EXPERIMENTAL TRIGEMINAL NEURALGIA (THE CONCEPT OF THE GENERATOR MECHANISM OF THE PAIN SYNDROME)

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A trigeminal pain syndrome was produced in experiments on albino rats by injecting tetanus toxin into the caudal nucleus of the spinal tract of the trigeminal nerve. Tetanus toxin was used as a substance disturbing inhibition. The syndrome described has the characteristic features of the clinically familar trigeminal neuralgia. It is concluded that this syndrome of experimental trigeminal neuralgia is based on the formation of a generator of pathologically increased excitation (a pathological dispatch† station) in the system of the caudal nucleus of the trigeminal nerve as a result of the disturbance of inhibition. Mechanisms similar in principle, a disturbance of inhibition and the formation of excitation generators in the corresponding parts of the CNS, are considered to lie at the basis of various pain syndromes.

KEY WORDS: caudal nucleus of the trigeminal nerve; trigeminal pain syndrome; tetanus toxin; generator of pathologically increased excitation; "dispatch" station phenomenon.

Previous investigations [6, 7, 9-11] have shown that a severe pain syndrome with all the characteristic features and with a profound disturbance of the catecholamine balance [5] can be produced by injecting tetanus toxin into the posterior horns of the gray matter of the lumbar spinal cord. Tetanus toxin has been used as a substance disturbing inhibitory processes [6, 14, 16, 17]. Analysis of the data obtained suggests that the induced pain syndrome is one form of pathological dispatch† station phenomenon [6-8], a basis for the formation of a generator of pathologically increased excitation.

The object of the investigation described below is to ascertain whether a trigeminal pain syndrome can be obtained by this method.

EXPERIMENTAL METHOD

Albino rats weighing 220 ± 20 g were used. Purified‡ tetanus toxin, in a dose of 0.1-1.0 MLD for rats was injected from a microinjector into the caudal nucleus of the spinal tract of the trigeminal nerve on the right side in a volume of 1×10^{-4} ml. Control animals received inactivated tetanus toxin under the same conditions. Glycine (20% solution, pH 5.6) was injected after the toxin into the same area of the nucleus; in the control experiments an 8% solution of NaCl, iso-osmotic with the glycine solution and with the same pH was injected. Clinical observations were made on the animal's behavior and its movements and postures were photographed. In some experiments a sound recording and an actogram of the animal

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†At the insistence of Professor G. N. Kryzhanovskii, the Russian term "stantsiya otpravleniya" is rendered in this manner – Translator.

‡The toxin was purified by O. P. Sakhalova, working in the authors' laboratory.

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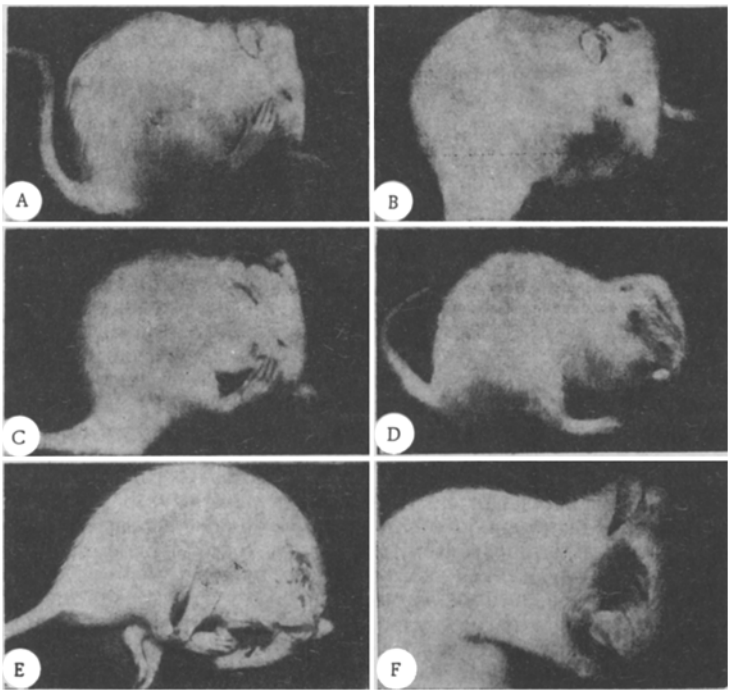

Fig. 1. Clinical picture of development of a trigeminal pain syndrome in a rat (explanation in text).

were obtained by the use of a specially constructed chamber with microphones and strain gauges. The electrical activity in the masticatory, temporal, and frontal muscles were recorded from some animals. The total number of rats tested exceeded 100.

