ACTION OF ANTIEPILEPTIC DRUGS ON MYOCLONIA OF SPINAL ORIGIN

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The theory of generator mechanisms of neuropathological syndromes characterized by hyperactivity of systems [8, 9] not only provides experimental models of neuropathological syndromes but is also the basis for elaboration of their specific pathogenetic treatment. Previous investigations in which a generator of pathologically enhanced excitation was created in the spinal part of the nociceptive system (the region of the posterior horns of the spinal cord) showed that a pain syndrome of spinal origin can be suppressed or totally eradicated by inhibitory mediators and antiepileptic drugs [2, 3, 10].

In the present investigation the effects of anticonvulsive (diphenylhydantoin, carbamazepine, diazepam) drugs were tested on generalized myoclonia of spinal origin, caused by the creation of a generator in the central horns of the spinal cord. The syndrome known as generalized myoclonia of spinal origin is characterized by paroxysms of clonic and tonic activity, resembling epileptiform discharges in epilepsy. This resemblance of electrical activity (EA) suggests that spinal myoclonia can be regarded as epilepsy at the spinal cord level.

EXPERIMENTAL METHOD

Experiments were carried out on noninbred albino rats weighing 200 g. A generator of pathologically enhanced excitation in the system of propriospinal neurons of the anterior horns of the lumbar segments of the spinal cord was created with the aid of tetanus toxin (TT) (40 MLD for mice), which was injected into the leg muscles. Under these conditions TT reached the anterior horns of the spinal cord via the regional neural pathway [6]. The vascular path of spread of TT was blocked by intravenous injection of antitoxin in a dose of 0.025 i.u. The generator was activated by stimulation (squeezing the skin and toes) of the limb on the side of injection of TT. EA was recorded on an 8-channel EEG-8.111 electroencephalograph (East Germany). Potentials were derived by bipolar needle electrodes. EA was recorded in the spinal and sacral muscles and the posterior group of femoral muscles on both sides. Experiments were carried out on animals with an intact spinal cord or on animals spinalized at the T2-T3 level. The spinal cord was divided under ether anesthesia 24 h before the experiment. Anticonvulsants were injected intramuscularly in the following doses: diphenylhydantoin 100 mg/kg, carbamazepine 30 and 50 mg/kg, diazepam 0.5-10 mg/kg. In control experiments, the universal solvent of the drugs was injected into the animals in the same volumes as when the drugs were given.

EXPERIMENTAL RESULTS

Periodic twitches appeared in the animals 96 h after injection of TT, and they were expressed on the EMG as paroxysmal synchronized bursts of EA, equal in amplitude and duration, and recorded in all groups of muscles; they were the clonic components of the syndrome. This phenomenon has been described under the name of "strychnine-like tetanus" [6, 7]. During stimulation of the limb on the side of injection of TT (the left hind limb) a burst of high-amplitude EA, tonic in character, was recorded in all the muscles, and in some experiments it was accompanied by a long after-effect. The complete syndrome described above has been called generalized myoclonia of spinal origin [9].

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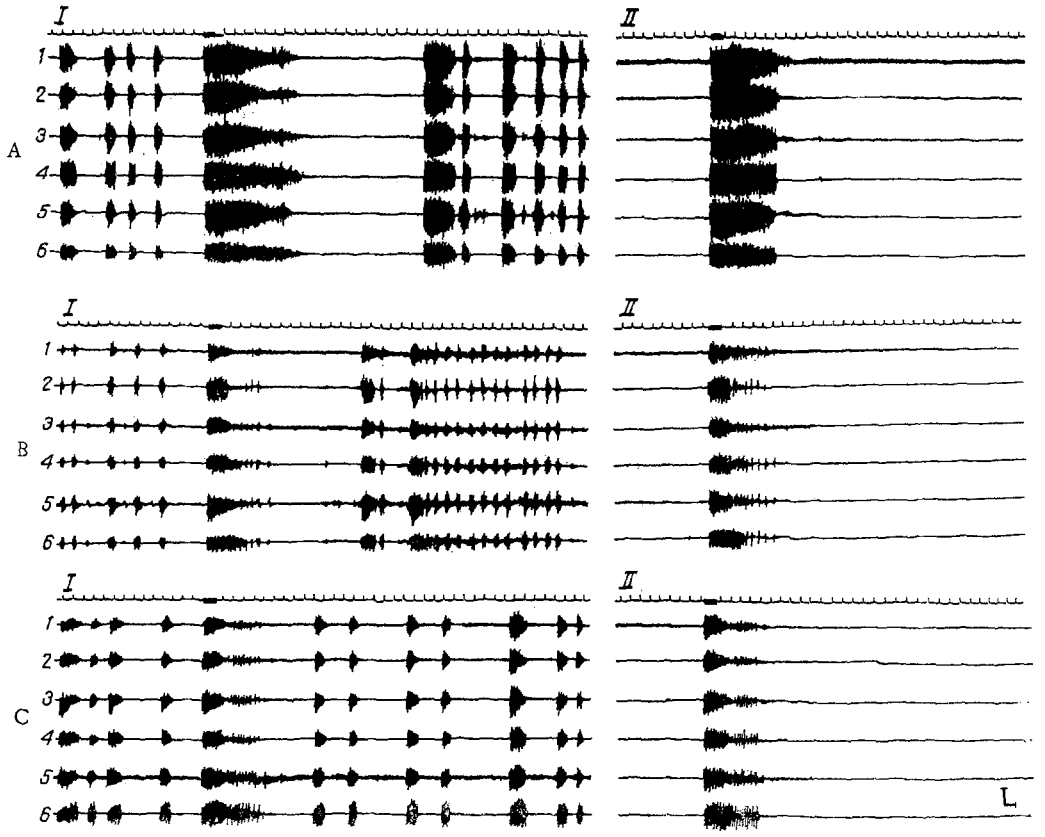

