

Morphological Changes of the Sensory Neurons in the Peripheral Neuropathy of Rat Tibial Nerve Using WGA-HRP Tracing Method

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Abstract : Neuropathy is a general term referring to disorders of nerves, and produces when the nerves are damaged. It is characterized by spontaneous pain, allodynia and hyperalgesia. The purpose of present study is to observe the number of WGA-HRP (wheat germ agglutinin-horseradish peroxidase) labeled sensory neurons of DRG (dorsal root ganglia), and distributions according to cell size of sensory neuron in tibial nerve ligation model (NLM).

The tibial nerve ligation was performed with 3-0 silk by the application of three tight ligatures at the mid-thigh level. In the neuropathy model of rat tibial nerve ligation, morphological changes of sensory neurons in DRG were observed using WGA-HRP.

Rats of NLM showed the neuropathic behaviors. Rats were shown guarding affected limb and limping. Their toes and ankle joint of operated limb were hyperflexed. Under light microscopy, tibial nerve showed degeneration of axons in NLM. In control and NLM, labeled sensory neurons of tibial nerve distributed L4 and L5 DRG. In control group, the labeled sensory neurons were round or oval in shape. They were large and small cells, and mixed pattern. Total number of labeled sensory neurons in NLM decreased significantly from control group. The number of labeled sensory neurons in L4 and L5 DRG decreased significantly from control group. Labeled large and small cells decreased significantly from control group.

Present study may serve as the basic information about the changes of DRG sensory neurons in NLM.

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Key words : Neuropathy, Tibial nerve, Sensory neuron, WGA-HRP, Nerve ligation model (NLM)

Introduction

Mitchell (1872) first described a painful syndrome-neuropathy, which occasionally develops following a nerve injury (Kim and Chung 1992). Neuropathy is a general term referring to disorders of nerves, and is produced when the nerves are damaged due to trauma, disease, metabolic disorder and toxins (Bennett and Xie

1988). Neuropathy confirms the occurrence of intense burning pain, pain evokes by normally innocuous stimuli (allodynia) and intense pain in response to painful stimuli (hyperalgesia) (Gautron et al. 1990, Choi et al. 1994). Neuropathy models are useful study method for nerve injury. In many neuropathy models, the abnormal behaviors were observed following complete nerve transection and ligation (Attal et al. 1990). Some neuropathy models are based on a unilateral ligation of the sciatic nerve or spinal nerves in the rat (the chronic constriction injury model, Bennett and Xie 1988; the partial sciatic nerve injury model, Seltzer et al. 1990;

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and the spinal nerve ligation model, Kim and Chung 1992). Comparison of neuropathy models within and between different laboratories has indicated that they show differences in (a) the time-course and the degree of allodynia and hyperalgesia against mechanical and/or thermal stimuli, (b) the occurrence of spontaneous pain, autotomy and inflammatory processes, (c) in the sensitivity to sympathectomy and pharmacotherapy (Hofmann et al. 2003). It can be assumed that part of this variation derives from differences in the degree of ligation, ligation material, differences in rat strain and differences in rat sciatic nerve anatomy. In the present study, we modified the method of Seltzer et al. (1990), and we focused that this tight nerve ligation model (NLM) reduces the variability in the results. In neuropathy models, there are many previous studies about behavioral observation, changes of neuropeptides and neurotransmitters, degeneration of axons, apoptosis and inflammation. Some studies (Baron et al. 1988, Swett et al. 1991, Swett et al. 1995) have reported distributions of sensory neurons in neuropathy model, but there may be no report about distributional changes of sensory neurons in neuropathy model and no report about changes of sensory neurons according to the cell body diameter in neuropathy model. Therefore, purpose of the present study is to observe the morphological changes of lumbar DRG (dorsal root ganglia) and tibial nerve, changes in the distributions according to cell size of WGA-HRP (wheat germ agglutinin-horseradish peroxidase) labeled sensory neurons in NLM.

Materials and Methods

1. Animal

Male Sprague-Dawley rats weighing between 280 ~ 340 grams at the beginning of the study were used. Each control and experimental groups was consisted of four male Sprague-Dawley rats.

