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Exercise reverses pain-related weight asymmetry and differentially modulates trabecular bone microarchitecture in a rat model of osteoarthritis

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ABSTRACT

There is great interest in developing and utilizing non-pharmacological/non-invasive forms of therapy for osteoarthritis (OA) pain including exercise and other physical fitness regimens.
Aims: The present experiments determined the effects of prior wheel running on OA-induced weight asymmetry and trabecular bone microarchitecture.
Main methods: Wheel running included 7 or 21 days of prior voluntary access to wheels followed by OA induction, followed by 21 days post-OA access to wheels. OA was induced with monosodium iodoacetate (MIA), and weight asymmetry was measured using a hind limb weight bearing apparatus. Bone microarchitecture was characterized using ex vivo μCT.
Key findings: Relative to saline controls, MIA (3.2 mg/25 μl) produced significant weight asymmetry measured on post-days (PDs) 3, 7, 14, 21 in sedentary rats. Seven days of prior running failed to alter MIA-induced weight asymmetry. In contrast, 21 days of prior running resulted in complete reversal of MIA-induced weight asymmetry on all days tested. As a comparator, the opioid agonist morphine (3.2–10 mg/kg) dose-dependently reversed weight asymmetry on PDs 3, 7, 14, but was ineffective in later-stage (PD 21) OA. In runners, Cohen's *d* (effect sizes) for OA vs. controls indicated large increases in bone volume fraction, trabecular number, trabecular thickness, and connective density in lateral compartment, and large decreases in the same parameters in medial compartment. In contrast, effect sizes were small to moderate for sedentary OA vs. controls.
Significance: Results indicate that voluntary exercise may protect against OA pain, the effect varies as a function of prior exercise duration, and is associated with distinct trabecular bone modifications.

1. Introduction

Osteoarthritis (OA) is a disease of musculoskeletal origin that is associated with debilitating chronic pain, and currently ranks as the most common form of arthritis. Symptoms include chronic pain and decreased mobility due to modification to subchondral bone and degeneration of joint cartilage [1,2]. Pharmacological treatments for OA patients include NSAIDs and/or opioids, which are associated with significant adverse side effects with chronic administration (reviewed in [3]). Further, some patients report OA pain associated with a persistent pain state that is NSAID resistant, referred to as advanced OA pain [4]. These patients often turn to joint replacement therapy that produces alleviation of OA symptoms including joint pain in many patients [5,6]. Alternative and less invasive/expensive methods for treatment are desirable. One potential treatment strategy may be the incorporation of exercise regimens to either reverse or attenuate symptoms of OA pain.

Exercise is the top recommended non-pharmacological treatment for OA patients, and recently there has been an increasing literature base on the protective effects of voluntary exercise in preclinical and clinical pain populations. Voluntary wheel running in rodents has been shown to enhance muscle viability and bone strength [7–9],

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attenuate allodynia and elevated IL-1β levels in a model of neuropathic pain [10], and increase protective CD206 macrophage production in a model of muscle pain, and decrease pain- and stress-related measures in a model of inflammatory pain [11,12]. Although there is an increasing literature base on exercise-pain interactions [10,11,13,14], less is known about how the behavioral mechanism of wheel running acquisition duration (i.e., prior wheel running) affects the expression of chronic pain-like behavior. Further, it is unknown if prior running + OA pain is associated with distinct modulation to trabecular bone, relative to a sedentary OA pain condition. Toward that end, the present set of studies addressed two issues. First, two voluntary wheel running protocols [15] that differed in prior access to wheels (7 days vs. 21 days) were used to determine if duration of prior wheel running would differentially affect OA-induced pain behaviors, measured by weight asymmetry of the hind-limbs. Second, the present study also characterized the effects of OA on trabecular bone microarchitecture in rats with or without access to running wheels.

In the present set of experiments, OA was chemically induced with monosodium iodoacetate (MIA), a validated preclinical model of OA pain that includes cartilage degradation and sub-chondral bone loss similar to that seen in human and veterinary patients [16–18]. A concentration of MIA (3.2 mg/25 μl) was selected that previously demonstrated tactile allodynia and weight asymmetry [15].

Given the reports on opioid treatment of human OA and MIA-induced OA [19–22], the relative effectiveness of wheel running to reverse OA-induced weight asymmetry was compared to that of the standard prescription mu opioid agonist morphine. Based on our earlier work, we hypothesized that a relatively longer duration of prior wheel running would reduce OA-induced weight asymmetry. Additionally, it was predicted that the magnitude of OA-induced changes to trabecular bone would be distinct in exercised rats compared to sedentary controls.

