Clinical and Experimental Pharmacology and Physiology (2008) **35**, 1197–1203 doi: 10.1111/j.1440-1681.2008.04979.x

COMPARATIVE EFFECTS OF TRAMADOL ON VASCULAR REACTIVITY IN NORMOTENSIVE AND SPONTANEOUSLY HYPERTENSIVE RATS

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SUMMARY

1. The aim of the present study was to determine the effects of tramadol on vascular reactivity in aortic rings from Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR).

2. Aortic rings, with or without endothelium, were obtained from male WKY rats and SHR (15–20 weeks old) and prepared for isometric tension recording. Aortic rings were precontracted with phenylephrine (10 μmol/L) or 40 mmol/L KCl and then exposed to cumulative concentrations of tramadol (0.1–1 mmol/L).

3. Tramadol produced a concentration-dependent relaxation of precontracted aortic rings from WKY rats and SHR, which was not dependent on functional endothelium. Vascular relaxation was significantly greater in rings from SHR than WKY rats.

4. The concentration of tramadol necessary to produce a 50% reduction of the maximal contraction to phenylephrine (IC_{50}) in rings with and without endothelium from SHR was 0.47 ± 0.08 and 0.44 ± 0.03 mmol/L, respectively ($P = 0.76$).

5. Tramadol attenuated the contracture elicited by Ca^{2+} in depolarized tissue, suggesting that it may inhibit L-type Ca^{2+} channels. However, pretreatment with nicardipine (1 μmol/L) prevented the relaxation induced by tramadol in aortic rings from WKY rats and partially reduced its inhibitory effect in aortic rings from SHR.

6. Pretreatment of endothelium-denuded aorta with glybenclamide (3 μmol/L), 4-aminopyridine (3 mmol/L), tetraethylammonium (3 mmol/L) and naloxone (100 μmol/L) did not affect tramadol-induced vasodilation of aortic rings from either WKY rats or SHR.

7. Intravenous administration of tramadol (10 mg/kg) to conscious SHR significantly reduced both systolic and diastolic blood pressure from 171.4 ± 5.3 to 129.3 ± 5.3 ($P = 0.002$) and from 125.0 ± 6.5 to 57.8 ± 8.9 mmHg ($P = 0.003$), respectively.

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Received 17 August 2007; revision 10 March 2008; accepted 25 March 2008.

Key words: blood pressure, spontaneously hypertensive rats, tramadol, vasodilation.

INTRODUCTION

Tramadol, (1RS, 2RS)-2-[(dimethylamino)-methyl]-1-(3-methoxyphenyl)-cyclohexanol hydrochloride, is a synthetic, centrally acting analgesic with efficacy comparable to codeine, pentazocine or dextropropoxyphene when used for pain relief.[1] The mechanism of its analgesic action involves a combination of binding to μ-opioid receptors and inhibition of the reuptake of serotonin and noradrenaline in pain pathways of the central nervous system. This dual mechanism of action has led to a description of tramadol as an 'atypical' opioid agent.[2] Tramadol ((+/–)-tramadol) is formulated as a racemic 1 : 1 mixture of (–)- and (+)-tramadol. The enantiomers differ in their potency to bind to μ-opioid receptors and to inhibit monoamine-reuptake: (+)-tramadol has the higher affinity for μ-opioid receptors, preferentially inhibits serotonin uptake and promotes increased serotonin release, whereas (–)-tramadol inhibits noradrenaline uptake.[3] The complementary and synergistic actions of the two enantiomers improve the analgesic efficacy profile of the racemate.[4] Unlike typical opioid analgesics, tramadol has not been associated with significant side-effects, such as respiratory depression or constipation,[5] and is considered haemodynamically stable.[6] Tramadol is effective in postoperative pain and in chronic pain consequent to prolonged inflammatory conditions or cancer. It provides additional analgesia to therapy with non-steroidal anti-inflammatory drugs (NSAIDs), contributing to a reduction in both their dose and side-effects.[7] In hypertensive individuals, especially in elderly and chronic pain patients, tramadol may be an advantageous analgesic because it does not inhibit prostaglandin synthesis, as do NSAIDs, which can limit the effectiveness of antihypertensive drugs.[8] Despite the large number of hypertensive patients who experience pain, no data are available on the cardiovascular effects of tramadol in those conditions. Hypertension is characterized by altered responses of the vessels to both vasoconstrictor and vasodilator agents.[9] Smooth muscle cells from hypertensive rats exhibit increased intracellular calcium concentrations, which are associated with decreased endothelium-dependent vasodilation.[10,11] It has been demonstrated that the vascular effects of some drugs are different in aortas isolated from spontaneously hypertensive rats (SHR) compared with normotensive rats.[12]

