Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry

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1Department of Physical Education and Exercise Science, Brooklyn College, Brooklyn 11210; 2Joan and Joel Smilow Cardiac Prevention and Rehabilitation Center, The Rusk Institute of Rehabilitation Medicine, 3Division of Pulmonary and Critical Care Medicine, Department of Medicine, and 4Department of Emergency Medicine, New York University School of Medicine, New York, New York 10016

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Sgherza, Anthony L., Kenneth Axen, Randi Fain, Robert S. Hoffman, Christopher C. Dunbar, and François Haas. Effect of naloxone on perceived exertion and exercise capacity during maximal cycle ergometry. J Appl Physiol 93: 2023–2028, 2002.—We assessed the effects of naloxone, an opioid antagonist, on exercise capacity in 13 men and 5 women (mean age = 30.1 yr, range = 21–35 yr) during a 25 W/min incremental cycle ergometer test to exhaustion on different days during familiarization trial and then after 30 mg (iv bolus) of naloxone or placebo (Pl) in a double-blind, crossover design. Minute ventilation (VE), O2 consumption (VO2), CO2 production, and heart rate (HR) were monitored. Perceived exertion rating (0-10 scale) and venous samples for lactate were obtained each minute. Lactate and ventilatory thresholds were derived from lactate and gas-exchange data. Blood pressure was obtained before exercise, 5 min postinfusion, at maximum exercise, and 5 min postexercise. There were no control-Pl differences. The naloxone trial demonstrated decreased exercise time (96% Pl; P ≤ 0.01), total cumulative work (96% Pl; P < 0.002), peak VO2 (94% Pl; P < 0.02), and HR (96% Pl; P = 0.01). Other variables were unchanged. HR and VE were the same at the final common workload, but perceived exertion was higher (8.1 ± 0.5 vs. 7.1 ± 0.5) after naloxone than Pl (P < 0.01). The threshold for effort perception amplification occurred at −60 ± 4% of Pl peak VO2. Thus we conclude that peak work capacity was limited by perceived exertion, which can be attenuated by endogenous opioids rather than by physiological limits.

peak oxygen consumption; lactate threshold; endogenous opioids; physiological fatigue

THE DISCOMFORT ASSOCIATED with skeletal muscle activity and/or with increased breathing during exercise in healthy fit people may determine when the exercise is terminated (8, 9). Sürbey et al. (22) have speculated that effort sensation, in turn, may be modulated by endogenous opioid release. The ventilatory component of discomfort is due, in part, to the disproportionate increase in minute venti-

lation (VE) relative to the increase in workload, which results from stimulation by H+ and CO2 formed during buffering of lactic acid released during high levels of exercise (24, 25). The ventilatory threshold (VT) denotes the work rate at which this disproportionate increase occurs. Robertson (16) speculated that during high-intensity, continuous exercise above VT, discomfort becomes a limiting factor. This level of work has also been associated with endogenous opioid release (23). Endogenous opioids, in turn, have been shown to reduce VE (15, 27) for a given workload, thereby diminishing respiratory discomfort. Similarly, these endogenous opioids would also diminish discomfort originating from exercising muscles (18, 19).

Although a small number of investigations have assessed the role of opioid blockade on maximum exercise capacity (5, 12, 20, 22), the effect in healthy subjects has not been thoroughly defined. To assess the possible impact of endogenous opioids on effort perception in determining maximum exercise capacity, we assessed the effects of a large dose of naloxone, a competitive opioid antagonist, on maximum exercise capacity and cardiopulmonary and metabolic parameters of exercise in a group of self-trained endurance athletes.

METHODS

The study’s aim and procedures were explained to the 13 men and 5 women, a sample of convenience consisting of self-trained endurance athletes, and signed informed consent was obtained. The evaluation was performed on 3 nonconsecutive days. The first day began with a medical examination consisting of a history, physical examination, and electrocardiogram. Subjects then performed a peak cycle ergometer test to exhaustion. This served to familiarize them with the overall procedure and establish a baseline level of fitness.

