

Remifentanil Preconditioning Protects against Ischemic Injury in the Intact Rat Heart

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Background: **Opioid receptors mediate cardiac ischemic preconditioning. Remifentanil is a new, potent ultra-short-acting phenylpiperidine opioid used in high doses for anesthesia. The authors hypothesize that pretreatment with this drug confers cardioprotection.**

Methods: **Male Sprague-Dawley rats were anesthetized and the chest was opened. All animals were subjected to 30 min of occlusion of the left coronary artery and 2 h of reperfusion. Before the 30-min occlusion, rats received either preconditioning by ischemia (ischemic preconditioning, 5-min occlusion, 5-min reperfusion × 3) or pretreatment with remifentanil, performed with the same regime (3 × 5-min infusions) using 0.2, 0.6, 2, 6, or 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ intravenously. The experiment was repeated with naltrindole (a selective δ-opioid receptor antagonist, 5 mg/kg), nor-binaltorphimine (a selective κ-OR antagonist, 5 mg/kg), or CTOP (a selective μ-opioid receptor antagonist, 1 mg/kg) administered before remifentanil-induced preconditioning or ischemic preconditioning, respectively. Infarct size, as a percentage of the area at risk, was determined by 2,3,5-triphenyltetrazolium staining.**

Results: **There was a dose-related reduction in infarct size/area at risk after treatment with remifentanil that was similar to that seen with ischemic preconditioning. This effect was prevented or significantly attenuated by coadministration of a μ, κ, or δ-opioid antagonist. The infarct-sparing effect of ischemic preconditioning was abolished by blockade of κ-opioid receptors or δ-opioid receptors but not by μ-opioid receptors.**

Conclusion: **Remifentanil mimics cardioprotection *via* all three opioid receptors. This differs from ischemic preconditioning, which confers cardioprotection *via* κ- and δ-, but not μ-opioid receptors. Part of the protective effect of remifentanil may be produced by μ-agonist activity outside the heart.**

OPIOID receptors (OR) are involved in cardiovascular regulation,[1–3] and several studies have found that activation of certain ORs can induce a cardioprotective effect similar to classic and delayed ischemic preconditioning (IPC).[4–6] It is believed that opioid-peptides exert this effect by interaction with Gi-protein coupled receptors.[7–9] There is evidence that both δ- (especially δ_1)[10,11] and κ[12,13]-ORs are involved in opioid-induced cardioprotection. Several studies have found that intravenous administration of morphine can mimic the effect of IPC to reduce infarct size (IS) in anesthetized open-chest rats.[9,10,14] Combined administration of isoflurane and morphine produces a synergistic reduction in myocardial IS in rats.[15] Fentanyl has been shown to alleviate postischemic ventricular dysfunction in rats with this cardioprotective effect apparently mediated by δ-ORs.[16,17]

Remifentanil is a new ultra-short-acting phenylpiperidine opioid analgesic agent that is rapidly metabolized by nonspecific blood and tissue esterases.[18] It has an analgesic potency similar to that of fentanyl and 100 times greater than morphine,[19] the opioids that have been most extensively studied in cardioprotection. Ligand-binding data show that remifentanil has a high degree of μ-OR selectivity (EC_{50} = 2.6 nM) with a lower affinity for δ (EC_{50} = 66 nM) and κ (EC_{50} = 6.1 μM) ORs,[20] and its effect on postischemic myocardium is still unknown.

The heart has δ-ORs and κ-ORs.[3,21,22] It has been shown that the cardioprotection of morphine preconditioning is mediated *via* the δ-OR,[11] and there is also evidence that it is mediated *via* both δ-ORs and κ-ORs.[13,23]

This study aimed to determine whether remifentanil, like morphine and fentanyl, confers cardioprotection against ischemia-induced injury and, if so, which ORs mediate this effect. We also compared the effects of remifentanil with those of ischemic preconditioning.

Materials and Methods

This study was conducted in accordance with our institutional guidelines on the use of live animals for research and the experimental protocol was approved by the Animal Care and Use Committee of the University of Hong Kong.

