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ORIGINAL ARTICLE

High-dose remifentanil increases blood pressure and heart rate mediated by sympatho-activation in conscious rats

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Abstract
Purpose The ultra-short-acting μ-opioid receptor agonist, remifentanil, is commonly used in clinical anesthesia; however, there are limited data about the hemodynamic effects of remifentanil itself without anesthetics. We investigated the effects of an ultra-short-acting μ-opioid receptor agonist, remifentanil, on cardiovascular and sympathetic function in conscious rats.
Methods The mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA) were recorded during continuous intravenous (i.v.) infusion of remifentanil at a moderate-dose (0.25 and 0.5 μg/kg/min) and a high-dose (1.0 and 2.0 μg/kg/min) in conscious intact and sino-aortic denervated (SAD) rats. Baroreflex sensitivity was examined during remifentanil administration. Rats were administered saline or naloxone to assess the involvement of the μ-opioid receptor in the remifentanil-induced responses.
Results High-dose remifentanil induced biphasic changes in MAP and HR. Mediated by sympatho-activation, these parameters increased after briefly decreasing once. Subpressor-dose remifentanil enhanced baroreflex sensitivity. Changes in MAP, HR, and RSNA induced by remifentanil were inhibited by naloxone.
Conclusions High-dose remifentanil decreases MAP and HR transiently and increases these parameters mediated by the activation of sympathetic nerve activity in conscious rats.

Keywords Remifentanil · Opioid · Sympathetic nerve activity · Sinoaortic-denervated rats

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Introduction

Remifentanil is a relatively new, potent, and titratable ultra-short-acting μ-opioid agonist [1]. Opioids and opiate receptors are located in specific brain nuclei known to regulate cardiovascular activity and to be involved in modulating sympathetic nervous system activity [2, 3] and baroreceptor reflex sensitivity [4]. Several studies have demonstrated that a combination of remifentanil and intravenous anesthetics has a dose-dependent cardiovascular depression with both bolus and continuous infusion [5–7]. Anesthesia is well known to profoundly affect the cardiovascular and autonomic nervous systems [8]. However, very few reports are available on the effects of remifentanil alone on the cardiovascular and sympathetic nerve activity (SNA) [9]. In this study, therefore, we investigated the effects of remifentanil on blood pressure (BP), heart rate (HR) and renal sympathetic nerve activity (RSNA) in conscious intact and sino-aortic denervated (SAD) rats.

Materials and methods

The experimental procedures (Ethical Committee No. 2008-528-2) were approved by the Ethics Committee on Animal Care of the Faculty of Medicine at the University of Miyazaki.

Male Wistar rats weighing 350–450 g each were given pentobarbital anesthesia (50 mg/kg i.p.). SP-31 tubing heat-coupled to an SP-50 and a PE-50 catheter was inserted into the abdominal aorta and the inferior vena cava from the left femoral artery and vein for measurement of BP and HR and for intravenous administration of drugs, respectively. In some rats, the right femoral vein was also cannulated using a PE-50 catheter for the intravenous infusion of saline (Peptide Institute, Osaka, Japan) or naloxone (Sigma Chemical, St. Louis, MO, USA). The arterial catheter, filled with heparinized (10 U/ml) saline solution, was connected to a Statham pressure transducer (Gould, Saddle Brook, NJ) and PowerLab (ADInstruments Pty Ltd, Australia) to monitor BP, and the venous catheter was sealed. For the measurement of RSNA, a left renal nerve bundle was dissected carefully via a retroperitoneal approach and freed from the surrounding tissue under stereoscopic microscopy. The nerve was placed on a bipolar electrode made of teflon-coated wire (Cooner Wire; Chatsworth, CA) and covered with silicone rubber (Semicosil 902A and B cement; Wacker Chemicals East Asia, Tokyo, Japan). Arterial and venous catheters and electrode leads for recording RSNA were tunneled under the skin to exteriorize at the nape of the neck. Spike potentials, which were amplified (Biophysioamplifier AVB-9; Nihon Kohden, Tokyo, Japan) and filtered (50–1,000 Hz), were monitored on a storage oscilloscope (Model VC-9A; Nihon Kohden) and continuously recorded on a DVD recorder (Sony, Tokyo, Japan). Through the window discriminator, impulses were then fed into a pulse counter (MET-1100; Nihon Kohden), and the output was digitized, printed as a histogram, and recorded simultaneously with BP and HR on a thermal rectigraph (San-Ei). The DVDs were later played back, and the RSNA waveforms were integrated after full-wave rectification using an amplitude analyzer (Series 5500; Concurrent, Fort Lauderdale, FL) with the sample-hold function reset to baseline by an internal timer set at 5 s. Absolute values for integrated RSNA were corrected before data analysis by subtracting the residual electrical output (background-noise level) recorded from the integrator after an intravenous injection of hexamethonium (20 mg/kg, i.v.). All burst-like activity in RSNA disappeared completely after the injection of hexamethonium, indicating that the recorded neural activity was the result of efferent but not afferent renal nerve fibers.

