

Exercise activates the endocannabinoid system

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Extensive documentation exists showing that exercise induces analgesia and sedation. Despite decades of research attempting to explicate a neurochemical basis for these phenomena, the mechanism underlying these changes is unknown. Using trained male college students running on a treadmill or cycling on a stationary bike for 50 min at 70–80% of maximum heart rate, we report

here the first evidence that exercise of moderate intensity activates the endocannabinoid system, suggesting a new mechanism for exercise-induced analgesia and possibly other physiological and psychological adaptations to exercise. *NeuroReport* 14:2209–2211
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INTRODUCTION

Physical exercise is known to suppress pain and induce sedation [1], but with the demise of the endorphin hypothesis [2,3], these remarkable changes lack a sound mechanistic explanation. Bearing on this long-standing gap in the knowledge base, we hypothesized that the endocannabinoid system might be implicated in exercise-induced analgesia.

The identification of two cannabinoid receptors, CB₁ and CB₂, and their naturally occurring ligands, anandamide and 2-arachidonylglycerol (2-AG), established the existence of an endogenous cannabinoid (endocannabinoid) system. Activation of this system reduces pain sensation at central and peripheral levels [4]. The hypothesis that exercise-induced analgesia is due to cannabinoid antinociception is strengthened by evidence linking the endocannabinoid system to stress-induced analgesia [5]. In addition, activation of the endocannabinoid system by exogenous cannabinoids such as THC, the psychoactive constituent of marijuana, induces changes in mental status that are similar to those reported by endurance athletes, such as sedation, anxiolysis, and a sense of well being [6].

MATERIALS AND METHODS

Participants: Twenty-four males (age 23.7±9.4 years; body mass 74.5±7.9 kg; height 183.7±6.2 cm; means±s.d.) volunteered to participate in this study. The training criterion for subject selection was ≥ 30 min of running or cycling, respectively, on ≥ 4 days/week for the previous 6 months.

Procedure: The experiment had three test conditions: running (*n*=8), cycling (*n*=8), and sedentary controls (*n*=8). Subjects satisfying the training criterion for running (*n*=12) were randomly assigned on a 2:1 basis to either the running or control condition, and subjects satisfying the cycling condition (*n*=12) were similarly assigned to either the cycling or control condition. All subjects gave written informed consent and the university's Institutional Review Board for the protection of human subjects approved the study protocol. All work was conducted in accordance with the Declaration of Helsinki.

To decrease variability due to arousal levels, all subjects reported to the laboratory on a day prior to the testing session to meet the investigators and practice on the exercise apparatus. Information about personal health and exercise training was obtained by questionnaire and followed up by interview. At the end of the familiarization session, pre-test instructions were given that asked each subject to not exercise on test day and to not eat or consume caffeinated beverages for ≥ 3 h prior to reporting. A 24 h history form, which requests information on diet, sleep, medications, exercise, and general feeling of well being, was completed on test day to verify compliance.

The exercise protocol was the same whether the subject was running on the treadmill (Quinton model Q65, Seattle, WA) or pedaling on the electronically braked cycle ergometer (Excalibur Sport, Lode, Netherlands). In a temperature controlled room (mean temperature 22°C), exercise began with a 5 min warm-up during which the work rate on the treadmill or cycle ergometer was slowly increased to elicit a heart rate in the range of 70–80% of maximum heart rate (~140–160 bpm). For endurance-

trained runners and cyclists this corresponds to a moderate training effort, an exercise intensity that is not easy, but not exhausting either. This represents a physiological steady state that a well-trained subject can continue for a prolonged duration. Once the desired exercise intensity was reached, the subject ran or cycled at this effort for 45 min. Subjects in the control condition were treated exactly the same except they were instructed to remain seated for 50 min in the same temperature-controlled room. All testing occurred at the same time of the day between 14.00 and 17.00 h.

Using standard procedures, blood was collected from all participants immediately prior to and following a session. The pre-post time interval was ~55 min for all subjects, including controls. The extraction and quantification of endocannabinoids from blood samples were performed according to protocols described elsewhere [7]. An ANOVA with *post hoc* Tukey tests was used for statistical comparisons.

RESULTS

A 3×2 mixed ANOVA with groups as the between-subject variable and anandamide as the within-subject variable revealed no significant effect for groups ($F(1,2)=0.87$, n.s.) or anandamide ($F(2,20)=1.14$, n.s.). The ANOVA revealed a significant interaction ($F(2,20)=6.46$, $p < 0.01$). Compared with pre-exercise levels, *post hoc* Tukey tests showed that plasma anandamide levels were significantly elevated in runners ($p < 0.01$) and cyclists ($p < 0.05$), but not sedentary controls. The *post hoc* comparison ($p < 0.05$) revealed no differences in anandamide levels among the groups prior to exercise. Pre-post hematocrit values did not differ significantly, eliminating the possibility that increases in anandamide were due to dehydration. All exercising participants displayed a post-exercise increase of anandamide levels, testifying to the robustness of the effect (Fig. 1). Although the analysis of plasma 2-AG showed a similar trend with increases for runners and cyclists but not controls, an ANOVA revealed no significant results. This difference may be attributable to functional divergences between anandamide and 2-AG, which are synthesized via different biochemical pathways and may be produced under different conditions [8].