Surgical Preparation

Male Sprague-Dawley rats weighing 300–350 g were used. The rats were anesthetized by intraperitoneal administration of pentobarbitone (50 mg/kg body weight) and maintained by repeat doses of 25 mg/kg every 60–90 min. All of the animals underwent tracheotomy and tracheal intubation. Mechanical ventilation was provided with a Harvard Apparatus Rodent Respirator (Harvard Apparatus, Boston, MA), and the rats were ventilated with room air at 60–70 breaths/min. Body temperature was monitored and maintained at 37 ± 1°C (mean ± SD) using a heating pad. The carotid artery was

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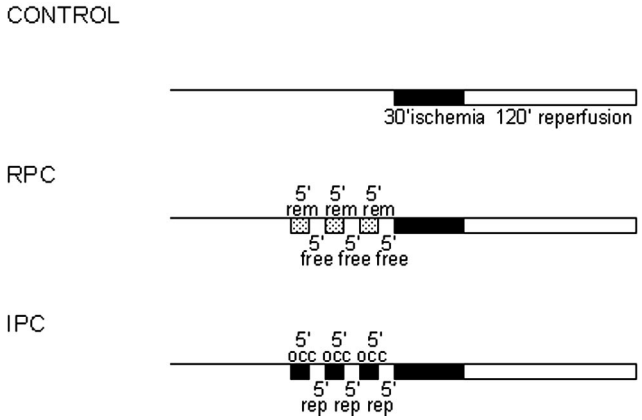

Fig. 1. All group hearts were subject to 30 min of occlusion and 120 min of reperfusion. Before ischemia, ischemic preconditioning (IPC) hearts were subject to three 5-min cycles of occlusion interspersed with 5 min of reperfusion, whereas remifentanil preconditioning (RPC) hearts were subject to three 5-min cycles of infusion of remifentanil (0.2, 0.6, 2, 6, or 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) interspersed with 5-min drug-free periods. *Occ* = occlusion of the left coronary artery; *rep* = reperfusion; *rem* = infusion of remifentanil, and *free* = drug-free periods.

cannulated to measure mean blood pressure *via* a pressure transducer, and a Lead-II electrocardiogram monitored heart rate *via* subcutaneous stainless steel electrodes. These were connected to a PowerLab monitoring system (ML750 PowerLab/4sp with MLT0380 Reusable BP Transducer; AD Instruments, Colorado Springs, CO). The right jugular vein was cannulated to infuse saline or drugs. A left thoracotomy was performed to expose the heart at the fifth intercostal space. After removing the pericardium, a 6–0 Prolene loop, along with a snare occluder, was placed at the origin of the left coronary artery. Regional ischemia was achieved by pulling the snare and securing the threads with a mosquito hemostat. Ischemia was confirmed by a substantial decrease in left ventricular pressure, electrocardiographic changes, and cardiac cyanosis. After surgical preparation, the rat was allowed to stabilize for 15 min.

Study Groups and Experimental Protocol

The current study consisted of two series of experiments. To determine whether the administration of remifentanil (GlaxoSmithKline Limited, Hong Kong) limits its myocardial infarct size, rats were randomly assigned to receive one of seven treatments (fig. 1): control (CON, saline vehicle), ischemic preconditioning (IPC) and remifentanil preconditioning (RPC) using five doses: 0.2, 0.6, 2, 6, and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$. All animals received 30 min of occlusion of the left coronary artery followed by 2 h of reperfusion. Before the 30-min occlusion, rats were subjected to either preconditioning by ischemia (IPC, 5-min occlusion, 5-min reperfusion × 3) or pretreatment with remifentanil with the same regimen (3 × 5-min infusions). These experiments will be referred to as Series 1.

Subsequently, to test which opioid receptor was involved in mediating the effects of remifentanil and ischemic preconditioning, rats were randomly assigned to one of 12 groups (fig. 2) as follows:

1. Control (CON, saline vehicle).
2. Naltrindole[10] (NTD, a selective δ-OR antagonist) 5 mg/kg intravenously 10 min before ischemia.
3. Nor-binaltorphimine[11] (nor-BNI, a κ-OR selective antagonist) 5 mg/kg intravenously 15 min before ischemia.
4. CTOP[24,25] (D-Phe-Cys-Tyr-D-Trp-Orn-Thr-Pen-Thr-NH_2, a μ-OR selective antagonist) 1 mg/kg intravenously 10 min before ischemia.
5. RPC.
6. IPC.
7. NTD+RPC.
8. NTD+IPC (5 mg/kg intravenously 10 min before RPC or IPC).
9. Nor-BNI+RPC.
10. Nor-BNI+IPC (5 mg/kg, intravenously 15 min before RPC or IPC).
11. CTOP+RPC.
12. CTOP+IPC (CTOP 1 mg/kg intravenously before RPC or IPC).