2. Nerve ligation model (Seltzer et al. 1990)

Under general anesthesia with 7% chloral hydrate (0.5 mL/100 g B. W, BDH Chemical Ltd., England), the right tibial nerve was exposed and was carefully freed from surrounding connective tissues. The ligation was performed with 3-0 silk by the application of three tight ligatures, applied 1 ~ 2 mm apart at the level of the bifurcation of the sciatic nerve at the mid-thigh level. The ligation of the tibial nerve was maintained during 1, 2 and 4 weeks, respectively.

3. Labeling technique

Rats were anesthetized with 7% chloral hydrate (0.5 mL/100 g B. W). After transection of the tibial nerve, the proximal end of tibial nerve stumps was soaked for about 5 min in 5 μ L of 2% aqueous wheat germ agglutinin-horseradish peroxidase (WGA-HRP, Sigma, USA) solution. After the application with the WGA-HRP, the nerve was returned to its original position. In control group, WGA-HRP was applied at the same level as in the experimental groups.

4. Histological preparations of the tibial nerve and the DRG

The rats were returned to normal condition for 3 days to allow transport and accumulation of WGA-HRP in sensory neurons of the DRG. After sacrificing the rat, a transcardial perfusion was performed with cold saline and 4% paraformaldehyde (Yakuri pure chemicals co., Ltd., Japan). Tibial nerve was identified, dissected and cut into following three segments along its length.

- Proximal tibial segment : above the proximal-most ligature
- Mid-tibial segment : within the ligature site
- Distal tibial segment : below the distal-most ligature

The segments of tibial nerve were post-fixed overnight. Following dehydration, clearing and embedding in paraffin, 5 μ m thick-sections were cut transversely

and stained with Hematoxylin-Eosin for light microscopy. From first lumbar DRG to sixth lumbar DRG were sampled. DRG were post-fixed overnight and stored in 20% sucrose in phosphate buffer for 24 hours at 4°C. All ganglia were cut by a freezing microtome (Cryostat, Leica, Germany) at 40 µm thickness. Forty micrometers were the most suitable thickness for marking reconstructions of rat sensory neuron populations. The sections were reacted with TMB (tetramethylbenzidine) as the chromogen.

5. Analysis of WGA-HRP labeled sensory neurons in DRG

All serial sections of L4 and L5 DRG counted for analysis. All serial sections were examined under light microscope using a ×100 objective lens. Only neuron profiles with a clear stained nuclei or cytoplasm were included in the study. WGA-HRP labeled neurons could be classified into large cells and small cells according to the cell body diameter. The sensory neurons of 25~45 µm in diameter were classified into large cells and the sensory neurons of 10~25 µm in diameter were classified into small cells. Any neurons smaller than 10 µm in diameter were ignored.

6. Statistical analysis

Data were expressed as mean ± SD. The data were analyzed by the student's t-test. Values of $P < 0.05$ are

regarded as significant.

Results

1. Behavioral changes following ligation of tibial nerve

Body weights of all rats gained normally (Fig. 1), and no signs of autotomy occurred in NLM. The rats in NLM walked without allowing the hind paw to touch the floor. Rats raised the affected hind paw from the floor and hold it in a protected position next to the flank while standing or sitting. The toes were held together

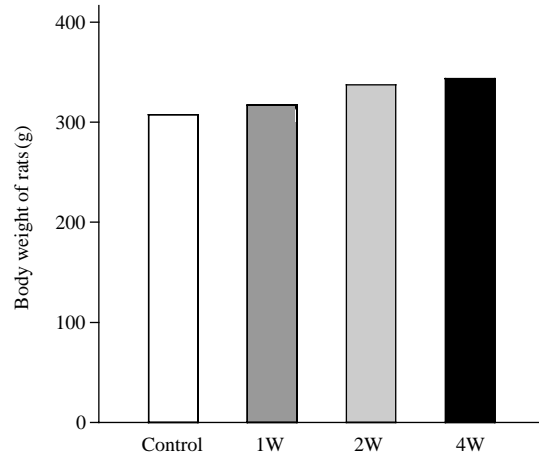


Fig. 1. The histograms body weight of the rats. Following the nerve ligation, rats do not lose their body weights.



