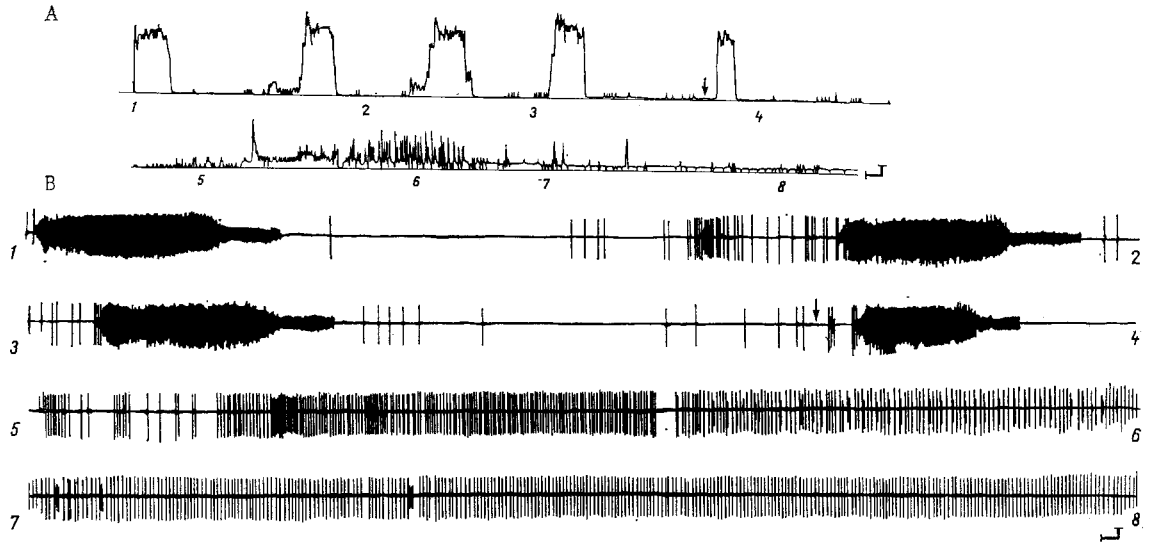

Fig. 2. Total suppression of EF and activation of IID following administration of mebicar in a dose of 500 mg/kg. Traces in A recorded 20 min after application of penicillin to cortex. Mebicar injected 55 min after application of penicillin. Remainder of legend as in Fig. 1.

EXPERIMENTAL RESULTS

Interictal discharges accompanied by contractions of muscles of the animal's contralateral limb appeared on the ECoG in the zone of the excitation generator 4-6 min after application of penicillin to the cortex. The frequency of the IID did not exceed 22 ± 3 min^{-1}. Regular EF with a mean frequency of 0.1 min^{-1} appeared 15-20 min later in the zone of penicillin application; the duration of each EF was 40 ± 5 sec. The total life of the epileptic focus from the time of penicillin application until the end of EF and IID averaged 240 min.

Mebicar, injected in a dose of 300 mg/kg 30-40 min after penicillin application, evoked initially a decrease in the frequency of the hitherto regular EF, combined with a decrease in their duration and an increase in the frequency of electrical activity during EF, followed by their total suppression after 10-15 min (Fig. 1). In the period of the inhibitory effect on EP an increase was found in the frequency of IID (Fig. 1: 5 and 6). In the dose specified mebicar depressed EF for 60-80 min, after which the EF were restored. After mebicar in a dose of 500 mg/kg the EF ceased completely, but at the same time the IID were activated (Fig. 2).

During continuous electrical stimulation of VPL, depending on conditions of stimulation (frequency and strength of the stimulating current) alternation of periods during which each stimulation of VPL evoked IID ("active" period) or did not evoke IID ("passive" period) could be obtained on the ECoG [8, 15]. If the "active" period was accompanied by high-frequency EF, injection of mebicar in a dose of 300 mg/kg did not affect alternation of the "active" and "passive" periods, but the high-frequency EF ceased completely (Fig. 3C). With an increase in the strength of stimulation of VPL conditions could be obtained under which each stimulus was accompanied by IID for a long period (Fig. 3A: 1, 2). Under these conditions injection of mebicar in a dose of 300 mg/kg reconverted the epileptic focus to the pattern of activity marked by alternation of "active" and "passive" periods.

Interaction between mebicar and convulsants such as strychnine nitrate (1.3 mg/kg, subcutaneously), metrazol (75 mg/kg, intraperitoneally), and camphor (200 mg/kg, subcutaneously) was studied previously and no anticonvulsant action of the drug was found on these models [3].

