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Different symptoms of neuropathic pain can be induced by different degrees of compressive force on the C7 dorsal root of rats

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Abstract

BACKGROUND CONTEXT: Neuropathic pain after nerve injuries is characterized by positive and negative sensory symptoms and signs. The extent of sensory fiber loss after nerve injuries has been demonstrated to correlate with symptoms of neuropathic pain by quantitative sensory testing and confirmed by biopsies of small nerve fibers. However, the relationship between the pathologic changes of large nerves on injuries and resulting pain symptoms remains unclear.

PURPOSE: To investigate the relationship between the extent of dorsal root injury and resulting symptoms of neuropathic pain.

STUDY DESIGN: Nerve injury and assessment of the following pain-related behaviors and neuropathologic changes.

METHODS: A total of 24 adult male Sprague-Dawley rats weighing 250 to 300 g were randomly divided into three groups (n=8 each): sham group operated on but without nerve compression, 70 gf group, and 180 gf group; a compression force of 70 or 180 g was applied to the right C7 dorsal root, separately. Threshold thermal and mechanical pains were measured before surgery (baseline) and on the first, third, fifth, and seventh day after surgery. On the seventh day after surgery, all rats were killed, and the structural alterations of nerve fibers within the compressed areas were examined.

RESULTS: A compression force of 70 g resulted in hyperalgesia, whereas a compression force of 180 g induced hypoalgesia in the ipsilateral forepaw in response to both mechanical and thermal stimulations within 7 days after injury. Light microscopy and electron microscopy revealed a mild to moderate sensory fiber loss after 70-gf compression and a more severe sensory fiber loss after 180-gf compression.

CONCLUSIONS: Transient injuries on sensory fibers can produce either positive or negative symptoms of neuropathic pain, and the different extent of sensory fiber loss after different degrees of injuries might account for the varied resulting symptoms of neuropathic pain.

Keywords: Nerve injury; Dorsal root; Neuropathic pain; Hyperalgesia; Hypoalgesia

FDA device/drug status: Not applicable.

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Introduction

Neuropathic pain arises from damage or disease within the nervous system and is clinically characterized by positive and negative sensory signs and symptoms [1,2]. The positive symptoms can manifest as spontaneous pain or stimulus-evoked types of pain, which are classified as allodynia (a pain evoked by normally innocuous stimuli) or hyperalgesia (an exaggerated or prolonged pain response to noxious stimuli). The negative sensory symptoms include abnormal sensation (paresthesia), sensory deficit (dysthesia), and sensory decrease (hypoesthesia/hypoalgesia) [3]. Because different symptoms may be related to a distinct pain mechanism [4–8] and respond differently to treatment, it is necessary to reveal the mechanism responsible for the generation of either positive or negative symptoms in a certain neuropathic pain condition.

Several previous studies used noninvasive quantitative sensory testing (QST) as a mechanism-based approach to study the sensory symptoms in neuropathic pain [4–6,9]. Results from these studies indicated that the extent of sensory fiber loss after nerve injuries correlated with the clinical signs and symptoms of neuropathic pain; a mild to moderate sensory fibers loss produced positive symptoms, whereas a more severe sensory fiber loss resulted in negative symptoms [9–11]. However, QST alone is not sufficient for the diagnosis of a neurologic lesion because of the lack of specificity of current QST databases [12]. Therefore, nerve biopsies have been used to assess the pathologic changes of small nerve fibers underlying the sensory symptoms in a neuropathic condition, and a correlation between results from nerve biopsies and QST was found [10,13]. However, pathologic changes of large nerve fibers such as nerve roots have not been examined previously, and the relationship between the large nerve injuries and resulting symptoms of neuropathic pain has yet to be investigated.

Because nerve biopsy is an invasive procedure that may lead to permanent nerve dysfunction, especially when a large nerve is involved, it is necessary to choose a proper animal model for study. In mammals, almost all large nerves are composed of sensory fibers, motor fibers, and sympathetic and/or parasympathetic fibers, except for the dorsal root, which is a small piece of large nerve consisting of only sensory fibers. To exclude the influence of motor or automatic nerve fibers, we used a rat model in which the C7 dorsal root was transiently compressed, with forces of two different strengths, to investigate the relationship between the extent of large nerve injury and resulting symptoms of neuropathic pain. Based on the behavioral sensitivities of the ipsilateral forepaw in response to mechanical and thermal stimulations and the structural alterations of compressed nerves, we hypothesized that a mild to moderate sensory fiber loss, caused by the weaker compression, might result in a positive sign of neuropathic pain, whereas a more severe sensory fiber loss, caused by the stronger compression, might lead to a negative sensory symptom.

Materials and methods

Animals

A total of 24 adult male Sprague-Dawley rats (250–300 g) were used for this study and randomly divided into three groups (n=8 each). In the sham-operated group, the right C7 dorsal root was exposed, and the wound was closed without further disruption of the nerve bed. In the 70 gf–treated group, a compression force of 70 g was applied to the right C7 dorsal root using an aneurysm clip (Aesculap AG & Co., Tuttlingen, Germany) for 15 minutes. In the 180 gf–treated group, a compression force of 180 g was applied to the right C7 dorsal root with an aneurysm clip for 15 minutes. Rats were housed in the Experimental Animal Center of the Central South University under a 12 hours light/dark cycle. Food and water were available ad libitum. All experimental procedures were performed in accordance with the National Institutes of Health Guide for the Care and Use of Laboratory Animals and approved by the Administrative Committee of Experimental Animal Care and Use of Central South University. The study adhered to the Ethical Guidelines of the International Association for the Study of Pain [14].

Surgical procedures

After being anesthetized with hydrated chloral (300–350 mg/kg, intraperitoneally), rats were placed in the prone position, and an incision was made in the skin from the base of the skull to the bony prominence of the second thoracic vertebra. Under a surgical magnifying glass, muscle and soft tissue were reflected to expose the C6 and C7 laminae. C6/C7 hemilaminectomy and partial facetectomy were performed to expose the spinal cord and the right C7 dorsal root. A compression force of 70 or 180 g was applied to the right dorsal root approximately 1 mm distal to the dorsal root ganglion with the aneurysm clip and was removed after 15 minutes. Sham procedures involved the same surgery as described previously but without nerve manipulation.

Assessment of hyperalgesia or hypoalgesia

Hyperalgesia or hypoalgesia to mechanical and thermal stimulations was assessed with methods adapted from previous studies on rats' C7 nerve root injury [15,16]. Rats were stimulated on the plantar surface of the ipsilateral forepaw.

Paw mechanical withdrawal threshold (PMWT) of the ipsilateral forepaw was determined in response to pressure from an electronic von Frey anesthesiometer (2390 series; IITC Instruments, Woodland Hills, CA, USA) as described previously [17]. The magnitude of pressure (in grams) needed to produce a paw withdrawal response was measured on each paw, three times, and separated by 3-minute intervals. Data from the three tests were averaged for each paw on a given day.