Peripheral μ-opioid receptors attenuate the augmented exercise pressor reflex in rats with chronic femoral artery occlusion

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Tsuchimochi H, McCord JL, Kaufman MP. Peripheral μ-opioid receptors attenuate the augmented exercise pressor reflex in rats with chronic femoral artery occlusion. Am J Physiol Heart Circ Physiol 299: H557–H565, 2010. First published June 11, 2010; doi:10.1152/ajpheart.00387.2010.—Recent studies have shown that opioid receptors are expressed on group III and IV afferents, which comprise the sensory arm of the exercise pressor reflex. Although the stimulation of opioid receptors in the central nervous system has been shown to attenuate the exercise pressor reflex, the effect on the reflex of their stimulation in the periphery is unknown. We therefore tested the hypothesis that the activation of peripheral μ-opioid receptors attenuates the exercise pressor reflex. The pressor responses to static contraction were compared before and after the injection of the μ-opioid receptor agonist [D-Ala², N-MePhe⁴, Gly⁵-ol-enkephalin (1 μg)] into the abdominal aorta of decerebrated rats in which one femoral artery had been occluded 72 h previously (n = 10) and in control rats whose femoral arteries were freely perfused (n = 8). DAMGO attenuated the peak pressor response to contraction in rats whose femoral arteries had been occluded (before: increase of 34 ± 3 mmHg and after: increase of 22 ± 2 mmHg, P = 0.008); the inhibitory effect of DAMGO was prevented by the injection of naloxone (100 μg) into the abdominal aorta (before: increase of 29 ± 5 mmHg and after: increase of 29 ± 5 mmHg, P = 0.646, n = 7). An intravenous injection of DAMGO (1 μg, n = 6) had no effect on the peak pressor response to contraction in both groups of rats. DAMGO had no effect on the peak pressor response to contraction in rats whose femoral arteries were freely perfused (before: Δ23 ± 4 mmHg, after: Δ23 ± 3 mmHg, n = 6) but appeared to have a small effect on topography of the response. DAMGO had no effect on the peak pressor response to tendon stretch in both groups of rats (both P > 0.05). We conclude that the stimulation of peripheral μ-opioid receptors attenuates the exercise pressor reflex in rats whose femoral arteries have been ligated for 72 h.

static contraction; thin fiber muscle afferents; ischemia; neural control of circulation

THE EXERCISE PRESSOR REFLEX plays an important role in evoking the cardiovascular responses to exercise in both physiological and pathophysiological states (5, 17, 20). The sensory arm of the reflex consists of thinly myelinated group III and unmyelinated group IV afferents (17), the endings of which are stimulated by both mechanical and metabolic stimuli arising in contracting muscles (13, 14). Group III and IV muscle afferents synapse on cells in laminae I and V of the dorsal horn of the spinal cord. These dorsal horn cells, in turn, relay to neural circuits in the both the ventrolateral medulla (6) and nucleus tractus solitarius (6), where they function to increase the sympathetic outflow to the vasculature and heart (34) as well as to decrease the parasympathetic outflow to the heart (18).

The stimulation of opioid receptors is known to inhibit transmission of nociceptive input to the spinal cord by both pre- and postsynaptic mechanisms (7, 12, 15, 26). The former mechanism is often attributed to opioid-induced inhibition of substance P release from the primary afferent terminals synapsing onto dorsal horn cells, whereas the latter is attributed to inhibition of these dorsal horn cells by enkephalin released from spinal interneurons (11, 16, 19). Recently, evidence has shown that opioid receptors are expressed not only on the central terminals of primary afferents but also on the peripheral endings of thinly myelinated and unmyelinated cutaneous sensory fibers (4). These opioid receptors are synthesized in cell bodies in the dorsal root ganglia and are then transported to the periphery (8, 21, 22). The activation of opioid receptors decreases the excitability of peripheral nerve terminals by inhibiting adenylate cyclase, which, in turn, decreases levels of cAMP, causing increased K⁺ efflux and decreased Ca²⁺ entry (38, 39, 40).