The SAD was performed according to the method of Krieger [10], as previously described [11]. The effectiveness of SAD was confirmed by the lack of bradycardia and sympathoinhibitory responses to phenylephrine (20 μg/kg, i.v.). The baroreflex control of RSNA was evaluated before (control) and 20 min after remifentanil (2.0 μg/kg/min) or remifentanil (2.0 μg/kg/min) plus naloxone (50 μg) infusion. Sodium nitroprusside (SNP) (15 μg/kg; 1 mg/ml, in 5 % dextrose in water) was used as a control baroreflex sensitivity test. Baroreflex sensitivity in response to SNP was assessed by calculating the ratio of maximum increase in RSNA (Δ RSNA) to the maximum reduction of MAP (Δ MAP) (Δ RSNA/Δ MAP).

For measuring arterial O_2 partial pressures (PaO_2), arterial CO_2 partial pressures ($PaCO_2$), and pH, arterial blood samples (0.2 ml) were withdrawn from the catheter that had been implanted into the abdominal aorta before and 20 min after the start of remifentanil i.v. infusion and analyzed with a gas analyzer (ABL-800, Radiometer, Copenhagen, Denmark).

Experimental protocol

We used thirty rats in this study. All experiments were performed in conscious, freely moving rats 1–5 days after surgery. After BP, HR, and RSNA stabilized, remifentanil (Jannsen Pharmaceutical K.K., Tokyo, Japan) was continuously administered intravenously into intact ($n = 8$) and SAD ($n = 8$) conscious rats through an infusion cannula connected to a 3 ml syringe by an automatic injector (LMS, Tokyo, Japan) for 20 min at a rate of 0.25, 0.5, 1.0, and 2.0 μg/kg/min. We diluted remifentanil with physiological saline so that it would be the same volume for each dose as much as possible. The concentrations of 0.25, 0.5, 1.0, and 2.0 μg/kg/min doses were diluted to be 5.0, 10.0, 20.0, and 40.0 μg/ml, respectively. We defined 0.25 and 0.5 μg/kg/min infusion rate as a moderate-dose, and 1.0 and 2.0 μg/kg/min infusion rate as a high-dose. Under similar experimental conditions in other intact rats ($n = 8$), the effect of treatment with naloxone hydrochloride or saline on remifentanil (2.0 μg/kg/min)-induced changes in MAP, HR, and RSNA was investigated. Naloxone (25 or 50 μg) dissolved in 0.4 ml of saline or vehicle (0.4 ml of saline only) was infused intravenously through the femoral vein catheter on the other side for 20 min at the same time as remifentanil administration. Vehicle (physiological saline), naloxone, or various doses of remifentanil were administered to each rat at random. We used other intact rats ($n = 6$) for measuring blood gases. Experiments were performed once daily on each rat. In antagonist-treatment studies, either vehicle or naloxone (25 or 50 μg) was administered once randomly to each rat. Chow and water were not available during the recording time.

Statistical analysis

All data are expressed as the mean ± SD, and statistical analyzes were performed using analysis of variance (ANOVA) for repeated measures followed by the Fisher's

