Disturbances of the Microcirculation under Conditions of the Permanent Development of the Deafferentation Pain Syndrome

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It has been shown previously that sciatic nerve transection leads to the development of the deafferentation pain syndrome (DPS) in rats, its clinical manifestation being self-mutilation (autotomy) of the extremities. DPS is accompanied by disturbances of the microcirculation, a rise of the venular permeability, and an increase of mast cell degranulation [2]. However, it has not been elucidated when the disturbances arise in the microcirculatory system, in what way they are connected with the phenomenon of autotomy and its intensity, how long the microcirculatory disorders are preserved, and whether there is any correlation between their disappearance and wound healing and claw regeneration. In addition, we considered that prolonged observations of animals with DPS would be interesting because, in spite of the fact that the model of the central pain syndrome (CPS) is widely used in experimental investigations, observations of animals have been performed for no longer than 7-10 weeks [5,6,8,9].

The aim of the present study was to observe the clinical course of DPS and the state of the microcirculation during the development of the syndrome beginning from the first week up to six months. The microcirculation changes were considered both from the standpoint of investigation of the mechanisms of DPS pathogenesis and from the standpoint of the development of methods for comprehensive pathogenetic therapy.

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MATERIALS AND METHODS

The experiments were carried out on 251 male Wistar rats weighing 160-200 g; the rats were maintained in the vivarium on a standard diet. The investigations were conducted from October to May, the operations and biomicroscopy being performed in the first half of the day. DPS was caused by transection of the left sciatic nerve, as described previously [2]. The terminal blood flow in the mesenteric microcirculatory bed was studied by biomicroscopy in nembutal-narcotized (5 mg/100 g) rats. The venular permeability for colloid carbon particles and the morphofunctional state of the mast cells were studied according to the methods described previously [1,2]. The experimental results were subjected to statistical analysis using Student's test.

RESULTS

As early as the first day postoperation, the onset of an autotomy was observed in 21% of the rats undergoing sciatic nerve transection, and one week later the

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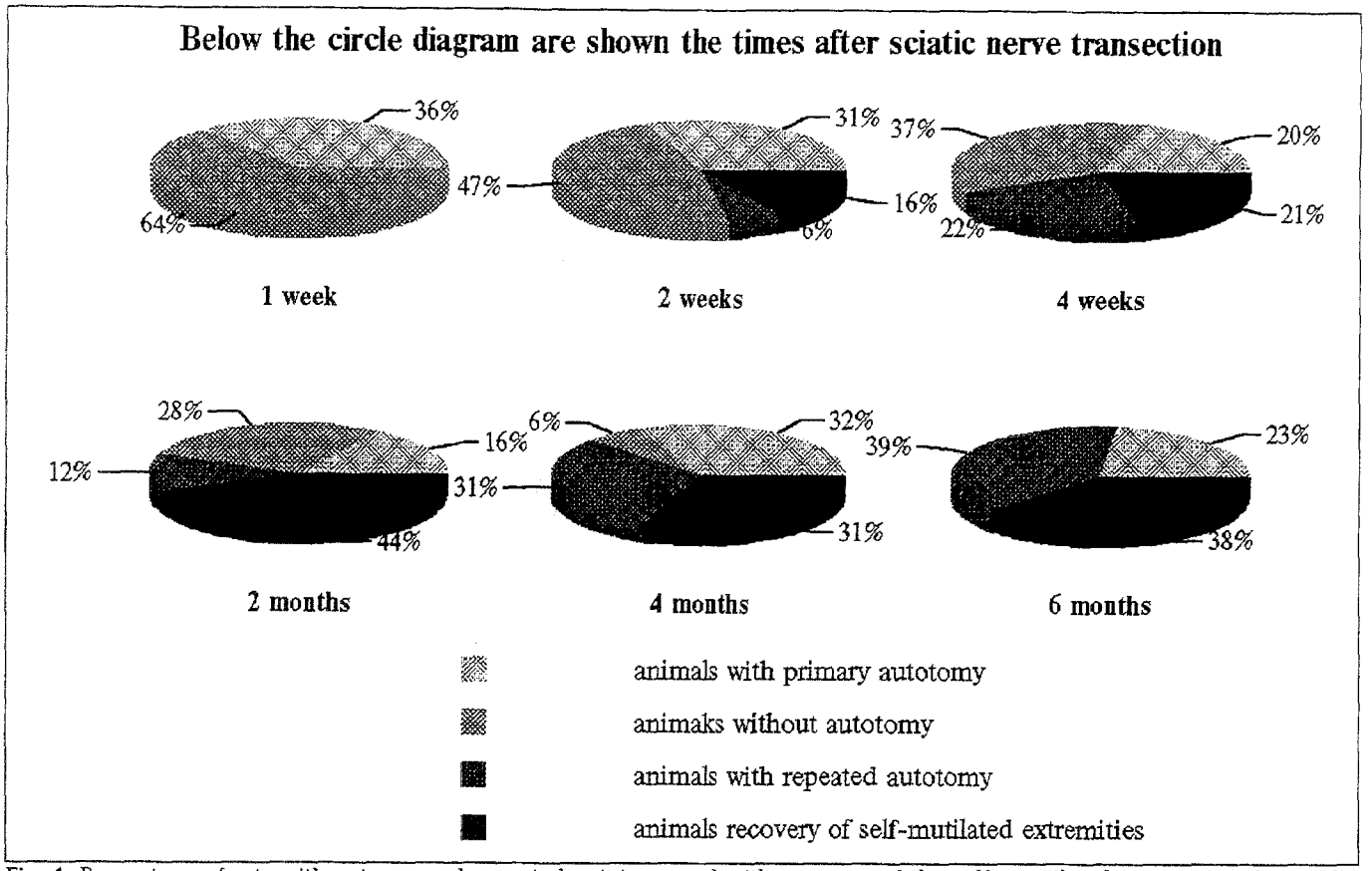

