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Behavioral Manifestation of Neuropathic Pain Following Sciatic Nerve Section in Rats

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ABSTRACT

The present study was performed to observe the time course of behavioral signs of painful sensations in sciatic neurectomy animal model and to test the effects of sympathectomy and saphenous nerve section on these behavioral signs. Sciatic nerve was ligated and cut at the mid-thigh level under gaseous anesthesia. The application of von Frey filaments to the medial plantar surface of foot revealed weak and long-lasting mechanical allodynia (until end of test period, 20 weeks PO). Acetone application to the plantar surface of foot was used ti measure the sensitivity to cold stimulation. Cold allodynia which is interpreted as increased response to acetone application developed fairly well and lasted the end of test period (20 weeks PO). The cumulative duration of foot lifts off neutral or cold plate was used to test spontaneous, ongoing pain and was increased until 16 weeks PO and 20 weeks PO respectively. These results suggest that sciatic neurectomy which has been widely used as chronic pain model shows behavioral signs suggsting painful sensations except autotomy, which has been used as index of pain in experimental animal. Surgical sympathectomy performed 1 week after sciatic neurectomy partially reduced the behavioral signs of mechanical allodynia and cold allodynia, suggesting behavioral changes developed following section of sciatic nerve was partially sympathetic dependent. Saphenous nerve section 1 week after sciatic neurectomy almost completely reduced mechanical allodynia and cold allodynia, but did not change spontaneous, ongoing pain. These results suggest that evoked responses such as mechanical and cold allodynia are mediated by saphenous nerve activity and activating and/or maintaining mechanisms of spontanous, ongoing pain and evoked pain may be different.

Key words: neuropathic pain, mechanical allodynia, sympathectomy, nerve injury

INTRODUCTION

Animal model standing for any disease in human is powerful tool to research of its mechanisms and treatment. Sciatic ligation and transection model has been used as a animal model for chronic pain (Basbaum, 1974; Wall et al., 1979; Wiesenfeld and Lindblom, 1980; Wiesenfeld and Hallin, 1983; Coderre et al., 1986). Following sciatic neurectomy, animals showed foot-biting and self-mutilation behaviors. Self-mutilation is called autotomy (Wall et al., 1979) and is likely pain-related behavior (Sweet, 1981; Coderre et al., 1986).

Total peripheral neurectomy in human produces dysesthesias. To be a good animal model for peri-

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pheral deafferentation model, a sciatic ligation and transection model should have similar painful sensations, which include spontaneous as well as evoked pain and aversive affect. And behaviors indicating painful sensations should be comparable to those which give rise to human dysesthesias.

Although sciatic neurectomy model has long been used, behavioral study has not extensively studied except autotomy behaviors.

The aim of this study was to observe behavioral manifestations in sciatic neurectomy model.

MATERIALS AND METHODS

Experimental animals and experimental groups

All experimental procedures were conducted in accordance with guidelines set by the Korea University College of Medicine Animals Research Policies Committee. Total 28 male rats (Sprague-Dawley) were used. Weights of rats were 150～200 gm at sciatic neurectomy. The animals were housed in groups of 3～4 in plastic cages with soft bedding under 12/12 hours day-night cycle. The animals were kept at least 7 days before surgery.

Sciatic nerve of the left leg was exposed and ligated with 6～0 silk thread at the mid-thigh level and sectioned just distal to the ligation under gaseous anesthesia with a mixture of enflurane (4% for induction and 2% for maintenance) and 1 : 2 flow ratio of N_2O and O_2. A 0.5 cm length of the distal nerve stump was removed to prevent regeneration. The wound was sutured in layer.

Rats were divided into 3 experimental groups;

Experimental group 1 (Time course of behaviors, n=12); Sciatic neurectomy was done as described above and their behaviors were observed up to 20 weeks.

