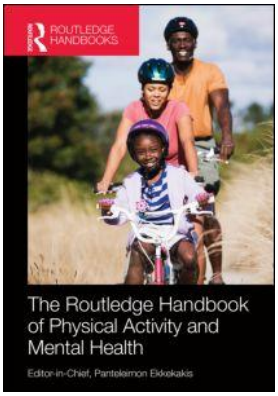

Routledge Handbook of Physical Activity and Mental Health

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Effects of Physical Activity on Laboratory Pain

Publication details
https://www.routledgehandbooks.com/doi/10.4324/9780203132678.ch25
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Published online on: 23 Apr 2013

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EFFECTS OF PHYSICAL ACTIVITY ON LABORATORY PAIN

Studies on animals

Kathleen A. Sluka

Pain is defined as a sensory and emotional experience associated with actual or potential tissue damage, or described in terms as such (www.iasp-pain.org). Chronic pain is a significant health problem affecting between 20% and 50% of the population; musculoskeletal pain is the most common. Chronic pain interferes with everyday activities including work, recreational activities, and activities of daily living. Acute pain, directly related to a tissue injury, also significantly impacts daily activities. Further, adequate treatment of acute pain is thought to prevent development of chronic pain. Interestingly, only 25% of respondents with pain participate in exercise: 45% of those with chronic pain and 14% of those with acute (for a review, see Sluka, 2009b). One effective treatment common for nearly all types of chronic pain, including those with musculoskeletal pain, is regular exercise (for a review, see Bement, 2009). Regular exercise also produces analgesia in uninjured animals and reduces pain behaviors after inflammatory, non-inflammatory, and neuropathic injury (Bement & Sluka, 2005; Blustein, McLaughlin, & Hoffman, 2006; Konarzewski, Sadowski, & Jozwik, 1997; Kuphal, Fibuch, & Taylor, 2007; Mathes & Kanarek, 2006; Shankarappa, Piedras-Renteria, & Stubbs, Jr., 2011; Stagg et al., 2011). In contrast to regular exercise, a single bout of exercise can enhance pain in both humans and animals (Lannersten & Kosek, 2010; Sluka & Rasmussen, 2010; Staud, Robinson, & Price, 2005; Vierck et al., 2001; Yokoyama, Lisi, Moore, & Sluka, 2007). Understanding the mechanisms that underlie these diverse effects of exercise will assist in the development of exercise protocols for patient populations.

As pain is a subjective experience in humans, measurement of pain in animals is inferred from the response of the animal to noxious stimuli. Several common tests are done that apply noxious heat or mechanical stimuli to a peripheral site (tail, paw, muscle, joint) and measure the withdrawal of the animal to the stimuli as latency (heat) or force (mechanical). Thus, a longer latency or greater force to withdrawal is indicative of analgesia and a shorter latency or lower force to withdrawal is indicative of pain and termed hypersensitivity (i.e., hyperalgesia). In addition, spontaneous pain behaviors – flinching or licking – are also measured in response to an acute injection of noxious chemical stimuli – formalin or acetic acid. To model pain conditions, several animal models have been developed. Neuropathic pain is induced by ligating a peripheral nerve and results in mechanical and heat hypersensitivity that lasts for months. Inflammatory pain is induced by injection of formalin, carrageenan, or complete Freund's adjuvant into paw, muscle, or joints. An initial acute inflammatory response is followed by a

chronic inflammatory response and results in decreased weight bearing, limb guarding, heat hypersensitivity, and mechanical hypersensitivity. Non-inflammatory chronic muscle pain is induced by two intramuscular acidic saline injections (2–5 days apart) and results in mechanical hypersensitivity without tissue damage. Spontaneous acute pain is induced by intraperitoneal acetic acid injections or intraplantar formalin injections and results in flinching and licking behaviors for 10–60 minutes.

Nociceptors respond to noxious stimuli and transmit information to the central nervous system for perception of pain; a schematic diagram of this pathway is shown in Figure 25.1A. Briefly, the nociceptors innervating peripheral tissue are activated by tissue injury, or noxious stimuli, and subsequently transmit this information to nociceptive neurons in the spinal cord dorsal horn. These neurons, termed spinothalamic (STT) cells, then send information to the thalamus and to the cortex for the perception of pain. The somatosensory cortices (SI and SII) are primarily involved in the sensation of pain in terms of quality, location, duration, and intensity, while the anterior cingulate and insular cortices (IC and CC) mediate the emotional component of pain (Hofbauer, Rainville, Duncan, & Bushnell, 2001; Rainville, Duncan, Price, Carrier, & Bushnell, 1997). Figure 25.1B shows a schematic diagram of descending inhibitory pathways thought to be involved in exercise-induced analgesia. In particular, the periaqueductal gray (PAG) in the midbrain sends input through the rostral ventromedial medulla (RVM) in the brainstem, which subsequently projects to the spinal cord. Activation of this pathway inhibits activity of nociceptive dorsal horn neurons as well as activity of nociceptors entering the dorsal horn. Understanding of the activation of different pathways and receptors by exercise, as well as how exercise may interact with these pathways, is important to a better understanding of the effects of exercise on pain. This could lead to improved exercise prescription for individuals with pain.

