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Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation

Kathleen A. Sluka

Laura Frey-Law

Marie K. Hoeger Bement

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Exercise-induced pain and analgesia? Underlying mechanisms and clinical translation

Kathleen A. Sluka
Department of Physical Therapy and Rehabilitation Science, The University of Iowa, Iowa City, IA
Neuroscience Institute, The University of Iowa, Iowa City, IA,
Pain Research Program, The University of Iowa, Iowa City, IA
Laura Frey-Law
Department of Physical Therapy and Rehabilitation Science, The University of Iowa, Iowa City, IA
Marie Hoeger Bement
Department of Physical Therapy, Marquette University, Milwaukee, WI

1. Introduction

Physical inactivity or a sedentary lifestyle is a significant health concern worldwide. The Centers for Disease Control (CDC) recommends 150 minutes per week of moderate to vigorous activity for health benefits.13 Worldwide, the great majority of the population does not meet these physical activity guidelines. Furthermore, physical inactivity is a recognized risk factor for many conditions including cardiovascular disease, diabetes, cancer, dementia, and depression 69 (Fig. 1). In fact, this has been

referred to as the "diseasome of physical inactivity."[69] Physical inactivity is also a risk factor for the development of pain.[50,51,89] The HUNT study performed a population-based analysis of 4219 subjects and showed that those with moderate levels' physical activity report less musculoskeletal pain.[50,51] Similarly, higher leisure-time physical activity is associated with a lower risk of chronic pelvic pain in men,[89] and those with a greater number of years of leisure physical activity decreased the risk of low back pain (LBP) during pregnancy.[63] Thus, physical inactivity may be a risk factor for the development of chronic pain, whereas physical activity reduces this risk.

Figure 1.Diagram representing the diseasome of physical inactivity. Physical inactivity is a risk factor for the development of a number of diseases including pain. Modified from Ref. 69, with permission from the publisher, John Wiley & Sons, Inc.

Regular physical activity can be achieved through regular lifestyle activity or by structured exercise. In chronic pain, prescribed exercise is an effective treatment for most pain conditions, and use of exercise and physical therapy has long been recognized for its effectiveness in reducing disability and health care costs.[40,42,84] Despite this, an acute bout of exercise can exacerbate pain, in those with chronic pain. As an example, we have shown that an upper-body fatiguing exercise increases pain by 3 points on a 10-point scale in those with fibromyalgia (FM) (Fig. 2A),[23] and isometric contractions in individuals with FM show no increase in pain thresholds that normally occur in healthy controls.[41,52] Furthermore, people with chronic pain are generally less active than age-matched healthy controls (Figs. 2B and C).[20,29,55,59]

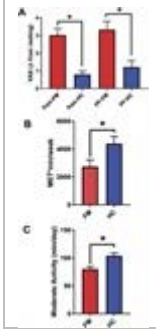

Figure 2. (A) Graphs showing the increase in pain and physical fatigue in people with fibromyalgia compared with healthy controls after a whole-body fatiguing exercise task. *P < 0.05. Data are mean ± SEM. Data are regraphed from Ref. 23. (B) Graph showing self-reported activity levels in METS*minute/week for those with fibromyalgia and healthy controls. *P < 0.05. Data are mean ± SEM. Data are graphic representations from tables in Ref. 59. (C) Graph showing moderate physical activity levels measured by accelerometry in fibromyalgia compared with healthy controls. *P < 0.05. Data are mean ± SEM. Data are graphic representations from tables in Ref. 59. FM, fibromyalgia; HC, healthy controls; METS, metabolic equivalents; PF, physical fatigue; VAS, visual analogue scale.

2. Effects of exercise on the central nervous system

We propose that regular physical activity changes the state of central pain inhibitory pathways and the immune system to result in a protective effect against a peripheral insult. This normal protective state that

occurs with regular physical activity is not found in physically inactive individuals and results in a greater risk of the development of chronic long-lasting pain.