The chemicals were purchased from Sigma Chemical Company (St. Louis, MO). These experiments will be referred to as Series 2.

Determination of Infarct Size

On completion of the reperfusion period, the heart was excised, transferred to a Langendorff apparatus, and perfused with normal saline for 1 min at a pressure of 100 cm H_2O to flush out blood. The snare was securely

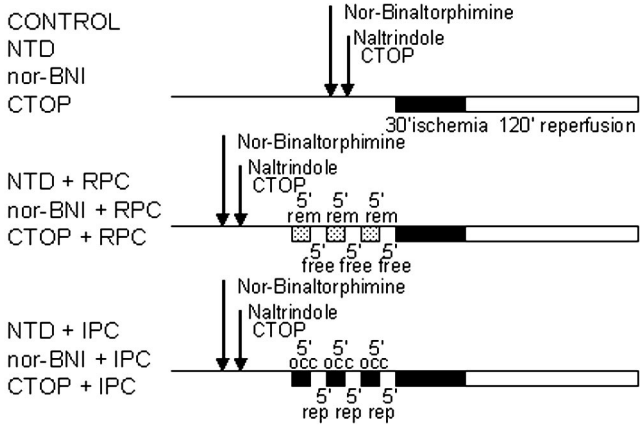

Fig. 2. Experimental protocol used to determine which opioid receptor mediates the cardioprotective effect of ischemic preconditioning (IPC) and remifentanil preconditioning (RPC, 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Naltrindole (NTD, a selective δ-OR antagonist, 5 mg/kg) and CTOP (a selective μ-OR antagonist, 1 mg/kg) intravenously 10 min before ischemia, IPC, or RPC. Nor-binaltorphimine (nor-BNI, a selective κ-OR antagonist, 5 mg/kg) intravenously 15 min before ischemia, IPC, or RPC. *Occ* = occlusion of the left coronary artery; *rep* = reperfusion; *rem* = infusion of remifentanil, and *free* = drug-free periods.

Table 1. Hemodynamic Parameters in Series 1

		Baseline			Treatment			30-min occlusion			2-h reperfusion		
	No.	HR	MBP	RPP	HR	MBP	RPP	HR	MBP	RPP	HR	MBP	RPP
Control	9	435 ± 54	82 ± 16	47 ± 10				446 ± 52	79 ± 13	45 ± 8	474 ± 52	63 ± 15	45 ± 13
IPC	9	428 ± 70	82 ± 14	44 ± 9	423 ± 40	88 ± 10	46 ± 10	435 ± 24	83 ± 8	43 ± 8	463 ± 29	81 ± 15	46 ± 10
RPC (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	5	383 ± 62	77 ± 10	38 ± 17	398 ± 38	73 ± 6	42 ± 5	423 ± 32	72 ± 7	41 ± 2	418 ± 52	74 ± 9	38 ± 8
RPC (0.6 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	6	436 ± 69	77 ± 15	46 ± 11	383 ± 117	67 ± 14‡	34 ± 12†	449 ± 59	65 ± 10*	45 ± 9	467 ± 96	58 ± 15	36 ± 13
RPC (2 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	8	460 ± 60	73 ± 7	45 ± 8	450 ± 59	63 ± 11‡	38 ± 9‡	486 ± 54	64 ± 13*	42 ± 11	514 ± 42	57 ± 18	39 ± 5
RPC (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	7	414 ± 28	70 ± 10	40 ± 4	324 ± 113†	64 ± 12†	28 ± 11‡	425 ± 28	69 ± 13	38 ± 6	423 ± 25	68 ± 16	37 ± 6
RPC (20 $\mu g \cdot kg^{-1} \cdot min^{-1}$)	6	439 ± 33	80 ± 10	47 ± 6	362 ± 29‡	64 ± 8‡	32 ± 3‡	430 ± 20	64 ± 10	41 ± 7	418 ± 34	64 ± 15	35 ± 9

Baseline = 15 min after surgery; Treatment = after remifentanil preconditioning (RPC) or ischemic preconditioning (IPC); 30-min occlusion = 30 min after regional ischemia; 2-h reperfusion = 2 hours after reperfusion; HR = heart rate (beats/min); MBP = mean arterial blood pressure (mm Hg); RPP = rate-pressure product (mm Hg/min per 1000).

