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SYMPOSIUM REVIEW

Does exercise increase or decrease pain? Central mechanisms underlying these two phenomena

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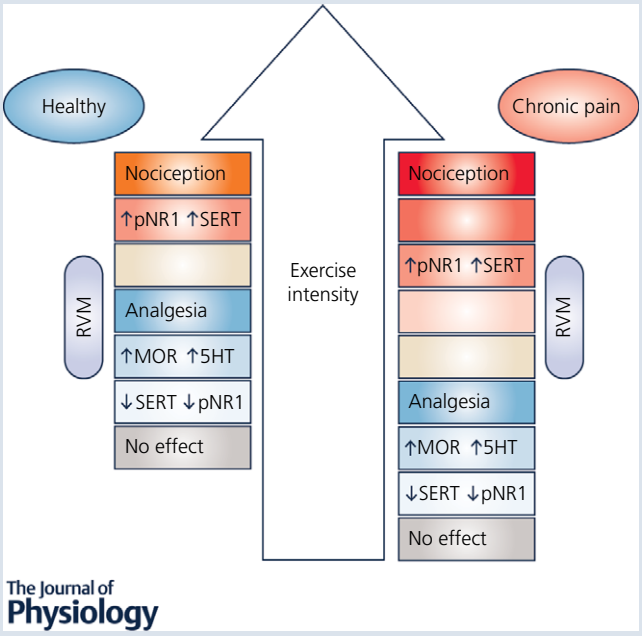

Abstract Exercise is an integral part of the rehabilitation of patients suffering a variety of chronic musculoskeletal conditions, such as fibromyalgia, chronic low back pain and myofascial pain. Regular physical activity is recommended for treatment of chronic pain and its effectiveness has been established in clinical trials for people with a variety of pain conditions. However, exercise can also increase pain making participation in rehabilitation challenging for the person with pain. Animal models of exercise-induced pain have been developed and point to central mechanisms underlying this phenomena, such as increased activation of NMDA receptors in pain-modulating areas. Meanwhile, a variety of basic science studies testing different exercise protocols, show

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exercise-induced analgesia involves activation of central inhibitory pathways. Opioid, serotonin and NMDA mechanisms acting in rostral ventromedial medulla promote analgesia associated with exercise. This review explores and discusses current evidence on central mechanisms underlying exercised-induced pain and analgesia.

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Abstract figure legend Summary of the mechanisms in the rostral ventromedial medulla underlying the nociceptive and analgesic effects as exercise intensity increases. Differences between healthy and chronic pain patients is demonstrated by the lower intensity level of exercise necessary to produce both analgesia and nociception in the chronic pain patients.

Abbreviations 5-HT, serotonin; NMDA, *N*-methyl-D-aspartate; NRM, nucleus raphe magnus; NRO, nucleus raphe obscurus; NRP, nucleus raphe pallidus; PAG, periaqueductal grey; RVM, rostral ventromedial medulla.

Introduction

Exercise not only reduces pain perception, but also has effects on mental health, such as mood elevation and reduction of stress and depression, which are often associated with chronic pain conditions (Bement & Sluka, 2016). Exercise is a powerful tool in the management of those conditions, especially considering the Centers for Disease Control and Prevention's new opioid-prescribing guidelines, recommending a focus toward non-opioid and non-pharmacological treatments (Dowell *et al.* 2016). In healthy subjects, exercise increases thresholds for experimentally induced pain (Bement & Sluka, 2016). In clinical populations, exercise promotes analgesia in conditions such as low back pain, osteoarthritis, myofascial pain, chronic fatigue syndrome and fibromyalgia (Bement & Sluka, 2016). However, exercise has also been shown to increase pain in experimental and clinical settings, especially when a musculoskeletal pain condition is already established (Staud *et al.* 2005). Patients with fibromyalgia show greater increases in pain and perceived fatigue after performing a physically fatiguing task when compared to healthy subjects (Dailey *et al.* 2015). This increased pain to exercise in chronic pain patients is often a barrier to regular exercise, leading to a sedentary lifestyle that worsens the painful conditions and makes treatment even more difficult (Damsgard *et al.* 2010). Interestingly, contraction of painful muscles fails to activate pain inhibitory mechanisms in myalgia and fibromyalgia patients while it increases pressure pain thresholds in healthy subjects (Lannersten & Kosek, 2010). Exercise is, in most cases, one of the best approaches for managing chronic pain conditions, so understanding the mechanisms of both pain and analgesia induced by exercise is important to better define physical activity-related treatment protocols for people with pain.

