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## Exercise induced hypoalgesia in pain-free and chronic pain populations

*State of the art and future directions*

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## Focus Article

# Exercise-Induced Hypoalgesia in Pain-Free and Chronic Pain Populations: State of the Art and Future Directions

David Rice,<sup>\*,†</sup> Jo Nijs,<sup>‡,§,¶</sup> Eva Kosek,<sup>||,\*</sup> Timothy Wideman,<sup>††</sup> Monika I Hasenbring,<sup>‡‡</sup> Kelli Koltyn,<sup>§§</sup> Thomas Graven-Nielsen,<sup>¶¶</sup> and Andrea Polli<sup>‡,§,¶,|||</sup>

<sup>\*</sup>Health and Rehabilitation Research Institute, Auckland University of Technology, Auckland, New Zealand

<sup>†</sup>Waitemata Pain Services, Department of Anaesthesiology and Perioperative Medicine, Waitemata District Health Board, Auckland, New Zealand

<sup>‡</sup>Pain in Motion International Research Group<sup>#</sup>

<sup>§</sup>Department of Physiotherapy, Human Physiology and Anatomy, Faculty of Physical Education & Physiotherapy, Vrije Universiteit Brussel, Brussels, Belgium

<sup>¶</sup>Department of Physical Medicine and Physiotherapy, University Hospital Brussels, Brussels, Belgium

<sup>||</sup>Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden

<sup>\*\*</sup>Stockholm Spine Center, Löwenströmska Hospital, Upplands Väsby, Sweden

<sup>††</sup>School of Physical and Occupational Therapy, McGill University, Montreal, Canada

<sup>‡‡</sup>Department of Medical Psychology and Medical Sociology, Faculty of Medicine, Ruhr-University of Bochum, Bochum, Germany

<sup>§§</sup>Department of Kinesiology, University of Wisconsin-Madison, Madison, Wisconsin

<sup>¶¶</sup>Center for Neuroplasticity and Pain (CNAP), Department of Health Science and Technology, Faculty of Medicine, Aalborg University, Aalborg, Denmark

<sup>|||</sup>Research Foundation – Flanders (FWO), Brussels, Belgium

**Abstract:** Exercise is considered an important component of effective chronic pain management and it is well-established that long-term exercise training provides pain relief. In healthy, pain-free populations, a single bout of aerobic or resistance exercise typically leads to exercise-induced hypoalgesia (EIH), a generalized reduction in pain and pain sensitivity that occurs during exercise and for some time afterward. In contrast, EIH is more variable in chronic pain populations and is more frequently impaired; with pain and pain sensitivity decreasing, remaining unchanged or, in some cases, even increasing in response to exercise. Pain exacerbation with exercise may be a major barrier to adherence, precipitating a cycle of physical inactivity that can lead to long-term worsening of both pain and disability. To optimize the therapeutic benefits of exercise, it is important to understand how EIH works, why it may be impaired in some people with chronic pain, and how this should be addressed in clinical practice. In this article, we provide an overview of EIH across different chronic pain conditions. We discuss possible biological mechanisms of EIH and the potential influence of sex and psychosocial factors, both in pain-free adults and, where possible, in individuals with chronic pain. The clinical implications of impaired EIH are discussed and recommendations are made for future research, including further exploration of individual differences in EIH, the relationship between exercise dose and EIH, the efficacy of combined treatments and the use of alternative measures to quantify EIH.

**Perspective:** This article provides a contemporary review of the acute effects of exercise on pain and pain sensitivity, including in people with chronic pain conditions. Existing findings are

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Address reprint requests to Dr David Rice, Health and Rehabilitation Research Institute, Auckland University of Technology, Private Bag 92006, Auckland, 1142, New Zealand. E-mail: [david.rice@aut.ac.nz](mailto:david.rice@aut.ac.nz)  
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*critically reviewed, clinical implications are discussed, and recommendations are offered for future research.*

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**Key words:** *Aerobic exercise, resistance exercise, hypoalgesia, chronic pain, hyperalgesia.*

Chronic pain is a pervasive condition, affecting an estimated 20% of all people worldwide.<sup>10,13,48</sup> It is typically defined as pain persisting beyond the expected time of healing (eg, after injury or surgery), or ongoing pain lasting for  $\geq 3$  months.<sup>132</sup> Exercise is considered an important component of effective chronic pain management. It has a number of potential benefits, including improving physical function<sup>84</sup> and mood,<sup>54</sup> as well as decreasing the risk of secondary health problems including cardiovascular, metabolic, bone, and neurodegenerative disorders.<sup>111</sup> Importantly for those suffering from chronic pain, exercise can also have a pain-relieving effect. There is a substantial and growing body of evidence that long-term exercise training can provide pain relief across many different chronic pain conditions, including fibromyalgia and chronic widespread pain,<sup>8,90</sup> osteoarthritis (OA),<sup>51,104</sup> chronic low back pain,<sup>49,144</sup> chronic neck pain,<sup>47</sup> and neuropathic pain.<sup>11,31</sup> Although regular exercise has many benefits in people with chronic pain conditions, the pain response to exercise can be variable in these populations,<sup>5,79,124</sup> particularly in the initial stages of training, where short-term exacerbations in pain can occur in some people.<sup>42,117,146,147,158,162</sup>

In healthy, pain-free participants, the typical response to an acute bout of exercise is a period of hypoalgesia. Exercise-induced hypoalgesia (EIH) is characterized by a decrease in sensitivity to painful stimuli, with variable duration, lasting  $\leq 30$  minutes after a single bout of exercise.<sup>65,101</sup> In laboratory-based research studies, EIH is usually quantified by applying a painful stimulus to the body before and after a defined dose of exercise and measuring changes in pain sensitivity, such as increased pain thresholds or decreased pain intensity to a standardized painful stimulus. Using these methods, EIH has been consistently demonstrated in healthy, pain-free populations,<sup>101</sup> with both aerobic and resistance exercise attenuating several different measures of pain sensitivity, including pressure, thermal, and electrocutaneous pain thresholds,<sup>101</sup> pressure pain tolerance,<sup>137</sup> and temporal summation of thermal<sup>14</sup> and mechanical pain.<sup>141</sup> Aerobic exercise more consistently elicits EIH at higher intensities (approximately 200 W or 70% maximal oxygen consumption).<sup>68</sup> Both dynamic and isometric resistance exercise induce EIH, with isometric loads as low as 10 to 30% of maximum voluntary contraction capable of inducing EIH, provided the duration of contraction is sufficient<sup>53</sup>—often held to exhaustion or for  $\leq 5$  minutes.<sup>71,77,131</sup> Aerobic exercise typically leads to widespread EIH while resistance exercise may lead to reduced pain sensitivity close to the site of muscle contraction (local EIH) and at remote sites of the body, distant to the contracting muscle (global EIH).<sup>71,77,143</sup>

The acute effect of exercise on pain sensitivity is more variable in chronic pain populations, with some studies demonstrating no change or even increased pain sensitivity in response to a single bout of exercise.<sup>15,41,56,66,71,77,95,96,119,123,131,147,158</sup> Increased pain sensitivity after exercise (ie, exercise-induced hyperalgesia) is thought to underlie flares in pain that can occur with exercise in some chronic pain populations.<sup>1,157,162</sup> In turn, pain exacerbation in response to exercise is likely to be a major barrier to adherence,<sup>55,57,117</sup> precipitating a cycle of physical inactivity that may lead to long-term worsening of both pain and disability. Thus, to optimize the therapeutic benefits of exercise, it is important to understand how EIH works, why it may be impaired in some people with chronic pain and how this should be addressed in clinical practice.