Figure 3 depicts 2 states of the nervous system for cells in the brainstem, which modulate pain. Brainstem sites, such as the rostral ventromedial medulla (RVM), both facilitate and inhibit nociceptive signals.[37,70] We suggest that in the sedentary condition, muscle insult results in increased phosphorylation of the NR1 subunit of the *N*-methyl-D-aspartate (NMDA) receptor, which would result in increased facilitation. There is substantial research suggesting that NMDA receptors in the RVM facilitate pain, and phosphorylation of the NMDA receptor enhances channel conductance and increases insertion of NMDA receptors into the synapse.[18,21,22,27,81,86,87] Simultaneously, we propose that there is an increased expression of the serotonin transporter (SERT), which would result in reduced inhibition. Classic studies show that injection of serotonin or a SERT inhibitor into the RVM is analgesic, blockade of serotonin receptors prevents analgesia by stimulation of the periaqueductal gray, and systemic morphine increases serotonin in the RVM.[47,48,56,57,78] Furthermore, in the sedentary condition, there is less opioid tone in the nervous system to prevent these excitatory effects. In the physically active state, we propose that activation of opioid receptors modulates neuron activity so that there is less phosphorylation of the NMDA receptor and less expression of the SERT. Basic research studies support this hypothesis. We show, in sedentary animals, that there is increased expression of the SERT and increased phosphorylation of the NR1 subunit of the NMDA receptor in the RVM in animals with nerve injury or chronic muscle pain.[2,8,54] These increases do not occur in physically active animals with nerve injury or chronic muscle pain.[2,8,54] Further blockade of opioid receptors systemically, in the periaqueductal gray or the RVM, prevents the protective effects of regular physical activity, and mu-opioid receptor knockouts do not develop analgesia to regular physical activity.[54] Furthermore, we show that naloxone-treated or mu-opioid receptor knockout physically active animals do not show the increases in SERT in the RVM, supporting an interaction between endogenous opioids and serotonin.[54] In human studies, greater exercise-induced analgesia was associated with a gene for stronger opioid signaling (OPRM1 G) in combination with weak 5-HT tone (5-HTT low/5-HT1a G), suggesting interactions between opioid and serotonergic mechanisms for exercise-induced analgesia.[82] Thus, regular physical activity prevents hyperalgesia through activation of opioids and serotonin to produce analgesia.

In humans, several studies have emerged suggesting that greater physical activity is associated with equal or reduced pain sensitivity across a wide range of assessments. Quantitative sensory testing is increasingly used as an indirect measure of centrally mediated pain processing. Healthy individuals routinely participating in vigorous activity demonstrate enhanced conditioned pain modulation, a measure of central pain inhibition, compared with less active individuals.[32,66] In people with osteoarthritis, a 12-week exercise program increased pain thresholds and decreased temporal summation.[38] However, in 1 study, temporal summation, a measure of central pain facilitation, to cold pain was unchanged,[32] whereas temporal summation to heat pain was reduced.[66] Similarly, a meta-analysis of athletes vs normally active adults indicates reduced pain sensitivity overall in athletes.[79] These studies suggest that engagement in regular physical activity is related to decreased pain sensitivity in healthy adults. However, few studies have examined associations between daily lifestyle physical activity and pain sensitivity in FM or other chronic pain populations.

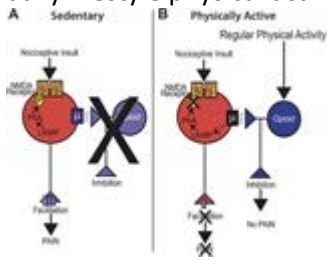

Figure 3. A schematic diagram representing the neurons in the brainstem, rostral ventromedial medulla, that facilitates and those that inhibits pain and how sedentary lifestyle (A) or physical activity (B) could modulate their activity. Based on data outlined in the text, we propose that in sedentary conditions, there is less opioid tone in the brainstem and overall less inhibition. This results in the neurons showing more facilitation after

nociceptive input with increases in phosphorylation of the NR1 subunit of the NMDA receptor and increased expression of the serotonin transporter. We further propose that regular physical activity increases release of endogenous opioids in the brainstem, which inhibit facilitatory neurons to reduce facilitation. This would be associated with less phosphorylation of the NR1 subunit of the NMDA receptor and reduced expression of serotonin transporter. Overall, in the physically active condition, there would be more inhibition from opioids and serotonin, and less excitation. NMDA, N-methyl-d-aspartate.