Centrally, the rostral ventromedial medulla (RVM) is a key relay for pain modulation, playing a major role in exercise-induced pain and analgesia (Sluka & Rasmussen, 2010; Stagg *et al.* 2011; Sluka *et al.* 2012, 2013). Within the caudal brainstem, the nucleus raphe magnus (NRM), nucleus raphe obscurus (NRO) and nucleus raphe pallidus (NRP) are involved in modulation of both pain and motor outputs (Fields *et al.* 1995; Porreca *et al.* 2002; Zhuo *et al.* 2002; Da Silva *et al.* 2010*a*), making these nuclei potential links between physical activity and pain perception. Other pain-processing areas such as the periaqueductal grey (PAG) (Mathes & Kanarek, 2006; Stagg *et al.* 2011) and cortical areas (de Oliveira *et al.* 2010) have been implicated in exercise-induced pain and analgesia. *N*-Methyl-D-aspartate (NMDA) glutamate receptors in the RVM also play a key role in chronic muscle pain, including exercise-induced pain (Da Silva *et al.* 2010*a*; Sluka *et al.* 2012). Phosphorylation of the NR1 subunits of NMDA receptors in the caudal brainstem mediates the hyperalgesia in animal models of chronic musculoskeletal pain and exercise-induced pain (Sluka *et al.* 2012). On the other hand, opioidergic and serotonergic neurons are both expressed in the RVM (Basbaum & Fields, 1984) and there is recent evidence for the involvement of these systems in the analgesia induced by exercise (Stagg *et al.* 2011; Bobinski *et al.* 2015). Figure 1 illustrates the known mechanisms of exercise-induced pain and analgesia.

This review discusses animal studies that explore the underlying central mechanisms of both exercise induced pain and analgesia from different exercise protocols. We discuss the evidence with respect to type, duration, and frequency of exercise using different pain models.

Fatiguing exercise enhances pain

Pain and fatigue interactions. Clinically, physical fatigue is a common complaint in chronic musculoskeletal pain conditions, while chronic pain is common in chronic fatigue conditions (Vierck *et al.* 2001; Whiteside *et al.* 2004; Staud *et al.* 2005; Kadetoff & Kosek, 2007). The overlap

between muscle fatigue and pain syndromes suggests an interaction between fatigue and pain such that fatigue may enhance pain. Pain may be a factor in reducing adherence to regular exercise and rehabilitation, leading the patient to a sedentary life (Damsgard *et al.* 2010). It is proposed that muscle fatigue promotes changes in central nervous system function that cannot be explained only in the muscle itself (Davis & Bailey, 1997).

Fatiguing exercise-induced pain models. Several animal models were developed to better understand the interaction between muscle fatigue and pain. For example, when an acute bout of running wheel activity (2 h) was combined with intramuscular doses of saline of different pH (pH 4.0, 5.0, 6.0 or 7.2), enhanced hyperalgesia developed bilaterally when the pH 5.0 injections were combined with the fatigue task – no cutaneous hyperalgesia developed with pH 5.0 injections without fatigue (Yokoyama *et al.* 2007). In the initial studies, two 2 h runs prior to the first intramuscular pH 5.0 injection, and two 2 h runs prior to the second intramuscular pH 5.0 injection of acid saline produced an enhanced muscle hyperalgesia. Subsequently it was shown that a single 2 h or 30 min run prior to the subthreshold muscle insult produced the same widespread hyperalgesia (Sluka *et al.* 2012). Despite a 10% reduction in grip force after the 2 h fatiguing exercise, there were no changes in muscle P_{CO_2} ,P_{O_2}, lactate, creatinine kinase MB and phosphate suggesting minimal fatigue metabolites were released during the fatiguing task. These results show that muscle fatigue enhances the probability of the development of mechanical hyperalgesia in mice in response to intramuscular acid saline without muscle histological changes.