The aim of this article was to provide a contemporary review of EIH in response to acute exercise, including in people with chronic pain. We begin by giving an overview of studies that have used a standardized exercise protocol and compared the EIH response in people with chronic pain and pain-free controls. Next, we explore possible biological mechanisms of EIH and the potential influence of sex and psychosocial factors on the EIH response—both in pain-free adults, and, where possible, in chronic pain populations. The clinical implications of impaired EIH are discussed and recommendations are made for future research on EIH, including in people with chronic pain.

## Overview of EIH in People With Chronic Pain

To provide an overview of studies exploring EIH in chronic pain conditions, a keyword list was developed (eg, exercise, aerobic, resistance, isometric, isotonic, hypoalgesia, analgesia, hyperalgesia, chronic pain, pain threshold, pain sensitivity, quantitative sensory testing). An initial check of the keyword list was made against several databases (CINAHL, MEDLINE, and Scopus) and, where appropriate, additional keywords were added and modifications to the keyword list were made. This was supplemented with a review of the bibliographies of past review articles on EIH, as well as the personal libraries of the contributing authors. Studies that compared the effects of a standardized, single bout of exercise on a measure of pain or pain sensitivity between a control group and a group with chronic pain are presented in [Table 1](#), with key findings summarized herein.

Compared with pain-free adults, several studies have demonstrated reduced EIH or, in some cases, exercise-induced hyperalgesia in response to either aerobic or

**Table 1. Acute Exercise-Induced Change in Pain Sensitivity or Pain Intensity After a Single Bout of Exercise in Studies Comparing Healthy Controls With Individuals With Chronic Pain**

PAIN CONDITION	FIRST AUTHOR, REFERENCE	EXERCISE TYPE	DOSE	PAIN MEASURE	CONTROL GROUP		PAIN GROUP	
					LOCAL EFFECT	GLOBAL EFFECT	LOCAL EFFECT	GLOBAL EFFECT
Chronic low back pain	Meeus <sup>96</sup>	Aerobic (cycle ergometer)	Incremental 20–130 W, 17–29 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		↓
Chronic neck pain	Christensen <sup>18</sup>	Resistance (dynamic shoulder abduction)	6 × 6 repeated bilateral shoulder abductions against gravity to a 140 degree angle	Pressure pain threshold (kPa)	↓	~	↑*	↑*
Chronic neck pain	Christensen <sup>18</sup>	Resistance (dynamic shoulder abduction)	6 × 6 repeated bilateral shoulder abductions against gravity to a 140 degree angle	Pain intensity (VAS)	~	N/A	↑*	N/A
Chronic wide-spread pain (chronic fatigue syndrome)	Whiteside <sup>158</sup>	Aerobic (treadmill)	Incremental incline, 5 km/h, 15 minutes	Pressure pain threshold (s)		↓		↑*
Chronic wide-spread pain (chronic fatigue syndrome)	Meeus <sup>96</sup>	Aerobic (cycle ergometer)	Incremental 20–130 W, 3–29 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		↑*
	Van Oosterwijk <sup>146</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min up to 75% HR <sub>max</sub> , approximately 3–5 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		↑*
	Van Oosterwijk <sup>146</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min up to 75% HR <sub>max</sub> , approximately 3–5 minutes	Pain intensity (VAS)		~		↑*
	Van Oosterwijk <sup>146</sup>	Aerobic (cycle ergometer)	Self-paced up to 80% of AT, approximately 5–9 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		↑*
	Van Oosterwijk <sup>146</sup>	Aerobic (cycle ergometer)	Self-paced up to 80% of AT, approximately 5–9 minutes	Pain intensity (VAS)		~		↑*
	Van Oosterwijk <sup>147</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 3–4 minutes	Pain intensity (VAS)		↓		~*
Chronic wide-spread pain (chronic fatigue syndrome)	Malfliet <sup>92</sup>	Aerobic (cycle ergometer)	50 W at 55–65 rpm, 12 minutes	Temporal summation of pressure pain (VAS)		↓		~
Chronic wide-spread pain (Gulf War syndrome)	Cook <sup>21</sup>	Aerobic (cycle ergometer)	70% VO <sup>2</sup> max 50–60 rpm, 30 minutes	Heat pain threshold (°C)		↓		↓
	Cook <sup>21</sup>	Aerobic (cycle ergometer)	70% VO <sup>2</sup> max, 50–60 rpm, 30 minutes	Pressure pain threshold (s)		↓		↓
	Cook <sup>21</sup>	Aerobic (cycle ergometer)	70% VO <sup>2</sup> max, 50–60 rpm, 30 minutes	Suprathreshold heat pain intensity (NRS)		~		↑*
Chronic wide-spread pain Fibromyalgia	Ghafouri <sup>42</sup>	Resistance (dynamic arm movement)	Repeated 30 cm movement of 11.8 g peg back and forth at 1.3 Hz for 20 minutes	Pain intensity (NRS)	~	N/A	↑*	N/A
	Vierck <sup>149</sup>	Aerobic (treadmill)	Incremental increase in incline, speed to exhaustion, approximately 11–14 minutes					

(continued on next page)