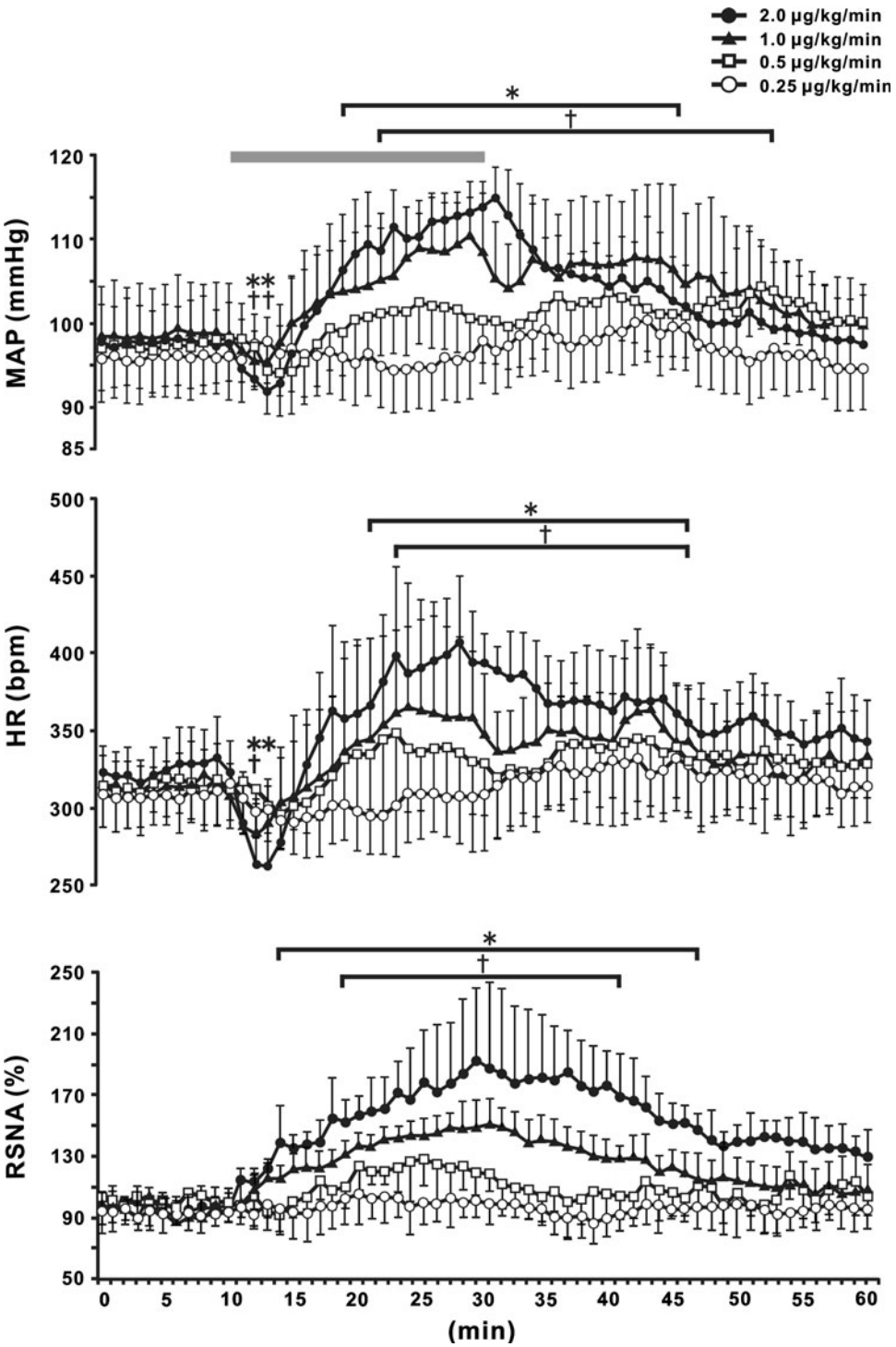

Fig. 1 Time course of changes in mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA) during the 60 min following intravenous administration of remifentanil (0.25, 0.5, 1.0, and 2.0 μg/kg/min) in conscious rats. *Bars* over data indicate times of intravenous administration of remifentanil for 20 min. *bpm* beats per min. All data are the mean ± SD; $n = 8$ in each dose. $^{*}P < 0.05$ versus baseline value at a rate of 2.0 μg/kg/min. $^{\dagger}P < 0.05$ versus baseline value at a rate of 1.0 μg/kg/min

PLSD test or the Bonferroni multiple comparison test. Maximum changes from baseline values were analyzed using a Student's *t* test. The Pearson's correlation coefficient was assessed, and a least squares linear regression line was fitted using Sigma Plot 11 (Systat Software, Inc., San Jose, CA, USA). $P < 0.05$ was considered statistically significant.

Results

High-dose remifentanil decreased MAP (4.2 ± 3.0, 7.9 ± 6.2 mmHg) and HR (37.2 ± 26.4, 79.0 ± 68.4 bpm) transiently and increased MAP (14.6 ± 4.2, 18.3 ± 6.0 mmHg), HR (69.2 ± 38.5, 101.2 ± 42.7 bpm), and RSNA (51.9 ± 16.4, 95.4 ± 45.1 %) from each baseline

