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AUTOTOMY PHENOMENON: EXPERIMENTAL MODEL OF NEURALGIC PAIN

Elena Kršljak,
Zoran Stajčić

Department of Physiology, Faculty of Stomatology
Dr Subotica 8, Belgrade, Serbia&Montenegro

Summary

Autotomy is phenomenon of deafferentation of the rat limb by transection of the sciatic and saphenous nerves, inducing an automutilation of the limb as a response to painful stimuli generated from the amputation neuroma. It was first described by Wall et al in 1979. Autotomy has been proposed as an experimental model for neuralgic pain. It was shown that implantation of a polyethylene tube around the proximal end of the sciatic nerve increases autotomy behaviour. Autotomy is easily quantified by using the degree of autotomy score. It has been shown that some drugs can prevent or decrease the degree of autotomy, such as: tricyclic antidepressant, anesthetics, glycerol, morphine, streptomycin, ampicillin.

Key words: Autotomy phenomenon, Sciatic nerve, Neuralgia

Introduction

Wall et al (1979)²⁵ have produced automutilation behaviour in rats after transection of the sciatic and saphenous nerves. As a result of this, animals start to attack their limbs. It is postulated that this behaviour is the result of the painful impulses sent to the CNS from the amputation neuroma formed at the end of the transected sciatic nerve. Animals usually start biting their nails, then phalanges, ending with mutilation of the entire foot. This occurrence is named autotomy phenomenon by Wall et al (1979)²⁵. The same behaviour has been observed following dorsal rhizotomy and named automutilation^{2,9}. Blumenkopf⁶ has speculated that autotomy phenomenon can be considered as a pathophysiological model of chronic pain and has introduced the term deafferentation. Wagner²⁴ has used the term neuropathic behavior for the same phenomenon. However the majority of investigators has accepted the term autotomy^{4,6,21,25}.

History

The autotomy phenomenon was introduced in the scientific literature by Wall et al (1979)²⁵. In this report rats and mice were taken as experimental animals and divided into 4 groups. In the first group both the sciatic and saphenous nerves were cut. In the second and the third group either sciatic or saphenous nerves were cut. In the fourth group nerves were sectioned and polyethylene (PE) tube

was placed around the proximal nerve stump. It was shown that the autotomy behaviour was most frequently recorded in the PE tube group.

Rats have been most commonly used experimental animals^{8,12,14,16,21}, followed by mice²⁵. Some investigators have sectioned both, the sciatic and the saphenus nerves as one stage procedure^{4,8,9,11,16}, whereas the others sectioned solely the sciatic nerve²⁵. After transecting the sciatic nerve, the proximal end of the nerve^{21,25} is gently pulled into the PE tube which distal end is sealed by sterile bone wax^{21,25} (Fig 1). The role of the PE tube is to prevent anastomosis of the nerve stump with adjacent nerve fibers. The PE tube can be used as a miniature cistern for different solutions to be investigated for their analgesic properties since they bathe the nerve stump for prolonged period of time. Barbera et al⁴ has injected such substances into the proximity of the nerve without implanting the PE tube. We have shown that frequency of the autotomy is much higher in animals where the PE tube is implanted¹¹. The peripheral nerve transection is followed by period of latency, for about 2 weeks, when animals start biting the denervated limb²⁵. Albe-Fessard et al², Caudaletti⁷ instead of peripheral nerve section performed dorsal rhizotomy of the suitable nerves in the cervical and thoracic part of the spinal cord.



Fig.1 The proximal end of the sciatic nerve is placed into the polyethylene tube

Possible causes of autotomy

There are two components of painful impulses that may cause the autotomy phenomenon. One is central¹⁰, related to brain activities and the other is peripheral associated with neuroma formation or abnormal activities of dorsal horn cells following rhizotomy.

There are opinions that the autotomy and “phantom pain” are the same phenomenon since it has been shown that substances reducing the phantom pain such as serotonin and triptofan also cause the suppression of the autotomy¹. Others state that there is significant difference between these two phenomena because autotomy has a latency period, whereas phantom pain starts immediately after amputation² lasting till the complete healing of the amputated part. The explanation for phantom pain is that this sensations of the amputated limbs, are represented in the thalamus, sensory and motor cortex(homunculus). It is obvious that these ² phenomena do not have the same mechanism of development.

