Published in final edited form as:

Anesth Analg. 2009 November ; 109(5): 1395–1402. doi:10.1213/ANE.0b013e3181b92201.

Acute Methadone Treatment Reduces Myocardial Infarct Size via the δ -Opioid Receptor in Rats During Reperfusion

Eric R. Gross, MD, PhD^{*}, Anna K. Hsu, BS[†], and Garrett J. Gross, PhD[†]

^{*}Department of Anesthesiology, Stanford University, Stanford, California

[†]Department of Pharmacology and Toxicology, Medical College of Wisconsin, Milwaukee, Wisconsin

Abstract

BACKGROUND—Methadone is an opioid agonist often given to manage acute and chronic pain. We sought to determine whether methadone compared with morphine dose dependently reduces myocardial infarct size (IS) and whether the mechanism is δ -opioid receptor mediated. Furthermore, we examined whether myocardial IS reduction varies with the timing of methadone administration or duration of induced ischemia.

METHODS—After surgical instrumentation, we divided male Sprague-Dawley rats into 3 sets. The first set was divided into groups, which received methadone (0.03–3 mg/kg), morphine (0.03–3 mg/kg), or water (placebo) 30 min before ischemia. Some animals of the first set also received the δ -opioid antagonist naltrindole (5 mg/kg) before methadone (0.3 mg/kg), morphine (0.3 mg/kg), or placebo administration. The second set of animals was divided into groups that received methadone (0.3 mg/kg) 5 min before reperfusion or 10 s after reperfusion. These 2 sets of animals were subjected to 30 min of myocardial ischemia by left anterior descending coronary artery occlusion and then 2 h of reperfusion. The third set of animals received placebo, methadone (0.3 mg/kg), or morphine (0.3 mg/kg) 5 min before reperfusion and were subjected to 45 min of ischemia by left anterior descending coronary artery occlusion with 2 h of reperfusion. Myocardial IS was assessed by staining myocardial tissue with triphenyltetrazolium chloride and expressed as a percentage of the area at risk (mean $\pm$ SEM).

RESULTS—Methadone or morphine administered before ischemia reduced myocardial IS. The greatest effect was achieved at a dose of 0.3 mg/kg (methadone, 46% $\pm$ 1%, $P < 0.001$ and morphine, 47% $\pm$ 1%, $P < 0.001$ versus placebo, 61% $\pm$ 1%, respectively). Naltrindole (5 mg/kg) blocked methadone-induced (0.3 mg/kg) and morphine-induced (0.3 mg/kg) cardioprotection (naltrindole + methadone, 58% $\pm$ 1%, $P < 0.001$ versus methadone; and naltrindole + morphine, 58% $\pm$ 1%, $P < 0.001$ versus morphine). Methadone (0.3 mg/kg) reduced myocardial IS when given 5 min before reperfusion (46% $\pm$ 1%, $P < 0.001$ versus placebo) but not 10 s after reperfusion (60% $\pm$ 1%, $P = 0.675$ versus placebo). No significant myocardial IS differences were seen for placebo when comparing the 45-min ischemia group (64% $\pm$ 1%) with the 30-min ischemia group (60% $\pm$ 1%, $P = 0.069$). The longer ischemia time of 45 min abrogated methadone-induced IS reduction (64% $\pm$ 2%, $P = 0.867$ versus 45-min ischemia placebo group) and morphine-induced IS reduction (65% $\pm$ 1%, $P = 0.836$ versus 45-min ischemia placebo group).

Copyright © 2009 International Anesthesia Research Society

Address correspondence and reprint requests to Garrett J. Gross, PhD, Department of Pharmacology and Toxicology, Medical College of Wisconsin, 8701 Watertown Plank Rd., Milwaukee, WI 53226. ggross@mcw.edu..

A portion of the preliminary data for this article was presented in abstract form at the International Anesthesia Research Society (IARS) annual meeting, San Francisco, CA, March 29 to April 1, 2008.

