Effect of morphine on sympathetic nerve activity in humans

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1Division of Cardiology, Department of Medicine, Pennsylvania State University College of Medicine, Hershey, Pennsylvania 17033; and 2Cardiovascular Center and Department of Internal Medicine, University of Iowa College of Medicine, Iowa City, Iowa 52242

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Carter, Jason R., Charity L. Sauder, and Chester A. Ray. Effect of morphine on sympathetic nerve activity in humans. J Appl Physiol 93: 1764–1769, 2002. First published August 2, 2002; 10.1152/japplphysiol.00462.2002.—There are conflicting reports for the role of endogenous opioids on sympathetic and cardiovascular responses to exercise in humans. A number of studies have utilized naloxone (an opioid-receptor antagonist) to investigate the effect of opioids during exercise. In the present study, we examined the effect of morphine (an opioid-receptor agonist) on sympathetic and cardiovascular responses at rest and during isometric handgrip (IHG). Eleven subjects performed 2 min of IHG (90% maximum) followed by 2 min of postexercise muscle ischemia (PEMI) before and after systemic infusion of morphine (0.075 mg/kg loading dose + 1 mg/h maintenance) or placebo (saline) in double-blinded experiments on separate days. Morphine increased resting muscle sympathetic nerve activity (MSNA; 17 ± 2 to 22 ± 2 bursts/min; P < 0.01) and increased mean arterial pressure (MAP; 87 ± 2 to 91 ± 2 mmHg; P < 0.02), but it decreased heart rate (HR; 61 ± 4 to 59 ± 3; P < 0.01). However, IHG elicited similar increases for MSNA, MAP, and HR between the control and morphine trial (drug × exercise interaction = not significant). Moreover, responses to PEMI were not different. Placebo had no effect on resting, IHG, and PEMI responses. We conclude that morphine modulates cardiovascular and sympathetic responses at rest but not during isometric exercise.

endogenous opioids; autonomic nervous system; blood pressure; isometric exercise

MORPHINE IS OFTEN ADMINISTERED to patients for pain management, but it is also recommended for acute myocardial infarction patients to reduce the elevated resting arterial blood pressure and sympathetic tone that is associated with cardiac ischemia. Although morphine is often recognized for its hypotensive effect, recent evidence suggests it may actually increase arterial blood pressure (16). The mechanism underlying morphine-induced increases in arterial blood pressure at rest remains equivocal. Because activation of the sympathoadrenal (11) and renin-angiotensin (1) systems has been suggested to contribute to increases in resting arterial blood pressure with morphine, it is possible that central sympathetic outflow is increased. To our knowledge, only one study has examined the effects of morphine on muscle sympathetic nerve activity (MSNA) at rest (13). Kirno et al. (13) report no change in either MSNA or arterial blood pressure. Because resting arterial blood pressure did not change, it is unknown whether changes in arterial blood pressure induced by morphine are associated with changes in MSNA.

The effect of morphine on cardiovascular and sympathetic responses during exercise is also not well documented. Exercise elicits marked increases in MSNA (15, 22) and also purportedly releases various endogenous opioids for analgesic actions (3). Several centers in the brain stem contain opioid receptors (21), including the ventrolateral medulla, which also receives skeletal muscle afferent input (17). Therefore, it is reasonable to speculate that endogenous opioids might modulate MSNA during exercise. Evidence is limited for endogenous opioid modulation of MSNA during exercise in humans. Most studies have used opioid receptor blockade to examine MSNA responses during exercise. The opioid-receptor antagonists naloxone and naltrexone have been reported to either increase (6) or not change (4, 23) MSNA responses during exercise. The effect of opioid receptor agonists on MSNA responses to exercise is less established. Only one study using the opioid-receptor agonist codeine reported no change in MSNA responses during dynamic handgrip (4). Moreover, this study did not examine MSNA responses during isolated activation of the muscle metaboreflex [i.e., postexercise muscle ischemia (PEMI)]. The effect of morphine, a potent opioid-receptor agonist, on MSNA during exercise has not been investigated in humans, but animals have demonstrated an attenuation of cardiovascular and sympathetic responses to exercise with morphine or the opioid-receptor agonist Met-enkephalin (10, 20).

