High-Intensity Extended Swimming Exercise Reduces Pain-Related Behavior in Mice: Involvement of Endogenous Opioids and the Serotonergic System

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Abstract: The present study examined the hyponociceptive effect of swimming exercise in a chemical behavioral model of nociception and the mechanisms involved in this effect. Male mice were submitted to swimming sessions (30 min/d for 5 days). Twenty-four hours after the last session, we noticed that swimming exercise decreased the number of abdominal constriction responses caused by acetic acid compared with the nonexercised group. The hyponociception caused by exercise in the acetic acid test was significantly attenuated by intraperitoneal (i.p.) pretreatment of mice with naloxone (a nonselective opioid receptor antagonist, 1 mg/kg), r-chlorophenylalanine methyl ester (PCPA, an inhibitor of serotonin synthesis, 100 mg/kg once a day for 4 consecutive days), and by bilateral adrenalectomy. Collectively, the present results provide experimental evidences indicating for the first time that high-intensity extended swimming exercise reduces pain-related behavior in mice. The mechanisms involve an interaction with opioid and serotonin systems. Furthermore, endogenous opioids released by adrenal glands probably are involved in this effect.

Perspective: Our results indicate that high-intensity extended exercise endogenously controls acute pain by activation of opioidergic and serotonergic pathways. Furthermore, these results support the use of exercise as a nonpharmacological approach for the management of acute pain.

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Physical exercise exerts many benefits for physical and mental health. It reduces disease incidence6; promotes neuroprotection, neuroplasticity,22,60 cognition improvement7; and has anxiolytic and antide-
eyes, heart, kidneys, gastrointestinal tract, spinal cord, and brain. In addition, chromaffin cells of the adrenal medulla have been well characterized as a rich source of endogenous opioids that may be useful in pain control. Pierce et al performed a study measuring plasma endorphin levels before and after endurance exercise, defined as 45 minutes of high-intensity aerobic. Results indicated a significant increase in endorphin levels after the exercise as compared with levels before exercise. Such findings support the idea that opioid peptides may be released as a result of exercising vigorously for a specific amount of time.

Published studies reveal that incremental graded and short-term anaerobic exercise leads to an increase in \( \beta \)-endorphin levels. The extent of this increase correlates with the lactate concentration. During incremental graded exercise \( \beta \)-endorphin levels increase when the anaerobic threshold has been exceeded or at the point of a disproportionate increase in lactate. In endurance exercise performed at a steady-state between lactate production and elimination, blood \( \beta \)-endorphin levels do not increase until exercise duration exceeds approximately 1 hour, with the increase being exponential thereafter.

Various intensities of exercise have been used in different studies, and it is currently unclear if there is a specific intensity of exercise that is necessary to produce hypoalgesia. However, it has been reported that high-intensity exercise produces hypoalgesia. Despite the growing amount of experimental data on physical exercise and nociception, the precise mechanisms through which high-intensity exercise causes hyponociception remain elusive. The specific neurochemistry of nonopioid hyponociception is unclear, but several neurotransmitters, such as serotonin and norepinephrine, have been implicated. Hoffmann et al 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 rats. But when the animals were pretreated with \( \rho \)-chlorophenylalanine methyl ester (PCPA), a serotonin synthesis blocker, the post-stimulatory analgesia was completely abolished, indicating that serotonin systems are involved in the analgesic response after muscle stimulation.

Thus, the aim of the present study was to investigate hyponociception after a high-intensity extended exercise protocol, as well as the potential mechanisms for this hyponociceptive response in mice. For this purpose, we used swimming exercise in the context of a chemical behavioral model of nociception. To address the mechanisms that underlie hyponociception after high-intensity extended swimming exercise, we treated mice with a nonselective opioid receptor antagonist (naloxone), a tryptophan hydroxylase enzyme inhibitor (\( \rho \)-chlorophenylalanine methyl ester) and adrenalectomy.

