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Similarities between exercise-induced hypoalgesia and conditioned pain modulation in humans

Henrik Bjarke Vaegter [a,b], Gitte Handberg [a], Thomas Graven-Nielsen [b,*]

[a] Pain Center South, University Hospital Odense, Odense, Denmark
[b] Center for Sensory-Motor Interaction (SMI), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

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ABSTRACT

Pain inhibitory mechanisms are often assessed by paradigms of exercise-induced hypoalgesia (EIH) and conditioned pain modulation (CPM). In this study it was hypothesized that the spatial and temporal manifestations of EIH and CPM were comparable. The participants were 80 healthy subjects (40 females), between 18 and 65 years of age in this randomized, repeated-measures cross-over trial that involved data collection on 2 different days. CPM was assessed by 2 different cold pressor tests (hand and foot). EIH was assessed by 2 intensities of aerobic bicycling exercises and 2 intensities of isometric muscle contraction exercises (arm and leg). Pressure pain thresholds (PPTs) were recorded before, during, after, and 15 minutes after conditioning/exercise at sites local to and remote from the extremity used for cold pressor stimulation and exercise. PPTs increased at local as well as at remote sites during both cold pressor tests and after all of the exercise conditions except low-intensity bicycling. EIH after bicycling was higher in women than in men. CPM and the EIH responses after isometric exercises were comparable in men and women and were not affected by age. The EIH response was larger in the exercising body part compared with nonexercising body parts for all exercise conditions. High-intensity exercise produced greater EIH responses than did low-intensity exercise. The change in PPTs during cold pressor tests and the change in PPTs after exercises were not correlated. The CPM response was not dominated by local manifestations, and the effect was seen only during the stimulation, whereas exercise had larger local manifestations, and the effects were also found after exercise.

1. Introduction

Several mechanisms play a role in the transition from acute to chronic pain, including imbalanced descending control, manifested as a net facilitory effect [54]. Descending pathways are of major importance in pain modulation because these pathways can inhibit or facilitate transmission of noxious information [45]. In humans, the ability to modulate pain is often assessed by paradigms of conditioned pain modulation (CPM) [36,47]. In human studies, CPM is typically triggered by applying a tonic noxious cold stimulus [36]. CPM causes an acute heterotopic decrease in the pain sensitivity, although homotopic hypoalgesias have been reported [12,35,43]. The CPM response dampens with increasing age [8,25,49], and studies of gender differences in pain modulation have indicated reduced CPM in women [34]. In subjects with chronic pain, reduced CPM seems to be common and to be predictive of acute and chronic postoperative pain [31,54,55].

Exercise-induced hypoalgesia (EIH) has been used to evaluate pain modulation in humans [3,24]. Experimental studies have examined the effect of acute exercise, and the majority have documented a multisegmental decrease in pain sensitivity during and following exercise in healthy subjects [30]. Aerobic exercise (eg, bicycling or running) produces a hypoalgesic effect when performed at moderate to high intensities for longer periods [15,18,40]. In contrast, isometric exercise (ie, a muscle contraction without joint movement) produces EIH at both low and high intensity and duration seems to be of less importance [13,46]. EIH is comparable in men and women [15,23,46], although greater effects have been shown in women [17,42]. EIH appears to be negatively correlated with age in female patients with fibromyalgia [14], but the effect of age on the EIH response in healthy subjects is unknown. In subjects with chronic pain, reduced EIH has been reported [3,21,24,29].

* Corresponding author. Address: Laboratory for Musculoskeletal Pain and Motor Control, Center for Sensory-Motor Interaction, Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Fredrik Bajers Vej 7D-3, Aalborg E 9220, Denmark. Tel.: +45 9940 9832; fax: +45 9815 4008.

E-mail address: tgn@hst.aau.dk (T. Graven-Nielsen).

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Similar mechanisms for CPM and EIH have been proposed. Systemic injection of naloxone, in both animals and humans, resulted in a reduction in the inhibitory effects after noxious thermal stimuli [27,53] and after exercise [1,16]. Reduced CPM has been reported in subjects treated with opioids [37] and lesser effects of opioids have been reported after long-term exercise [41]. Thus, activation of opioidergic descending inhibitory pathways is a potential mechanism for both CPM and EIH.

Similarities exist among studies of CPM and EIH; however, the 2 paradigms have never been compared directly. A direct comparison has the potential to reveal whether pain modulation differs within individuals depending on type of stimulus. Thus, the purpose of this study was to compare pressure pain thresholds (PPTs) in healthy subjects before and after different types of exercises as well as before and after cold pressor tests at varying locations. It was hypothesized that (1) exercise and conditioning pain stimuli would cause a multisegmental decrease in PPTs; (2) the CPM and EIH responses would be correlated; (3) the effects of exercise and cold pressor test on PPTs would be reduced in older subjects; (4) the effect of exercise on PPTs would be increased in women; and (5) greater inhibition of PPTs would be observed with higher intensity and longer duration of exercise.