Therefore, the purpose of this study was to examine the effect of the opioid-receptor agonist morphine on arterial blood pressure and MSNA responses at rest and during isometric handgrip (IHG) and PEMI. We
hypothesized that morphine would increase arterial blood pressure and MSNA at rest and would attenuate sympathetic and cardiovascular responses during IHG and PEMI. Our results indicate that morphine modulates arterial blood pressure and MSNA at rest but not during exercise.

METHODS

Subjects. Twelve healthy men (age 18–35 yr) volunteered to participate in the study. Subjects abstained from nicotine, alcohol, and caffeine for a minimum of 8 h before the experiment. After verbal explanation of the testing procedures, all participants signed a written informed consent approved by the Institutional Review Board at the University of Iowa.

Experimental design. On each experimental day, subjects performed two bouts of exercise. The first exercise bout was designated as the control trial because no drug intervention was performed. During the second exercise bout, morphine or saline was administered as an intravenous bolus infusion into the nonexercising arm over a 10-min period. The two exercise bouts were conducted in the same order on each day and were separated by at least 35 min of rest. Morphine and saline were administered on separate days, and both the investigator and the subjects were blinded with regard to the drug intervention until analysis of data was completed.

During each exercise bout, subjects performed 2 min of IHG (30% maximum voluntary contraction) followed by 2 min of PEMI before (control) and after systemic infusion of morphine (0.075 mg/kg loading dose + 1 mg/h maintenance) or placebo (saline). This morphine dose has been shown to significantly elevate arterial blood pressure (16). The maximal voluntary contraction level was established on each test day by using the peak force generated from three maximal efforts. PEMI was induced 5 s before the cessation of exercise by inflating a blood pressure cuff on the arm to 250 mmHg. Each exercise trial began and ended with a 5-min baseline and 2-min recovery.

Measurements. Multifiber recordings of MSNA were made by inserting a tungsten microelectrode into the peroneal nerve at the head of the fibula of a resting leg; a different leg was used for the morphine and placebo trials. A reference electrode was inserted subcutaneously 2–3 cm from the recording electrode. Both electrodes were connected to a differential preamplifier and then to an amplifier (total gain between 40,000–80,000), where the nerve signal was band-pass filtered (700–2,000 Hz) and integrated (time constant, 0.1 s) to obtain a mean voltage display of the nerve activity. Satisfactory recordings of MSNA were defined by spontaneous, pulse-synchronous bursts that increased during end-expiratory apnea and did not change during stroking of the skin or auditory stimulation (yell).

Continuous heart rate (HR) was recorded with a three-lead electrocardiogram. A pneumograph bellows was wrapped around the subject’s chest to monitor respiratory rate and to ensure subjects avoided a Valsalva maneuver during IHG. After local anesthesia, a 20-gauge catheter was inserted into a forearm vein for systemic infusion of morphine or saline. Mean arterial pressure (MAP) was derived by using a Finapres positioned on the middle digit of the subject’s nonexercising hand. The mean voltage neurograms were displayed together with an electrocardiogram and respiratory pattern on a chart recorder (model ES2000, Gould) at a paper speed of 5 mm/s. The nerve traffic was also routed to a storage oscilloscope and a loudspeaker for monitoring during the study.

Data analysis. Successful nerve recordings were obtained in 11 subjects during both the morphine and placebo trials. All data were analyzed in 1-min segments. Baseline data for the morphine and placebo trials were compared by using a paired t-test, and the exercise and PEMI data were analyzed by using a two-within-factor (drug × exercise bout) repeated analysis of variance. Significance was accepted at the P < 0.05 level. All data are presented as means ± SE.

RESULTS

Preexercise values for all measured variables are presented in Table 1. Preexercise values between the control and saline trials were not different. However, morphine significantly increased MSNA (17 ± 2 to 22 ± 2 bursts/min; P < 0.01) and MAP (87 ± 2 to 91 ± 2 mmHg; P < 0.02) at rest, whereas HR (61 ± 4 to 59 ± 3 beats/min; P < 0.01) decreased. Morphine did not elicit any noticeable side effects.