Subjects were studied in an air-conditioned room (68°F) with continuous monitoring of heart rate and rhythm (via telemetry). During the last two sessions, a venous catheter was placed in the antecubital vein for administration of a
EFFECT OF NALOXONE ON MAXIMAL CYCLE ERGOMETRY

Table 1. Pre- and postinjection resting values

<table>
<thead>
<tr>
<th></th>
<th>Placebo Preinjection</th>
<th>Placebo Postinjection</th>
<th>Naloxone Preinjection</th>
<th>Naloxone Postinjection</th>
</tr>
</thead>
<tbody>
<tr>
<td>$V_O_2$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>4.8 ± 0.3</td>
<td>5.7 ± 0.8</td>
<td>4.5 ± 0.3</td>
<td>5.2 ± 0.4</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>61 ± 4.0</td>
<td>68 ± 2.6</td>
<td>62 ± 2.3</td>
<td>67 ± 2.3</td>
</tr>
<tr>
<td>$V_E$, l/min</td>
<td>13.4 ± 0.6</td>
<td>14.2 ± 0.9</td>
<td>12.8 ± 0.9</td>
<td>13.5 ± 0.9</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>0.9 ± 0.05</td>
<td>0.9 ± 0.05</td>
<td>0.8 ± 0.07</td>
<td>0.9 ± 0.09</td>
</tr>
<tr>
<td>Blood pressure (systolic/diastolic), mmHg</td>
<td>120 ± 2/77 ± 2</td>
<td>118 ± 3/78 ± 2</td>
<td>124 ± 3/79 ± 2</td>
<td>120 ± 3/77 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. $V_O_2$, $O_2$ consumption; HR, heart rate; $V_E$, minute ventilation.

30-ml bolus of either 30 mg naloxone in saline or a placebo of saline alone. The effective mean dose was 0.42 mg/kg for men and 0.49 mg/kg for women. The bolus was injected over a 5-min period before the start of exercise. Injection order was randomly determined, and the investigators were blinded as to the order. The catheter was also used for drawing blood samples for lactate (La$^-$) analysis.

Blood pressure measurements (by sphygmomanometry) were obtained while the subjects were resting on the cycle, 5 min after injection, at peak exercise, and at 5 min postexercise. Ventilatory and gas-exchange data were measured by an automated breath-by-breath aerobic analyzer (Fitco Max-1 Aerobic Testing System) using 10-s averaging intervals. Blood samples for La$^-$ analysis were drawn before injection, 5 min after injection, at the end of each minute during exercise, immediately on stopping exercise, and 5 and 10 min postexercise.

At the end of each minute of exercise, subjects were asked to rate their perceived exertion (PE) by using the Borg 0-10 category ratio (CR-10) scale, which ranges from 0 (nothing at all) to 10 (maximal, very hard). This follows prior evaluations of PE (1). This scale provides a measure related to absolute sensory magnitude based on quantitative semantics (e.g., "moderate," "severe," "very severe") that maintains an approximate ratio relationship between value judgements (i.e., if one stimulus is perceived to be twice as intense as another, the subject selects an evaluative level that is twice as great (1)). The CR-10 scale thus provides a useful estimate of absolute magnitude, permits comparisons among subjects, and is simple to use. After exercise, participants responded to verbal questions regarding reason for stopping, nature of fatigue, and symptoms of physical discomfort.

The ergometer’s saddle and handlebars were adjusted to each subject’s height so that knee was flexed between 15 and 30° when the foot was at its lowest point. Because the power output of the electrically braked ergometer is independent of pedaling frequency between 40 and 120 rpm, subjects were allowed to choose their own cadence. After an initial 3-min period of pedaling against no resistance, the load was incremented by 25 W at the end of each minute. Exercise was stopped when subjects either said they were unable to continue or were unable to maintain a minimum pedaling frequency of 40 rpm.

La$^-$ was analyzed within 2 min of sampling by using the YSI model 1500 Sport lactate analyzer. La$^-$ threshold (LT), defined as the workload at which La$^-$ begins to accumulate above average resting levels, was determined visually from logarithmic transformations of La$^-$ concentration plotted against corresponding workloads.

VT, defined as the beginning of excess $CO_2$ output generated from the buffering of $H^+$ arising from lactic acid production, was determined by the V-slope method (21). Initially, the point of departure from linearity of the $CO_2$ production ($VCO_2$) to $O_2$ uptake ($VO_2$) plot was graphically determined (21); then regression lines were calculated for lines above and below this point. In accordance with previous work (21), this point was adjusted to minimize the residual sums of squares obtained by linear regression analysis.