Fig. 1. Percentage of rats with primary and repeated autotomy and with recovery of the self-mutilated extremities during the development of DPS.

self-mutilations were found in 36% of animals. In the second week autotomies ceased in 22% of animals (out of 53% rats with autotomy), while total restoration of the claws was observed in the rats which had bitten them off, and complete wound healing occurred in the animals which had bitten off the toe phalanges. At this time one more interesting phenomenon was discovered: a repeated autotomy (the second "wave") began in 6% of rats (out of 22% animals with restoration). During the following six months of observations a gradual increase was observed of the number of animals demonstrating repeated autotomy and restoration after the first autotomy (Fig. 1). Later on (after the second "wave" of autotomy), further relapses were also observed in the rats against the background of repeated remissions. The maximum number of repeated autotomies was six, and their duration was 5-68 days. Thus, a remission was followed by a relapse of DPS. The duration of remissions was 7-73 days on the average. Another group comprised animals demonstrating a continuous autotomy (with incomplete remission), neither total restoration of the claws nor complete healing of the wounds being observed in this group. Beginning from the second week postoperation, the animals were divided into the following groups (7): 1) rats undergoing a sham operation; 2) rats undergoing sciatic nerve transection and exhibiting no autotomy; 3) rats with mild autotomies (no more than half of the claw); 4) rats with marked autotomies (more than half of the claw or phalanx); 5) rats demonstrating restoration of the extremities; 6) rats with repeated autotomies; 7) rats with continuous autotomy.