Some authors explain the autotomy behaviour as a dermatome rule¹. The others describe autotomy as excitability changes of the spinal cord and brain cells^{7,8}. Futhermore, it has been shown that autotomy can be produced after dorsal rhysotomy^{7,8}. Seltzer et al¹⁸ were able to produce autotomy by electric stimulation on the A-alpha and C sciatic nerve fibres. Interestingly, autotomy behaviour started immediately after such stimulation.

The prevail opinion in the literature is that autotomy phenomenon is caused by painful impulses originating from neuroma at the proximal end of the cut nerve^{1,4,8,16,18,21,25} (Fig 2). Histopathological examination of the animals that developed autotomy revealed neuroma formation^{4,18,21,25}. Barbera et al⁴ also proved neuroma formation after reentry and were able to produce painful impulses by small pressure on neuroma. Wagner et al²⁴ noticed that Wallerian – like degeneration at the proximal end of the sciatic nerve influences the reduction the painful transmission and prevents the onset of autotomy phenomenon which was proved in our studies^{11,22}. (Fig.3) Based on current findings it can be strongly suggested that artificially created neuroma closed in PE tube is directly responsible for the autotomy behavior in experimental animals since the latency period of two weeks corresponds to the time required for neuroma to be formed.

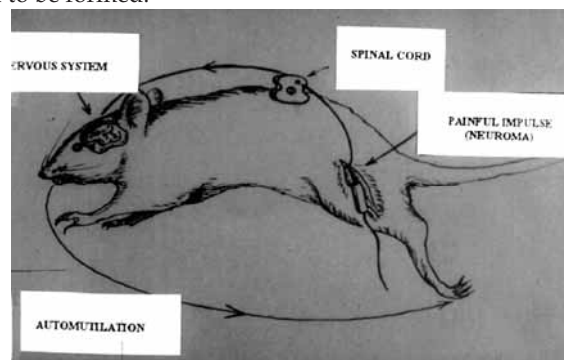


Fig.2 Autotomy phenomenon is based on the neuroma transmitting painful impulses to the CNS

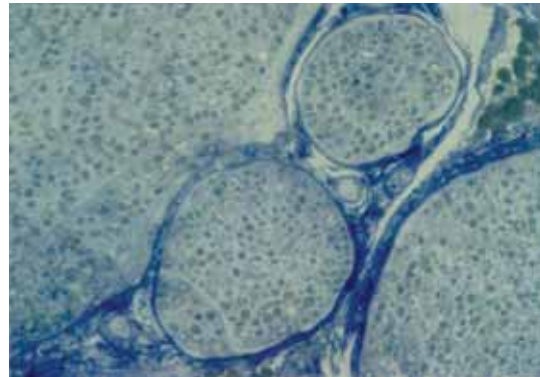


Fig.3 Wallerian like degeneration on the proximal end of the transecting nerve

Autotomy scores

Wall et al²⁵ introduced a method for measuring the severity of autotomy by using numerical values which was based on the degree of damage of the foot. Minimal autotomy score was 0 and maximal 13. A0 describes the absence of autotomy. Scores from one to five (A1-A5) denote bitten nails (Fig.4). Scores



Fig.4 Four nails bitten

from five to ten (A5-A10) correspond to damaged phalanges (Fig.5). The maximal autotomy score (A13) is given to the destroyed entire foot (Fig.6). There has been unanimous use of autotomy score by investigators.