Fig. 2. Photographs of legs of control (A) and NLM (B-1, B-2). Rat of NLM show hyperflexion of ankle joint and toes.

and ventroflexed (Fig. 2B-1, B-2). The movements of rats reduced. No autotomization was observed in NLM.

2. The histological changes of tibial nerve

When the silk ligation was removed, the proximal tibial segment were swollen and mid tibial segment

was covered with new connective tissues. The mid tibial segment was shown thinner diameter than control group, and there was a local inflammatory reaction. The distal tibial segment of the ligated site was shown little swelling. In the light microscopic analysis, degeneration of axons was present in distal tibial segment. Many axons disappeared and myelin sheaths were

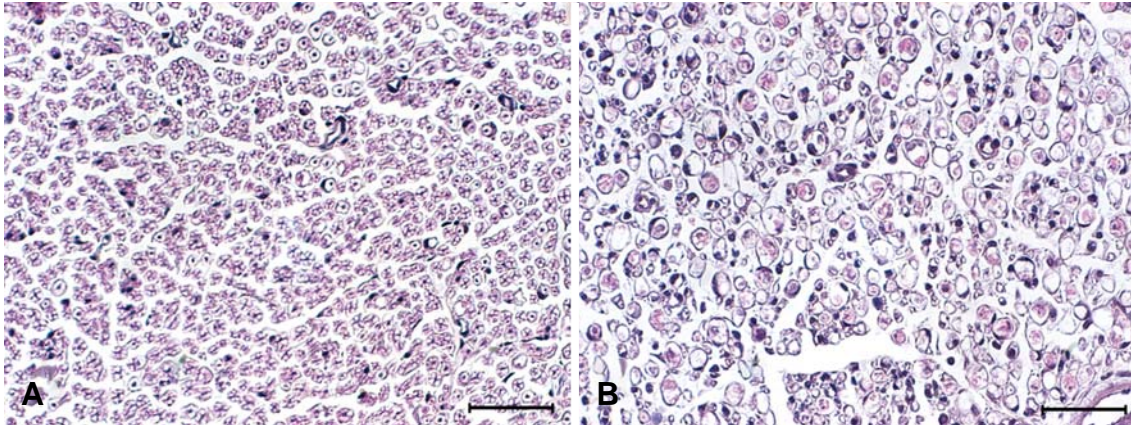


Fig. 3. Transverse sections of tibial nerve at the distal tibial segment. A : control, B : 1 week after nerve ligation. Hematoxylin-Eosin stain. In B, some axons become swollen and lose their myelin sheath. Scale bars=50 μ m.