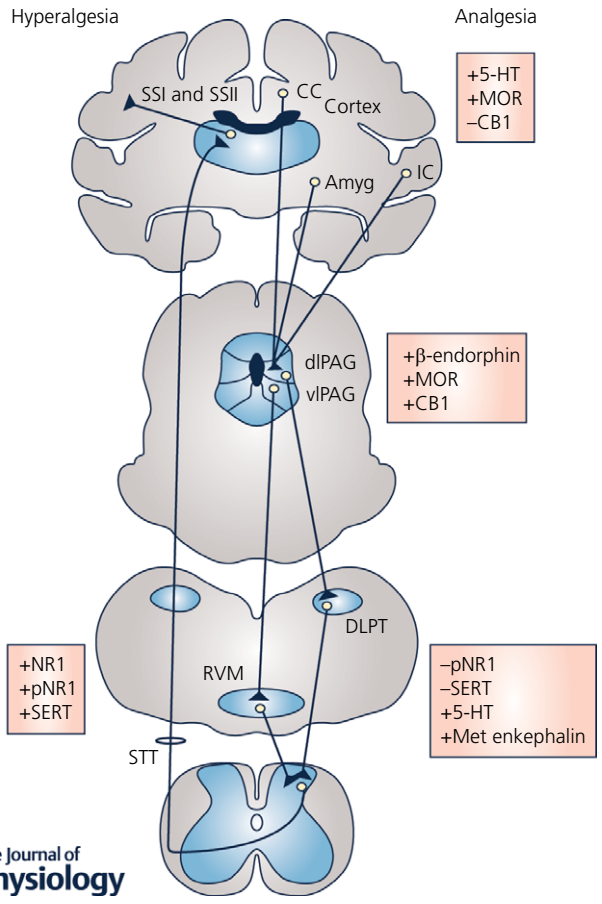

Figure 1. Overview of the underlying mechanisms of exercise-induced pain and analgesia
Known neurotransmitters and receptors that have been shown to be involved at different areas of the central nervous system are listed. The majority of studies have focused on the PAG and the RVM. Increases in serotonin and opioids, and activation of μ-opioid (MOR) and cannabinoid-1 (CB1) receptors are implicated in the exercise-induced analgesia. Further, the normally increased phosphorylation of the NR1 subunit of the NMDA receptor and the increased expression of serotonin transporter (SERT) that is increased by acute exercise are reduced by regular physical activity. +, increase; −, decrease; 5-HT, serotonin; CB1, cannabinoid receptor 1; DH, dorsal horn; MOR, μ-opioid receptor; PAG, periaqueductal grey; p-NR1, phosphorylated NR1; RVM, rostral ventromedial medulla.

Similarly, combining an acute bout of running wheel exercise with a low dose of intramuscular carrageenan injection (0.03%) produced widespread mechanical hyperalgesia. Interestingly, injection of carrageenan either 2 h before or 2 h after the fatigue task produced the same degree of mechanical hyperalgesia of the paw, but not the muscle (Sluka & Rasmussen, 2010). There was also an enhanced hyperalgesia in female mice that was eliminated by ovariectomy, suggesting oestradiol contributed to the development of exercise-induced hyperalgesia in this model.

To test if localized fatigue of the injected muscle was sufficient to induce the hyperalgesia, electrical stimulation of the muscle replaced the whole-body fatiguing task. When combining this electrically induced isometric contraction with pH 5.0 injections there was a significant hyperalgesia that developed in the ipsilateral muscle of male mice and bilaterally in the female mice (Gregory *et al.* 2013). Interestingly, the hyperalgesia was longer lasting and easier to induce in female mice. Hyperalgesia lasted for 2 weeks in males and over 1 month in females. Temporally separating the fatigue task and the muscle insult by 24 h resulted in bilateral hyperalgesia only in female mice, which suggests that the attenuation in response to muscle fatigue does not occur in females. Spatially separating the fatigue task and muscle insult by giving the fatigue task in the muscle contralateral to the injection also resulted in bilateral hyperalgesia only in female mice. In this case, ovariectomy had no effect on the sex differences suggesting oestradiol was not involved in the development of exercise-induced hyperalgesia in this model. It may be that the isometric fatiguing task favours a peripheral mechanism that results in release of fatigue metabolites

like acidic pH in muscle that subsequently activate acid sensing ion channels (ASICs). Indeed, we showed that blockade of ASIC3 prevents and ASIC3 knockout mice do not develop hyperalgesia in this localized fatigue-induced pain model (Gregory *et al.* 2016).

In summary, the studies described above show that fatiguing exercise can enhance hyperalgesia in both male and female mice, and this enhancement is greater in females. Interestingly, whole body exercise produced the female phenotype through oestradiol while the localized fatigue exercise task produces the enhancement in an oestradiol-independent manner. This highlights the complicated nature of nociceptive processing in males and females and suggests that there are task-dependent mechanisms involved in the enhancement of hyperalgesia by exercise.