Experimental group 2 (Surgical sympathectomy group, n=8); One week after sciatic neurectomy, under gaseous anesthesia with a mixture of halothane (2% for induction and 0.8% for maintenance) and 1 : 2 flow ratio of N_2O and O_2, the lumbar sympathectic chain was identified through a transperitoneal approach. The identification of the exact level of the sympathetic ganglia was made by finding the reliable landmarks described by Baron et al (1988). The sympathetic chains along with ganglia of both sides were removed from L2 to L6 levels.

Experimental group 3 (Saphenous nerve resection group, n=8); One week after sciatic nerve ligation and transection, saphenous nerve was cut at the mid-thigh level.

Behavioral tests

Behavioral tests were conducted in experimental group 1 at 1 day before nerve injury, 1, 3, 5 and 7 days postoperatively (PO) and biweekly until 4 weeks PO; quatriweekly until 20 week in expermertal group 1. In experimental group 2 and 3, behavioral tests were done on 1 day prior to sciatic neurctomy, 1, 3, 5 and 7 days postoperatively and 1, 3, 5, 7, 14 days after surgical sympathectomy or saphenous neurectomy, respectively.

Behavioral signs of three different kinds of neuropathic pain were measured as previously described in detail (Choi et al., 1994): mechanical allodynia, cold allodynia, and ongoing pain. To quantify mechanical sensitivity of the foot, brisk foot withdrawal in response to normally innocuous mechanical stimulus was measured. Innocuous mechanical stimulus was applied with two different strength of von Frey filaments (8.4 mN, 0.8 g; 54.4 mN, 5 g). The rats were placed under the plastic dome (8×8×24 cm) on a metal mesh floor and von Frey filaments were applied to the medial portion of plantar surface of the foot. Each von Frey filament was applied 10 times to each hind paw. The interval between each stimulus was about 3～4 sec. The frequency of foot withdrawal was expressed as a percent (number of foot withdrawals/number of trial ×100).

To measure cold sensitivity of the foot quantitatively, brisk foot withdrawal in response to acetone application was determined. The rat was placed under the plastic dome on a metal mesh floor and acetone was applied to the plantar surface of the foot. Acetone was applied five times to each paw. The interval between each application was at least 5 min. The frequency of foot withdrawal was expressed as a percent (number of foot withdrawal to acetone/number of trial ×100).

Two different kinds of test were performed to measure ongoing pain. Each rat was placed under the transparent plastic dome on a brass plate kept a neutral (30±0.5°C) or cold temperature (5±0.5°C). After 5 min. of adaptation, the cumulative duration of time that the rat lifted the foot off the plate for the next 5 min. was measured. The foot lifts associated with locomotion or reposition of body were not counted. These tests reflect spontaneous pain and cold-stress induced ongoing pain, respectively (Choi et al., 1994).

Statistics

Data are expressed mean standard error of mean (S.E.M.). Statistical treatments were made by using non-parametric statistics including the Friedman analysis by rank followed by multiple comparison tests. p values less than 0.05 were considered to be significant.

RESULTS

Time course of neuropathic behaviors

Twelve rats were used for this study. Sciatic ligation and transection produced foot deformities which were moderately inverted or everted foot and moderately ventroflexed toes. Limping gait was seen especially first one to two weeks and was recovered to normal gait after 2 weeks PO. Autotomy was firstly seen at 3 days PO in 1 rat out of 12 rats. Cumulative percentage of rats which showed autotomy was 25.0% (3 of 12) at 5 days PO, 33.3% (4 of 12) at 7 days PO, 41.7% (5 of 12) at 2 weeks PO and 66.7% (8 of 12) at 4 weeks PO. The autotomy was confined to the tips of one or more nails in all affected animals.

The results of the behavioral tests for spontaneous pain and cold-stress induced ongoing pain are shown in Fig. 1A and 1B. The rats lifted the foot off the neutral temperature plate (30^{o}C) on operated side for at least 12 weeks PO as compared to the preoperative period. When the rats were placed on a cold plate (5^{o}C), they lifted the foot on the injured side. The foot lifting was increased at least 20 weeks PO as compared to the preoperative control period. The contralateral foot was not responsive throughout the test period either on neutral or on cold temperature plate.

