PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

Dynamics of Electrical Activity of the Cortex in Rats with Neuropathic Trigeminal Neuralgia

G. N. Kryzhanovskii, V. K. Reshetnyak, and V. G. Dolgikh

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According to the theory of generator and systemic mechanisms of pain syndromes [3,5,13], the appearance of a generator of pathologically enhanced excitation (GPEE) in the corresponding nociceptive structure lies at the basis of any pathological pain. As a result, this structure becomes hyperactivated and assumes the role of a determinant which induces the formation of a pathological algical system involving the higher structures of the nociceptive system, in particular, the brain cortex. The latter is evidenced by the appearance of spontaneous epileptiform activity in the somatosensory zone of the cortex that was demonstrated in a model of trigeminal neuralgia of neuropathic [1] and central [6] origin.

The present study was aimed at investigating the dynamics of development of epileptiform activity in the cortex in rats infraorbital nerve compression (the model of trigeminal neuralgia of neuropathic origin).

MATERIALS AND METHODS

The study was performed on 119 male Wistar rats. The experimental group included 93 rats that were subjected to unilateral loose ligation of the infraorbital nerve under ether. The control group included 26 animals that underwent the sham operation (sham animals). We studied the character of evoked potentials (EP) in the somatosensory cortex of both hemispheres at different periods during 6 months. The animals were prepared for the operation under ether anesthesia with subsequent administration of a myorelaxant and artificial ventilation of the lungs. Electrical excitation of the infraorbital nerve was accomplished via needle-shaped electrodes implanted at symmetrical points of the muzzle in the region of the infraorbital foramen with rectangular current pulses of 0.1 msec duration and differing intensity. EP were recorded with silver spherical electrodes with a diameter of 1.0 mm in the focus of maximal activity in the symmetrical somatosensory regions of the cortex of both hemispheres.

RESULTS

In rats with infraorbital nerve compression we registered background spontaneous epileptiform activity in the somatosensory regions of the cortex that was characterized by acute waves and peak-wave complexes. This activity was recorded as soon as the first

Istitute of General Pathology and Pathophysiology, Russian Academy of Medical Sciences, Moscow

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week after compression and the frequency of its recording increased with time. Epileptiform activity was recorded more often in the hemisphere contralateral to the compressed nerve (Fig. 1). The differences between the operated and sham animals in the frequency of activity recording in the contralateral hemisphere acquired a reliable character only 3 months after nerve compression (see Table 1).

Excitation of the infraorbital nerve on the side of compression with an electrical current of differing intensity led to exaltation of EP in the contralateral hemisphere and afterdischarges of 12-17 Hz frequency and 1 sec duration in both hemispheres. During the first two weeks after compression a significant increase in contralateral EP amplitude ($p<0.05$) was registered only for non-nociceptive stimulation of the injured nerve in comparison with stimulation of the intact side of the muzzle. During the next month an increase in EP amplitude acquired a reliable character for nociceptive stimulation of the injured nerve as well and in comparison with the control group of animals. In 3-6 months after nerve compression the amplitude of EP induced by nociceptive stimulation gradually decreased and asymmetry of contralateral EP upon nociceptive and non-nociceptive stimulation of the injured and intact nerves became less expressed (smoothed out).

Rhythmic afterdischarge could be registered during the very first week after nerve compression. During the whole period of observation the frequency of its recording was higher in the contralateral hemisphere in cases where the injured nerve was excited. Similarly, afterdischarge was recorded, though with a somewhat lower frequency (see Table 1), in the hemisphere contralateral to the compressed nerve when the intact nerve was stimulated. The frequency of afterdischarge recording in the hemisphere ipsilateral to the compressed nerve was much lower than that in the contralateral hemisphere under stimulation of either the injured or intact nerve. The highest frequency of afterdischarge recording was registered 3-6 weeks after compression (see Table 1). An increase in stimulation intensity was followed by an increase in EP amplitude but led to inhibition of afterdischarge in both hemispheres (Fig. 2). This phenomenon was observed 1, 5, and even 6 months after nerve compression.