Central mechanisms of fatiguing exercise-induced hyperalgesia. To examine potential brain sites that underlie exercise-induced hyperalgesia, C-fos immunostaining, as a marker of neuron activation, in the caudal brainstem was investigated. C-fos immunoreactivity showed an increase in the number of cells in the NRM, NRO and NRP after a 2 h running-wheel task, suggesting the caudal raphe might be involved in the development of exercise-induced hyperalgesia (Sluka *et al.* 2012). Since NMDA receptors in the RVM are involved in pain facilitation (Sluka & Rasmussen, 2010), NMDA receptors were blocked in the NRO/NRP during the fatiguing task when combined with 0.03% carrageenan. NMDA receptor blockade during the fatiguing task prevented the development of exercise-induced hyperalgesia. On the other hand, over-expression of the NR1 subunit of the NMDA receptor in the RVM, using a feline immunodeficiency virus expressing the complementary DNA to NR1, produced bilateral mechanical hyperalgesia of the paw and muscle (Da Silva *et al.* 2010*b*), supporting a role for NR1 in development of hyperalgesia. Since phosphorylation of NMDA receptors can enhance neuron excitability (Chen & Roche, 2007), the expression of the phosphorylated NR1 subunit was investigated. In the exercise-induced pain model induced by whole-body running wheel activity combined with 0.03% carrageenan or pH 5.0 injections, there was an increase in the number of cells stained for phosphorylated NR1 in the NRO, NRM, and NRP (Sluka *et al.* 2012; Lima *et al.* 2016). However, there were no differences in the number of p-NR1 labelled cells in the electrically stimulated fatigue task combined with two pH 5.0 injections (Gregory *et al.* 2013), suggesting different mechanisms in this model. Thus, NMDA receptor activation and phosphorylation of NMDA receptors underlies the development of hyperalgesia from a whole-body fatiguing task, but not from a localized fatigue task.

Exercise-induced analgesia

Mechanistic studies in human subjects. Exercise-induced analgesia and the underlying mechanisms have been investigated in several studies using healthy control human subjects and more recently in patient populations. Early studies show that high intensity running, or bicycle ergometry produced analgesia that was reversed by systemic naloxone, suggesting the involvement of opioids in exercise-induced analgesia (Janal *et al.* 1984; Olausson *et al.* 1986). Using a fatiguing isometric contraction, there were decreases in pain thresholds that were accompanied by a reduction in cortical excitability and motor evoked potentials assessed by transcranial magnetic stimulation (Bement *et al.* 2009). High levels of physical activity correlate with greater conditioned pain modulation, which is thought to measure central inhibition, in healthy controls (Geva & Defrin, 2013). Conditioned pain modulation is higher in athletes (Flood *et al.* 2017), and predicts exercise-induced analgesia in healthy subjects (Ellingson *et al.* 2014; Lemley *et al.* 2015; Stolzman & Bement, 2016). In people with osteoarthritis, there were significant increases in pressure pain thresholds in those with normal conditioned pain modulation, and decreases in pressure pain thresholds in those with reduced conditioned pain modulation, suggesting exercise and conditioned pain modulation use similar mechanisms (Fingleton *et al.* 2017). Further, both conditioned pain modulation and exercise-induced hypoalgesia predict greater pain relief 6 months after total knee replacement (Vaegter *et al.* 2017). Lastly, several studies show a reduction in temporal summation, a measure of central excitability, in healthy subjects and patient populations following aerobic and isometric exercise protocols (Koltyn *et al.* 2013; Henriksen *et al.* 2014; Naugle & Riley, 2014; Lemley *et al.* 2015; Stolzman & Bement, 2016; Vaegter *et al.* 2017). Thus, in human subjects there is evidence to support modulation of central nervous system function with enhanced inhibition and reduced excitation. A number of chronic pain conditions are associated with a loss of conditioned pain modulation and increased temporal summation, and thus lack of immediate effects of exercise, or even increases in pain with acute exercise, could be explained by this lack of inhibition and enhanced excitability. It is further likely that repeated regular exercise could restore the loss of conditioned pain modulation.