RPC hearts were subject to three cycles of 5 min infusion periods of remifentanil (0.2, 0.6, 2, 6 or 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$) interspersed with drug-free periods.

* $P < 0.05$ versus control group; † $P < 0.05$; ‡ $P < 0.01$ versus baseline.

retightened and 0.25% Evan blue dye was injected to stain the normally perfused region of the heart. This procedure allowed visualization of the normal, nonischemic region and the area at risk (AAR). The heart was then weighed, frozen, and cut into 2-mm slices. Thereafter, the slices were stained by incubation at 37°C for 20 min in 1% 2,3,5-triphenyltetrazolium (Sigma Chemical Co.)[11,13,14] in phosphate buffer (pH 7.4), and then were immersed in 10% formalin to enhance the contrast of the stain. The areas of infarct (2,3,5-triphenyltetrazolium negative) and risk zone (2,3,5-triphenyltetrazolium stained) for each slice were traced and digitized using a computerized planimetry technique (SigmaScan 4.0, Systat Software Inc., Richmond, CA). The volumes of the left ventricles, IS, and AAR were calculated by multiplying each area with slice thickness and summing the product. The IS was expressed as a percentage of the AAR (IS/AAR).

Statistical Analysis

Data analysis was performed with a personal computer statistical software package (Prism v4.0; GraphPad Software, San Diego, CA). Data were expressed as mean ±SD. Hemodynamics were analyzed using two-way analysis of variance with Bonferroni *post hoc* test for multiple comparisons if significant *F* ratios were obtained. IS (expressed as percentage of the area at risk) were analyzed between groups using analysis of variance with a Student-Newman-Keuls *post hoc* test for multiple comparisons. Sigmoid dose-response nonlinear regression was used for remifentanil-treated rats. Statistical differences were considered significant if the *P* value was <0.05.

Results

A total of 107 animals were used in the study. Animals were omitted from further data analysis if severe hypotension (arterial mean blood pressure less than 30 mmHg) or intractable ventricular fibrillation occurred. Consequently, five were excluded because of intractable ventricular fibrillation: one each in the control, RPC (0.2 $\mu g \cdot kg^{-1} \cdot min^{-1}$), NTD, NTD+IPC, and NTD+RPC groups. One animal in the CTOP+RPC group and one in the nor-BNI+IPC group were excluded because of severe hypotension. One animal in the IPC group was excluded because of an excessively large AAR volume (>0.550 mm^3). A total of 99 animals completed the study.

Effects of Remifentanil or Ischemic Preconditioning on Myocardial Infarct after Ischemia and Reperfusion

As shown in table 1, remifentanil at 6 and 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ significantly reduced the heart rate. At 0.6–20 $\mu g \cdot kg^{-1} \cdot min^{-1}$ it also significantly reduced the mean blood pressure and rate pressure product. There was no difference in any of the hemodynamic parameters between control and treatment groups during ischemia and reperfusion with two exceptions: a slight, but significant drop in mean blood pressure in the groups preconditioned with 0.6 and 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ RPC.

The AAR ranged from 0.384 ± 0.084 cm^3 to 0.434 ± 0.117 cm^3. There was no difference between the control and treatment groups. As shown in figure 3 the IS, expressed as a percentage of the AAR, of the control group was 52.7 ± 5.5% (n = 9). In groups subjected to IPC and RPC the infarct sizes were significantly reduced. The reduction in IS in groups subjected to remifentanil PC in the range of 0.6–6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ were dose related, with a peak reduction at 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$. The ED_{50} was 2.69 $\mu g \cdot kg^{-1} \cdot min^{-1}$ according to the sigmoid equation $Y = 15.18 + 17.76/[1 + 10^{(-2.57-x)}]$, $r = -0.898$.

