Opiate receptor blockade by naltrexone and mood state after acute physical activity

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Acute mood changes occur with various forms of physical activity. Increased levels of endogenous opioids (endorphins) in response to exercise may mediate activity-induced shifts in mood state. Thirteen female and six male aerobics class participants aged 20–46 years received the opiate receptor antagonist naltrexone and a placebo in randomized, double-blind crossover fashion on two separate occasions at the same 75-min high-intensity aerobics class. Mood states were assessed before and after each class, which were spaced 5 days apart, using the Profile of Mood States questionnaire (POMS), a mood adjective checklist, and a Visual Analogue Scale (VAS) which measured mood in relation to several emotional extremes. Mood changes over the course of each aerobics class were compared in the naltrexone and placebo groups. For men and women, significant differences between conditions were observed in overall mood by both the POMS ($P < 0.005$) and VAS ($P < 0.02$). There were significant differences between conditions for most subscales of each mood instrument ($P < 0.05$); with the placebo, mood states became calmer, more relaxed and pleasant, tending away from depression, anger and confusion. Positive mood shifts did not occur when subjects were preloaded with naltrexone, suggesting that activity-generated mood changes are mediated through endorphinergic mechanisms.

Keywords: Endorphin, mood, aerobics, exercise

A number of studies have demonstrated altered endorphin immunoreactivity and increased plasma concentrations of endorphin and lipotropic hormones in response to physical activity. Acute responses of endogenous opioids have been reported following running events[1,2], graded exercise tests[3,4], bicycle ergometer tests[5,6] and swimming[7], typically resulting in a two–five-fold increase in endorphin levels. Observations such as these suggest that the phenomenon of the 'runner's high', an acute positive shift in mood state, might be related to changes in endorphin levels with physical activity. Such a hypothesis is supported by the observations that individuals who exercise regularly do so to relieve negative feelings of discomfort, irritability, frustration and nervousness[8], and that increases in endorphin-like immunoreactivity after running correlate with the shift to a feeling of pleasantness[9]. The phenomenon of the 'runner's high' might, therefore, be more appropriately termed the 'runner's calm', since these changes in mood more closely resemble an opioid state characterized by 'calm' than a euphoric 'high', but whether mood is influenced at all by endorphin response to exercise has not been established.

Using opiate receptor antagonists to block any endorphin effect, and various psychological instruments to assess mood state, several studies have failed to observe differences in mood between blocked and unblocked conditions following physical activity[10–14]. Some studies have demonstrated that certain subscales of mood were more positive after exercise when opiate receptors were not blocked, but have failed to demonstrate a significant difference in overall mood[15,16]. Only Allen and Coen[17] have implicated endogenous opiates as exercise-induced modulators of mood: administration of the opiate receptor antagonist naloxone resulted in no change in mood following treadmill running, but positive shifts in mood were observed overall and for each subscale of mood when a placebo was administered.

Weak relationships and discrepancies between these studies could be a result of difficulties in quantifying subtle psychological changes; most available mood instruments are best suited for assessment of pathological conditions with large variation in scores. But results are also heavily influenced by differences in the selection and characteristics of subjects for study, the nature, amount and intensity of the exercise, and the manner in which investigators attempt to block opiate receptors. For example, whereas investigators reporting no differences in mood state between blocked and unblocked opiate receptor conditions have typically used low dosages of a receptor antagonist, Allen and Coen[17] used high dosages of naloxone administered intravenously first as a bolus and then by continuous drip throughout the exercise periods. That they observed significant differences between conditions might also be attributable to the fact that their subjects exercised at 75% of maximal oxygen consumption ($\dot{V}O_{2\,max}$); a critical intensity of 70% $\dot{V}O_{2\,max}$ has been reported by Goldfarb *et al.*[6] as necessary to elevate β-endorphin

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levels, and few studies have observed an effect at less than this.

Inconsistencies regarding a link between an endorphin response to exercise and positive post-exercise mood shifts indicate the need for further investigation. Furthermore, all studies to date have compromised external validity in an effort to maintain internal validity; results of these studies cannot be generalized since all were conducted within tightly controlled environments. As McMurray *et al.*[3] have recently demonstrated, this is important when measuring endorphin changes related to exercise. However, if opiate receptor activity due to exercise-induced endorphin production can be controlled by administration of an opiate receptor antagonist, then exercise in its usual form and environment appears a more valid and reliable means than standardized testing under controlled laboratory conditions by which to observe any related mood shift. Toward this end, we report here the results of a cross-sectional study in which men and women participating in an aerobics class were administered an opiate receptor antagonist and a placebo in randomized, double-blind crossover fashion on two separate occasions, with mood states assessed before and after each class.