value at a rate of 1.0 and 2.0 μg/kg/min, respectively, in intact rats (Fig. 1). The maximum changes from the baseline values during (20 min) and after (30 min) intravenous administrations of remifentanil were compared for each dose (Fig. 2). Significant differences were observed in increase in MAP ($P < 0.0001$), HR ($P = 0.0052$), and RSNA ($P < 0.0001$) between 0.25 and 1.0 μg/kg/min. There are also significant differences in increase in MAP ($P = 0.021$), HR ($P = 0.015$), and RSNA ($P < 0.0001$) between 0.5 and 2.0 μg/kg/min. Remifentanil (2.0 μg/kg/min) decreased PO_2 compared with control value ($P = 0.0069$, Table 1). In SAD rats, remifentanil (2.0 μg/kg/min) decreased MAP (34.1 ± 15.8 mmHg; $P = 0.013$) and HR (74.9 ± 35.3 bpm; $P < 0.0001$) transiently and increased RSNA (52.1 ± 15.7 %; $P = 0.0056$, Fig. 3). However, these effects disappeared at a 1.0 μg/kg/min dose, and remifentanil did not increase MAP and HR at any dose (Fig. 3). In the relationship between sympathetic nerve activity and cardiovascular responses in intact rats, there was a statistically significant correlation between RSNA and MAP or HR ($r = 0.73$, $P = 0.025$ and $r = 0.79$, $P = 0.008$, respectively) at a rate of 2.0 μg/kg/min (Fig. 4). A subpressor dose (0.5 μg/kg/min) of remifentanil enhanced the baroreflex sensitivity (Δ RSNA/Δ MAP) from 4.8 ± 0.8 to 6.4 ± 1.1 %/mmHg ($P = 0.035$), and it (from 5.1 ± 0.3 to 4.9 ± 0.8 %/mmHg; $P = 0.68$) was blocked by naloxone (50 μg). Remifentanil (0.25 μg/kg/min) did not affect the baroreflex sensitivity. Simultaneous infusion of naloxone (25 or 50 μg) blocked the cardiovascular and sympathetic responses induced by remifentanil (2.0 μg/kg/min) in a dose-dependent manner (Fig. 5).