Previously, we investigated the vasodilatory action of tramadol and its enantiomers in aortas from normotensive rats and found that

the vasodilation caused by tramadol was mediated by both endothelium-dependent and -independent processes.[13] However, vascular relaxation has not been studied in the hypertensive condition. Thus, the present study compared the effects of tramadol on the vascular reactivity of isolated aortas from normotensive Wistar-Kyoto (WKY) rats and SHR. We also observed haemodynamic parameters in conscious WKY rats and SHR after a single intravenous injection of tramadol.

METHODS

The protocols used in the present study were approved by the Animal Care and Use Committee at Universidade Federal do Rio de Janeiro. Wistar-Kyoto rats and SHR were purchased from the Centro Multidisciplinar para Investigação Biológica (CEMIB; Universidade de Campinas, São Paulo, Brazil).

In vitro experiments

Preparation of aortic rings and protocols

Thoracic aortas were rapidly removed from 15–20-week-old male WKY rats and SHR, cleaned of connective tissue and cut into 2–3 mm rings. Aortic rings were placed in vertical chambers (internal volume 10 mL) filled with saline solution (composition (in mmol/L): NaCl 120; KCl 5.9; $MgCl_2$ 1.2; NaH_2PO_4 1.2; $NaHCO_3$ 18; $CaCl_2$ 2.5; glucose 11, pH 7.4) and oxygenated with carbogen gas at 37.0 ± 0.5°C. Each ring was mounted between two hooks, of which one was attached to a force transducer (model FT-03; Grass Instruments, West Warwick, RI, USA) whose signal was conditioned by a Cyberamp (Axon Instruments, Union City, CA, USA) so that contractile responses could be displayed and stored on a computer for future analysis using Axoscope software (Axon Instruments). Preparations were stabilized under 1 g resting tension for 2 h before the experimental protocol was started. After the equilibrium period, aortic rings were contracted with phenylephrine (10 μmol/L), followed by exposure to acetylcholine (ACh; 10 μmol/L) to test the integrity of the endothelium. The presence of an intact endothelium was confirmed by the observation of ACh-induced relaxation > 60%.[14] In some experiments, the endothelium was removed mechanically by gently rubbing the internal surface of the vessel. Removal of the endothelium was confirmed by a lack of relaxation (< 5%) in response to ACh (10 μmol/L). To investigate the ability of tramadol to induce relaxation of precontracted aorta from WKY rats and SHR, intact or endothelial-denuded rings were contracted with a single concentration of phenylephrine (10 μmol/L) or 40 mmol/L KCl and then exposed to increasing concentrations of tramadol (0.1–1.0 mmol/L). In experiments with high K^+, the isotonic 40 mmol/L KCl saline solution was prepared by equimolar replacement of NaCl.

The next step was to examine the effect of tramadol on Ca^{2+} influx in the smooth muscle, which could explain tramadol-induced relaxation. After the stabilization period, denuded rings were allowed to equilibrate in Ca^{2+}-free saline solution for 15 min, which was then replaced with Ca^{2+}-free/high-K^+ solution (40 mmol/L). Aortic rings were maintained in this depolarized state for a period of 15 min, in the presence or absence of either 0.2 or 0.5 mmol/L tramadol, followed by the addition of increasing concentrations of $CaCl_2$ (10^{-6}–10^{-3} mol/L). To determine the involvement of L-type Ca^{2+} channels, opioid receptors and different K^+ channels in the relaxation response to tramadol, nicardipine (1 μmol/L), naloxone (100 μmol/L), glybenclamide (3 μmol/L), 4-aminopyridine (4-AP; 3 mmol/L) and tetraethylammonium (TEA; 3 mmol/L) were added to the solution 20 min before the addition of phenylephrine. Because pretreatment with some K^+ channels inhibitors increased the amplitude of phenylephrine-induced contracture, 5 μmol/L phenylephrine was used in these experiments to induce a contracture of a similar amplitude to those in the other groups.