The results obtained provide evidence for the early formation of the pathological system after infraorbital nerve compression. The main manifestations of the process (spontaneous epileptiform activity, exaltaation of EP and afterdischarges) may be recorded as soon as the first week after nerve compression. As shown in the model of peripheral neuropathy induced by compression of the sciatic

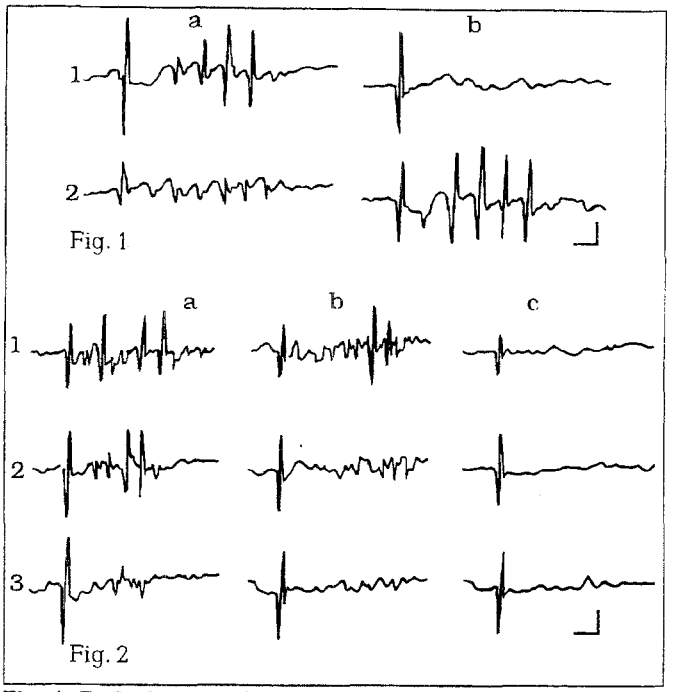

Fig. 1. Evoked potentials and afterdischarges in rats cortex with neuropathic trigeminal neuralgia. *a*) electrical stimulation of injured nerve; *b*) electrical stimulation of intact nerve. 1) recording in contralateral hemispheres; 2) recording in ipsilateral hemispheres. Calibration 1 mV. 100 msec.

Fig. 2. Variation of evoked cortical activity for an increased intensity of electrical stimulation of the infraorbital nerve. *a*) recording in somatosensory cortex of contralateral hemisphere for stimulation of injured nerve; *b*) recording in somatosensory cortex of contralateral hemisphere for stimulation of intact nerve; *c*) recording in contralateral hemisphere for stimulation of sham-operated nerve. 1) intensity of stimulation of 2nd threshold of EP occurrence in contralateral hemisphere for stimulation of intact nerve; 2) intensity of stimulation of 4th threshold; 3) intensity of stimulation of 8 thresholds. Calibration 1 mV, 100 msec.

nerve, pathological impulsation appears first in the A-β and A-Δ fibers of the injured nerve just 24 h after compression [12] and only toward the 10th day do spontaneous changes in activity become more pronounced in nonmedullated fibers [14]. These peculiarities may account for the appearance of the exalted EP registered in this study during the first two weeks after compression predominantly in response to non-nociceptive stimulation of the innervation zone of the injured nerve, while under nociceptive stimulation this phenomenon could be reliably recorded only after 3 weeks. It may be suggested that ectopic impulsation from the injured nerve center (as a peripheral generator) plays an important role at the first stage promoting further formation of central GPEE [4,5]. This suggestion is supported by the following observations: impulsation in injured peripheral fibers in cats [8] and rats [11] becomes extinct in 1 month, while the epileptiform activity in the brain cortex in our experiments could be registered for as long a period as 6 months. An analogous increase in EP amplitude

TABLE 1. Peculiarities of Electrical Activity in the Cortex in Rats with Neuropathic Trigeminal Neuralgia.

