CHANGES IN CORTICAL ELECTRICAL RESPONSES IN RATS WITH A DEAFFERENTATION PAIN SYNDROME

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Injection of penicillin or tetanus toxin into the central zones of the brain nociceptive system causes the animal to develop a marked pain syndrome [1]. This is due to the formation of a generator of pathologically enhanced excitation (GPEE), which is a group of hyperactive neurons with disturbed inhibitory control and with lowered thresholds of excitability [1], in these brain zones. We know from numerous clinical observations that in man after peripheral nerve trauma lasting pain syndromes develop, and their character and course point to involvement of central nervous formations in the pathological process, and suggest that a GPEE is formed in them [4, 6]. The aim of this investigation was to study changes in spontaneous and evoked cortical electrical activity of the rat brain during the development of a pain syndrome in the animals after sciatic nerve injury.

EXPERIMENTAL METHOD

Experiments were carried out on 23 noninbred male rats weighing 200-220 g. The sciatic nerve was divided under hexobarbital anesthesia at the level of the popliteal fossa distally to the site of the ligature. The proximal end of the divided nerve was placed in a polyethylene tube with a soldered end and was left in the sutured wound. In control experiments animals underwent a mock operation, which included all the manipulations carried out on the experimental animals except sciatic nerve trauma. The thresholds of the nociceptive responses of all the animals were determined by the hot plate test, based on the response of licking the limbs (surface temperature of the plate 55°C). Recording of brain electrical activity began 20-25 days after division of the sciatic nerve, on the appearance of signs of autotomy on the traumatized limb, evidence of the development of a pain syndrome. Under ether anesthesia the animals were fixed in a stereotaxic apparatus, immobilized with suxamethonium, and maintained on artificial ventilation of the lungs. Evoked potentials (EP) during electrical stimulation of tissues of the hind- and forelimbs were recorded by silver surface electrodes with a tip 0.8 mm in diameter, in the somatosensory cortex of both hemispheres, in the focus of their maximal activity (FMA), where the positive-negative EPs had the shortest latent period and the greatest amplitude. The reference electrode was secured in the region of the frontal sinus. Electrical stimulation of the tissues of the fore- and hind-limbs was applied through bipolar needle electrodes, introduced subcutaneously at symmetrical points on the right and left sides, with square pulses 0.1 msec in duration. Electrical stimulation of tissues of the hind limbs was applied above the point of division of the sciatic nerve. Evoked potentials were averaged and analyzed by specialized computer, using 10 presentations.

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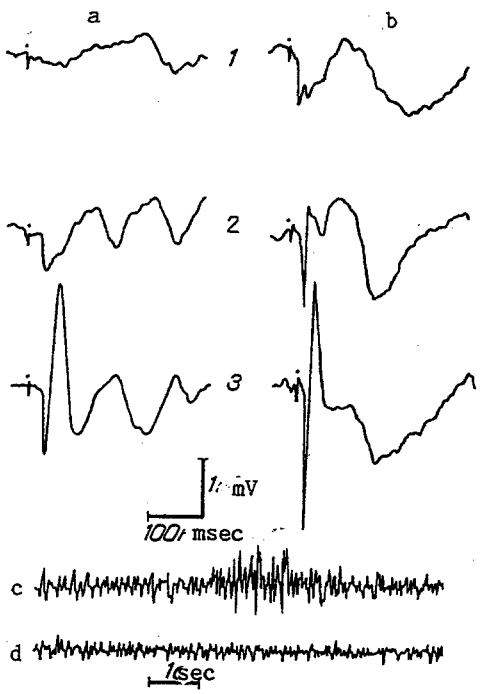

Fig. 1. Spontaneous and evoked electrical activity in somatosensory cortex of rats with pain syndrome after division of sciatic nerve: a) contralateral EP in response to stimulation of tissues of healthy hind limb; b) contralateral EP to stimulation of tissues of limb with divided nerve; 1: b) threshold appearance of EP in contralateral hemisphere in response to stimulation of tissues of limb with divided nerve; a) absence of response in contralateral hemisphere to similar stimulation of tissues of intact limb; 2: a and b) EP to stimulation of twice threshold intensity; 3: a and b) EP to stimulation 3 times the threshold of intensity; c) spontaneous electrical activity in hemisphere contralateral to intact limb; d) spontaneous electrical activity in hemisphere contralateral to limb with divided nerve.