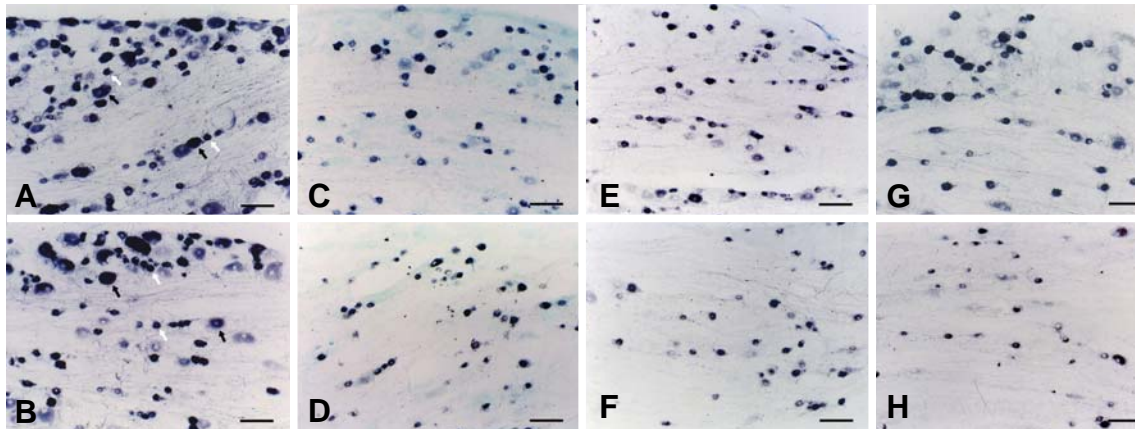


Fig. 4. Photomicrographs of WGA-HRP labeled sensory neurons in control and NLM. A : L4 DRG of control, B : L5 DRG of control, C : L4 DRG of 1 week, D : L5 DRG of 1 week, E : L4 DRG of 2 weeks, F : L5 DRG of 2 weeks, G : L4 DRG of 4 weeks and H : L5 DRG of 4 weeks group. Sensory neurons of tibial nerve distribute in L4 and L5 DRG. Large and small cells are mixed (black arrows : large cell, white arrows : small cell). In NLM, WGA-HRP labeled large and small cells decrease from control group. Scale bars=50 μ m.

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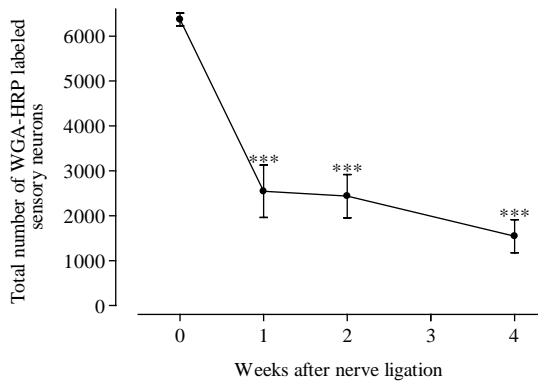


Fig. 5. Total number of WGA-HRP labeled sensory neurons in NLM. Total number of labeled sensory neurons in 1, 2 and 4 weeks groups decrease significantly from control group. 0 week is control group. *** $P < 0.001$.

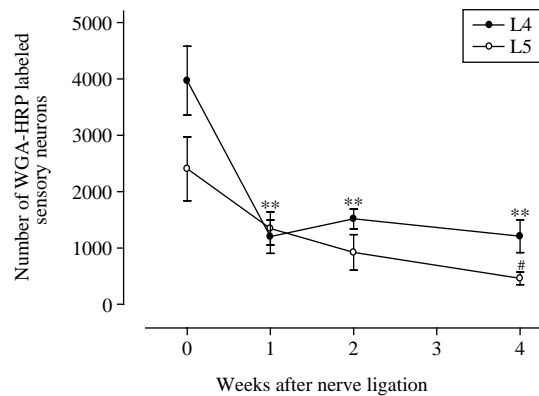


Fig. 6. The number of WGA-HRP labeled sensory neuron of L4 and L5 DRG in NLM. In L4 DRG, the number of labeled sensory neurons in 1, 2 and 4 weeks groups decrease significantly from control group. In L5 DRG, the number of labeled sensory neurons decrease significantly in only 4 weeks group from control group. 0 week is control group. # $P < 0.05$, ** $P < 0.01$.

Table 1. Total number of WGA-HRP labeled sensory neurons in control and NLM

	Nerve ligation model			
	Control	1W	2W	4W
L4	3,967 ± 612.1	1,200 ± 296.9	1,517 ± 177.5	1,209 ± 289.9
L5	2,404 ± 567.3	1,346 ± 295.7	919 ± 315.6	460 ± 110.9
Total	6,372 ± 139.6	2,546 ± 584.4	2,437 ± 481.2	1,544 ± 367.3

swollen and irregular in the distal tibial segment (Fig. 3B).

3. Distributions of labeled sensory neurons

In a preliminary examination, from L1 DRG to L6 DRG were sampled, and distributions of WGA-HRP labeled sensory neurons were observed. In control group, labeled sensory neurons of tibial nerve distributed in L4 and L5 DRG (Fig. 4). These labeled sensory neurons showed strong staining of the nuclei and cytoplasm with violet colors. The labeled sensory neurons were round or oval in shape. There were two kinds of cells in labeled sensory neurons; large cells (25 ~ 45 μm in diameter) and small cells (10 ~ 25 μm in diameter). The large and small cells were shown a mixed

pattern in DRG (Fig. 4A, B). In NLM, labeled sensory neurons of tibial nerve distributed in L4 and L5 DRG. These labeled sensory neurons were round or oval in shape, and showed a mixed pattern in DRG (Fig. 4C-H).