During the six months of the DPS investigation, a continuous course of this CPS was found to be clinically manifested in a wavelike autotomy development or a development without any remissions. Such a phenomenon has not been described previously, probably due to the short-term observations (up to 10 weeks) of other workers [5,8,9]. However, observations during more than a year have shown that the self-mutilations of deafferentated extremities correlated at first with a spontaneous hyperactivity in the spinal cord (up to 3 months) of rats with dorsal rhizotomy. Later, the clinical signs disappeared but the neuronal hyperactivity was recorded in the spinal cord for up to six months. Beginning from the sixth month and up to one year an abnormal burst activity was observed in the thalamic nuclei. The workers assumed that translocation of the neuronal hyperactivity occurs beginning from the lower to the upper levels by

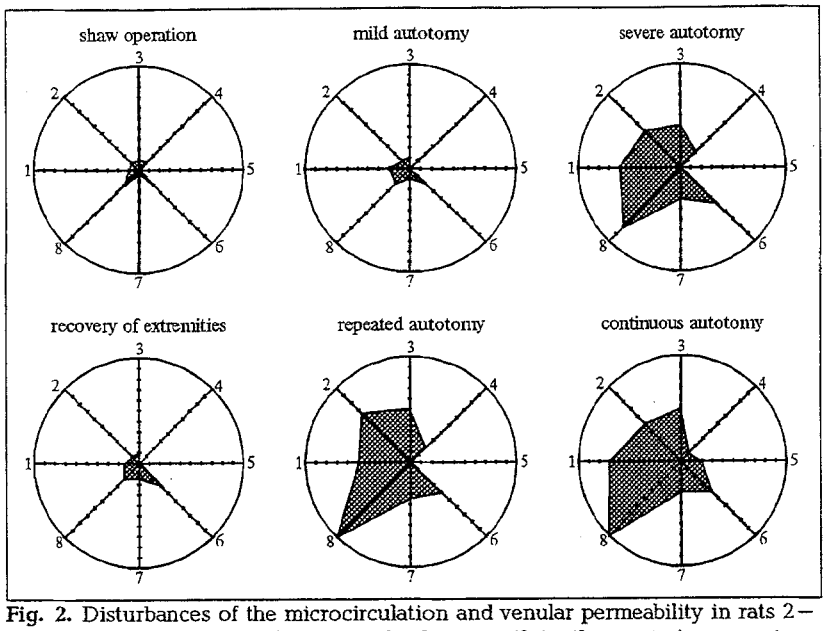

Fig. 2. Disturbances of the microcirculation and venular permeability in rats 2–6 months postoperation. In the circle diagram (0 in the center): percentage intensity of a certain symptom (symptom presence in all rats within the groups is taken as 100%). Radius: 1) blood flow slowing in venules; 2) erythrocyte aggregation in capillaries; 3) erythrocyte aggregation in venules; 4) "plasmatic" vessels; 5) stasis; 6) leukocyte adhesion to walls of venules; 7) abundance of venular permeability disorders; 8) intensity of venular permeability disturbances.

means of progressive kindling [3,4,7,8]. Probably, under the conditions of our model the wavelike course of the syndrome was related to a similar translocation of the focus of neuronal hyperactivity.

One week postoperation, during investigation of the microcirculation, it was found that the disturbances observed in the rats with sciatic nerve transection were the same as in the animals undergoing a sham operation: a decrease of the blood flow in the venules, erythrocyte aggregation in the capillaries and venules, plasmatization, stasis, extravasation of erythrocytes out of the venules, increase of the venular permeability for colloid carbon particles, and an increase of mast cell degranulation. In some of the rats autotomy was observed together with a tendency toward increased erythrocyte aggregation in the microvessels, although no significant difference of the microcirculation was found in these animals vis-a-vis the rats without autotomies and the rats undergoing a sham operation. Obviously, the microcirculatory disturbances were largely the result of postoperative injury. It is interesting that an adrenal hypertrophy was observed in both groups of rats one week postoperation.

No statistically significant difference of the mesenteric circulation, venular permeability, or morphofunctional state of the mast cells was discovered between the animals of groups 2, 3 and 5; however, in the rats of groups 3 and 5 a tendency for the microcirculatory parameters to differ was observed (Figs. 2, 3). A decrease of the blood flow in the venules, erythrocyte aggregation in the capillaries, plasmatization, stasis, leukocyte adhesion to the walls of the venules, an increase of the venular permeability for colloid carbon particles, and increased degranulation of the mast cells were noted in the rats with severe autotomy. No disturbances of the microcirculation or venular permeability and no increase of mast cell degranulation were found in the animals with "restored" extremities, i.e., an absence of the clinical signs of DPS correlated with a normalization of the microcirculation.