Experiments *in vivo*

Male WKY rats and SHR (15–20 weeks old) were anaesthetized with ether and a catheter was placed into the right carotid artery for arterial blood pressure (BP) measurement using a calibrated pressure transducer (P022; Statham, Oxnard, CA, USA). A pair of external electrodes was placed on the chest of rats to enable recording of the electrocardiogram (ECG). In addition, a catheter was placed in a jugular vein for the intravenous (i.v.) injection of tramadol. Two hours after the surgical procedures, rats were treated with a bolus injection of tramadol (10 mg/kg). Both BP and ECG were recorded continuously on a polygraph (Grass model 7400; AstroMed, West Warwick, RI, USA) before and during the administration of tramadol.

Compounds

Tramadol hydrochloride and naloxone were kindly donated by Cristália Produtos Químicos e Farmacêuticos (São Paulo, SP, Brazil). Phenylephrine, ACh, nicardipine, glybenclamide, 4-AP and TEA were purchased from Sigma Chemical (St Louis, MO, USA). All compounds were dissolved in distilled water, except for glybenclamide, which was dissolved in dimethyl sulphoxide, and tramadol, which was dissolved in saline for the *in vivo* experiments. The final concentration of DMSO tissues were exposed to was 0.0003% and this concentration had no effect on its own.

Statistics

Relaxation induced by tramadol was expressed as percentage of maximal tension. All data are expressed as the mean±SEM. Differences between different concentrations were considered statistically significant when $P < 0.05$ using one-way analysis of variance (ANOVA) followed by a post hoc Dunnett's test. For the comparison of multiple groups, ANOVA followed by Newman–Keuls' test was used. Paired Student's *t*-test was used for comparisons between two groups (*in vivo* experiments). The concentration–response curves for calcium were fitted to the equation $y = y_o + a/(1 + e^{-(x - xo/b)})$, where y_o is y_{min}, x_o is the EC_{50}, $a = Y_{max} - Y_{min}$ and b is the slope (y_{min}, percentage of isometric tension at lowest drug concentration; y_{max}, percentage of isometric tension at highest drug concentration).

RESULTS

Effects of tramadol on vascular smooth muscle from SHR

The vasodilator activity of tramadol was investigated in aortic rings from WKY rats and SHR. Figure 1 shows typical recordings of the maximal contractile response induced by phenylephrine (10 μmol/L) in aorta with (Fig. 1a) and without (Fig. 1b) endothelium from SHR, followed by exposure to cumulative concentrations of tramadol. Maximal tension induced by phenylephrine in aortic rings from SHR and WKY rats was 1.4 ± 0.1 and 1.5 ± 0.2 g, respectively, for endothelium-intact rings ($P > 0.05$) and 1.2 ± 0.1 and 1.6 ± 0.2 g, respectively, for endothelium-denuded rings ($P > 0.05$). Tramadol caused a concentration-dependent relaxation of precontracted aortic rings from both WKY rats and SHR. However, the relaxation was greater in SHR than WKY rats (Fig. 1c); maximal relaxation in the presence of 1 mmol/L tramadol was 81.3 ± 6.3 versus 20.7 ± 4.3% in SHR compared with WKY rats, respectively ($n = 6$; $P < 0.001$). Removal of the endothelium from aortic rings from WKY rats and SHR had no effect on the relaxation induced by tramadol, indicating that its relaxant effect was not dependent on the integrity of the vascular endothelium (Fig. 1c). The IC_{50} for tramadol against phenylephrine-induced contractions in endothelium-intact and -denuded rings from SHR was 0.47 ± 0.08 and 0.44 ± 0.03 mmol/L, respectively ($P > 0.05$) in. In another series of experiments, the effects of tramadol on the K^+-induced contraction were investigated. The high K^+ induces membrane depolarization, which, in turn, opens voltage-dependent L-type Ca^{2+} channels, leading to increased intracellular concentrations of Ca^{2+} and subsequent contraction.[15] In aortic rings from both WKY