With the exception of La$^-$ data, statistical significance at termination of exercise was determined by using repeated-measures ANOVA followed by a Tukey post hoc analysis. A two-tailed paired $t$-test was used for the La$^-$ analysis. Comparisons with theoretical populations were done by using Z score analysis. Nonparametric comparisons were done with Fisher’s exact test.

RESULTS

As a group, our subjects were significantly more fit than a published (24), randomly selected age-comparable sample ($Z$ score = 2.1, $P < 0.05$). There were no significant differences between resting cardiopulmonary parameters after injection of the placebo or naloxone (Table 1), nor were there significant differences between baseline and placebo in either physiological parameters or PE at any exercise level (Table 2). Similarly, there were no postplacebo or postnaloxone dif-

Table 2. Peak exercise response

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Placebo</th>
<th>Naloxone</th>
<th>Significance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise time, s</td>
<td>748.3 ± 38.6</td>
<td>740.1 ± 36.7</td>
<td>709.8 ± 33.9</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>Maximum power, W</td>
<td>322.1 ± 14.4</td>
<td>323.6 ± 15.5</td>
<td>309.7 ± 14.5</td>
<td>$P &lt; 0.02$</td>
</tr>
<tr>
<td>$V_O_2$, ml·kg$^{-1}$·min$^{-1}$</td>
<td>49.6 ± 1.9</td>
<td>50.7 ± 2.8</td>
<td>45.6 ± 2.6</td>
<td>$P &lt; 0.02$</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>174.7 ± 2.0</td>
<td>171.2 ± 2.7</td>
<td>164.2 ± 2.1</td>
<td>$P &lt; 0.01$</td>
</tr>
<tr>
<td>$V_E$, l/min</td>
<td>125.5 ± 4.5</td>
<td>124.3 ± 6.1</td>
<td>117.4 ± 4.5</td>
<td>NS</td>
</tr>
<tr>
<td>Lactate, mmol/l</td>
<td>8.1 ± 0.5</td>
<td>7.8 ± 0.4</td>
<td>NS</td>
<td>NS</td>
</tr>
<tr>
<td>Blood pressure (systolic/diastolic), mmHg</td>
<td>177 ± 3/74 ± 3</td>
<td>179 ± 3/74 ± 3</td>
<td>174 ± 5/75 ± 2</td>
<td>NS</td>
</tr>
<tr>
<td>$P_E_{max}$</td>
<td>7.8 ± 0.5</td>
<td>8.0 ± 0.4</td>
<td>8.1 ± 0.5</td>
<td>NS</td>
</tr>
<tr>
<td>PE</td>
<td>7.0 ± 0.4</td>
<td>7.1 ± 0.5</td>
<td>8.1 ± 0.5</td>
<td>$P &lt; 0.01$</td>
</tr>
</tbody>
</table>

Values are means ± SE. PE, perceived exertion compared with last common work level completed; $P_E_{max}$, maximal PE; NS, not significant.
ferences in any physiological parameter during submaximal exercise.

After naloxone injection, however, maximum exercise time was significantly reduced by 31 s (P < 0.01) and maximum work rate was reduced by 14 W (P < 0.02), as shown in Table 2. This was accompanied by a significant reduction in \( \dot{V}O_2 \) peak of 5.1 ml·kg\(^{-1}\)·min\(^{-1}\) (P < 0.01), equivalent to nearly 1.5 metabolic equivalents, and a reduction in peak heart rate of 7 beats/min (P < 0.01). Average reductions in \( \dot{V}E \) and \( \dot{V}O_2 \) did not reach statistical significance. Blood pressure increased equally under both conditions. Postexercise PE at the end of exercise was similar in both placebo and naloxone trials. At the last common work rate, however, PE was greater after naloxone than after placebo (8.1 ± 0.5 and 7.1 ± 0.5; P < 0.01).

Naloxone did not have a significant effect on either VT or LT. The PE divergence between naloxone and placebo, which occurred at a \( \dot{V}O_2 \) equivalent to ~60% of the placebo \( \dot{V}O_2 \) peak (Table 3), strongly suggests that the endogenous opioid release threshold coincided with VT and LT. When questioned after each exercise session, 15 of the 18 participants had subjective complaints of fatigue (n = 8), nausea (n = 5), dizziness (n = 4), and/or headaches (n = 2) after receiving naloxone. In comparison, only two subjects had postexercise complaints after placebo (1 each, headache and fatigue) (P < 0.001, Fisher’s exact test).

