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Analgesia Following Exercise
A Review

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Abstract

Over the past 20 years a number of studies have examined whether analgesia occurs following exercise. Exercise involving running and cycling have been examined most often in human research, with swimming examined most often in animal research. Pain thresholds and pain tolerances have been found to increase following exercise. In addition, the intensity of a given pain stimulus has been rated lower following exercise. There have been a number of different noxious stimuli used in the laboratory to produce pain, and it appears that analgesia following exercise is found more consistently for studies that used electrical or pressure stimuli to produce pain, and less consistently in studies that used temperature to produce pain. There is also limited research indicating that analgesia can occur following resistance exercise and isometric exercise. Currently, the mechanism(s) responsible for exercise-induced analgesia are poorly understood. Although involvement of the endogenous opioid system has received mixed support in human research, results from animal research seem to indicate that there are multiple analgesia systems, including opioid and non-opioid systems. It appears from animal research that properties of the exercise stressor are important in determining which analgesic system is activated during exercise.

Stressful conditions have been found to be a natural stimulus which can trigger pain suppression.[1] A number of anecdotal observations suggest that pain perception is altered during exposure to various stressors, and the phenomenon has been referred to as stress-induced analgesia. Among the earliest reports of stress-induced analgesia are results published by Beecher,[2,3] who found that soldiers severely wounded in battle reported little pain, and required considerably less analgesic medication com-

pared with civilians undergoing similar surgery. Stress-induced analgesia appears to be elicited by a wide range of stressors. Research has been conducted with humans and animals, and some of the stressors that have been studied include thermal challenges, restraint, rotation, electric shock and exercise.

Dramatic anecdotes from dancers and athletes who continue strenuous exercise in the face of severe injuries, and later report that they felt no pain, have contributed to the notion that exercise can alter pain perception. Some investigators have referred to this as exercise-induced analgesia. One of the early reports of analgesia following exercise was published by Black et al.,[4] who found that pain threshold was elevated immediately following 40 minutes of running in a single individual. Over the past 20 years a number of studies have examined whether analgesia occurs following exercise. Exercise such as running and cycling has been examined most often in human research, with swimming being examined most often in animal research. Typically, a noxious stimulus is applied before and following exercise to see if analgesia occurs following exercise. There have been a number of different noxious stimuli used in the laboratory to produce pain, including electrical, ischaemic, temperature and pressure stimulation. Investigators have also examined potential mechanisms that may be responsible for the analgesic response following exercise. The most commonly tested hypothesis for exercise-induced analgesia has been that activation of the endogenous opioid system during exercise may be responsible for the analgesic response that occurs following exercise. Naloxone (an opioid antagonist) has been administered in some of the studies to test for this possibility, but other potential mechanisms, such as growth hormone (GH) and corticotropin (adrenocorticotropic hormone) have also been examined.

The purpose of this paper is to summarise the human and animal research that has been conducted in this area. Two previous review papers have been published examining exercise-induced analgesia in humans.[5,6] The intent of including findings from animal research in this review is to provide an additional perspective which may expand our understanding of exercise-induced analgesia and the mechanisms responsible for this response.

1. Human Research

1.1 Cycling, Running and Step Exercise

1.1.1 Noxious Stimulation: Electrical

A number of investigators have studied changes in pain perception following cycling exercise using noxious dental pulp stimulation techniques. For example, Pertovaara et al.[7] assessed changes in dental pain thresholds during and following exercise at different intensities. Dental pain thresholds were determined with a Bofors Pulp Tester, in which a cathode was attached to an upper tooth, and assessments were completed before, during and following exercise. Four different levels of exercise (50, 100, 150 and 200W) were completed on a bicycle ergometer by 6 men. Workloads were increased stepwise without rest between the different levels, and each work period lasted 8 minutes. It was reported that dental pain thresholds tended to increase with the increasing workloads. However, a significant increase in pain thresholds was only evident at the 200W workload. Dental pain thresholds remained elevated 30 minutes following exercise.

Similar results were found in a study by Kemppainen et al.[8] Seven men cycled continuously for 8 minutes at workloads of 100, 200, 250 and 300W. Heart rate, blood pressure, dental pain threshold and blood samples were taken before, during, and 15 and 30 minutes following exercise. A significant increase in dental pain thresholds became apparent between 200 and 250W, and remained elevated for approximately 15 minutes. In addition, thermal sensitivity was decreased following exercise, with a more marked decrease in leg sensitivity compared to thermal sensitivity of the hand. These changes in pain perception were correlated positively with heart rate, blood pressure and GH levels.

Kemppainen et al.[9] next examined the association between pain threshold elevation found with exercise and GH release. Six men completed cycle ergometry exercise at workloads of 200, 250 and

300W in 2 randomly assigned conditions. One condition consisted of administration of cyproheptadine [a serotonin (5-hydroxytryptamine; 5-HT) receptor antagonist] which has been shown to inhibit GH release, and the other condition consisted of the administration of a placebo every 6 hours, beginning 2 days before testing. Dental pain thresholds were determined with a constant current tooth stimulator, and heart rate, dental pain threshold and blood samples were assessed before exercise, at each workload, and 15 and 30 minutes following exercise. Pain thresholds were found to be significantly higher at 300W than before exercise in both conditions. Cyproheptadine was not found to have a significant effect on dental pain thresholds, although it suppressed the exercise-induced GH release. The investigators concluded that exercise-induced analgesia was not associated with GH release in this study.

Results from another study by Kemppainen et al.[10] indicated that mechanisms related to the release of corticotropin are involved in exercise-induced analgesia. Corticotropin is released concomitantly with β-endorphin,[11] and can be selectively blocked with dexamethasone administration. Six men performed cycle ergometer exercise at workloads of 100, 150 and 200W in 2 randomly assigned conditions consisting of the administration of dexamethasone or saline 60 minutes before exercise. It was found that dental pain thresholds were significantly elevated in the placebo condition at workloads of 100, 150 and 200W and remained elevated for 30 minutes following exercise. However, dental pain thresholds were significantly elevated only at a workload of 200W in the dexamethasone condition. The authors concluded that dexamethasone attenuated pain threshold elevations, indicating that corticotropin is potentially involved in exercise-induced analgesia.