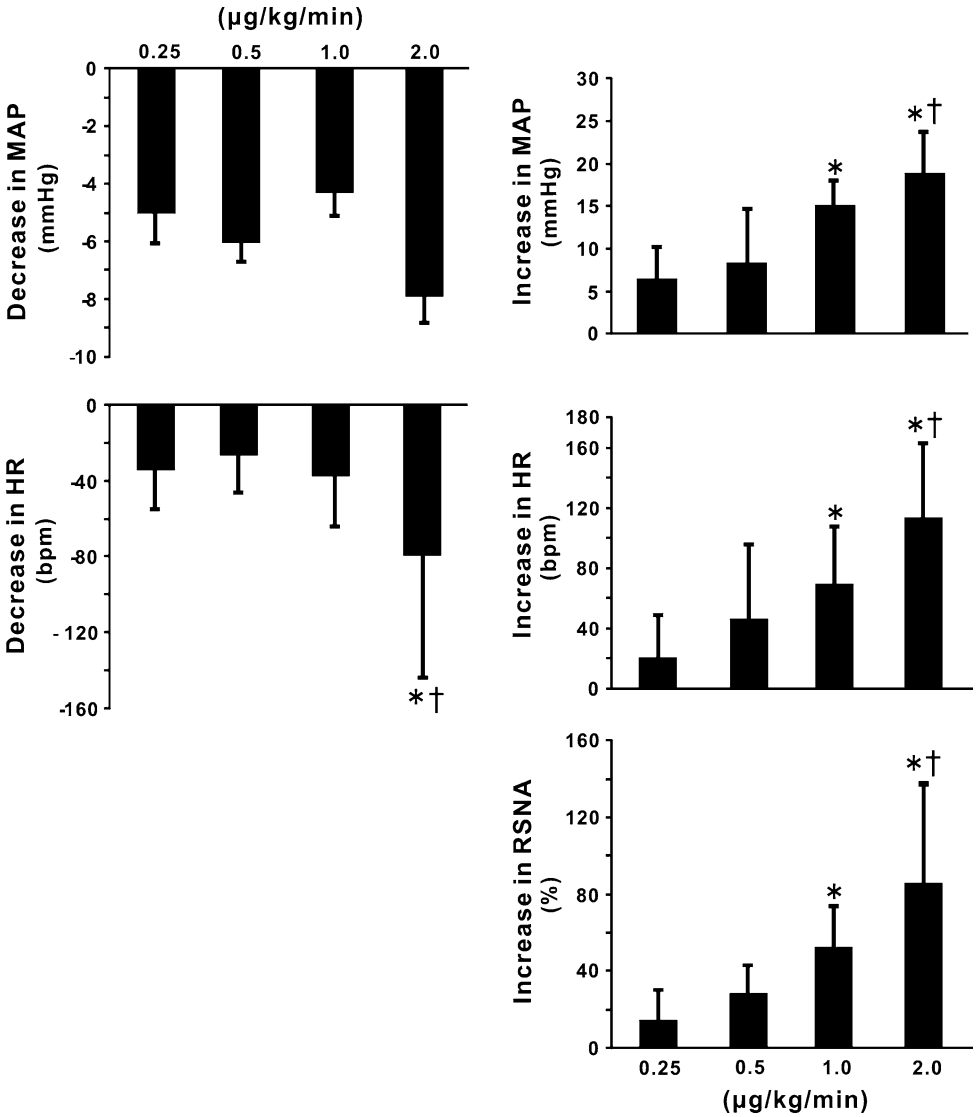

Fig. 2 *Bar graph* showing maximal changes from baseline values for MAP, HR, and RSNA during (20 min) and after (30 min) intravenous administration of remifentanil (0.25, 0.5, 1.0, and 2.0 μg/kg/min) in conscious rats; *bpm* beats per min. All data are the mean ± SD; $n = 8$ in each dose. *$P < 0.05$ versus 0.25 μg/kg/min. †$P < 0.05$ versus 0.5 μg/kg/min

Table 1 Effects of high-dose remifentanil on blood gases in intact rats

Remifentnail dose	1.0 μg/kg/min		2.0 μg/kg/min	
	Control	20 min	Control	20 min
PaO_2 (mmHg)	96.2 ± 4.8	90.7 ± 3.0	95.5 ± 5.5	84.2 ± 3.1*
$PaCO_2$ (mmHg)	35.7 ± 0.7	36.6 ± 1.5	36.6 ± 1.4	37.8 ± 1.0
pH	7.45 ± 0.07	7.44 ± 0.08	7.46 ± 0.05	7.41 ± 0.03

All data are the mean ± SD; $n = 8$ in each dose

* $P < 0.05$ versus control

Discussion

This is the first study demonstrating that high-dose remifentanil increased BP and HR mediated by an increase in SNA in conscious rats.

Remifentanil is usually administered as a continuous i.v. infusion in clinical anesthesia because it is a very short-acting opioid agonist [1]. Continuous infusion of high-dose remifentanil induced biphasic changes in MAP and HR. The MAP and HR decreased transiently soon after the start of infusion. These results were in agreement with previous

