Electrophysiological properties of spinal wide dynamic range neurons in neuropathic pain rats following spinal nerve ligation

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Abstract: Objective The present study aimed to investigate the electrophysiological properties of wide dynamic range (WDR) neurons in spinal dorsal horn of rats with neuropathic pain induced by lumbar 5 (L5) spinal nerve ligation (SNL) in a large size of samples. **Methods** Adult Sprague-Dawley rats were divided into normal and SNL groups. Electrophysiological technique was used to record the characteristics of WDR neurons in the spinal dorsal horn. **Results** Compared with the WDR neurons in normal rats, the WDR neurons in SNL rats showed an increase in excitability, manifested by an enlargement of the receptive field size, an increase in the proportion of neurons that exhibited spontaneous activities, decreases in the C-response threshold and latency, and an increase in the C-response duration. In addition, the numbers of A_β- and C-fiber-evoked discharges were smaller in SNL rats than in normal rats. **Conclusion** The excitability of spinal WDR neurons increased in rats with neuropathic pain induced by L5 SNL. The increase in excitability of WDR neurons may contribute to the development of neuropathic pain.

Keywords: wide dynamic range neuron; spinal dorsal horn; spinal nerve ligation; neuropathic pain

1 Introduction

Peripheral nerve injury leads to neuropathic pain including spontaneous pain and evoked pain, such as allodynia and hyperalgesia^[1]. The mechanisms underlying neuropathic pain remain still elusive^[2,3]. There has been evidence that neuropathic pain is related to the sensitization of dorsal horn neurons. In the spinal dorsal horn, wide dynamic range (WDR) neurons are a reasonable population for correlative

studies of neuropathic pain^[4]. The properties of WDR neurons are altered following lumbar 5 (L5) spinal nerve ligation (SNL), including the enlargement of the receptive field and increases in spontaneous activities^[5-8]. Electrical stimulation on sciatic nerve is a commonly used method in studying the properties of spinal WDR neurons. However, inconsistencies still exist on the results of studies regarding the electrically evoked WDR responses. For example, some researchers reported that after SNL, the C-fiber-evoked responses were unchanged^[8-11], while others reported reduced^[5]. Thus, in the present study, the changes in electrophysiological properties of spinal WDR neurons in rats with neuropathic pain after L5 SNL were investigated in a large sample size.

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2 Materials and methods

2.1 Animals Male Sprague-Dawley rats (weighing 220-250 g at the beginning of the experiment) were provided by the Department of Experimental Animal Sciences, Peking University Health Science Center. Rats were housed in separate cages at $(24 \pm 1)^\circ\text{C}$ under a natural light/dark cycle, with free access to food and water. All animal experiments were conducted in accordance with the guidelines of the International Association for the Study of Pain^[12] and were approved by the Animal Care and Use Committee of Peking University.

2.2 SNL procedure Under general anesthesia with chloral hydrate (0.3 g/kg, i.p.), the left L5 spinal nerve distal to the dorsal root ganglion (DRG) was tightly ligated with 4-0 silk sutures as described by Kim and Chung^[13-15]. Animals were allowed to recover for 7 d before electrophysiological recordings. Rats exhibiting any motor deficiency or lacking tactile allodynia were excluded from the study.

2.3 Assessment of mechanical allodynia Mechanical allodynia, a behavioral measurement of neuropathic pain, was assessed by measuring 50% paw withdrawal threshold (PWT) as described in the previous reports^[16,17]. The 50% PWT in response to a series of von Frey filaments was determined by the up and down method^[18] and was calculated as previously described^[19]. The 50% PWT was recorded in all animals one day before SNL surgery and at day 7 after SNL surgery, respectively. Only rats with significant mechanical allodynia, whose 50% PWT in ipsilateral hind limb was lower than 4.0 g, were selected for further electrophysiological studies.