Animal models of exercise-induced analgesia. The first evidence of centrally mediated mechanisms came from animal studies using swimming as the exercise stimulus in healthy, non-injured rodents (Cooper & Carmody, 1982; Girardot & Holloway, 1984; Koltyn, 2000). Different protocols have been tested, testing different water temperatures and exercise durations (3–10 min). Although longer exercise protocols and colder water

temperatures seemed to produce a stronger analgesic effect (Cooper & Carmody, 1982; O'Connor & Chipkin, 1984), swimming interventions as short as 15 s and in warm water promoted increases in pain thresholds that were at least partially reversed by the opioid antagonist naloxone (Cooper & Carmody, 1982). These studies in healthy animals performed a single bout of the exercise task to produce analgesia. Similar results were found in the formalin model, where as little as 3 min of swimming with a single bout of exercise produced a reduction of pain behaviours that was reversed by naloxone (Carmody & Cooper, 1987; Kuphal *et al.* 2007). Since most studies showed that opioid antagonists only partially reversed exercise-induced analgesia, especially when lower temperatures and longer exercise times were used (Cooper & Carmody, 1982; Girardot & Holloway, 1984; Terman *et al.* 1986), it seems that other mechanisms could be involved, but also conditions other than exercise itself might have influenced the results, like changes in body temperature and stress (Koltyn, 2000).

Forced treadmill running in rodents has also been studied as an exercise stimulus and it excludes the temperature bias from swimming protocols. In a neuropathic pain model, 5 weeks of treadmill running with different frequencies (3 or 5 days week^{-1}) and intensities (10 or 16 m min^{-1} speeds) reversed the injury-induced hyperalgesia in an intensity- but not frequency-dependent manner (Stagg *et al.* 2011). A 5-day treadmill (15–30 min day^{-1}) protocol found similar results in a chronic muscle pain model, with reduction in bilateral mechanical hyperalgesia occurring as soon as immediately after the first session (Bement & Sluka, 2005). In both studies, the effects of exercise were reversed by administration of opioid antagonists, showing evidence of opioid mechanisms underlying the observed exercise-induced analgesia.

While treadmill running allows one to control the degree of physical activity each animal performs, it can produce a stress component (Contarteze *et al.* 2008), which itself could produce analgesia through activation of endogenous opioid and serotonergic systems (Yesilyurt *et al.* 2015), and thus confound interpretation of the results. One way to avoid this is by using running wheels placed in the animals' home cages. Rodents voluntarily exercise in running wheels in a consistent manner (Sherwin, 1998). Recent studies used running wheels to investigate exercise-induced analgesia (Smith & Yancey, 2003; Sluka *et al.* 2013; Grace *et al.* 2016; Leung *et al.* 2016) to isolate the effects of exercise from the influence of other stimuli. Different durations of running wheel activity, ranging from 5 consecutive days to 8 weeks and performed before or after the insult have been tested in different models, such as non-inflammatory chronic muscle pain (Sluka *et al.* 2013), exercise-induced pain (Sluka *et al.* 2013), acute inflammatory muscle pain (Sluka *et al.* 2013), neuropathic pain (Grace *et al.* 2016) and healthy control animals (Kanarek *et al.* 1998; Mathes & Kanarek, 2006). These studies showed the efficacy of running wheel activity in producing analgesia in healthy non-injured animals, but more importantly, in preventing and reversing hyperalgesia in different pain models. There is a duration-dependent effect. Importantly, in the studies investigating different pain models, the running wheels were removed from the cages at the time of induction of the model, and thus these studies compared physically active animals to physically inactive animals. Five days of wheel running prevents secondary, but not primary hyperalgesia, in the exercised-induced pain model and has no effect on hyperalgesia in a chronic non-inflammatory muscle pain model. On the other hand, 6–8 weeks of physical activity prevents both primary and secondary hyperalgesia in an exercise-induced pain model, a chronic non-inflammatory muscle pain model and a neuropathic pain model (Sluka *et al.* 2013; Grace *et al.* 2016), but not in an acute inflammatory pain model (Sluka *et al.* 2013). Further, 2 weeks of voluntary wheel running was unable to reverse hyperalgesia in mouse models of neuropathic pain and formalin-induced acute pain (Sheahan *et al.* 2015), but longer duration wheel running (6 weeks) successfully prevented and reversed hyperalgesia from a neuropathic pain model (Grace *et al.* 2016). Table 1 summarizes the exercise protocols used in animal studies. Thus, multiple different protocols have been used to produce analgesia in uninjured animals and in multiple pain models. These include swimming, treadmill exercise, and wheel running with a single bout of exercise producing analgesia to multiple days and weeks. The analgesic effects depend on duration (days or weeks), with longer training protocols producing more significant results. Further, while protocols applied after the injury can reverse the hyperalgesia, intriguingly making animals physically active prior to the insult prevents the development of the hyperalgesia in both neuropathic pain and muscle pain models.