4. The number of labeled sensory neurons

1) Total number of WGA-HRP labeled sensory neurons in DRG

Total number of labeled sensory neurons in 1, 2 and 4 weeks groups decreased significantly (Fig. 5, Table 1).

2) The number of WGA-HRP labeled sensory neurons in L4 and L5 DRG

The number of labeled sensory neurons of L4 DRG in 1, 2 and 4 weeks groups decreased significantly. The number of labeled sensory neurons of L5 DRG in 4 weeks group decreased significantly. The number of labeled sensory neurons of L5 DRG showed no significant difference in 1 and 2 weeks groups (Fig. 6, Table 1).

3) The number of WGA-HRP labeled large cells

Total number of labeled large cells in 1, 2 and 4 weeks groups decreased significantly. The number of labeled large cells of L4 DRG in 1, 2 and 4 weeks groups decreased significantly in NLM. The number of labeled large cells of 2 and 4 weeks groups in L5 DRG decreased significantly. The number of labeled large cells of L5 DRG in 1 week group showed no significant difference in NLM (Fig. 7, Table 2).

4) The number of WGA-HRP labeled small cells

Total number of labeled small cells in 1, 2 and 4 weeks groups decreased significantly in NLM. The number of labeled small cells of L4 DRG in 1, 2 and 4 weeks groups decreased significantly. The number of labeled small cells of L5 DRG in 4 weeks group decreased significantly. The number of labeled small cells in L5 DRG showed no significant difference in 1 and 2 weeks groups (Fig. 7, Table 2).

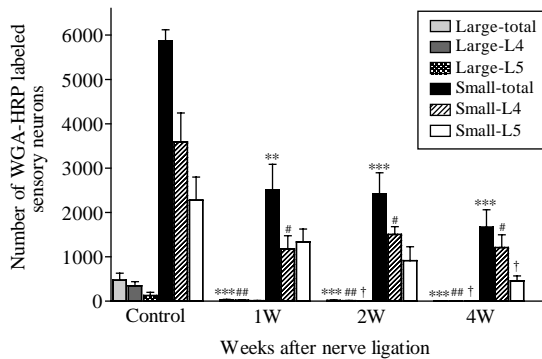


Fig. 7. The number of WGA-HRP labeled large and small cells in NLM. Total number labeled large cells in 1, 2 and 4 weeks groups decrease significantly. The number of labeled large cells of L4 DRG in 1, 2 and 4 weeks groups decrease significantly from control group. The number of labeled large cells of L5 DRG in 2 and 4 weeks groups decrease significantly from control group. Total number of labeled small cells in 1, 2 and 4 weeks groups decrease significantly from control group. The number of labeled small cells of L4 DRG in 1, 2 and 4 weeks groups decrease significantly from control group. The number of labeled small cells of L5 DRG in 4 weeks group decrease significantly from control group. *, #, †*P* < 0.05, **, ##*P* < 0.01, ****P* < 0.001.

Discussion

Neuropathy is a debilitating condition that often results from partial injury to a nerve. The development of animal models of nerve injury-induced pain contributes significantly to the analysis of mechanisms that contribute to neuropathic pain syndromes (Shields et al. 2003).