2.4 Electrophysiological recording

2.4.1 Surgery Rat was initially anesthetized with urethane (1.2-1.5 g/kg, i.p.). The trachea was cannulated to allow mechanical ventilation with room air. A catheter was inserted into the right jugular vein for continuous infusion of Tyrode's solution containing (in mmol/L) NaCl 137, KCl 2.7, CaCl_2 1.4, MgCl_2 1.0, NaHCO_3 6.0, NaH_2PO_4 2.1, and *D*-(+)-glucose 6.5 (pH 7.4), at a rate of 1.0-1.5 mL/h. The rectal temperature was maintained at 36.5 - 37.5°C via a feedback-controlled underbody heating pad. A pair of bipolar silver hook electrodes was placed under the sciatic nerve immediately proximal to

the trifurcation for electrical stimulation. The vertebral column was rigidly fixed in the frame with 2 clamps. The lumbar enlargement of the spinal cord was exposed by laminectomy at the vertebrae thoracic 13 (T13) and lumbar 1 (L1), and the dura covering lumbosacral spinal segments was carefully removed. The exposed spinal tissue was covered with warm (37°C) paraffin oil. After surgery, the animal was artificially ventilated with a small animal ventilator and paralyzed with curare (2.0 mg/kg, i.v.). Anesthesia state and paralysis were maintained with urethane (0.10-0.15 g/kg per hour) and curare (0.20 mg/kg per hour) during the experiment. The depth of anesthesia was monitored by examination of pupillary size and reflex. The physiological condition of the animal was monitored by recording the electrocardiogram (330-460 beats/min), end-expiratory CO_2 (3.5%-4.5%), and rectal temperature (36.5 - 37.5°C), and maintained within these ranges^[20,21].

2.4.2 Extracellular recording Single-unit extracellular recordings were made from the lumbar dorsal horn neurons within the depth of 1 300 μm from the dorsal surface of the spinal cord with 2-5 M Ω parylene-coated tungsten microelectrodes (Frederick Haer & CO., Bowdoinham, ME, USA). The microelectrode was inserted perpendicularly into the dorsal horn from a point approximately midway between the midline and the medial edge of the dorsal root entry zone. During electrode advancement, electrical pulses (0.5 Hz, 0.3-ms pulse width, 0.4 mA) were applied to the ipsilateral sciatic nerve as search stimuli so that a neuron with no spontaneous firing could be identified. Once a single unit was identified, the receptive field and response characteristics were determined by a range of mechanical stimuli at varying intensities, including brushing or touching the skin with a cotton brush, light pressure with a probe, and pinching a fold of skin with a toothed forceps. Neuron responding to innocuous tactile stimuli, light pressure and noxious pinch in a graded manner was identified as the WDR neuron and selected for further investigation^[22,23]. A train of 10 stimuli (0.5 Hz, 0.5-ms pulse width, 0.5-5.0 mA in density which was approximately twice of the C-fiber response threshold) were applied repeatedly to the sciatic nerve with 5-min intervals, and post-stimulus histograms were constructed.

Data were captured and analyzed by a Cambridge Elec-

tronic Design (CED) 1401 interface (Cambridge, UK) coupled to a Pentium computer with Spike 2 software. The recorded signals were amplified with an AC pre-amplifier, filtered with a passing bandwidth of 500-1 000 Hz, displayed on an oscilloscope, and fed into a Pentium computer via a CED 1401 interface for off-line analysis. Electrically-evoked responses were classified on the following criteria: A_β-fiber: 0-20 ms, A_δ-fiber: 20-45 ms, and C-fiber: 45-300 ms post stimulation. Responses evoked within 300-800 ms post stimulation were classified as post-discharge of the neuron. Single cell recording was confirmed based on the amplitude and shape of the action potentials. The electrically-evoked responses were expressed as the average of 3 values from consecutive trains of test stimuli. Neurons showing variation of less than 20% were selected for further experiments.

2.4.3 Mapping of the receptive field The non-nociceptive receptive field (low-threshold receptive field) was mapped with a blunt probe, moving from outside loci to within the receptive field. Based on the response of each WDR neuron, the area of the receptive field was mapped on paper. Field size was measured with a planimeter.

2.4.4 Recording site confirmation At the end of each experiment, the recording site was marked by electrolytic lesion (20.0 μ A positive depolarizing DC current for 20 s), and the animal was subsequently euthanized with an overdose of pentobarbital sodium. The spinal cord was fixed in 4% paraformaldehyde at 4 °C overnight, and sectioned into 20 μ m-thick transverse sections on a cryostat. The recording site was then identified and plotted on a schematic representation of the lumbar spinal cord.