The analgesic effects of the stimulation of peripheral opioid receptors have been previously reported (22, 36). Using an in vitro glabrous skin-nerve preparation, Wenk et al. (36) examined the effect of morphine, an opioid receptor agonist, on the discharge properties of single afferent fibers innervating normal and inflamed skin. They found that morphine reduced the responses of most nociceptors to noxious mechanical and thermal stimuli in inflamed skin but had little effect on the responses of nociceptors to these stimuli in normal skin. The reduction was found to depend on the concentration of the opioid and was prevented by naloxone, an opioid receptor antagonist. In addition, Tegeder et al. (31) demonstrated that a local infusion of a low dose of morphine-6β-glucuronide, which does not readily penetrate the blood-brain barrier (2), significantly reduced muscle hyperalgesia by a series of concentric and eccentric muscle contractions in human subjects.

Based on these previous studies, we hypothesized that the activation of peripheral opioid receptors desensitizes group III and IV muscle afferents and thereby attenuates the exercise pressor reflex. Therefore, we examined the peripheral effect of a μ-opioid receptor agonist on the exercise pressor reflex in decerebrated rats. As suggested in the previous studies, the role of peripheral opioid receptors in the exercise pressor reflex may be different if the exercising muscles are either stressed or damaged (31, 36). Previously, we (33) have shown that the pressor response to static contraction of a hindlimb whose ipsilateral femoral artery was occluded for 72 h before the start of an experiment was greater than the pressor response to contraction of the contralateral freely perfused hindlimb. Thus, we compared the effect of an intra-arterial injection of a μ-opioid receptor agonist on the pressor reflex to static con-
traction in rats whose femoral arteries were ligated for 72 h before the experiment with the effect of the opioid agonist on the reflex in control rats whose hindlimb was freely perfused.

METHODS

All procedures were reviewed and approved by the Institutional Animal Care and Use Committee of the Hershey Medical Center of Pennsylvania State University. Adult male rats (Sprague-Dawley, n = 49, weighing between 344 and 565 g) were used in this study. Rats were housed in a temperature-controlled room (24 ± 1°C) with a 12:12-h light-dark cycle. Rats were fed a standard diet and tap water ad libitum. Seventy-two hours before an experiment, 29 of 49 animals underwent surgery to induce unilateral femoral artery occlusion according to procedures described elsewhere (23, 37). Briefly, rats were anesthetized with a mixture of 4% isoflurane and 100% oxygen; one femoral artery was isolated and then tightly ligated just distal to the inguinal ligament. Using radiolabeled microspheres, it has been shown that this femoral artery ligation procedure reduced blood flow reserve capacity to ~10–20% of normal but allowed sufficient blood flow to meet resting requirements (23, 37). Rats were allowed to recover 72 h before the experiments were started. Femoral artery occlusion has been reported to have no effect on normal cage activity (30).

Surgical preparation. On the day of the experiment, rats were anesthetized with a mixture of 4% isoflurane and 100% oxygen. The right jugular vein and common carotid artery were cannulated for the delivery of drugs and fluids and the measurement of arterial blood pressure, respectively. The carotid arterial catheter was connected to a pressure transducer (model P23 XL, Statham). Heart rate (HR) was calculated beat to beat from the arterial pressure pulse (Gould Bio-Tach). The trachea was cannulated, and the lungs were ventilated mechanically (Harvard Apparatus). Arterial blood gases and pH were measured by an automated blood gas analyzer (model ABL-700, Radiometer). Pco2 and arterial pH were maintained within normal ranges either by adjusting ventilation or through an intravenous administration of sodium bicarbonate (8.5%). A rectal temperature probe was inserted, and the core body temperature of the animal was maintained at 37–38°C by a water-perfused heating pad and a lamp.

In 37 of 49 experiments, we cannulated (polyethylene-10 tubing) the right femoral artery in a retrograde direction and advanced the tip to the bifurcation of the abdominal aorta. This allowed us to administer drugs into the arterial supply of the left hindlimb. A reversible vascular occluder was placed around the abdominal aorta and the inferior vena cava just above the aortic bifurcation. When tightened, this occluder helped to keep the injectate within the circulation of the left hindlimb.