EXPERIMENTAL RESULTS AND DISCUSSION

Soon after injection of the toxin (the actual length of this period depended on the dose of the toxin injected) the animals began to scratch particular parts of the face or head. In some cases (as a rule, if the toxin was injected deeper into the nucleus) the scratching movements were preceded by washing movements with the forelimbs. Scratching of areas of the face of head was accompanied by a corresponding movement of the hind limb but only on the side of injection of the toxin (Fig. 1A); after each scratching the rats carefully "cleaned" the digits of that paw just as during an ordinary scratch reflex (Fig. 1B). In the intervals between scratching the rats were quiet. With the course of time the bouts of scratching became more frequent, they lasted longer, and their intensity increased. The bouts were paroxysmal in character; they were not provoked by external stimulation of any sort, but were "silent" in character.

Later the scratching movements became violent, the rats squeaked loudly and began to scratch desperately the same area as before. The animals became restless and aggressive, they dashed about the cage and flung themselves against its walls. The seizures increased in frequency; as before they were paroxysmal in character but now they were easily provoked by a stimulus applied to the zone of scratching. The seizures could be provoked by tactile stimuli of different strengths, even light, applied to this zone; their intensity and duration were virtually identical in every case and were independent of the strength of stimulation. The zone of scratching, which was not the zone of facilitated induction of the seizure, increased in size. The skin of this zone was injured by the scratching and the air was removed from it (Fig. 1C); in the late stages the zone increased in area and sometimes an extensive part of the face was injured (Fig. 1E, F); often the animals lacerated the tissues in the region of this zone. The animals' posture in the period between seizures was characteristic: they would sit or lie on their side, with the forelimbs or paws held tightly against the face (Fig. 1D). The palpebral fissure on the side of injection of the toxin was narrowed and sometimes lacrimation and increased discharge from the nose were observed. The intensity and the rate of increase of the symptoms depended on the dose of toxin injected: if relatively large doses (1 MLD) were given the syndrome developed rapidly and the symptoms were severe; if a dose of 0.1 MLD was given the syndrome developed slowly and it could be observed for 2-3 days. The main cause of death of the animals was evidently tetanus poisoning, although the role of catecholamine inbalance, leading to paralysis of the heart, as took place in the spinal pain syndrome [5, 9], cannot be ruled out.

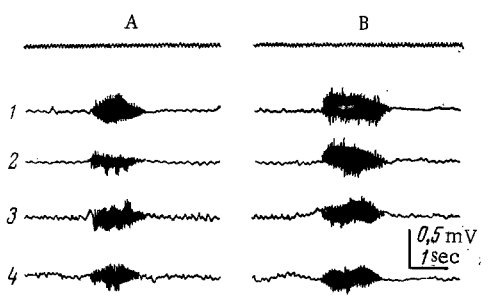

Fig. 2

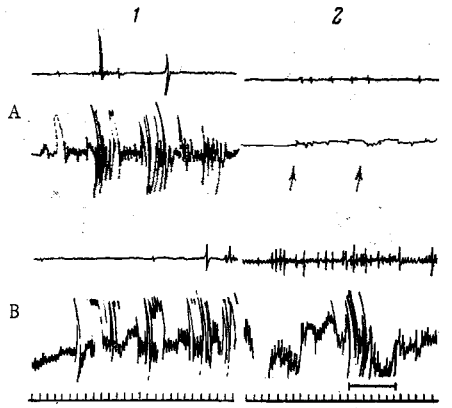

Fig. 3

Fig. 2. Bursts of electrical activity in the facial muscles of an animal with a trigeminal pain syndrome during attacks of pain. Activity recorded 2 (A) and 7 h (B) after injection of toxin into caudal nucleus of spinal trigeminal tract on the right side. Scheme of recording: 1, 2) masticatory muscles on the right and left; 3, 4) frontal muscles on the right and left.