Materials and Methods

Animals

Male Swiss mice (25 to 35 g) obtained from Federal University of Santa Catarina (UFSC), were maintained at constant room temperature of 22° ± 2° C under a 12-hour light/dark cycle (lights on at 6:00 AM), with access to food and water ad libitum. Mice (n = 8 to 10 animals per group) were used only once and were acclimatized to the laboratory for at least 1 hour before testing, which was conducted during the light cycle. The experiments were performed after approval of the protocol by the Institutional Ethics Committee for Animal Research of Federal University of Santa Catarina. All experiments were conducted in accordance with current guidelines for the care of laboratory animals and the ethical guidelines for investigations of experimental pain in conscious animals. The number of animals and intensities of noxious stimuli used were the minimum necessary to demonstrate a consistent effect of the exercise.

Swimming Exercise Protocol

Animals were placed in a plastic box divided in eight compartments (170 × 100 mm), filled with 35 L of water at 37° C. Liquid soap (8 mL) was added to reduce surface tension and to abolish the “floating” behavior. After each exercise session, animals were gently dried with a cloth towel. Control (nonexercised) mice were allowed to swim for just 30 seconds each day and were then gently dried. Another nonexercised group was exposed to shallow water (3 cm of depth) for 30 minutes each day, mice could stand normally with their head out of the water, did not need to swim.

The swimming exercise protocol was adapted from Kuphal et al, as illustrated in Table 1. Mice were randomly assigned to nonexercised or exercised groups. Mice in the exercised group were exposed to water for 30 seconds twice on the first day and for 2 minutes twice on the second day. Mice were thus acclimated to the new environment. On the third and fourth days, the animals were submitted to intermittent exercise. They swam for 10 minutes and had a 5-minute rest on the third day; swam for 15 minutes and had a 5-minute rest on the fourth day. In total, mice performed 30 minutes of swimming exercise. On the fifth, sixth and seventh days the animals swam continuously for 30 minutes. On the eighth day (24 hours after the last session of exercise) mice were submitted to behavioral testing.

Physical Exercise Intensity (Blood Lactate Concentration in Mice)

Blood lactate level was determined from 25 \( \mu \)L of tail capillary blood during the last session of exercise. The blood lactate concentration was analyzed at rest and then at 10, 20, and 30 minutes during swimming exercise (Table 2). The separate blood samples were put onto a glass fiber fleece where the erythrocytes were retained and placed in 1.5-mL Eppendorf tubes containing 50 \( \mu \)L sodium fluoride (1%). To avoid blood lactate dilution with residual water in the tails of the animals, the mice
were dried with a towel immediately before blood collection. The lactate concentrations were determined with a lactate analyzer (YSI Model 2700 SPORT; YSI, Yellow Springs, OH). Before each test, the equipment was calibrated according to the manufacturer’s instructions.

Behavioral Testing
Each exercise training session was conducted in the morning and the behavioral testing occurred in the morning of the next day, thus providing a 24-hour rest period. This time interval minimized the potentially confounding factor of stress-induced antinociception (SIA), which occurs on the order of minutes, not hours.54

Abdominal Constriction Induced by Acetic Acid and Peritoneal Capillary Permeability in Mice

The abdominal constrictions were induced according to procedures described previously5,52 and resulted in the contraction of the abdominal muscle together with a stretching of the hind limbs in response to an intraperitoneal (i.p.) injection of acetic acid (.6%, 0.45 mL/mouse) at the time of the test. In the beginning of the experiment, mice were pretreated intravenously with 2.5% Evans blue dye solution (10 mL/kg), used as a marker of peritoneal capillary permeability.36 One hour later the animals received the acetic acid injection and were then individually placed in glass cylinders of 20-cm diameter. The abdominal constrictions were counted cumulatively over a period of 20 minutes. The hyponociceptive activity was expressed as the reduction in the number of abdominal constrictions, for example, comparing control animals (nonexercised 30 seconds and nonexercised 30 minutes, shallow water) with exercise animals.

