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TRIGEMINAL NEURALGIA OF NEUROPATHIC ORIGIN

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In trigeminal neuralgia the onset of the disease is often associated with compression of a root [19] or of the II-III branches of the trigeminal nerve [3]. The development of gross destructive changes in the nerve is accompanied by a change of the disease into a neurotic stage, in which pain becomes continuous in character and is described by the patients as aching, stabbing, and burning.

To create models of trigeminal neuralgia, various neurochemical agents are widely used (tetanus toxin, penicillin, strychnine, picrotoxin), applied to the caudal trigeminal nucleus [6, 18]. These procedures lead to insufficiency of the mechanisms of inhibitory control and hyperactivation of neurons, and this is connected with the formation and activity of a generator of pathologically enhanced excitation (GPEE) [7]. Clinical physiological studies also have shown that the pathogenesis of trigeminal neuralgia is based on the formation of a GPEE in central structures of the trigeminal nerve system [5, 12].

Since the initial pathogenetic mechanism leading to the formation of a central GPEE in most cases is damage to peripheral portions of the trigeminal nerve system [5, 9], the aim of the investigation described below was to create models

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of trigeminal neuralgia of neuropathic origin in rats by compression of the infraorbital nerve or by damage to the trigeminal ganglion. With a model of this kind, it is impossible to observe the vivid nociceptive reactions found in animals without special methods of testing [11]. In order to assess the adequacy of this model, we therefore used instrumental methods of investigation of nociceptive responses, and we also studied the state of the microcirculatory system, disturbances of which have been demonstrated when a pain syndrome of trigeminal [10] and spinal [8] origin is present.

EXPERIMENTAL METHOD

Experiments were carried out on male Wistar rats weighing 180-200 g. Compression of the left infraorbital nerve was carried out on 60 animals, under ether anesthesia, by inserting two incomplete ligatures and applying aluminum filings in the region of the perineurium. Stereotaxic coagulation of part of the trigeminal ganglion was carried out on eight animals. The localization of the electrodes was monitored by recording evoked potentials in the ganglion during electrical stimulation of the rat's upper lip. The animals' behavioral responses were studied by the open field test, and also by placing them for 30 min in a transparent chamber measuring 30 × 30 × 30 cm. Ability to hold on to a vertical mesh surface also was assessed. Nociceptive sensitivity was assessed by the tail withdrawal test and the hotplate test, on specialized instruments from "Ugo Basile" (Italy), and also on a specially designed system for applying nociceptive thermal stimulation with a focused beam of light on symmetrical parts of the left and right sides of the rat's snout. In rats anesthetized with pentobarbital, the microcirculation in the mesentery was studied under the biomicroscope by means of a system based on the "Docuval" microscope (Karl Zeiss, West Germany). The morphological and functional state of the mast cells was assessed after fixation of part of the mesentery with 96% ethanol followed by staining with 0.5% toluidine blue. The venular permeability of the microvessels was studied by the "labeled vessels" method, using intravenous injection of colloidal carbon. The intensity of the stress-pain response also was estimated by the change in weight of the adrenals, thymus, and spleen (calculated per 100 g body weight). The control animals underwent a mock operation with compression of the nerve (20 rats) or damage to the ganglion (eight rats), and also 20 intact rats.

EXPERIMENTAL RESULTS

The parameters tested did not differ significantly in animals undergoing the mock operations and intact rats. Observation of the animals of the experimental group showed that 1.5 months after the operation of compression of the infraorbital nerve some degree of inhibition of investigative activity of the rats in the open field was noted. The number of rearings on the hind limbs was significantly reduced (from 10.9 ± 0.6 to 4.2 ± 0.4; $p < 0.05$). The time during which the rats could hold on to a vertical mesh surface also was reduced (from 90.7 ± 3.8 to 61.9 ± 0.6 sec; $p < 0.05$). Observation of the animals' behavior in the experimental chamber revealed increased scratching of both sides of the snout by the hind limbs. In a period of observation lasting 30 min this response averaged 20.1 ± 0.6 sec compared with 12.1 ± 2.5 sec in the control animals ($p < 0.05$). In some animals, increased rubbing of both sides of the snout by the forelimbs was observed, and in 40% of animals undergoing the operation multiple scratching of the snout took place with injury to the skin and with scab formation. These scratches were most frequently at the corners of the mouth, on the lower jaw, and in the region of the throat, and less frequently in the projection region of the nerve damage. Some rats responded aggressively to touching the vibrissae.

The study of nociceptive sensitivity relative to thermal stimulation of symmetrical parts of the snout on the intact side and on the side of nerve damage revealed lowering of the pain threshold on the side of nerve damage in 60% of rats on average by 38.5 ± 1.7%. Meanwhile, investigation of general pain responses by the hotplate and tail withdrawal tests revealed no significant differences compared with the control.

The biomicroscopic study of the mesenteric microcirculation showed that in rats with compression of the nerve (by contrast with the control animals) disturbances of the terminal blood flow also developed, such as slowing of the flow in the venules, aggregation of erythrocytes in the form of rouleaux in the capillaries, and the appearance of plasmatic capillaries. A tendency was noted for aggregation of erythrocytes in the venules (diameter 15-60 μ) to increase. All the animals had disturbance of venular permeability for colloidal carbon particles in preparations of the mesentery (Table 1).