Bennett and Xie (1988) introduced animal neuropathy model (well-known method of 4 loose ligatures around the sciatic nerve) based on injury of sciatic nerve. In methodology described by Bennett and Xie (1988), only about 30~40% of total number of ligated rats developed the neuropathic syndrome. The degree to which the nerve has to be constricted (loosely tied) in order to produce the neuropathic syndrome is not quantitatively defined, which can lead to an important variability in the results (Kupers et al. 1992). Neuropathy model by Seltzer et al. (1990) was tight ligation of sciatic nerve. Present study modified the method of Seltzer et al. (1990), and this tight ligation model re-

Table 2. The number of large and small cells of WGA-HRP labeled sensory neurons in control and NLM

	Nerve ligation model					
	Large cell			Small cell		
	L4	L5	Total	L4	L5	Total
Control	347 ± 92.5	127 ± 72.1	474 ± 157.3	3,595 ± 649.3	2,052 ± 708.4	5,872 ± 246.7
1W	18 ± 6.3	11 ± 3.7	29 ± 10.1	1,182 ± 293.0	1,335 ± 293.2	2,516 ± 577.9
2W	11 ± 4.4	6 ± 3.6	17 ± 6.7	1,505 ± 174.2	913 ± 312.3	2,419 ± 474.9
4W	0.5 ± 0.5	0.75 ± 0.75	1.25 ± 1.25	1,209 ± 289.7	459 ± 110.7	1,668 ± 395.0

duced the variability in the results. Tibial nerve was tied carefully for maintaining normal blood circulation.

1. Behavioral changes following ligation of tibial nerve

Sciatic nerve injury model showed characteristic features—the loss of ankle plantar flexion, foot invertors, toe flexors, foot intrinsic, and the footprint (Bain et al. 1989). Features related to sciatic nerve injury model were observed in the present study. Rats of nerve transection or sciatic nerve ligation showed serious weight loss and autotomized digits (Bennett and Xie 1988, Kovačič et al. 2003). Autotomy is explained sudden licking of the hindpaw on the operated side, accompanied by gentle biting or pulling on the nails with the mouth (Kim and Chung 1992). Hofmann and colleagues (2003) informed advantage of tibial NLM. Hofmann et al. (2003) reported that rat of tibial NLM shows normal growth and no sign of autotomy. In present study, there was no weight loss and no autotomy. All animals of NLM appeared healthy, although some changes in gait, posture and guarding behaviors were evident after nerve injury. Ventroflexed toes and foot drop of operated side was markedly observed. Rats walk with a limp, placing less pressure on the hind paw on the nerve-ligated side. They frequently raised the nerve-damaged hind paw off the ground. It was similar phenomenon with previous studies (Bennett and Xie 1988, Attal et al. 1990, Seltzer et al. 1990, Kim and Chung 1992, Shields et al. 2003).

2. The histological changes of tibial nerve

Tied nerves suffer strong inflammatory reaction and axons of myelinated fiber are accompanied with degeneration (Basbaum et al. 1991, Myers et al. 1996). In the present study, tibial nerve in NLM had an irregular arrangement of axons, and myelins and axons were swollen and shrunken in NLM. Myelinated and unmyelinated axons of all sizes were degenerated. Neuropa-

thy is closely related to the axon type. Coggeshall et al. (1993) found that a loss of all axon types, with a preferential loss of large myelinated axons in unilateral ligation of the sciatic nerve in the rat, is associated with the development of heat hyperalgesia. Other researchers (Basbaum et al. 1991, Maves et al. 1993, Myers et al. 1996) also observed loss of large myelinated axons, and they hypothesized about relation of myelinated axon changes and hyperalgesia following neuropathic condition. Denervated Schwann cell produces many neuroactive cytokines and growth factors including tumor necrosis factor- α that may potentially act on the intact axon, and contribute to the pain (Sorkin et al. 1997).

3. Distributions of labeled sensory neurons

Tibial nerve contains the largest number of DRG sensory neurons according for 45% of all sciatic sensory DRG neurons. The L4 and L5 DRG contains 99% of the tibial nerve DRG neurons with the L4 DRG containing more than twice the number of tibial neurons than the L5 DRG (Swett et al. 1991). Hofmann et al. (2003) reported that all sensory neurons of L5 DRG are affected by tibial nerve injury, whereas L4 DRG is only partially affected. Any profiles smaller than 10 μm in diameter were ignored because no DRG sensory neurons of the size exist in the rat (Swett et al. 1991). In the present study, WGA-HRP labeled sensory neurons of the tibial nerve distributed on L4 and L5 DRG in control and NLM.