Table 1. Continued

PAIN CONDITION	FIRST AUTHOR, REFERENCE	EXERCISE TYPE	DOSE	PAIN MEASURE	CONTROL	GLOBAL	PAIN	GLOBAL
					GROUP LOCAL EFFECT	EFFECT	GROUP LOCAL EFFECT	EFFECT
Fibromyalgia	Vierck <sup>149</sup>	Aerobic (treadmill)	Incremental increase in incline, speed to exhaustion, approximately 11–14 minutes	Heat pain aftersensations (VAS)		↓		↑*
	Staud <sup>124</sup>	Aerobic (arm ergometer)	60 W, 60 rpm up to 15 minutes or exhaustion	Pain intensity (VAS)		~		~
	Staud <sup>124</sup>	Aerobic (arm ergometer)	60 W, 60 rpm up to 15 minutes or exhaustion	Suprathreshold heat pain (VAS)		↓		↓
	Staud <sup>124</sup>	Aerobic (arm ergometer)	60 W, 60 rpm up to 15 minutes or exhaustion	Pressure pain threshold (kPa)		↓		↓
	Kosek <sup>71</sup>	Resistance (Isometric knee extension)	25% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓		↑*	
	Staud <sup>123</sup>	Resistance (isometric gripping)	30% of MVC, 90 seconds	Pressure pain threshold (kPa)	↓	↓	↑*	↑*
	Staud <sup>123</sup>	Resistance (isometric gripping)	30% of MVC, 90 seconds	Suprathreshold heat pain intensity (VAS)	↓	↓	↑*	↑*
	Kadettoff <sup>63</sup>	Resistance (isometric knee extension)	10–15% of MVC, up to 15 minutes or to exhaustion	Pressure pain threshold (kPa)	~	↓	~	↓
	Lannersten <sup>77</sup>	Resistance (isometric shoulder rotation)	20–25% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	~*	~*
	Lannersten <sup>77</sup>	Resistance (isometric knee extension)	20–25% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↑*	~*
Local shoulder myalgia	Ge <sup>41</sup>	Resistance (isometric shoulder abduction)	Hold shoulder at 90 degrees of abduction against gravity to exhaustion	Pressure pain threshold (kPa)	↓	~	~*	↑*
	Tour <sup>131</sup>	Resistance (isometric knee extension)	30% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	nc	↓	N/A	↓*
	Lannersten <sup>77</sup>	Resistance (isometric shoulder rotation)	20–25% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↑*	↑*
	Lannersten <sup>77</sup>	Resistance (isometric knee extension)	20–25% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↓	↓
Osteoarthritis	Ghafouri <sup>42</sup>	Resistance (Dynamic arm movement)	Repeated 30-cm movement of 11.8 g peg at 1.3 Hz for 20 minutes	Pain intensity (NRS)	~	N/A	↑*	N/A
	Kosek <sup>73</sup>	Resistance (isometric knee extension)	50% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↓	↓
Osteoarthritis	Burrows <sup>15</sup>	Resistance (isotonic upper limb exercises)	60% of 1 RM, 3 sets of 10 contractions	Pressure pain threshold (kg/cm <sup>2</sup> )	↓	↓	↓	↓
	Burrows <sup>15</sup>	Resistance (isotonic upper limb exercises)	60% of 1 RM, 3 sets of 10 contractions	Pressure pain tolerance (seconds)	N/A	~	N/A	~
	Burrows <sup>15</sup>	Resistance (isotonic lower limb exercises)	60% of 1 RM, 3 sets of 10 contractions	Pressure pain threshold (kg/cm <sup>2</sup> )	↓	↓	~	~
	Burrows <sup>15</sup>	Resistance (isotonic lower limb exercises)	60% of 1 RM, 3 sets of 10 contractions	Pressure pain tolerance (s)	~	N/A	~	N/A
Painful diabetic neuropathy	Knauf <sup>66</sup>	Resistance (isometric gripping)	25% of MVC, 3 minutes	Suprathreshold heat pain (NRS)	↓	N/A	~*	N/A

(continued on next page)

Table 1. Continued

PAIN CONDITION	FIRST AUTHOR, REFERENCE	EXERCISE TYPE	DOSE	PAIN MEASURE	CONTROL	PAIN		
					GROUP LOCAL EFFECT	GLOBAL EFFECT	GROUP LOCAL EFFECT	GLOBAL EFFECT
	Knauf <sup>66</sup>	Resistance (isometric gripping)	25% of MVC, 3 minutes	Heat pain temporal summation ( $\Delta$ NRS)	↓	N/A	~*	N/A
Rheumatoid arthritis	Fridén <sup>37</sup>	Resistance (isometric knee extension)	30% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↓	↓
	Löfgren <sup>88</sup>	Resistance (isometric knee extension)	30% of MVC, up to 5 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↓	↓
Whiplash-associated disorder	Van Oosterwijk <sup>147</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–5 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		↑*
	Van Oosterwijk <sup>147</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–5 minutes	Pain intensity (VAS)		↓		↑*
	Van Oosterwijk <sup>147</sup>	Aerobic (cycle ergometer)	Self-paced up to 80% of AT, approximately 10–13 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		~*
	Van Oosterwijk <sup>147</sup>	Aerobic (cycle ergometer)	Self-paced up to 80% of AT, approximately 10–13 minutes	Pain intensity (VAS)		↓		~
	Ickmans <sup>56</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–6 minutes	Pressure pain threshold (kg/cm <sup>2</sup> )		↓		~*
	Ickmans <sup>56</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–6 minutes	Pressure pain threshold (mm Hg)		~		~
Whiplash-associated disorder	Ickmans <sup>56</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–6 minutes	Suprathreshold pressure pain (mm Hg)		~		~
	Ickmans <sup>56</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–6 minutes	Temporal summation ( $\Delta$ VAS)		~		~
	Ickmans <sup>56</sup>	Aerobic (cycle ergometer)	Incremental, 25 W/min to 75% of HR <sub>max</sub> , approximately 4–6 minutes	Conditioned pain modulation ( $\Delta$ VAS)		~		~
	Smith <sup>119</sup>	Aerobic (cycle ergometer)	75% of age-predicted HR <sub>max</sub> , 30 minutes	Pressure pain threshold (kPa)		~		~
	Smith <sup>119</sup>	Resistance (isometric wall squat)	Static squat 100 degrees of knee flexion, up to 3 minutes or to exhaustion	Pressure pain threshold (kPa)	↓	↓	↓	↓
Whiplash-associated disorder	Christensen <sup>18</sup>	Resistance (dynamic shoulder abduction)	6 × 6 repeated bilateral shoulder abductions against gravity to a 140 degree angle	Pressure pain threshold (kPa)	↓	~	↑*	↑*
	Christensen <sup>18</sup>	Resistance (dynamic shoulder abduction)	6 × 6 repeated bilateral shoulder abductions against gravity to a 140 degree angle	Pain intensity (VAS)	~	N/A	↑*	N/A

Abbreviations: ↓, decrease in pain sensitivity or pain intensity; ↑, increase in pain sensitivity or pain intensity; ~, equivocal findings or no change in pain sensitivity or pain intensity; VAS, visual analogue scale; rpm, revolutions per minute; N/A, measurement not available (not completed); AT, anaerobic threshold; NRS, numerical rating scale; 1 RM, 1 repetition maximum; MVC, maximum voluntary contraction; HR<sub>max</sub>, maximum heart rate;  $\Delta$ , change; W, Watt; Hz, Cycles per second. \*Significantly impaired exercise-induced hypoalgesia response compared with healthy controls ( $P < .05$ ). Local effect = pain measurement at a site local to the contracting muscle group. Global effect = pain measurement at a site remote to the contracting muscle group.

NOTE: As aerobic exercise involves contraction of several muscle groups and induces a widespread hypoalgesic response, its effects were considered global.

resistance exercise in chronic pain populations, including fibromyalgia<sup>41,71,77,95,123,131,149</sup> and chronic widespread pain associated with chronic fatigue syndrome<sup>96,145,158</sup> and Gulf War syndrome.<sup>21</sup> Those with widespread body pain often demonstrate both a local and a global EIH dysfunction in response to resistance exercise, with pain sensitivity increasing or remaining unchanged at remote body sites (ie, distant to the muscle[s] undergoing contraction) as well as sites local to the contraction.<sup>41,77,123</sup> In contrast, patients with a localized shoulder myalgia showed impaired EIH during isometric contractions of pain-afflicted muscles,<sup>42,77</sup> but normal EIH when contracting remote, nonafflicted muscles.<sup>77</sup> Similarly, people with painful knee OA had an intact EIH response to dynamic resistance exercise of the upper limb, but impaired EIH when resistance exercise was undertaken in the painful lower limb.<sup>15</sup> These findings suggest that, even in the presence of impaired EIH, people with localized pain conditions might be able to obtain pain-relieving effects by exercising remote, nonpainful parts of the body, because this strategy may still elicit EIH.

