ANALGESIC EFFECTS OF ANTIEPILEPTIC DRUGS IN A PAIN SYNDROME OF SPINAL ORIGIN

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A pain syndrome of spinal origin was induced by the formation of a generator of pathologically enhanced excitation (GPEE) in the dorsal horns of the lumbosacral segments of the rat spinal cord by means of disinhibitors (tetanus toxin, strychnine, penicillin) and depolarizers (KCl and ouabain), applied to one side of the dorsal surface of the spinal cord in a 1% agar wafer. The investigations showed that the "analgesic" action of the anticonvulsants was determined by the nature of the GPEE thus formed. Diphenylhydantoin had no significant effect on the development of pain syndromes induced by disinhibitors but abolished those due to the action of depolarizers. Carbamazepine abolished pain syndromes associated with the formation of a GPEE by depolarizers, lengthened the latent period of appearance of the syndrome following the formation of a GPEE by tetanus toxin, shortened the duration of the pain syndrome produced by a "strychnine" generator but did not abolish the syndrome produced by a "penicillin" generator. Seduxen had a similar action to carbamazepine and the depth of the effect depended on dose. Phenazepam, a new Soviet tranquilizer, had a stronger action than seduxen. It is concluded that the activity of a generator located in the nociceptive system and the spread of pathologically enhanced excitation produced by the generator over this system can be inhibited by means of antiepileptic drugs, and in that way a pain syndrome of spinal origin can be abolished. The results are in agreement with the theory of the generator mechanisms of central pain syndromes.

KEY WORDS: determinant structure; generator of pathologically enhanced excitation; pain syndrome of spinal origin; antiepileptic drugs.

It has been shown that a pain syndrome of spinal origin can be induced by creating a generator of pathologically enhanced excitation (GPEE) in the posterior horns of the spinal cord [5-7]. The GPEE can be created by means of substances disturbing inhibitory mechanisms or by substances inducing depolarization of neurons [5]. In every case a pain syndrome with a characteristic and consistent clinical picture arises, although the pathogenetic nature of the GPEE is different in each case. It was shown previously [4] that the GPEE can be depressed by local action on the region affected by it by means of inhibitory mediators; this effect, moreover, is specific and corresponds to the pathogenetic nature of the GPEE. On depression of the GPEE the whole pain syndrome also is abolished for the time of action of the mediators. Since the pathogenetic basis of this pain syndrome is the formation of a hyperactive structure – a GPEE in the posterior horns of the spinal cord – it was decided to investigate the effects of various antiepileptic drugs (diphenylhydantoin, carbamazepine, seduxen, phenazepam) on this pain syndrome.

EXPERIMENTAL METHODS

Experiments were carried out on albino rats weighing 200-220 g. A pain syndrome of spinal origin was induced by the use of drugs disturbing various types of inhibition (tetanus toxin, strychnine, penicillin), and depolarizing agents (KCl and ouabain). The substances were deposited in 1% agar, a wafer of which was applied to the surface of the spinal cord (the agar wafer method, see [4]). A wafer measuring 10 × 4 × 1.5 mm was

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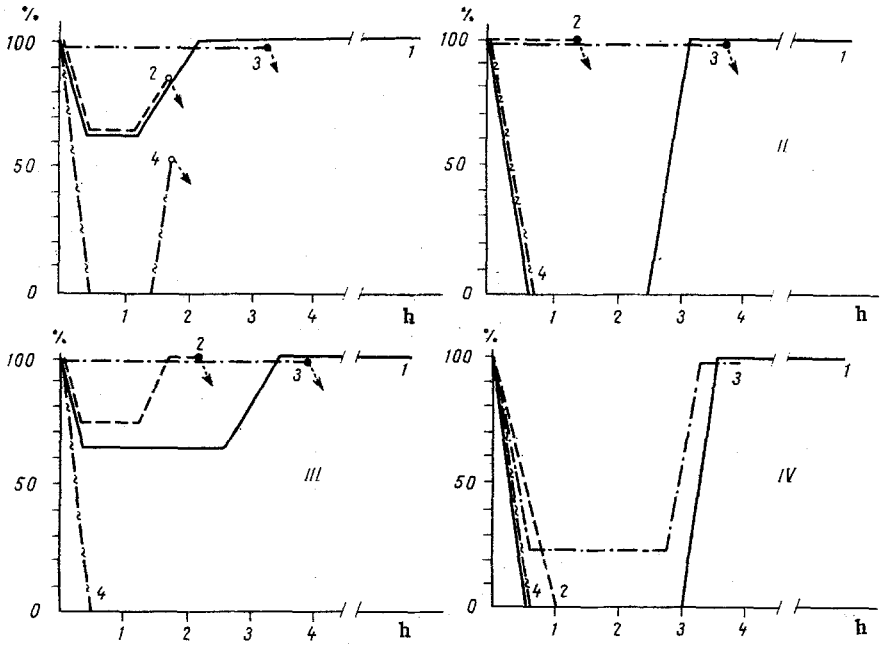