Fig. 3. Effect of glycine when injected into caudal nucleus of the trigeminal nerve after tetanus toxin. In A and B top curves are sound recordings, bottom curves actograms recorded from rats with a trigeminal pain syndrome before (1) and 20 min after (2) injection of 20% glycine solution (A) and 8% NaCl solution (control; B) into the caudal nucleus of the spinal tract of the trigeminal nerve in a volume of 1×10^{-4} ml per injection, 72 h after injection of the toxin (0.1 MLD) into the caudal nucleus of the spinal tract of the trigeminal nerve. Tape winding speed (horizontal line) 3 cm/5 min.

The recording of the EMG of the facial muscles showed that during the attacks a burst of electrical activity appeared in the masticatory, temporal, and frontal muscles (Fig. 2). In some animals these bursts were equal in intensity and duration on both sides; in others they were more marked on the side of the lesion. In some cases increased spontaneous activity was recorded and this also was a little stronger on the side of injection of the toxin.

Injection of glycine into the previously poisoned trigeminal nucleus led to complete suppression of the syndrome during the period of action of the glycine (Fig. 3A): the paroxysmal attacks disappeared, the animal became quiet, it ceased to scratch or to lacerate the particular zone concerned, and the application of a stimulus to that zone no longer provoked an attack of pain. The syndrome returned as soon as the action of the glycine came to an end. In control experiments administration of 8% NaCl solution gave no effect (Fig. 3B). Comparison of the observations described above with the clinical symptoms of trigeminal neuralgia [1, 2, 4, 12, 13, 15, 21] leads to the conclusion that the syndrome has all the characteristic features of a trigeminal pain syndrome. The syndrome of trigeminal neuralgia was thus reproduced experimentally.

Previous investigations [6, 7, 8], in which tetanus toxin was used as a substance disturbing inhibition [6, 14, 16, 17], showed that suppression of the inhibitory mechanisms in a certain group of neurons causes that neuron pool to begin to function as a generator of pathologically increased excitation; the intensity of the excitation rises as inhibition is progressively disturbed and as the number of neurons forming the generator increases. These mechanisms lie at the basis of the spinal pain syndrome described earlier [6, 7, 9-11], caused by injection of tetanus toxin into the posterior horns of gray matter of the lumbar segments of the spinal cord. The same mechanisms evidently also lie at the basis of the trigeminal pain syndrome produced by the injection of tetanus toxin into the caudal nucleus of the trigeminal nerve we have just examined, for this nucleus has a structure similar to that of the posterior horns and it is functionally connected with pain sensation [3, 19, 20, 24, 26]. Disturbance of inhibition in the neuron system of the caudal nucleus, just as in the neuron system of the posterior horns, brings these systems into a state of readiness for explosive excitation that arises in response to triggering stimulation. It is these features that determine the paroxysmal character of the attack of neuralgia. The triggering stimulus may be some

form of afferent impulsation, but the most effective form is impulsation arriving via a particular afferent channel associated with the facilitated induction of reflex attacks of pain (known in clinical medicine as trigger zones). The role of triggering stimulation diminishes with increasing severity of the disturbance of inhibition and increasing excitability of the generator. The presence of a generator mechanism accounts for the comparatively longer duration of the attack of pain and its increase as the generator continues to form, as well as the possibility that attacks may arise even in the absence of reinforcing stimulation from the periphery, as was shown in the case of the spinal pain syndrome [9-11]. Injection of glycine, inducing postsynaptic inhibition [18, 25], suppresses the generator and causes the disappearance of the pain syndrome during the period of its action, as was found also in other forms of the "dispatch station" phenomenon when the excitation generator was suppressed by glycine [8, 11].

The theory of the portal control of pain [22, 23], the most widely held theory at the present time and one which has been applied also to the system of the trigeminal nerve nuclei [10], despite its advantages cannot completely explain the special features and mechanisms of the pathological pain syndrome. The concept of the generator mechanism of the pain syndrome could be an important addition to this theory. The formation of generators of pathologically increased excitation in the system of pain sensation is worthy of consideration as a highly important pathogenetic mechanism of various pain syndromes.

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