The rat was placed in a Kopf stereotaxic frame. Dexamethasone (0.2 mg) was injected intravenously just before the decerebration procedure to minimize brain stem edema. The left common carotid artery was tied off, and a precollicular decerebration was performed. All neural tissue rostral to the section was removed. To minimize cerebral hemorrhage, small pieces of oxidized regenerated cellulose (Ethicon, Johnson & Johnson) were placed on the internal skull surface, and the cranial cavity was packed with cotton. In our experiments, rats were decerebrated instead of anesthetized because the preponderance of the evidence indicates that anesthesia prevents the reflex in this species (27, 32, 35).

A laminectomy exposing the lower lumbar and sacral portions of the spinal cord (L1–L5) was performed. The rat was then secured in a customized spinal frame by clamps placed on rostral lumbar vertebrae and the pelvis. Using the skin on the back, we formed a pool, which was filled with warm (37°C) mineral oil. The dura was cut and reflected, allowing the visual identification of the spinal roots. The left L4 and L5 ventral roots were identified and cut close to their exits.
from the spinal cord. The calcaneal bone of a left hindlimb was
severed, and the triceps surae muscles were isolated. Once the sur-
geries had been completed, the anesthesia was withdrawn, and the
lungs were ventilated with room air. A minimum recovery period of
90 min was used after decerebration before any experimental protocol
was started.

Experimental protocols. The L4 and L5 ventral roots were placed
on shielded stimulating electrodes. The cut end of each calcaneal

Table 1. Baseline MAP and HR before and after the administration of DAMGO, saline, and naloxone with DAMGO

<table>
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<tr>
<th>Group</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
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<tr>
<td>Freely perfused group</td>
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<tr>
<td>Intra-arterial administration (DAMGO treatment)</td>
<td>8</td>
<td>90.4 ± 6.7</td>
<td>436.4 ± 14.4</td>
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<tr>
<td>Control</td>
<td>8</td>
<td>8.14 ± 3.8</td>
<td>444.5 ± 16.5</td>
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<tr>
<td>Intravenous administration</td>
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<td></td>
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<tr>
<td>Control</td>
<td>6</td>
<td>73.6 ± 11.1</td>
<td>470.7 ± 25.8</td>
</tr>
<tr>
<td>DAMGO</td>
<td>6</td>
<td>76.3 ± 11.3</td>
<td>476.1 ± 17.9</td>
</tr>
<tr>
<td>Intra-arterial administration (saline treatment)</td>
<td>6</td>
<td>79.8 ± 4.6</td>
<td>491.3 ± 18.4</td>
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<tr>
<td>Control</td>
<td>6</td>
<td>74.8 ± 2.4</td>
<td>493.8 ± 15.3</td>
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72-h occluded group

<table>
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<th>Group</th>
<th>n</th>
<th>MAP, mmHg</th>
<th>HR, beats/min</th>
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<tr>
<td>Intra-arterial administration (DAMGO treatment)</td>
<td>10</td>
<td>89.7 ± 4.7</td>
<td>404.1 ± 9.0</td>
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<tr>
<td>Control</td>
<td>10</td>
<td>92.7 ± 1.7</td>
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<td>Control</td>
<td>6</td>
<td>86.7 ± 4.6</td>
<td>421.5 ± 10.5</td>
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<tr>
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<td>6</td>
<td>86.0 ± 5.0</td>
<td>410.4 ± 6.9</td>
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<td>Intra-arterial administration (saline treatment)</td>
<td>6</td>
<td>86.1 ± 2.4</td>
<td>392.2 ± 16.3</td>
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<tr>
<td>Control</td>
<td>6</td>
<td>86.2 ± 5.0</td>
<td>403.3 ± 13.6</td>
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<tr>
<td>Saline</td>
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<tr>
<td>Intra-arterial administration (DAMGO + naloxone treatment)</td>
<td>7</td>
<td>77.5 ± 4.3</td>
<td>406.8 ± 10.0</td>
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<tr>
<td>Control</td>
<td>7</td>
<td>85.6 ± 5.3</td>
<td>411.6 ± 12.9</td>
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</table>

Values are means ± SE; n, no. of rats/group. MAP, mean arterial pressure; HR, heart rate; DAMGO, [α-Ala²,N-MePhe⁴,Gly-ol⁵]enkephalin; freely perfused group, control rats whose hindlimb was freely perfused; 72-h occluded group, rats whose femoral artery had been ligated 72 h before the start of the experiment.