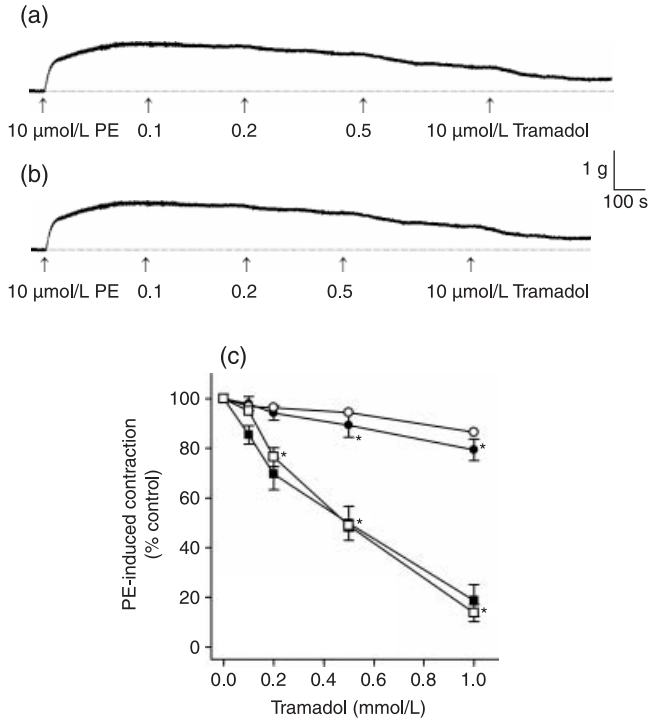

Fig. 1 Effects of tramadol on aortic rings from Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR). (a,b) Representative tracings of isometric tension of aortic rings from SHR with (a) and without (b) endothelium in response to phenylephrine (PE). (c) Concentration–response curves for tramadol in endothelium-denuded (open symbols) and -intact (filled symbols) aortic rings from WKY rats (●, ○) and SHR (■, □). Data are the mean±SEM ($n = 6$). *$P < 0.01$ compared with control.

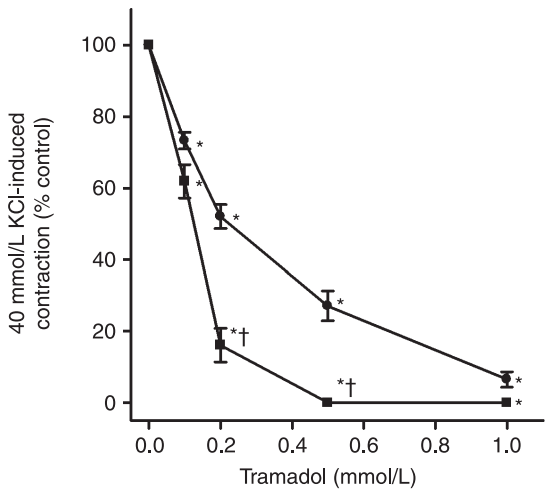

Fig. 2 Effects of tramadol on aortic rings from Wistar-Kyoto (WKY) rats (●) and spontaneously hypertensive rats (■) precontracted with 40 mmol/L KCl. Data are the mean±SEM ($n = 6$). *$P < 0.01$ compared with control; †$P < 0.01$ compared with WKY rats.

rats and SHR, the tramadol-induced relaxation was greater after exposure to high K^+ than to phenylephrine. The concentration–response curve for tramadol was shifted leftwards and the IC_{50} for tramadol was 0.22 ± 0.02 and 0.12 ± 0.01 mmol/L in aortic rings from WKY rats and SHR, respectively (Fig. 2; $P < 0.001$). To investigate whether tramadol impaired extracellular calcium influx through