Fig. 1. Effects of antiepileptic drugs on pain syndrome of spinal origin. Abscissa, degree of development of pain syndrome (in %, maximum of manifestation of syndrome taken as 100%); ordinate, duration of pain syndrome (in h). Effect of diphenylhydantoin (I), carbamazepine (II), seduxen (III), and phenazepam (IV) on pain syndromes induced by GPEE created by tetanus toxin (1), strychnine (2), penicillin (3), and KCl (4). Empty circles indicate stopping action of anticonvulsant; syndrome thereupon goes into a decline as a result of termination of the action of the substance inducing the pain syndrome (arrows). Filled circles denote stopping action of substance inducing pain syndrome; syndrome thereafter gradually goes into decline (arrows). After application of tetanus toxin to produce a GPEE the pain syndrome continues to increase progressively and the animals die after 18-25 h.

applied to one side of the dorsal surface of the spinal cord in the region L2-L6. The following substances were added to 1 ml of 1% agar: 1 ml tetanus toxin containing 15-50 MLD for rats; 1 ml 0.1% strychnine; 1 ml penicillin, containing 15,000 units; 1 ml 75 mM KCl, 1 ml 0.5 mM ouabain. The behavior of the animals was observed and in some cases a sound recording and actogram were made before and after injection of the drugs, using a specially constructed chamber with acoustic detectors and strain gauges. The drugs were injected at the height of the pain syndrome in the following doses: diphenylhydantoin 100 mg/kg intramuscularly, carbamazepine 50 mg/kg intramuscularly, seduxen 2-5 mg/kg intravenously, phenazepam 2 mg/kg intravenously. The doses selected had only a sedative and not a narcotic effect. In one series of experiments carbamazepine in a dose of 200 mg/kg was given by mouth in liquid starch to the animals 30 min before application of the substance inducing the formation of the GPEE so that the carbamazepine concentration would reach a maximum at the time of maximal manifestation of the pain syndrome. In the control experiments the animals received injections of the solvent (70% propylene glycol and 30% ethyl alcohol by volume) in the same volume as was used to inject the anticonvulsants. The spinal cord was exposed under ether anesthesia. The latent period of the pain syndrome and its duration were measured from the time of application of the substances inducing the pain syndrome. The maximum of the manifestation of each pain syndrome, i.e., the highest frequency and longest duration of the paroxysms, was taken as 100% (Fig. 1).

EXPERIMENTAL RESULTS

The investigations showed that after application of the disinhibitors and depolarizers to the dorsal surface of the lumbar segments of the spinal cord a pain syndrome developed. The syndrome was characterized by a group of symptoms consistent with that described previously [3, 6, 7] when tetanus toxin was used. When a certain time (30-50 min) had elapsed after application of the substances (in the doses chosen) the animals

began to lick an area of the limb on the side of application. These areas were trigger zones. Application of stimuli to them readily induced a fit: The animals cried and attacked the limb; or the fits appeared spontaneously. As the syndrome developed the spontaneous paroxysms of pain increased in frequency, the fits became more and more severe, and the animals cried, ran from place to place, attacked the limb on the side of application, and licked or even bit the limb tissues.

The clinical picture of the pain syndrome induced by different substances showed certain special features. When strychnine and penicillin were used the syndrome developed practically immediately after the animals recovered from the anesthetic: They began to bite the limb; the severity of the syndrome increased rapidly for 20-30 min; the duration of the pain syndrome following application of penicillin was twice as long, and the animal "nursed" the corresponding limb (held it semiflexed). Pain syndrome induced by application of KCl and ouabain (under these experimental conditions) appeared after a longer latent period (30-40 min) and the spontaneous fits were weaker in intensity than in the strychnine and penicillin syndromes.

The experimental results are illustrated in Fig. 1. They show that diphenylhydantoin (Phenytoin) had a weak action on the development of pain syndromes induced by disinhibitors (tetanus toxin, strychnine, penicillin) and inhibited the pain syndrome due to the action of depolarizers (KCl). Carbamazepine (Tegretol, Finlepsin) lengthened the latent period of onset of the pain syndrome associated with a GPEE created with tetanus toxin and strychnine, abolished (during the action of the drug) the pain syndrome of a tetanus generator at the height of its development, but did not abolish the strychnine pain syndrome under these conditions, and it was ineffective against a penicillin generator.