CONCLUSIONS—These findings demonstrate that methadone and morphine produce similar myocardial IS-sparing effects that are δ -opioid receptor mediated and that are dependent on the duration of myocardial ischemia.

Methadone is a μ -selective opioid receptor agonist and *N*-methyl-D-aspartate receptor antagonist frequently prescribed in doses ranging from 30 to 120 mg per day to patients with chronic pain or to subjects addicted to heroin. Methadone has an extended half-life (24–36 h) and relatively low cost compared with other opioids. In the United States, retail sales of methadone have increased 1177% from 1997 to 2006, the largest percentage change for grams of opiate medication sold.¹ The heightened popularity of prescribing methadone for chronic pain warrants further investigation regarding its potential secondary effects, particularly on the cardiovascular system. An autopsy analysis from the Chief Medical Examiner of New York City revealed that long-term opiate exposure, predominantly with methadone, reduced the extent of age-, race-, and gender-adjusted coronary artery disease compared with nonopiate exposure.²

Our prior studies suggest that when morphine, a μ_1 - and δ -receptor agonist, is given before myocardial ischemia or reperfusion, the size of the myocardial infarction is reduced, predominately via a δ_1 -opioid receptor-mediated mechanism.^{3,4} It is unknown, however, whether methadone, which has low affinity for κ - or δ -opioid receptors, possesses similar cardioprotective properties.⁵ Furthermore, there are few data determining whether morphine's and possibly methadone's cardioprotective effects are dose dependent or contingent upon the duration of myocardial ischemia or the timing of administration.

Our aim was to compare whether methadone limits myocardial infarct size (IS) to a similar extent as morphine. We determined specifically what effects the dose and timing of administration of both opioids have on myocardial IS reduction compared with placebo. Because both the δ - and κ -opioid receptors, but not the μ -opioid receptor, are present in rat cardiomyocytes, we used a rat model of myocardial infarction to determine whether methadone-induced IS reduction is mediated by the δ -opioid receptor.^{6,7}

METHODS

The experimental protocol was approved by the Animal Care and Use Committee of the Medical College of Wisconsin, and it conformed to the National Institutes of Health Guide for the Care and Use of Laboratory Animals.

Experimental Protocol

The experimental protocol is outlined in Figure 1. Eight-wk-old male Sprague-Dawley rats (Charles River Laboratories, Wilmington, MA) were anesthetized with thiobutabarbital sodium (Inactin, 100 mg/kg IP, Sigma, St. Louis, MO). A tracheotomy was performed, and the lungs were mechanically ventilated (model CV-101, Columbus Instruments, Columbus, OH) at 38–45 breaths/min using an air-oxygen mixture. The respiratory rate and tidal volume were adjusted on the basis of arterial pH, P_{CO_2} , and P_{O_2} measurements (obtained before myocardial ischemia, during ischemia, and 2 h after myocardial reperfusion). Body temperature was kept between 36.5°C and 37.5°C with a heating pad and surgical lamps.

The left jugular vein was cannulated to administer drugs and the left common carotid artery to measure arterial blood pressure and heart rate via a PE23 pressure transducer (Gould, Cleveland, OH) connected to a polygraph monitored continuously throughout the experiment. Heart rate, mean arterial blood pressure, and rate pressure product were measured at baseline, after 15 min of myocardial ischemia, and 2 h after myocardial reperfusion.