As exercise can both reduce pain and increase pain, it is important to understand the different contexts and mechanisms underlying both phenomena to better manage people with painful conditions. To understand these mechanisms, animal models have been developed for both exercise-induced analgesia and exercise-induced pain. Recently several studies have begun to study these phenomena in more detail, and this chapter will review the underlying mechanisms for exercise-induced analgesia and exercise-induced pain focusing on animal models.

Exercise-induced analgesia

Effects of exercise on pain behaviors

There are a number of different types of exercises that have been used in animals to produce analgesia. These include (1) increased physical activity by allowing animals free access to running wheels in their cages generally for several weeks, (2) strengthening exercises where rats do resisted exercise training, and (3) aerobic conditioning exercises using either treadmill running or swimming. In general, these tasks have been done repetitively over days or weeks. More specifically, allowing rats free access to running wheels for 3 weeks increases withdrawal responses to noxious heat stimuli applied to the tail (tail flick) (Kanarek, Gerstein, Wildman, Mathes, & D'Anci, 1998; Mathes & Kanarek, 2006). Similarly, in mice bred for high running wheel activity, withdrawal thresholds to noxious heat (tail flick) are higher than control mice (Li, Rhodes, Girard, Gammie, & Garland, 2004). A single swimming exercise task at either a low intensity or high intensity also increases withdrawal responses to noxious heat (tail flick) (Blustein et al., 2006). A resistance strengthening exercise program for 12 weeks in rats increases the paw withdrawal latency to noxious mechanical stimulation; this analgesic effect lasts for 15 minutes after ending

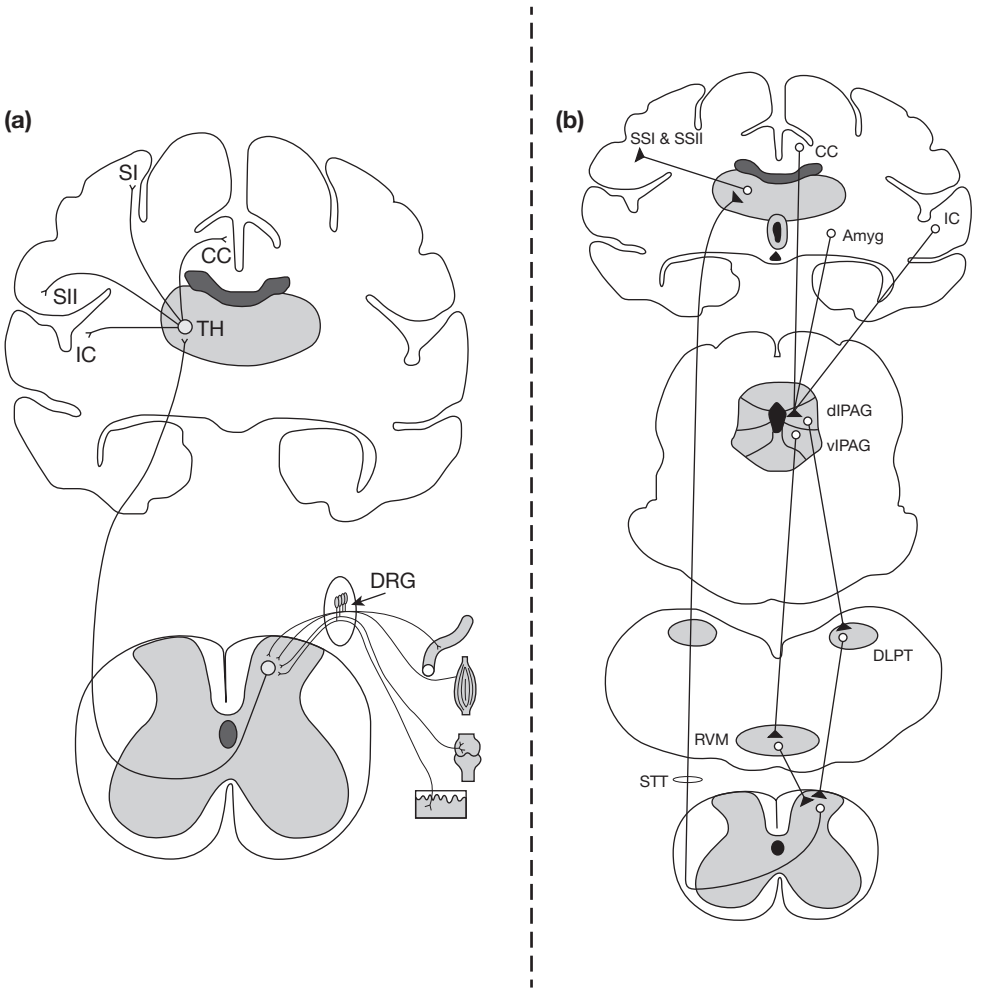

Figure 25.1 Schematic diagrams showing ascending nociceptive pathways (a) and inhibitory pathways (b). Nociceptors (first-order neuron) innervating joints send input to the spinal cord dorsal horn and synapse on spinothalamic tract cells (STT) (second-order neuron). STT cells then project supraspinally to the thalamus to synapse on a thalamic neuron (third-order neuron), which then projects to cortical sites, somatosensory cortex (SI, SII), insular cortex (IC), and anterior cingulate cortex (CC), resulting in perception of pain. B. Descending inhibitory pathways include the periaqueductual gray matter (vlPAG and dlPAG), which projects to the rostroventomedial medulla (RVM) and the dorsolateral pons (DLPT). The RVM and the DLPT then project to the spinal cord and inhibit activity in nociceptive neurons.

the task (Mazzardo-Martins et al., 2010). Thus, in uninjured rats, studies show that wheel running, swimming, and resistance training result in analgesia.