It is important to emphasize that not all chronic pain populations consistently demonstrate an impaired EIH response and different measures have been used to quantify EIH (eg, clinical pain intensity vs pressure pain threshold) that may influence both the underlying mechanism and observed response to exercise. Although limited to a few studies, impaired EIH has also been observed in painful diabetic neuropathy<sup>66</sup> and chronic neck pain,<sup>18</sup> whereas a normal EIH response has been observed in those with rheumatoid arthritis<sup>37,88</sup> and chronic low back pain.<sup>96</sup> Furthermore, in contrast with the findings of Burrows et al,<sup>15</sup> Kosek et al<sup>73</sup> observed intact local and global EIH in individuals with end-stage hip and knee OA. Impaired EIH has been observed after repeated shoulder movements in people with whiplash-associated disorder (WAD),<sup>18</sup> whereas a normal EIH response was seen after an isometric leg muscle contraction.<sup>119</sup> In contrast, impaired EIH is typically,<sup>56,119,147</sup> observed in patients with WAD after aerobic exercise, highlighting the variability of the EIH response in chronic pain populations and suggesting a possible difference in EIH according to the type of exercise and pain condition.

To further explore the individual variability of EIH among people with chronic pain, Vaegter et al<sup>140</sup> split people with chronic musculoskeletal pain of various etiologies into 2 groups based on their widespread sensitivity to pressure pain. Interestingly, the high pain sensitivity group showed a decreased EIH compared with the low pain sensitivity group. Similarly, Fingleton et al<sup>35</sup> examined EIH in people with knee OA according to their conditioned pain modulation response. Although pressure pain sensitivity decreased after exercise in both controls and those with knee OA who had a normal conditioned pain modulation response, it increased after both isometric and aerobic exercise in those with deficient conditioned pain modulation, indicating impaired EIH in this subgroup of patients. Although preliminary, these findings suggest that impaired EIH occurs more

frequently in individuals with augmented central nociceptive processing, indicated by widespread pain sensitivity and an imbalance in endogenous descending pain inhibitory or facilitatory function.

## Biological Mechanisms That May Contribute to EIH

Currently, the mechanisms responsible for EIH are not entirely understood, either in healthy adults or individuals with chronic pain (Table 2). Historically, the opioid hypothesis has received the most attention, which states that activation of the endogenous opioid system during exercise may be responsible for EIH. A number of studies have been conducted in which an opioid receptor antagonist was administered before and/or during an exercise session (for a review see<sup>67</sup>). Most of the early research in this area involved either pain-free adults or animals. Results from human research seems to be equivocal, with more consistent support for the opioid hypothesis in the animal research.<sup>67</sup> However, EIH that is insensitive to opioid antagonists can also occur, providing evidence for nonopioid mechanisms in EIH.<sup>23,67,69,86</sup> In the sections below, we discuss some additional biological mechanisms that may contribute to the EIH response in humans, with a focus on recent findings. It is important to note that other mechanisms may also be involved and that much of the research regarding the potential mechanisms of EIH has been performed in healthy, pain-free adults. However, where possible, we include studies undertaken in people with chronic pain and discuss their potential relevance to EIH in these populations.

### *The Role of Endocannabinoid System in EIH*

The specific neurochemistry of nonopioid hypoalgesia is not fully understood, but it has been suggested that the endocannabinoid system may be involved.<sup>29</sup> The endocannabinoid system is a neuromodulatory system composed of cannabinoid receptors (CB1, CB2), their endogenous ligands, that is, the endocannabinoids (N-arachidonyl ethanolamine [AEA] and 2-arachidonoylglycerol [2-AG]), and proteins responsible for their metabolism. The presence of cannabinoid receptors in nociceptive-processing areas of the brain and spinal cord suggests that endocannabinoids contribute to the control of pain through the activation of CB1 receptors. Exercise increases circulating levels of endocannabinoids and there is evidence of increased expression of CB1 receptors in the brains of rodents that exercised,<sup>39,40</sup> with cannabinoid receptor antagonists preventing the EIH response in animals.<sup>40</sup> In pain-free human adults, Koltyn et al<sup>69</sup> examined endocannabinoid and opioid mechanisms of EIH. Participants completed pain testing and had their blood drawn before and following isometric exercise in 2 conditions, that is, administration of an opioid antagonist and administration of a placebo. Results indicated that nonopioid mechanisms contribute to EIH and there were significant increases in circulating

**Table 2. Overview of Main Biological Mechanisms Explored in Relation to EIH in Pain-Free Adults and Those With Chronic Pain Conditions**

SYSTEM	MECHANISM EXAMINED	POPULATION	MAIN FINDINGS [REFERENCE]
Opioid system	OPRM1 gene polymorphism	Pain-free adults People with Fibromyalgia	OPRM1 polymorphism alone is not associated with EIH in either group. <sup>131</sup>
	Endogenous opioid activity	Pain-free adults	Opioid antagonists have either no or limited effects in reducing EIH. <sup>23,67,69</sup>
Endocannabinoid system	Endocannabinoid ligands circulation	Pain-free adults	AEA and 2-AG concentrations increase after exercise. Opioid antagonists block AEA increase, while they have no effect on 2-AG. Relationship between endocannabinoid ligands and EIH not reported. <sup>23</sup>
	Interstitial endocannabinoid related lipids	Pain-free adults, people with localized shoulder myalgia, people with CWP	Lower levels of PEA and SEA associated with increased pain after exercise in localized myalgia and CWP groups. <sup>42</sup>
Serotonergic system	HTR1a and 5-HTT gene polymorphisms	Pain-free adults, people with fibromyalgia	Neither of the serotonergic polymorphisms alone are associated with EIH in either group. <sup>132</sup> However, the combination of genetically inferred strong opioid tone (ORPM1 G genotype) and weak serotonergic signaling (5HT1a G genotype and low expressing 5-HTT) was associated with more pronounced EIH in both groups. <sup>132</sup>
Immune system	IL-10 gene expression	Pain-free adults, people with CFS and CWP	IL-10 gene expression increased more after exercise in people with CFS and CWP than controls and was moderately correlated with postexercise pain. <sup>85</sup>
	TLR-4 gene expression	Pain-free adults, people with CFS and CWP	TLR-4 gene expression increased more after exercise in people with CFS and CWP than controls but was not correlated with postexercise pain. <sup>85</sup>
	Complement system	Pain-free adults, people with CFS and CWP	C4a products increase soon after exercise in people with CFS and CWP. Relationship to EIH not reported. <sup>121</sup>
	Oxidative stress	Pain-free adults, people with CFS and CWP	Exercise may increase pro-oxidants such as TBARS and reduce antioxidants such as heat shock protein, in people with CFS and CWP. Relationship to EIH not reported. <sup>58,59</sup>
Autonomic nervous system	Heart rate variability	Pain-free adults, people with CFS and CWP	Heart rate variability is reduced after exercise, with no difference between groups and no association with EIH. <sup>92</sup>
	Cerebral blood flow	Pain-free adults, people with CFS and CWP	Cerebral blood flow increases with exercise, with no difference between groups and no association with EIH. <sup>92</sup>

Abbreviations: ORPM1, mu opioid receptor; EIH, exercise induced hypoalgesia; AEA, N-arachidonylethanolamine; 2-AG, 2-arachidonoylglycerol; CWP, chronic widespread pain; PEA, palmitoylethanolamide; SEA, stearoylethanolamide; 5HT1a, serotonin-1a receptor; 5HTT, serotonin transporter; CFS, chronic fatigue syndrome; TLR-4, Toll-like receptor 4; TBARS, thiobarbituric acid-reactive substances; IL-10, Interleukin 10; C4a, complement component 4a.

endocannabinoids and their associated lipids suggesting that these could contribute to EIH after isometric exercise. Thus, there is converging human and animal research supporting of the role of endocannabinoids in EIH. Furthermore, there is evidence of an interplay between the endocannabinoid and opioid systems, such that the activation of one system is mediated by the other system.<sup>24</sup> For example, preclinical studies in animals involving exogenous administration of cannabinoids and opiates have indicated significant interactions between opioid and endocannabinoid systems in pain responses,<sup>156</sup> but little research has examined the interaction between these systems in EIH.

