Opioid Involvement in the Perception of Pain Due to Endurance Exercise in Trained Man

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Abstract The purpose of this study was to evaluate the role of endogenous opiates in modulating physical performance during dynamic exercise in conscious man. The plasma concentration of $\beta$-endorphin (BEP) and of adrenocorticotropic hormone (ACTH) along with muscle pain (McGuill Pain Questionnaire) were assessed in 17 trained, male runners before and after running the longest possible distance within 12 min (i.e., the Cooper test). Each runner participated twice in the test (double-blind cross-over design), with a 1-week interval—with or without an injection of the opiate antagonist naloxone (0.8 mg i.v.). The average (SEM) distance reached was 3,198 (45) m in the naloxone test and 3,240 (38) m in the placebo test. The BEP increased significantly during the tests by a factor of 4.1 on naloxone and by 2.8 on placebo (from the normal resting averages of 1.7 and 2.1 pmol/l, respectively). The ACTH also increased significantly by a factor of 2.0 on naloxone and 2.5 on placebo (from the normal resting averages of 19.3 and 16.8 pmol/l, respectively). There were no significant differences between the naloxone and the placebo test with respect to the increments of BEP or ACTH by exercise. However, the perception of muscle pain was enhanced with naloxone. The increased perception of pain did not decrease the athletes ability to perform in terms of the distance run. We conclude that endogenous opiates are involved in the perception of pain associated with exhaustive exercise and may subserve psychological rather than physiological functions during exercise.

Key words: opiates, exercise, pain, adrenocorticotropic hormone, $\beta$-endorphin.
The endogeneous opiate \( \beta \)-endorphin (BEP) is released from the pituitary during acute dynamic exercise (FRAIOLI et al., 1980; GAMBERT et al., 1981). The physiological role of exercise-induced elevation of BEP plasma concentration remains unresolved. This role may be studied indirectly at the present stage of knowledge by blocking the specific opiate binding sites with an opiate antagonist, naloxone. Naloxone enhances pulmonary ventilation at high work intensities (GROSSMAN et al., 1984), which conforms to the inhibitory effects of endogeneous opiates on ventilatory regulation demonstrated by POKORSKI and LAHIRI (1981) and by POKORSKI et al. (1981). Naloxone also enhances, by an as yet undetermined mechanism, exercise-induced release of a number of hormones and neuromodulators (FRAIOLI et al., 1980; GAMBERT et al., 1981; GROSSMAN et al., 1984). GROSSMAN et al. (1984) and SURBEY et al. (1984) have hinted at an increased perception of effort and pain during exercise with naloxone. This opens up yet another avenue of a possible role of the endogenous opioid system in exercise, i.e., in the psychological events accompanying exercises.

Endurance training is known to elevate the threshold for pain (SCOTT and GIJSBERS, 1981), and BEP release is facilitated in trained humans during exercise (CARR et al., 1981). A delayed development and reduced intensity of muscle pain during exhaustive exercise would likely increase the ability to perform. Accordingly, if the perception of pain is mediated by opiate receptors, the opiate antagonist naloxone would be expected to impair performance. The purpose of the present study was therefore to determine the effect of naloxone on the perception of pain and on the related capability of sustaining submaximal exercise in highly trained athletes. Additionally, changes of plasma BEP and of adrenocorticotropic hormone (ACTH) were evaluated. Our results indicated that endogenous opiates were involved in the perception of pain during exercise, which, however, did not affect the athletes’ physical performance.

