

Exercise-Induced Hypoalgesia Profile in Rats Predicts Neuropathic Pain Intensity Induced by Sciatic Nerve Constriction Injury

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Abstract: The aim of this study was to investigate the predictive value of exercise-induced hypoalgesia (EIH) profile on pain intensity induced by nerve injury in a rat model. EIH was tested by evaluating the percentage of withdrawal responses to a train of 30 mechanical stimuli on the hind paw before and after 180 seconds of exercise on a rotating rod. The rats were grouped into low, medium, and high EIH based on their reduction in the percentage of withdrawal responses before and after exercise. Rats from each group then underwent left sciatic nerve constriction injury. Mechanical allodynia, mechanical hyperalgesia, and heat allodynia were assessed in the affected and contralateral hind paws prior to and 3 and 7 days following the procedure. The low EIH rats demonstrated increased hypersensitivity at baseline and developed significantly more severe heat allodynia, mechanical allodynia, and hyperalgesia 3 and 7 days following the injury compared to the medium and high EIH rats. Moreover, the low EIH rats developed contralateral heat allodynia following the injury. The EIH of habituated and nonhabituated rats was compared to study the role of stress on the hypoalgesic effect. No significant differences were found between the habituated and nonhabituated rats at baseline and 1 and 5 minutes after the exercise.

Perspective: EIH profile was found to be predictive of pain severity following nerve injury. It may suggest that selected patients with faulty pain modulation are at risk for developing chronic pain following injury or surgical procedures. EIH may represent a preoperative means to detect this predisposition and enable proactive management.

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Key words: Exercise-induced hypoalgesia, neuropathic pain, pain modulation, nerve injury.

Pain is a complex sensory and emotional experience often initiated by peripheral nociceptors. Prior to arriving at the somatosensory cortex, peripherally generated signals may undergo modulation in the central nervous system. Similar external stimuli can evoke different pain experiences, depending on processes within the central nervous system. The perception of pain varies among subjects and is affected by emotional status, concurrent painful stimuli, and exercise or physical activity.

Various chronic pain conditions such as fibromyalgia,^{19,47,56,57} tension-type headache, musculoskeletal

pain,^{4,29,46} migraine,⁶⁷ chronic low back pain,²⁸ irritable bowel syndrome,²⁷ and temporomandibular disorder^{38,39,49-52} have been shown to be associated with faulty pain modulation, specifically, deficient inhibition and often increased facilitation. Among healthy subjects, pain modulation efficiency is reduced in older subjects¹⁴ and increased in patients with fewer reports of past pain,¹³ and it seems to be more efficient in males than females.¹⁶

Conditioned pain modulation (CPM) protocols assess pain inhibition in the laboratory by using 2 remote noxious stimuli, with the “conditioning” pain inhibiting the “test” pain.⁴⁸

The predictive value of pain modulation on the development of chronic pain has been recently demonstrated in patients that underwent thoracotomy. Patients with efficient CPM had less chronic postthoracotomy pain.⁶⁹ Further research has shown that patients with less efficient CPM experienced greater therapeutic efficacy from duloxetine than patients with normal CPM,⁷⁰

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suggesting that pain modulation can be a factor for predicting individual pain management outcomes.

Exercise is considered a trigger for pain modulation and has been used to evaluate CPM.³⁵ The effect of physical activity on pain perception is commonly termed exercise-induced hypoalgesia (EIH).⁷ Studies have shown increased pain thresholds after aerobic exercise for both mechanical^{21-23,68} and thermal⁵⁵ stimuli and increased generalized pressure pain thresholds following isometric muscle contraction.^{21,32}

The exact mechanisms of EIH are unknown; however, it is widely believed that activation of the endogenous opioid system and release of peripheral and central beta-endorphins^{5,53} play a major role in this phenomenon. Other suggested mechanisms include activation of neurotransmitters such as serotonin and norepinephrine,¹² involvement of the adenosinergic system,⁴⁴ and interactions with the cardiovascular system.³⁷

The increased pain threshold following exercise appears to be more consistent when the painful stimulus is mechanical or electrical and less consistent for thermal painful stimuli. Other factors that may affect EIH are the intensity of the performance, duration, and emotional status (stress).³⁰ The analgesic effect of exercise led to specific treatment protocols for painful conditions such as fibromyalgia, neck pain, low back pain, and arthritis.^{9,26,58,64} However, questions were raised regarding the effect of exercise on patients with faulty modulation systems.^{33,65,66}

The goal of this study was to investigate the predictive value of the EIH profile on pain intensity in a rat model of nerve injury. Extrapolating from studies on CPM, we hypothesized that rats with less efficient EIH would develop more severe pain following nerve injury.