Subjects and methods

Subjects

Men and women from a high-intensity, high-impact aerobics class at a municipal recreation facility took part in the study; all were regular participants (attending 3–4 times per week) and had been so for at least 6 months. Potential participants were informed of the nature and extent of any involvement, but were not told the experimental hypotheses. Of 28 volunteers, 25 completed a screening questionnaire after which six were excluded due to: (a) history of or current use of opioid medications; (b) use of prescription or non-prescription drugs within 1 month of participation in the study; (c) history of any endocrine abnormality; (d) poor general health; and (e) in the case of the women, menstrual cycles less than 21 or greater than 36 days. The final sample size was thus 19 (13 women and six men). All subjects provided their informed written consent, and the research protocol was approved by the Simon Fraser University Ethics Committee for the Protection of Human Subjects.

Materials

The opiate receptor antagonist naltrexone,[18] (Du Pont, Wilmington, Delaware, USA) was administered orally in 50 mg tablet form on one occasion; a placebo similar in appearance, taste and texture was administered on another. Like naloxone, a more commonly used opiate receptor blocker, naltrexone is highly effective but, unlike naloxone, does not require subcutaneous or intravenous administration, a protocol unsuitable for this investigation.

Two mood state instruments were used as psychological tools to assess mood state before and after an aerobics class on each of two separate occasions: the Profile of Mood States (POMS)[19], and a Visual Analogue Scale (VAS)[20]. The POMS is a 65-item mood adjective checklist in which each adjective is scored from 0 (absent) to 4 (very much). Following standard scoring methods, six mood scales are derived: tension–anxiety, depression–dejection, confusion–bewilderment, vigour–activity, anger–hostility and fatigue–inertia. Subjects were generally able to complete the POMS within 10 min. The POMS has been used in previous studies concerning exercise, endogenous opiates and mood changes[10, 12, 17]. The VAS was adapted from that used by Allen and Coen[17], based on the scale developed by Janal *et al*[15]. Subjects made a vertical slash mark on a horizontal line between two extremes of mood for each of six scales arranged in random order: depressed–euphoric, regretful–joyful, pleasant–miserable, very uncalm–very calm, relaxed–uptight and disturbed–at peace. The intersection of the vertical slash mark with the horizontal line between the two extremes of mood was measured with a ruler (yielding continuous data); the positive mood end was always taken as the zero position. The VAS generally required about 5 min to complete.

Design

Naltrexone or the placebo was administered in a double-blind crossover fashion on two separate occasions at the same high-intensity, high-impact aerobics class. The same instructor conducted each class. Components of each 75-min class were as follows: 7-min warm-up, 31-min cardiovascular session, 4-min cooldown, 28-min muscular strength and endurance session and 5-min stretch and flexibility session, all set to music. Subjects did not exercise at all for 5 days before the first aerobics class, nor did they exercise in the 5 days between the first and second classes. On each occasion, subjects arrived at the gym at least 45 min before the aerobics class began. They ingested orally either naltrexone or the placebo with some water and immediately completed pre-class POMS and VAS questionnaires. Subjects then participated in the aerobics class and completed post-class POMS and VAS questionnaires (identical to pre-class forms) as soon as the class concluded. Study design included a crossover, such that each subject received naltrexone for one class and the placebo for the other; administration of naltrexone or placebo was double-blind and randomized. For the women, timing of the menstrual cycle was not standardized with timing of the interventions.

Statistical analysis

Data analysis consisted of descriptive and inferential statistics; differences in mood disturbances were assessed by paired *t*-tests (two tailed), since both the POMS and VAS scales yielded continuous data. Statistical significance was set at the 0.05 level of probability. The total mood disturbance POMS and the global VAS were calculated for each instrument by subtracting the sum of all post-class results from

the sum of all pre-class results. For the total mood disturbance POMS value, the vigour scale was negatively weighted since it pertains to an effectively positive mood that is opposite in nature to the negative emotional experiences assayed by the other five scales. StatView SE+ Graphics (Abacus Concepts, Berkeley, California, USA) software was used for statistical analysis of the data on a Macintosh SE/30 microcomputer (Apple Computer, Cupertino, California, USA).