Repeated physical activity or exercise training prevents the development of acute pain behaviors to noxious stimuli, and reverses pain behaviors in animal models of muscle and nerve pain. For example, 5–9 days of swimming activity at moderate intensity prevents spontaneous pain-like behaviors induced by intraperitoneal acetic acid injection (Mazzardo-Martins et al., 2010) and by intraplantar formalin injection (Kuphal et al., 2007). In animals, repeated aerobic

exercise tasks like swimming and treadmill running reduce neuropathic pain induced by nerve injury or diabetes, and chronic muscle pain induced by repeated acid injections (Bement & Sluka, 2005; Korb et al., 2010; Kuphal et al., 2007; Shankarappa et al., 2011; Sharma, Ryals, Gajewski, & Wright, 2010; Stagg et al., 2011). For example, after development of non-inflammatory muscle pain induced by repeated acid injections, 15–30 minutes of treadmill running for 4 days (6m/min; low intensity) reverses the existing mechanical hypersensitivity when compared to sedentary rats; this effect occurs after the first 15-minute task and continues throughout 4 days of exercise (Bement & Sluka, 2005). In the same model of non-inflammatory muscle pain, moderate-intensity treadmill running for 30–45 minutes (13–16m/min) attenuated development of mechanical hypersensitivity when compared to sedentary mice (Sharma et al., 2010). In this study, it is unknown if moderate intensity had an immediate effect since changes were not measured until after 1 week of exercise training. In animals with diabetic neuropathy induced by streptozotocin, treadmill running for 60 minutes/day, 5 days per week (18m/min; high intensity), started at the time of induction of diabetes, delays the onset of hypersensitivity to noxious heat without changing blood sugar concentration (Shankarappa et al., 2011). Similarly, in animals with neuropathic pain induced by sciatic nerve injury, treadmill running (16m/min, 8% grade, high intensity), started at the time of injury or 3 weeks later, decreased the duration of mechanical and heat hypersensitivity with significant reductions starting 3 weeks after exercise (Figure 25.2A) (Stagg et al., 2011). The analgesic effects were similar if the animals exercised 3 days per week or 5 days per week, but did not occur at a lower intensity (10m/min). In animals with neuropathic pain (sciatic nerve injury), a 2-week training session of 90 minutes/day forced swimming was performed prior to injury. Rats continued to swim for 90 minutes per day after the nerve injury. By the third week rats showed reduced hypersensitivity to noxious cold and heat stimuli when compared to sedentary animals (Kuphal et al., 2007). These studies show that regular exercise can prevent or reduce the duration of hypersensitivity in animal models of pain. It should be noted that forced exercise tasks such as treadmill running or swimming may produce analgesia through a stress response, and it is well known that stress can produce analgesia without the exercise task (Blustein et al., 2006; Hopkins, Spinella, Pavlovic, & Bodnar, 1998; King, Devine, Vierck, Rodgers, & Yezierski, 2003; Konarzewski et al., 1997). Exercise also produces a variety of effects that may influence pain including affecting the sympathetic, cardiovascular, and motor systems (Danion, Latash, Li, & Zatsiorsky, 2001; Morimoto, Tan, Nishiyasu, Sone, & Murakami, 2000; Roveda et al., 2003; Sacco, Hope, Thickbroom, Byrnes, & Mastaglia, 1999; Spierer et al., 2007). In summary, a variety of exercise programs in animals produce analgesia in uninjured animals, prevent the development of pain behaviors to acute noxious stimuli, and reduce pain behaviors in animals with chronic pain conditions.

Mechanisms underlying exercise-induced analgesia

Opioid mechanisms

It is generally thought that exercise produces analgesia by activating endogenous opioid mechanisms. Centrally, this classical opioid analgesic pathway involves activation of the PAG in the midbrain, which projects through the RVM and subsequently to the spinal cord to inhibit nociceptive information (for a review, see Sluka, 2009a) (Figure 25.1B). Endogenous opioid peptides include β-endorphin, endomorphins, enkephalins, and dynorphins. These peptides are located in the PAG, RVM, and spinal cord and bind to opioid receptors (μ, δ, or κ) located on central neurons and nociceptors. When the endogenous opioids bind their receptors they inhibit activity of the target neuron and reduce pain in humans and animals.