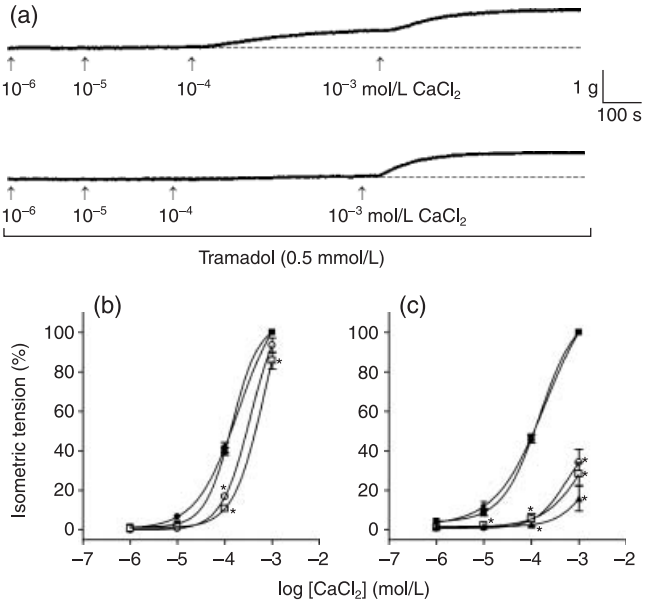

Fig. 3 Effects of tramadol on Ca^{2+}-induced contraction of depolarized denuded aorta from Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR). (a) Representative tracings of isometric tension of aortic rings from SHR in response to increasing concentrations of Ca^{2+} in the absence and presence of 0.5 mmol/L tramadol. (b,c) Effects of 0.2 and 0.5 mmol/L tramadol, respectively, on the concentration–response curve for Ca^{2+} in WKY rats and SHR. Nicardipine (10 nmol/L) was used as a blocker of L-type Ca^{2+} channels. Contractions were taken as 100% in the presence of 10^{-3} mol/L $CaCl_2$ (control curve). (●), WKY rats; (○), WKY rats + tramadol; (■), SHR; (□), SHR + tramadol; (▲), nicardipine. Data are the mean±SEM ($n = 6$). *$P < 0.05$, compared with control.

voltage-dependent calcium channels, concentration–response curves for Ca^{2+} were obtained in the absence and presence of tramadol. The experimental protocol consisted of pretreatment of aortic rings with 0.2 or 0.5 mmol/L tramadol and subsequent depolarization of the tissue in the absence of extracellular Ca^{2+}. After that, increasing concentrations of Ca^{2+} were added to the bath and the Ca^{2+}-induced contraction was observed in depolarized aorta from SHR (Fig. 3a). Tramadol was effective in attenuating the contractile response to Ca^{2+} in aortic rings from both WKY rats and SHR (Fig. 3b,c). In the presence of tramadol (0.5 mmol/L), the maximal contraction of aortic rings from WKY rats and SHR induced by 1 mmol/L $CaCl_2$ was reduced to 34.1 ± 6.8 and 28.3 ± 5.8%, respectively (Fig. 3c; $P < 0.001$). Tramadol produced similar rightward shifts in the calcium concentration–response curve in aortic rings from WKY rats and SHR, suggesting that its vasorelaxant effect is mediated, at least in part, through inhibition of the entry of extracellular calcium. Figure 3c also shows the inhibitory effect of 10 nmol/L nicardipine, an L-type Ca^{2+} channel blocker on aorta from SHR.

Based on these results, we tested the effect of tramadol on aortic rings precontracted with phenylephrine in the presence of nicardipine (1 µmol/L), an L-type Ca^{2+} channel blocker. At this concentration, nicardipine totally abolished the K^+-induced contraction (data not shown). In the presence of nicardipine, tramadol did not relax aortic rings from WKY rats that had been precontracted with phenylephrine (Fig. 4a). In contrast, in the presence of nicardipine only a partial reduction in the tramadol-induced relaxation of phenylephrine-precontracted aortic rings from SHR was observed. At

Table 1 Effects of intravenous administration of tramadol on systolic and diastolic blood pressure of conscious Wistar-Kyoto and spontaneously hypertensive rats

	WKY rats SBP (mmHg)	DBP (mmHg)	SHR SBP (mmHg)	DBP (mmHg)
Control	144.0 ± 4.3	105.0 ± 2.7	171.4 ± 5.3**	125.0 ± 6.5*
Tramadol (10 mg/kg)	135.0 ± 2.2	100.0 ± 3.5	129.3 ± 5.3†	57.8 ± 8.9†

Data are the mean±SEM ($n = 6$). *$P < 0.05$, **$P < 0.01$ compared with Wistar-Kyoto (WKY) rats; †$P < 0.001$ compared with control.
SBP, systolic blood pressure; DBP, diastolic blood pressure; SHR, spontaneously hypertensive rats.