2. Materials and methods

2.1. Subjects

Adult male Sprague-Dawley rats (Harlan, Indianapolis, IN), 200–250 g at the start of the experiment, were used for all studies. Rats were randomly assigned to six separate groups: three different saline-treated groups (saline sedentary/n = 7, saline runner with 7 day acquisition/n = 7, saline runner with 21 day acquisition/n = 7) and three different osteoarthritis MIA-treated groups (MIA sedentary/n = 7, MIA runner with 7 day acquisition/n = 8, MIA runner with 21 day acquisition/n = 8). All rats were initially housed in groups of two to three in standard Plexiglas containers with food and water available ad libitum. Following 7 days of acclimation to the animal facility, runners were then moved to individual cages with running wheels attached; sedentary controls rats were also moved to individual cages at the same time. Animals were maintained in a temperature and humidity controlled colony on a 12-h light/dark cycle (lights on at 8:00). All experiments were conducted in accordance with the Guide for the Care and Use of Laboratory Animals as adopted by the National Institutes of Health. The University of New England Institutional Animal Care and Use Committee (IACUC) approved all protocols involving animals.

2.2. Wheel running protocols

Wheel running was measured using an activity wheel monitoring system (Lafayette Instruments, Lafayette, IN). In running wheel experiments, rats were singly housed in a chamber that contained an activity wheel. Each rat had 24 h voluntary access to its own running wheel for the duration of the experiment, and the total distance traveled (m) in the wheels by each rat was recorded. Two separate running wheel protocols were evaluated. Each protocol consisted of three phases: a) an acquisition phase of 7 or 21 days, b) an osteoarthritis induction phase consisting of a single intra-articular injection of either saline or 3.2 mg MIA into the left hind knee, and c) a post-injection observation phase which lasted 21 days [15]. Rats had continuous access to running wheels each day from the beginning of acquisition through the end of post-observation.

2.2.1. Acquisition phase

The length of the acquisition phase (number of days access to wheels before saline or MIA injection) was chosen based on our previous experience with MIA-depressed wheel running protocols [15]. Two different wheel running protocols with distinct acquisition durations were evaluated: a 7-day acquisition period + 21-day post-induction period (protocol 7-21), and a 21-day acquisition period + 21-day post-induction period (protocol 21-21).

2.2.2. Osteoarthritis model

A single intra-articular injection of MIA (3.2 mg/25 μl) into the left hind knee was administered to induce a localized arthritis of the knee joint [15,16]. Control subjects received a single intra-articular injection of saline (25 μl). All i.a. injections occurred between 9:00–9:30 am, and running rats were then returned to the wheels. Sedentary rats were returned to separate cages with no access to wheels.

2.2.3. Post-MIA phase

The post-MIA phase consisted of a 21-day observation phase in which the effects of MIA-induced osteoarthritis or saline on wheel running were recorded daily. On post-days 3, 7, 14 and 21, rats were removed from their activity wheel monitoring system cages and brought into a separate room for testing on the Incapacitance tester [15,23]. After habituation to the testing room and Plexiglas chamber, weight bearing data were recorded as described above. Incapacitance testing was conducted for ~1 h starting at 12:00 pm. Test trials for each rat were approx. 30–60 s.

2.3. Weight bearing assay

An Incapacitance tester (Columbus Instruments, Columbus, OH) was used to determine hind paw weight distribution. Rats were placed in a custom-made, angled Plexiglas chamber so that each hind paw rested on a separate force plate. The change in hind paw weight distribution was automatically calculated by the Incapacitance tester. The apparatus calculates an average weight distribution over the span of 5 s, and three recordings are taken for each rat. All three recordings are then automatically averaged and a mean score is displayed. The primary dependent measure was % weight on ipsilateral hind limb, and represented the percentage of weight on ipsilateral hind paw following a treatment condition (MIA sedentary, MIA sedentary + morphine, MIA + wheel running) subtracted from the percentage of weight on ipsilateral hind paw following the baseline saline condition, and was determined by the following formula:

$$[\text{baseline force (g) of left hind paw} \div (\text{baseline force (g) of left hind paw} + \text{baseline force (g) of right hind paw}) * 100] - [\text{treatment force (g) of left hind paw} \div (\text{treatment force (g) of left hind paw} + \text{treatment force (g) of right hind paw}) * 100]$$

After habituation to the Plexiglas chamber, baseline recordings were determined. Following baseline determinations, sedentary rats were removed from their home cage and injected with 3.2 mg of intra-articular monosodium iodoacetate (MIA) or intra-articular saline (controls) into the left hind knee, returned to their home cages, and allowed to recover. Similarly, wheel running rats were removed from their running cages and injected with 3.2 mg of i.a. MIA or saline (controls) into the left hind knee, and returned to their wheel cages. The concentration of