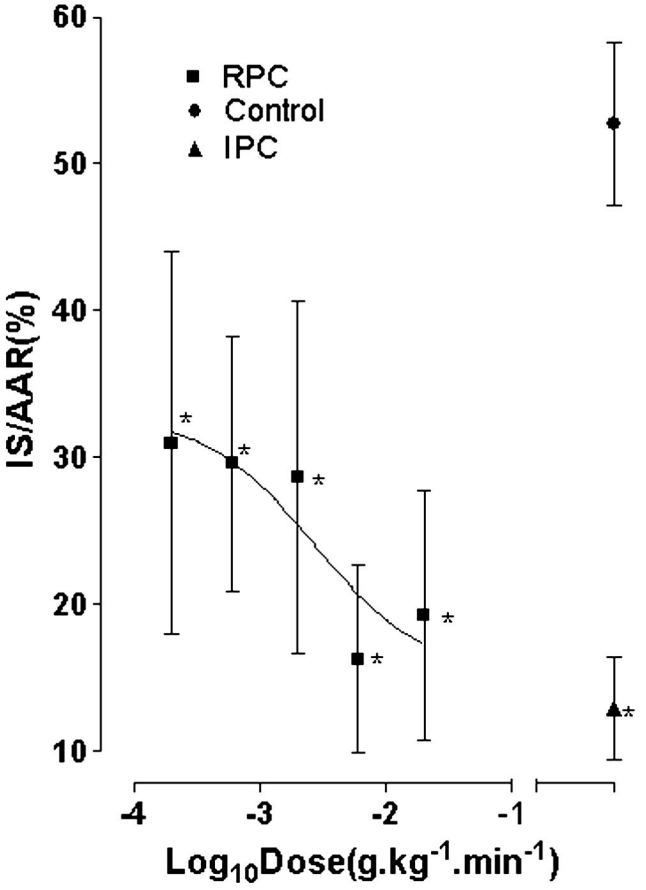

Fig. 3. Curve illustrating the relationship between IS/AAR and the dose of remifentanil. Infarct size (IS) expressed as a percentage of the area-at-risk (AAR). ED_{50} is 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$; sigmoid equation $Y = 15.18 + 17.76/[1 + 10^{(-2.57-x)}]$, $r = -0.898$. *IPC* = ischemic preconditioning; *RPC* = remifentanil preconditioning. Values are means ± SD. **P* < 0.01 *versus* control.

Effects of Remifentanil or Ischemic PC on Myocardial Infarct after Ischemia and Reperfusion with Blockade of Opioid Receptors

There were no differences in hemodynamic parameters between control and treatment groups (data not shown). Nor was there any difference in AAR, which ranged from 0.329 ± 0.015 to 0.499 ± 0.092 cm^3. IPC and RPC (6 $\mu g \cdot kg^{-1} \cdot min^{-1}$) markedly reduced IS/AAR from 52.7 ± 5.5% (n = 9) to 12.9 ± 3.4% (n = 9, $P <$ 0.01 *versus* control) and 16.2 ± 6.4% (n = 7, $P < 0.01$ *versus* control), respectively. 1 mg/kg CTOP, a selective μ-OR antagonist, or 5 mg/kg NTD, a selective δ-OR antagonist, administered 10 min before RPC completely abolished the cardioprotective effect of RPC (IS/AAR: CTOP+RPC 58.5 ± 4.6%, n = 5; NTD+RPC 47.4 ± 8.5%, n = 5, $P > 0.05$ *versus* control). 5 mg/kg nor-BNI, a selective κ-OR antagonist, administered 15 min before RPC attenuated the cardioprotective effect of RPC (IS/AAR: 33.1 ± 7.7%, n = 6, $P < 0.01$ *versus* control and RPC) (fig. 4). In the IPC group, blockade of the δ-OR abolished, whereas blockade of the κ-OR attenuated, the protection (IS/AAR: NTD+IPC 47.6 ± 8.3%, n = 5, $P >$ 0.05 *versus* control; nor-BNI+IPC 31.9 ± 5.7%, n = 6, $P < 0.01$ *versus* control and IPC) (fig. 5). Blockade of the μ-OR did not alter the cardioprotective effect of IPC (IS/AAR: 18.4 ± 3.2%, n = 5, $P < 0.01$ *versus* control and $P > 0.05$ *versus* IPC, respectively). The three antagonists did not change IS/AAR when either agent was administered to non-PC hearts (IS/AAR: NTD 51.6 ± 4.7%, n = 5, nor-BNI 50.3 ± 8.3%, n = 6, and CTOP 47.2 ± 5.3%, n = 6, $P >$ 0.05 *versus* control, respectively) (fig. 5).

