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Effects of Prior Anaesthesia on Autotomy Following Sciatic Transection in Rats

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Summary

The animal model for chronic pain following sciatic nerve section in the rat has been studied varying the sensory afferents prior to nerve section, using the anaesthetic blocking of the sciatic nerve. The experimental parameters used were the day of onset of autotomy and the time course of autotomy. The results show that the anaesthetic blocking prior to nerve section significantly reduces the degree of autotomy.

Introduction

Pain due to deafferentation has been defined by Tasker [14] as that produced by a lesion to the central or peripheral nervous system, with an accompanying loss of sensitivity. The pathophysiology of deafferentation pain is unknown, although central as well peripheral factors must be considered in order to explain certain clinical features [11,12,14].

In the case of amputations, it has been pointed out that phantom limb pain appears more readily if the patient experienced severe pain prior to amputation. Surgical section of the nerves during amputation produces a massive discharge of nociceptive afferents. This discharge, followed by a sudden absence of afferents, could stimulate the central cells into a state of continuous discharge, thus explaining why certain patients experience pain immediately after amputation. It has also been suggested that pain establishes engrams or memories of pain in the central nervous system which would continue to exist even without peripheral afferents.

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Wall et al. [16,18] have proposed the animal model of sciatic nerve section as a model for chronic pain due to deafferentation. In this model, pain can be quantified indirectly by evaluating the degree of autotomy [16]. The aim of this experimental study is to evaluate the autotomy in the chronic model of deafferentation pain through sciatic nerve section in the rat when the sensory afferents are varied prior to surgery, using the anaesthetic blocking of the sciatic nerve.

Methods

A total of 30 male Sprague–Dawley rats were used, weighing 250–300 g at the start of the experiment. The animals were anaesthetised with ketamine and atropine sulphate.

In 20 animals, a simple section of the left-side sciatic nerve in the thigh was performed. About 5 mm of the distal stump of the nerve was removed to avoid spontaneous distal reinnervation (control group, CoG, 20 rats). Following surgical exposure of the left-side sciatic nerve in the thigh of 10 animals, the surgical field was bathed with a 1% solution of mepivacaine. Cotton wool impregnated with the same local anaesthetic was left in place for 2 h and, after sciatic nerve section and the opening of a gap between the proximal and distal stumps, the surgical area was soaked with 1 ml of the anaesthetic solution. Mepivacaine is a local anaesthetic which takes effect within 2–8 min of application and which lasts 2–3 h (anaesthetic blocking group, ABG, 10 rats). In all animals the surgical wound was closed in layers. All animals were individually housed under standard colony conditions, regarding feeding, day–night cycle and temperature. No drugs were administered.

Every 48 h, the animals were examined by a member of the team, who was unaware of the group of origin of each animal. The extent of autotomy was assessed in accordance with the scale of points proposed by Wall et al. [16]: one point for the autotomy of one or more nails, a further point for each half digit attacked, one point for the autotomy of the metatarsus and another for the autotomy of the tarsal area. The maximum autotomy score was 13 points. The parameters used in the experiment were the day of onset of autotomy and the time course of the autotomy, which was assessed weekly for 10 weeks. Those animals which obtained a maximum autotomy score were sacrificed immediately; the others were sacrificed at the end of the observation period. The terminal neuroma was removed in all animals for pathological study. The results were compiled into statistical studies using the Student's t test, the Mann–Whitney test and the chi-square test with Yates' correction. The level of significance was set at $P < 0.05$.

Results

The surgical technique used was uneventful. Trophic changes were observed in the denervated limbs, namely temporary oedema, desquamation or hypertrophy of the unautotomised nails. The contralateral limb did not display lesions or trophic changes.

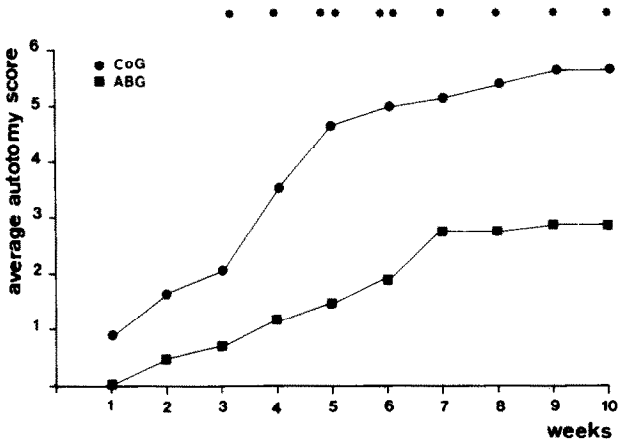

Fig. 1. Graphical illustration of the weekly average autotomy score in the control group (CoG) and the anaesthetic blocking group (ABG). Significant differences appear from the third week onwards. Mann–Whitney test. * $P < 0.05$, ** $P < 0.01$.