Crombie et al<sup>23</sup> examined endocannabinoid and opioid system interactions in EIH in pain-free human adults. Participants were administered an opioid antagonist (naltrexone) and placebo before pain testing and exercise. Concentrations of cannabinoid ligand 2-AG increased significantly after exercise and were unaffected by naltrexone pretreatment. In contrast, increases in AEA found in the placebo condition were

blocked by pretreatment with naltrexone. These results suggest that 2-AG, in particular, may be the endocannabinoid involved in EIH after isometric exercise. Moreover, the block of exercise-induced increases in AEA by naltrexone pretreatment suggests the opioid system may be involved in AEA release after exercise. Very little research has explored the role of the endocannabinoid system in EIH among people with chronic pain. Ghafouri et al<sup>42</sup> examined endocannabinoid-related lipids palmitoylethanolamide and stearoylethanolamide in the trapezius muscle of 3 groups of women, including women with chronic localized shoulder myalgia, women with chronic widespread pain, and healthy controls before and after exercise consisting of 20 minutes of repetitive arm movement. Pain was found to increase during arm movement for the women with localized myalgia and chronic widespread pain, in contrast with the control group. The increase in pain intensity was found to be associated with lower levels of interstitial palmitoylethanolamide and stearoylethanolamide, consistent with the hypothesis that reduced activation of the



endocannabinoid system may be associated with impaired EIH. Additional research is required to further our understanding of the role of endocannabinoids and related lipids in EIH, both in pain-free and chronic pain populations.

### **The Role of Serotonergic and Opioid System Interactions in EIH**

Animal experiments have indicated that opioid and serotonergic mechanisms may also interact to produce EIH.<sup>86</sup> This finding is in line with reports of antagonistic effects of mu-opioid receptor and the serotonergic serotonin 1A receptor agonists.<sup>20</sup> Genetic association studies offer a unique method to assess the importance of opioid and serotonin interactions for EIH in humans without depending on invasive or pharmacologic interventions. Tour et al<sup>131</sup> investigated the effects of 3 functional genetic polymorphisms on EIH, both in healthy pain-free controls (n = 134) and in people with fibromyalgia (n = 130). These polymorphisms were 1) the single nucleotide polymorphism *rs1799971* in the OPRM1 gene, regulating the activation of the mu-opioid receptor (G-allele associated with increased tone in the endogenous opioid system), 2) the single nucleotide polymorphism *rs6295* in the HTR1a gene regulating serotonin 1A receptor expression (G-allele associated with reduced serotonergic tone), and 3) the polymorphisms *5-HTTLPR* and *rs25531* of the serotonin transporter (5-HTT) gene that jointly modulate 5-HTT expression. EIH was assessed by having the participants perform isometric contractions (knee extension) corresponding with 30% of their individual maximal voluntary force. The contractions were performed until exhaustion (maximum of 5 minutes). Pressure pain thresholds were determined at the deltoid muscle before and during the contraction, and the relative increase in pressure pain thresholds at the end of contraction compared with baseline was calculated as EIH. The fibromyalgia group had reduced EIH compared with controls, but none of the single polymorphisms had an effect on EIH in either group. However, significant gene-to-gene interactions were found between different combinations of opioid and serotonin genes, without statistically significant group differences. The results were in agreement with the hypothesis of antagonistic effects of opioid and serotonergic signaling on EIH as the combination of genetically inferred strong opioid tone (ORPM1 G genotype) combined with weak serotonergic signaling (5HT1a G genotype and low expressing 5-HTT) resulted in more pronounced EIH. The fibromyalgia group did not differ from controls in these respects, despite demonstrating significantly less EIH. Therefore, the data do not support an altered interaction between opioid and serotonergic polymorphisms as the basis for impaired EIH in fibromyalgia. The opposite interaction, that is, that genetically inferred low opioid tone combined with high serotonergic signaling, would yield better EIH was less consistently observed. The only statistically significant finding in this direction was that healthy controls with genetically inferred

weaker opioid tone (ORPM1 AA genotype) had more pronounced EIH if they also had a stronger serotonergic tone (5HT1a CC genotype) compared with those with weak serotonergic tone (5HT1a G genotype).

### **The Relationship Between EIH and Conditioned Pain Modulation**

Exercise is often painful,<sup>28</sup> particularly at high intensity or in the presence of muscle fatigue, where muscle nociceptors are activated.<sup>130</sup> Nociception is known to trigger the activation of endogenous descending inhibitory and facilitatory pathways from the brain,<sup>150</sup> which can be assessed using the conditioned pain modulation paradigm. Experimentally, conditioned pain modulation is measured by comparing pain sensitivity at one site in the body (ie, test stimulus), first in the absence of and then during or immediately after a second painful input (ie, conditioning stimulus) is applied to an anatomically distant body part.<sup>46</sup> Similar to EIH, in pain-free controls the conditioned pain modulation paradigm typically induces a multisegmental decrease in pain sensitivity that may involve both serotonergic<sup>17,133</sup> and opioidergic<sup>78,163</sup> mechanisms. Moreover, similar to EIH, conditioned pain modulation is often impaired in chronic pain populations.<sup>83</sup> Hence, it has been suggested that EIH and conditioned pain modulation may have shared mechanisms and that EIH occurs, at least in part, due to the activation of the same descending inhibitory pathways involved in conditioned pain modulation, which are triggered by exercise-induced activation of muscle nociceptors.<sup>33,72,80,136</sup>

To further explore the similarities between conditioned pain modulation and EIH, Ellingson et al<sup>33</sup> examined changes in heat pain sensitivity in pain-free female participants under 3 conditions: quiet rest, nonpainful aerobic exercise, and matched intensity painful aerobic exercise, achieved through the partial occlusion of blood flow to the exercising lower limbs. Interestingly, both painful and nonpainful exercise decreased heat pain sensitivity, whereas quiet rest had no effect. Although statistically significant differences were not observed consistently between the EIH response to painful and nonpainful exercise, the effect size of the EIH response was greater with painful exercise, and a moderate linear relationship was reported between the peak muscle pain reported during exercise and the magnitude of EIH. These findings are supported by other studies that have reported a significant association between the magnitude of conditioned pain modulation and EIH, both in healthy controls<sup>82,126,142</sup> and chronic pain populations.<sup>35,140</sup> However, the strength of the association is typically weak to moderate, and findings are not always consistent, with other studies reporting no relationship between conditioned pain modulation and EIH.<sup>116,136</sup> Furthermore, because conditioned pain modulation only occurs with a painful conditioning stimulus, it cannot explain EIH observed after nonpainful exercise.<sup>33</sup>

Finally, more in-depth experiments in pain-free adults have demonstrated differences in both the time course and spatial distribution of EIH and conditioned pain

modulation. Vaegter et al<sup>136,142</sup> found that conditioned pain modulation only occurred during a painful stimulus, whereas in the same group of participants, EIH continued 15 minutes after isometric contraction, at a time when conditioned pain modulation was absent. Moreover, the magnitude of EIH was greatest at sites local to the exercising muscles and weakest at remote body sites.<sup>136</sup> In contrast, the magnitude of conditioned pain modulation was greatest at remote sites and weaker at sites closer to the painful conditioning stimulus.<sup>136</sup> Thus, although it is possible that the same descending pain inhibitory pathways contribute to conditioned pain modulation and EIH during painful exercise, spatial and temporal differences in these responses and the presence of EIH during nonpainful exercise suggests that the neurophysiological mechanisms explaining EIH may be at least partly independent of those involved in conditioned pain modulation.