Fig. 2. Time courses of the average changes in MAP and triceps surae muscle tension during static contraction before and after the intra-arterial injection of DAMGO. A: although the intra-arterial injection of DAMGO did not attenuate the peak levels of the pressor response to static contraction, it attenuated the subsequent pressor response in rats whose hindlimbs were freely perfused. B: on the other hand, the intra-arterial injection of DAMGO attenuated both the peak and subsequent pressor responses to static contraction in rats whose femoral artery had been ligated for 72 h previously. The time courses of the muscle tension were the same before and after the administration of DAMGO into the hindlimb circulation. Note that the maximum values of the increase in MAP obtained by averaging the consecutive data points were smaller than the averaged peak increase of MAP shown in Fig. 1, because the time points when MAP values reached their peak during static contraction were different in each trial. Values are means ± SE. *MAP values were significantly increased from their respective baselines (P < 0.05). †Values at the same time point were significantly different from each other (P < 0.05).
RESULTS

As previously shown (33), the pressor response to static contraction in rats whose femoral artery was ligated 72 h before the start of the experiment was significantly greater than the pressor response in control rats whose hindlimbs were freely perfused \( (P < 0.05; \text{Fig. 1}) \). The intra-arterial injection of either DAMGO \( (1 \, \mu g) \) or saline had no significant effect on either baseline MAP or HR in either treatment group (Table 1). Although 5 min of occlusion of the abdominal aorta and inferior vena cava by the inflation of the vascular occluder transiently decreased MAP and increased HR, these parameters returned to their baseline levels within 15 min of the reperfusion period. In control rats \( (n = 8) \) whose hindlimb was freely perfused, the average peak pressor response to static contraction \( (22 \pm 4 \, \text{mmHg}) \) was not affected by the intra-arterial injection of DAMGO \( (23 \pm 3 \, \text{mmHg}, P = 0.979; \text{Fig. 1}) \). Likewise, the peak increase in HR during static contraction \( (14 \pm 3 \, \text{beats/min}) \) was not affected by the intra-arterial injection of DAMGO \( (14 \pm 2 \, \text{beats/min}, P = 0.929) \). In contrast, in rats \( (n = 10) \) whose femoral artery was occluded 72 h before the start of the experiment, the average peak pressor response to static contraction \( (34 \pm 3 \, \text{mmHg}) \) was attenuated by the intra-arterial injection of DAMGO \( (22 \pm 2 \, \text{mmHg}, P = 0.008) \). On the other hand, the peak increase in HR during static contraction \( (26 \pm 4 \, \text{beats/min}) \) in these rats was

![Fig. 3. Effect of the coadministration of the \( \mu \)-opioid receptor antagonist naloxone with DAMGO on the pressor reflex to static contraction in the hindlimb whose femoral artery had been ligated for 72 h. The coadministration of naloxone \( (100 \, \mu g) \) with DAMGO \( (1 \, \mu g) \) into the hindlimb circulation antagonized the inhibitory action of DAMGO on the pressor response to static contraction in the hindlimb whose left femoral artery had been occluded for 72 h previously \( (P = 0.646) \). Peak increases of HR during static contraction were not affected by the coadministration of naloxone with DAMGO \( (P = 0.716) \) in the same rats. Values are means \( \pm \text{SE}; n = 7 \). The pressor responses to contraction were significantly increased from their respective baselines \( (*P < 0.05) \).](http://ajpheart.physiology.org/)

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not affected by the intra-arterial injection of DAMGO (21 ± 2 beats/min, *P* = 0.073).