Epidemiological investigations also support the protective nature of physical activity on the development of chronic pain, which may be due to peripheral or central mechanisms. A population-based study from Norway showed that chronic musculoskeletal pain incidence was 10% to 38% less in individuals participating in moderate leisure-time activity 1 to 3 times per week compared to those with no leisure-time activity.[50,51] However, in patient populations, the relationships between regular physical activity and central pain processing are less clear. Increasing physical activity and exercise reduces symptomology in a variety of patient population, and is a first-line treatment in a number of chronic pain populations, from FM to LBP.[58,71] Furthermore, nonpharmacological therapies, in general, are considered first-line treatments, with exercise having strong support.[58,71] However, quantitative sensory testing and physical activity levels have not been routinely investigated in patient populations. In a small study of 18 women with FM, fitness levels, as assessed by cycle ergometry or the 6-minute walk test, were not associated with pain thresholds or temporal summation assessments.[25] However, this area of study remains sparse and may be limited by the reduced range of lifestyle physical activity levels observed in many chronic pain populations.

3. Effects of exercise on the immune system

We also propose that regular physical activity modulates the immune system locally at the site of insult, systemically, and in the central nervous system. In the physically inactive condition, there are more inflammatory cytokines and less anti-inflammatory cytokines. After regular physical activity, this balance shifts to more anti-inflammatory cytokines and less inflammatory cytokines. Inflammatory cytokines activate receptors on nociceptors to produce pain, whereas anti-inflammatory cytokines reduce activity of nociceptors to prevent pain.[26,33,46,90] Figure 4 shows our theory that physical activity levels modulate phenotype of macrophages in muscle. Macrophages are located in muscle and release inflammatory or anti-inflammatory cytokines depending on 2 relevant phenotypes: classically activated (M1) macrophages release inflammatory cytokines and regulatory (M2) macrophages release anti-inflammatory cytokines.[65] In support, we show that in uninjured animals, physically active animals show an increased proportion of M2 macrophages.[53] Similarly, in animals with nerve injury, sedentary animals show an increased proportion of M1 and less M2 macrophages at the site of injury, whereas physically active animals show increases in M2 and less M1 macrophages.[3] The analgesia produced by regular physical activity and exercise is prevented by blockade of either IL-10 (muscle insult) or IL-4 (nerve injury).[3,53] Thus, at the peripheral site of insult, there are alterations in macrophage phenotype that underlies the analgesia produced by regular exercise.

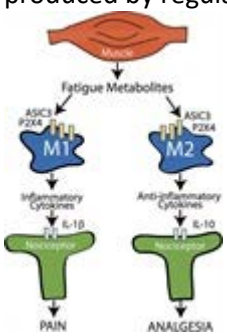

Figure 4. A schematic diagram representing the interaction between muscle, macrophages, and nociceptors in the peripheral nervous system. Macrophages, found in local tissue, can be polarized to and M1 phenotype that releases proinflammatory cytokines that activate nociceptors, or an M2 phenotype that releases anti-inflammatory cytokines that inhibit nociceptors. Our data support that there are greater M1

macrophages at the site of insult or injury in the sedentary state and that regular physical activity increases the proportion of M2 macrophages. Our data further support the notion that regular physical activity changes the state of the immune system so that there is a greater proportion of M2 macrophages and greater anti-inflammatory cytokine that mediates the analgesia of regular physical activity.