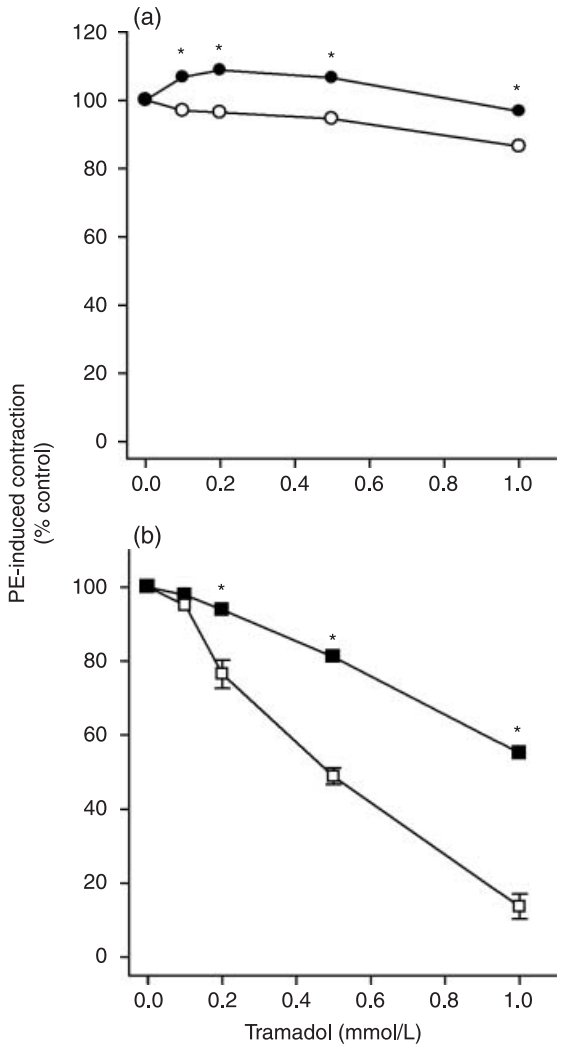

Fig. 4 Effects of tramadol on phenylephrine (PE)-precontracted aortic rings from (a) Wistar-Kyoto (WKY) rats and (b) spontaneously hypertensive rats (SHR) precontracted with phenylephrine in the presence (●, ■) and absence (○, □) of 1 μmol/L nicardipine. Data are the mean±SEM ($n = 5$). *$P < 0.01$ compared with control.

1 mmol/L, tramadol reduced phenylephrine-induced contractions of aortic rings from SHR to 55.1 ± 0.8% of control ($n = 4$; $P < 0.001$; Fig. 4b). These results suggest that, in SHR, vasodilation induced by tramadol involves, in part, inhibition of extracellular Ca^{2+} influx.

In order to test the possible role of K^+ channels in the tramadol-induced vasodilation, endothelium-denuded aortic rings were exposed to different K^+ channels blockers before being exposed to phenylephrine. Pretreatment of aortic rings with 3 μmol/L glybenclamide, 3 mmol/L 4-AP and 3 mmol/L TEA, inhibitors of ATP-sensitive K^+ channels, voltage-sensitive K^+ channels and Ca^{2+}-activated K^+ channels, respectively, did not inhibit the vasodilation induced by tramadol in aortic rings from either WKY rats or SHR (Fig. 5). Pretreatment of SHR aorta with TEA produced a significant reduction in the IC_{50} from 0.44 ± 0.03 to 0.28 ± 0.02 mmol/L ($P < 0.05$), which may be due to the membrane depolarization induced by TEA.[16] Moreover, the increased potency of tramadol to relax high K^+-contracted aortic rings also suggests that activation of K^+ channels may not be involved in the vasodilation in response to tramadol. Similarly, pretreatment with 100 μmol/L naloxone, an opioid receptor antagonist, had no effect on tramadol-induced vasodilation in aorta from WKY rats and SHR (Fig. 6).

Effects of tramadol on the blood pressure in SHR

We also investigated the effects of intravenous administration of tramadol on the BP of conscious WKY rats and SHR. Systolic BP (SBP) was significantly higher in SHR than WKY rats (171.4 ± 5.3 *vs* 144.0 ± 4.3 mmHg, respectively; $P < 0.01$). Figure 7 shows typical BP and ECG recordings before and after intravenous injection of vehicle (saline) or tramadol (10 mg/kg) in SHR. No changes were observed in systolic and diastolic BP after injection of tramadol in WKY rats (Table 1). In contrast, tramadol produced significant changes in these haemodynamic parameters in SHR. Rapid and transitory reductions of SBP and diastolic BP (DBP), as well as changes in the ECG pattern, were observed after injection of tramadol in SHR. Systolic BP and DBP were both reduced significantly (from 171.4 ± 5.3 to 129.3 ± 5.3 mmHg for SBP; and from 125.0 ± 6.5 to 57.8 ± 8.9 mmHg for DBP; both $P < 0.001$).