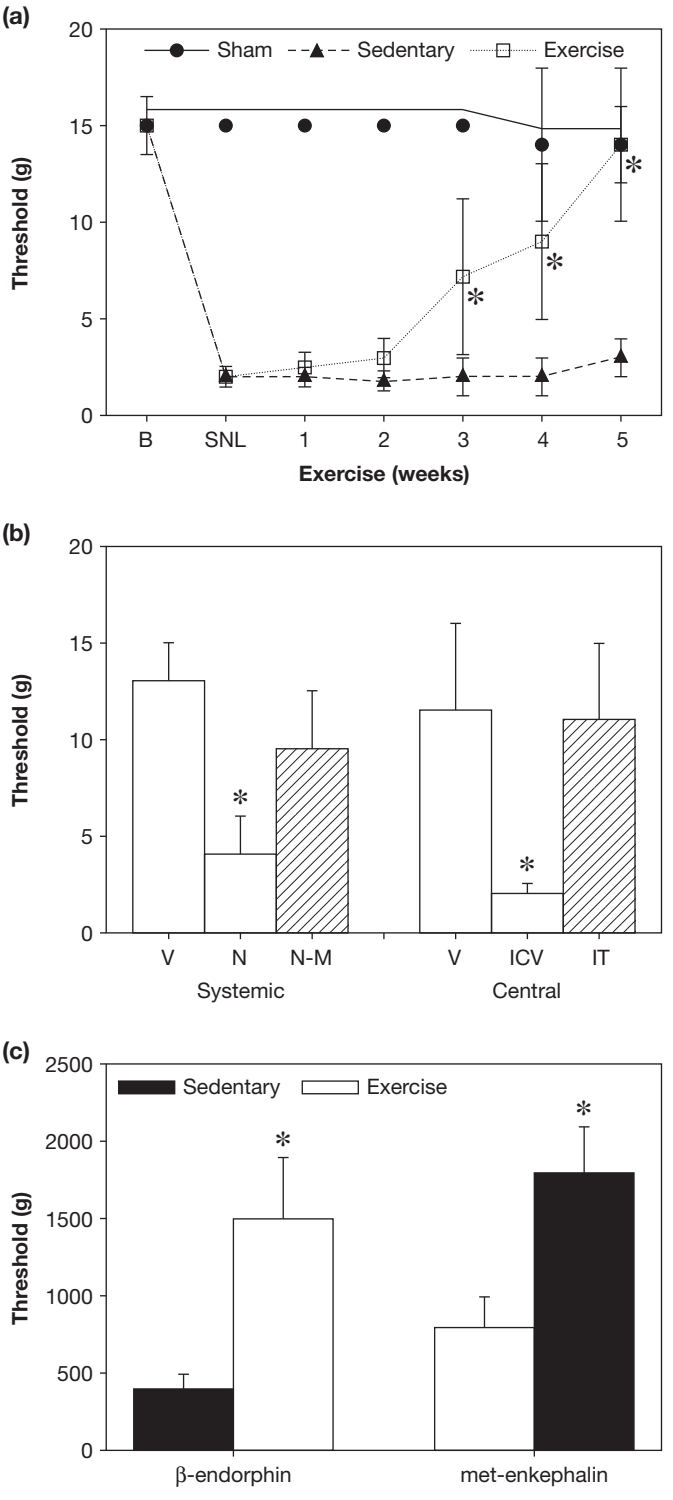

Figure 25.2 Treadmill running 5 days per week reverses the reduced mechanical withdrawal threshold induced by nerve injury when compared to sedentary rats with nerve injury. Normal withdrawal thresholds of the paw were 15 g; withdrawal thresholds decreased to between 2 and 3 g after nerve injury. B. Systemic naloxone (N) reversed the analgesic effects of exercise when compared to vehicle injection (V). Injection of naloxone methiodide (N-M) systemically, to block peripheral opioid receptors only, had no effect on the analgesia. C. Naloxone methiodide delivered supraspinally (i.c.v.) but not spinally (i.t.) reversed the analgesia produced by exercise in animals with neuropathic pain when compared to vehicle (V). D. Exercise increased the expression of β-endorphin in the PAG and met-enkephalin in the RVM when compared to sedentary rats. Data are mean ± S.E.M. ⋆, $P<0.05$ (redrawn from data presented in Stagg et al., 2011.)

In uninjured animals, β-endorphins are produced in a wide range of tissue types, including the PAG, RVM, spinal cord, and muscle (Denning et al., 2008; Sluka, 2009a). In human subjects, serum levels of β-endorphin increase in response to aerobic exercise; there is a minimum threshold of exercise duration and intensity for this release (Colt, Wardlaw, & Frantz, 1981; Rahkila, Hakala, Alen, Salminen, & Laatikainen, 1988; Rahkila, Hakala, Salminen, & Laatikainen, 1987). Blockade of opioid receptors systemically, reduces analgesia produced by chronic running wheel activity and by strength training in animals without tissue injury (Li et al., 2004; Mazzardo-Martins et al., 2010). In rats, 3 weeks of running wheel activity reduces the effectiveness of μ- and κ-opioid agonists given systemically or into the PAG in the midbrain (D'Anci, Gerstein, & Kanarek, 2000; Kanarek et al., 1998; Mathes & Kanarek, 2001, 2006; Smith & Yancey, 2003). Together these data support a role for opioid receptors in the analgesia produced by exercise.