Immediately after the test, mice were killed by cervical dislocation; the peritoneal cavity was washed with 1.5 mL of sterile saline plus heparin (25 IU/mL); peritoneal liquid was then collected with automatic pipettes. Total leukocyte counts were performed using a Neubauer chamber via optical microscopy after diluting a sample of the peritoneal fluid with Türk solution (1:20). A sample of the collected fluid (1 mL) was centrifuged at 1000 rpm for 10 minutes, and the absorbance of the supernatant was read at 610 nm with an ELISA analyzer. The peritoneal capillary permeability induced by acetic acid is expressed in terms of dye (µg/mL), which leaked into the peritoneal cavity according to the standard curve expected for Evans blue dye.36 The procedure described above was accomplished in the following groups: 1) non-exercised 30 seconds in water and 2) exercised, exposed to intense swimming exercise protocol.

Measurement of Locomotor Activity
To exclude any unspecific locomotor effect caused by the exercise, the locomotor activity was evaluated. Ambulatory behavior was assessed in an open-field test11,50,51. The apparatus consisted of a wooden box measuring 40 × 60 × 50 cm. The floor of the arena was divided in 12 equal squares. At the start of each trial, a mouse was placed in the left corner of the field and was allowed to freely explore the arena. The number of squares crossed with all paws (crossing) was counted in a 6-minute session. The apparatus was cleaned with a solution of 10% ethanol between tests to hide animal clues.

Involvement of Endogenous Opioids
To investigate the role played by endogenous opioids in the hyponociceptive effect of exercise, nonexercised mice were pretreated with naloxone (1 mg/kg, i.p., a non-selective opioid receptor antagonist) or saline (.9% NaCl solution, 10 mL/kg, i.p.). After 20 minutes, the animals received an intraperitoneal injection of acetic acid. Another group of control mice received an injection of saline (10 mL/kg, i.p.) or naloxone (1 mg/kg, i.p.); after 20 minutes, they received morphine (5 mg/kg, subcutaneous, s.c.), and 30 minutes later, the acetic acid was intraperitoneally administered. The exercised group was pretreated with saline (10 mL/kg, i.p.) or naloxone (1 mg/kg, i.p.); after 20 minutes, the animals received an intraperitoneal injection of acetic acid. The abdominal constrictions were counted for 20 minutes.52

Role of Endogenous Opioid Release by Adrenal Glands
To evaluate the involvement of endogenous opioid release from adrenal glands in the hyponociceptive effect caused by swimming exercise animals were anesthetized with xylazine (10 mg/kg, i.p.) and ketamine (80 mg/kg, i.p.); both adrenal glands were removed through a dorsal
incision, as described previously. No postoperative analgesia was used because it can interfere with experimental results. After the surgery, the animals were returned to their cages and had free access to food and drink. The water was replaced with saline to maintain a physiological plasma sodium concentration. One week later, the animals were submitted to the swimming exercise protocol and then injected with acetic acid. For this experiment, the following groups were used: i) nonexercised, 30 seconds of swimming, ii) nonexercised/sham-operated, dorsal incision, iii) sham-operated/exercised group, 30 minutes/5 days of swimming and dorsal incision, iv) nonexercised/adrenalectomy, both adrenal glands removed through dorsal incision, and v) adrenalectomy/exercise.

**Involvement of the Serotonergic System**

To assess the possible contribution of endogenous serotonin to the hyponociceptive effect of exercise, animals were pretreated with \( \beta \)-chlorophenylalanine methyl ester (PCPA, 100 mg/kg, i.p., an inhibitor of serotonin synthesis) or with vehicle, once a day for 4 consecutive days. Then, 24 hours after the last PCPA or vehicle injection, animals were tested in the acetic acid–induced abdominal constriction test. For this experiment, the following groups were used: i) nonexercised group, ii) nonexercised/PCPA group, iii) exercised group, iv) morphine group, v) PCPA/morphine group, and vi) PCPA/exercise group.

**Drugs**

The following substances were used: morphine hydrochloride, acetic acid (Merck, Darmstadt, Germany), naloxone hydrochloride, \( \beta \)-chlorophenylalanine methyl ester (PCPA), sodium fluoride, xylazine, and ketamine (purchased from Sigma Chemical Company, St Louis, MO, USA). NaCl was supplied by Merck (Haar, Germany). Drugs were dissolved in isotonic saline solution (NaCl .9%) immediately before use. The drugs were administered by intraperitoneal and subcutaneous routes.