A left-sided anterior thoracotomy was performed at the fifth intercostal space, the pericardium opened, and a silk ligature placed around the proximal left anterior descending coronary artery distal to the left atrial appendage. Myocardial ischemia was induced by tightening the ligature to occlude the left anterior descending coronary artery. Coronary occlusion was confirmed by the presence of myocardial dyskinesia and epicardial cyanosis distal to the occluded coronary artery. After 30 or 45 min, the ischemic myocardium was reperfused by loosening the ligature. After 2 h of reperfusion, the left anterior descending coronary artery was again occluded and patent blue dye was injected into the jugular vein, staining blue the myocardial tissue outside the area at risk (AAR). The heart was then excised, dissected into 4–5 slices (1–2 mm in thickness), and separated into the blue-stained normal zone and the myocardium AAR for injury. The myocardial pieces were then incubated in 1% 2,3,5-triphenyltetrazolium chloride for 15 min at 37°C staining viable tissue red, whereas nonviable infarct tissue failed to stain and remained white. The heart was then placed overnight in 10% formaldehyde. The next day the infarct tissue was dissected from the AAR under a microscope. IS and the AAR were assessed gravimetrically and expressed as a percent of AAR (IS/AAR%).

Methadone and Morphine Dose-Response Curves

Morphine sulfate and methadone (Sigma Biochemicals) were dissolved in water in varying concentrations to achieve a final volume between 0.2 and 0.3 mL. All agents and placebo were administered as a bolus via the right jugular vein. Eleven groups of rats ($n = 6$ –8/group) were used, with 1 group administered placebo (water), 5 groups given methadone (doses of 0.03, 0.10, 0.30, 1, or 3 mg/kg), and 5 groups given morphine (doses of 0.03, 0.10, 0.30, 1, or 3 mg/kg) 30 min before coronary artery occlusion. Rats then underwent 30 min of myocardial ischemia and 2 h of reperfusion followed by determination of myocardial IS.

Opioid Receptor Antagonism with Naltrindole

Rats were administered the δ -opioid antagonist naltrindole (5 mg/kg) (Tocris, Ellisville, MO) 5 min before receiving methadone (0.3 mg/kg), morphine (0.3 mg/kg), or placebo given 30 min before coronary artery occlusion. Rats then underwent 30 min of myocardial ischemia and 2 h of reperfusion followed by determination of myocardial IS.

Timing of Methadone Administration

Rats were administered methadone (0.3 mg/kg) 5 min before reperfusion or 10 s after reperfusion. The rats underwent 30 min of myocardial ischemia and 2 h of reperfusion followed by determination of myocardial IS.

Length of Ischemia

A final set of rats subjected to 45 min of myocardial ischemia were administered methadone (0.3 mg/kg), morphine (0.3 mg/kg), or placebo 5 min before myocardial reperfusion. Myocardial IS was determined after 2 h of reperfusion.

Statistical Analysis

An experimental group size of 6 animals was determined necessary to achieve at least a 15% minimal difference in myocardial IS ($\alpha < 0.05$, $\beta < 20\%$). All values were noted as mean $\pm$ SEM. GraphPad Prism Software (GraphPad, La Jolla, CA), including the QuickCalcs online calculator, was used to perform statistical analysis and to calculate P values. To determine statistical significance for myocardial IS and hemodynamics, we performed a 1-way analysis of variance with Bonferroni correction comparing each group to the placebo-treated group. In addition, the rats receiving naltrindole + morphine or naltrindole + methadone were statistically compared using a 1-way analysis of variance with Bonferroni correction with groups treated

with morphine (0.3 mg/kg given 30 min before ischemia) or methadone (0.3 mg/kg given 30 min before ischemia), respectively.

RESULTS

We used 159 animals to obtain 152 successful experiments. Five rats were excluded secondary to intractable ventricular fibrillation during myocardial occlusion or reperfusion (1 placebo undergoing 30 min of ischemia, 1 morphine at the 3.0 mg/kg dose, 1 naltrindole + morphine, 1 naltrindole + methadone, and 1 placebo with 45 min of ischemia). Two additional rats were excluded secondary to the suture breaking during patent blue staining to determine the AAR (1 morphine at the 3.0 mg/kg dose and 1 morphine at the 0.1 mg/kg dose).