DISCUSSION

The present study demonstrated that tramadol induced a concentration-dependent relaxation of precontracted aorta from WKY rats and SHR and that this effect was significantly greater in SHR than in WKY rats. In addition, intravenous administration of tramadol reduced BP only in conscious SHR.

Structural and functional changes in vascular smooth muscle are found in all forms of spontaneous and experimental hypertension. The vascular endothelium plays an important role in the control of vascular tone because it produces a number of relaxant and

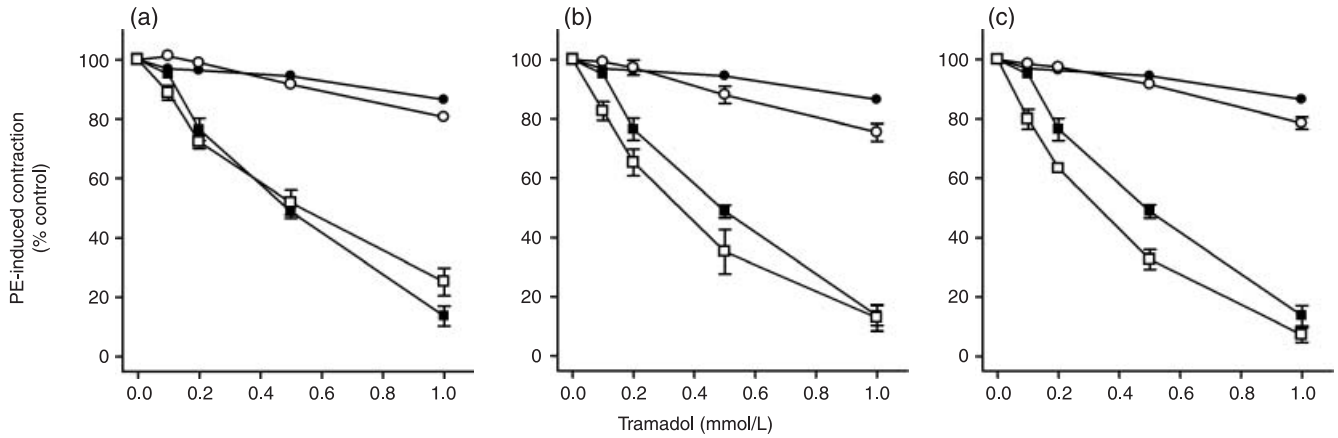

Fig. 5 Effects of K^+ channel inhibitors on the tramadol-induced relaxation of phenylephrine (PE)-precontracted aortic rings from Wistar-Kyoto (WKY) rats (●, ○) and spontaneously hypertensive rats (SHR; ■, □). Concentration–response curves were constructed to tramadol in the absence (●, ■) and presence (○, □) of (a) 3 μmol/L glibenclamide, (b) 3 mmol/L 4-amynopiridine and (c) 3 mmol/L tetraethylammonium. Data are the mean±SEM ($n = 5$).

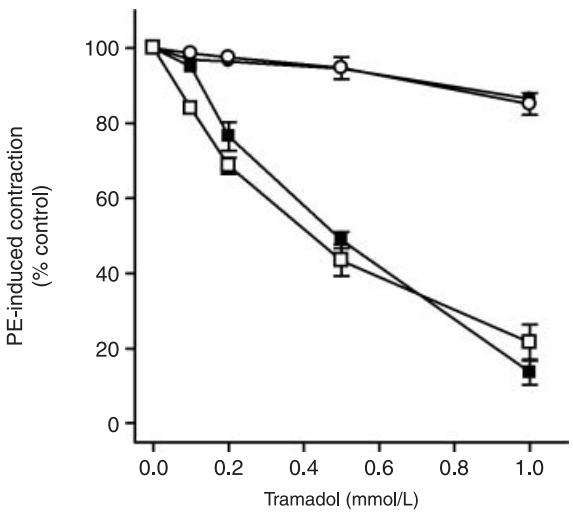

Fig. 6 Effect of naloxone on the tramadol-induced relaxation of phenylephrine (PE)-precontracted aortic rings from Wistar-Kyoto (WKY) rats and spontaneously hypertensive rats (SHR). (●), WKY rats; (○), WKY rats + naloxone; (■), SHR; (□), SHR + naloxone. Data are the mean±SEM ($n = 5$).