Methods

The experimental procedures and protocols were approved by the Institutional Animal Care and Use Committee of the University of Medicine and Dentistry of New Jersey (currently Rutgers School of Medicine) protocol no. 12093E0216.

Animals

A total of 96 adult male Sprague Dawley rats were sourced from a single breeder and housed in the on-site animal facility under veterinary supervision. The rats were fed a standard rodent chow, given ad libitum access to reverse osmosis water, and maintained on a 12-hour light-dark cycle.

Study Overview

The study was performed in 2 phases. In the first, EIH was tested by evaluating percentage of responses to a train of mechanical stimuli before and after 180 seconds of exercise on a rotarod (Roto-Rod; Stoelting Inc, Wood Dale, IL). Based on the difference in the response rates before and after the exercise, the rats were divided into low, medium, and high EIH responders. The effect of habituation on EIH score was studied on a group of

rats that was not exposed to the rotating rod apparatus prior to the EIH test (ie, did not go through the habituation protocol). In the second phase, rats from each group (low, medium, and high EIH) underwent constriction injury of the left sciatic nerve. The postoperative pain level was evaluated and compared between the groups.

Assessment of Exercise-Induced Analgesia

For exercise, the rats were placed on a rotarod, a rotating surface that requires the rat to walk against the motion of the rotating drum for 180 seconds, with the speed accelerating from 8 to 16 rpm over 100 seconds and maintaining the 16 rpm for an additional 80 seconds.

Thirty mechanical stimuli were applied to the rats' hind paw with a 60-g-force von Frey fiber at the rate of 1 Hz. A positive response was recorded when the rat withdrew the paw following the stimulus. If the filament passively elevated the paw (without paw withdrawal by the rat) the stimulus was considered a nonresponse.

The number of responses was counted and the percentage was calculated (30 out of 30 was considered a 100% response). The response to the mechanical stimuli was evaluated before the exercise and at 1, 5, and 10 minutes following the cessation of exercise. Pre- and postexercise measurements were obtained daily over 3 days and averaged so as to counteract reversion-to-the-mean errors. The percentage difference between the stimuli response before and after exercise represented the EIH.

Prior to testing, rats were habituated to the Rotarod and to walking against the rotating drum for 3 consecutive days. Habituation involved slow and gentle exposure to the exercise equipment: first the rats were allowed to sniff around for several minutes, after which the drum was turned by hand to familiarize the rats with the motion of the Rotarod. The machine was then run for cycles of increasing time intervals with 10 seconds rest in between. The exercise cycles began with 10 seconds and the walk time was doubled until the rat successfully completed a 180-second exercise cycle. The majority of the rats were able to walk on the rod for the entire 180-second test period during their first exposure to the device. Across the 3 days, all the rats were able to walk for 180 seconds without failure. To study the possible role of stress on the EIH, a separate group of 18 rats naïve to the Rotarod underwent a similar protocol (test, exercise, test after 1, 5, and 10 minutes) but without the habituation period.

Pain Behavior Assessment

Three types of validated behavioral assays were performed: tactile allodynia, mechanical hyperalgesia, and heat allodynia. Rats were habituated preoperatively by allowing them 30 minutes daily inside the sensory-testing apparatus for 1 week. As part of the habituation, the rats were stimulated with a blunted acupuncture needle, von Frey filaments, and hot stimuli in the hind paw area and then returned to their cages.

The behavioral assays (pain assessments) were performed on the rat's midplantar hind paw (sciatic nerve

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