Hemodynamic Results

Heart rate, mean arterial blood pressure, and rate pressure product results are shown in Table 1. The methadone groups receiving 1.0 or 3.0 mg/kg doses had significant differences in heart rate and rate pressure product during myocardial ischemia and reperfusion compared with the placebo group. Mean arterial blood pressure was lower in the methadone 3.0 mg/kg group than in the placebo group during myocardial ischemia. Mean arterial blood pressure and rate pressure product at reperfusion were different in the morphine 0.3 mg/kg group compared with the placebo group. A difference in rate pressure product occurred in the morphine + naltrindole group compared with the placebo group at reperfusion.

Myocardial IS Results

Methadone and Morphine Dose Response—Myocardial IS for the methadone, morphine, and control groups treated before induced myocardial ischemia are shown in Figure 2A. Several methadone doses reduced myocardial IS compared with the placebo group. The largest reduction in IS occurred with the 0.3 mg/kg methadone dose (versus placebo, $P < 0.001$). IS reduction for the morphine doses was similar to methadone doses, with maximal reduction of IS with the 0.3 mg/kg morphine dose (versus placebo, $P < 0.001$).

δ -Opioid Receptor Inhibition via Naltrindole—Myocardial IS/AAR% for the methadone, morphine, and placebo groups with or without naltrindole administration are shown in Figure 2B. The presence of naltrindole abrogated the reduction in myocardial IS from methadone (naltrindole + methadone, $P < 0.001$ versus methadone) and morphine (naltrindole + morphine, $P < 0.001$ versus morphine). Naltrindole given alone had no effect on myocardial IS ($P = 0.1498$ versus placebo).

Timing of Methadone Treatment—Myocardial IS results for animals given methadone (0.3 mg/kg) before myocardial ischemia, before reperfusion, or after reperfusion are shown in Figure 3A. Methadone reduced myocardial IS when administered 5 min before reperfusion compared with placebo; however, methadone did not abrogate IS when given 10 s after reperfusion ($P < 0.001$ and $P = 0.675$ versus placebo, respectively).

Myocardial IS After 30 or 45 min of Induced Ischemia—Myocardial IS results after administration of methadone (0.3 mg/kg) or morphine (0.3 mg/kg) given 5 min before reperfusion after either 30 or 45 min of myocardial ischemia are shown in Figure 3B. We observed no difference in myocardial IS between rats given placebo that underwent 30 or 45 min of ischemia ($P = 0.069$). However, administration of either methadone or morphine failed to salvage the myocardium after 45 min of ischemia ($P = 0.867$ and $P = 0.836$ versus placebo with 45 min of ischemia, respectively).

DISCUSSION

Our results demonstrated that methadone, similar to morphine, reduces myocardial IS in an *in vivo* rat model in a dose-dependent manner. The δ -opioid receptor mediates myocardial protection observed with methadone when given either before or during myocardial ischemia. Neither methadone nor morphine reduced myocardial IS when the myocardial ischemic time was lengthened to 45 min.

We found that both methadone and morphine demonstrated maximal myocardial IS-sparing effects at a dose of 0.3 mg/kg. The opioid-induced myocardial salvage effect was blocked by the δ -opioid antagonist naltrindole, which has a reported affinity approximately 200 times greater for δ -opioid receptors compared with μ -or κ -opioid receptors.⁸ Our findings are consistent with previous studies evaluating morphine in intact rats and in isolated cardiomyocytes that have demonstrated cardioprotection via δ -opioid receptor activation.^{3,4,9} In addition, other studies have shown that the μ -opioid receptor agonists remifentanyl and fentanyl provide myocardial IS reduction by activation of the δ -opioid receptor.^{10,11}

We noted reduced myocardial protection for methadone and morphine at doses larger than 0.3 mg/kg. These findings are consistent with other studies using the selective δ -opioid receptor agonist fentanyl isothiocyanate and the μ -selective agonist remifentanyl, which both showed a lesser degree of myocardial salvage when doses larger than the optimal IS reduction dose were given.^{12,13} The mechanisms causing an attenuated myocardial protection for opioids at a dose larger than the optimal are not known.