2.4.5 Statistical analysis All data were expressed as mean $\pm$ SEM. Two-tailed unpaired Student's *t*-test and χ^2 test were used for the comparison between normal group and SNL group. $P < 0.05$ was considered as statistically significant.

3 Results

3.1 General characteristics of WDR neurons A total of 175 WDR neurons were recorded from 133 normal rats. Most of the neurons (136/175, 77.7%) were located at the depth of 550-1 250 μ m [(849.7 $\pm$ 22.5) μ m] below the dorsal surface of the spinal cord, corresponding to laminae IV-VI of the dorsal

horn (Fig. 1). A total of 143 WDR neurons were recorded from 99 SNL rats. Most of the neurons (118/143, 82.5%) were located at the depth of 550-1 250 μ m [(850.1 $\pm$ 21.4) μ m] below the dorsal surface of the cord. The distributions of the recorded neurons were similar between normal and SNL rats (Table 1).

In normal rats, non-nociceptive receptive fields of most WDR neurons were on the ipsilateral hindpaw and covered from 2 toes to nearly the whole hindpaw [(125.7 $\pm$ 10.6) mm², $n=175$]. In SNL rats, the receptive fields of the WDR neurons were significantly larger. The receptive fields of all WDR neurons in SNL rats almost encompassed the entire ipsilateral hindpaw and hindlimb [(406.3 $\pm$ 23.3) mm², $n=143$, $P < 0.001$].

Most of the WDR neurons in normal and SNL rats exhibited background activities in the absence of stimulation,

Fig. 1 A: A schematic illustration of the laminae of the spinal cord. B: A representative site of extracellular recording of a WDR neuron in the deep layer of the spinal dorsal horn, as indicated by electrolytic lesion in the spinal dorsal horn. The arrow indicated the electrolytic lesion site.

ranging from 0.03 to 48.9 impulses/s in frequency. The averaged frequencies of the background activities of WDR neurons were similar between normal rats [(9.0±1.8) impulses/s, $n=38$] and SNL rats [(8.4±1.2) impulses/s, $n=45$], but interestingly, the proportion of WDR neurons that exhibited spontaneous activities was much higher in SNL rats (45/143, 31.5%) than in normal rats (38/175, 21.7%) ($P<0.05$) (Table 1).

3.2 Responses of WDR neurons to electrical stimulation

In normal rats, A_{β} -, A_{δ} - and C-fiber evoked (53.9±1.6), (6.0±0.7) and (88.6±3.6) impulses per ten stimuli in the WDR neurons, respectively. The post-discharge value was (45.9±4.3) impulses per ten stimuli ($n=175$). The threshold, latency and duration of the C-responses were (1.2±0.1) mA, (84.1±1.6) ms and (153.8±2.9) ms ($n=175$), respectively (Table 1). A representative detailed post-stimulus histogram of one WDR neuron in normal group was presented in Fig. 2A.

In SNL rats, A_{β} -, A_{δ} - and C-fibers evoked (45.8±1.7), (7.1±0.9) and (76.3±3.1) impulses per ten stimuli in the WDR neurons, respectively. The post-discharge value was (34.8±3.7) impulses per ten stimuli ($n=143$). The averaged numbers of A_{β} - and C-fiber-evoked responses in SNL rats were significantly lower than those in normal rats ($P<0.001$, $P<0.05$, respectively) (Fig. 3). The averaged C-response threshold [(0.8±0.1) mA] and the latency of the C-responses [(76.1±1.5) ms] were significantly decreased, compared with those in normal rats ($P<0.001$). The duration of the C-responses [(172.5±3.0) ms] increased in SNL rats compared with that in normal rats ($P<0.001$). Fig. 2B showed a representative post-

Fig. 2 Post-stimulus histograms (ten stimuli) showing the typical responses of WDR neuron to electrical stimuli delivered to the sciatic nerve in normal (A) and SNL (B) rats. Inserts were oscilloscope records showing a single sweep. Bin value: 2 ms.