Fig. 1. Effect of antiepileptic drugs on EA of muscles of spinalized animals with spinal myoclonia. EA of muscles of rat before (I) and 15 min after (II) intramuscular injection of diphenylhydantoin in a dose of 100 mg/kg (A), carbamazepine in a dose of 50 mg/kg (B), and diazepam in a dose of 2 mg/kg (C). Derivations: 1, 2) right and left spinal muscles, respectively; 3, 4) right and left sacral muscles, respectively; 5, 6) posterior group of muscles of right and left thigh, respectively. Calibration: 250 μV, 1 sec. Marker of stimulation is thickened region along line of time marker.

In animals with an intact spinal cord diphenylhydantoin suppressed clonic EA (in 80% of cases) or slowed its frequency and reduced the amplitude and duration of single discharges (in 20% of cases) but had no significant effect on evoked tonic activity. After division of the spinal cord the character of the action of the drug was unchanged, but in some experiments the duration of the after-effect on tonic activity was reduced (Fig. 1A).

In animals with an intact spinal cord carbamazepine had a similar action: It either inhibited clonic activity (50% of cases) or reduced its frequency, but left the amplitude of evoked tonic activity unchanged. Carbamazepine also had a similar effect after spinalization of the animal (Fig. 1B). It is a noteworthy fact that in some experiments an increase in the amplitude and duration of each clonic discharge was observed simultaneously with a decrease in their frequency. Unlike diphenylhydantoin, carbamazepine caused no change in the after-effect.

In the minimal threshold dose (0.5 mg/kg) in animals with an intact spinal cord diazepam slowed the frequency of the clonic discharges, but with an increase in the dose (1 mg/kg) it completely abolished them. A further increase in the dose of the drug (to 5 mg/kg) led to a decrease in the amplitude of the tonic EA also, in the spinal muscles on both sides and in the right sacral muscles, i.e., in regions more remote from the generator of pathologically enhanced excitation (Fig. 2A). Only in a large dose (10 mg/kg) did diazepam abolish tonic EA almost completely, and in that case also in muscles innervated by segments of the spinal cord in which the generator was located, and also in adjacent regions (left sacral muscles), EA of low activity and very short duration was preserved (Fig. 2B). In animals with an intact spinal cord diazepam (2 mg/kg) acted in the same way as the drugs described above (Fig. 1C). An increase in the dose to 10-15 mg/kg did not change the effect of the drug.