In our study, methadone failed to salvage myocardium when given immediately after reperfusion. Our previous studies showed that both the κ -opioid agonist, U-54086, and morphine failed to salvage myocardium when given immediately after reperfusion.^{14,15} However, BW373U86 (a δ_1 -specific opioid agonist that has a 10-fold greater binding affinity for δ -opioid receptors than μ -opioid receptors), unlike μ -selective and κ -selective opioid agonists, can salvage the myocardium when given immediately after reperfusion.^{15,16} Hence, a more selective δ -opioid receptor agonist such as BW373U86 may provide a longer window of myocardial salvage compared with morphine and methadone (which both have approximately 1000 times lower affinity for the δ -opioid receptor compared with the μ -opioid receptor⁵).

The consequence of the duration of myocardial ischemia on pharmacological or ischemic myocardial protection is largely understudied. Our results showed that lengthening myocardial ischemia from 30 to 45 min duration inhibited the cardioprotective effects of morphine and methadone. A previous study in canines showed a preconditioning stimulus of either 1 or 4 cycles of 5 min myocardial ischemia and 5 min reperfusion failed to reduce myocardial IS when the ischemia time was lengthened from 60 to 90 min.¹⁷ Taken together, these data suggest that both opioids and ischemic preconditioning-induced myocardial protection are limited by the duration of myocardial ischemia. Additional myocardial salvage modalities, such as ischemic postconditioning or other pharmacological agents, need to be evaluated.

Our study has several potential limitations that need to be considered while interpreting the data. Naltrindole is a nonspecific δ_1 - and δ_2 -opioid receptor antagonist; therefore, the specific opioid receptor subtype that elicits myocardial IS reduction cannot be concluded from this study. Previous data from isolated cardiomyocytes and intact rat hearts suggest that the δ_1 -opioid receptor is primarily involved in myocardial IS reduction.^{4,14,15} Furthermore, the κ -opioid receptor was not investigated in this study; however, the κ -opioid receptor antagonist, norbinaltorphimine, partially abrogated remifentanyl-induced IS reduction.¹⁰ We did not investigate the role of various molecular signaling cascades activated by methadone in myocardial ischemic protection. Nonetheless, signaling pathways of myocardial IS reduction

via δ -opioid receptor activation have been studied, indicating that the mechanism involves inhibition of glycogen synthase kinase 3β and the mitochondrial permeability transition pore.^{18,19} Different animal species and humans could cause variability for the dose-response curves of morphine and methadone-induced myocardial IS reduction as observed in our study.²⁰

Presuming that daily methadone or morphine does not downregulate cardiac δ -opioid receptors, our findings indicate that myocardial protection occurs even with repeated methadone or morphine doses. A previous study in mice with implanted morphine tablets showed that myocardial ischemic protection is enhanced with continuous drug infusion, an effect that may be independent of opioid tolerance.²¹ Therefore, our data support future studies as to whether daily opioid users have improved myocardial salvage after myocardial infarction compared with nonopioid users.

Acknowledgments

The authors thank Patricia Rohrs for proofreading the manuscript.

Supported by NIH grants HL08311 and HL074314 (to GJG) and a resident research career development award by Stanford University (to ERG).

