# PATHOLOGICAL PHYSIOLOGY AND GENERAL PATHOLOGY

# Formation of a Pathological System in Rats with Neuropathic Trigeminal Neuralgia

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It was shown previously [4] that incomplete compression of the infraorbital nerve in rats induces an experimental trigeminal neuralgia that is manifested clinically in scratching of the pain projection zones on the facial skin. In such animals, various types of epileptiform activity are recordable from the somatosensory cortex of the brain [2], and microcirculatory disorders characteristic of pathological pain are present [4].

The purpose of the study reported here was to compare the above-mentioned signs of the trigeminal pain syndrome at various stages of its development.

## MATERIALS AND METHODS

For the study, 81 male Wistar rats weighing 150-200 g initially were used. In 61 of the rats, the infraorbital nerve was incompletely compressed by means of two ligatures under ether anesthesia. The remaining 20 rats were sham-operated to serve as controls. All animals were observed for 6 weeks after the operation. Clinical manifestations of trigeminal neuralgia were rated according to severity by noting the size of skin scratches at the corner of the mouth and on the cheek and neck on the operated side. The 81 rats were classified into four groups as follows: rats without skin scratches over the entire observation period (group 1); those with scratches at the times when electrophysiological or biomicroscopic studies were undertaken (group 2); those with healed scratches by the time of the studies (group 3); and sham-operated rats (group 4).

Bioelectrical activity was recorded in rats made immobile by a muscle relaxant and artificially ventilated. The operative preparation of the animals for the recordings was carried out under ether anesthesia. The infraorbital nerve on both sides of the face was stimulated via needle electrodes with rectangular pulses of 0.1 msec duration and of variable intensity. Bioelectrical activity was recorded from the surface of the cerebral cortex with spherical silver electrodes 1.0 mm in diameter placed at symmetrical sites of the somatosensory areas in both hemispheres.

Biomicroscopy was mainly used to study the microcirculation. In addition, procedures described by us earlier [1,4] were applied.

## RESULTS

Scratches began to appear on the skin 3 to 6 days after infraorbital nerve compression. The proportion

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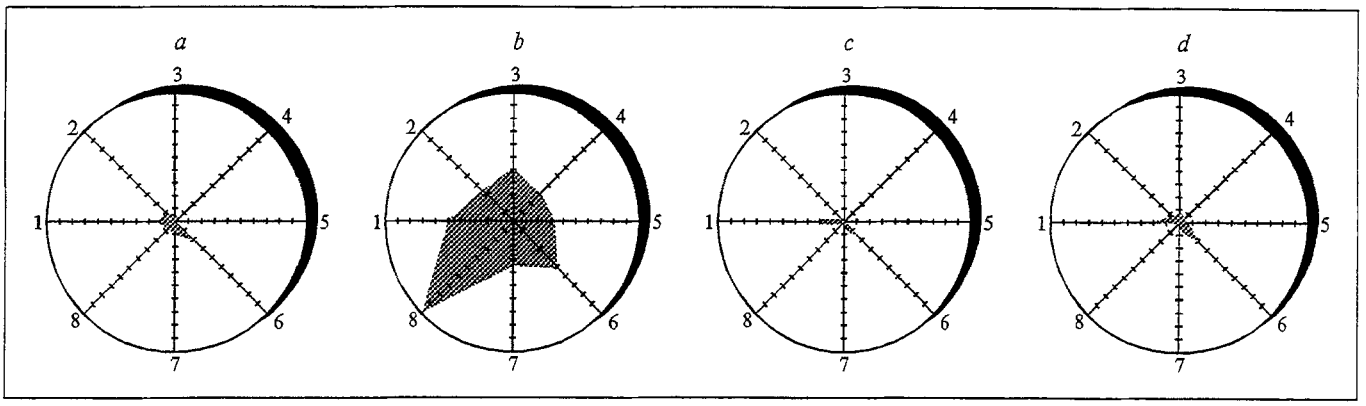


Fig. 1. Signs of disordered microcirculation and venular permeability in rats of four groups with neuropathic trigeminal neuralgia. The eight (1 to 8) radii in these circular diagrams represent the magnitudes (in %) of particular signs (the presence of a given sign in all rats of the group being taken as 100%), as follows: 1) slowed venular blood flow; 2) erythrocyte aggregation in capillaries; 3) erythrocyte aggregation in venules; 4) vessels with abundant plasma cells; 5) stasis; 6) leukocyte adherence to venular walls; 7) extent of venular permeability disturbances; 8) severity of venular permeability disturbances.

of operated (test) rats with skin scratches was 7% in the first week postcompression, 13% in the second, 25% in the third, and 33% in the fourth to sixth weeks. All rats with scratches were assigned to group 2. Healing of the skin was observed in 3% of these rats starting with the fourth week after nerve compression (group 3).

Biomicroscopic examination of the mesentery one week postcompression revealed impaired terminal blood flow, increased venular permeability, and intensified mast cell degranulation in both the test and control (sham-operated) rats, which did not differ in these respects. Two to six weeks after surgery, the rats without scratches did not have any microcirculatory disturbances, while those with scratches (group 2) showed slowed venular blood flow, increased erythrocyte aggregation in the capillaries, a large number of plasma cells, and increased venular permeability to colloidal carbon particles.