Results

The mean(s.d.) age of all participants was 31.1(7.4) years (range 20–46 years). There was no significant difference in age between the men (32.2(6.4) years) and the women (30.6(7.8) years). All subjects were within the college norms for the POMS[19] and tended toward the lower or 'emotionally stable' end of the scale; no norms were available for the VAS. Though women demonstrated slightly greater variability than men, pre-class mood state values between the naltrexone and placebo classes were not significantly different for either the women or the men ($P > 0.46$); mood states were similar for each sex at the start of each class.

For men and women separately, there were significant differences in the magnitude of mood state shifts after the aerobics class as assessed by the pre-minus post-class POMS results (*Table 1*) and the VAS results (*Table 2*) between the naltrexone and placebo conditions. By scale, the POMS results for men showed significant differences in depression ($P < 0.05$), anger ($P = 0.05$), fatigue ($P < 0.05$) and confusion ($P < 0.005$) between the naltrexone and placebo conditions; decreases in these negative mood states occurred with the placebo, but not naltrexone. Changes in tension and vigour were of borderline significance ($P = 0.056$ and $P = 0.061$, respectively). The total mood disturbance POMS for men indicated an overall positive mood shift following the placebo class relative to the naltrexone class ($P < 0.005$). For women, there were significant differences in tension ($P < 0.02$), depression ($P < 0.002$), anger ($P < 0.002$) and confusion ($P < 0.005$) between the naltrexone and placebo conditions, but there were no significant differences in vigour and fatigue. As with men, decreases in negative mood states occurred with the placebo but not with naltrexone, and the total mood disturbance POMS showed a positive mood shift overall ($P < 0.002$).

Results obtained using the VAS were in agreement with results obtained using the POMS. By scale, the VAS results for men indicated significant differences in responses between the extremes of miserable–pleasant ($P < 0.05$), very uncalm–very calm ($P < 0.005$), uptight–relaxed ($P = 0.02$) and disturbed–at peace ($P < 0.02$), but there were no significant changes in depression–euphoria and regretful–joyful. Overall, the global mood VAS indicated a significant positive mood shift for men upon completion of the placebo class relative to the naltrexone class ($P < 0.02$). Women were characterized by significantly different responses between the extremes of depression–euphoria ($P < 0.02$), miserable–pleasant ($P < 0.05$) and uncalm–very calm ($P < 0.02$), but there were no significant changes in responses between the extremes of regretful–joyful, uptight–relaxed and disturbed–at peace. The global mood VAS indicated a significant positive mood shift overall upon completion of the placebo class relative to the naltrexone class in women ($P < 0.02$).

There were significant positive Pearson product–moment correlations between the total mood disturbance POMS and the global VAS in both the placebo ($r = 0.82$, $P = 0.0001$) and naltrexone ($r = 0.54$, $P < 0.02$) conditions.

Table 1. Probability values for differences in mood before and after exercise between the naltrexone and placebo groups in an aerobics class using the POMS questionnaire

Mood source	*Men (n = 6)*	*Women (n = 13)*
Tension–anxiety	0.056	0.013
Depression–dejection	0.046	0.001
Anger–hostility	0.050	0.001
Vigour–activity	0.061	0.329
Fatigue–inertia	0.038	0.169
Confusion–bewilderment	0.003	0.003
Total mood disturbance	0.002	0.001

Table 2. Probability values for differences in mood before and after exercise between the naltrexone and placebo groups in an aerobics class using the VAS questionnaire

Mood source	*Men (n = 6)*	*Women (n = 13)*
Depression–euphoria	0.198	0.011
Regretful–joyful	0.125	0.394
Miserable–pleasant	0.024	0.048
Uncalm–calm	0.003	0.012
Uptight–relaxed	0.020	0.057
Disturbed–at peace	0.019	0.102
Global mood change	0.015	0.017

Discussion

The data demonstrate clearly that exercise in a high-intensity aerobics class for 75 min was followed by significant changes in mood in both men and women; mood states became calmer, more peaceful, more relaxed and pleasant, tending away from tension, depression, anger, fatigue and confusion. This overall positive mood change did not occur when subjects were preloaded with a 50-mg dose of naltrexone, an opiate receptor blocker, suggesting that activity-generated mood changes are mediated through endorphinergic mechanisms.