In a study by Olausson et al.,[12] the separate effects of exercise and transcutaneous nerve stimulation (TNS) on pain threshold were studied. Dental pain thresholds were assessed in 8 men and 3 women before and following 20 minutes of leg and arm exercise, as well as after low frequency TNS of the hands or face in 2 conditions (naloxone and placebo administration). Pain thresholds increased significantly following leg and arm exercise, and gradually decreased to baseline levels by 50 minutes after exercise. Also, pain thresholds increased significantly following electrical stimulation of the face and hands. Changes in pain thresholds were unaffected by injections of naloxone (0.8mg) that were administered after exercise. However, naloxone administration did result in a short-lasting attenuation of analgesia following arm exercise.

Dental pulp and finger pain thresholds and plasma hormone levels (β-endorphin, cortisol, and catecholamines) were measured in 10 men before, during and following exercise by Droste et al.[13] Participants completed cycle ergometer exercise to exhaustion (approximately 15 minutes) following naloxone (20mg) and placebo administration. Plasma β-endorphin, cortisol and catecholamines were found to be significantly elevated at maximal exercise in both conditions. Dental pulp and finger pain thresholds were also found to be significantly elevated at maximal exercise in both conditions, with a gradual return to baseline levels by 60 minutes after exercise. In addition, magnitude estimates of the pain stimuli using a visual analogue scale were found to be significantly lower following exercise, indicative of an analgesic response in both naloxone and placebo conditions. Results from this study indicate that naloxone administration did not influence the analgesic response that occurred following exercise.

In a study examining analgesia following exercise in patients with silent and symptomatic myocardial ischaemia, Droste et al.[14] did not find significant changes in pain thresholds following exercise. Eight men with symptomatic myocardial ischaemia and 9 men with asymptomatic myocardial ischaemia completed cycle ergometer exercise to exhaustion in naloxone (6mg) and placebo conditions administered immediately prior to exercise in a double-blind fashion. Ischaemic and finger pain thresholds were assessed before, during and following exercise with plasma β-endorphin, cortisol and catecholamines assessed at the same time-points. Results in-

dicated that ischaemic and electrical pain thresholds were higher in the asymptomatic patients compared with symptomatic patients at baseline. A moderate, but statistically insignificant, increase in pain thresholds was found following exercise. Naloxone administration was found to attenuate ischaemic pain thresholds following exercise but had no effect on finger pain thresholds. Plasma β-endorphins were found to increase during exercise with significantly higher increases in the asymptomatic patients compared with symptomatic patients. Naloxone administration was found to attenuate the β-endorphin increase in the asymptomatic patients, and the investigators concluded that 'there may be quantitative differences in the endorphinergic regulation of pain in patients with symptomatic and asymptomatic myocardial ischaemia'.

Guieu et al.[15] used electrical stimulation of the sural nerve to assess changes in the threshold of the nociceptive flexion reflex following cycle ergometer exercise. Thresholds were assessed at rest in 8 non-athletes, and at rest, as well as following 20 minutes of cycling, in 6 high level athletes who regularly participated in national or international athletic competitions. Pain thresholds at rest were found to be significantly higher in the athletes compared to the non-athletes. Also, cycle ergometry exercise resulted in a significant increase in the thresholds of the nociceptive reflex in the athletes.

1.1.2 Noxious Stimulation: Temperature

Even though there appears to be evidence in support of analgesia following exercise, Padawer and Levine[16] contend that analgesia following exercise may be an artifact of the pre-test exposure to a noxious stimulus that occurs when pre-test/post-test designs are employed. Studies investigating exercise-induced analgesia usually involve exposing participants to a pre-test measurement of pain, then to exercise, and finally to a post-test pain measurement. Exposure to a painful stimuli can result in reduced sensitivity to subsequent exposures of the noxious stimulus, and Padawer and Levine suggest that previous exercise-induced analgesia studies did not control for this possibility. Padawer and Levine[16] tested 91 participants using a Solomon design, in which some participants were pre- and post-tested, while other participants were post-tested only in exercise and control conditions to determine if exercise or pre-testing with a cold pressor stimulus would produce analgesia. Results indicated no significant analgesic response associated with exercise, but there was a significant analgesic response found for the pre-exposure to the pain stimulus, and the investigators concluded that the 'so-called exercise-induced analgesia effect may be entirely, or in part, a pain test-reactivity artifact'.

Pertovaara and Kemppainen[17] and Droste and Greenlee[18] responded to the issues raised by Padawer and Levine,[16] and questioned whether the exercise intensity (50 and 70% of maximum heart rate) selected by Padawer and Levine was sufficient to provoke an analgesic response. Previously, Kemppainen reported that the lowest workload which was found to be associated with an analgesic response was a workload of 74% of maximum aerobic capacity. Also, use of the cold pressor stimulus was criticised because the replicability of analgesia with repeated cold pressor tests has been mixed. For example, Janal et al.[19] showed using multiple pain stimuli that cold pressor pain was not influenced by exercise, although in the same participants thermal and ischaemic pain were attenuated following exercise. In this study, 12 runners completed a 10km run at 85% of maximal aerobic capacity in naloxone (0.8mg in 2ml vehicle each) and placebo conditions administered after each session in a double-blind fashion. Sensory decision theory analyses were employed to assess both discriminability of pain stimuli, as well as pain report criterion to 3 different stimuli (thermal, ischaemic and cold pressor). Discriminability represents how well a person can distinguish between different intensities of painful stimuli, while pain report refers to the person's willingness to report a stimulus as painful. Results indicated that an analgesic response occurred following exercise because thermal discriminability and ischaemic discriminability were significantly reduced following running. However, there was no significant analgesic response found for the cold pressor test. Naloxone was found to reverse the

post-run analgesic response for ischaemic stimulation but not for thermal stimulation.

On the other hand, Sternberg et al.[20] did find significant reductions in pain reports on the cold pressor test in athletes following an athletic competition. Male and female basketball players, fencers and track runners were exposed to cold pressor and noxious heat stimuli 2 days before, immediately following and 2 days after an athletic competition. Cold pressor pain ratings decreased immediately following the competition, and it was also reported that withdrawal latencies to noxious heat were altered by competition. No changes in pain reports were observed across time in the non-athletes who participated in the study.

Mixed results regarding the analgesic effect of exercise on cold pain sensitivity in pilots were found by Kemppainen et al.[21] Eight pilots who had previously experienced acute in-flight neck pains and 8 pilots who had not previously experienced acute in-flight neck pains (controls) completed cycle ergometry exercise at increasing workloads (50 to 200W). Pain thresholds were found to increase significantly following exercise at 200W in the pilots who had previously experienced acute in-flight neck pains, but not in the control pilots. However, ratings of pain intensity and unpleasantness were found to decrease significantly following exercise at 200W in both groups of pilots.