These signs of abnormal microcirculation were significantly more pronounced in rats with more strongly marked scratches, and in such rats increased erythrocyte aggregation in the venules was also observed, as was stasis. Mesenteric biomicroscopy in rats with healed skin scratches (group 3) indicated normalization of the microcirculation (Fig. 1). The character or type of microcirculatory disorders within each group did not depend on the time that had elapsed after the operation.

Rats with scratches also developed adrenal hypertrophy (+18% to +62%) 2 to 6 weeks postsurgery.

Alterations in bioelectrical activity after infraorbital nerve compression were characterized by the appearance of spontaneous epileptiform activity in the form of sharp waves and peakwave complexes and of afterdischarges and by increased amplitudes of evoked potentials in the somatosensory cortex of the hemisphere contralateral to that of nerve compression. In group 1, increased amplitudes of evoked potentials with or without evoked or spontaneous epileptiform discharges were registered in 50% of the animals 1 to 2 weeks after the operation, in 44% after 3-4 weeks, and in 22.2% after 5-6 weeks. In group 2, evoked potentials of increased amplitude and epileptiform discharges were recorded in 100% of the rats, while in group 3 they were recorded in 75% during the 4th and 5th postoperative weeks. A more detailed description of epileptiform activity development in rat cerebral cortex with time is presented by us in another article [5].

In summarizing the results of the present study, the following points should be noted. First, the incidence of abnormal cortical electrical activity declined with time in the group without skin scratches (group 1), whereas it rose in animals with such scratches, whether unhealed (group 2) or healed by the time of recording (group 3); in the latter two groups, the number of rats with scratches increased with time. Second, epileptiform activity was also present in rats with healed scratches, although the microcirculation in these rats was normal or almost so. Third, there was a good correlation between the extent of scratches and the microcirculatory disturbances.

According to the theory of generator and systemic mechanisms [3], the pathogenetic basis of a neuropathological syndrome is a pathological system. The pathological algetic system (PAS) proper, which is responsible for the pain syndrome in question, includes peripheral nerve fibers, nuclei of the trigeminal complex, the thalamus, and the somatosensory region of the cerebral cortex. The epileptiform activity recorded from the cerebral

cortex in the first two weeks after nerve compression reflects an early stage in the establishment of a PAS, namely the formation in the nervous system of a generator of pathologically enhanced excitation that then involves other CNS structure in the pathological response. Using animal models of sciatic nerve neuropathy, other authors have described pathological changes in the activity of peripheral nerve fibers [7], dorsal horns of the spinal cord [8], and the thalamus [6], while we have described such changes in an animal model of trigeminal neuropathy [2,5].

A more complex pathological system involves, in addition, other CNS structures responsible for various pathological responses (behavioral, autonomic, and others). Such a "polysystem" also has outlets to internal organs and to the microcirculatory system which all become peripheral target organs. That a polysystem of this kind developed in the rats with compressed infraorbital nerve is evidenced by the presence in them of both scratches (as a manifestation of the motor response to pain) and microcirculatory disturbances. The absence of skin scratches and microcirculatory abnormalities in some rats after nerve compression suggests either that a pain syndrome had not developed or - if epileptiform activity was present in the cerebral cortex - that a complex pathological system with outlets to peripheral target organs had not formed, possibly because the controlling antisystems were active and/or the target organ(s) was (were) resistant to the PAS. The healing of skin scratches in some rats (group 3) and the normalization of the microcirculation in them may also be taken as evidence that such controlling mechanisms were active and the PAS did not have outlets to the target organs. The presence of cortical epileptiform activity in these rats indicates that the PAS proper was operational.

If so, then reactivation of the complex pathological system with repeated involvement of the effector organs may occur under certain circumstances. In our study, a second "wave" of scratches together with microcirculatory abnormalities were observed in 10% of group 3 rats six weeks after infraorbital nerve compression.

## REFERENCES

1. M. P. Gorizontova, O. V. Alekseev, and A. M. Chernukh, *Byull. Eksp. Biol.*, **79**, № 3, 22-25 (1975).
2. V. G. Dolgikh, V. K. Reshetnyak, and G. N. Kryzhanovskii, *Ibid.*, **113**, № 5, 458-459 (1992).
3. G. N. Kryzhanovskii, *Zh. Nevropatol. Psikhiatr.*, **90**, № 10, 3-10 (1990).
4. G. N. Kryzhanovskii, V. K. Reshetnyak, V. G. Dolgikh, M. P. Gorizontova, and T. V. Speranskaya, *Byull. Eksp. Biol. Med.*, **112**, № 8, 120-122 (1991).
5. G. N. Kryzhanovskii, V. K. Reshetnyak, and V. G. Dolgikh, *Ibid.*, № 2, 125-127 (1993).
6. G. Guilbaud, J. M. Benoist, F. Jazat, *et al.*, *J. Neurophysiol.*, **64**, 1537-1554 (1990).
7. K. C. Kajander and G. J. Bennett, *Soc. Neurosci. Abstr.*, **14**, 912 (1988).
8. J. Palecek, V. Palecekova, P. M. Dougherty, *et al.*, *Soc. Neurosci. Abstr.*, **17**, 437 (1991).