MATERIALS AND METHODS

Seventeen well-trained male athletes volunteered for the study. They had a median age (range) of 26 (22–32) years. For the weight, height, and indirect maximum oxygen uptake (Harvard step test) the medians (range) were: 79 (66–90) kg, 1.80 (1.79–1.93) m, and 59 (46–66) ml O\(_2\) (STPD)/(min·kg), respectively. The procedure complied with the rules of the Helsinki Declaration, and informed consent was obtained from each person. The study was approved by the institutional ethical committee for human research. A double-blind cross-over trial was designed, consisting of two Cooper tests arranged with a 1-week interval. Nine athletes received naloxone before the first competition and eight athletes before the second. The test consisted of a 12-min run on a track, while each person tried to reach the longest distance possible with total exhaustion as the endpoint. The performance was maximal. All runners were students from the Danish Military Academy’s School of Physical Training and Education, and were therefore
accustomed to the Cooper test. The many supervisors conducted the test with military precision. The athletes were running at the velocity range of 15.1 to 17.4 km/h corresponding to a calculated oxygen uptake (mean ± S.D.) of 58 ± 2 ml STPD/(kg·min). Before each test, the runner warmed up with 10-min muscle extension (with a heart rate below 100 beats/min). The venous blood sample was collected, and 2 ml of either sterile physiological saline or 0.8 mg naloxone (also 2 ml in volume) was injected intravenously as a bolus. About 10 min after the injection, the Cooper test was started. At the end of the 12-min run, the distance accomplished was recorded, and another blood sample was obtained—the blood sampling was completed 267 s (placebo) and 287 s (naloxone) after the test, as an average.

Venipuncture was chosen as opposed to an indwelling catheter during the track run, as the runners were less anxious about this well-known procedure, and because we wanted to avoid catheter complications. Both tests were performed at the same time of day, and both days were sunny and windless. Experiments (such as pain and nervousness) were evaluated on the basis of results from a modified McGuill Pain Questionnaire (MELZACK, 1975). This questionnaire quantifies the degree of pain and other unpleasant experiences. We used 11 questions analyzed with a maximum score of 4 points per experience, i.e., a maximum of 44 points for maximal pain and discomfort. In the present situation a non-parametric statistical method must be used, and Fishers exact test is the choice. The BEP and ACTH in circulating blood (plasma) were measured with specific radioimmunoassays as described elsewhere (FENGER, 1986; BACH et al., 1987). The distribution of the measured running distances and concentrations was, with a good approximation, shown to be normal (Gaussian) and accordingly, a Student’s t-test for paired variables was used.

Results from the McGuill questionnaire were analyzed with a nonparametric test (Fishers exact test). A level of 2p less than 0.05 was chosen as statistically significant.

RESULTS

We compared four variables (running distance, BEP, ACTH, and pain score) from the two Cooper tests on naloxone and on placebo. In the placebo Cooper test, the distance was 3,249 (SEM, 38) m, which was not statistically different from the naloxone test at 3,198 (SEM, 45) m (p = 0.08). Both these results were comparable with an average running distance of a routine Cooper test of 3,233 (SEM, 34) m recorded at the School of the Danish Military Academy before our study. The velocity of running implied a calculated energy expenditure equal to the maximum oxygen uptake plus a small anaerobic energy component. The BEP increased significantly (Fig. 1) during the placebo Cooper test (factor 2.8), and also during the naloxone Cooper test (factor 4.1), but the difference between these increments was not statistically significant (Table 1). The total score of unpleasant experiences, including pain (during and following the running), is given on the scale with a maximum of 44 points. Since each of the 17 subjects answered with almost identical
total scores for nociception following the two runs (Fig. 2), the differences between the tests is not statistically significant for the total score ($2p > 0.9$). However, the claim of pain only in the naloxone test was significantly more frequent (12 out of 17) than in the placebo running (3 out of 17), which is a statistically significant difference ($2p < 0.05$ with Fishers exact test). The pain was mainly located in the exercising leg muscles. The rise in ACTH during the Cooper tests is shown in Fig. 3. From the baseline levels of 16.8 and 19.3 pmol/l the increments in concentration were 2.5-fold and 2-fold in the placebo and naloxone tests, respectively. Both increments were statistically significant (Table 2), but the difference between the tests was not ($p > 0.95$). The resting levels of BEP and ACTH in plasma were in the

**Table 1.** The rise in endogenous opiate $\beta$-endorphin concentration (pmol/l plasma) from rest to the end of exercise (Cooper tests) with naloxone and with placebo.

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<th>Naloxone test</th>
<th>Placebo test</th>
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<td></td>
<td>Rest</td>
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<tr>
<td>$X$</td>
<td>1.7</td>
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<td>S.E.M.</td>
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Fig. 2. The total score of unpleasant experiences (pain and discomfort) during and following the exercise. The claim of pain only is not illustrated as it is just part of the total.

