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Research article

Nerve injury induced activation of fast-conducting high threshold mechanoreceptors predicts non-reflexive pain related behavior

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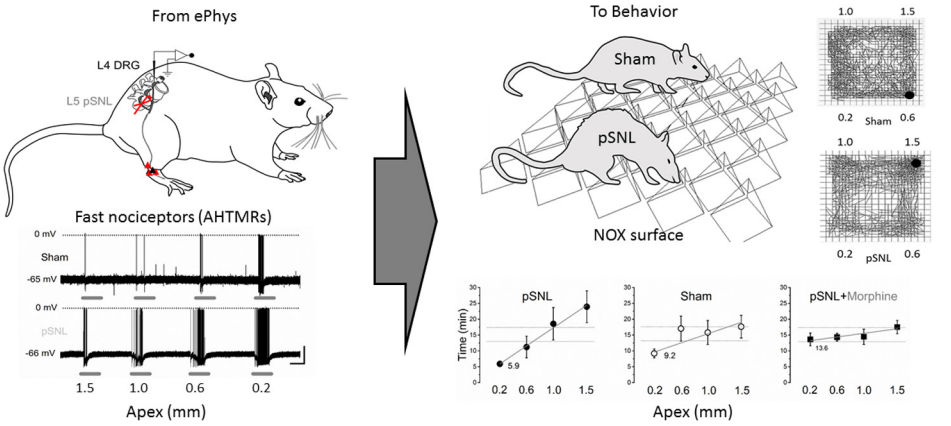
HIGHLIGHTS

- Graded fast conducting high threshold mechanoreceptor activation can be elicited.
- Induced neuronal activity in this subset is further increased after nerve injury.
- Activity of these neurons predicts pain related place aversion.
- This nerve subset may contribute to pain beyond acute pain signaling.
- Consideration of these neurons in chronic pain may further knowledge and treatment.

GRAPHICAL ABSTRACT



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ABSTRACT

The role of specific subsets of peripheral nerves in pain related behavior remains unclear. To better understand the contribution of differential activation of fast-conducting, high-threshold mechanoreceptor (AHTMR) input, we hypothesized that neuronal activation would be distinct with nerve injury, and that nociceptive input would predictt behavior in the freely exploring animal. A series of surfaces was used to deliver mechanical input to the hindpaws of rats upon voluntary movement and exploration. Neuronal activation increased as apex surface decreased (0.2, 0.6, 1.0 and 1.5 mm) using *in vivo* recording in L4 DRG neurons, and this relationship was enhanced following partial ligation of L5 (pSNL). In behaving animals, apex size was correlated to time spent on each surface following pSNL, but not with sham. Morphine normalized the discriminatory behavior following pSNL. These data indicate that noxious mechanical activation of AHTMR upon normal movement predicts behavior using paradigms that do not rely on reflexive withdrawal responses suggesting that AHTMR activation and central nervous system input contribute to higher order pain behavior after nerve injury beyond the immediate early pain input long attributed to these neurons.

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1. Introduction

The withdrawal response elicited by a threshold stimulus is the most common endpoint in evaluation of pain in the laboratory [1]. Withdrawal is divided into response to thermal or mechani-

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cal force and is based on the evoked response component of pain [2,3]. Withdrawal to mechanical force is based on the development of hyperalgesia and allodynia from tissue and nerve injury [4–7]. This is an evoked response that is fundamentally reflexive and is largely a function of spinal cord circuitry based on motor responses to nociceptive input. Ascending inputs seem to be required and the response is influenced by higher order central nervous system (CNS) inputs through descending modulation to spinal cord circuitry, but conscious decision-making about pain or discomfort as part of its character or occurrence is likely absent [8–10]. Furthermore, in neuropathic pain patients, hyperalgesia alone may not tell the whole story and the predominant functional symptom of pain is likely the quality and character, which may be more related to the spontaneous and persistent component of pain [11–13].

Spontaneous, or non-reflexive, measures of pain likely provide different information about the nociceptive input and its impact to the whole animal, more along the lines of the subjective description of actual pain [14,15]. However, some types of non-reflexive or spontaneous pain behaviors in the animal may still rely predominantly on a reflexive pathway in the spinal cord. Decision-making can be a component of escape and avoidance or place preference and may include attention-related responses [16–19]. These behaviors involve higher levels in CNS and reflect the influence and impact globally to the animal. This emerging consideration of higher level CNS modulation has resulted in greater use of novel approaches to measure the extent to which nociceptive information changes non-elicited behavioral outputs in freely behaving animals [16–18,20–23].