EXPERIMENTAL RESULTS

Recording the thresholds of nociceptive response in the animals during the first 3 weeks after division of the sciatic nerve revealed a gradual lowering of the thresholds of the nociceptive response and the development of hyperalgesia, which reached maximal intensity after 20-25 days. Meanwhile the animals' behavior changed: they became restless, they licked and bit the limb with disturbed innervation vigorously. As a rule, the development of hyperalgesia coincided in time with the appearance of signs of autotomy, evidence of the presence of a pain syndrome in the rats [2]. The study of spontaneous electrical activity of these rats in the somatosensory cortex showed that, by contrast with the control animals, paroxysmal high-amplitude (700-800 μV) synchronized discharges were recorded in the hemisphere contralateral to the divided nerve in the experimental animals, in the form of groups of pointed waves (Fig. 1c). The appearance of these groups of waves 1-2 sec in duration was irregular. Similar changes in EEG activity also are observed in patients with a phantom pain syndrome [3]

Marked changes in electrical activity in rats with the pain syndrome were found when EP were recorded also. The latent periods of onset of contralateral EP to stimulation of tissues of the hind limbs with divided and intact nerves did not differ significantly, but amounted to 14.8 ± 1.2 and 14.2 ± 1.6 msec respectively. An important sign distinguishing the contralateral EP to electrical stimulation of tissues of the limb with a divided nerve from the contralateral EP to stimula-

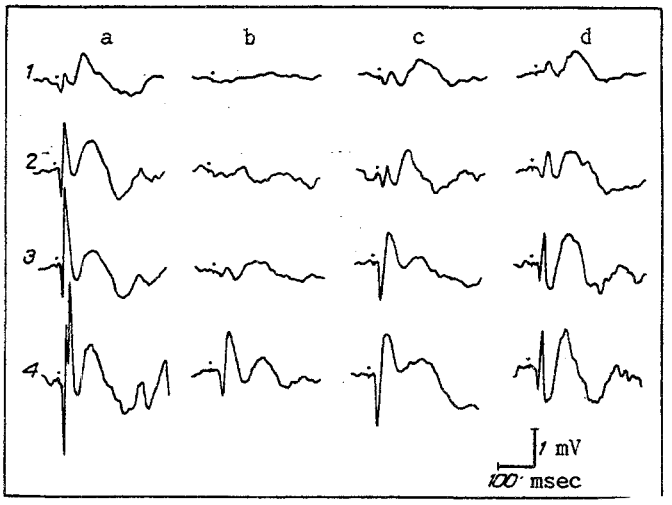

Fig. 2. Contralateral and ipsilateral EP in animals with pain syndrome in response to stimulation of tissues of limbs with damaged and intact sciatic nerve. EP in contralateral (a) and ipsilateral (b) somatosensory cortex to stimulation of tissues of limb with divided nerve. EP in contralateral (c) and ipsilateral (d) somatosensory cortex to stimulation of tissues of limb with intact nerve. 1) EP to threshold stimulation; 2-4) EP to stimulation of 2, 3, and 4 thresholds in intensity.