In animal models of pain, several studies show that opioid receptors are also involved in the analgesia produced by regular exercise. There is release of β-endorphin in the PAG and enkephalin in the RVM after treadmill running in animals with neuropathic pain (Stagg et al., 2011) (Figure 25.2D). Systemic blockade of opioid receptors reverses the analgesia produced by regular aerobic exercise in neuropathic pain, chronic muscle pain, and acetic acid-induced pain (Bement & Sluka, 2005; Mazzardo-Martins et al., 2010; Shankarappa et al., 2011; Stagg et al., 2011) (Figure 25.2B). Blockade of opioid receptors centrally, giving naloxone intracerebroventricularly (i.c.v.) to block brainstem receptors, also reduces the analgesia produced by exercise in animals with neuropathic pain (Stagg et al., 2011) (Figure 25.2C). On the other hand, blockade of peripheral opioid receptors (naloxone methiodide) has no effect on the analgesia produced by treadmill running in animals with neuropathic pain (Stagg et al., 2011). In animals with chronic muscle pain, the analgesia produced on the first day of treadmill exercise is reduced by systemic naloxone and repeated exercise is reversed by daily naloxone injections, suggesting an acute release of endogenous opioid peptides (Bement & Sluka, 2005). In animals with diabetic neuropathy, analgesia produced by 2 weeks of treadmill running is reversed by a single injection of naloxone to block opioid receptors (Shankarappa et al., 2011), again supporting that opioids are continuously released in response to repeated exercise training. Together these data suggest that regular exercise reduces pain by activation of opioid receptors in descending inhibitory pathways in the central nervous system. However, recent studies show peripheral expression of opioid peptides in muscle (Denning et al., 2008), suggesting that exercise may also produce its effects by activation of peripheral opioid receptors.

Hippocampal changes

Interestingly, running wheel exercise increases c-fos expression (Lee et al., 2003; Oladehin & Waters, 2001), increases cell proliferation (Boehme et al., 2011; Ra et al., 2002; Sahay et al., 2011; Shors, Anderson, Curlik, & Nokia, 2012), and increases opioid receptor expression in the

hippocampus (de Oliveira et al., 2010), a brain structure involved in learning and memory. In fact regular running wheel activity increases learning and memory and neurogenesis (Boehme et al., 2011; Shors et al., 2012). In contrast, blockade of μ-opioid receptors reduces cell proliferation or neurogenesis induced by running wheel activity (Persson et al., 2004). Together these data suggest that regular exercise activates hippocampal neurons and may alter learning and memory through activation of opioid receptors. Voluntary exercise also reduces depressive behaviors in mice with concomitant changes in brain-derived neurotrophic factor (BDNF) in the hippocampus (Duman, Schlesinger, Russell, & Duman, 2008). Cognitive dysfunction and depression are co-morbid symptoms found in people with chronic pain conditions (Glass, 2009; Van, Kempke, & Luyten, 2010), and thus benefits of regular exercise in people with chronic pain could be to improve learning and reduce depression.

Serotonin

Serotonin is a major neurotransmitter found in descending inhibitory pathways and has been implicated in exercise-induced analgesia. Swimming-induced prevention of acetic-acid-induced spontaneous behavior is prevented by prior depletion of serotonin with p-chlorophenylalanine (PCPA) (Mazzardo-Martins et al., 2010). In contrast, nerve injury increases serotonin in the dorsal raphe nucleus of the midbrain, and this increase is prevented by regular treadmill exercise (Korb et al., 2010). Serotonin produces its effects through multiple different receptors, and is found in several different brain sites as well as the spinal cord and the periphery (Sluka, 2009a, 2009c). Future studies should investigate the role of serotonin receptors and different brain sites to more fully characterize the role of serotonin in exercise-induced analgesia and exercise-induced pain.

Ion channels

It is also possible that exercise has effects peripherally, reducing nociceptor activity. Enhanced activity of calcium channels would result in increased nociceptor excitability, which would be manifested as hypersensitivity to noxious stimuli. A recent study recorded calcium currents in dorsal root ganglia neurons (DRG) in animals with diabetic neuropathy, as a measure of excitability of nociceptive afferents (Shankarappa et al., 2011). Diabetic mice show enhanced calcium current density for both low- (T-; LVA) and high-voltage calcium currents (N-, P/Q, L-; HVA), indicative of increased calcium channel availability and activation. Treadmill running reduces the enhanced current densities of HVA and LVA calcium channels, suggesting reductions in nociceptor activity. Since prior studies show that genetic and pharmacological reduction of LVA or HVA calcium channels reduces pain behaviors in a variety of animal models (Chaplan, Pogrel, & Yaksh, 1995; Malmberg & Yaksh, 1994; Sluka, 1997, 1998; Todorovic & Jevtovic-Todorovic, 2011; Wang, Pettus, Gao, Phillips, & Bowersox, 2000), it is possible that regular exercise reduces pain hypersensitivity by normalization of enhanced ion channel activity of nociceptors.