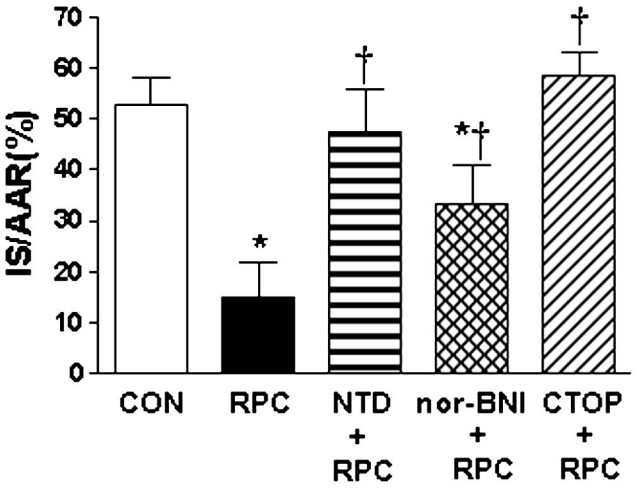

Fig. 4. The effect of opioid antagonists on remifentanil preconditioning. Infarct size (IS) expressed as a percentage of the area-at-risk (AAR). Infarct sizes in rat hearts subjected to control, remifentanil preconditioning (RPC, remifentanil 6 $\mu g \cdot kg^{-1} \cdot min^{-1} \times 3$), naltrindole (5 mg/kg, intravenous; NTD + RPC) given 10 min before the RPC, nor-binaltorphimine (5 mg/kg, intravenous; nor-BNI + RPC) given 15 min before the RPC, or CTOP (1 mg/kg, intravenous; CTOP + RPC) given 10 min before the RPC. Values are means ± SD. **P* < 0.01 *versus* control; †*P* < 0.01 *versus* RPC.

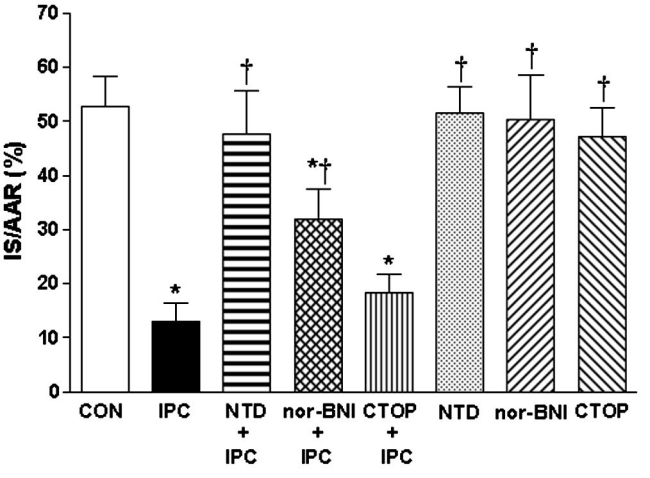

Fig. 5. The effect of opioid antagonists on ischemic preconditioning. Infarct size (IS) expressed as a percentage of the area-at-risk (AAR). Infarct sizes in rat hearts subjected to control, NTD or NTD+IPC (naltrindole 5 mg/kg, intravenous; 10 min before ischemia or IPC), CTOP or CTOP+IPC (CTOP 1 mg/kg, intravenous; 10 min before ischemia or IPC), nor-BNI or nor-BNI+IPC (nor-binaltorphimine, 5 mg/kg, intravenous; 15 min before ischemia), ischemic preconditioning (IPC). Values are means ± SD. **P* < 0.01 *versus* control; †*P* < 0.01 *versus* IPC.

Discussion

Remifentanil reduced IS dose-dependently in open chest anesthetized rats; this is the first time that a preconditioning effect has been demonstrated with remifentanil. More interestingly, the protective effect of RPC was abolished by all three OR antagonists CTOP, NTD, and nor-BNI, indicating that the effect of remifentanil is mediated *via* μ-, δ-, and κ-ORs.

A previous study has shown that a brief infusion of morphine can produce a preconditioning effect.[10,14] Because the half-life of morphine is long, its effect may last beyond the preconditioning period. Therefore it is not clear whether the protective effect of morphine was a direct effect of morphine itself or the effect of preconditioning triggered by morphine. In the current study, we used an ultra-short acting μ-opioid agonist, remifentanil, and found that it also confers cardioprotection. However, in view of the extremely short half-life, it is likely that this drug mimics ischemic preconditioning.