The results of the present investigation are evidence that mebicar exerts an anticonvulsant effect on focal models of epilepsy. The significance of the experimental model of epilepsy for manifestation of the anticonvulsant action of drugs also was noted previously. In particular, the use of strychnine or penicillin [4, 12] as epileptogens, which disturb different synaptic mechanisms, also is responsible for the difference in the mechanisms of action of anticonvulsants on epileptic foci. A study of the anticonvulsant action of diphenylhydantoin showed that this substance suppresses generalized EF but does not affect IID [11] or may even activate them [12]. The same pattern was found by the present writers when studying the anticonvulsant action of diazepam on models of both primary generalized epilepsy [6] and focal cortical epilepsy [7-9]. In a discussion of the mechanisms of IID and EF generation in the epileptic focus [7-9] it was suggested that they may be based on different processes, on which pharmacological agents may have different effects. Comparison of the action of diazepam and mebicar on the epileptic focus indicates that they have something in common. Both diazepam and mebicar act in opposite directions on EF and IID: both drugs depress and activate IID formation. The writers showed previously [9] that besides its action on GABA-ergic inhibition [16], diazepam also activates Na,K-ATPase of synaptosomal membranes of the brain in a penicillin-induced focus of epileptic activity, and thereby facilitates a fall in the extracellular K^+ concentration, an increase in which is a factor in EF formation [14]. At the same time, activation of the Na,K-pump makes inhibitory interaction between neurons in the epileptic focus less effective [5], and on the one hand this may cause an increase in the frequency of IID and on the other hand a decrease in synchronization of neuronal discharges and an increase in the variability of their amplitude. The fact that the amplitude of IID remains constant as their frequency rises under the influence of mebicar indicates that the mechanism of synchronization of neurons, on which their inhibitory interaction is based, is preserved in the region of the focus. Depression of EF under the influence of mebicar is evidently mainly due to the increased effectiveness of synaptic inhibition of the neurons in the epileptic focus. The general level of neuronal excitability remains high, and it is this which causes an increase in the frequency of IID.

The mechanism of action of mebicar on a GPEE in the cerebral cortex can thus be represented as follows. On the one hand, potentiation of synaptic inhibition of neurons in the epileptic focus disturbs the formation of the epileptic pool of neurons, thus preventing the formation of EF, and on the other hand, against the background of a high level of excitability of neurons in the epileptic focus, strengthening of inhibitory interaction between neurons promotes their synchronization, which is manifested as stabilization of the amplitude of IID.

On the basis of the results of a study of the anticonvulsant action of mebicar described in this paper widening of the spectrum of its clinical application, especially as an anticonvulsant, can be recommended.

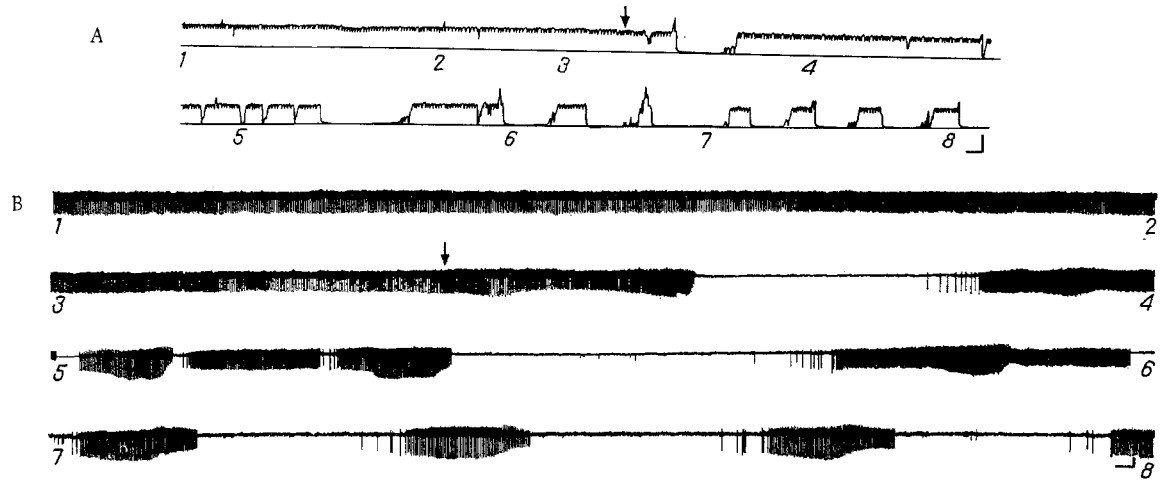

Fig. 3. Inhibition of high-frequency cortical epileptic discharges during continuous thalamic stimulation following injection of mebicar in a dose of 300 mg/kg (C). High-frequency components of "active" period depressed by injection of mebicar, duration of "active" period also reduced. A) Histogram of momentary frequency of IID in epileptic focus during continuous thalamic stimulation; B) corresponding cuts on ECoG. Before injection of mebicar each thalamic stimulation evoked IID in the cortex, but after injection of mebicar in a dose of 300 mg/kg alternation of "active" and "passive" periods occurred. Remainder of legend as in Fig. 1.

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