Fuller and Robinson[22] used a signal detection analysis of pain perception in a post-test only design with endurance athletes in a naturalistic setting. Twenty-two men completed 2 randomly assigned conditions, including an exercise condition where participants completed a 10km run outdoors, and a control condition consisting of sitting quietly in a laboratory for 40 minutes. Radiant heat was applied to the forearm following each condition, and results indicated that discriminability measures from intensities of 44° and 46°C were significantly lower following exercise in comparison to the control condition. This finding was reported to be consistent with discriminability decreases seen with the administration of analgesic chemicals such as morphine and nitrous oxide. However, discriminability measures at a temperature of 48°C were not significantly different from the control condition.

1.1.3 Noxious Stimulation: Pressure

Haier et al.[23] examined the effects of a 1-mile run on pressure pain thresholds in 9 men and 6 women. A 3lb weight was rested on the first joint of the index finger until the participant reported pain, and assessments were completed before and following a 1-mile run at self-selected intensities. Naloxone administration (2mg) and saline administration were administered in a double-blind fashion right before the run. Results indicated that although pain thresholds increased following exercise in both conditions, the increase was found to be significantly higher in the naloxone condition. A second study was then conducted employing a larger dose of naloxone (10mg) administered before exercise to examine the influence of naloxone dosage on exercise-induced analgesia. In this study, 4 men and 2 women completed a 1-mile run following naloxone or placebo administration, and results indicated that 10mg of naloxone completely blocked the analgesic response following exercise.

Gurevich et al.[24] employed a Solomon 4 group design in which 60 men were randomly assigned to: (i) an experimental pre/post-test group; (ii) an experimental post-test only group; (iii) a control pre/post-test group; or (iv) a control post-test only group. The experimental groups completed 12 minutes of step exercise at approximately 63% of maximal oxygen uptake (VO_{2max}), while the control group completed 2 unrelated questionnaires which required approximately 12 minutes to complete. Pain tolerance was assessed by the amount of time that participants could endure 2300g of pressure to the index finger of the dominant hand. Participants also rated the intensity of the pain stimulus using an 11-point scale. Results showed no significant analgesic response for the pain pre-test. However, there was a significant analgesic response found for exercise, with the exercise groups having higher pain tolerances and lower pain ratings following exercise in comparison to the control group.

Koltyn et al.[25] found increases in pressure pain thresholds following exercise. Fourteen men and 2

women completed 2 randomly assigned conditions including exercise and no-exercise control sessions. Exercise consisted of 30 minutes of cycle ergometer exercise at 75% of $\dot{V}O_{2max}$, while the control condition consisted of resting quietly in a sound-dampened chamber for 30 minutes. Pressure was applied to the finger with the Forgione-Barber pressure stimulator before, immediately following and 15 to 20 minutes following the exercise and control conditions. Pain thresholds were found to be significantly elevated immediately, as well as 15 to 20 minutes following exercise, compared with no change in pain thresholds following the no-exercise control condition. In addition, pain ratings were found to be significantly lower following exercise in comparison to the control condition.

There is one report of a hyperalgesic response following exercise. Vecchiet et al.[26] examined muscular pain sensitivity following 30 minutes of exercise in 10 healthy men. The intensity of pain was reported with a visual analogue scale every 30 seconds after the injection of: (i) 1ml of 10% sodium chloride hypertonic solution at rest; (ii) 1ml of 20% sodium chloride hypertonic solution at rest; and (iii) 1ml of 10% sodium chloride hypertonic solution 1 minute and 60 minutes following submaximal exercise. The injection of 10% sodium chloride solution 1 minute after exercise was associated with an increase in pain, similar to that induced by the 20% sodium chloride solution given during rest. The investigators concluded that exercise produced a hyperalgesic response because pain was elevated 1 minute following exercise.

1.2 Resistance Exercise

There have been only a limited number of studies that have examined whether analgesia occurs following a resistance exercise session. Bartholomew et al.[27] investigated the effects of 20 minutes of self-selected exercise on pressure pain thresholds and pain tolerance. Seventeen men who were regular exercisers completed a self-selected exercise session in a gym and a control session in a laboratory. Exercise consisted of 13 of the participants completing 20 minutes of resistance exercise (circuit weight training), while 4 participants performed stationary cycling. There were significant increases in pressure pain tolerances following exercise in comparison to the control condition. However, pain thresholds were not found to change following exercise or control conditions. It is unclear why pain tolerances changed following exercise but pain thresholds remained unchanged.

Koltyn and Arbogast[28] examined whether analgesia occurred following a resistance exercise session in comparison to a no-exercise control session. Thirteen participants completed 2 randomly assigned conditions (resistance exercise and control), and pressure pain thresholds and pain ratings were assessed immediately before, as well as 5 and 15 to 20 minutes following the 2 conditions. Resistance exercise consisted of 45 minutes of lifting 3 sets of 10 repetitions at 75% of the individual's 1 repetition maximum, with the control condition consisting of sitting quietly in a room free from distractions for 45 minutes. Pain thresholds were found to increase significantly 5 minutes following resistance exercise, with a return to baseline by 15 to 20 minutes following exercise. Pain ratings were found to be lower 5 minutes following resistance exercise, and this was observed in conjunction with changes in blood pressure and heart rate following resistance exercise. Pain thresholds and pain ratings were not found to change significantly following quiet rest.

1.3 Isometric Exercise

Several studies have examined changes in pain perception following isometric exercise. Pressure pain thresholds were examined before, during and following isometric contractions of the quadricep by Kosek and Ekholm.[29] Fourteen women completed an isometric contraction to exhaustion (maximum = 5 minutes) of the quadricep at 21% of maximal voluntary contraction. Pressure pain thresholds of the quadriceps were assessed before, every 30 seconds during, immediately following and 5 minutes following isometric exercise. Pain thresholds were found to increase significantly during isometric exercise, and remained elevated during the 5-minute recovery period. In a subsequent

study, Kosek et al.[30] examined the effect of submaximal isometric exercise on pressure pain thresholds in 14 patients with fibromyalgia and 14 healthy volunteers. The same design was employed in this study, and results showed that pain thresholds increased significantly during isometric exercise and remained elevated during the 5-minute recovery period in the healthy control participants. In comparison, pain thresholds decreased significantly during isometric exercise and remained below precontraction levels during the 5-minute recovery period in the patients with fibromyalgia. The results for the patients with fibromyalgia are in agreement with results reported by Bengsston et al.,[31] who found that lower body pain reports were elevated following cycle ergometry exercise performed at 80% of the participant's estimated $\dot{V}O_{2max}$.