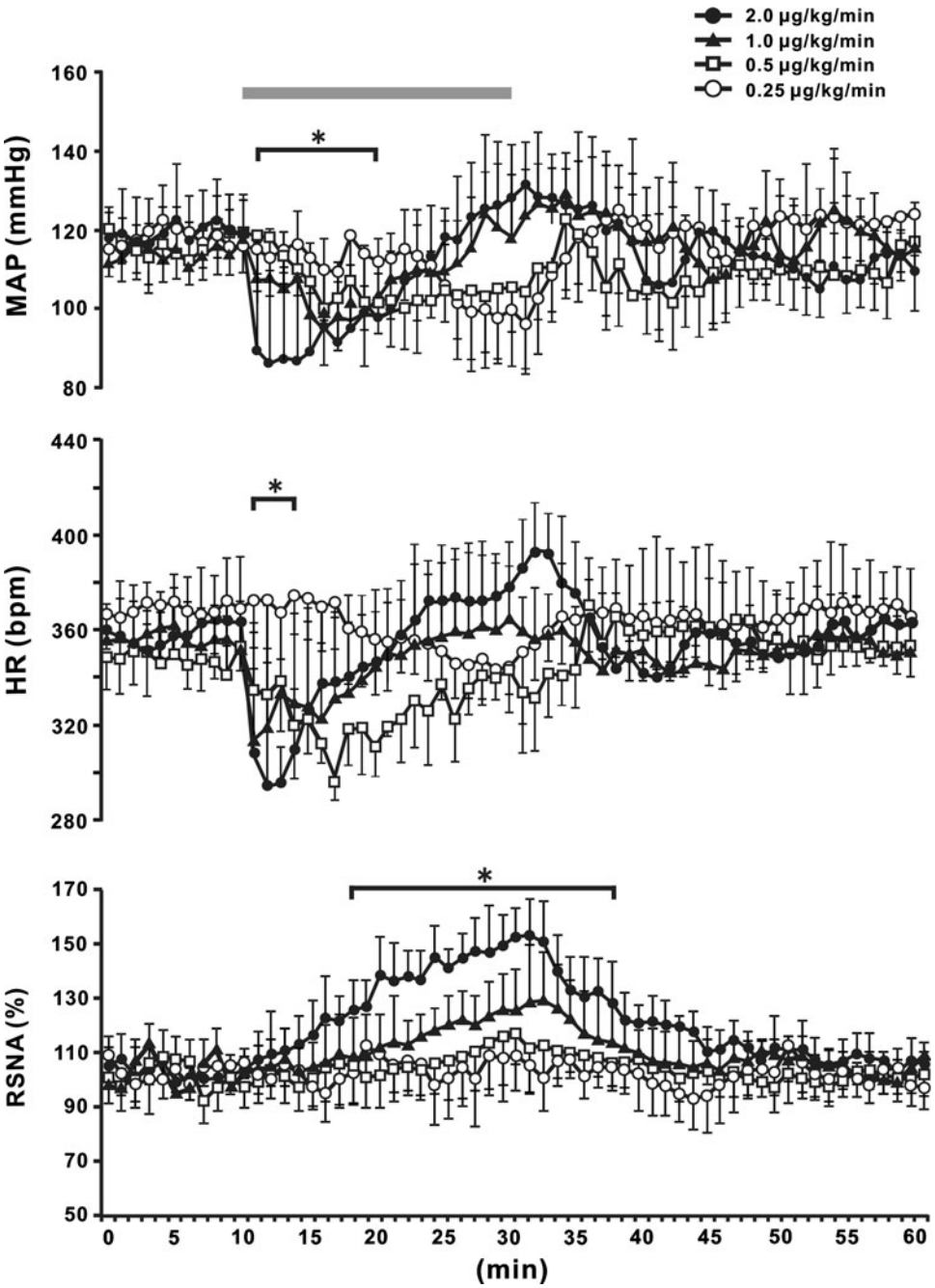

Fig. 3 Time course of changes in mean arterial pressure (MAP), heart rate (HR), and renal sympathetic nerve activity (RSNA) during the 60 min following intravenous administration of remifentanil (0.25, 0.5, 1.0, and 2.0 μg/kg/min) in SAD rats. *Bars* over data indicate times of intravenous administration of remifentanil for 20 min. *bpm* beats per min. All data are the mean ± SD; $n = 8$ in each dose. *$P < 0.05$ versus baseline value at a rate of 2.0 μg/kg/min

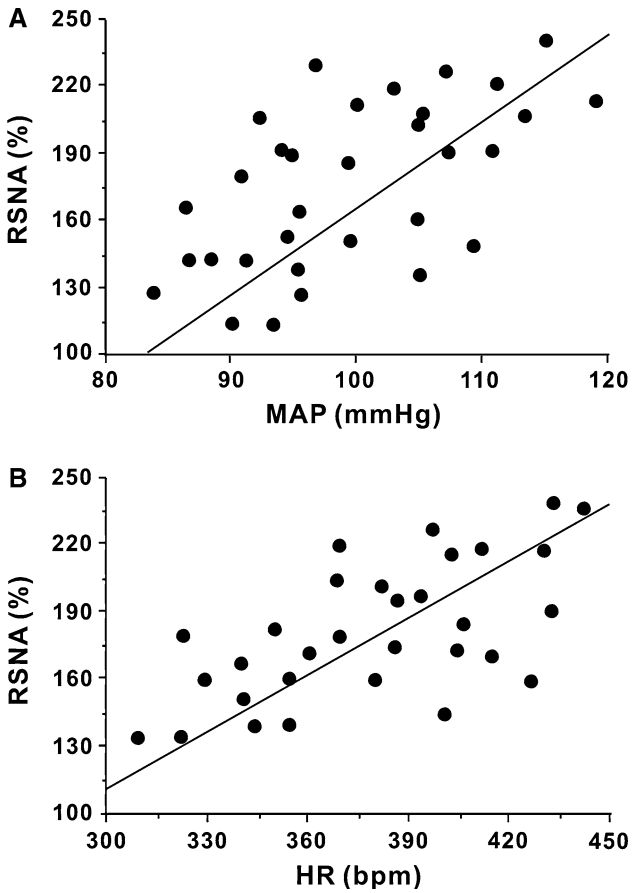

Fig. 4 These graphs indicate the relationship of renal sympathetic nerve activity (RSNA) and mean arterial pressure (MAP) (**a**) or heart rate (HR) (**b**) in RSNA significantly increased periods. There was a statistically significant correlation between RSNA and MAP or HR ($r = 0.73$ and $r = 0.79$, respectively; both P values <0.05) in the remifentanil (2.0 μg/kg/min)-infused group