Table 1. Characteristics of WDR neurons in normal and SNL rats

	Normal	SNL
Depth (μ m)	849.7±22.5	850.1±21.4
Receptive field (mm^2)	125.7±10.6	406.3±23.3***
Proportion of WDR neurons with spontaneous activity	21.7%	31.5%*
Background activity (impulses/s)	9.0±1.8	8.4±1.2
C-threshold (mA)	1.2±0.1	0.8±0.1***
C-latency (ms)	84.1±1.6	76.1±1.5***
C-duration (ms)	153.8±2.9	172.5±3.0***

* $P<0.05$, *** $P<0.001$ vs normal control rats.

Fig. 3 An averaged post-stimulus histogram of the responses of dorsal horn WDR neurons to electrical stimuli delivered to the sciatic nerve. Data of spike numbers per ten stimuli were expressed as mean±SEM. * $P<0.05$, *** $P<0.001$ compared with normal group. A_{β} : A_{β} -fiber responses (0-20 ms post stimulation), A_{δ} : A_{δ} -fiber responses (20-45 ms post stimulation), C: C-fiber responses (45-300 ms post stimulation), PD: post-discharge (300-800 ms post stimulation). $n=175$ in normal group, $n=143$ in SNL group.

stimulus histogram of one WDR neuron in SNL rat group.

4 Discussion

The mechanical allodynia in the SNL rats with neuropathic nociception was comparable to the results reported earlier^[16,17,21,22]. Here the electrophysiological studies showed that L5 SNL resulted in sensitization of spinal WDR neurons, including an enlargement of receptive field size, an increase in the proportion of WDR neurons that exhibited spontaneous activity, decreases of C-response threshold and latency and an increase in the C-response duration. Besides, L5 SNL also resulted in decreases in A_β- and C-fiber-evoked discharges.

In the present study, the mean size of non-nociceptive receptive field in the SNL rats with neuropathic nociception was significantly increased, which is consistent with the previous reports. The mean size of the receptive fields on the ipsilateral hindpaw, mapped using low-intensity stimulation with 1 g^[23] or 9 g^[8] von Frey hair, increased significantly in the SNL rats. In addition, an enlarged non-nociceptive receptive field has also been described in other neuropathic or inflammatory pain models^[24-26]. It is well known that expansion of receptive field is an indicator of central sensitization^[1]. Enlarged receptive fields of the WDR neurons imply that “submodality” segregation within the receptive fields is altered, and a given low-intensity stimulus may recruit more neurons. In neuropathic pain animals, the dorsal horn network is shown to be more prone to synchronous network activity compared with that in normal control animals^[27]. Simultaneous activation of many adjacent neurons after a light intensity of stimulation could lead to greater additive responses transmitted supraspinally, therefore further amplifying the effect of the receptive field enlargement. Here, the expansion of the receptive field in the neuropathic pain rats might be explained by the increase in neural excitability and/or the decrease of intraspinal inhibition. In the SNL rats, L5 spinal nerve was selectively ligated, and a remarkable reduction in the number of afferent fibers was induced. As a result, the L4-L5 spinal segment received less afferent input^[28,29]. This may induce a marked compensatory hyperexcitability within the spinal cord via NMDA receptor activa-

tion and/or spinal disinhibition, e.g., via reduced GABAergic inhibitory activity in the spinal cord^[30]. Another possibility is structural reorganization with spinal cord. Following peripheral nerve injury, sprouting in A_β-fibers to superficial dorsal horn induced an increase of receptive field size for touch^[31]. However, this finding has been recently questioned^[29].

Most of the WDR neurons in normal and SNL rats exhibited some background activities. The average frequencies of background activities of WDR neurons were similar between normal and SNL rats. However, the proportion of WDR neurons that exhibited spontaneous activities in SNL rats was higher than that in normal rats. A previous study reported that the proportion of spinal neurons exhibiting spontaneous activities and the frequency of the spontaneous activities were both significantly higher after SNL^[5]. The proportion of WDR neurons that exhibited spontaneous activities was also significantly higher after SNL^[32]. In the present study, the extent of ongoing pain behavior following SNL was not assessed, but this pain behavior may be related to the increased spontaneous activities of spinal neurons in SNL rats. The origination of the spontaneous activities of WDR neurons is elusive, and the following possibilities have been proposed. One possibility is the ectopic firings from the injured site of L5 and the DRG^[33]. Another possibility is the spontaneous activities in the uninjured L4 primary afferent fibers adjacent to the injured fibers^[34]. The third possibility is the central mechanism, such as microglial activation in the spinal cord, disinhibition of the descending inhibition system and activation of descending facilitatory system^[2,35]. After peripheral nerve injury, local anesthetic blockade of peripheral inputs to the spinal cord, which completely blocks the evoked activities, only partially reverses the heightened level of spontaneous WDR firing. Thus, besides the peripheral mechanisms, the central mechanisms also possibly contribute to the maintenance of the hyperactive state of WDR neurons^[36].