Central mechanisms involved in exercise-induced analgesia. The RVM comprises, with the PAG and dorsal horn, a descending pain inhibitory system that both facilitates and inhibits noxious stimuli (Porreca *et al.* 2002). Within the RVM, NRM, NRO and NRP are nuclei known to be involved in pain modulation but are also involved in modulation of motor responses, making them potential key areas involved in exercise-induced analgesia mechanisms (Fields *et al.* 2006). Three types of cells exist in the RVM: ON-cells promote nociception when activated, OFF-cells inhibit nociception when activated, and neutral cells do not respond to noxious stimuli (Fields *et al.* 2006). We propose that a shift in the balance between ON- and OFF-cell activation defines hyperalgesia or analgesia from an exercise task. As discussed previously,

Table 1. Summary of studies examining exercise-induced analgesia

Pain model	Exercise intervention	Duration	Effect	Study
Healthy animals	Swimming (15 s to 7.5 min)	Single bout	Reduction in thermal hyperalgesia	Cooper & Carmody (1982)
	Cold water swim 3.5 min, 2°C	Single bout	Reduction in thermal hyperalgesia	Girardot & Holloway (1984)
	Swimming 3 min warm water, 2 min cold water	Single bout	Reduction in thermal hyperalgesia	O'Connor & Chipkin (1984)
	Voluntary wheel running	6 weeks	Reduction in thermal hyperalgesia	Smith & Yancey (2003)
		20 days	Increase in thermal hyperalgesia	Kanarek *et al.* (1998)
		24 h	No effect	
		3 weeks	Reduction in thermal hyperalgesia	Mathes & Kanarek (2006)
	Resistance exercise, 3 sets of 10 repetitions, 3 times week^{-1}	12 weeks	No effect	Galdino *et al.* (2010)
	Resistance exercise, 15 sets of 15 repetitions	1 day	Reduction in mechanical hyperalgesia	Galdino *et al.* (2014*a*)
	Treadmill running, 20 m min^{-1} speed, until fatigue (average of 49.06 $\pm$ 3 min)	Single bout	Reduction in thermal and mechanical hyperalgesia	Galdino *et al.* (2014*b*)
	Cold water swimming, 5 min, 1°C	Single bout	Reduction in thermal hyperalgesia	Vaswani *et al.* (1988)
Formalin test	Voluntary wheel running	2 weeks	No effect	Sheahan *et al.* (2015)
	Cold water swimming	Single bout	Reduction in pain scores and thermal hyperalgesia	Terman *et al.* (1986)
	Swimming 3 min warm water	Single bout	Reduction in pain scores	Carmody & Cooper (1987)
	Swimming 37°C water for 90 min day^{-1}	9 days	Reduction in pain scores	Kuphal *et al.* (2007)
Neuropathic pain	Swimming	18–25 days	Reduction in pain ratings, cold allodynia and thermal hyperalgesia	
	Treadmill running, 3 or 5 days week^{-1}, 16 m min^{-1} speed	5 weeks	Reduction in mechanical hyperalgesia	Stagg *et al.* (2011)
	Voluntary wheel running	6 weeks	Prevention of allodynia	Grace *et al.* (2016)
	Treadmill running, 30 min, 5 days week^{-1}, 10 m min^{-1} speed	2 weeks	Reduction in mechanical hyperalgesia	Bobinski *et al.* (2015)
	Voluntary wheel running	2 weeks	No effect	Sheahan *et al.* (2015)
	30 min day^{-1}, 5 days a week, 8–20 m min^{-1} speed	4 weeks	Reduction in thermal hyperalgesia and mechanical allodynia	Kim *et al.* (2015)
	Treadmill running, 20–60 min day^{-1}, 9 m min^{-1} speed	4 weeks	Reduction in mechanical allodynia	Korb *et al.* (2010)
Chronic muscle pain model	Treadmill running, 15–30 min day^{-1}, 6–10 m min^{-1} speed	5 days	Reduction in mechanical hyperalgesia	Bement & Sluka (2005)
	Voluntary wheel running	8 weeks	Prevention of primary and secondary hyperalgesia	Sluka *et al.* (2013)
		5 days	No effect	
		8 weeks	Prevention of primary and secondary hyperalgesia	Leung *et al.* (2016)
Exercise-enhanced pain	Voluntary wheel running	5 days	Prevention of secondary hyperalgesia	Lima *et al.* (2016)
		8 weeks	Prevention of secondary hyperalgesia	Sluka *et al.* (2013)
		5 days		
Acute muscle inflammation	Voluntary wheel running	8 weeks	No effect	Sluka *et al.* (2013)
		5 days		
Chemically induced nociception	Swimming, 30 min day^{-1}	5 days	Reduction in pain behaviours (abdominal constrictions)	Mazzardo-Martins *et al.* (2010)
	Swimming, 10–30 min day^{-1}	2 weeks	Reduction in pain behaviours (paw-licking) and mechanical hyperalgesia	Martins *et al.* (2017)

