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Nociception Before and After Exercise In Rats Bred for High and Low Aerobic Capacity

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Abstract

Exercise and stress are known to influence pain perception. However, little is known about how level of fitness influences pain perception and the experience of pain. In the present study, pain perception before and after exercise to exhaustion was examined in 6 rats systematically bred to have a high aerobic capacity (HCR animals) and 6 rats systematically bred to have a low aerobic capacity (LCR animals). HCR animals had significantly higher pain thresholds compared to LCR animals before and after exercise (7.66 s compared to 6.01 s, $t = -3.07$, $p < .05$; and 6.89 s versus 4.73 s, $t = -3.73$, $p < .01$, respectively). In addition, both groups of animals displayed evidence of hyperalgesia following exercise compared to baseline. However, the pain thresholds of HCR animals returned to baseline levels faster than LCR animals following exercise. The findings support the hypothesis that level of fitness plays a role in the perception of pain. In addition, a higher level of fitness may serve as buffer against the effects of stress and help to reduce or prevent the experience of clinical pain. Further research is needed to examine the mechanisms that underlie this phenomenon.

Keywords

Hyperalgesia; Fitness; Pain Perception; Exercise; Thermal Pain

INTRODUCTION

Studies in humans and animals demonstrate that aerobic exercise provides temporary relief from pain. This phenomenon, termed exercise-induced analgesia, has been reported using a variety of painful stimuli including heat,[4,19,20,38] cold,[19,20,21,36] pressure,[9,28,29] electric stimulation,[5,6,7,8,13,23,24,25,35,37] and ischemia.[8,19,20,21] Outcomes, however, appear to vary depending on the type of noxious stimuli given and the intensity and duration of exercise.[27] Some studies report that this effect can be blocked by administration of naloxone, suggesting that the effect is mediated by endogenous opioids.[1,19,27] However, animal studies indicate that exercise activates several antinociceptive systems, and that activation of specific systems appears to be dependent on the nature of the stressor.[27] While the majority of research on this phenomenon has been conducted in healthy persons, recent

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studies have shown that exercise alters pain perception in persons with chronic low back pain (CLBP) [17] and in rats with induced chronic muscle pain.[1]

Relatively little is known as to whether long-term exercise or fitness level also plays a role in pain perception. Monnier-Benoit et al.[33] examined pressure pain responses among sedentary students and cyclists before and after exercise and found no differences between the two groups at either time. In contrast, a longitudinal study of runners followed over 14 years found that consistent exercise was associated with a 25% lower incidence of musculoskeletal pain compared to sedentary controls.[2] Ylinen et al.[51] found that persons with chronic neck pain who underwent neck muscle endurance or strength training displayed significantly higher pressure pain thresholds in the neck after 1-year compared to control subjects. Further research is needed to determine if fitness level plays a significant role in pain perception.

Koch and Britton[26] have bred strains of rats selected for low and high aerobic treadmill running capacity. The low-capacity runners (LCR) and high capacity runners (HCR) have been shown at generation 10 to differ in running capacity by 347%.[47] Comparing the nociceptive responses of these two animal strains following exercise provides a controlled way to examine the role of fitness on pain perception. In the present study, heat pain thresholds (HPTs) were obtained from these animals before and after aerobic exercise. We hypothesized that the HCR animals would display significantly greater HPTs compared to LCR rats. In addition, consistent with other studies examining exercise-induced analgesia, we predicted that HPTs in both groups would significantly increase following exercise.

MATERIALS AND METHODS

Animals

The development of LCR and HCR rats has been described previously in detail.[26] Briefly, two-way artificial selection of a heterogenous rat population from the N:NIH stock (National Institutes of Health) produced rat strains differing in inherent aerobic capacity. Endurance running capacity was assessed at 11 wk of age using run time and distance to exhaustion on a treadmill (15 degree incline; initial velocity 10 m/min and increased 1 m/min every 2 min) as parameters. From the founder population of 186 rats, the top 20% of each sex was randomly bred to initiate the HCR strain, whereas the bottom 20% was mated to initiate the LCR strain. Each subsequent generation was stratified and bred in a similar fashion with precaution being taken to minimize inbreeding (<1%/generation).