There were no significant drug × exercise interactions for either the morphine (P = 0.43) or placebo trial (P = 0.63) for total MSNA. Similarly, there was no significant interaction observed for MAP and HR. Exercise did significantly increase MSNA, MAP, and HR (all P < 0.01) across all exercise bouts (Fig. 1). PEMI elicited comparable responses for all variables during both the morphine and placebo trials. Increases in MSNA and MAP during exercise were maintained during PEMI, whereas HR returned to baseline levels. Repeated-measures ANOVA revealed a main effect for drug during the morphine trial for burst frequency (P = 0.02) but not for any other variable. Figure 2 shows that MSNA responses during the first minute of IHG were less with morphine than without (P < 0.05), but responses during the second minute of IHG and PEMI were not different. During the placebo trial, MSNA, MAP, and HR responses to IHG and PEMI were not different between the two exercise bouts.

Table 1. Preexercise baseline values during the morphine and placebo trials

<table>
<thead>
<tr>
<th>Variable</th>
<th>Control</th>
<th>Morphine</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>MSNA, bursts/min</td>
<td>17 ± 2</td>
<td>22 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>19 ± 2</td>
</tr>
<tr>
<td>Total MSNA, sum of burst amplitudes</td>
<td>151 ± 27</td>
<td>207 ± 26&lt;sup&gt;a&lt;/sup&gt;</td>
<td>182 ± 29</td>
</tr>
<tr>
<td>MAP, mmHg</td>
<td>87 ± 2</td>
<td>91 ± 2&lt;sup&gt;a&lt;/sup&gt;</td>
<td>90 ± 3</td>
</tr>
<tr>
<td>HR, beats/min</td>
<td>61 ± 4</td>
<td>59 ± 3&lt;sup&gt;a&lt;/sup&gt;</td>
<td>58 ± 3</td>
</tr>
</tbody>
</table>

Values are means ± SE. MSNA, muscle sympathetic nerve activity; MAP, mean arterial pressure; HR, heart rate. Morphine and placebo trials were randomized. <sup>a</sup>Significantly different from corresponding control value, P < 0.05.
variables returned to preexercise levels during recovery (not shown).

DISCUSSION

The primary findings of this study are that 1) morphine modulates MSNA, MAP, and HR at rest in humans and 2) cardiovascular and MSNA responses to IHG and PEMI are not altered by the opioid-receptor agonist morphine. The present study provides the first evidence of concurrent increases in resting arterial blood pressure and MSNA with morphine in humans. Furthermore, our results suggest that morphine does not modulate cardiovascular or MSNA responses during exercise.

Responses at rest. Morphine has been recognized for its hypotensive effect (2, 12). Previous studies suggest that morphine decreases arterial blood pressure as a result of multiple mechanisms, including decreases in cardiac and renal sympathetic nerve activity (7, 18), an increase in vagal tone (26), histamine release (5, 19),
and venous and arterial vasodilation (14). Although morphine has been reported to predominantly decrease arterial blood pressure, morphine has also been reported to elevate arterial blood pressure in humans (1, 11, 16). Mildh et al. (16) recently reported that intravenous injection of morphine increased MAP, but in this study morphine was injected during ischemia-induced pain (300-mmHg upper arm tourniquet), not at rest. Bailey et al. (1) and Hoar et al. (11) demonstrated that morphine increased arterial blood pressure at rest, but these studies were performed with surgical subjects who were under the influence of other drugs (e.g., diazepam and nitrous oxide). Moreover, the mechanisms responsible for increases in MAP during morphine administration remain equivocal. Previous studies have attributed increases in arterial blood pressure to elevation of the sympathoadrenal (11) and renin-angiotensin (1) systems. Another mechanism that could contribute to the rise in arterial blood pressure with morphine is a direct increase in central sympathetic outflow. To our knowledge, only one study has previously examined the effect of morphine on resting MSNA in humans (13). These authors reported that baseline MSNA did not change with intrathecal administration of morphine (0.4 mg) with no change in arterial blood pressure or heart rate. Because of these findings, the mechanisms responsible for the elevated arterial blood pressure with morphine could not be ascertained by the authors.