Next, we examined the effect of DAMGO on the topography of the pressor response to static contraction. We did so by plotting at 2 s, 5 s, and every 5-s interval thereafter from the onset of static contraction, the change in MAP from baseline values for 90 s. Before DAMGO was given, static contraction of the hindlimb, regardless of whether its femoral artery had been occluded or not, rapidly increased MAP, effects that reached their peak levels at ~10 s from the onset of tension development (Fig. 2). Subsequently, the increases in MAP gradually decreased from their peak levels even though the hindlimb muscles continued to contract. DAMGO had minimal statistically significant effects on the topography of the pressor response to static contraction in the rats whose hindlimbs were freely perfused (Fig. 2). Specifically, the only time point that was affected by DAMGO was at 15 s into the contraction period. At this point, the pressor response to contraction was significantly above baseline before DAMGO but was not significantly above baseline after DAMGO.

In contrast to the rats whose hindlimbs were freely perfused, DAMGO had significant effects on the topography of the pressor response to static contraction in rats whose femoral artery had been ligated 72 h before the start of the experiment (Fig. 2). Specifically, the pressor response to contraction before DAMGO was at 15 s into the contraction period. At this point, the pressor response to contraction was significantly above baseline before DAMGO but was not significantly above baseline after DAMGO.

The intra-arterial injection of naloxone with the concomitant administration of DAMGO completely blocked the attenuating effect of DAMGO on the augmented pressor response to static contraction in rats whose left femoral arteries were ligated for 72 h before the start of the experiment (*P* = 0.646; Fig. 3). Naloxone in conjunction with DAMGO also did not affect the peak HR response to static contraction in the hindlimb whose femoral artery had been occluded 72 h previously (*P* = 0.716).

An intravenous injection of DAMGO at the dose we used in this study (1 μg) did not affect either the pressor or HR responses to static contraction regardless of whether the femoral artery had been occluded for 72 h previously or not (Fig. 4). Likewise, TTIs were not affected by any drugs regardless of its route of administration or whether the femoral artery had been ligated for 72 h before the start of the experiment or not (Table 2).

### Table 2. TTIs during static contraction

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<th>TTI, kg·s⁻¹</th>
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<tr>
<td></td>
<td><em>n</em></td>
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<tr>
<td><strong>Freely perfused group</strong></td>
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<tr>
<td>Intra-arterial DAMGO</td>
<td>8</td>
</tr>
<tr>
<td>Intravenous DAMGO</td>
<td>6</td>
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<tr>
<td>Intra-arterial saline</td>
<td>6</td>
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<td><strong>72-h occluded group</strong></td>
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<td>Intravenous DAMGO</td>
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<td>Intra-arterial saline</td>
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<tr>
<td>Intra-arterial naloxone and DAMGO</td>
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Values are means ± SE; *n*, no. of rats/group. TTI, tension-time index.
We next examined the effect of DAMGO (1 μg), injected into the femoral artery, on the reflex pressor response to tendon stretch (28). The intra-arterial injection of DAMGO (1 μg) had no significant effect on either baseline MAP or HR in either treatment group (Table 3). DAMGO also had no effect on either the pressor or cardioaccelerator responses to stretch in either the freely perfused limbs or in those whose femoral arteries were ligated for 72 h before the start of the experiments (Fig. 5). TTIs during tendon stretch were not different before and after the administration of DAMGO (Table 3).

Finally, neither peak pressor nor cardioaccelerator responses to static contraction were altered by the intra-arterial injection of saline regardless of whether or not the femoral artery had been occluded for 72 h previously or not ($P > 0.05$; Fig. 6).

**DISCUSSION**

We found that DAMGO, a μ-opioid receptor agonist, injected into the arterial supply of a hindlimb whose femoral artery had been ligated for 72 h before the start of the experiment, significantly attenuated the exercise pressor reflex. In contrast, DAMGO had only a minimal effect on the reflex in rats whose hindlimbs were freely perfused. We also found that the attenuation by DAMGO of the exercise pressor reflex in the rats whose femoral arteries were ligated was prevented by naloxone, an opioid receptor antagonist. Moreover, the reflex was not attenuated when DAMGO was injected intravenously, a finding that indicates that DAMGO did not exert its attenuating effect by circulating to the spinal cord or brain stem.