Neurotrophic factors

Pain is influenced by neurotrophic factors, particularly members of the nerve-growth factor (NGF) family of neurotrophins, which include brain-derived neurotrophic factor (BDNF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4). Increases in NT-3 are thought to be analgesic. After 3 weeks of exercise in mice with non-inflammatory muscle pain, there is increased expression of NT-3 mRNA and protein in the muscle tissue (Sharma et al., 2010), the same time period when significant reductions in pain behaviors are observed. Increased intramuscular expression of NT-3 (transgenic mice) or intramuscular injection of NT-3 reduces mechanical

hypersensitivity induced by intramuscular acid injections (Gandhi, Ryals, & Wright, 2004). Together, these data suggest that increases in NT-3 could be one mechanism by which regular exercise produces analgesia.

Future directions

While research has begun to address the role of physical activity or exercise in animal models of pain there is limited data on mechanisms underlying the analgesic effects. Both central factors and peripheral factors need to be investigated in more detail in animal models of pain. For example, the data examining opioid receptor involvement in the analgesic effect of pain is primarily based on systemic delivery of naloxone, although one recent study showed an effect when given supraspinally. It is unclear which opioid receptors mediate the exercise-induced analgesia (μ, δ, or κ), or the location of opioid receptors (i.e., PAG, RVM, spinal cord, nociceptor) in the analgesic effect. Further comparisons between forced (swimming and treadmill) and voluntary exercise (running wheels) is critical to gain a better understanding of underlying mechanisms. In addition, peripheral effects of exercise on reducing injury-induced changes in nociceptor excitability are intriguing and suggest that exercise may have long-term effects. Could exercise change expression of factors at the peripheral level that can then inhibit nociceptor activity, such as NT-3, endogenous opioid peptides, or opioid receptors? While it is recognized that exercise has effects on a variety of systems including sympathetic, cardiovascular, and motor, in addition to the nociceptive system, it is unclear if these effects are directly related to the analgesia. Lastly, could regular physical activity prevent the development of chronic pain, or the conversion of acute pain to chronic pain? Understanding the molecular and cellular mechanisms underlying exercise-induced analgesia will help identify potential patient populations for treatment, and identify protocols that could be effective in treatment of painful conditions.

Exercise-induced pain

Eccentric exercise-induced pain

Exercise-induced pain in animals has been induced by eccentric exercise and running wheel activity. Eccentric exercise, lengthening contractions, produces pain and muscle soreness to pressure for several days in humans and has been termed delayed onset muscle soreness (DOMS) (Frey Law et al., 2008; Slater, Arendt-Nielsen, Wright, & Graven-Nielsen, 2005). Animal models have been developed to study the underlying mechanisms of eccentric exercise-induced pain (Alvarez, Levine, & Green, 2010; Dessem et al., 2010; Fujii et al., 2008). Eccentric exercise in animals is generally produced by electrically stimulating a muscle and having the joint movement occur in an eccentric manner. Eccentric exercise results in increased sensitivity to mechanical stimulation of the muscle measured behaviorally in awake animals (Dessem et al., 2010; Taguchi, Matsuda, & Mizumura, 2007; Taguchi, Sato, & Mizumura, 2005). In parallel, electrophysiological recordings from muscle nociceptors show increased sensitivity to mechanical stimulation of the muscle after eccentric exercise (Taguchi et al., 2005). Eccentric exercise results in muscle damage, increased pro-inflammatory cytokine release in muscle, and infiltration of inflammatory cells to muscle (Alvarez et al., 2010; Dessem et al., 2010; Fujii et al., 2008). Muscle nociceptors also show increased expression of the neuropeptide calcitonin gene-related peptide (CGRP) and of the ATP-receptor P2X3 (Dessem et al., 2010). Release of pro-inflammatory cytokines, neuropeptides, or ATP in response to eccentric exercise can directly activate and alter excitability of muscle nociceptors to result in mechanical hypersensitivity. In particular, the following

potential mediators could be directly related to the observed behavioral increases in hypersensitivity – heat, decreases in pH, lactic acid, or ATP. Each of these mediators can bind specific receptors to produce their effects – transient receptor potential vanilloid receptor (TRPV1), acid sensing ion channels (ASICs), or purinergic receptors (P2X). Pharmacological blockade of TRPV1 channels (heat-effect) or ASICs (decreased pH/lactic acid-effect) prevents the eccentric exercise-induced mechanical hypersensitivity (Fujii et al., 2008). However, recording from nociceptive afferents after eccentric exercise shows no changes in response to decreases in pH or lactic acid, ATP, or heat (Taguchi et al., 2005). This would suggest that while these substances may be released and activate nociceptors their responses are not sensitized. Together the data suggest that eccentric exercise results in release of inflammatory mediators that subsequently activate nociceptors to result in enhanced sensitivity to mechanical stimuli and pain.