The effect of isometric leg exercise and cycle ergometer exercise on skin sensitivity was examined by Paalasmaa et al.[32] Skin sensitivity to innocuous and noxious thermal stimuli was examined using a thermostimulator which could be warmed or cooled, and electrical stimulation was used to examine tactile sensitivity in 11 men. Isometric exercise consisted of pressing the right foot against a static load of 30 and 70% of maximum force for approximately 2 minutes, while cycle ergometer exercise consisted of pedalling 6 to 8 minutes at increasing levels of intensities (100, 150, 200, 250W). Isometric exercise produced an attenuation of thermal stimuli of the exercised limb to innocuous stimuli, but did not have an effect on tactile or heat pain thresholds. In comparison, cycle ergometer exercise produced an intensity-dependent multisegmental attenuation of tactile and thermal sensitivity lasting approximately 15 to 30 minutes following exercise.

1.4 Summary

Analgesia following exercise has been found by a number of investigators using a variety of noxious stimuli, and results have been summarised in table I. Increased pain thresholds and tolerances, as well as lower pain ratings, have been found to occur following exercise, and 2 other reviews of literature have also reported similar results.[5,6] The results for exercise-induced analgesia appear to be more consistent for studies that used electrical or pressure stimuli to produce pain, and less consistent for studies that used temperature stimulation to produce pain. The equivocal results for temperature stimulation may be due to changes in skin and body temperature that can occur during exercise depending upon the intensity and duration of the exercise. Previously, it has been shown that with an increase in skin temperature, both warm and cool thresholds are obtained at a higher stimulation temperature.[32,33] However, Kojo and Pertovaara[33] also reported that heat pain thresholds were only minimally, if at all, influenced by a change in skin or body temperature. It is currently unclear how changes in skin or body temperature associated with exercise interacts with heat or cold pain thresholds. Thus, additional research is needed in this area. Analgesia following exercise appears to be most consistent when the exercise stimulus involves exercise performed at higher intensities (i.e. > 70% of maximal aerobic capacity). Currently, the mechanism(s) for analgesia following exercise are poorly understood. Results from studies that have examined the involvement of the endogenous opioid system in the analgesic response following exercise are mixed. Some investigators have found that naloxone administration attenuated the post-exercise analgesic response.[12,14,19,23] However, other investigators did not find that analgesia following exercise was affected by naloxone administration.[4,12,13,19]

2. Animal Research

The most compelling evidence to support analgesia following exercise and the involvement of the endogenous opioid system have been provided by animal experimentation. Most of this research has investigated whether exercise-induced analgesia is mediated by endogenous opioid mechanisms, and the predominant exercise stimulus used in the animal research has been swimming. For example, Bodnar et al.[34] examined whether different doses of naloxone would eliminate analgesia produced by cold water swims in 18 male rats. Naloxone at doses of 0, 1, 5, 10 and 20 mg/kg were adminis-

Table I. Human studies of exercise-induced analgesia

Investigators	Participants	Exercise stimulus	Results
Electrical stimulus			
Pertovaara et al.[7]	6 men	Cycle ergometer (50-200W)	Increase in dental pain thresholds at 200W
Kemppainen et al.[8]	7 men	Cycle ergometer (100-300W)	Increase in dental pain thresholds at 200W
Kemppainen et al.[9]	6 men	Cycle ergometer (200-300W), placebo and cyroheptadine conditions	Increase in dental pain thresholds at 300W in both conditions
Kemppainen et al.[10]	6 men	Cycle ergometer (100-200W) placebo and dexamethasone conditions	Increase in dental pain thresholds at 100-200W in placebo condition but only at 200W in dexamethasone condition
Olausson et al.[12]	8 men, 3 women	Arm and leg ergometer (20 minutes), placebo and naloxone conditions	Increase in dental pain thresholds in placebo and naloxone conditions
Droste et al.[14]	17 men with myocardial ischaemia	Cycle ergometer (to exhaustion), placebo and naloxone condition	No increase in finger pain thresholds in placebo or naloxone conditions
Droste et al.[13]	10 men	Cycle ergometer (to exhaustion), placebo and naloxone conditions	Increase in dental and finger pain thresholds in placebo and naloxone conditions
Guieu et al.[15]	6 athletes	Cycle ergometer (20 minutes)	Increase in the thresholds of the nociceptive reflex
Temperature stimulus			
Padawer & Levine[16]	91 men and women	Cycle ergometer (50 and 70% of HR_{max})	No analgesic response for cold pressor stimuli following exercise
Janal et al.[19]	12 runners	10km run at 85% of max, placebo and naloxone conditions	Analgesic response following exercise for thermal and ischaemic pain stimuli but not for cold pressor stimuli
Sternberg et al.[20]	34 male athletes, 33 female athletes	Athletic competition	Decrease in pain reports following competition for cold pressor stimuli
Kemppainen et al.[21]	8 pilots with pain, 8 pilots without pain	Cycle ergometer (50-200W)	Increase in pain thresholds for pilots with pain. Pain ratings decreased for both groups
Fuller & Robinson[22]	22 men	10km run	Discriminability decreased for 44 and 46°C radiant heat but not for 48°C
Paalasmaa et al.[32]	11 men	Isometric and cycle ergometer	Increase in heat thresholds following cycle exercise but not for isometric exercise
Pressure stimulus			
Haier et al.[23] (study 1)	9 men, 4 women	1-mile run, placebo and naloxone conditions	Increase in pain thresholds for both conditions
Haier et al.[23] (study 2)	4 men, 2 women	1-mile run, placebo and naloxone conditions	Increase in pain thresholds for placebo condition
Gurevich et al.[24]	60 men	12 minutes step exercise at 63% of maximum	Increase in pain tolerance and lower pain ratings following exercise
Koltyn et al.[25]	14 men, 2 women	30-minute cycle ergometer (75% of maximum)	Increase in pain thresholds and decrease in pain ratings following exercise
Bartholomew et al.[27]	17 men	20 minutes self-selected exercise (cycle ergometer or resistance exercise)	Increase in pain tolerances but not pain thresholds
Koltyn & Arbogast[28]	7 men, 6 women	45 minutes resistance exercise at 75% of maximum	Increase in pain thresholds and decrease in pain ratings following exercise
Kosek & Ekholm[29]	14 women	Isometric exercise at 21% of maximum to exhaustion	Increase in pain thresholds during and following exercise
Kosek et al.[30]	28 women (14 with fibromyalgia, 14 healthy controls)	Isometric exercise at 21% of maximum to exhaustion	Increase in pain thresholds during and following exercise in the healthy control women but not in the women with fibromyalgia
Other stimulus			
Vecchiet et al.[26]	10 men	30 minutes cycle ergometer at 70% HR_{max}	Increase in pain associated with an injection of 10% sodium chloride after exercise

HR_{max} = maximum heart rate.

tered at weekly intervals immediately preceding cold water swims (3.5 minutes in 2°C water). Alterations in flinch jump-thresholds were determined 30 minutes following the swims. Thresholds were found to be elevated following cold water swimming in comparison to a control condition, and naloxone produced a mild, dose-dependent reduction in analgesia following the swim. However, even at doses normally sufficient to block opiate analgesia, naloxone did not fully reverse the analgesia, which may indicate the possible existence of a parallel non-opiate system.