These findings indicate that the stimulation of μ-opioid receptors accessible from the femoral arterial supply to the hindlimb muscles was responsible for the attenuation of the exercise pressor reflex. Thus, the simplest conclusion to draw from our findings is that DAMGO stimulated μ-opioid receptors on the endings of group III and IV muscle afferents to attenuate the exercise pressor reflex.

Little is known both about the effects of opioids on the discharge properties of group III and IV muscle afferents. Likewise, little is known about the effects of opioids in the periphery either on alleviating pain arising from skeletal muscle or on attenuating the exercise pressor reflex. In contrast, the role played by opioids on cutaneous and articular nociception has received considerable attention. Consequently, interpreting

<table>
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<tr>
<th></th>
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<th>MAP, mmHg</th>
<th>HR, beats/min</th>
<th>TTI, kg·s</th>
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<tr>
<td><strong>Freely perfused group</strong></td>
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<tr>
<td>Control</td>
<td>5</td>
<td>86.6 ± 7.1</td>
<td>427.8 ± 11.8</td>
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<tr>
<td>Intra-arterial DAMGO</td>
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<td><strong>72-h occluded group</strong></td>
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<tr>
<td>Control</td>
<td>8</td>
<td>85.1 ± 3.5</td>
<td>401.3 ± 17.5</td>
<td>31.9 ± 1.2</td>
</tr>
<tr>
<td>Intra-arterial DAMGO</td>
<td>8</td>
<td>89.4 ± 3.6</td>
<td>391.9 ± 14.4</td>
<td>33.9 ± 0.7</td>
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Values are means ± SE; $n$, no. of rats/group.

Fig. 5. Effect of the intra-arterial injection of DAMGO on reflex increases in MAP and HR during tendon stretch. A and B: peak increases of MAP and HR during tendon stretch were not affected by the intraarterial injection of DAMGO in both groups [freely perfused hindlimb (A) or 72-h ligated (B) groups]. Values are means ± SE. The pressor responses to tendon stretch in each group were significantly increased from their respective baselines ($*P < 0.05$).
our findings in muscle based on what is known about skin might be informative and might allow us to draw some useful parallels. In particular, our finding that DAMGO had only modest effects on the exercise pressor reflex in freely perfused hindlimbs seems to parallel the lack of effect of opioids on cutaneous nociception in noninflamed skin (22). In general, opioids applied to healthy tissues have been shown to have substantially less analgesic effects than when they are applied to damaged tissue (29). Taking these findings into consideration, we speculate that stimulation of peripheral opioid receptors expressed on the group III and IV muscle afferents would play a role in alleviating the augmented exercise pressor reflex only when the contracted muscles are stressed or damaged.

Although four major subtypes (δ, κ, μ, and nociceptin/orphanin FQ) of opioid receptors have identified to date, the functional differences among these receptors are still not well characterized. Inflammation in tissues such as the skin and joints is known to increase μ-opioid receptor numbers in dorsal root ganglion cells. For example, an injection of the rat hindpaw with Freund’s complete adjuvant increased the mRNA in dorsal root ganglion cells for μ-opioid receptors but had no effect on the mRNA for δ-opioid receptors (24). Moreover, axonal transport of μ-opioid receptors from the cell nucleus in the dorsal root ganglion to sensory endings in the periphery was enhanced after the hindpaw injection of Freund’s complete adjuvant. In noninjected control rats, μ-opioid receptor RNA levels have been shown to be about seven times higher than δ-opioid receptor RNA levels in lumbar dorsal root ganglion cells (3, 24), a finding that provides a strong rationale for examining, in our experiments, the effect of μ-opioid receptor agonists, such as DAMGO, on the exercise pressor reflex.