The results of the behavioral tests for cold sensitivity of the hind paw are shown in Fig. 1C. Before surgery, the rats rarely responded to acetone application. After sciatic neurectomy, the ipsilateral hind paw became sensitive to acetone application.

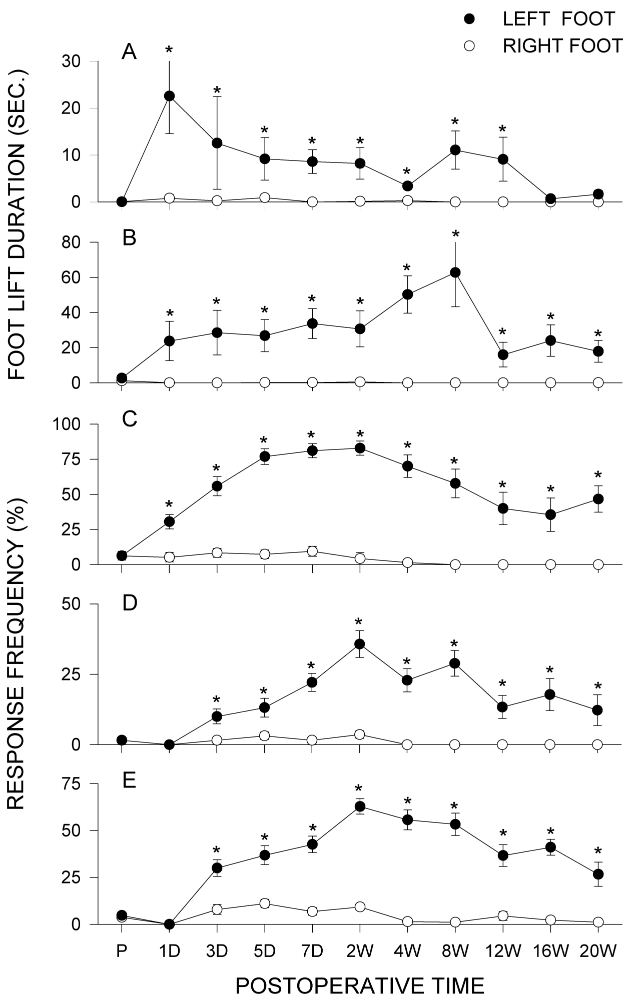

Fig. 1. Time course of the behavioral signs of painful sensations following sciatic neurectomy (Group 1). Behavioral signs of spontaneous pain (A), cold-stress induced ongoing pain (B), cold allodynia (C), and mechanical allodynia (D; 8.4 mN, E; 54.4 mN von Frey filament). Postoperative time is expressed as P for the preoperative test period or as D and W for days and weeks after sciatic neurectomy. Asterisks indicate values significantly different from the preoperative value ($p<0.05$ by Friedman analysis of variance by ranks followed by multiple comparisons). Number of animals: 12.

When acetone was applied to the plantar surface of the foot, it sometimes spreaded to dorsum of foot and ankle region.

The results of the behavioral tests for mechanical sensitivity are shown in Fig. 1D and 1E. Fig. 1D shows the results obtained to mechanical stimuli applied with the weaker von Frey filament (8.4 mN, 0.9 g). This von Frey filament makes the light touch sensation when applied to human skin. Before surgery, rats did not respond to application of this mechanical stimuli to the hind paw. After sciatic nerve was sectioned, the most area of plantar surface was anesthetic and only small area of plantar surface along the medial edge including first digit was responsive to pin-prick. Mechanical stimulation with von Frey filaments was applied to plantar surface which responded to pin-prick test. After sciatic nerve was sectioned, the ipsilateral paw became sensitive to mechanical stimulation. Compared to increased mechanical sensitivity occurred in partial peripheral neuropathic models (Kim and Chung, 1992; Choi et al., 1994; Kim et al., 1997), the responsiveness to von Frey filament was not prominent and slowly developed. Fig. 1E shows the results obtained to mechanical stimuli applied with the stronger von Frey filament (54.4 mN, 5.5 g). The strength of this von Frey filament produces pressure sensation when applied to this stimuli. After surgery, ipsilateral paw became responsive to this mechanical stimulation and this increased sensitivity was maintained throughout the test period.