REFERENCES

1. Manchikanti L, Singh A. Therapeutic opioids: a ten-year perspective on the complexities and complications of the escalating use, abuse, and nonmedical use of opioids. *Pain Physician* 2008;11:S63–88. [PubMed: 18443641]
2. Marmor M, Penn A, Widmer K, Lenin RI, Maslansky R. Coronary artery disease and opioid use. *Am J Cardiol* 2004;93:1295–7. [PubMed: 15135709]
3. Schultz JJ, Hsu AK, Gross GJ. Ischemic preconditioning and morphine-induced cardioprotection involve the delta-opioid receptor in the intact rat heart. *J Mol Cell Cardiol* 1997;29:2187–95. [PubMed: 9281450]
4. Liang BT, Gross GJ. Direct preconditioning of cardiac myocytes via opioid receptors and KATP channels. *Circ Res* 1999;84:1396–400. [PubMed: 10381891]
5. Raynor K, Kong H, Chen Y, Yasuda K, Yu L, Bell GI, Reisine T. Pharmacological characterization of the cloned kappa-, delta-, and mu-opioid receptors. *Mol Pharmacol* 1994;45:330–4. [PubMed: 8114680]
6. Ventura C, Bastagli L, Bernardi P, Calderera CM, Guarnieri C. Opioid receptors in rat cardiac sarcolemma: effect of phenylephrine and isoproterenol. *Biochem Biophys Acta* 1989;987:69–74. [PubMed: 2557082]
7. Wittert G, Hope P, Pyle D. Tissue distribution of opioid receptor gene expression in the rat. *Biochem Biophys Res Commun* 1996;218:877–81. [PubMed: 8579608]
8. Portoghese PS, Sultana M, Takemori AE. Design of peptidomimetic delta opioid receptor antagonists using the message-address concept. *J Med Chem* 1990;33:1714–20. [PubMed: 2160538]
9. McPherson BC, Yao Z. Morphine mimics preconditioning via free radical signals and mitochondrial K(ATP) channels in myocytes. *Circulation* 2001;103:290–5. [PubMed: 11208691]
10. Zhang Y, Irwin MG, Wong TM, Chen M, Cao CM. Remifentanyl preconditioning confers cardioprotection via cardiac kappa- and delta-opioid receptors. *Anesthesiology* 2005;102:371–8. [PubMed: 15681953]
11. Kato R, Foex P. Fentanyl reduces infarction but not stunning via delta-opioid receptors and protein kinase C in rats. *Br J Anaesth* 2000;84:608–14. [PubMed: 10844838]
12. Gross ER, Peart JN, Hsu AK, Auchampach JA, Gross GJ. Extending the cardioprotective window using a novel delta-opioid agonist fentanyl isothiocyanate via the PI3-kinase pathway. *Am J Physiol Heart Circ Physiol* 2005;288:H2744–9. [PubMed: 15653765]
13. Zhang Y, Irwin MG, Wong TM. Remifentanyl preconditioning protects against ischemic injury in the intact rat heart. *Anesthesiology* 2004;101:918–23. [PubMed: 15448525]