4. The number of labeled sensory neurons

Gautron et al. (1990) presented that alterations of nociceptive test in sciatic nerve neuropathy model (4 loose ligation) begin at 1 week after surgery, are maximum at 2 weeks, recovery starting after 3 weeks and being usually complete by 8~10 weeks. In present study, we used NLM and total number of labeled sensory neurons were continuous decreasing by time-course.

NLM may be stronger neuropathic condition than 4 loose ligation model. In NLM, the number of labeled sensory neurons in L4 DRG and labeled sensory neurons in L5 DRG were 62~70% loss and 55~81% loss from control group. The results of the present study also showed 91~99% loss of large cells and 57~72% loss of small cells in NLM. The neuropathic condition seemed to affect characteristic selective loss of large cells of L4-L5 DRG in NLM. Although there is not a precise correlation between the diameter of the sensory neuron cell body and the diameter of the axon, most of the large neurons have large myelinated axons (Donnerer 2003). So, NLM may affect more large myelinated axons than unmyelinated axons.

The use of neuropathy animal models develops as one possible way of trying to elucidate the mechanisms of pain and associated processes following injury to nerves. Neuropathy models were used as a valuable method of various studies. There was histological changes of neurons (Grant et al. 1979, Song et al. 2003) and morphological changes of axons (Gautron et al. 1990, Basbaum et al. 1991, Myers et al. 1996) following neuropathy. Several studies of neuropathy model focused behavioral changes of treated animals by time-course (Bennett and Xie 1988, Attal et al. 1990, Seltzer et al. 1990, Kupers et al. 1992, Choi et al. 1994, Shields et al. 2003). But, there may be no reports about the anatomical changes of tibial NLM using neural tracers. Present study may serve as the basic information about the changes of DRG sensory neurons in neuropathy models.

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정강신경의 말초신경병증에서 WGA-HRP를 이용한 감각신경의 형태학적 변화

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간추림 : 신경병증은 신경이 손상을 받았을 때 일어나는 신경의 이상을 뜻하는 용어로 작열통, 통각과민, 이질통증을 특징으로 한다. 본 연구는 말초신경병증 흰쥐에서 WGA-HRP (wheat germ agglutinin-horseradish peroxidase)에 표지된 척수신경절의 신경세포체 수와 분포의 변화를 관찰하기 위해 시행되었다.

흰쥐의 오른쪽 정강신경을 결찰하여 신경결찰모델을 만들었다. 신경병증을 유발한 흰쥐의 절단된 정강신경 끝에 WGA-HRP를 묻힌 후 척수신경절에서 표지된 세포의 개수와 크기에 따른 분포 등을 관찰하여 다음과 같은 결과를 얻었다.

신경결찰모델의 흰쥐는 신경을 묶은 다리를 보호하는 행동을 보이고 다리를 절름거리리는 등 신경병증의 특징을 보였고, 발가락과 무릎관절에서는 과다굽힘을 관찰할 수 있었다. 결찰된 정강신경은 축삭이 부풀어 오르고, 말이집이 손실된 것을 관찰할 수 있었다. 대조군과 신경결찰모델 모두에서 WGA-HRP에 표지된 신경세포체는 네번째와 다섯번째 허리척수신경절에 분포하고 있었으며, 크고 작은 세포체가 섞여서 분포하고 있었다. 표지된 신경세포체는 원형 또는 타원형이었다. 신경결찰모델에서 WGA-HRP에 표지된 신경세포체의 총갯수는 대조군에 비해서 감소했으며, 네번째와 다섯번째 허리척수신경절에서 표지된 신경세포체의 수는 각각 감소했다. 크기가 큰 세포체와 크기가 작은 세포체의 수는 대조군에 비하여 감소했다.

본 연구를 통해 신경결찰모델의 척수신경절에서 신경세포체의 변화에 관한 결과는 신경병증에 따른 척수신경절세포의 변화에 대한 기초적인 정보를 제공할 것으로 생각된다.

찾아보기 낱말 : 신경병증, 정강신경, 감각신경세포체, WGA-HRP, 신경결찰모델