**Statistical Analysis**

All experimental results are given as mean ± SEM. Comparisons between experimental and control groups were performed by \( t \) test, 1-way ANOVA followed by the Newman-Keuls test, or 2-way ANOVA followed by Tukey HSD test for post hoc comparison when appropriate. A value of \( P < .05 \) was considered significant.

**Results**

**Animals Performed a High-Intensity Extended Swimming Exercise Protocol**

Endurance capacity can, from a metabolic point of view, be regarded as the highest steady-state energy supply from oxidative phosphorylation. Therefore, another approach to assess aerobic endurance performance is the determination of the highest constant exercise intensity that can be maintained for a longer period of time without a continuous rise in blood lactate. The maximal lactate steady state (MLSS) is presumably the highest blood lactate concentration at which equilibrium between lactate formation and elimination can be achieved during prolonged exercise at constant work load.

An increase in blood of not more than 1 mmol/L between 10 and 30 minutes during the constant-load trials appears to be the most reasonable procedure for MLSS determination. The MLSS represents the upper border of constant load endurance training. Intensities above the MLSS have been used to guide interval training sessions in different endurance sports.

At the end of the last day of the exercise protocol, the blood lactate level in the swimming exercise group was 3.43 ± .57 mmol/L at 10 minutes and 7.84 ± 1.40 mmol/L at 30 minutes. We observed an increase in lactate blood concentration of more than 1 mmol/L between 10 and 30 minutes during the constant-load swimming exercise. This suggests that the mice in our study performed the exercise at above-MLSS intensity.

**Abdominal Constriction Response Caused by Intraperitoneal Injection of Acetic Acid and Peritonitis in Mice**

The results presented in Fig 1 show that swimming exercise reduced the acetic acid-induced abdominal constrictions in mice by 44% ± 3% when compared with the control group (nonexercised). Notably, the 2 control groups (nonexercised 30 seconds and nonexercised 30 minutes in shallow water) had a similar response. Therefore, subsequent experiments were performed using only the nonexercised 30-second control group.

The swimming exercise, in the same conditions that caused inhibition of acetic acid-induced nociception in mice, did not alter cell migration (Fig 2A, 2B, and 2C) or
the Evans blue dye diffusion induced by acetic acid when compared with the nonexercised group (Fig 2D).

**Evaluation of Locomotor Activity**

The swimming exercise did not affect locomotor activity in the open-field test when compared with the nonexercised group. The mean ± SEM for crossing number was 74.4 ± 7 and 82.7 ± 4 for the nonexercised and exercised groups, respectively.

**Involvement of Endogenous Opioids**

Two-way ANOVA revealed significant main effects of naloxone pretreatment \([F(1,27) = 2.30; \ P < .05]\) and exercise \([F(1,27) = 14.92; \ P < .001]\), and a naloxone pretreatment x exercise interaction \([F(1,27)=6.16; \ P < .05]\). Post hoc analyses indicated that the pretreatment of mice with naloxone prevented \((P < .05)\) the antinociceptive effect elicited by swimming exercise (Fig 3).

The results presented in Fig 4 show that the pretreatment of mice with naloxone (1 mg/kg, i.p., a nonselective opioid receptor antagonist), given 20 minutes beforehand, completely reversed the antinociceptive effect caused by morphine (2.5 mg/kg, s.c., used as a positive control) \([F(1,27) = 354.74; \ P < .001]\).

**Involvement of the Endogenous Opioids Released by the Adrenal**

Two-way ANOVA revealed significant main effects of bilateral adrenalectomy of the animals \([F(1,29) = 2.41; \ P < .13]\) and exercise \([F(1,29) = 4.57; \ P < .05]\), and bilateral adrenalectomy of the animals x exercise interaction \([F(1,29) = 20.16; \ P < .001]\). Post hoc analyses indicated that the bilateral adrenalectomy of mice prevented \((P < .001)\) the antinociceptive effect induced by swimming exercise (Fig 5).