In the present study, morphine increased baseline MAP and MSNA and reduced HR. Differences between our study and the findings of Kirmo et al. (13) might be due to different administration routes (intravenous vs. intrathecal). Neural and cardiovascular effects of exogenous opioids appear to be dependent on the dose, the route of administration, and the type of opioid administered (2, 12). However, results from the present study are enhanced by several aspects of our research design. First, both the investigators and subjects were blinded with regard to the drug intervention to minimize bias. Second, the same subjects were used for both the placebo and morphine trials to reduce variability that might be observed by using a second random sample of subjects. Therefore, the results from the present study provide new evidence for a possible mechanism responsible for morphine-induced increases in arterial blood pressure at rest.

**Responses during exercise.** The role of endogenous opioids on sympathetic responses during exercise remains equivocal. Farrell et al. (6) reported that the endogenous opioid-receptor antagonist naloxone augments MSNA responses during IHG in humans. In contrast, several studies have failed to report differences in cardiovascular and sympathetic responses to dynamic or static exercise after administration of an opioid-receptor antagonist (4, 8, 9, 23, 25). Specifically, Ray and Pawelczyk (23) and Cook et al. (4) found no effect of either naloxone or naltrexone on MSNA during ischemic and dynamic handgrip in humans. One limitation of previous opioid antagonistic studies examining MSNA during exercise is that the exercise muscle mass (small) and duration (brief) may have prevented activation of the endogenous opioid system. Because opioid-receptor antagonists block, rather than activate, opioid receptors, an interaction between sympathetic responses during exercise and the endogenous opioid system would only be observed if the exercise stimulus were sufficient to activate the opioid system. In humans, it is not currently possible to artificially evoke endogenous neurotransmitter release during exercise. However, exogenous administration of an opioid agonist, such as morphine, should activate opioid receptors during exercise.

Currently, the influence of opioid-receptor agonists on sympathetic responsiveness during exercise is not well documented. Using animals, Pomeroy et al. (20) and Hill and Kaufman (10) demonstrated that intrathecal administration of the opioid-receptor agonists morphine and Met-enkephalin analog attenuated sympathetic and cardiovascular responses to exercise. In contrast, Cook et al. (4) demonstrated that codeine (60 mg) does not alter MSNA responses during dynamic handgrip in humans. Because of this apparent conflict in data, we examined MSNA responses during exercise in humans after the intravenous administration of the more potent opioid-receptor agonist morphine.
Morphine predominantly activates μ-receptors, which are distributed throughout the rostral and caudal ventrolateral medulla (21). Because the ventrolateral medulla also receives skeletal muscle afferents (17), it is possible that the neural interaction during simultaneous stimulation of μ-receptors and skeletal muscle afferents may influence ventrolateral medulla output of MSNA. However, our results suggest that morphine does not alter MSNA responses during IHG. Although changes in MSNA appear to be attenuated during the first minute of IHG during the morphine trial, MSNA responses during the second minute were not different. One explanation for the attenuation observed during the first minute could be related to the elevated baseline MSNA and MAP during the morphine trial. The elevated MAP may have prevented the small increase in MSNA observed in the control trial (24). It is also possible that morphine had a specific effect on skeletal muscle reflexes. However, if morphine did have a specific effect on the skeletal muscle reflexes, it would be expected that the effect would have persisted during the second minute of IHG, but this was not observed. Therefore, we conclude that MSNA responses during brief periods of IHG are not altered by stimulation of opioid receptors. It should be recognized that we cannot exclude a role for δ-receptors during exercise because morphine does not bind to this receptor (2).

Because IHG engages both mechanoreceptors and metaboreceptors, PEMI was performed to isolate the effects of the muscle metaboreflex. To our knowledge, the influence of an opioid agonist during PEMI has not been reported previously. Morphine did not affect MSNA responses during PEMI. This finding indicates that the muscle metaboreflex, the primary mechanism for MSNA increases during exercise, is unaltered by activation of opioid receptors.

**Summary.** In summary, intravenous injection of the opioid-receptor agonist morphine increases arterial blood pressure and MSNA at rest but does not modulate cardiovascular and sympathetic responses to IHG and PEMI. These findings suggest that central sympathetetic outflow contributes to increases in arterial blood pressure with morphine. Moreover, we conclude that the activation of endogenous opioid receptors does not modulate cardiovascular and sympathetic responses during forearm exercise in humans.

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**REFERENCES**