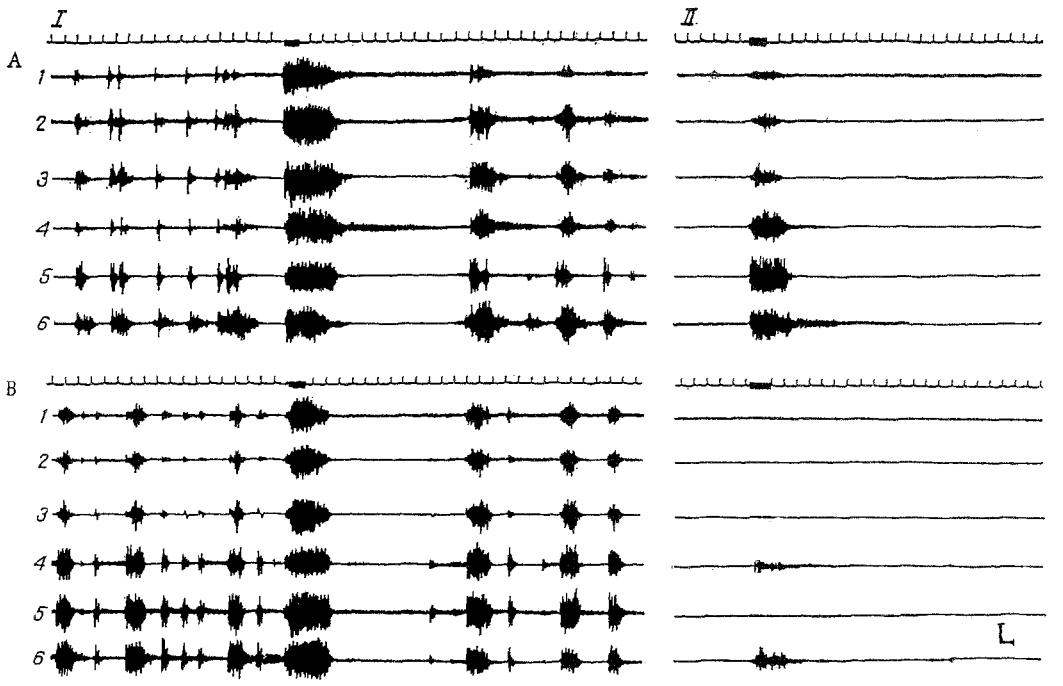

Fig. 2. Effect of diazepam on EA of muscles in animals with spinal myoclonia EA of muscles of rats before (I) and 10 min after (II) intramuscular injection of diazepam in doses of 5 (A) and 10 mg/kg (B) into animals with intact spinal cord. Remainder of legend as to Fig. 1.

The antiepileptic drugs tested acted mainly on clonic seizure discharges, either reducing their frequency (carbamazepine, diazepam in small doses), or abolishing them completely (diphenylhydantoin, carbamazepine, diazepam in average doses). Evoked tonic EA, however, was resistant to the action of these drugs. Only diazepam, in large doses, led to the abolition of all types of paroxysmal EA because of its sedative effect.

It is important to note that the drugs tested were active after division of the spinal cord, i.e., they acted at the spinal level.

The results can be explained both by the specific character of the action of the drugs and by the particular features of the neurochemical organization of the excitation generator that plays the role of hyperactive determinant structure [9]. Diphenylhydantoin has a direct inhibitory action on spinal polysynaptic reflexes, it inhibits synaptic transmission in the spinal cord [23], it can stabilize the normal level of the threshold of excitability of the hyperactivated neuron [4], and it reduces posttetanic potentiation at the spinal level [20]. Interoceptive inhibition, realized through a system of interneurons, is very sensitive to diphenylhydantoin [1].

Similar results also were obtained when the other anticonvulsants (carbamazepine, diazepam) were tested. Carbamazepine is effective in various forms of pathology connected with paroxysmal activity [18, 22]. It reduces the frequency of seizure discharges [5] and is effective in the treatment of tonico-clonic convulsions and complex seizure discharges [12]. Like diphenylhydantoin, carbamazepine inhibits posttetanic potentiation at the spinal level [17]. Diazepam is highly active against myoclonic spasms [13, 15], it is highly effective against generalized seizure discharges [19], and it limits the spread of seizure activity [14, 21]. At the same time, it has been shown that none of these antiepileptic drugs has any significant effect on the basic focus of epileptic activity [11, 16].

All these data agree with the results of our own investigations. The drugs tested abolished generalized myoclonic discharges but did not suppress the burst of tonic paroxysmal activity. The action of the anticonvulsants on the excitation generator itself was less effective than on other parts of the pathological system, evidently on account of the high level of excitation of the generator and the particular features of its functional organization. Not all neurons were inhibited to the same degree; "leading" neurons could remain active and formed the basis for functional recovery of the generator and the syndrome evoked by it [9]. Such neurons may be suppressed by the action of anticonvulsants in very large

doses, as was shown in the experiments with diazepam, which proves to be the most effective of all the drugs we used.

The results of these experiments agree in principle with those obtained previously [2], which showed that the syndrome evoked by an excitation generator created in another system and, in particular, in the posterior horns of the spinal cord, can be suppressed by anticonvulsants.

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