The present study tested 6 LCR and 6 HCR males from generation 17 that were between 17 and 18 weeks old. Each rat was provided food (Ralston Purina, diet 5001) and water ad libitum and placed on a 12:12-h light-dark cycle with the light cycle coinciding with daytime. Rats were caged individually or in pairs according to size. The entire experimental protocol was reviewed and approved by the University of Michigan Committee for the Use and Care of Animals and this study strictly adhered to the *National Institute of Health Guide for the Care and Use of Laboratory Animals* (NIH Publications No. 80-23, revised 1996).

Exercise to exhaustion

The rats were not allowed to exercise outside of the cage prior to testing. During the first week of testing they were exposed to the treadmill and trained to run. Running duration and velocity were gradually increased within each daily run. Failure to keep pace caused the rat to slide off of the moving belt onto a 15 × 15-cm electric shock grid that delivered 1.2 mA of current at 3 Hz. The rats were left on the grid for about 1.5 s and then moved forward onto the moving belt. This process was repeated until the rats learned to run to avoid the mild shock. The next week rats were tested before and after exercise to exhaustion with the treadmill set at a constant slope

of 15° and an initial velocity of 10 m/min, increasing by 1 m/min every 2 min. Exercise to exhaustion was defined as the third time a rat could no longer keep pace with the speed of the treadmill and remained on the shock grid for 2 s rather than run.

Measurement of thermal sensory threshold

All tests were performed by the same experimenter on the same apparatus. It was not possible to blind the experimenter given the morphological differences between the HCR and LCR animals. Thermal pain thresholds were determined by measuring paw withdrawal latencies (PWL) according to the methods of Hargreaves et al.[14] Animals were individually placed into Plexiglas chambers (22 × 17 × 14 cm) comprising the Hargreaves device (Model 336T. IITC Life Science, Inc.; Woodland Hills, CA) and allowed to habituate to the environment for 60 min. All animals were tested in the same room at the same ambient temperature. A radiant heat source located beneath the Plexiglas was focused directly under the hind paw. The heat source and an electronic timer were activated simultaneously. At the moment the animal lifted its hind paw, the heat source and the timer were stopped by the experimenter and the PWL was recorded. To avoid thermal injury to the animal, the cut-off latency was set to automatically shut off the thermal stimulus at 10 s. Baseline measurements were obtained in five consecutive tests taken 5 min apart. After the last baseline PWL measurement, the animals were placed onto the treadmill and exercised to exhaustion. Duration and total distance of run were recorded. Immediately following exercise animals again were placed into the Plexiglas chambers and PWL measurements were taken 10 min, 20 min, 30 min, 45 min, and 60 min post exercise. A total of three tests were performed at each time point alternating between left and right paws. The results of the three tests were averaged to determine mean PWL at each time point.

RESULTS

The mean PWL for all of the baseline and post-exercise assessments combined for HCR and LCR rats are presented in Table 1. Repeated measures MANOVA was used to examine the between-subjects effect of group (LCR versus HCR), the within-subjects factor of time (baseline versus post-exercise), and the interaction. The MANOVA revealed a significant main effect of group ($F(1,10) = 14.1$, $p = .004$) and time ($F(1,10) = 19.5$, $p = .001$). The interaction effect was not statistically significant. Post-hoc independent samples t-tests revealed that HCR rats had significantly higher PWL compared to LCR rats at both baseline and post-exercise. Based on matched-pairs t-tests, PWL significantly decreased for LCR rats post-exercise compared to baseline ($t(5) = 4.73$, $p = .005$), but the decline for HCR animals was not statistically significant.