Effects of sympathectomy

Eight rats were used for this study to investigate if painful behaviors measured in the present study were dependent on the sympathetic efferent function one week after sciatic neurectomy. Fig. 2A and 2B show the behavioral signs of the spontaneous pain. Sympathetic block did not change the behavioral signs indicating spontaneous pain. Fig. 2C shows the results of lumbar sympathectomy on behavioral signs of cold allodynia. Cold sensitivity of paw did not change. Fig. 2D and 2E show the behavioral signs of mechanical allodynia after surgical sympathectomy. Sympathetomy reduced signs of mechanical allodynia at least first 5 days (lighter von Frey filament) or 7 days (stronger von Frey filament), but decreased mechanical sensitivity following sympathectomy was temporary and eventually recoverd at 2 weeks after sympathectomy, which was the end of the test period.

Effects of saphenous nerve section

Eight rats were used for this study to see the roles of saphenous nerve in sciatic sectioned animal. Fig. 3A and 3B show the behavioral signs of ongoing pain which was not changed after saphenous nerve section. Fig. 3C shows the results of behavioral signs of cold allodynia. Cold sensitivity

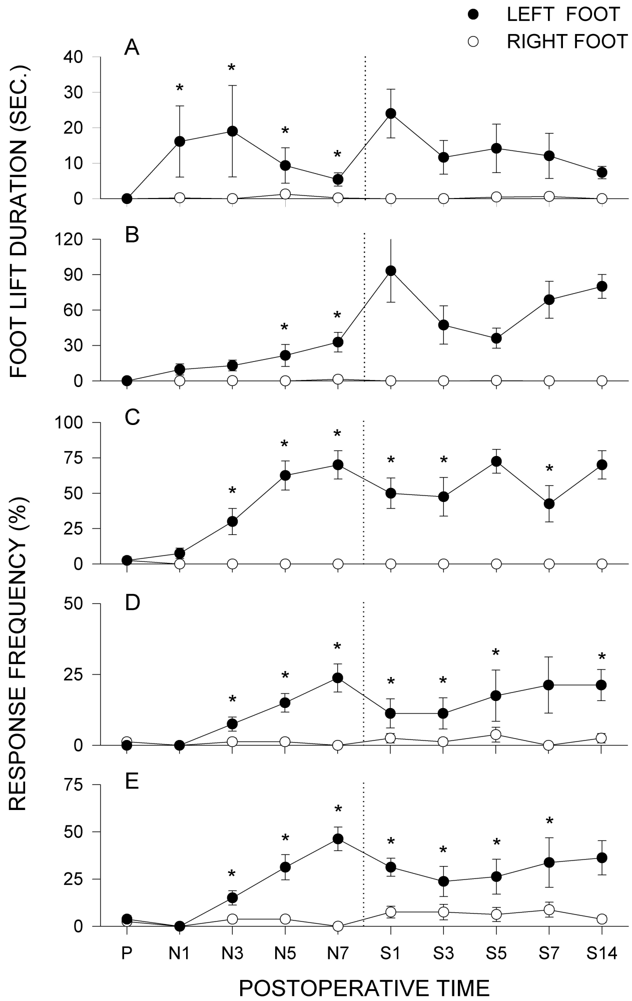

Fig. 2. Effects of surgical sympathectomy on behavioral signs of spontaneous pain (A), cold-stress induced ongoing pain (B), cold allodynia (C), and mechanical allodynia (D; 8.4 mN, E; 54.4 mN von Frey filament) (Group 2). One week after sciatic neurectomy, a lumbar sympathectomy was perform (at dotted line) and behavioral tests were continously performed next 2 weeks. Postoperative time is expressed as P for the preoperative test period or as N and S for post-neurectomy period and post-sympathectomy