**DISCUSSION**

Perceived effort was assessed in a double-blind, crossover design by using 18 fit subjects performing incremental cycle ergometer tests to self-reported exhaustion on 2 days after an intravenous bolus of either placebo or naloxone. This was done to assess the perceptual impact of naloxone, an opioid antagonist, on maximum exercise capacity. \( \dot{V}E \), \( \dot{V}O_2 \), heart rate, and blood \( L_a \) concentration were obtained, from which VT and LT were determined. In accord with other published work evaluating effort (2, 14, 19), we used the modified Borg CR-10 scale (2) to evaluate individual PE.

In humans, endogenous opioids appear not to have a tonic effect under normal physiological conditions unless challenged by a variety of stressors, among them exercise. It is increasingly evident that a moderately high-intensity exercise threshold [between 60 and 75% maximal \( \dot{V}O_2 \) (\( \dot{V}O_2 \) max)] is needed to stimulate the release of \( \beta \)-endorphins (23). Our data indicating that PE was similar during both the placebo and naloxone trials until ~60% of the placebo \( \dot{V}O_2 \) peak and then increased more steeply with increasing workload after naloxone, are in agreement with the notion of such an opioid release threshold. This, combined with the significant presence of postexercise symptoms (i.e., fatigue, nausea, dizziness, and headaches) consistent with the effects of naloxone in the presence of opioids, further indicates that endogenous opioids were indeed released and that naloxone effectively antagonized their effects.

Several investigations that used naloxone to study the role of endogenous opioids on maximum exercise capacity (5, 12, 20, 22) concluded that endogenous opioids do not have a significant role in the circulatory or ventilatory response to exercise in healthy humans. Although these studies do not agree with our demonstration that naloxone results in premature cessation of exercise (Fig. 1F), the differences in conclusion may result from the following methodological variations.

1) The dose of naloxone used previously, ranging from 0.4 to 10.5 mg, is substantially less than the 30 mg used in this investigation and may have been inadequate. The effects of endogenous opioids (e.g., \( \beta \)-endorphin) are mediated through their actions on membrane-bound receptors found in multiple brain nuclei, the spinal cord, and peripheral organs. The presence of three opiate receptors (OP1, OP2, and OP3 receptors, previously termed \( \mu \), \( \delta \), and \( \kappa \) is widely accepted. Although the OP1 receptor requires relatively low doses of naloxone to antagonize endorphins, the OP2 and OP3 receptors can be blocked only by higher doses (11). Because naloxone has a relatively short half-life [30–100 min, mean = 65 min (11)], too low a dose will not permit potential effects to develop. Conversely, excessively high doses, in the milligram per kilogram range, elicit clinically significant behavioral effects. Consequently, the 30-mg dose chosen for this study was high enough to maintain effective opioid inhibition levels over the 16-min exercise protocol but significantly less than that used to produce gross mood and memory effects. Consistent with our observations, this relatively high dose of naloxone has not been shown to exert any significant effect on resting heart rate, ventilation (26), or blood pressure (17).

2) Because the criteria defining maximum exercise capacity differed among these studies, small changes in exercise time may have been missed. Our subjects exercised until they said they were unable to continue or until they were unable to maintain a pedaling frequency of 40 rpm. In contrast, Gullestad et al. (5) used the ability to maintain pedaling frequency of 60 rpm along with an exertion rating of 19 of 20, Staessen et al. (20) asked volunteers to cycle for 3 min at 100% of their previously determined maximum exercise capacity, McMurray et al. (12) required subjects to signal when they felt unable to complete more than one further minute of work, and it is not clear what criteria Surbej et al. (22) used to determine maximum exercise capacity.