Willow et al.[35] examined the analgesic response following swimming in female mice. Changes in pain thresholds were assessed by placing mice on a hot plate maintained at 56°C, and recording the time it took for a flick of a hind limb to occur. Two groups of mice were swum in 20°C for 3 minutes. One group received 100 μg/kg of naloxone 1 hour prior to the swim, while the other group received saline. Results indicated that there was a significant increase in pain thresholds in the saline group but no increase in pain thresholds in the group that received naloxone. The investigators concluded that the stress of swimming, or some consequence of the swimming, was sufficient to activate a mechanism which reduced sensitivity to pain. This effect was greater than the analgesia obtained with the injection of 15 mg/kg of morphine. Furthermore, since analgesia following swimming was eliminated by naloxone, 'it seems likely that this mechanism involves enkephalins, endorphins or some comparable endogenous opioid'.

Changes in tail flick latencies following warm water swims were examined by Christie et al.[36] Female mice were swum for 3 minutes in 32°C water. Results indicated a significantly longer tail flick latency after swimming compared to control mice which did not swim. The leu-enkephalin (LE) binding to brain homogenates was also examined, and it was found that the LE binding was significantly reduced following swimming compared with the control condition, which may suggest involvement of endogenous opioids.

Cooper and Carmody[37] examined the time course of analgesia induced by swimming, as well as the effect of water temperature on body temperature and the analgesic response in mice. Male mice were swum for different time periods in different water temperatures, and pain thresholds were assessed before and following the swim by recording the time of a flick of a hind limb after the animal was placed on a hot plate. Results showed that pain thresholds were increased significantly 1 minute after the swim, with a linear decline in pain thresholds through 30 minutes. A swim as short as 15 seconds was associated with a significant increase in pain thresholds, and with longer swims (up to 7.5 minutes) the magnitude of analgesia was found to increase. Pain thresholds were found to be elevated following swims in water temperatures of 31 and 38°C in the absence of a significant change in body temperature, and with further decreases in water temperature, body temperature dropped and the magnitude of the analgesic response increased significantly.

O'Connor and Chipkin[38] investigated the effects of warm and cold water swims on tail flick latencies in male mice. Response latencies were measured by shining a radiant heat lamp on the middle section of the tail and measuring the withdrawal response time before and after warm (32°C) and cold (2°C) water swims. To first determine the appropriate control group, tail flick latencies of dry versus wet mice were compared. Separate groups of mice were tested in 3 different conditions: (i) dry; (ii) briefly (< 2 seconds) dunked in water with excess moisture wiped from the tails; and (iii) tails that were moistened with water outside the bath and then dried. Results indicated that the dry mice had significantly shorter tail flick latencies than the wet mice, implying that the dampness of the tail can contribute to the increase in tail flick latencies. Therefore, in the next study, wet mice were used as the relevant control group and were compared to the group of mice that were swum. Cold water swimming was associated with a significant increase in tail flick latencies which was not blocked by naloxone. Warm water swimming up to 3 minutes produced an inconsistent effect on tail flick latencies, and naloxone was found to atten-

uate the response. These results suggested the analgesic effect following exercise in warm and cold water may be mediated by different mechanisms.

Examination of the influence of various parameters of cold water (2°C) swims on exercise-induced analgesia were conducted by Giradot and Holloway.[39] Male rats were exposed to: (i) various durations of cold water swims; (ii) intermittent *vs* continuous cold water swims; and (iii) 60 consecutive cold water swims in naltrexone and saline conditions. Naltrexone administered 10 minutes before the swim partially antagonised continuous cold water swim analgesia, but only at high doses of naltrexone (21 mg/kg). However, at lower doses (14 mg/kg) naltrexone did significantly antagonise intermittent cold water swims and enhanced the analgesic response produced by 60 consecutive swims. These results demonstrate that naltrexone differentially influences cold water swim analgesia depending upon specific parameters of the exercise condition, including the duration of the swim, whether the swim was intermittent or continuous, or whether a large number of consecutive cold water swims were completed.

Examination of the interaction between exercise and water temperature in determining the opioid or non-opioid analgesic response to swimming was investigated by Terman et al.[40] Seventy-two male rats were divided into 6 groups (n = 12), and swam in water of different temperatures (10, 15, 20 or 40°C water) for either 3, 5 or 10 minutes. Half of the rats received naltrexone hydrochloride and the other half received saline. Pain sensitivity was assessed using the tail-flick test, with analgesia defined as a significant increase in response latency time relative to baseline. No significant changes in tail-flick latencies were found following swimming in 40°C water for 5 minutes. However, there were significant increases in tail-flick latencies following swimming in the other water temperatures. Naltrexone was found to significantly attenuate the analgesic response for the 3 and 5 minute swims in 15 and 20°C water, but had no effect on the analgesic response for the 10-minute swims in 15°C water or for the 5-minute swims in 10°C water. Thus, analgesia from the longest duration or coldest water swims was insensitive to naltrexone, whereas analgesia induced by briefer or warmer water swims was reduced by naltrexone. It appears that the severity of the stressor plays a role in determining the neurochemical mediation of analgesia.

Carmody and Cooper[41] examined the influence of swimming on chronic pain in mice. Chronic pain can be induced in mice with subcutaneous formalin injections, and Carmody and Cooper found that 3 minutes of swimming in 20 to 21°C water produced a significant reduction in pain behaviours which persisted for 30 minutes following the swim. Also, this analgesia appears to be opioid in nature since naloxone (1 mg/kg) abolished the analgesic response following swimming.