A second repeated measures MANOVA was conducted to examine the time course of PWL at different time points following exercise in LCR and HCR animals. The MANOVA again revealed a main effect of time ($F(5,6) = 10.9$, $p = .006$) and group ($F(1,10) = 14.5$, $p = .003$). The interaction effect of time and group approached statistical significance ($F(5,6) = 3.4$, $p = .086$). To examine the course of recovery after exercise within and between each of the animal strains, independent and matched-pairs were conducted on the data taken at 10 min, 20 min, 30 min, 45 min, and 60 min post-exercise, and the mean of all the baseline measurements. Independent samples t-tests conducted between the groups revealed that HCR rats had significantly longer PWL at 10 minutes ($t(10) = 2.17$, $p = .05$), 20 minutes ($t(10) = 3.09$, $p < .05$), 30 minutes ($t(10) = 3.93$, $p < .01$); 45 minutes ($t(10) = 3.40$, $p < .01$), and 60 minutes ($t(10) = 4.26$, $p < .01$) post-exercise compared to LCR animals. Within-group comparisons revealed that HCR rats had significantly lower PWL compared to baseline at 10 minutes ($t(5) = 4.77$, $p < .01$), but none of the remaining time points were significantly different from baseline. Conversely, LCR rats had significantly lower PWL compared to baseline at 10

minutes ($t(5) = 3.85$, $p < .05$), 20 minutes ($t(5) = 8.46$, $p < .001$), 30 minutes ($t(5) = 5.63$, $p < .01$), and 45 minutes ($t(5) = 4.58$, $p < .01$).

Changes in the time course of return to baseline are readily visualized when PWL is expressed as percent change from baseline using the equation: (experimental PWL−baseline PWL) ×100. Figure 1 shows that PWL in the HCR returned to baseline significantly faster than PWL in the LCR.

DISCUSSION

Fitness is believed to play a role in the development and maintenance of pain conditions, especially chronic pain syndromes, although the mechanisms by which it influences pain are varied and may change over the time. For example, fitness may decrease the likelihood of sustaining a musculoskeletal injury and facilitate recovery. For persons with chronic pain, exercise may decrease fear/avoidance beliefs, leading to increased function and improved conditioning.[30] Lastly, physical fitness or aerobic capacity may influence systemic neuropeptides or other neurochemicals that influence pain transmission and perception.

Research has demonstrated that obesity is a risk factor for developing chronic back pain following an occupational injury.[11] While cross-sectional studies find that persons with chronic pain tend to be more obese and have poorer aerobic capacity compared to controls,[16,48] it is difficult to discern whether this is a cause or a consequence of having chronic pain. Despite this, there is accumulating evidence that exercise is beneficial in the treatment of chronic pain. Randomized, controlled trials indicate that exercise is an effective intervention for fibromyalgia,[3,12,40] chronic neck pain,[41,50] osteoarthritis,[32,43] and chronic low back pain.[15,31,45] More research is needed to determine the mechanisms by which exercise impacts chronic pain.

As hypothesized, HCR animals displayed significantly higher heat thresholds compared to LCR animals. This finding supports the notion that fitness plays a role in pain perception, and better fitness may serve as a buffer against the experience of clinical pain. Further research is needed to elucidate the mechanisms that underlie this phenomenon. While much is known about the acute effects of exercise on neurotransmitters such as endorphins and the hypothalamo-pituitary-adrenocortical (HPA) axis, little research has been conducted to examine tonic or long-lasting changes produced by consistent exercise. One study in humans examined the influence of exercise on plasma levels of beta-endorphin, cortisol, human growth hormone, prolactin, and the experience of labor pain in pregnant women.[46] In a group of women who underwent aerobic conditioning, plasma beta-endorphin levels were consistently higher in women who exercised regularly throughout pregnancy, and these women also experienced less labor pain compared to women who did not exercise. This study suggests that regular exercise may influence tonic levels of neuropeptides, altering pain perception.