3) By using 10-s averages of breath-by-breath analysis, we were better able to discriminate changes in the

**Table 3. Threshold assessment**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Naloxone</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ventilatory threshold</td>
<td>61.0 ± 2.3</td>
<td>61.8 ± 2.1</td>
</tr>
<tr>
<td>Lactate threshold</td>
<td>58.4 ± 2.6</td>
<td>57.9 ± 1.9</td>
</tr>
<tr>
<td>PE threshold*</td>
<td>58.9 ± 3.8</td>
<td></td>
</tr>
</tbody>
</table>

Values are means ± SE given as percent peak \( \dot{V}O_2 \) (%\( \dot{V}O_2 \) peak). *%\( \dot{V}O_2 \) peak of placebo at which postnaloxone PE diverges from placebo PE.
last stage of exercise than the 1-min averages of mixed air used in the other studies. This is supported by the data of McMurray et al. (12) demonstrating no significant differences in cardiovascular and respiratory response between placebo and naloxone during the last minute of the last completed stage but finding significant reduction in heart rate and ventilation as well as trends toward reduced duration, $V_{O_2 \text{ max}}$, and blood $L_a$ at maximal exertion. McMurray et al. noted that “Although there were not statistically significant differences in exercise duration, the naloxone trials averaged 30 s less... Therefore, the lower ventilation, respiratory frequency, heart rates and higher $P_{ET CO_2}$ during peak exertion for the naloxone trial may have been explained by shorter duration.” These data closely parallel our observations, and their failure to observe a statistical postnaloxone reduction in maximum exercise likely represent an insufficient number of subjects (6 compared with our 18).

The present data, demonstrating that the observed physiological responses to exercise are virtually identical in both the naloxone and placebo conditions (Fig. 1, A–D) but that effort above the putative point of endogenous opioid release is perceived as greater after naloxone administration (Fig. 1E), are consistent with the suggestion of Surbey et al. (22) that the endogenous opioid system may alter the perception of discomfort associated with high-intensity exercise, thus significantly affecting maximum exercise capacity without changing the physiological response to exercise.

A conceptual model based on one developed by Levine and Everhart (10) to explain the possible role of endogenous opioids in improving performance is illustrated in Fig. 2. Simultaneous sensory input to the perception of exertion during dynamic exercise arises locally from sensation of muscle activity and centrally from cardiovascular and respiratory activity in the mid- and hindbrain. This combined sensory information is processed preconsciously along with psychological (e.g., mood, anxiety, neurosis, depression, etc.) and cognitive elements (e.g., prior experience at a given level of effort, cultural pattern, etc.). This preconscious processing selectively filters the information that emerges to conscious awareness and determines the conscious decision on continuing the exercise. Endogenous opioids and their receptors have been demonstrated in structures associated with respiration (15), cardiovascular control, behavior and mood (7), and pain (3). Inhibition of sensory information or modulation of mood by endorphins at any of these locations

Fig. 1. Data obtained from a representative subject illustrating the absence of differences between naloxone and placebo in the evolution of heart rate (A), minute ventilation ($V_e$; B), $O_2$ consumption ($V_{O_2}$; C), and lactic acid (D) over the range of common work rates. In contrast, at high levels of work effort, perception was greater (E) and total work time was shorter (F) after naloxone than after placebo.
would result in reduced discomfort and/or pain perception, thus allowing for continued effort.

Although we cannot rule out a direct effect of naloxone in reducing maximum exercise capacity, the majority of previous observations indicate that, on the contrary, naloxone tends to block the inhibitory cardiorespiratory effects of endogenous opioids (14). It is highly unlikely, therefore, that the reduction in peak exercise capacity seen here could be attributed to reduced physiological function. As it appears that exercise was volitionally terminated before the subjects reached physiological limits, we conclude from these data that maximum exercise capacity, in healthy fit subjects under laboratory conditions, is usually determined by individual effort perception rather than by physiological limitations.

Although our finding that the small but significant increase in exercise tolerance after placebo administration (i.e., when the opioid response remains intact) suggests that attenuation of discomfort by appropriate endogenous opioid release during competition might provide a small but important edge for athletes at critical stages in performance, these data also raise a conundrum. The endogenous opioid system appears to have two diametrically opposed effects. On one hand, it diminishes awareness of pain and thus allows subjects to continue their effort. On the other hand, it inhibits sympathetic activity in favor of parasympathetic activation, which theoretically would inhibit the physiological response to increasing exercise demands. Finally, cognitive factors may supercede the effects of effort perception on exercise performance (✓) irrespective of opioid presence or absence. $V_{\text{O}2_{\text{max}}}$.
individual’s PE, which can be attenuated by endogenous opioids, rather than by physiological fatigue.

REFERENCES