Tierney et al.[42] examined the influence of the duration of swim on the analgesic response. Female mice completed swims between 15 seconds and 5 minutes in 20 to 22°C water. Half of the animals were pre-treated with naloxone (5 mg/kg) and the other half were pre-treated with saline. Results indicated that there was a significant increase in analgesia as measured by tail-flick latencies following the 15-second swim, and this analgesia increased progressively as the swim duration was extended to 5 minutes. No significant differences were found between the naloxone and saline conditions following the 15-second swim. However, an opioid analgesia was reported to develop as the duration of swim increased. The investigators concluded that the duration of the swim influences the nature of the analgesia, and that there appears to be multiple analgesia systems (opioid and non-opioid) involved in this type of analgesia.

Shyu et al.[43] conducted one of the few studies that has used a running protocol rather than a swimming protocol as the exercise stimulus. Male spontaneously hypertensive (SHR) and normotensive (WKY) rats were trained to run spontaneously in running wheels. After 3 to 4 weeks of training, pain sensitivity (squeak threshold to electrical stimulation) was measured between 8 and 9am when the animals were at the end of their running activity during the dark phase. Squeak thresholds were found to be significantly elevated in the early morning in

those rats that ran during the dark phase. The magnitude of change of squeak thresholds varied across animals, and was found to correlate significantly (r = 0.80) with the amount of running activity. Also, the effect of naloxone and saline administration on squeak thresholds was examined between 8 and 9am in 6 SHR rats. Saline administration was not found to change squeak thresholds, but naloxone administration was found to decrease squeak thresholds to baseline levels, indicating involvement of the endogenous opioid system.

Hoffman et al.[44] investigated whether skeletal muscle stimulation in the rat would alter pain thresholds, because it has been suggested that the analgesic effect of exercise is mediated by activation of group III and/or IV afferents from skeletal muscle. Sixty minutes of low frequency muscle stimulation of the hind leg was found to increase pain thresholds in male SHR rats. The analgesic response peaked after 120 minutes following stimulation, and lasted for an additional 2 hours. Additionally, 1 group of rats was pretreated with dl-p-chlorophenylalanine (PCPA), a serotonin synthesis blocker, to examine the role of serotonin in the analgesic response to muscle stimulation. Results indicated that PCPA completely abolished the post-stimulatory analgesia, indicating that serotonin systems are involved in the analgesic response following muscle stimulation.

Yao et al.[45] activated group III muscle afferents using prolonged low frequency stimulation of the sciatic nerve, and examined the role of endorphin and serotonin systems on pain thresholds and blood pressure responses. Pain thresholds, blood pressure and heart rate were assessed before and following 30 minutes of low frequency stimulation of the sciatic nerve in adult, male, SHR rats. Sciatic stimulation significantly elevated pain thresholds, and a dose of naloxone (1 ml/kg IV) had an immediate antagonistic effect on the analgesic response. However, a larger dose of naloxone (10 to 15 mg/kg IV) was required to attenuate the blood pressure responses following stimulation. Furthermore, serotonin was found to be involved in the blood pressure responses following sciatic stimulation.

Very little is known about the neurochemical basis of non-opioid analgesia. Marek et al.[46] examined the involvement of *N*-methyl-*D*-aspartic acid (NMDA) subtype of excitatory amino acid receptors in non-opioid analgesia. The influence of a NMDA antagonist dizocilpine (MK-801) on the analgesic response following swimming was studied in control (C) mice, and in mice selectively bred for high (HA) or low (LA) swim-induced analgesia. Mice (C, HA and LA) were randomly assigned to 1 of 4 groups consisting of: (i) naloxone; (ii) dizocilpine; (iii) a combination of naloxone and dizocilpine; and (iv) saline administered 20 minutes before the baseline assessment of hot-plate latencies. The mice then completed 3 minutes of swimming in water temperatures of 15, 20 and 32°C in 3 separate experiments. Dizocilpine was found to attenuate the analgesic response following the swim in 15°C water in which naloxone was ineffective, but had no influence on the analgesic response following the swim in 32°C water, which naloxone blocked completely. A combination of naloxone and dizocilpine was found to attenuate the analgesic response following swimming in 20°C water in the C and HA mice. It was concluded that dizocilpine selectively blocked non-opioid mechanisms of analgesia following swimming in 15°C water.

In summary, exercise-induced analgesia has been demonstrated in male rats and male and female mice, and results from this research are summarised in table II. However, most of the research has employed a forced swimming protocol, and a question has arisen regarding whether the analgesia produced following swimming is a result of the stressful nature of forced swimming itself or secondary to changes in body temperature (i.e. hypothermia) produced by the swim.[40,46] However, Terman et al.[40] and Marek et al.[46] argue against the notion that analgesia is a result of hypothermia due to a number of different reasons including: (i) swim-induced analgesia and hypothermia can be pharmacologically dissociated in that naloxone can block the analgesic response following swimming but not the hypothermic response;[40] (ii) analgesia has been found to occur following swimming in the absence of a significant

Table II. Animal studies of exercise-induced analgesia

Investigators	Study animals	Exercise stimulus	Results
Electrical stimulus			
Bodnar et al.[34]	Male albino rats	3.5-minute swim in 2°C water, various naloxone conditions	Increase in flinch jump thresholds, but naloxone produced dose-dependent decrease in analgesia
Christie et al.[36]	Female QS mice	3-minute swim in 32°C water	Increase in tail flick latency
Shyu et al.[43]	Male SHR and normotensive rats	Wheel running during dark phase	Increase in squeak thresholds but naloxone attenuated the analgesic response
Yao et al.[45]	Male SHR rats	60-minute muscle stimulation, control and PCPA groups	Increase in squeak threshold but PCPA blocked analgesic response
Terman et al.[40]	Male rats	Swim in various water temperatures, placebo and naltrexone conditions	Increase in tail flick latencies in all water temperatures except 40°C. Naltrexone attenuated analgesic response in 15 and 20°C water
Hoffman et al.[44]	Male SHR rats	60-minute muscle stimulation, control and PCPA groups	Increase in squeak threshold but PCPA blocked analgesic response
Temperature stimulus			
Willow et al.[35]	Female albino mice	3-minute swim in 20°C water, placebo and naloxone conditions	Increase in hind limb flick when exposed to hot plate in placebo but not naloxone group
Cooper & Carmody[37]	Male mice	Swims of different durations and water temperatures	Increase in hind limb flick in all conditions
O'Connor & Chipkin[38]	Male mice	Swim in 2 and 32°C water, placebo and naloxone conditions	Increase in tail flick latency in 2°C water but inconsistent effects in 32°C. Naloxone blocked response in 32°C water
Giradot & Holloway[39]	Male albino rats	Various swims in 20-21°C water, placebo and naltrexone conditions	Mixed results
Tierney et al.[42]	Female albino mice	Swims of various durations in 20-22°C water, placebo and naloxone groups	Increase in tail flick latencies. However, naloxone attenuated increase in longer duration swims
Marek et al.[46]	Male and female mice	3-minute swim in 15, 20 and 32°C water, placebo, dizocilpine and naloxone conditions	Dizocilpine blocked analgesia in 15°C water, naloxone blocked analgesia in 32°C water, combination blocked analgesia in 20°C water
Other stimulus			
Carmody & Cooper[41]	Male mice	3-minute swim in 20-21°C water, placebo and naloxone conditions	Decrease in pain behaviour and naloxone abolished the response