In contrast to our hypothesis, both animal strains displayed evidence of hyperalgesia following exercise (Table 1). Prolonged exercise in animals has been found to produce transient muscle hyperalgesia,[22] and various stressors have been found to produced both transient and long-lasting hyperalgesia in animals.[18,39] In the present study, the duration and intensity of exercise may have been great enough such that it produced the hyperalgesia observed, rather than the hypothesized analgesia. The additional stress of shocking the animals to achieve exercise to exhaustion may also have contributed to the hyperalgesic response. In humans, anxiety and fear have been found to be related to heightened experiences of both clinical and experimental pain.[34,44] It would be beneficial to examine the animals in an alternative exercise paradigm that has been shown in other animal studies to produce analgesia. It is

possible that the HCR and LCR animals may show different analgesic responses to such an exercise paradigm.

An interesting finding was that HCR animals displayed faster recovery of their pain threshold following exercise compared to LCR animals (Figure 1). It is possible that such recovery, or lack of recovery, may influence the development of long-lasting hyperalgesia following stress in animals, or the development of chronic pain in humans. Fitness may influence HPA activity or recovery following stress or exercise, or may play a role in the release of endogenous opioids or catecholamines influencing analgesia and pain perception.[18] Studying the factors that underlie these recovery differences may provide insight into how neuroendocrine factors influence lasting changes in pain perception and the development of chronic pain.

Some limitations of the present study deserve mention. For example, it is possible that morphologic or other differences between the HCR and LCR animals may have been responsible for the findings, as the LCR animals are heavier and larger than the HCR animals. While these factors may influence sensation produced by stimulation of deep tissues, it is unlikely that these differences would influence the perception of a cutaneous stimulation such as heat. In addition, the animals reached the same behavioral outcome (i.e., exercised to exhaustion), but it took HCR animals longer to reach this outcome compared to the LCR animals as these animals exercise significantly longer.[25] This may have produced greater changes in blood pressure and skin temperature, which in turn may influence heat responsiveness. In addition, it is possible that tonic differences in these factors may have influenced the findings. While blood pressure has been suggested to influence pain perception, France[10] suggests that this is not due to a direct influence of blood pressure. He argues that this finding is likely due to a central nervous system factor that regulates both blood pressure and pain perception, as altered pain perception is found in persons at risk for hypertension prior to any observed elevations in blood pressure. Studies examining the influence of ambient temperature or skin temperature on pain perception in both humans and rodents have reported highly variable findings: some suggest hotter or colder skin produces hyperalgesia, some report it produces analgesia, and some report skin temperature makes little or no difference in pain perception [42,49].

It should also be noted that the HCR and LCR animals may have genetic differences in their nociceptive processing systems that are responsible for the findings, as HCR animals displayed evidence of hypoalgesia at baseline compared to LCR animals. This decrease in nociception observed in HCR animals may account for at least some of their increased ability to tolerate exercise compared to LCR animals. Further research is needed to examine the factors that underlie this difference and whether they play a role in exercise tolerance. For example, if nociception in HCR animals is opioid mediated, administration of an opioid antagonist should increase pain sensitivity in these animals and reduce running time.

In summary, the HCR and LCR animal strains may serve as a model for examining the influence of fitness on pain perception and the development of pain conditions. The strains provide a large difference in fitness level, and the use of animals allows for manipulations to produce chronic pain and physiologic manipulations to examine mechanisms that underlie differences between the strains. The findings of the present study support the notion that these animals display inherent differences in the perception of pain and recovery from stress. Future research should examine mechanisms that underlie this phenomenon, such as altering the opioid and other nociceptive systems to determine if they mediate this observed relationship. In addition, studies are needed to examine whether the strains are differentially susceptible to manipulations known to produce chronic pain. Such research may help to further our understanding of the influence of exercise on clinical pain, and how fitness may play a role in reducing or preventing clinical pain.