### ***The Potential Role of the Immune System in Impaired EIH***

The interactions between the immune and the nervous systems have been thoroughly discussed in recent decades.<sup>154</sup> Peripheral immune cells like macrophages and glial cells in the central nervous system can increase excitability of the nociceptive system by releasing pro-inflammatory mediators, such as IL-6.<sup>30,43,45</sup> People with chronic widespread pain often show altered levels of innate and adaptive markers of immune function such as the complement system, tumor necrosis factor- $\alpha$ , tumor necrosis factor-, IL-11, IL-6, IL-8, interferon (INF)- $\gamma$ , C-reactive protein, and oxidative stress, whereas anti-inflammatory markers might be reduced or unaltered.<sup>3,9,110,114,134</sup> A systematic review on the effect of exercise on the immune system of people with chronic inflammatory diseases showed that a single session of exercise aggravated inflammation (IL-6 and tumor necrosis factor- $\alpha$ ).<sup>112</sup> Importantly, altered immune responses may occur within minutes of a single exercise session.<sup>58,59,75</sup> Inflammatory mediators released in the periphery or in the central nervous system have the potential to activate nociceptive neurons and glial cells, contributing to sensitization and lowered pain thresholds.<sup>30,43,45</sup> Thus, it is possible that a further increase in inflammation could contribute to impaired EIH and/or the postexercise flare in pain that may be observed in some people with chronic pain conditions.<sup>16,101,107</sup> Indeed, complement system,<sup>120,121</sup> oxidative stress,<sup>59</sup> IL-10 and toll-like receptor-4 gene expression<sup>85,107</sup> have been found to be associated with symptom exacerbations after a single bout of exercise in people with chronic widespread pain associated with chronic fatigue syndrome.

However, the effects of altered immune responses on impaired EIH and/or postexercise pain is far from conclusive. Other studies in people with chronic widespread pain associated with chronic fatigue syndrome failed to find an exercise-induced alteration of complement system or toll-like receptor-4, despite exercise induced symptoms worsening.<sup>64,108</sup> Furthermore, in people with knee OA, a single session of resistance exercise was

shown increase the level of IL-10, an anti-inflammatory cytokine.<sup>50</sup> A similar anti-inflammatory response has also been reported in a study of people with fibromyalgia.<sup>12</sup> Unfortunately, no clinical measures were taken in these studies to allow the relationship between immune system changes and pain to be evaluated. More work exploring the potential link between the immune system and impaired EIH in different chronic pain populations is warranted.

### ***The Potential Role of the Autonomic Nervous System in EIH, Including Cerebral Blood Flow***

Both pain and exercise activate the body's stress response systems, including the hypothalamus-pituitary-adrenal axis and autonomic nervous system.<sup>19,74</sup> This results in the release of stress hormones like (nor) adrenaline and cortisol, which exert analgesic effects at the level of the brain (eg, noradrenaline is an important neurotransmitter for enabling descending nociceptive inhibition<sup>98</sup>) and spinal cord (eg, dorsal horn neurons contain glucocorticoid receptors, having nociceptive inhibitory capacity<sup>94</sup>). In addition, the autonomic nervous system is responsible for cardiac output and blood distribution (vasodilatation) to the exercising muscle, which has potential implications for muscle fatigue, ischemia, and muscle nociceptor activation in the context of EIH. In people with chronic widespread pain, lower parasympathetic activity rather than dysregulated sympathetic tone is associated with greater pain intensity, suggesting that intense pain is a chronic stressor interfering with parasympathetic activity.<sup>4</sup> Autonomic nervous system function can be evaluated by measuring heart rate variability (ie, the variation over time of the period between consecutive heartbeats), with a greater heart rate variability corresponding with better parasympathetic tone.

Heart rate variability is also related to cerebral blood flow.<sup>61</sup> Cerebral autoregulation aims at maintaining an adequate and stable cerebral blood flow. During exercise, perfusion pressure may exceed the autoregulatory range (60–160 mm Hg),<sup>109</sup> which in turn requires activation of the baroreceptor reflex to restore "normal" cerebral blood flow.<sup>99</sup> Available evidence suggests that experimentally induced pain leads to a decrease in global cerebral blood flow (velocity).<sup>97</sup> However, less is understood about cerebral blood flow in chronic pain conditions or whether autonomic dysfunction is related to EIH. To investigate this hypothesis, a recent study examined cerebral blood flow and heart rate variability changes in response to exercise and emotional stress in healthy, pain-free controls and patients suffering from chronic widespread pain associated with chronic fatigue syndrome.<sup>92</sup> It was found that both groups display a similar and normal decrease in heart rate variability during physical exercise, which normalizes (back to baseline values) during emotional stress.<sup>92</sup> Likewise, none of the cerebral blood flow parameters differed between groups, and both groups showed a similar cerebral blood flow evolution over the different experimental

conditions, despite an impaired EIH response being observed in the group with chronic widespread pain.<sup>92</sup> Neither changes in heart rate variability nor cerebral blood flow were associated with EIH efficacy or symptoms of postexertional malaise.<sup>92</sup> These results fail to provide evidence of a role for dysregulated autonomic control of cerebral blood flow or heart rate variability in explaining pain exacerbations after exercise or emotional stress in people with chronic widespread pain associated with chronic fatigue syndrome.

## Sex Effects on EIH

As outlined in different reviews,<sup>6,34,135</sup> there is substantial evidence of sex differences in chronic pain, with higher prevalence rates among women in many chronic pain diagnoses and, at least in some studies, greater pain intensity ratings in females. A higher female prevalence occurs in many chronic pain conditions where an impaired EIH response also has been observed, including fibromyalgia, chronic widespread pain, and WAD (Table 1). Thus, it could be hypothesized that sex differences may at least partly explain the impaired EIH that is often observed in these conditions.