NMDA receptors in the RVM play a role in facilitation of nociception with an increase in phosphorylation of the NR1 subunit playing a critical role (Da Silva *et al.* 2010*a*, *b*; Sluka *et al.* 2012). Exercise-induced analgesia promotes the opposite response. Either 5 days or 8 weeks of wheel running prevented the increase in phosphorylation of NR1 in the RVM of mice induced with chronic non-inflammatory muscle pain or exercise-enhanced pain when compared to induced sedentary mice (Sluka *et al.* 2013). These data suggest that regular physical activity reduces facilitation in the caudal brainstem by modulating NMDA receptor function.

There is strong evidence that opioid mechanisms mediate exercise-induced analgesia in both human and animal studies (Koltyn, 2000). Several studies showed that the opioid antagonist naloxone, given systemically, blocks the analgesic effects of swimming and resistance exercise in healthy, uninjured animals (Cooper & Carmody, 1982; O'Connor & Chipkin, 1984; Galdino *et al.* 2010; Mazzardo-Martins *et al.* 2010; Martins *et al.* 2017), and treadmill running in chronic muscle pain (5-day running) and neuropathic pain models (5-weeks running) (Bement & Sluka, 2005; Stagg *et al.* 2011). Subsequent studies show that supraspinal naloxone blocks the analgesia produced by 5 weeks of treadmill running in a neuropathic pain model (Stagg *et al.* 2011). Further, there are increased concentrations of endogenous opioids systemically in both human subjects and in animals (Wildmann *et al.* 1986; Vaswani *et al.* 1988; Debruille *et al.* 1999; Stagg *et al.* 2011; Bidari *et al.* 2016), in the PAG and RVM in animals (Commons, 2003; Stagg *et al.* 2011; Kim *et al.* 2015), and increased μ-opioid receptor expression in the hippocampus of rats after both acute (7 days) and chronic (45 days) treadmill or wheel running (de Oliveira *et al.* 2010). Further, 4–6 weeks of voluntary wheel running produces cross-tolerance to μ-opioid agonists and physical dependence, effects similar to those resulting from chronic use of opioids (Kanarek *et al.* 1998; Smith & Yancey, 2003) and 3 weeks of wheel running attenuates the analgesia from morphine injected into the PAG of rats (Mathes & Kanarek, 2006). Thus, regular physical activity and exercise use central opioid receptors to produce analgesia.

Serotonin (5-HT) has also been implicated in exercise-induced analgesia. One hour of swimming increases 5-HT levels in the brainstem and hypothalamus, while 4 weeks of swimming extended this increase to the cerebral cortex (Dey *et al.* 1992). Similarly, 8 weeks of treadmill running showed increased levels of 5-HT in the midbrain and cortex (Brown *et al.* 1979), and 4 weeks of treadmill running increases 5-HT expression in the RVM (Korb *et al.* 2010). More recently, we extended these studies by examining the role of serotonin in a neuropathic pain model. We show that 2 weeks of low-intensity treadmill running in a neuropathic pain model increased 5-HT levels in the caudal brainstem, decreased expression of the serotonin transporter in the NRM, NRO and NRP, and altered serotonin receptor expression in the brainstem (Bobinski *et al.* 2015). Importantly, in neuropathic pain models there is an increase in serotonin transporter expression and a decrease in 5-HT in the brainstem; 2 weeks of treadmill running reversed these injury-induced changes. Further, systemic depletion of serotonin prevents the analgesia produced by treadmill running in neuropathic pain (Bobinski *et al.* 2015) and by high intensity swimming (30 min to 5 days) in the acetic acid writhing test (Mazzardo-Martins *et al.* 2010). Thus, there is emerging evidence that increases in supraspinal serotonin release, along with reductions in the serotonin transporter, play a significant role in the analgesia produced by regular exercise.