PCPA = dl-p-chlorophenylalanine; **SHR** = spontaneously hypertensive.

change in body temperature;[37] and (iii) analgesia has been found following other stressors, including footshock and rotation, that do not result in a change in body temperature.[40] Furthermore, in order to address the question of whether analgesia following swimming is a function of the forced nature of the swim, Shyu et al.[43] used spontaneous wheel running as the exercise stimulus, and found analgesia to occur in those animals that ran spontaneously.

It appears from animal research that multiple analgesia systems exist (opioid and non-opioid) and that properties of the exercise stressor are important in determining which system is activated during exercise. It has been shown that by manipulating the parameters of the exercise stressor, it is possible to elicit either naloxone-reversible or naloxone-insensitive analgesia following exercise. Some of the parameters that have been manipulated in the animal research include: (i) duration of the exercise session; (ii) using continuous *vs* intermittent exercise; and (iii) varying the water temperature for the swim protocols. Naloxone has been found to attenuate the analgesic response following exercise in warmer water temperatures but has not had a consistent effect on analgesia following exercise in colder water temperatures. These results suggest that multiple analgesia systems, including opioid and non-opioid systems, exist in this type of anal-

gesia. The specific neurochemistry of non-opioid analgesia is unclear, but several neurotransmitters, such as serotonin and norepinephrine (noradrenaline), have been implicated.[44] Also, NMDA has recently been examined for its potential involvement in non-opioid analgesic responses that occur following exercise.[46]

3. Discussion and Conclusions

Analgesia following exercise has been found to occur in humans and animals by a number of investigators. Running, cycling and swimming have consistently been associated with an analgesic response following exercise, although analgesia following swimming has only been studied in rodents. Research with other modes of exercise, such as resistance exercise and isometric exercise, has been very limited. However, preliminary results indicate that analgesia can occur following resistance exercise and isometric exercise, but the time course of the analgesic response following these types of exercise needs further examination. More research is needed to expand our understanding of analgesic responses following different modes of exercise. Also, the mechanisms underlying exercise-induced analgesia have proven to be complex, and the exact mechanism(s) responsible for exercise-induced analgesia are not entirely clear at this time. The most commonly tested hypothesis in both the human and animal literature is that activation of the endogenous opioid system during exercise may be responsible for the analgesic response following exercise. However, the data regarding this hypothesis are mixed in human research. There appears to be more consistent support for involvement of endogenous opioids in exercise-induced analgesia in animal research, but non-opioid analgesia following exercise has also been identified in animals. Additional research is needed to clarify and expand our understanding of the mechanisms responsible for exercise-induced analgesia. Furthermore, application of the latest neural imagining techniques (e.g. positron emission tomography, regional cerebral blood flow) could potentially expand our understanding of the brain circuitry involved in analgesia following exercise.

There is also a need for more research examining whether analgesia occurs following exercise in women. Most of the research in this area has involved the testing of men. In several of the studies that have been conducted, a mixed sample of men and women were used, but the number of women in these studies was very small. In the general pain literature, there are reports of gender differences in experimentally-induced pain.[47-49] Currently, it is unclear if men and women differ in exercise-induced analgesia because very little research has been conducted in this area. Further research is needed examining exercise-induced analgesia in women, and whether men and women differ in analgesic responses following exercise.

Research is also needed to examine whether analgesia occurs following exercise in individuals experiencing chronic painful conditions. Most of the exercise-induced analgesia research has involved the testing of healthy individuals who regularly exercise, and it is currently unclear whether individuals who are experiencing a chronic painful condition will experience analgesia following an exercise session. It is possible that exercise may exacerbate an already existing painful condition, and there is some research with patients with fibromyalgia to support this possibility.[30,31] However, there are a number of different chronic conditions (e.g. low back pain, arthritic pain, headache pain) and research is needed to determine if exercise can serve as an effective pain management intervention.

References

1. Terman GW, Shavit Y, Lewis JW, et al. Intrinsic mechanisms of pain inhibition: activation by stress. Science 1984; 226: 1270-7
2. Beecher HK. Pain in men wounded in battle. Ann Surg 1946; 123: 96-105
3. Beecher HK. Relationship of significance of wound to pain experienced. JAMA 1956; 161: 1609-13
4. Black J, Chesher GB, Starmer GA. The painlessness of the long distance runner. Med J Aust 1979; 1: 522-3
5. Janal MN. Pain sensitivity, exercise and stoicism. J R Soc Med 1996; 89: 376-81
6. O'Connor PJ, Cook DB. Exercise and pain: the neurobiology, measurement, and laboratory study of pain in relation to exercise in humans. Exerc Sport Sci Rev 1999; 27: 119-66
7. Pertovaara A, Huopaniemi T, Virtanen A, et al. The influence of exercise on dental pain thresholds and the release of stress hormones. Physiol Behav 1984; 33: 923-6