Exercise-enhanced pain

Interestingly, Levine and colleagues show that a prior eccentric exercise task enhances the response to a subsequent injection of the inflammatory mediator prostaglandin E-2 (PGE-2) (Alvarez et al., 2010), sometimes termed a priming effect. Specifically, after the hyperalgesia to eccentric exercise resolves, intramuscular injection of PGE-2 results in a long-lasting hyperalgesia (days) when compared to injection of PGE-2 without eccentric exercise (hours) (Alvarez et al., 2010). Reduction of the intracellular messenger protein kinase Cε (PKCε) or the inflammatory cytokine receptor to interleukin-6 in nociceptors (with oligonucleotide antisense injected intrathecally) prevents the enhanced effect of eccentric exercise-induced hyperalgesia to PGE2. This suggests that eccentric exercise results in a sensitization of nociceptors that involves IL-6 receptors and activation of PKCε so that a subsequent noxious stimulus results in an enhanced pain response.

Similarly, a non-damaging exercise stimulus in combination with a subthreshold muscle insult produces mechanical hypersensitivity. In this model the non-damaging exercise task was 2 hours of running wheel activity where animals were encouraged to continuously run (Sluka, Danielson, Rasmussen, & Dasilva, 2012; Sluka & Rasmussen, 2010; Yokoyama et al., 2007). This task alone did not produce mechanical hypersensitivity (Sluka & Rasmussen, 2010). However, when combined with a subthreshold muscle insult that does not produce hypersensitivity on its own, mechanical hypersensitivity develops 24 hours later (Sluka et al., 2012; Sluka & Rasmussen, 2010; Yokoyama et al., 2007) (Figure 25.3A). The muscle insult used in these studies was either two intramuscular pH 5.0 acid injections or intramuscular 0.03% carrageenan. These studies subsequently showed that the exercise task could be given up to 2 hours before or up to 2 hours after the muscle insult, and a 30-minute exercise task could produce the same enhanced hypersensitivity (Sluka et al., 2012; Sluka & Rasmussen, 2010). Further, while the effect occurs in both male and female mice, when 0.03% carrageenan is combined with the 2-hour fatigue task, female mice show greater hypersensitivity (Sluka & Rasmussen, 2010); ovariectomy prevents the enhanced hypersensitivity observed in females so that now the hyperalgesia is similar to that observed in males (Sluka & Rasmussen, 2010). Interestingly, there is no observable muscle damage, and no change in pH, lactic acid, creatinine kinase, phosphate, or oxygen in the muscle immediately after the exercise task. Although a 10% fatigue occurs with the 2-hour exercise task, no fatigue occurs with the 30-minute exercise task. Together these data suggest that non-damaging exercise can enhance pain to a subthreshold muscle insult and that peripheral metabolic factors related to fatiguing exercise do not mediate this enhanced hyperalgesia.

Using this model of exercise-induced pain, changes indicative of enhanced neuron excitability are observed in the central nervous system. Specifically, the 2-hour exercise task increases