14. Gross ER, Hsu AK, Gross GJ. Acute aspirin treatment abolishes, whereas acute ibuprofen treatment enhances morphine-induced cardioprotection: role of 12-lipoxygenase. *J Pharmacol Exp Ther* 2004;310:185–91. [PubMed: 14993258]
15. Gross ER, Gross GJ. Ligand triggers of classical preconditioning and postconditioning. *Cardiovasc Res* 2006;70:212–21. [PubMed: 16448635]
16. Knapp RJ, Santoro G, DeLeon IA, Lee KB, Edsall SA, Waite S, Malatynska E, Varga E, Calderon SN, Rice KC, Rothman RB, Porreca F, Roeske WR, Yamamura HI. Structure-activity relationships for SNC80 and related compounds at cloned human delta and mu opioid receptors. *J Pharmacol Exp Ther* 1996;277:1284–91. [PubMed: 8667189]
17. Gumina RJ, Buerger E, Eickmeier C, Moore J, Daemmgen J, Gross GJ. Inhibition of the Na(+)/H(+) exchanger confers greater cardioprotection against 90 minutes of myocardial ischemia than ischemic preconditioning in dogs. *Circulation* 1999;100:2519–26. discussion 2469–72. [PubMed: 10604890]
18. Gross ER, Hsu AK, Gross GJ. Opioid-induced cardioprotection occurs via glycogen synthase kinase beta inhibition during reperfusion in intact rat hearts. *Circ Res* 2004;94:960–6. [PubMed: 14976126]
19. Obame FN, Plin-Mercier C, Assaly R, Zini R, Dubois-Rande JL, Berdeaux A, Morin D. Cardioprotective effect of morphine and a blocker of glycogen synthase kinase 3 beta SB216763 [3-(2,4-dichlorophenyl)-4(1-methyl-1*H*-indol-3-yl)-1*H*-pyrrole-2,5-dione], via inhibition of the mitochondrial permeability transition pore. *J Pharmacol Exp Ther* 2008;326:252–8. [PubMed: 18434587]
20. Pagel PS, Krolikowski JG, Amour J, Warltier DC, Weihrauch D. Morphine reduces the threshold of helium preconditioning against myocardial infarction: the role of opioid receptors in rabbits. *J Cardiothorac Vasc Anesth*. Feb 19;2009 epub ahead of print.
21. Peart JN, Gross GJ. Morphine-tolerant mice exhibit a profound and persistent cardioprotective phenotype. *Circulation* 2004;109:1219–22. [PubMed: 14993125]

Figure 1.

Schematic representation of the experimental protocol, with *n* values for each group in parentheses. Of note, the last 3 groups underwent 45 min rather than 30 min of myocardial ischemia. 45 = 45 min of ischemia; pre-r = agent administered 5 min before reperfusion. *For the morphine dose-response curve experiments, the *n* values for each group are as follows: 0.03 mg/kg (*n* = 7), 0.1 mg/kg (*n* = 7), 0.3 mg/kg (*n* = 8), 1.0 mg/kg (*n* = 8), and 3.0 mg/kg (*n* = 6).

Figure 2.

A, Myocardial infarct size expressed as a percentage of area at risk (IS/AAR%) for varying doses (mg/kg) of methadone (darker gray bars) and morphine (lighter gray bars) versus placebo (black bar). B, IS/AAR% for methadone (0.3 mg/kg) or morphine (0.3 mg/kg) in the presence and absence of the δ -selective opioid antagonist naltrindole (5 mg/kg) versus placebo. Prior treatment with naltrindole abolished myocardial IS reduction with either methadone or morphine. * $P < 0.01$ versus placebo, + $P < 0.01$ versus methadone, x $P < 0.01$ versus morphine. The IS/AAR% as mean $\pm$ SEM is listed above each individual bar of the bar graph.

Figure 3.

A, Myocardial infarct size expressed as a percentage of area at risk (IS/AAR%) for methadone (0.3 mg/kg) administered 30 min before ischemia (pre-I), 5 min before reperfusion (pre-R), or 10 s after reperfusion (post-R) versus placebo. B, IS/AAR% for rats undergoing either 30 min (I-30, darker bars) or 45 min (I-45, lighter bars) of myocardial ischemia in the presence of either morphine (0.3 mg/kg) or methadone (0.3 mg/kg) administered 5 min before reperfusion versus placebo. * $P < 0.01$ versus I-30. The IS/AAR% as mean $\pm$ SEM is listed above each individual bar of the bar graph.