There are reasons to believe that the opioid and serotonergic mechanisms are not independently activated by exercise, but rather they interact to promote analgesia. Serotonergic neurons receive input from endogenous opioid peptides and both coexist in RVM neurons (Fields *et al.* 2006). Further evidence of this interaction is shown by blockade of analgesia from systemic or RVM-injected morphine following systemic depletion of serotonin, or blockade of serotonin receptors in the RVM (Schul & Frenk, 1991; Carruba *et al.* 1992). We recently tested this hypothesis by performing immunohistochemistry for serotonin transporter in μ-opioid receptor knockout mice induced with exercise-induced pain and comparing these to wild-type mice (Lima *et al.* 2016). μ-Opioid receptor knockout and wild-type mice were exposed to 5 days of wheel-running prior to induction the exercise-induced pain model, and compared to sedentary mice. Wheel running prevented the increase in the serotonin transporter in the RVM induced by the muscle insult in wild-type mice. However, in μ-opioid receptor knockout mice, wheel running had no effect on the increased serotonin transporter expression induced by muscle insult. Thus, these data suggest that μ-opioid receptor activation by exercise reduces expression of the serotonin transporter in the caudal brainstem to promote analgesia.

Endocannabinoids in the central nervous system also play a role in exercise-induced analgesia (Dietrich & McDaniel, 2004). Endocannabinoid receptors are present in pain-modulating areas of the brain and spinal cord (Herkenham *et al.* 1991) and activation of endocannabinoid receptors produces analgesia (Dietrich & McDaniel, 2004). Further, exercise increases circulating levels of the endocannabinoid *N*-arachidonylethanolamine in healthy human subjects (Koltyn *et al.* 2014). After both aerobic and resistance exercise tasks, there is an increased expression of the cannabinoid receptor CB_1 in the brain, including the PAG, in healthy uninjured animals. This effect is prevented by systemic and central blockade with cannabinoid

receptor antagonists (AM251 and AM630) (Galdino *et al.* 2014*a*, *b*). Since endocannabinoids have synergistic interactions with opioids to produce antinociception (Navarro *et al.* 1998), one could speculate that the same interaction occurs during exercise-induced analgesia. Thus, there is emerging evidence that endogenous endocannabinoids in the central nervous system contribute to the analgesia produced by regular exercise.

Conclusion

A single bout of fatiguing exercise in the presence of a chronic pain condition can exacerbate pain that is characterized by increased phosphorylation of NMDA receptors in the RVM, suggesting enhanced central facilitation. On the other hand, regular exercise promotes pain relief and is characterized by reduced NMDA receptor phosphorylation, suggesting reduced central facilitation. Further regular exercise reduces serotonin transporter expression, increases serotonin levels, and increases opioids in central inhibitory pathways including the PAG and RVM, suggesting exercise utilizes our endogenous inhibitory systems to reduce pain (Fig. 1). We propose that there is a balance between inhibition and excitation in the central nervous system that determines whether exercise will promote analgesia or promote pain. Several factors, such as fitness level, physical activity levels, and state of the injury or pain condition influence this balance. The great majority of the animal studies examining pain mechanisms are performed in physically inactive animals, and nearly all the exercise studies are focused on aerobic exercise. Further, there is no consistency regarding intensity, duration, frequency or exercise type making interpretation difficult. Understanding the mechanisms underlying different forms of exercise, as well as the different intensities and duration of exercise that produce analgesia, will be critically important to translate animal studies to human subjects, particularly those with acute and chronic pain.

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Additional information

Competing interests

All authors declare no conflict of interest

Author contributions

L.V.L: designed, wrote and reviewed the manuscript; T.S.S.A.: wrote and reviewed the manuscript; K.A.S.: designed, wrote and reviewed the manuscript. All authors contributed to the writing of the manuscript and approved with the final version. All designated authors qualify for authorship, and all those who qualify for authorship are listed.

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