8. Kemppainen P, Pertovaara A, Huopaniemi T, et al. Modification of dental pain and cutaneous thermal sensitivity by exercise in man. Brain Res 1985; 360: 33-40
9. Kemppainen P, Pertovaara A, Huopaniemi T, et al. Elevation of dental pain threshold induced in man by physical exercise is not reversed by cyproheptadine-mediated suppression of growth hormone release. Neurosci Lett 1986; 70: 388-92
10. Kemppainen P, Paalasmaa P, Pertovaara A, et al. Dexamethasone attenuates exercise-induced dental analgesia in man. Brain Res 1990; 519: 329-32
11. Guillemin R, Vargo T, Rossier J, et al. Beta-endorphin and adrenocorticotropin are secreted concomitantly by the pituitary gland. Science 1997; 197: 1367-9
12. Olausson B, Eriksson E, Ellmarker L, et al. Effects of naloxone on dental pulp pain threshold following muscle exercise and low frequency transcutaneous nerve stimulation: a comparative study in man. Acta Physiol Scand 1986; 126: 299-305
13. Droste C, Greenlee MW, Schreck M, et al. Experimental pain thresholds and plasma beta-endorphin levels during exercise. Med Sci Sports Exerc 1991; 23: 334-42
14. Droste C, Meyer-Blankenburg M, Greenlee MW, et al. Effect of physical exercise on pain thresholds and plasma beta-endorphins in patients with silent and symptomatic myocardial ischemia. Eur Heart J 1988; 9: 25-33
15. Guieu R, Blin O, Pouget J, et al. Nociceptive threshold and physical activity. Can J Neurol Sci 1992; 19: 69-71
16. Padawer WJ, Levine FM. Exercise-induced analgesia: fact or artifact? Pain 1992; 48: 131-5
17. Pertovaara A, Kemppainen P. Comments on Padawer and Levine [letter]. Pain 1992; 50: 239-40
18. Droste C, Greenlee MW. Comments on Padawer and Levine [letter]. Pain 1992; 50: 241
19. Janal MN, Colt EWD, Clark WC, et al. Pain sensitivity, mood and plasma endocrine levels in man following long distance running: effects of naloxone. Pain 1984; 19: 13-25
20. Sternberg WF, Bailin D, Grant M, et al. Competition alters the perception of noxious stimuli in male and female athletes. Pain 1998: 76: 231-8
21. Kemppainen P, Hamalainen O, Kononen M. Different effects of physical exercise on cold pain sensitivity in fighter pilots with and without the history of acute in-flight neck pain attacks. Med Sci Sports Exerc 1998; 30: 577-82
22. Fuller AK, Robinson ME. A test of exercise analgesia using signal detection theory and a within-subjects design. Percept Mot Skills 1993; 76: 1299-310
23. Haier RJ, Quaid K, Mills JSC. Naloxone alters pain perception after jogging. Psychiatry Res 1981; 5: 231-2
24. Gurevich M, Kohn PM, Davis C. Exercise-induced analgesia and the role of reactivity in pain sensitivity. J Sports Sci 1994; 12: 549-59
25. Koltyn KF, Wertz AL, Gardiner RL, et al. Perception of pain following aerobic exercise. Med Sci Sports Exerc 1996; 28: 1418-21
26. Vecchiet L, Marini I, Colozi A, et al. Effects of aerobic exercise on muscular pain sensitivity. Clin Ther 1984; 6: 354-63
27. Bartholomew JB, Lewis BP, Linder DE, et al. Post-exercise analgesia: replication and extension. J Sports Sci 1996; 14: 329-34
28. Koltyn KF, Arbogast RW. Perception of pain after resistance exercise. Br J Sports Med 1998; 32: 20-4
29. Kosek E, Ekholm J. Modulation of pressure pain thresholds during and following isometric contractions. Pain 1995; 61: 481-6
30. Kosek E, Ekholm J, Hansson P. Modulation of pressure pain thresholds during and following isometric contraction in patients with fibromyalgia and in healthy controls. Pain 1996; 64: 415-23
31. Bengtsson M, Bengsston A, Jorfeld L. Diagnostic epidural opioid blockade in primary fibromyalgia at rest and during exercise. Pain 1989; 39: 171-80
32. Paalasmaa P, Kemppainen P, Pertovaara A. Modulation of skin sensitivity by dynamic and isometric exercise in man. Eur J Appl Physiol 1991; 62: 279-85
33. Kojo I, Pertovaara A. The effects of stimulus area and adaptation temperature on human heat pain and warm thresholds. Int J Neurosci 1987; 32: 875-80
34. Bodnar RJ, Kelly DD, Spiaggia KA, et al. Dose-dependent reductions by naloxone of analgesia induced by cold-water stress. Pharmacol Biochem Behav 1978; 8: 667-72
35. Willow M, Carmody J, Carroll P. The effects of swimming in mice on pain perception and sleeping time in response to hypnotic drugs. Life Sci 1980; 26: 219-24
36. Christie MJ, Chesher GB, Bird KD. The correlation between swim-stress induced antinociception and [3H] Leu-enkephalin binding to brain homogenates in mice. Pharmacol Biochem Behav 1981; 15: 853-7
37. Cooper K, Carmody J. The characteristics of the opioid-related analgesia induced by the stress of swimming in the mouse. Neurosci Lett 1982; 31: 165-70
38. O'Connor P, Chipkin RE. Comparisons between warm and cold water stress in mice. Life Sci 1984; 35: 631-9
39. Giradot MN, Holloway FA. Cold water stress analgesia in rats: differential effects of naltrexone. Physiol Behav 1984; 32: 547-55
40. Terman GW, Morgan MJ, Liebeskind JC. Opioid and non-opioid stress analgesia from cold water swim: importance of stress severity. Brain Res 1986; 372: 161-71
41. Carmody J, Cooper K. Swim stress reduces chronic pain in mice through an opioid mechanism. Neurosci Lett 1987; 74: 358-63
42. Tierney G, Carmody J, Jamieson D. Stress analgesia: the opioid analgesia of long swims surpasses the non-opioid analgesia induced by short swims in mice. Pain 1991; 46: 89-95
43. Shyu BC, Andersson SA, Thoren P. Endorphin mediated increase in pain threshold induced by long-lasting exercise in rats. Life Sci 1982; 30: 833-40
44. Hoffman P, Skarphedinsson JO, Delle M, et al. Electrical stimulation of the gastrocnemius muscle in the spontaneously hypertensive rat increases the pain threshold: role of serotonergic receptors. Acta Physiol Scand 1990; 138: 125-31
45. Yao T, Andersson S, Thoren P. Long-lasting cardiovascular depressor response following sciatic stimulation in spontaneously hypertensive rats: evidence for the involvement of central endorphin and serotonin systems. Brain Res 1982; 244: 295-303
46. Marek P, Mogil JS, Sternberg WF, et al. N-Methyl-D-Aspartic acid (NMDA) receptor antagonist MK-801 blocks non-opioid stress-induced analgesia: II. Comparison across three swim-stress paradigms in selectively bred mice. Brain Res 1992; 578: 197-203
47. Riley JL, Robinson ME, Wise EA, et al. Sex differences in the perception of noxious experimental stimuli: a meta-analysis. Pain 1998; 74: 181-7
48. Fillingim RB, Maixner W. Gender differences in the responses to noxious stimuli. Pain Forum 1995; 4: 209-21
49. Berkley KJ. From psychophysics to the clinic? Pain Forum 1995; 4: 225-7

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