The results presented in Fig 5 show that bilateral adrenalectomy of the animals did not significantly affect acetic acid-induced writhing in nonexercised mice.
Moreover, the nociceptive response caused by acetic acid did not significantly differ between nonexercised and sham-operated/nonexercised groups (data not shown).

Involvement of the Serotonergic System

Two-way ANOVA revealed significant main effects of PCPA pretreatment \[F(1,31) = 11.00; P < .01\] and exercise \[F(1,31) = 23.52; P < .001\], and a PCPA pretreatment \times\ exercise interaction \[F(1,31) = 18.23; P < .001\]. Post hoc analyses indicated that the pretreatment of mice with PCPA prevented \(P < .001\) the antinociceptive effect caused by swimming exercise (Fig 6).

The results presented in Fig 7 show that the pretreatment of animals with PCPA (100 mg/kg, i.p., for 4 consecutive days) completely reversed the antinociceptive effect caused by morphine (2.5 mg/kg, i.p., used as a positive control) \[F(1,30) = 154.62; P < .01\].

Discussion

The results presented here show for the first time that high-intensity exercise produces hypnociceptive effects on chemical models of nociception in mice. The most relevant findings of the present work are the following: i) intense swimming exercise reduced the nociceptive response elicited by acetic acid and ii) the hypnociceptive effect of exercise in the acetic acid test was significantly reversed by intraperitoneal treatment of animals with naloxone (a nonspecific opioid receptor antagonist), PCPA (a tryptophan hydroxylase inhibitor) or bilateral adrenalectomy. Our data support the hypothesis that high-intensity extended swimming exercise reduces acute pain via opioid and serotonergic systems.

Exercise Reduces Acetic Acid-Induced Abdominal Constrictions

The results reported here indicate for the first time that intense swimming exercise, at an intensity that did not produce any important motor dysfunction or any detectable side effects, produced a marked hyponociceptive effect on acetic acid-induced visceral nociception. Moreover, acetic acid injection in the peritoneal cavity of mice promotes the release of many inflammatory mediators such as prostaglandin, bradykinin, substance P, tumor necrosis factor-α (TNF-α), interleukin-1β, interleukin-8, and others. In addition, these substances stimulate primary afferent neurons, enhancing aspartate and glutamate release in the cerebrospinal fluid. It has been demonstrated that swimming (particularly in cold water) produces the well-known phenomenon of stress-induced antinociception (SIA), which is mediated by both opioid and nonopioid mechanisms. A nonopioid mechanism includes the release of endogenous corticosteroids. Additionally, corticosteroids plays a critical role in the regulation of the inflammatory response, such that they can suppress inflammation, in part, by reducing cellular infiltration and plasma protein extravasation. The results of the present study also demonstrated that intense swimming exercise, at levels that cause hyponociception, was not capable of reducing leukocyte infiltration and plasma protein extravasation (Evans blue dye diffusion) induced by acetic acid in...
The present study showed that the opioid system probably is involved in the hyponociceptive effect of swimming exercise. This conclusion is derived from the fact that pretreatment of animals with naloxone, a nonselective opioid receptor antagonist, at a dose that produced no significant effect on acetic acid-induced visceral pain, completely inhibited the hyponociceptive effect of exercise. Therefore, we suggest that swimming exercise releases endogenous opioids like encephalin, endorphin or others that are responsible for hyponociception. This is in agreement with previous findings that strongly proposed activation of the opioid system as responsible for the analgesic response that occurs after exercise. ϒ-Endorphins can be released into the circulation by the pituitary gland or can be projected into various areas of the brain through nerve fibers. In addition, exercise of adequate intensity and duration was demonstrated to increase circulating ϒ-endorphin levels. Exercise generating >60% maximal oxygen consumption (VO₂ max) is needed to increase circulating ϒ-endorphin levels. Endorphins are primarily synthesized within the hypothalamus, the anterior pituitary gland and spinal nerves. Furthermore, chromaffin cells of the adrenal medulla store opioid peptides in several mammalian species. The results of the current study also revealed that the hyponociceptive effects of intense swimming exercise were inhibited by the bilateral adrenalectomy of mice, indicating that endogenous opioids released by adrenal glands might contribute to the hyponociceptive effect.
It is well known that serotonin (5-HT) pathways within the CNS arise from a series of nuclei situated in the midline of the brain stem, the raphe nuclei, which represent the richest source of neuronal 5-HT synthesized in the mammalian brain. In addition, several studies have shown that the bulbar serotonin nuclei that project to the spinal dorsal horn may suppress incoming noxious input to the spinal cord and inhibit pain transmission. Moreover, multiple 5-HT receptor types within the spinal cord appear to fulfill different roles in the control of nociception.