Like diphenylhydantoin, carbamazepine also abolished the pain syndrome induced by depolarizers – KCl and oubain. The effect of seduxen (diazepam, Valium) on the pain syndromes also was similar to that of carbamazepin. The strength of action of the drug depended on its dose. Pain syndromes induced by depolarizers could be completely abolished by the use of small doses (2 mg/kg) of seduxen. In pain syndromes induced by tetanus toxin and strychnine, small doses of seduxen led only to slight reduction in the intensity of the pain syndromes: a reduction in the frequency and strength of the attacks of pain. The action of small doses of seduxen on a tetanus generator was stronger than on a strychnine generator. Large doses of the drug (5 mg/kg) completely abolished the attacks of pain. Seduxen had virtually no action on the penicillin generator. All that could be observed was that the animals were less aggressive after receiving large doses of seduxen. The effect of phenazepam (a drug of the benzodiazepine series similar in chemical structure to seduxen [1, 2]) differed from those of seduxen in their depth and duration, and the dose required to give its maximal effect was only one-third to one-half of that of seduxen: Phenazepam in small doses (2 mg/kg) completely abolished (in four of seven experiments) or considerably weakened (in three of seven experiments) the pain syndrome following application of tetanus toxin, as shown by a marked decrease in the frequency and intensity of the paroxysms and disappearance of the animal's aggressiveness. The duration of action of phenazepam could be up to 4 h. Against a strychnine generator phenazepam was not effective immediately: During the first 15-30 min the painful manifestations weakened in the animals but did not disappear completely, but after 20-30 min the pain syndrome ceased and did not return (the duration of action of the strychnine itself was 2 h). As regards the penicillin generator, against which seduxen was virtually inactive, phenazepam led to marked weakening of the pain syndrome, so that the animal did not bite the affected limb, although it still squeaked and showed some degree of motor excitation. The pain syndrome due to the action of depolarizers was abolished by phenazepam immediately after injection and did not subsequently return. The solvent had virtually no action on the pain syndromes. Only in the case of intravenous injection was there a temporary (15-20 min) and slight weakening of the pain syndrome.

The specific features of these effects of the various drugs were connected with the nature of the generator formed, i.e., they depended on which inhibitory systems in the neuron populations of the GPEE were inactivated or weakened, and how this was brought about. Tetanus toxin is known to disturb the release of inhibitory transmitters (GABA and glycine), but without blocking receptors on the postsynaptic membrane [9, 11, 13]; strychnine disturbs inhibition by blocking the glycine receptors of the postsynaptic membrane [12]; penicillin blocks GABA receptors on the post- and presynaptic membranes [15]; there is also evidence that strychnine and penicillin and certain other convulsants are not true competitors for glycine and GABA respectively, and that the disturbance of inhibition is evidently due to blocking of membrane channels for Cl ions [18, 20]. Hyperactivity of neurons induced by KCl and ouabain is connected with the direct depolarizing action of these agents [17] and with potentiation of mediator liberation from nerve endings.

It can accordingly be suggested that the effects of carbamazepine are connected with the inhibitory action of GABA. Penicillin, which blocks GABA receptors, prevents the action of carbamazepine. Besides its supra-

spinal action, carbamazepine is also known to influence spinal structures: It inhibits spinal polysynaptic reflexes, depresses synaptic transmission [16], and reduces posttetanic potentiation, which may lead to weakening both of the GPEE itself and of its effects, which are realized at the supraspinal level in the form of pain syndromes. Seduxen also depresses spinal reflexes and considerably reduces responses to repetitive stimulation [19]. The effects of seduxen on the pain syndromes described above can probably be explained by increased affinity of GABA for its specific receptors brought about under the influence of the drug; large doses of seduxen delay GABA liberation [8, 14, 21]; it is also suggested that seduxen can act presynaptically, facilitating GABA liberation from nerve endings [10]. Phenazepam (a derivative of seduxen – bromine and methyl groups are introduced into the formula of seduxen [1]), has a stronger action. Phenazepam has a distinct effect even on the "penicillin" generator when GABA receptors are blocked. Its action probably leads to activation of inhibitory mechanisms, which are weakly activated by seduxen. It can tentatively be suggested that the point of application of all the anticonvulsants tested is the polysynaptic connections entering and leaving the GPEE. In the writers' latest experiments these same anticonvulsants were shown to have a similar inhibitory action on other syndromes due to a GPEE in the anterior horns and in the system of propriospinal connections. The facts described above explain the analgesic effect of antiepileptic drugs which are not true analgesics in the pharmacological sense. The results are also in agreement with the theory of generator mechanisms of central pain syndromes [5, 6], for which they provide further substantiation.

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