In chronic pain conditions, systemic inflammation is suggested as an underlying pathology.[60,75,76] Systemically, immune cells, ie, peripheral blood mononuclear cells are highly plastic, can alter levels of cytokines systemically or locally in tissue, and secrete inflammatory or anti-inflammatory cytokines based on their phenotype. In support, people with FM show enhanced circulating inflammatory cytokines and enhanced evoked release of inflammatory cytokines from circulating monocytes.[5,6,30,67,68] By contrast, a 4- or 8-month aquatic exercise program for individuals with FM decreases circulating and stimulated release from monocytes of inflammatory cytokines of IL-8, IL-1[beta], and tumor necrosis factor.[5,67,68] In healthy controls, exercise training also reduces the percentage of inflammatory monocytes in healthy men and women.[80] However, it should be noted that the number of subjects in most of these studies was low, and there are mixed results in the literature, likely a result of low sample size, use of mixed populations of immune cells, use of different stimuli to evoke cytokine release from immune cells.[61,76,83] Thus, preliminary studies show that exercise can alter systemic cytokines, and reduce systemic inflammation, a proposed mechanism of chronic pain.

In the central nervous system, glia cells modulate inflammatory and anti-inflammatory cytokines, and play a significant role in a variety of pain conditions.[62] In animals with nerve injury, there is activation of glial cells, increases in inflammatory cytokines, and decreases in anti-inflammatory cytokines.[3,34,62,85] Regular physical activity and exercise reduce glial cell activation, reduce inflammatory cytokines, and increase anti-inflammatory cytokines in the spinal cord dorsal horn.[3,34] Specifically, the enhanced astrocyte (glial fibrillary acidic protein) and microglial (Iba-1) immunoreactivity produced by nerve injury was significantly reduced by treadmill running.[3] In parallel, decreases in the anti-inflammatory cytokines-IL-4, Il-1ra, and IL-5-induced by nerve injury are reversed by treadmill running.[3] On the other hand, the increase in inflammatory cytokine IL-1beta is reduced by regular physical activity.[34] Furthermore, there are increases in transcription factors that regulate IL-1[beta], NF[kappa]B, and NLRP3 inflammasome, which are also reduced by regular physical activity.[34] Thus, regular exercise normalizes neuroimmune signaling in the central nervous system to prevent and reverse the development of hyperalgesia.

4. Effects of exercise on psychological comorbidities

In addition to the beneficial effects of exercise on immune health, people who participate in regular physical activity typically have enhanced mental health and psychological well-being, whereas individuals who are physically inactive are more likely to experience depression and anxiety. Specific to chronic pain, individuals who report low levels of physical activity are more likely to report higher kinesiophobia, fear avoidance beliefs, and pain catastrophizing compared with those who report higher physical activity levels.[28,49] However, in a cohort of patients with nonspecific LBP, fear of movement was not associated with subjective and objective (ie, questionnaire and accelerometry, respectively) measures of physical activity.[17] Therefore, the relation between physical activity and psychological health is less clear for individuals with chronic pain.

Despite the frequent recommendation of exercise in the treatment of depression and anxiety,[16,19] the prescription of exercise on improving psychological functioning for individuals with chronic pain is equivocal. In an overview of Cochrane Reviews to determine the effectiveness of physical activity and exercise interventions for adults with chronic pain,[31] only 5 of the 21 reviews included psychological well-being (ie, mental health, anxiety, and depression). Variable effects were reported, which included positive and no effects of exercise on psychological health.

The variability in the response may be related to how exercise is incorporated with other interventions in promoting psychological well-being. For example, in a systematic review and meta-analysis, the strongest

effects for reducing pain catastrophizing in adults with chronic noncancer pain were with multimodal treatment that included cognitive behavioral therapy and exercise.[74] The authors propose several explanations such that participating in exercise produces positive benefits that subsequently promote cognitive restructuring, increases self-efficacy by encouraging self-management, attenuates rumination through increased attentional demands of exercise, and decreases pain through activation of descending inhibitory systems. Similarly, in patients with chronic LBP, a multimodal program that included cognitive behavioral training and exercise produced better effects than exercise alone in improving quality of life and reducing disability and fear avoidance beliefs.[64] It is important to note that improvements occur with exercise alone; participating in regular physical activity that included both aerobic and strength training reduced pain catastrophizing in patients with chronic LBP, which mediated the improvements in disability and depression.[77] Thus, exercise prescription that incorporates a biopsychosocial approach that addresses the multitude of factors that occur with prolonged pain is important to maximize the overall positive effects.[4,40]