reports [7] that an i.v. bolus injection of remifentanil decreased MAP and HR briefly in a dose-dependent manner in rabbits under urethane anesthesia. However, continuous increases after transient decreases of these parameters observed in our study were not observed in their study, showing that MAP and HR did not change in spite of RSNA increase. In humans, remifentanil (2, 5, 15, or 30 μg/kg) induced a reduction in only BP and HR under isoflurane anesthesia [6]. These differences may be due to the use of anesthesia and differences in the method of drug administration. Cardiovascular and autonomic functions are significantly affected by anesthetics [8], and responses to certain interventions are quite different between unanesthetized and anesthetized animals [12], which is the reason for the use of conscious rats. Remifentanil increased RSNA in a dose-dependent manner in intact rats. The potent μ opioid receptor agonist fentanyl has been reported to induce a dose-dependent increase in RSNA under urethane or halothane anesthesia [13] and noradrenaline and adrenaline plasma concentrations [14]. These results suggest a central activation of the sympathetic outflow by a μ-opioid receptor agonist. Propofol is frequently used as a sedative with remifentanil in clinical anesthesia and has inhibitory effects on BP, HR and RSNA in conscious rats [15]. Therefore, the sympatho-excitatory effects of remifentanil may be counteracted by propofol in clinical anesthesia. There was a statistically significant correlation coefficient between RSNA and MAP or HR. These results suggest that increases in MAP and HR induced by remifentanil are mediated by central sympathetic nerve activation. The μ-opioid receptors in the nucleus tractus solitarius (NTS) produce pressor responses mediated by increased SNA [16]. Sympatho-activation by remifentanil may be mediated by the stimulation of μ-opioid receptors in the NTS. The doses (0.25 or 0.5 μg/kg/min) of remifentanil did not affect RSNA. These data are consistent with the previous report that a sedative dose of remifentanil did not change the sympathetic outflow in humans [9].

The autonomic nervous system regulates circulatory reflexes via the arterial and cardiopulmonary baroreceptors located in the major blood vessels [17]. The signal is integrated in the rostral ventrolateral medulla (RVLM)/nucleus ambiguous complex, NTS, or vasomotor center and leads to compensatory adjustments in sympathetic and parasympathetic nerve activity [18]. To explore the direct action of remifentanil on cardiovascular and sympathetic responses, we used SAD rats. Increases in MAP and HR were not observed in SAD rats in spite of RSNA increase. These results suggest that baroreflex activity induces an increase in MAP and HR mediated by the modulation of remifentanil. Subpressor-dose remifentanil enhanced baroreflex sensitivity in our study. Increased baroreflex sensitivity might accelerate an increase in MAP and HR in intact rats. This is inconsistent with previous reports on remifentanil [7] and the other μ-opioid agonist, fentanyl [19]. On the other hand, Matsumura et al. [20] demonstrated that an intracerebroventricular injection of the μ-opioid agonist increases baroreflex sensitivity in conscious rabbits. The effect of opioids on cardiovascular responses and the baroreceptor reflex is divergent, depending on the use of anesthesia [21, 22] and the differences between opioid receptor subtypes [20]. The difference may be due to the use of anesthesia. Remifentanil induces systemic arterial vasodilation and increases regional blood flow at a clinical dose [23]. A hypotensive effect induced by vasodilation might also accelerate an increase in RSNA mediated by a baroreceptor reflex.

Remifentanil decreases HR and MAP by its central vagotonic effect [7]. Brief hypotension and bradycardia soon after a start of an infusion of high-dose remifentanil observed in our study may be mediated by centrally mediated vagotonic action and peripheral action. Morphine and fentanyl have also been reported to induce central vagal