Fig. 3. ACTH concentrations (pmol/l plasma) just following exercise. The normal resting averages were 19.3 and 16.8 pmol/l before the naloxone and placebo tests, respectively.
DISCUSSION

This study demonstrated that the opiate antagonist naloxone, enhanced the subjective perception of pain during submaximal exercise in the trained male athletes. Since plasma β-endorphin was markedly elevated we may infer that opiate receptors blocked by naloxone were involved in pain perception during exercise.

There is other evidence pointing to the possible involvement of endogenous opiates in pain perception during exercise. SURREY et al. (1984) have reported that affective pain, i.e., emotional components of pain perception, were adversely affected by naloxone, which was accompanied by an impaired exercise performance. GROSSMAN et al. (1984) have found an intensified feeling of effort with naloxone for the same work load.

One would expect that if the subject perceives the unpleasant feeling of pain more, he would terminate his running stint faster. It is uncertain, however, if changes in pain perception relate causally to impaired performance. Our subjects, although they had a greater sense of pain with naloxone, tolerated the feeling well enough to achieve a distance comparable with that on placebo.

It is possible that the time limit set for our runners was too short, or that the progressively incremental work of running was not intense enough to render the adverse effect of enhanced pain perception on performance apparent. All our subjects were trained also in submaximal work (i.e., sprint, circuit training, etc.) and were thus accustomed to painful performances.

The determinants of the achievable distance for runners have more likely to do with energy metabolism than with endogenous opiates and the psychology of pain. The opiates might, however, modulate the performance indirectly, counteracting the plausible detrimental effect of increased pain. Naloxone increases pulmonary ventilation at high work intensities (GROSSMAN et al., 1984). This might increase, through alterations in blood gas content, the anaerobic threshold and facilitate

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Table 2. The change in ACTH concentration (pmol/l plasma) from rest to the end of exercise (Cooper tests) with naloxone and with placebo.

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<td></td>
<td>Rest</td>
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<tr>
<td>$X$</td>
<td>19.3</td>
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<tr>
<td>S.E.M.</td>
<td>1.9</td>
<td>4.3</td>
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<td>$p &lt; 0.05$</td>
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normal range reported for humans, and naloxone did not influence these resting levels appreciably.
exercise performance. Naloxone also increases exercise-induced release of various hormones, like catecholamines (GROSSMAN et al., 1984), which are stimulatory for ventilation. Thus, although the submaximal performance of this study seemed to have been unrelated to the level of pain reported, the data do not allow exclusion of other actions of endogenous opiates opposing the possible adverse effect of increased sense of pain on performance.

We used trained athletes for this study, since training increases exercise-induced secretion of β-endorphin (CARR et al., 1981; FARRELL et al., 1987). We confirmed that the athletes have a substantial increase in the plasma concentration of β-endorphin. It is noteworthy that the brain concentration of β-endorphin might be higher, since the brain-blood barrier offers resistance to endorphin penetration (GROSSMAN and SUTTON, 1985). We reasoned that an effect of naloxone would easier come to light in the trained condition. We found that naloxone influenced neither the resting level nor the exercise-induced secretion of β-endorphin or ACTH. This suggests that their release during both rest and exercise is independent of the function of the opiate system. Recently, however, HOFFMANN et al. (1987) have reported an increase in β-endorphin in the cerebrospinal fluid during exercise.

Previous reports have shown that naloxone increases plasma ACTH at rest in man (VOLAVKA et al., 1979), and that sufficiently intense exercise enhances ACTH release (FRAIOLI et al., 1980; GAMBERT et al., 1981). The seemingly discordant result of the lack of naloxone effect on resting plasma ACTH might depend on the naloxone dosage. The naloxone dose in our study was about 12 times smaller than the lower dose used in the report of VOLAVKA et al. (1979). Our small dose is believed to have only antagonistic actions, whereas high doses may exhibit direct agonistic activity (HILL, 1981), confounding the physiological effects of endogenous opiates-opiate receptors interaction. The increased pain perception with naloxone observed in our study argues for an adequate amount of the drug being bound to opiate receptors in the brain to exert an effect.

In conclusion, our study suggests that endorphins released during high-intensity submaximal running are involved in the psychological elaboration of pain perception. The role of endogeneous opiates in the physiological components sustaining exercise performance remains undetermined at present.

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