period. Asterisks appeared before dotted line indicate values significantly different from the preoperative value and asterisks appeared after dotted line indicate values significantly different from the pre-sympathectomy value ($p<0.05$ by Friedman analysis of variance by ranks followed by multiple comparisons). Number of animals: 8.

was well developed following sciatic neurectomy and these behavioral signs were significantly reduced after saphenous nerve section and was remained low until the next 2 weeks, which was the ens of the test period. Fig. 3D and 3E show the effects of saphenous neurectomy on the mechanical sensitivity developed following sciatic neurectomy. Section of saphenous nerve significantly reduced

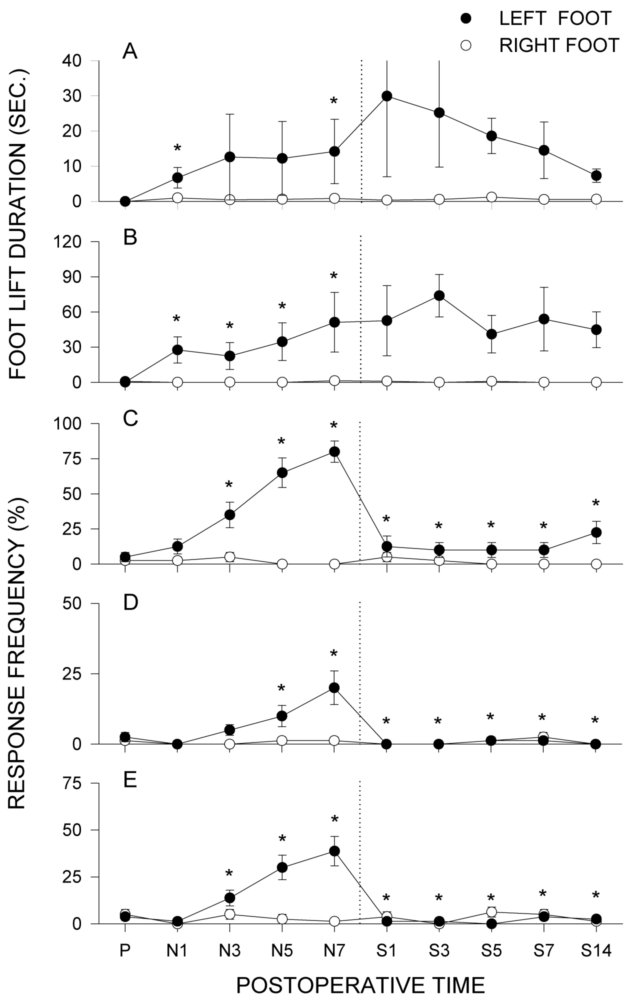

Fig. 3. Effects of section of saphenous nerve on behavioral signs of spontaneous pain (A), cold-stress induced ongoing pain (B), cold allodynia (C), and mechanical allodynia (D; 8.4 mN, E; 54.4 mN von Frey filament) (Group 3). One week after sciatic neurectomy, saphenous nerve was cut at the mid-thigh level (at dotted line) and behavioral tests were continously performed next 2 weeks. Postoperative time is expressed as P for the preoperative test period or as N and S for post-neurectomy period and post-saphenous neurectomy period. Asterisks appeared before dotted line indicate values significantly different from the preoperative and asterisks appeared after dotted line indicate values significantly different from the pre-saphenous nerve section value ($p < 0.05$ by Friedman analysis of variance by ranks followed by multiple comparisons). Number of animals: 8.

the behavioral signs of mechanical allodynia, almost completely, which was maintained throughout the test period.