Onset of autotomy

The mean time for onset of autotomy and the standard deviation was 15.1 ± 12.3 days (ranging from 3 to 48 days) in the control group and 25.4 ± 13.9 days (ranging from 8 to 49 days) in the anaesthetic blocking group. There are no significant differences between the experimental groups ($t = 1.86$; $P < 0.10$). At the end of the period of observation, 100% (n = 20) of the animals in the control group and 80% (n = 8) of the anaesthetic blocking group had begun the autotomy of the denervated limb (autotomy score ≥ 1; $\chi^2 = 1.67$, P n.s.), 90% (n = 18) of rats in the CoG and 50% (n = 5) in the ABG had an autotomy score ≥ 3 ($\chi^2 = 3.94$, $P < 0.05$) and, finally, 60% (n = 12) in the CoG and 10% (n = 1) in the ABG had an autotomy score ≥ 6 ($\chi^2 = 4.90$, $P < 0.05$).

Time course of autotomy

The average autotomy score increases progressively in all groups until the final weeks, when it levels out. If experimental groups CoG and ABG are compared, then significant statistical differences are seen from the third week onwards (Fig. 1).

Pathological findings

Study under surgical microscope of the terminal neuromas at the moment of sacrifice did not show any differences among the experimental groups. Microscopic study of the neuromas proved to be similar in all animals, with axon sprouts growing anarchically inside a connective scar and among the neighbouring muscle tissue.

Discussion

Sciatic nerve section and dorsal cervico-thoracic and lumbar rhizotomy in the rat have been proposed as animal models of deafferentation pain [9,16,18]. The most

striking clinical consequence of deafferentation in the animal model is the self-cannibalism or autotomy of the denervated ending, whose quantification has been considered as a means of evaluating the pain, disaesthesia or, at least, discomfort experienced by the deafferentated animal [9,16]. Unlike the response of animals in the acute pain test, autotomy entails a complex behavioural disturbance involving the cerebral structures. The same phenomenon occurs in chronic pain in humans.

The physiopathological basis of deafferentation pain and autotomy is unclear. Some authors do not support the relationship between autotomy and deafferentation, pointing out that autotomy would simply be the animal's response to rid itself of a useless limb [10,13]. However, in the deafferentation pain models through dorsal rhizotomy, epileptiform discharges have been described in the spinal cord cells following sudden deafferentation [1], and the autotomy is controlled by the use of diphenylhydantoin [6]. In the deafferentation pain model through peripheral nerve section, Wall and Gutnick [17] have described new electrophysiological properties in the nerve fibres which regenerate in the neuroma, that appear to be the physiological substrata of pain and autotomy [3,4,15,17]. Furthermore, autotomy has been modified through the use of techniques which act on peripheral levels, such as centro-central anastomosis [7], transcutaneous neurostimulation [20] or the administration of guanethidine [5]. But autotomy has also been modified with changes in the animals' environment such as housing in groups [2], stress [19] or genetic factors [8]. These findings support the idea that autotomy represents a complex behavioural change and that we must not restrict ourselves to considering only localised mechanisms in the spinal cord or peripheral nerves.

Our experimental results show that anaesthetic blocking prior to and at the moment of sciatic nerve section in the rat significantly reduces autotomy scores, without changes in the day of onset of autotomy or in the structure of terminal neuroma. This indicates that blocking of sensory afferents during nerve section has an influence on the later discomfort of the animal, whereas the onset of autotomy remains unchanged because it is probably related to limb anaesthesia and abnormal neural activity generated in the neuroma [3,4,15–18]. Although the cutaneous anaesthesia is present immediately after nerve transection, the peripheral abnormal electrical activity starts later [3] and would not be modified by the anaesthetic blocking. Then, one might speculate that nerve injury produces immediate functional central changes, the intensity of which is reduced by means of anaesthetic blocking. Some immediate central changes, such as retrograde neuronal reaction and transsynaptic reaction, have been considered by Sunderland [12] to explain certain features of the causalgic pain.

These experimental findings support the idea that in experimental deafferentation pain and autotomy, both central and peripheral mechanisms are involved.

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