Recently, μ-opioid receptors on cutaneous sensory nerves in mice have been shown to be distributed exclusively on peptidergic (i.e., substance P containing) C-fiber afferents, whereas δ-opioid receptors have been shown to be distributed exclusively on nonpeptidergic Aδ- and C-fiber afferents (25). Moreover, the selective distribution of opioid receptors was found on both the peripheral and central terminals of these thin fiber afferents. In these mice, the stimulation of δ-opioid receptors with DAMGO reduced responsiveness to noxious heat stimulation but had no effect on responsiveness to noxious mechanical stimulation. In contrast, the stimulation of μ-opioid receptors with SCN80, a potent and highly selective μ-opioid receptor agonist, reduced responsiveness to noxious mechanical stimulation but had no effect on responsiveness to noxious heat stimulation (25). The above findings concerning cutaneous sensation might provide a useful context with which to view our results concerning static contraction, which is both a mechanical and metabolic stimulus to group III and IV muscle afferents, and stretch, which is solely a mechanical stimulus, to these thin fiber afferents (28). Extending the findings of Scherrer et al. (25) to those of our own, we offer the speculation that DAMGO attenuated the augmented exercise pressor reflex in limbs whose femoral arteries were ligated by inhibiting the responsiveness of group IV metaboreceptors (13, 14) to contraction. We further speculate that DAMGO had no effect on

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**Fig. 6.** Effect of the intra-arterial injection of saline on reflex increases in MAP and HR during static contraction. A: the intra-arterial injection of saline (200 μl) did not affect the peak increases in both MAP and HR during static contraction in control rats. B: the intra-arterial injection of saline (200 μl) also had no effect on the peak increases in MAP and HR during static contraction in rats whose left femoral artery had been occluded for 72 h previously. Values are means ± SE; n = 6. The pressor and cardioaccelerator responses to contraction in each group were significantly increased from their respective baselines (*P < 0.05).
the responsiveness of group III mechanoreceptors (13, 14) to contraction. This last conclusion, nevertheless, needs some qualification. Specifically, only about half of the group III mechanoreceptors that respond to tendon stretch also respond to static contraction (9). Consequently, tendon stretch is not an adequate tool with which to test the responsiveness of group III mechanoreceptors to static contraction. Nevertheless, the fact that DAMGO had no effect on the pressor reflex evoked by tendon stretch is consistent with the theory postulated by Scherrer et al. (25): that μ-opioid receptors are not found on mechanoreceptors.

One limitation of our findings is that they only apply to the effect of peripheral μ-opioid receptors on the exercise pressor reflex. Among others, δ- and κ-opioid receptors may also have a role to play in the periphery in attenuating the reflex. In particular, δ-opioid receptors may be important in controlling input from group III mechanoreceptors. Indeed, an injection of a specific agonist to δ-opioid receptors onto the surface of the spinal cord near the entry point of the dorsal roots has been found to attenuate the exercise pressor reflex (10). The possibility exists that this δ-opioid receptor agonist acted presynaptically to decrease neurotransmitter and/or neuromodulator release from the terminals of group III mechanoreceptors responding to static contraction. It remains to be shown that the peripheral stimulation of δ-opioid receptors on the sensory endings of thin fiber muscle afferents can also attenuate the reflex.

In any event, we have shown that the stimulation of peripheral μ-opioid receptors on thin fiber muscle afferents plays a role in attenuating the exercise pressor reflex in rats whose femoral arteries have been occluded for 72 h. We have also shown that these peripheral μ-opioid receptors play a very modest role in attenuating the reflex in freely perfused muscles. The preparation we used in our experiments is the same as the one developed by Terjung and colleagues (23, 30) and is viewed by some as an animal model of peripheral vascular disease. To the extent that this is the case, then the stimulation of μ-opioid receptors in the periphery may prove useful in the treatment of the pain and excessive cardiovascular responses induced by exercise in patients with peripheral vascular disease (1).

ACKNOWLEDGMENTS

The authors thank Jennifer Probst and Sarah Simmonds for technical assistance.

GRANTS

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DISCLOSURES

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