However, studies to date provide no evidence that EIH is less efficient in females. A number of laboratory studies in pain-free adults have addressed the question of sex differences in pain sensitivity and endogenous pain inhibition, including the EIH response. Although early reviews suggested increased pain sensitivity in women,<sup>34,135</sup> a comprehensive systematic review analyzing 172 articles published between 1998 and 2008 came to the conclusion that sex differences in pain sensitivity are dependent on the type of stimulus.<sup>113</sup> Although men and women showed comparable thresholds for cold and ischemic pain, thresholds for pressure pain seem to be lower in females.<sup>113</sup> Furthermore, pain tolerance times for thermal and pressure pain were shorter for women compared with men, but comparable for ischemic pain.<sup>113</sup> Studies examining sex differences in the severity of delayed onset muscle soreness after exercise are also equivocal.<sup>27,36</sup> With respect to EIH in pain-free adults, some studies report no sex differences,<sup>14,69,103</sup> whereas, surprisingly, several other studies report more robust EIH in women after both isometric<sup>38,70,81,82</sup> and aerobic exercise.<sup>125,136</sup> Although the potential mechanisms remain unclear, it is possible that this effect may be at least partially ascribed to lower baseline pain thresholds in women (eg, <sup>70,82</sup>), potentially leading to a larger relative change in pain sensitivity with exercise. However, other studies observed stronger EIH in females despite no baseline sex differences in pain sensitivity.<sup>38,81</sup> Thus, results of laboratory research in pain-free adults remain inconclusive regarding possible sex differences in EIH, leaving findings of impaired EIH in chronic pain disorders with a greater prevalence in women (eg, fibromyalgia and WAD) largely unanswered. When it comes to sex differences in EIH among chronic pain populations, much less is known. One study explored possible sex differences in EIH in patients with chronic WAD, but failed to find any differences.<sup>56</sup>

## Psychosocial Influences on EIH

Research indicates that psychosocial factors contribute to the experience of pain in both healthy and patient populations.<sup>44,60</sup> However, less is known regarding the impact of psychosocial factors on EIH. Only a limited number of studies have been conducted in this area, but some studies in healthy, pain-free adults suggest that EIH can be influenced by psychosocial factors. Pain catastrophizing, for example, which is characterized by maladaptive emotional and cognitive processes (ie, perception of helplessness, rumination, and magnification of painful sensations) has been found to attenuate the EIH response and was associated with increased ratings of perceived exertion and muscle pain during exercise in healthy adults.<sup>14,103,155</sup> Fear of pain and mood disturbance have also been reported to attenuate the hypoalgesic response after exercise in healthy adults.<sup>14</sup> Furthermore, family-related factors such as family environment and a family history of chronic pain seem to influence EIH. Positive family environments were found to predict greater EIH, whereas negative and chronic pain-present family environments predicted worse pain and EIH outcomes.<sup>14</sup>

Less is known regarding the relationship between psychosocial factors and EIH in adults with chronic pain. However, findings to date provide no evidence that selected psychosocial factors are associated with EIH in chronic pain populations. For example, in adults with chronic musculoskeletal pain, anxiety, depression, and pain catastrophizing did not predict changes in pressure pain thresholds after exercise,<sup>140</sup> and kinesiophobia (ie, fear of movement or injury) was not found to be associated with EIH.<sup>143</sup> Similarly, no relationship was found between state anxiety and EIH in women with fibromyalgia<sup>52</sup> and in adults with chronic WAD, the relationship between selected psychosocial factors (ie, pain catastrophizing, kinesiophobia, and stress symptoms) and EIH were examined, and results indicated no significant associations between the change in pressure pain sensitivity and psychosocial factors.<sup>119</sup>

Exercise should be considered both a physiological and a psychological stressor. However, whether the way exercise is perceived changes the EIH response is relatively unexplored. People who perceive exercising as potentially harmful or uncontrollable might respond differently to exercise. The stress literature offers interesting insights on this. Animal studies show that voluntarily wheel running improves health, reducing stress and inflammation.<sup>32</sup> On the contrary, forced—and thus uncontrollable—exercise can induce detrimental effects, including increased inflammation and a heightened stress response.<sup>22,129</sup> In healthy, pain-free humans, a minor increase (10%) in exercise intensity beyond the level that the participants would choose for themselves can significantly decrease pleasantness, with no additional fitness gains.<sup>87</sup> In general, increasing perceived control alleviates stress and increases activity levels.<sup>7</sup>

Very little of this evidence has been transferred to the context of EIH. However, in pain-free adults when a physical stimulus is perceived as more threatening, pain

tolerance decreases.<sup>153</sup> In addition, specific education about the beneficial and hypoalgesic (thus safe) effects of exercise, seems to increase the magnitude of EIH, at least in healthy controls.<sup>62</sup> The evidence is less clear in chronic pain populations. Van Oosterwijck et al<sup>146</sup> manipulated exercise intensity in patients with chronic widespread pain associated with chronic fatigue syndrome. Although one exercise was a submaximal one, the other was a self-paced, physiologically limited bout of exercise. Both exercises had negative effects on participants, increasing pain and worsening their other symptoms such as fatigue. This finding seems to contradict the evidence cited, because the second bout of exercise was specifically design to decrease threat and increase safety. A possible explanation is that people with chronic fatigue syndrome are arguably the people that fear physical activity the most. Exercise itself—even if self-paced and controllable—may be perceived as harmful, facilitating negative responses. Additional research is required to further explore other psychosocial factors and different chronic pain conditions to expand our understanding of the relationship between psychosocial factors and EIH, both in pain-free adults and chronic pain populations.

## How Should We Address Impaired EIH in Clinical Practice?

Although it is clear that impaired EIH occurs in some people with chronic pain, how should this issue be addressed in clinical practice? The vast majority of the literature on exercise prescription in the context of rehabilitation focuses on matching exercise parameters to fitness levels. In this context, exercise is designed to reverse deconditioning and may be based on factors relating to strength, cardiovascular function, biomechanics, and/or flexibility. However, basing exercise prescription on fitness levels alone will likely be problematic for people with impaired EIH.<sup>25,105,160,161</sup> For these people, pain exacerbations are a major barrier to activity engagement that likely needs to be addressed for them to benefit from treatment. Unfortunately, there is currently very little evidence to specifically inform us how to tailor the parameters of exercise prescription for those people with impaired EIH.

Although the role of psychosocial factors in impaired EIH remains unclear, the broader literature exploring how to increase exercise engagement among people living with pain suggests that decreasing the threat value of pain and movement may be an effective way of helping these people.<sup>89,100,151,152,159</sup> For instance, recent work has highlighted the potential advantages of applying therapeutic neuroscience education and cognitive interventions (eg, graded exposure) within the context of physical activity to specifically help people with chronic pain reappraise the threat value that they associate with pain and movement.<sup>91,106</sup> As a starting point, clinicians can explain EIH when delivering a pain neuroscience education intervention before delivering a therapeutic exercise program. For instance, when

explaining descending nociceptive inhibition clinicians can use a Socratic-style dialogue<sup>118</sup> to explain that exercise can activate it, resulting in hypoalgesia. Clinicians can also highlight that people with chronic pain may experience hyperalgesic responses to the early stages of an exercise program, which can result in more pain. Again, Socratic-style dialogue can be used to discuss the threat value of such pain flares after exercise (eg, Does it imply more damage in the muscles or joints?). When integrated in a comprehensive pain neuroscience education program, people with impaired EIH are expected to benefit through decreases in their catastrophic thinking about potential exercise-induced symptom flares, increased acceptance about such flares, and improved confidence that these negative reactions will dissipate with time.