A geometric surface based on single cell fast-conducting, high-threshold mechanoreceptor (AHTMR) threshold to mechanical force after nerve or tissue injury was used to activate peripheral neuronal input [24,25]. We hypothesized that increasing calibrated force, related to reducing the size of the surface activated by a given pressure, would activate AHTMR differently due to nerve injury induced hypersensitivity. Furthermore, we hypothesized that the surface induced mechano-activation of AHTMR in the face of nerve injury would induce injury related nociceptive peripheral input to higher order CNS structures in the brain that rely on decision making and this would result in pain related altered place avoidance in a freely behaving animal.

2. Methods

2.1. Surgical procedures

A total of 48 male Sprague-Dawley rats (Postnatal day 45) were used in the study. A power analysis per se was not performed. However, based on previous studies in our laboratory, a minimum of 12 animals are required in each group to detect a meaningful difference using open field (OF). Three groups of 12 animals in each group were used for OF testing (nerve injury, sham, and nerve injury with morphine) and 2 groups of 11 animals in each group were used for electrophysiology (sham and nerve injury) (also based on previous studies of electrophysiologically determined responses of a single neuron). Animals were randomly assigned to receive surgery or sham and morphine with nerve injury or nerve injury only. OF and electrophysiology groups were done at separate times while animal groups within these experiments were all done at the same time. The use and handling of animals were in accordance with guidelines provided by the National Institutes of Health and received approval from the Institutional Animal Care and Use Committee of the Wake Forest University Health Sciences.

2.2. Partial spinal nerve ligation (pSNL)

Animals underwent right L5 pSNL and recovery as previously described [25]. In a sham control group, the surgical procedure was identical to that described except that the left L5 spinal nerve was not injured.

2.3. Behavioral testing

Individuals blinded to treatment determined mechanical withdraw threshold (MWT) by application of calibrated von Frey hairs to the plantar surface of the paw as previously described [25]. MWTs were determined before and 1 week after pSNL (postoperative day 7 [POD7]). All animals were included in the data analysis.

2.4. Electrophysiology

A week after either pSNL or Sham surgery, cellular recordings were made under anesthesia, after a dorsal midline incision was made in trunk skin and the L4 dorsal root ganglion (DRG) and adjacent spinal cord were exposed by laminectomy as previously described (illustrated in Fig. 1A) [26]. The tissue was continuously superfused with oxygenated artificial cerebrospinal fluid as described [26].

The electrophysiological recordings from L4 DRG neurons were limited to of 71 min. DRG soma were impaled with borosilicate microelectrodes (80–250 MΩ) containing 1 M potassium acetate. Intracellular penetrations with a resting membrane potential of ≤ -40 mV were characterized further as previously described [26–28]. Only cells capable of generating a somatic action potential (AP) (by current somatic injection, 25 and 500 ms pulses) and with impalements stable long enough to adequately explore the full extent of the skin at the L4 dermatome (>2 min) were included. In the electrophysiology studies the investigator could not be blinded to treatment since the change in neural thresholds of different nerve populations made it clear which animals had nerve injury.

2.5. Cellular classification protocol

To identify the receptor field (RF), the skin was searched and a cellular classification process was performed to determine afferent identity as previously described [26–28]. The results of this procedure were combined with specific cellular properties (action potential [AP] shape and somatic passive characteristics) to assign every cell into one of three simplified categories: Low threshold MR (LTMR), AHTMR, c-nociceptors (CHTMR), based on the strongest defining characteristics [27]. For the purpose of this study, only cells classified as AHTMR were studied further. In all cases, RFs were characterized (Fig. 1A).

2.6. Somatic electrical properties

Active and passive membrane properties of AHTMR neurons were analyzed as previously described [27]. All included cells satisfied the following requirements: resting membrane potential more negative than −40 mV, AP amplitude $\geq$30 mV and the presence of AHP. Passive membrane properties indicative of poor (extremely low Ri and/or Tau) impalement were also reasons for exclusion.

2.7. Conduction velocity (CV) and receptive field (RF)

Spike latency was obtained by stimulating the RF at the skin surface using a bipolar electrode following all natural stimulation to prevent potential alterations in RF properties by electrical stimulation as previously described [26–28]. After establishing the afferent identity as AHTMR subtype, the RF was carefully searched with

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