Our observations are in agreement with those of Allen and Coen[17], who noted similar responses in male runners within a controlled laboratory environment. Taken together, these studies are strong evidence for exercise-induced endorphin-mediated mood changes in humans, especially since they demonstrate external and internal validity, respectively. That Allen and Coen[17] used intravenous naloxone whereas we used oral naltrexone as a means of blocking opiate receptors suggests both

naloxone and naltrexone have similar effects upon the opiate receptors subserving mood state, but these specific receptors remain to be defined. Farrell *et al.*[13], using naltrexone, failed to implicate an endorphin link between exercise and mood, as have similar investigations using naloxone[10–14].

That the present investigation observed significant results whereas most others have not, might be attributable to the environment within which subjects were observed; we did not require participants to exercise under unfamiliar conditions in a clinical laboratory situation where associated stress may have influenced answers to questions regarding mood state. For example, because psychological stress invokes significant increases in plasma levels of β-endorphin and other hormones released in association with adrenocorticotropin[21,22], a foreign environment and unfamiliar activity may profoundly influence the validity and reliability of mood state responses and measurements of endorphin levels. In this manner, baseline levels of endorphin and mood may be distorted such that no difference is observed between the pre- and post-exercise conditions.

The uniqueness of observing participants in an aerobics class deserves comment. We are not aware of any investigations of exercise-induced mood shifts involving aerobics classes. Exercise intensity in the present study can only be speculated on but, though subjective, it is worth stating that the 75-min aerobics class was worthy of its 'high-intensity' rating, presenting a unique challenge unmatched by most other classes. It is a reasonable assumption that the subjects were working at a relatively high percentage of their $\dot{V}O_{2\,max}$ at least for most of the 31-min cardiovascular portion of the class, but no claim can be made as to how this approximated the critical intensity of 70% $\dot{V}O_{2\,max}$ reported by Goldfarb *et al.*[6] as necessary to increase levels of β-endorphin. The additional stipulation by Goldfarb *et al.*[6] of a 15-min minimum duration of exercise was exceeded by subjects in the present study in both the cardiovascular and muscular endurance portions of the aerobics class, and it is also possible that lactate production during the muscular endurance portion of the class might have contributed to endorphin response, since lactate and β-endorphin levels are positively correlated[23].

Although we observed similar shifts in mood with both the POMS and VAS, we feel that results of the POMS should be weighted more heavily than those of the VAS, even given our observations of significant correlations between the total mood disturbance POMS and global VAS in both the naltrexone and placebo conditions. Also, while the VAS appeared to assess mood changes rather well in relation to the POMS in the placebo condition ($r = 0.82$), the lower correlation coefficient of the VAS with the POMS in the naltrexone condition ($r = 0.54$) suggests some degree of inadequacy in the ability of the VAS to measure negative mood state with the refinement of the POMS. The POMS is a validated psychological tool, the VAS is not. As a 65-item mood adjective checklist from which six basic mood scales are derived, the POMS ensures considerable difficulty in biasing responses, but even when mood extremes are arranged in random order on the VAS it is still possible to demonstrate a bias.

However, this is not to say that the POMS is without problems. The measure of vigour did not show a significant shift in either men or women in this study, and female values for change in fatigue were not significant. It may be that psychological and physical responses to questions concerning vigour and fatigue were confused: a subject may physically perceive fatigue and a lack of vigour, even when psychologically feeling refreshed and vigorous. Irrespective of the perceived validity of these mood subscales, the total mood disturbance POMS, which is the best indicator of mood shift between the placebo and naltrexone conditions, still indicated highly significant differences. Another problem with the POMS is that the vigour scale pertains to an effectively positive mood that is opposite in nature to the negative emotional experiences assayed by the other five scales; we resolved this by giving the vigour scale a negative weight in calculating the total mood disturbance POMS value. Thus, for all five scales, a downward or lower score indicated a positive mood shift.

In conclusion, the present investigation of both men and women found significant differences in mood state following a high-intensity aerobics class between conditions in which naltrexone, an opiate receptor antagonist, and a placebo were administered. Post-class mood was characterized by a calm, unstressed frame of mind when subjects received the placebo, but these positive mood shifts did not occur with administration of naltrexone. The results implicate endogenous opioids as mediators of activity-generated mood changes.