## Future Research Perspectives

An important question that remains largely unexplored is whether combining exercise with other interventions might help to restore impaired EIH. For example, pain neuroscience education emphasizing the hypoalgesic effects of exercise seems to enhance the EIH response in healthy controls,<sup>62</sup> but this has not yet been examined in chronic pain populations with decreased EIH. Similarly, the use of centrally acting analgesics (eg, serotonin-noradrenaline reuptake inhibitors) in combination with exercise interventions has been suggested, especially in the early phase of exercise programs.<sup>105</sup> Yet studies exploring this combination are currently lacking. Emerging work suggests that certain analgesic interventions may have unique benefits for decreasing pain during activity.<sup>122</sup> For instance, several placebo-controlled studies suggest that transcutaneous electrical nerve stimulation can specifically improve movement-related pain, even when levels of pain at rest remain unchanged.<sup>26,115,148</sup> These findings may have particular clinical importance for rehabilitation professionals, because transcutaneous electrical nerve stimulation is commonly used at rest and may have some added value when used in conjunction with exercise.

To date, most studies of EIH have focused on comparing between-group differences among people living with different chronic pain conditions versus individuals who are pain free.<sup>25,102,105</sup> This type of research is essential to better understand and characterize the mechanisms that underlie EIH. However, it provides little guidance in understanding and characterizing the within-group clinical differences related to EIH. For instance, it remains unclear whether the prognoses of patients with similar pain conditions (eg, nonspecific low back pain) differ based on their individual levels of EIH. The development of this within-group line of research is essential to characterize the clinical prognostic profiles related to EIH and to subsequently develop tailored interventions for people with impaired EIH. Preliminary findings suggest that such an approach holds promise.<sup>139</sup>

Establishing the measurement reliability of the EIH response is also fundamental for understanding its

future clinical implications. At this time, only one study has assessed the test–retest reliability of the EIH response, measured using the change in pressure pain threshold in response to aerobic exercise in healthy subjects.<sup>138</sup> Although pressure pain threshold measurements alone showed excellent reliability (intraclass correlation coefficients of  $>.8$ ), the between-session reliability of the EIH response was only fair (intraclass correlation coefficient of  $.45$ ) and agreement in EIH responders between sessions was not significant. Further research examining the test–retest reliability of the EIH response is needed, including in chronic pain populations and with other forms of exercise (ie, dynamic and/or isometric resistance exercise). Moreover, rather than assessing EIH as an isolated phenomenon, it should be combined with other quantitative sensory testing measures of pronociceptive and antinociceptive function. This research is important both for improving the mechanistic understanding of EIH and for developing an individualized approach that may better predict those patients who are likely to be EIH responders.

Few studies have actively explored the effects of varying exercise dose on EIH in chronic pain populations. Some studies<sup>146,147</sup> have directly compared the EIH response after a prescribed aerobic exercise intensity (eg, 75% of heart rate maximum) with a condition where aerobic exercise intensity is self-selected. Despite self-selection leading to a significantly decreased exercise intensity and lower ratings of perceived exertion, these studies have largely failed to find a difference in the magnitude of EIH between prescribed and self-selected exercise intensities.<sup>146,147</sup> In addition, many studies exploring EIH in chronic pain populations have used exercise doses that may not accurately reflect clinical practice. For example, several have used aerobic exercise protocols that last  $<15$  minutes in duration.<sup>56,92,96,145–147,149</sup> Furthermore, EIH studies using resistance exercise have often used isometric, rather than dynamic, resistance exercises and, typically, these are performed at low loads (10–30% of maximum voluntary contraction), with a single muscle contraction held for several minutes.<sup>63,71,77,88,123,131</sup> Although known to induce EIH in healthy adults,<sup>53,68</sup> these exercise protocols do not reflect current exercise guidelines, making the clinical relevance of their findings difficult to interpret. More research exploring the effects of varying exercise dose on EIH in chronic pain populations is needed. Future EIH studies may also wish to examine the effects of exercise protocols that more closely mimic clinical practice.

Finally, the bulk of the literature has focused on quantifying EIH by evaluating the change in pressure pain thresholds before and after an acute bout of exercise. Using pressure pain thresholds as a proxy for pain sensitivity is a useful way of anchoring these measures within the literature on mechanisms related to pain and exercise.<sup>2,102</sup> However, in clinical settings, self-reported pain symptoms (typically quantified through self-reports of pain intensity) are arguably the most important indicator of a pain problem. Although pain thresholds and self-reported pain intensity are often correlated, they are

functionally distinct constructs.<sup>2</sup> This distinction raises the question of whether exercise-related changes in pain thresholds or self-reported pain is the best clinical proxy of EIH and whether the choice of pain measurement influences both the underlying mechanism and observed response to exercise. An emerging line of clinically oriented research has quantified EIH using exercise-related changes in self-reported pain and shows promising results.<sup>76,93,127,128,160,161</sup> Additional research that focuses on the direct comparison between the predictive value of these 2 approaches to quantifying EIH will help shed light on their respective clinical value.

## Summary and Conclusions

In healthy, pain-free populations, a single bout of aerobic or resistance exercise typically leads to EIH, a generalized decrease in pain sensitivity that occurs during exercise and for a short time afterward. EIH is more variable in chronic pain populations and may be impaired in some people, with pain sensitivity remaining unchanged or even increasing in response to exercise.

The physiological mechanisms underlying EIH remain incompletely understood and known mechanisms explaining the reduced EIH that can occur in some chronic pain populations are currently lacking. In general, interactions between the opioid and endocannabinoid systems and between the opioid and serotonergic systems seem to be important in determining EIH, with recent findings suggesting some of the individual variability in the EIH response is heritable and at least partly determined by polymorphisms in the ORPM1, 5HTP1a, and 5HTTR genes. Although other established descending pain control systems (eg, those assessed by conditioning pain modulation) may contribute to EIH during painful exercise, the mechanisms explaining EIH appear to be at least partly independent of conditioned pain modulation. The role of the autonomic and immune systems in the EIH remains unclear, although it is possible that a proinflammatory effect of acute exercise is involved in impaired EIH or the postexercise flares in pain that can occur in some people with chronic pain. Psychosocial factors such as fear of pain, pain catastrophizing, and beliefs about the perceived threat of exercise may also have important influences on EIH, although evidence supporting this is so far confined to healthy, pain-free populations.

Further work is required to establish why EIH may be impaired in some people with chronic pain (and not others) and how to apply this knowledge to clinical practice. This research could explore within-group differences in EIH in people with the same chronic pain condition and the use of combined interventions (eg, centrally acting analgesics and exercise) to restore impaired EIH. Although cognitive-behavioral strategies (eg, pain neuroscience education) that aim to diminish the threat value of exercise may improve adherence in chronic pain populations, their effect on EIH remains largely unknown and should be explored further.

Finally, much of the existing EIH research has used exercise doses that do not reflect recommendations in exercise guidelines and focused on the acute effect of exercise on a single laboratory-based measure of pain sensitivity (eg, pressure pain threshold). Future research may wish to further explore shared mechanisms between EIH and other pronociceptive and antinociceptive measures, establish key factors affecting the test–retest reliability of the EIH response, use more clinically relevant exercise protocols, and better determine

the relationship between exercise-induced changes in pain sensitivity and self-reported measures of pain intensity, because the latter may be more relevant to people with chronic pain.

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## Supplementary data

Supplementary data related to this article can be found at <https://doi.org/10.1016/j.jpain.2019.03.005>.

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