Both δ-ORs and κ-ORs are present in the heart.[21,22] This study, in accordance with previous studies, has shown that these two receptors in the heart mediate the cardioprotection of IPC.[12,13,23,26] There is no evidence of μ-ORs in the rat heart from binding studies[21,22,27] or physiologic studies,[28,29] and in the current study we also found that blockade of the μ-opioid receptor with its antagonist, CTOP, did not alter the cardioprotective effect of ischemic preconditioning, suggesting that an intracardiac μ-opioid receptor is not involved in the cardioprotection of ischemic preconditioning. We found that blockade of any of the three opioid receptors by systemic administration of selective opioid receptor antagonists abolished or attenuated the protective effect of remifentanil in the anesthetized rat. Therefore, the action of remifentanil may be mediated, at least partly, *via* the cardiac δ-ORs and κ-ORs but not by a cardiac μ-OR. It is possible that a μ-OR that is located outside the myocardium may also mediate the effect of remifentanil. One possibility is the central nervous system. During myocardial ischemia, there is an accumulation of norepinephrine in the myocardium as a result of an increased nonexocytotic release from sympathetic nerve terminals, which induces injury.[30–33] There is evidence that activation of the μ-OR by morphine administered intrathecally reduces IS in a rat model of myocardial ischemia reperfusion injury[34] and also depresses the somatocardiac reflex.[35] It is possible that activation of the μ-OR in the central nervous system may inhibit the sympathetic influence on the heart, thus reducing the release of norepinephrine and injury during ischemia. This is supported by the clinical observation of decreased heart rates in patients receiving remifentanil-based anesthesia[36] and could be an interesting area for further study.

Brief renal, mesenteric, or skeletal muscle ischemia of remote origin can effectively precondition the heart ("remote preconditioning").[37] This concept is consistent with the fact that regional cardiac ischemia can initiate global protection and render remote myocardium resistant to infarction ("preconditioning at a distance").[38] Therefore, another possibility is that remifentanil may have some effect on other organs that indirectly renders remote myocardium resistant to infarction.

A previous study showed that morphine, a predominantly μ-OR agonist, acts on the heart *via* κ-ORs and δ-ORs.[23] It is, therefore, not surprising that remifentanil, also a μ-OR agonist, acts *via* κ-ORs and δ-ORs.

It is interesting that blockade of one of the three receptors abolished or markedly attenuated the effect of preconditioning. This is most likely attributable to the fact that activation of any one of the receptors leading to cardioprotection involves the same final common pathway, which may be cytosolic Ca^{2+} overload, believed to be a precipitating factor of injury. If activation of one of the receptors leads to a significant reduction of Ca^{2+} overload induced by ischemia, cardioprotection is achieved. Activation of another receptor in or outside the heart will not necessarily confer additional protection.

We also observed that remifentanil decreased heart rate, mean blood pressure, and rate pressure product in agreement with previous observations.[36,39,40] However, other than a slight but significant reduction in mean blood pressure during ischemia in the groups preconditioned with 0.6 and 2.0 $\mu g \cdot kg^{-1} \cdot min^{-1}$, there were no differences in any of the hemodynamic parameters between the control and treatment groups during ischemia and reperfusion. This observation suggests that it is unlikely that the effect of preconditioning on myocardial infarct is related to alterations in hemodynamic parameters.

We found the effect of remifentanil on reducing infarct size was dose dependent. Given in clinically relevant larger doses to rats (from 0.2 to 20 $\mu g \cdot kg^{-1} \cdot min^{-1}$), remifentanil produces its maximum effect at a dose of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ with an ED_{50} of 2.7 $\mu g \cdot kg^{-1} \cdot min^{-1}$, although it is difficult to extrapolate such doses from a small animal model to the human. Remifentanil is now being increasingly used in anesthesia because its unique pharmacokinetic profile allows it to be given in very high doses during surgery without fear of postoperative respiratory depression.[18]

In summary, this study has provided evidence for the first time that RPC confers protection against injury induced by ischemia in the intact rat heart. All three subtypes of ORs, namely μ-ORs, δ-ORs, and κ-ORs, mediate the action of remifentanil, although the μ-OR effect is likely to be initiated extracardiac.

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