DISCUSSION

These findings provide the first evidence that exercise activates the endocannabinoid system and are suggestive of a new neurohumoral mechanism for exercise analgesia. Because exercise dramatically elevates anandamide levels in the systemic circulation, we hypothesize that this compound may be produced in extraneural tissues and acts on peripheral sensory fibers to relieve pain. This hypothesis is supported by two findings. First, anandamide is synthesized in and released from a variety of peripheral cells, including sensory neurons [9]. Second, anandamide causes profound antinociceptive and antihyperalgesic effects, which are mediated by CB₁ cannabinoid receptors located on pain-sensing C fibers [4,10]. Since anandamide is rapidly inactivated in peripheral tissues, the elevations in circulating anandamide levels observed in the present study

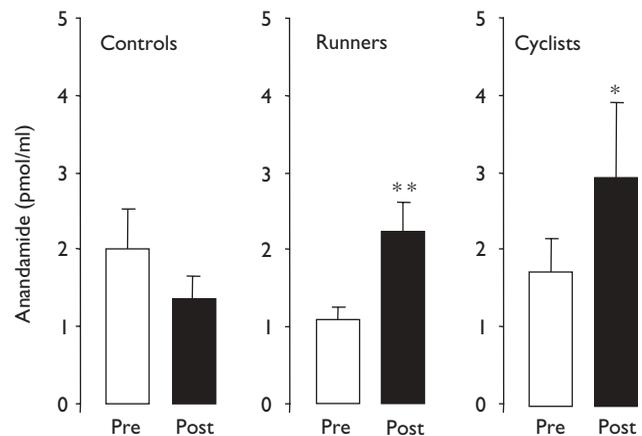


Fig. 1. Anandamide levels are elevated for runners and cyclists but not sedentary controls following 1 h of moderate intensity exercise. * $p < 0.05$; ** $p < 0.01$.

are likely to be an underestimate of the local concentrations of anandamide at its sites of action.

Anandamide binds to the CB₁ receptor, which is densely expressed in brain regions implicated in the control of motor functions, emotion and cognition [11]. Due to its highly lipophilic properties, anandamide crosses the blood-brain barrier readily, avoiding the principal problem that plagued the endorphin hypothesis. Activation of central CB₁ receptors by exogenous cannabinoids such as THC causes intense subjective experiences similar to those reported by endurance athletes such as analgesia, sedation (post-exercise calm), anxiolysis, and a sense of well being. It is intriguing to speculate that rises in systemic anandamide levels during exercise may occur in parallel with a central engagement of the endocannabinoid system, which might help account for the psychological counterparts of exercise analgesia, either directly or by interacting with other neurotransmitter systems such as opioids or catecholamines. Irrespective of the speculation that endocannabinoids might play a contributory role in the phenomenon popularly known as the runner's high, our finding suggests a plausible mechanism for exercise analgesia and opens unexpected perspectives in exercise physiology.

REFERENCES

1. Cook DB and Koltyn KF. Pain and exercise. *Int J Sports Psychol* **31**, 256–277 (2000).
2. Kolata G. Runner's high? Endorphins? Fiction say some scientists. *NY Times* 2002, May 21.
3. Harbach H, Hell K, Gramsch C, Katz N, Hempelmann G and Teschemacher H. β -Endorphin (1–31) in the plasma of male volunteers undergoing physical exercise. *Psychoneuroendocrinology* **25**, 551–562 (2000).
4. Richardson JD. Cannabinoids modulate pain by multiple mechanisms of action. *J Pain* **1**, 2–14 (2000).
5. Hohmann AG, Tsou K and Walker JM. Cannabinoid suppression of noxious heat-evoked activity in wide dynamic range neurons in the lumbar dorsal horn of the rat. *J Neurophysiol* **81**, 575–583 (1999).
6. Chaperon F and Thiebot MH. Behavioral effects of cannabinoid agents in animals. *Crit Rev Neurobiol* **13**, 243–281 (1999).
7. Giuffrida A, Rodríguez de Fonseca F and Piomelli D. Quantification of bioactive acylethanolamides in rat plasma by electrospray mass spectrometry. *Anal Biochem* **280**, 87–93 (2000).

8. Stella N, Schweitzer P and Piomelli D. A second endogenous cannabinoid that modulates long-term potentiation. *Nature* **388**, 773–778 (1997).
9. Ahluwalia J, Yaqoob M, Urban L, Bevan S and Nagy I. Activation of capsaicin-sensitive primary sensory neurones induces anandamide production and release. *J Neurochem* **84**, 585–591 (2003).
10. Calignano A, La Rana G, Giuffrida A and Piomelli D. Control of pain initiation by endogenous cannabinoids. *Nature* **394**, 277–281 (1998).
11. Glass M, Dragunow M and Faull RLM. Cannabinoid receptors in the human brain: a detailed anatomical and quantitative autoradiographic study in the fetal, neonatal and adult human brain. *Neuroscience* **10**, 1665–1669 (1997).