Period after operation, weeks	Spontaneous epileptiformic activity, %		Amplitude of contralateral EP, mV				Afterdischarges, %			
			non-nociceptive stimulation		nociceptive stimulation		stimulation of intact nerve		stimulation of injured nerve	
	contralateral hemisphere	ipsilateral hemisphere	intact nerve	injured nerve	intact nerve	injured nerve	contralateral cortex	ipsilateral cortex	contralateral cortex	ipsilateral cortex
1–2 Exp.	28.6	0	1.7±0.4	3.1±0.4*	2.7±0.4	5.4±1.3	28.6	28.6	42.9!	14.3
Control	0	0	2.0±0.5	2.2±0.7	3.8±0.8	3.8±0.4	16.7	0	0	14.3
3–4 Exp.	40.0	10.0	1.2±0.2	3.3±0.4**!	2.2±0.5	5.9±0.6**!	14.3	42.9!	100.0**!	28.6
Control	28.6	0	1.2±0.1	1.5±0.5	2.4±0.3	2.9±0.4	14.3	0	42.9	0
5–6 Exp.	33.3	11.1	1.1±0.2	2.9±0.4**!	3.3±0.6	6.1±0.5**!	44.4	66.7!!	66.7!	55.6!!
Control	25.0	0	1.4±0.2	1.3±0.6	2.1±0.7	3.6±0.4	50.0	0	25.0	0
10–12 Exp.	83.3!!	33.3	1.3±0.2	3.0±0.8*!	1.7±0.3	3.6±0.5*!	16.7	33.3	66.7	33.3
Control	0	0	1.4±0.2	1.3±0.6	2.1±0.7	2.6±0.4	14.3	0	42.9	0
24–26 Exp.	60.0!	40.0	0.8±0.3	1.1±0.5	1.2±0.6	2.5±0.6	20.0	40.0	60.0	20.0
Control	0	0	1.4±0.2	1.3±0.6	2.1±0.7	2.6±0.4	25.0	0	25.0	0

Note: * – reliability level in comparison with the second hemisphere; *! – $p<0.05$; ! – reliability level in comparison with the control; ** or !! – $p<0.01$

and the appearance of epileptiform activity and afterdischarges were registered in clinical trials [2,7].

Afterdischarges may be also regarded as one of the forms of induced epileptiform activity, their appearance testifying to the formation of central GPEE. It is noteworthy that afterdischarges in the cortex fade away with an increase in the intensity of excitation of the infraorbital nerve in rats. This phenomenon correlates well with clinical observations testifying that paroxysm of pain in patients with trigeminal neuralgia is evoked by a mild excitation of the skin but not by intensive nociceptive stimulation [10]. Experiments performed on sections of rat cortex demonstrated that the epileptiform activity registered from the cortex surface developed for just 10-15% suppression of intracortical inhibition. Besides, the epileptiform activity correlated with the synaptic activity of neurons of layers II and III which, in its turn, decreased with an increase in the stimulation intensity as a result of the formation of inhibitory postsynaptic potentials [9]. It cannot be ruled out that the above-described phenomenon is based on an analogous mechanism.

Thus, the experiments show that the pathological process becomes generalized with time: spontaneous epileptiform activity can be recorded, first, only in the contralateral hemisphere with respect to the injured nerve but later on in the ipsilateral hemisphere as well. Excitation of the intact nerve, along with stimulation of the injured nerve, induces afterdischarges in the contralateral hemisphere in an increasing number of rats. Gradually the ipsilateral hemisphere of the brain becomes involved where afterdischarges arise predominantly upon excitation on the side of compression. This dynamics is evidence of the formation of a pathological system including both the projectional and the opposite somatosensory regions of both hemispheres and, probably, higher structures of the nociceptive system together with the limbic structures. This problem is awaiting further investigation.

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