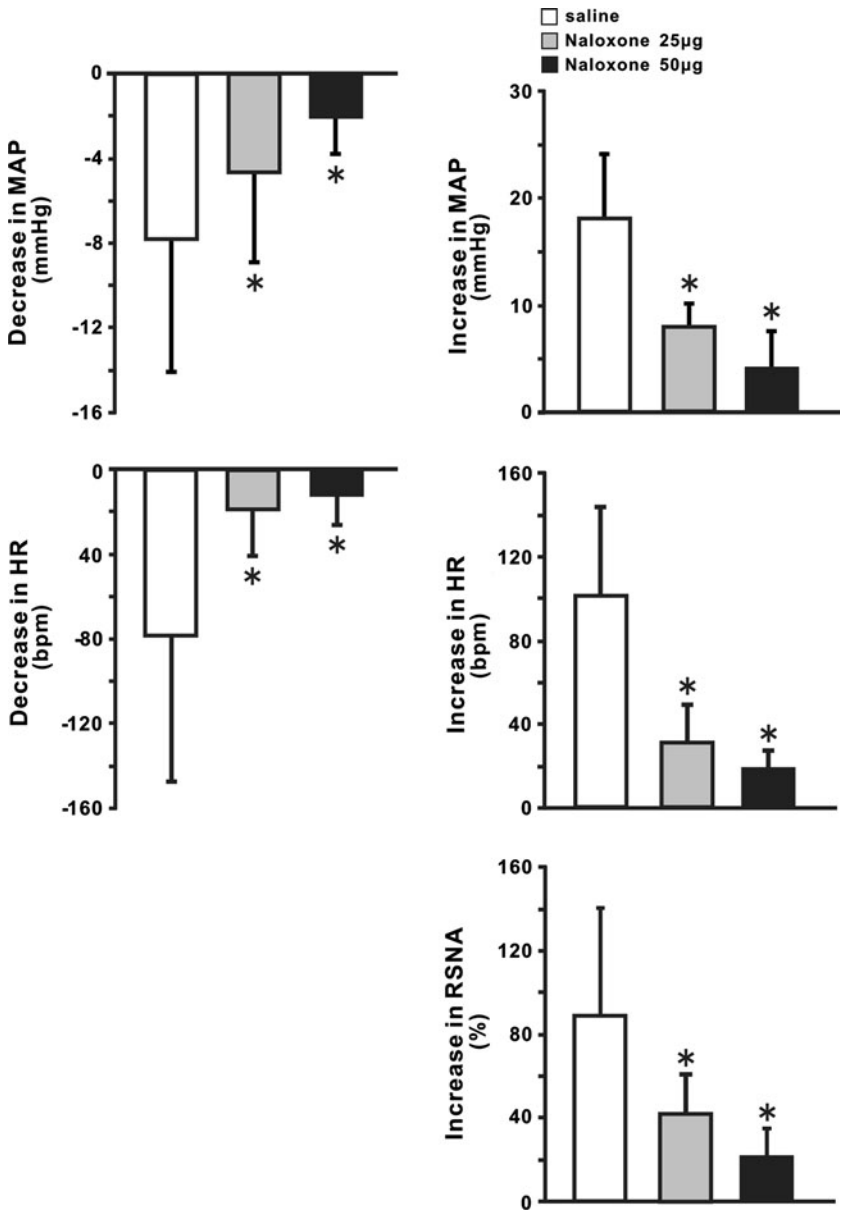

Fig. 5 *Bar graph* showing maximal changes from baseline values for MAP, HR, and RSNA during (20 min) and after (30 min) intravenous administration of remifentanil (2.0 μg/kg/min) and saline or naloxone (25 or 50 μg) in intact rats; *bpm* beats per min. All data are the mean ± SD; $n = 8$ in each dose. $^*P < 0.05$ versus saline

activation [13, 21]. These results suggest that stimulation of μ-opioid receptors may activate central vagus nerve activity. Remifentanil produces a dose-dependent vasodilator in rat thoracic aortic rings in vitro [24]. Morphine, fentanyl, and remifentanil produce concentration-dependent and endothelium-independent relaxations in human radial artery rings [25]. These results suggest that remifentanil induces hypotension mediated by direct vasodilator effects. Opioids, such as fentanyl and remifentanil have been shown to induce a direct negative chronotropic effect in isolated rat heart [26]. Remifentanil has greater depressant effects on HR than fentanyl [26] and suppresses sinoatrial conduction and sinus node automaticity under propofol-based anesthesia [27]. Negative chronotropic action by remifentanil may be counteracted by sympathoactivation in our study.

Although we defined high doses as 1.0 and 2.0 μg/kg/min infusion rate, these doses may be not high for rats. Haidar et al. [28] collected blood samples and evaluated the pharmacokinetics of remifentanil infusion at 25 μg/kg/min in spontaneously breathing rats. Respiratory depression and/or muscle rigidity must occur in humans at this infusion rate [29]. Cox et al. [30] showed that the pharmacodynamic parameter concentration at the half-maximal EEG effect of remifentanil was 9.4 and 19.5 ng/ml in rats and humans, respectively. It may be possible that the effects and plasma concentrations of remifentanil on rats differ from those on humans at the same infusion rate.

A limitation of our study is related to the fact that respiratory depression is the most common serious side effect of opioid drugs [31]. Hypoxia leads to increases in SNA and BP [32]. Remifentanil at a rate of 2.0 μg/kg/min decreased PO_2, however, PO_2 was preserved within normal range. Remifentanil did not induce hypoxia or hypercapnia. Thus, changes in blood gas parameters would not affect SNA and BP.

Finally, receptors associated with remifentanil-induced responses were examined in conscious rats treated with the classical opioid receptor antagonist, naloxone. Naloxone blocked cardiovascular and sympathetic responses induced by remifentanil in a dose-dependent manner. These results suggest that remifentanil induced cardiovascular and sympathotonic action mediated by μ-opioid receptors.

In conclusion, high-dose remifentanil increased BP and HR by an increase in SNA mediated by μ-opioid receptors in conscious rats.

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