DISCUSSION

Behavioral manifestation

This study provides behavioral evidence that sciatic ligation and transection model produces pain-related behaviors. The presence of behavioral signs suggestive of spontaneous pain is shown in this study. To test spontaneous, ongoing pain, the duration of the foot lift off a plate at 30°C was measured. The cumulative duration of foot lift off a neutral temperature plate has been used as an index of spontaneous pain after subcutaneous injection of formalin (Dubuisson and Dennis, 1977; Coderre et al., 1993) and spontaneous pain in partial peripheral nerve injury model (Attal et al., 1990; Choi et al., 1994; Kim et al., 1997). Because most area of plantar surface is anesthetic following sciatic nerve section, foot lift may be related to spontaneous pain without any overt external stimuli. It is not certain whether the the cumulative duration of foot lift accurately reflects the amount or severity of pain.

The cumulative duration of foot lifting off a cold plate (5°C) was used to quantify the cold-stress induced ongoing pain. In this study, behavioral signs of cold-stress induced ongoing pain was present until end of test, 20 weeks PO. This behavior is proposed likely to be related to a form of spontaneous, ongoing pain because 1) plantar surface of foot in sciatic neurectomy rat was anesthetic and 2) the same test has been used as a behavioral test for ongoing pain in partial peripheral nerve injury model (Choi et al., 1994). It was proposed that this behavioral test may be helpful to find the effect of therapeutic treatment, since the absolute value of behavioral test for spontaneous pain was too small.

Behavioral signs of mechanical allodynia were also present in this study. Mechanical allodynia was quantified by measuring the frequency of foot withdrawal to application of von Frey filament to the medial plantar surface of the foot. Two von Frey filaments were used in this study have weak bending forces so that their application to normal human skin produces a faint sense of touch (the weaker one) or pressure (the stronger one). Application of these von Frey filaments to the plantar surface of the foot are innocous to normal rats because the rats rarely respond to such stimulation before surgery. After ligation and transection of sciatic nerve, rats withdraw their foot to same stimuli. Foot withdrawal is not evident right after denervation of hindpaw and is being increased to reach its peak at 2 weeks PO. Although mechanical allodynia was developed after sciatic nerve section, its degree was much less than mechanical allodynia following experimental causalgia model (Choi et al., 1994; Kim et al., 1997). The development of mechanical hyperalgesia was reported following sciatic nerve section in lateral portion of the affected paw (Kingery and Vallin, 1989).

The frequency of the foot withdrawals to acetone application to the plantar surface of the foot was measured as a behavioral test for cold allodynia. Acetone application has been used to detect the presence of cold allodynia in human (Frost et al., 1988; Davis et al., 1991) and in experimental neuropathic pain model (Choi et al., 1994). The presence of behavioral signs suggestive of cold allodynia is shown in this study. Normal rats are rarely responsive to the application of acetone to the plantar surface of foot. Beginning 1 day PO, rats withdrew their foot to acetone application and this response lasted at least 20 weeks PO, which was the end of test. Because acetone applied to the plantar surface of foot sometimes spreaded to the dorsum of foot, behavioral response to acetone application is exactly not the reflection of sensation changes localized in the plantar surface of foot.

Effects of sympathectomy

The results of this study show that behavioral changes following sciatic nerve section are partially reduced by surgical sympathectomy. Because the lumbar sympathetic ganglia were often fused and the innervation of sympathetic nerve to hindpaw in rat is controversial (Peterson and Norvell, 1985; Baron et al., 1988) surgical sympathectomy was done by removing the sympathetic chains along with the ganglia on both sides from L2 to L6.