tion of the symmetrically opposite point on the intact limb (Fig. 1) was the lower threshold of their onset (0.71 ± 0.1 and 1.2 ± 0.17 mA respectively; $p < 0.05$). Other features distinguishing EP in rats with a pain syndrome were the greater amplitude of the early components and the presence of late components in contralateral EPs, arising in response to stimulation of tissues of the limb with a divided nerve compared with EP in response to stimulation of the symmetrically opposite point of the intact limb. With an increase in the strength of the stimulating current to twice or three times the threshold strength or more, predominance of amplitude of the responses to stimulation of the limb with the divided nerve was preserved (Fig. 2). Meanwhile, extension of the FMA of the contralateral EP also was observed in response to stimulation of the tissues of the limb with a divided nerve, which was 2-3 times larger than FMA of the contralateral EP to stimulation of tissues of the intact hind limb. Moreover, high-amplitude positive-negative responses to stimulation of the forelimb, and also ipsilateral responses to stimulation of the intact hind limb were observed in animals with a pain syndrome in the zone of representation of the hind limb in the hemisphere contralateral to the limb with the divided nerve. The threshold of onset of ipsilateral EP in response to stimulation of the intact hind limb did not differ from the threshold of onset of the contralateral EP. During stimulation of tissues of the limb with the divided nerve the threshold of onset of responses in the contralateral cortex was more than 3.5 times lower than the threshold of onset of EP in the ipsilateral hemisphere (Fig. 2). These changes can be explained by an increase in excitability of the neurons and by activation of additional, previously nonfunctioning inputs from neighboring regions to deafferented neurons; the plastic modifications on which these processes are based, moreover, can take place not only at the spinal cord level [7], but also at the level of cortico-subcortical and intracortical connections [8], as is shown by the appearance of low-threshold responses to stimulation of the ipsilateral forelimb and contralateral hind limb, in the somatosensory cortex contralateral with respect to the divided nerve, in the region of representation of the hind limb.

The appearance of late components in the evoked responses in animals with a pain syndrome to low-threshold stimulation of the limb with the divided nerve was due to increased excitability of neurons in nonspecific brain structures, involved in the conduction and analysis of somatosensory signals. All the data described above, namely the appearance of spontaneous paroxysmal high-amplitude pointed waves in the cortex, an increase in the amplitude of EP and lowering of the thresholds of their appearance, and enlargement of FMA of responses of the somatosensory cortex of the hemisphere contralateral relative to the divided nerve, are evidence of an increase in the degree of excitability and the number of neurons responding to nociceptive stimulation and of the ability of the population of these neurons to generate spontaneous discharges. It can be concluded from these characteristics that after division of the sciatic nerve a GPEE is formed in

the nociceptive system. The identity of the central structures of the nociceptive system in which the GPEE is formed requires further study.

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EFFECT OF NEUROTROPIN ON SEIZURE ACTIVITY IN PICROTOXIN KINDLING

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The study of the effect of neurotropin on models of generalized seizures, induced by various epileptogens, has demonstrated its antiepileptic activity in picrotoxin-induced seizures [5]. It was decided to study the anticonvulsant activity of neutrotropin on other models of epileptic activity (EpA). One model of progressively increasing EpA and prolonged and enhanced seizure activity is picrotoxin kindling [3]. Furthermore, to continue the study of the mechanisms of the anticonvulsant action of neurotropin, its effects were studied when protein synthesis was blocked by cycloheximide [4].

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 220-320 g. Each group consisted of 10 animals. Pharmacologic kindling was produced by daily single intraperitoneal injections of picrotoxin ("Sigma," USA) in a dose of 1.0 mg/kg body weight [3]. The intensity of the seizures was judged by the use of the adopted scale and expressed in points [2]. Neurotropin ("Nippon Zoki," Japan) was injected 24 h after the 20th injection of picrotoxin. The injection was given under open ether anesthesia under stereotaxic conditions [10] into the lateral cerebral ventricles in a volume of 12.5 or 25 μl, or intraperitoneally (1.0 ml per animal). Animals of the control groups, under similar conditions received 0.9% sodium chloride solution. Starting with the day after injection of neurotropin, seizure responses to injection of a testing dose of picrotoxin (1.0 mg/kg) were investigated daily. The latent period of the first seizures, of convulsions, and the mean intensity

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