Skeletal muscle tissue consumes branched chain amino acids (BCAAs; ie, leucine, isoleucine, and valine). This consumption of BCAAs is increased during exercise; the BCAA concentration in blood will then tend to decrease. BCAAs enter the brain via the same carrier as tryptophan. Thus, if BCAA concentration goes down without a corresponding change in tryptophan level, more tryptophan will enter the brain. Tryptophan is the precursor of serotonin. Prolonged exercise has two effects. First, BCAA concentration decreases, thereby altering the ratio of tryptophan-BCAA entering the brain in favor of tryptophan. Second, prolonged exercise leads to increased levels of fatty acids in the blood. The increase in free fatty acids causes an increase in the ratio of free versus bound plasma tryptophan, which in turn causes a further increase in the amount of tryptophan entering the brain. The increased levels of brain tryptophan lead to an increase in the effects of serotonergic transmission.

Physical exercise results in an increase in the availability of brain neurotransmitters (dopamine, noradrenalin, and serotonin) that typically are reduced in depressive patients. Similarly, studies involving animals and humans have indicated that exercise increases levels of serotonin in the brain. Thus, the mechanisms underlying the antidepressant-like effect of exercise are similar to those obtained in the present study. This assertion is supported by the demonstration that the depletion of endogenous serotonin using a tryptophan hydroxylase inhibitor PCPA, at a dose known to decrease cortical levels of serotonin and reverse morphine antinociception, largely antagonized the hyponociceptive effect of physical exercise.

Of note is one discrepancy between our results and those reported by Quintero et al. Whereas Quintero et al demonstrated that rats subjected to 10 to 20 minutes of forced swimming in cool (24 °C to 26 °C) water for 3 days presented thermal and chemical hyperalgesia, which according to the authors was an effect mediated by reduction in central serotonin activity. This might be explained primarily by the differences in animal species (rats vs mouse) and modalities tested (formalin and hot plate vs acetic acid models), which could be encoded by different nociceptive signaling mechanisms. Furthermore, the differences in exercise protocol can also explain this opposite results, such as: the intensity of stress-induced hyperalgesia (SIH) may inversely correlate with water temperature. Of fact, swimming in cooler water may facilitate SIH, whereas swimming in warmer water facilitates exercise-induced antinociception.

However, the stress during initial swim sessions of the present study might induce SIH; we speculate that these would dissipate as the animal habituates. Indeed, we observed a decrease in feces in the water over the first few swim sessions. Finally, the intensity of exercise, in the Quintero et al study, the rats did not swim all the time (20 minutes), whereas in the present study, the soap added prevented floating behavior. However, future studies are expected to determine the exact the mechanisms that are involved in exercise-induced hyponociception.

In summary, the present results provide convincing evidence that high-intensity extended swimming exercise exerts a pronounced hyponociceptive effect, as revealed by the suppression of nociceptive responses generated by acetic acid in mice. These experiments are the first to show that high-intensity extended swimming exercise activates several mechanisms to reduce pain-related behavior in mice. Extended swimming exercise reversed the nociceptive response to acetic acid in an acute visceral pain model through the activation of opioid and serotonin receptors. Endogenous opioid release by adrenal glands is likely to be involved in this effect.

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