TABLE 1. Disturbances of Components of the Microcirculatory System of Rats with Experimental Trigeminal Neuralgia

Experimental conditions	Severity of microcirculatory disturbances, number of cases in per cent of							Venular permeability							
	slowing of blood flow in venules	Aggregation of erythrocytes		plasmatic vessels	stasis	extravasation of erythrocytes from	pavmenting of leukocytes in venules	number of mesenteric fenestrae, per ce			number of rats with label of different degrees of intensity, per cent of total number of rats				
		capillaries	venules					without label	1-10 labeled vessels	more than 10 labeled	0	I	II	III	IV
Control (n = 10)	20	0	0	0	0	0	40	96	4	0	80	20	20	0	0
Compression of nerve	78*	28*	21	28	0	0	43	82*	13*	5*	23*	77*	77*	69*	46*
Injury to trigeminal ganglion (n = 8)	100*	50*	50*	24	24	20	50	69*	25*	6*	0*	100*	100*	88*	72*

Legend. Asterisk indicates values where $p < 0.05$ compared with control; n) number of animals.

The study of the morphological and functional state of the mast cells showed that in animals undergoing the operations there was a significant increase in mast cell degranulation: 3.4 ± 0.2% compared with 1.2 ± 0.3% in the control ($p < 0.05$). An increase in the number of contractions of the walls of the lymphatic microvessels 80-100 μ in diameter was observed: 8.7 ± 0.8 compared with 4.8 ± 1.3 in 1 min ($p < 0.05$). In the animals with compression of the nerve, significant hypertrophy of the adrenals and involution of the thymus and spleen were observed. The weight of the adrenals (calculated per 100 g body weight) was 7.0 ± 0.2 g (6.1 ± 0.1 g in the control; $p < 0.05$), of the thymus 106.1 ± 4.5 g (158.8 ± 7.4 g in the control; $p < 0.05$), and the spleen — 246.9 ± 9.0 g (305.1 ± 10.8 g in the control; $p < 0.05$).

Similar changes in behavior, sensitivity to pain, and the microcirculation also were found in animals with damage to the trigeminal ganglion. Disturbances of venular permeability and involution of the thymus and spleen were significantly more marked (compared with compression of the infraorbital nerve).

The experiments showed that long-term compression of the infraorbital nerve or damage to the trigeminal ganglion is accompanied by a series of various changes in the animals' behavior, their sensitivity to pain, their microcirculatory system, and the state of their stress-sensitive organs. A certain number of animals develop a state of hyperalgesia, manifested as lowering of the pain thresholds on the snout on the site of injury and intensified scratching of the snout with the hind limbs and rubbing it with the forelimbs, until the skin is injured. These phenomena of hyperalgesia have been described in patients with trigeminal neuralgia [17], and also in rats undergoing chronic compression of the sciatic nerve [13]. Laceration and damaging scratching of the snout by the limbs as a response of the animals to spontaneous and evoked pain also are found after injection of formalin beneath the skin of the snout [14] and when the trigeminal pain syndrome is created by direct application of neurochemical agents to the caudal trigeminal nucleus, giving rise to a GPEE in it [6, 7, 18].

Disturbances of the microcirculatory system are evidence of the formation of a pain syndrome. In this and previous investigations [10] we demonstrated changes in many different components of the general microcirculatory system: the terminal blood flow, permeability of the walls of the venules and capillaries, contractility of the lymphatic microvessels, and secretory activity of the mast cells. Incidentally, we observed similar changes in rats with an experimental model of a pain syndrome of spinal origin [8]. In patients with trigeminal neuralgia, at the time of an attack increased platelet aggregation and hypercoagulation are observed [4].

A characteristic feature of the development of a stress response to chronic pain as a result of compression of the nerve or damage to the trigeminal ganglion is hypertrophy of the adrenals, together with involution of the thymus and spleen. We showed previously that linked changes of this type in the microcirculatory system and the internal organs (adrenals, thymus, spleen) also take place during prolonged painful electrical stimulation in animals [1]. A common feature of the adhesive neuropathies is the inhibition of general motor and orienting activity observed in such animals [13]. In the modern view, chronic compression of a nerve or root, or their direct injury causes demyelinization of nerve fibers, followed by their degeneration, and may lead to neuroma formation [2, 3]. The neuroma, like areas of local demyelinization, is a source of ectopic activity in nerve fibers [15]. During compression of the nerve, its appearance is observed also on the day

after the operation [16]. The formation of a peripheral focus of ectopic activity after compression of the nerve or damage to the ganglion is the initial pathogenetic mechanism which, with the course of time, leads to the formation of a GPEE in the central structures of the nociceptive system [9].

The results of these experiments thus demonstrate that a pain syndrome of trigeminal neuropathy is formed in response to compression of the infraorbital nerve or injury to the trigeminal ganglion. This model can be regarded as appropriate for the study of the mechanisms of trigeminal neuralgia of neuropathic origin.

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