If the autotomy behavior is produced after the dorsal root section of the forelimb, the denervated limb is divided into 10 zones. The ablation by biting one of the portions of the arm is counted 1. The ventral side is subdivided in the same way. The total of the forearm ablation is counted as 16, the

ablation of one digit as 1 and half of a digit as 5. The complete mutilation of the forelimb is scored 2423 (Fig.6)



Fig.5 An animal limb without two phalanges

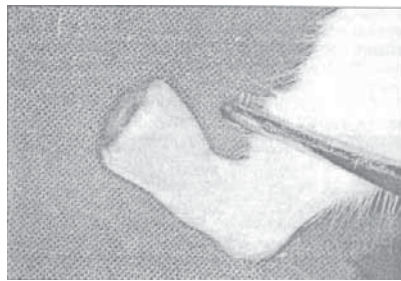


Fig.6 The whole foot bitten off

Effects of drugs on autotomy phenomenon

Published studies have been focused on substances and drugs blocking pain receptors or excitatory neurotransmitter receptors. The tested drug have been applied either systematically or topically at the free end of the transected nerve. Intra-neural injection of RCA I, reduces the release of Substance P, which causes the decrease of painful impulses and autotomy behavior in rats. The opioid application and cryotherapy have been known to reduce the autotomy scores and suppress it, which Puke et al22 ascribed to the opiate inhibitory effect on the substance P release in the gelatinous substance. Seltzer et al18 has shown that amitriptyline, tricyclic antidepressant is an effective analgesic against neuropathic chronic pains in humans. These drugs when applied in experimental animals reduce the autotomy behavior by inhibition of prostaglandin E2 and blocking H1 receptors. Puke et al17 pointed out the role of descending inhibitory pain control in the autotomy control showing that clonidine dexmedetomidine alpha2 adrenoceptor agonists effectively suppress autotomy when administered on 14th and 21st day of the nerve sections. Local anesthetics and blockers of the nerve transmission in the C-fibers and also cause the suppression of the autotomy phenomenon. 10,18. Glycerol was shown by Rappaport et al16 to reduce autotomy and prevent ectopic activity in A-alpha and C-fibers by two possible modes. It could firstly, preferentially eliminate demyelinated large fibers through an osmotic action and secondly, reduce their excitability. Gonzales et al8 were able to show that 20-day application of phenobarbital could reduce the degree of autotomy. The same authors performed the anesthetic blockade of the cut nerve with local anesthetic placed between the nerve ends (1% solution of mepivacaine), which

resulted in a significant suppression of the autotomy scores. Kauppala et al (9) injected anesthetic, lidocaine and bupivacaine, before the nerve section, at the place of the future lesion, which influenced the reduction of the autotomy scores and postponed occurrence of this phenomenon. Seltzer et al (18) reduced the autotomy scores by application of local anesthetic blocks. The autotomy behaviour in rats was reduced with a perineural infusion of lidocaine (6). An Intrathecal lidocaine injection, before the nerve section, also resulted in the postponed occurrence of autotomy. Cryotherapy applied to block peripheral nerve functions and concurrently to prevent the autotomy phenomenon was used by Wagner et al (24).

The suppression of the autotomy phenomenon was caused with the aid of morphine dissolved in water in the rats with the sciatic nerve transection resulted in the reduction of the autotomy behavior (14).

Saudeau et al (23) noticed, after unilateral section of the dorsal roots C5 to T1, that subcutaneous application of chloramphenicol and amoxicillin significantly reduced autotomy. Stajčić (28) showed that topically applied streptomycin after the sciatic nerve section in rats significantly reduced the autotomy phenomenon. Kršljak (11,13) has also shown that streptomycin and ampicillin injected into the PE tube significantly reduced the autotomy phenomenon (Tab 1). The mechanism of the protective effect of ampicillin against autotomy is largely unknown. It could be suggested that ampicillin as well as streptomycin, produces some degenerative changes of the nerve stump, which have been confirmed by Stajčić et al (2002) (22).

Tab.1

Statistical parameters	Antibiotics 0,01ml - 50% solution			
	streptomycin	ampicillin	chloramphenicol	saline
No. of animals	15	15	15	15
Minimal autotomy score	1	2	5	5
Maximum autotomy score	7	13	13	13
Medial	4***	7.**	10	10

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*** p < 0.001 Statistical significance compared streptomycin in relation to saline

** p < 0.01 Statistical significance compared ampicillin in relation to saline

Sporel et al speculate that all drugs that reduced autotomy behavior can be considered anti-neuralgic drugs in humans. However, we think that the autotomy phenomenon is a reliable experimental model for neuralgic pain, which can be used for testing new analgesic substances.

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