Chronically injured sensory axons ending in a neuroma produced by sciatic nerve section generate ectopic impulse (Wall and Gutnick, 1974; Govrin-Lippmann and Devor, 1978; Devor and Jänig, 1981; Scadding, 1981; Korenman and Devor, 1981; Wall and Devor, 1983). Spontaneous neuroma activity had been proposed to relate the behavioral evidence of pain or dysesthesia (autotomy) after sciatic nerve section (Wall and Gutnick, 1974; Govrin-Lippmann and Devor, 1978; Wall et al., 1979; Korenman and Devor, 1981; Scadding, 1981; Wall and Devor, 1983). This activity is observed as early as 2 to 3 days after sicatic nerve section experimentally and is increased to topical or systemic application of -adrenergics. In addition, if guanethidine, sympathetic blocking agent, is given from 4 to 9 days after sciatic nerve division, autotomy is abolished while anesthesia and paralysis persist (Wall et al., 1979). This suggests that blocking sympathetic efferent activity to neuroma reduces ongoing activity and correlative painful behaviors. In present study, surgical sympathectomy partially reduced behavioral signs of mechanical and cold allodynia but did not diminish behavioral signs of spontaneous, ongoing pain. This results suggest that spontaneous pain and evoked pain may have different activation or maintaining mechanism, which was also proposed in experimental neuropathic model (Yoon et al., 1996). In view of previous reports, surgical sympathectomy is expected to reduce the behavioral signs of painful sensations. Partial reduction of painful behaviors may be partially due to too early sympathectomy, this assumption is supported by 1) spontaneous ectopic activity generated in neuroma, which may be related to painful sensations, is increased as time passes after sciatic nerve division (Korenman and Devor, 1981) 2) abnormal responsiveness of spontaneous discharge to systemic injection of noradrenaline, epinephrine, or phenylnephrine develops only several days after nerve injury (Scadding, 1981) 3) sprouing of sympathetic postganglionic fibers into dorsal root ganglia is progressive after sciatic ligation (McLachlan et al., 1993). It is suggested that behavioral signs of painful sensations following sciatic neurectomy may be sympathetically independent in the early phase of time course, but may be retained sympathetic dependency later.

Effects of saphenous nerve section

The present study shows that saphenous nerve plays a role in the behavioral signs of evoked pain such as mechanical allodynia and cold allodynia. After sciatic nerve is cut, the responsive area of saphenous nerve which is a only nerve to innervate the plantar surface of foot in rat, expand (Devor et al., 1979). To detect cutaneous stimuli for rats in plantar surface of foot, it is necessary that intact nerve fiber must exist. So behavioral signs of mechanical and cold allodynia developed following section of sciatic nerve in this study is related to saphenous nerve. Behavioral sign of spontaneous, ongoing pain is not reduced by saphenous nerve section, suggesting that the generating and/or maintaining mechanisms of spontaneous pain is different from those of evoked pain. Decreased reflex withdrawal time to cold and hot water produced by loose ligation of sciatic nerve was not developed if saphenous nerve was cut (Ro and Jacobs, 1993), suggesting saphenous nerve plays a role in the behavioral changes following incomplete sciatic nerve injury.

Autotomy

Peripheral nerve transection model has been most widely used animal model of chronic pain (Wall et al., 1979; Rodin and Kruger, 1984; Levitt, 1985). The animals mutilate the denervated paw following nerve section and this behavior is called autotomy (Wall et al., 1979). Autotomy is thought as an animals' attempts to remove their unplesant sensations arising in denervated extremities (Coderre et al., 1986) and have been used as an index of pain severity (Wall et al., 1979; Wiesenfeld-Hallin, 1984; Wiesenfeld-Hallin et al., 1987). Although autotomy is one of good behavioral signs suggesting presence of painful sensations, it has several problems; 1) because autotomy is accumulative and irreversible phenomenon, pharmacological interventions to increase or decrease the autotomy is restricted. 2) autotomy is rarely seen in human.

The behavioral signs of painful sensations presented here provide a reproducible behavioral tests developed following sciatic neurectomy.

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