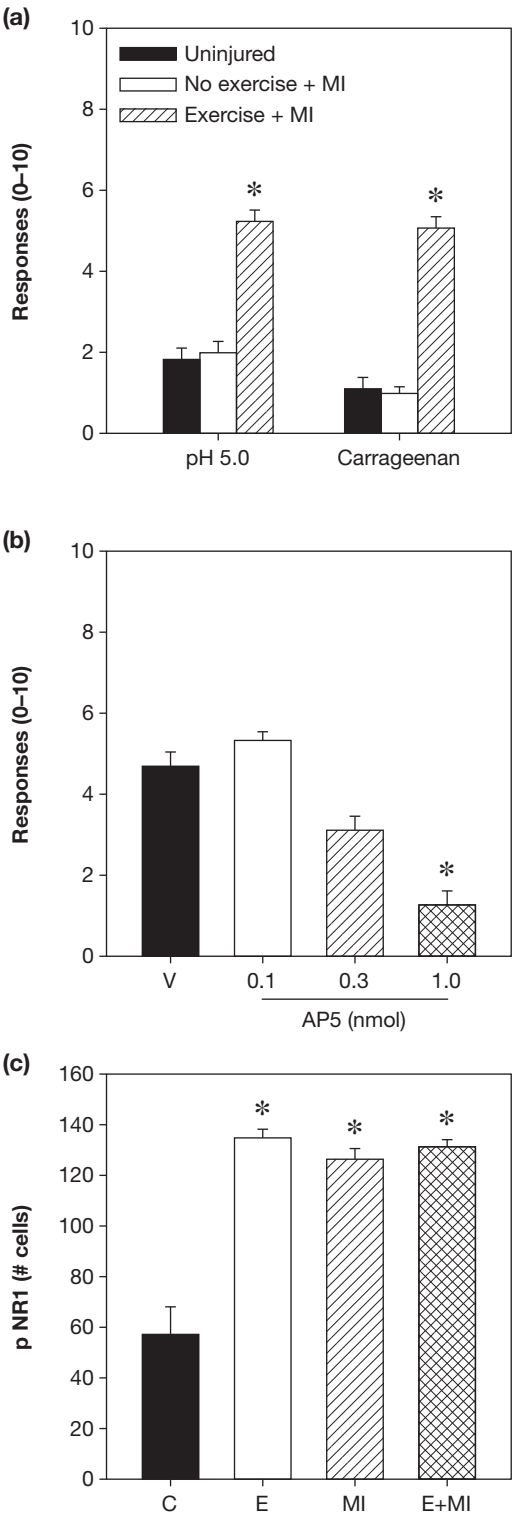

Figure 25.3 (a) Number of withdrawals to repeated mechanical stimuli (0.4 mN) applied to the paw of mice in uninjured animals, in animals that received a subthreshold muscle insult of either two injections of pH 5.0 into the gastrocnemius muscle or 0.03% carrageenan, or animals that received a 2-hour exercise task prior to the subthreshold muscle insult. Increased mechanical sensitivity occurred in the group that received muscle insult in combination with exercise (⋆, $p<0.05$). (b) Microinjection of an NMDA receptor antagonist (AP5) into the caudal raphe nuclei (nucleus raphe pallidus and obscurus) during the exercise task prevents the development of mechanical sensitivity to the combination of exercise with a subthreshold muscle insult (0.03% carrageenan). ⋆, $p<0.05$. (c) The number of cells in the caudal raphe (NRM, NRO, and NRP) labeled for p-NR1 (NMDA receptor phosphorylation) are significantly increased after the exercise task (E), after the subthreshold muscle insult (MI; 0.03% carrageenan), and after the exercise task in combination with the subthreshold muscle insult (E+MI). Data are mean ± S.E.M. ⋆, $p<0.05$ (figures modified from data presented in Sluka, Danielson, Rasmussen, & daSilva, 2012; Sluka & Rasmussen, 2010).

activation of cells in the caudal raphe nuclei of the medulla–nucleus raphe magnus (NRM), nucleus raphe pallidus (NRO), and nucleus raphe obscurus (NRO) – as measured by c-fos expression (Sluka & Rasmussen, 2010). In addition to inhibiting pain, the caudal raphe nuclei are also involved in enhancement of pain (Porreca, Ossipov, & Gebhart, 2002; Tillu, Gebhart, & Sluka, 2008) (Figure 25.3B) and thus may underlie the exercise-induced pain in this model. The NRM is classically thought to modulate pain while the NRO and NRP are classically thought to modulate motor activity. However, the NRM can modulate motor responses and the NRO/NRP can respond to noxious stimuli. Thus, these nuclei may be ideal for an interaction between exercise and pain.

Glutamate is a major excitatory neurotransmitter within the nervous system and the NMDA glutamate receptor plays a critical role in pain modulation within the caudal raphe. In the caudal raphe, overexpression of NMDA glutamate receptors (NR1-subunit) enhances mechanical hypersensitivity in uninjured animals (da Silva, Walder, Davidson, Wilson, & Sluka, 2010) and blockade of NMDA glutamate receptors in the caudal raphe during the 2-hour exercise task prevents the development of exercise-induced muscle pain (Sluka et al., 2012). Phosphorylation of the NMDA receptor (p-NR1; increasing cAMP production) in nociceptive neurons enhances NMDA currents, enhances channel conductance, and increases trafficking of the NMDA receptor complex to the cell membrane (Chen & Roche, 2007; Ehlers, Tingley, & Huganir, 1995; Lin, Wu, & Willis, 2002) – thus phosphorylation of NR1 enhances neuron excitability. In response to the exercise task, there is enhanced p-NR1 in the caudal raphe nuclei, which occurs immediately after the 2-hour exercise task, 2 hours after the 2-hour exercise task, or immediately after the 30-minute exercise task (Sluka et al., 2012) (Figure 25.3C). Together these data suggest increased activation and sensitization of NMDA receptors on excitatory neurons in the caudal raphe are necessary for development of exercise-induced pain.

Future directions

Future research examining exercise-induced pain should focus on potential brain sites where exercise could enhance neuron hyperexcitability (as shown in the RVM) and the underlying neurotransmitters and receptors involved in this process. Exercise-induced pain could also involve changes peripherally and could enhance pain through fatigue-related factors, or through factors released from exercising muscle, either locally or systemically (as shown with IL-6). The role of the sympathetic system in modulating pain behaviors is well known, as is the role of the sympathetic system in exercise effects. Thus, future experiments should determine if changes in the sympathetic system underlie the effects of exercise-induced pain, as well as exercise-induced analgesia.

Summary

Animal models have begun to decipher the underlying mechanisms of exercise-induced analgesia and exercise-induced pain. Evidence suggests that exercise-induced analgesia involves activation of central opioid receptors, utilizes serotonin, and may normalize nociceptor hypersensitivity by modulating ion channels and growth factors. Regular exercise also produces neurogenesis in the hippocampus, which may underlie the improvements in learning and depressive symptoms. Eccentric exercise results in pain and enhances the nociceptive response to subsequent stimuli. Evidence suggests that changes associated with muscle damage and inflammation likely mediate the pain response – this includes increases in pro-inflammatory cytokines, ATP, and neuropeptides after eccentric exercise. Further, a subthreshold muscle insult combined with a non-

damaging exercise task results in enhanced mechanical hypersensitivity that involves neuron excitability in the central nervous system. Thus, exercise has multiple effects and can modulate pain by either preventing or reversing pain, or by enhancing pain. Understanding the underlying mechanisms of exercise-induced analgesia and exercise-induced pain can assist with management of individuals with chronic pain.

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