2. Methods

2.1. Subjects

The study included 80 healthy subjects: average age, 37.9 years [range, 18–65 years]; average body mass index (BMI) 24.2 kg/m^2 [range, 19–35]; 10 left-handed; 40 women). There was no significant difference in age or BMI between female and male subjects (Mann-Whitney U test; $P > 0.3$). Subjects were recruited by advertisement at the local university and the local university hospital and through a local newspaper. None of the included subjects suffered from neurological, psychological or cardiovascular diseases or had any pain or used any pain medication during the week prior to participation. All subjects were asked to refrain from physical exercise, coffee and nicotine on the days of participation. The study was conducted in accordance with the Declaration of Helsinki and approved by the local ethical committee (S-20110070), and all subjects provided written informed consent.

2.2. Procedure

The subjects participated in 2 sessions at approximately the same time of day and separated by 1 to 3 weeks. In the first session, subjects were introduced to the procedures. Conditioned pain modulation was assessed by 2 different cold pressor test conditions. Exercise-induced hypoalgesia was assessed by 2 different aerobic cycling exercises and 4 different isometric muscle contraction conditions. Each session lasted approximately 150 minutes and comprised 4 different conditions. A 20-minute recovery interval was maintained between each condition. The order of the 8 conditions was randomized and counterbalanced between the 2 sessions with 1 cold pressor test, 1 bicycling, and 2 isometric contractions in each session (Fig. 1).

PPTs were used to assess the efficacy of the cold pressor stimulation and exercise. PPTs were recorded before, 1 minute after starting, immediately after, and 15 minutes after the cold pressor tests. In the exercise paradigm, PPTs were recorded before the exercise, immediately after the first bout of exercise, immediately after the second bout of exercise, and 15 minutes after the end of the exercise.

2.3. Pressure pain threshold assessment

PPTs were assessed using a handheld pressure algometer (Somedic, Hörby, Sweden) with a stimulation area of 1 cm^2. The rate of pressure increase was kept to approximately 30 kPa/s, and the first time the pressure was perceived as pain, the subject pressed a button and the pressure intensity defined the PPT. Two PPT assessments were completed for each site, and the average was used for statistical analysis. Intervals of 20 seconds between assessments were maintained. PPT measurements were conducted with the subject seated on a plinth without foot support and with both arms resting on the thighs.

Three assessment sites were located and marked. Site 1 was located in the middle of the dominant quadriceps muscle, 20 cm proximal to the base of the patella. Site 2 was located in the middle of the dominant biceps brachii muscle, 10 cm proximal to the cubital fossa. Site 3 was located in the nondominant upper trapezius muscle, 10 cm from the acromion in direct line with the neck.

2.4. Cold pressor test

In the 2 sessions, the subjects completed a cold pressor test with the dominant hand and a cold pressor test with the dominant foot, respectively. The cold pressor tests were performed with the subject comfortably seated while immersing the hand or foot into a tank containing circulating ice water at 1°C to 2°C. The subject immersed the hand or foot 5 cm above the wrist or ankle joint for 2 minutes. Just before removing the limb, the subject was instructed to rate the pain intensity caused by the cold water on a 0 to 10 numerical rating scale (NRS), with 0 defined as no pain and 10 as the worst imaginable pain. After 2 minutes, the limb was removed from the tank, and pain assessments were performed immediately afterward, as described. After the pain assessments were performed, the subject sat quietly on the plinth for a 15-minute recovery period, which concluded with a final set of pain assessments.

2.5. Bicycling exercise

The 2 bicycling conditions (ie, low and high intensity) each lasted for 2 × 10 minutes. In the beginning of the first session, the age-related target heart rates for the low- and high-intensity bicycling exercises were determined. In short, based on a previously described method [44], the relationship between heart rate and VO_2 was used to determine the age-related target heart rate corresponding to 75% VO_{2max} and 50% VO_{2max}. The seat post of the stationary cycle (Ergomedic 928E; Monark Exercise, Vansbro, Sweden) was adjusted so that the subject had approximately a 5-degree bend at the knee during the bottom phase of the pedal stroke. A heart rate monitor (Monark) was strapped around the subject's chest. Subjects were instructed to maintain a pedal rate as close to 80 rounds per minute as possible throughout the 2 × 10 minutes. The first 2 minutes of each session were used as warmup, and the intensity was kept below the target heart rate corresponding to low intensity. Resistance was then increased over the next 3 minutes until the target heart rate was achieved by the beginning of the fifth minute, whereafter the subject continued bicycling for 5 minutes. Heart rate was monitored constantly, and resistance was manipulated if necessary to keep the heart rate at the desired level. After 10 minutes of bicycling, pain assessments were performed as described, and the subject went back to the bicycle and exercised at the target heart rate for another 10 minutes, followed by another set of pain assessments. After the pain assessments were performed, the subject sat quietly on the plinth for a 15-minute recovery period, which concluded with a final set of pain assessments. Ratings of Perceived Exertion (Borg 6-20 RPE scale) scores were obtained after 10 minutes and 2 × 10 minutes of bicycling.