Table 1

Hemodynamics Results for Experimental Groups

	<i>n</i>	Baseline			15 min ischemia			2 h reperfusion		
		HR	MAP	RPP	HR	MAP	RPP	HR	MAP	RPP
Placebo	8	375 ± 6	131 ± 3	57 ± 2	379 ± 5	117 ± 4	50 ± 2	353 ± 6	82 ± 3	36 ± 1
Methadone (0.03)	8	373 ± 10	137 ± 4	59 ± 3	383 ± 9	113 ± 6	49 ± 3	355 ± 11	82 ± 3	37 ± 1
Methadone (0.1)	8	384 ± 8	140 ± 3	61 ± 2	379 ± 10	120 ± 5	51 ± 3	345 ± 10	77 ± 5	34 ± 2
Methadone (0.3)	8	370 ± 5	131 ± 3	55 ± 1	361 ± 14	93 ± 7	40 ± 3	329 ± 7	75 ± 4	32 ± 2
Methadone (1.0)	8	358 ± 6	122 ± 3	51 ± 1	330 ± 7*	92 ± 4	36 ± 2*	318 ± 11*	68 ± 2	29 ± 1
Methadone (3.0)	8	361 ± 10	131 ± 2	56 ± 2	340 ± 6*	88 ± 6*	36 ± 3*	315 ± 15*	80 ± 3	33 ± 2
Morphine (0.03)	7	357 ± 7	133 ± 5	56 ± 2	366 ± 5	104 ± 8	44 ± 3	346 ± 4	83 ± 2	36 ± 1
Morphine (0.1)	7	389 ± 7	117 ± 7	52 ± 3	373 ± 8	90 ± 8	39 ± 3	361 ± 7	82 ± 9	37 ± 4
Morphine (0.3)	8	366 ± 7	141 ± 6	60 ± 3	388 ± 11	129 ± 7	57 ± 3	379 ± 8	109 ± 9*	48 ± 3*
Morphine (1.0)	8	381 ± 14	131 ± 5	57 ± 3	380 ± 9	110 ± 7	47 ± 3	351 ± 12	83 ± 3	36 ± 2
Morphine (3.0)	6	365 ± 9	126 ± 6	53 ± 3	368 ± 3	105 ± 10	44 ± 4	350 ± 7	81 ± 8	35 ± 2
Naltrindole + methadone	8	378 ± 3	138 ± 6	60 ± 3	349 ± 4	101 ± 5	42 ± 2	330 ± 5	67 ± 4	30 ± 2
Naltrindole + morphine	6	368 ± 5	144 ± 5	61 ± 3	368 ± 7	111 ± 12	46 ± 5	370 ± 7	102 ± 5	44 ± 2*
Naltrindole	8	370 ± 10	129 ± 6	55 ± 4	360 ± 8	105 ± 8	44 ± 3	338 ± 6	76 ± 3	33 ± 1
Methadone (Pre-R)	8	376 ± 8	127 ± 6	56 ± 3	398 ± 6	121 ± 3	52 ± 2	349 ± 4	79 ± 3	36 ± 1
Methadone (Post-R)	8	371 ± 9	124 ± 3	53 ± 2	381 ± 10	111 ± 4	47 ± 3	336 ± 6	77 ± 5	32 ± 2
Morphine (Pre-R)	7	361 ± 11	118 ± 5	56 ± 2	361 ± 7	96 ± 4	40 ± 2	328 ± 11	77 ± 5	32 ± 2
Placebo (45)	8	358 ± 12	120 ± 6	50 ± 3	365 ± 11	102 ± 5	43 ± 3	335 ± 10	76 ± 5	32 ± 2
Methadone (Pre-R, 45)	8	376 ± 5	121 ± 6	50 ± 2	381 ± 5	104 ± 10	46 ± 4	356 ± 4	94 ± 7	40 ± 2
Morphine (Pre-R, 45)	7	386 ± 7	129 ± 5	57 ± 2	388 ± 9	109 ± 7	47 ± 3	361 ± 8	90 ± 3	38 ± 1

Numbers in parentheses correspond to doses of morphine or methadone (mg/kg).

n = number of animals per group; HR = heart rate (bpm); MAP = mean arterial blood pressure (mm Hg); RPP = rate pressure product (mm Hg/1000); pre-I = drug administered before ischemia; pre-R = agent administered before reperfusion; post-R = drug administered 10 s after reperfusion; 45 = 45 min of ischemia.

* $P < 0.01$ represents significance compared with placebo group.