In the present study, complex changes in the responses of WDR neurons to electrical stimulation were observed in SNL rats. The averaged number of A_β- and C-fiber-evoked

responses in SNL rats was significantly lower than that in normal rats. A previous study reported that the magnitude of the C-fiber-evoked neuronal responses of SNL rats decreased significantly at days 14-17 after L5 SNL^[5]. In addition, neuronal responses evoked by brush, prod, or 25 g and 50 g von Frey weights were also significantly reduced in SNL rats^[5]. The L4 and L5 spinal segments would receive less unmyelinated and myelinated afferent inputs as a result of L5 SNL^[29]. The L4 spinal segment would be likely to receive approximately 40% less fine fibers input as a result of L5 and L6 SNL^[28]. Despite the approximate 40% loss of afferent inputs from fine fibers in the L4 spinal segment, there was only a 14% decrease in the C-fiber-evoked responses of WDR neurons after nerve injury in the present study, indicating a marked compensatory hyperexcitability of the WDR neurons. Further analysis revealed that the C-response threshold and latency were decreased and the C-response duration was increased. These results also support the compensatory hyperexcitability in the spinal cord for the marked loss of afferent inputs produced in this model. However, previous studies reported that the responses of WDR neurons to electrical stimulation were similar among SNL, sham-operated and normal control rats^[8-11]. Causes for these discrepancies remain uncertain, but differences in the sample size might play a role. Experiments with a small size of samples ($n < 12$) showed that the C-fiber-evoked responses remained unchanged after SNL^[9-11]. In an experiment with a relatively larger sample size, Suzuki *et al.* reported that the C-fiber-evoked responses in SNL rats were not significantly changed compared with those in control rats, but showed a tendency of decrease ($n \geq 31$)^[8]. However, in another experiment with a relatively larger sample size, Chapman *et al.* reported that the C fiber-evoked responses were reduced after SNL ($n \geq 35$)^[5]. Here, we employed a large sample size ($n \geq 143$), and results also showed that the C-fiber-evoked responses were reduced after SNL. Obviously, a larger sample size will probably give more accurate explanations for these complex responses of WDR neurons after SNL.

In summary, by using electrophysiological recordings, our present study revealed that L5 SNL could result in an increased excitability of WDR neurons, manifested by an

enlargement of receptive field size, an increase in the proportion of WDR neurons that exhibited spontaneous activities, decreases of C-response threshold and latency, and an increase in C-response duration. Besides, SNL also resulted in decreases in A_β- and C-fiber-evoked discharges. The increase in WDR neuron excitability may contribute to the development of neuropathic pain.

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脊神经结扎神经痛大鼠脊髓背角广动力范围神经元的电生理学特性

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摘要：目的 探讨腰5脊神经结扎(spinal nerve ligation, SNL)后, 大鼠脊髓背角的广动力范围(wide dynamic range, WDR)神经元电生理学特性的改变。方法 将健康雄性 Sprague-Dawley 大鼠分为正常组和 SNL 组, 利用细胞外电生理学方法记录脊髓背角的 WDR 神经元放电。结果 与正常大鼠相比, SNL 组大鼠 WDR 神经元兴奋性增加, 表现为感受野扩大、有自发放电的神经元比例增加, 以及 C 纤维诱发放电的阈值降低、潜伏期缩短、发放时程增加。此外, SNL 组大鼠 WDR 神经元 A_β 和 C 纤维诱发放电数目较正常大鼠降低。结论 大鼠腰5脊神经结扎后主要引起 WDR 神经元的兴奋性增加。WDR 神经元的兴奋性增加可能参与神经病理痛的发生。

关键词：广动力范围神经元; 脊髓背角; 脊神经结扎; 神经病理痛