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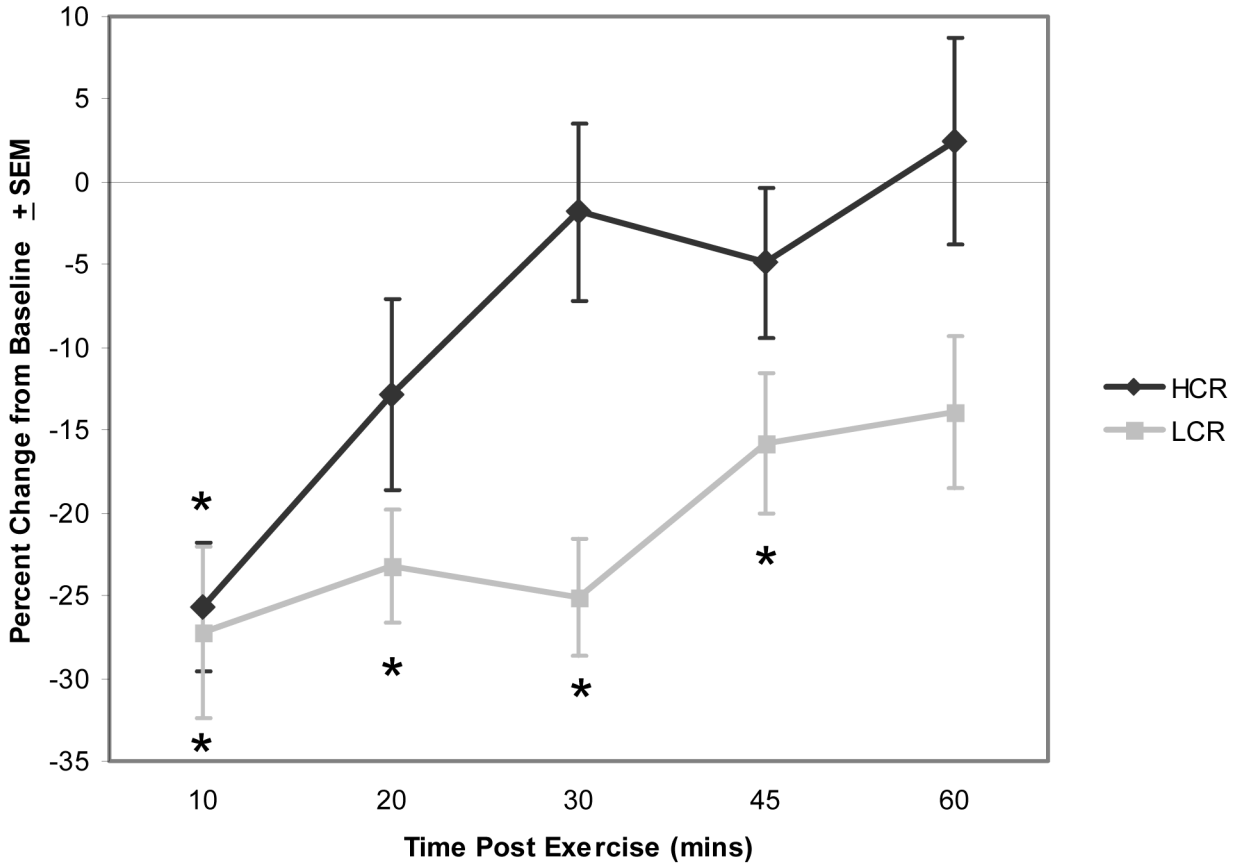

Figure 1.
Percent Change from Baseline in PWL for HCR and LCR Animals. * Denotes that the mean PWL at a given time point is significantly different from baseline.

Table 1

Mean (SD) Paw Withdrawal Latencies (in seconds) by Group at Baseline and Following Exercise

	Group		
Time	HCR	LCR	t-value
Baseline	7.66 (1.2)	6.01 (0.4)	−3.07*
Post-Exercise	6.89 (1.2)	4.73 (0.7)	−3.73**

* Notes: $p < .05$

** $p < .01$.