The intensity of microcirculatory disorders correlated not only with the autotomy intensity but also with the number of preceding "waves" of autotomies (Fig. 2). For example, an increased erythrocyte aggregation in the capillaries and venules in the rats enduring the third "wave" of autotomy was observed vis-a-vis the animals enduring the second "wave," whereas the clinical signs of DPS were identical in these rats. In the group of animals with continuous autotomy the changes of the microcirculation were more pronounced compared to the microcirculatory disorders in the rats with the third "wave" of autotomy: the number of microvessels with stasis and the percentage of degranulated mast cells rose in them (Figs. 2, 3).

A correlation was found between the weight changes of the stress-sensitive organs and both the intensity of the clinical manifestations and the degree of microcirculatory disorders. For example, 2-6

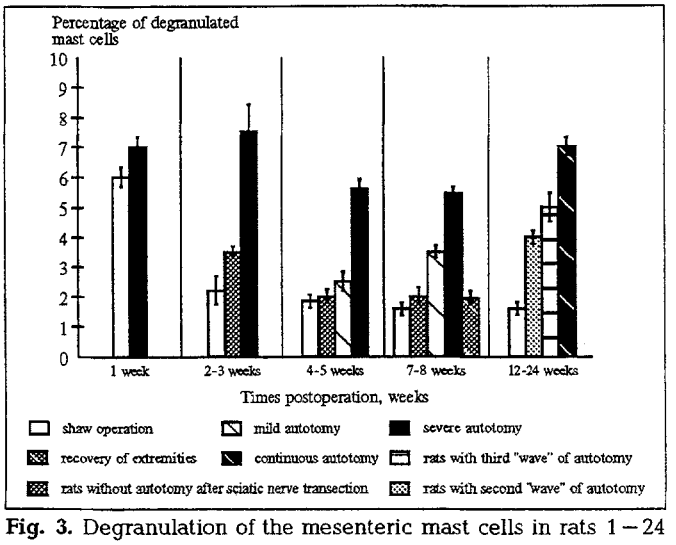

Fig. 3. Degranulation of the mesenteric mast cells in rats 1–24 weeks postoperation.

weeks postoperation, 22-26% thymus involution was observed in the animals with marked autotomy. Adrenal hypertrophy was found 2-6 weeks postoperation in the rats with severe autotomy, 7-8 weeks postoperation in the rats with severe and mild autotomies, and in the animals with repeated autotomies.

Thus, the model of DPS caused by transection of the sciatic nerve showed the onset of autotomies in all the operated rats by the 5th month postoperation. It was established that DPS is a constant process, the course of autotomy being wavelike or continuous. The microcirculatory disorders observed two weeks to six months after sciatic nerve transection were shown to be the result of the development of DPS. These disturbances were found in the animals with marked autotomies and did not depend upon whether these were primary or repeated. The healing of the self-mutilated extremities correlated with the normalization of the microcirculation. The microcirculatory disorders observed in the group of animals with continuous autotomy were comparable to those observed during the repeated autotomies; however, in the latter case the number of microvessels with stasis rose significantly and degranulation of the mast cells increased.

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Characteristics of Neurons of the Nodose Ganglion with Constant Spike Activity

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Information from the receptors of the cardiovascular system is conducted to the CNS along myelinated and unmyelinated fibers of the vagus nerves. Best studied is the impulse activity from the motor receptors of the atria, ventricles, and blood vessels, which is transmitted along myelinated fibers and is synchronized to the heart rhythm [2,5,8,10]. It has been shown that the nodose ganglion neurons discharging in the heart rhythm receive afferent information transmitted at the speed of excitation conductance (17-32 m/sec) along fibers of the vagus nerve [4]. A constant impulse from the heart receptors and not

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