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References

1 Colt EWD, Wardlaw SL, Frantz AG. The effect of running on plasma beta-endorphin. *Life Sci* 1981; **28**: 1637–40.
2 Bortz WM, Angwin P, Mefford IN. Catecholamines, dopamine and endorphin level during extreme exercise. *N Engl J Med* 1981; **305**: 466–7.
3 McMurray RG, Forsythe WA, Mar MH, Hardy CJ. Exercise intensity-related responses of beta-endorphin and catecholamines. *Med Sci Sports Exerc* 1987; **19**: 570–8.
4 Viswanathan M, Van Dijk JP, Graham TE *et al.* Exercise- and cold-induced changes in plasma beta-endorphin and beta-lipotropin in men and women. *J Appl Physiol* 1987; **62**: 622–7.
5 Carr DB, Bullen BA, Skrinar GS. Physical conditioning facilitates the exercise-induced secretion of beta-endorphins and beta-lipotropin in women. *N Engl J Med* 1981; **305**: 560–3.
6 Goldfarb AH, Hatfield BD, Armstrong D, Potts J. Plasma beta-endorphin concentration: response to intensity and duration of exercise. *Med Sci Sports Exerc* 1990; **22**: 241–4.

7 Russell JB, Mitchell DE, Musey PI, Collins, DC. The role of beta-endorphins and catechol estrogens on the hypothalamic–pituitary axis in female athletes. *Fertil Steril* 1984; **42:** 690–5.

8 Carmack MA, Mertens R. Measuring commitment to running: a survey of runners' attitudes and mental states. *J Sport Psychol* 1979; **1**: 25–42.

9 Wildmann J, Kruger A, Schmole M. Increase of beta-endorphin-like immunoreactivity correlates with the change in feeling of pleasantness after running. *Life Sci* 1986; **38**: 997–1033.

10 Markoff RA, Ryan P, Young T. Endorphins and mood changes in long-distance running. *Med Sci Sports Exerc* 1982; **14**: 11–15.

11 Grossman A, Bouloux P, Price P, Drury PL. The role of opioid peptides in the hormonal responses to acute exercise in man. *Clin Sci* 1984; **67**: 483–91.

12 DeMeirleir K, Arentz T, Smitz J. Effect of opiate antagonism on physiological and hormonal responses to acute dynamic exercise. *Med Sci Sports Exerc* 1985; **17:** 235.

13 Farrell PA, Gustafson AB, Garthwaite TL. Influence of endogenous opioids on the response of selected hormones to exercise in humans. *J Appl Physiol* 1986; **61**: 1051–7.

14 Goldfarb AH, Hatfield D, Sforzo FA, Flynn G. Serum β-endorphin levels during a graded exercise test to exhaustion. *Med Sci Sports Exerc* 1987; **19**: 78–82.

15 Janal MN, Colt EWD, Clark WC. Pain sensitivity, mood and plasma endocrine levels in man following long-distance running: effects of naloxone. *Pain* 1984; **19**: 13–25.

16 McMurray RG, Berry MJ, Hardy CJ, Sheps DS. Physiologic and psychologic responses to a low dose of naloxone administered during prolonged running. *Ann Sports Med* 1988; **4**: 21–5.

17 Allen ME, Coen D. Naloxone blocking of running-induced mood changes. *Ann Sports Med* 1987; **3**: 190–5.

18 Crabtree BL. Review of naltrexone, a long-acting opiate antagonist. *Clin Pharm* 1984; **3**: 273–80.

19 McNair DM, Lorr M, Droppleman LF. *Profile of Mood States Manual.* San Diego: Educational and Industrial Testing Service, 1971.

20 Bond A, Lader M. The use of analogue scales in rating subjective feelings. *Br J Med Psychol* 1974; **47:** 211–18.

21 Meyerhoff JL, Oleshansky MA, Mougey EH. Psychologic stress increases plasma levels of prolactin, cortisol, and POMC-derived polypeptides in man. *Psychosom Med* 1988; **50:** 295–303.

22 Mutti A, Ferroni C, Vescovi PP *et al.* Endocrine aspects of psychological stress associated with neurobehavioural performance testing. *Life Sci* 1989; **44:** 1831–6.

23 DeMeirleir K, Naaktgeboren N, Van Steirtegham A, *et al.* Beta-endorphin and ACTH levels in peripheral blood during and after aerobic and anaerobic exercise. *Eur J Appl Physiol* 1986; **55**: 5–8.