5. Clinical implications

Pain with activity is a significant barrier to activity participation.[11-13] We routinely show that in sedentary animals, there is an increase in hyperalgesia with a single bout of fatiguing exercise.[11,35,36,88] We further show that in human subjects, there is a significant increase in pain with fatiguing exercise in people with FM.[23] Treatments designed to reduce pain with activity have the potential to improve participation in regular activity. We recently show that application of transcutaneous electrical nerve stimulation (TENS) to the spine in people with FM reduces movement-evoked pain but has no effect on resting pain.[24] Similarly, in people with postoperative pain, Rakel and Frantz [72] applied TENS and showed a reduction in movement-evoked pain but not in resting pain. Thus, TENS may be an effective treatment to reduce movement-evoked pain to encourage activity participation in individuals with chronic pain.

The type of exercise may be less important than the act of doing exercise. Several studies have compared different types of exercise for different types of pain and show no difference between active exercise interventions.[15,39,45,73] For example, in individuals with LBP, comparison of spinal stabilization exercises to conventional physical therapy that included general exercise showed no differences between groups.[14] For those with neck pain, comparison of proprioceptive training to craniocervical flexion showed no differences in outcomes between groups.[45] Similarly, comparison of graded exercise and graded exposure for those with chronic LBP showed similar effects.[15] Furthermore, significant effects of strengthening and aerobic exercise are shown in LBP, osteoarthritis, and FM, and are both part of recommended guidelines for these conditions.[1,9,10,12,58,71] In fact, a recent Cochrane review comparing motor control exercise with other forms of exercise for those with chronic LBP concluded "Given the evidence that motor control exercise is not superior to other forms of exercise, the choice of exercise for LBP should probably depend on patient and therapist preferences, therapist training, costs, and safety."[73] We suggest that this lack of specificity of exercise may be related to the multiple and widespread mechanisms by which exercise works to reduce pain.

6. Future research directions

Basic science studies have only just begun to examine the underlying mechanisms of exercise. A better understanding of the molecular and cellular mechanisms of how exercise can lead increase pain or decrease pain will help to develop novel strategies to address chronic pain and improve implementation and adherence for this important intervention for chronic pain. It is abundantly clear that regular exercise and physical activity are effective for reduction in pain. It has also become increasingly clear that the type of exercise for reduction in pain is less important than doing the exercise. Although the CDC recommends 150 minutes of moderate physical activity per week and 2 days of strengthening per week for health benefits,[13] it is unclear whether this dose is needed for pain relief.[4] Indeed, multiple clinical trials use less time and lower intensities and still produce clinical effects in those with chronic pain.[40] However, we do not know the most effective dose, or the minimal effective dose. Furthermore, like all interventions, adherence and compliance with the program is extremely important to producing an effect. Barriers to exercise adherence include pain with

exercise, low levels of physical activity, low self-efficacy, psychological dysfunction, and poor social support.[43] Supervised exercise, individualized therapy, and self-management techniques may improve adherence; however, the quality of trials assessing these interventions is low.[44] Thus, future clinical studies will need to determine the most effective and minimally effective doses of exercise, if physical activity is equally beneficial to regular prescribed exercise, and develop methods and programs to improve adherence. Finally, although accepted that exercise is an important intervention for chronic pain, it is often not used as a first-line treatment, relying rather on medication prescriptions. The CDC opioid prescribing guidelines recommend the use of nonpharmacological approaches as the preferred approach to chronic pain (CDC guidelines). As much as 50% of all visits to primary care practitioners are for chronic pain,[7] yet nonpharmacological treatments are underutilized. Therefore, future studies should develop innovative methods to improve utilization of nonpharmacological treatments by health care practitioners for both acute and chronic pain.

Conflict of interest statement

The authors have no conflict of interest to declare.

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