constrictor factors. It is well known that, in hypertension, the balance between these factors is altered and that this is central to the maintenance of elevated BP.[17] Removal of the endothelium in the present study did not alter the vasorelaxant effect of tramadol in aortic rings from either WKY rats or SHR, suggesting that the endothelium does not mediate the vascular effects of tramadol in either WKY rats or SHR. Rather, it may act directly on vascular smooth muscle.

In addition to endothelial modifications, there is some evidence that enhanced Ca^{2+} influx may play an important role in the pathogenesis of hypertension. Voltage-dependent calcium channels play a central role in the regulation of vascular tone, especially L-type channels in myogenic reactivity and vasomotion.[16] Abnormal calcium handling in vascular smooth muscle from hypertensive rats has already been reported and free cytosolic calcium concentrations have been shown to be increased in SHR.[18] There is direct evidence that the expression and activity of calcium channels are augmented in vascular smooth muscle from SHR.[19] In the present study, tramadol induced a concentration-dependent relaxation of K^+-contracted aortic rings from WKY rats and promoted complete relaxation of the K^+-induced contraction in aortic rings from SHR, which was associated with a threefold reduction of the IC_{50}. The contractile response induced by high K^+ in smooth muscle is consequent to the influx of extracellular Ca^{2+} through L-type voltage-dependent Ca^{2+} channels. Thus, tramadol showed a significantly

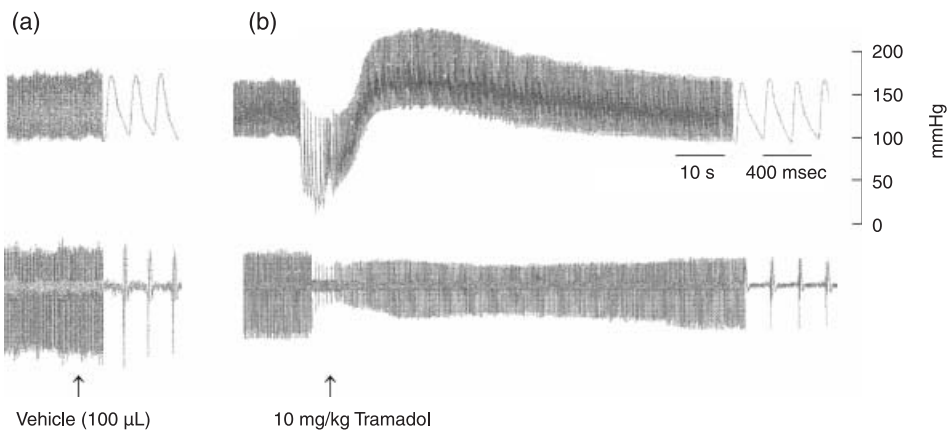

Fig. 7 Typical recording of arterial blood pressure (upper panel) and electrocardiogram (lower panel) before and after intravenous injection of (a) vehicle (saline) or (b) 10 mg/kg tramadol in spontaneously hypertensive rats.

greater relaxant effect when contractions of aortic rings from both WKY rats and SHR were induced by high K^+, suggesting that tramadol may act, in part, by blocking the influx of Ca^{2+} through the voltage-dependent Ca^{2+} channels.

Vascular relaxation induced by tramadol in WKY rats seems to be mediated through voltage-dependent Ca^{2+} channels because the action of tramadol is abolished in the presence of nicardipine. However, in SHR, tramadol seems to have an additional mechanism of action because it produced a slight vasodilation of aortic rings even after pretreatment with nicardipine.

Because tramadol produces analgesia partly through activation of μ-opioid receptors, we investigated the involvement of opioid receptors in the vascular effects of tramadol in SHR. Mahinda *et al*.[20] showed that subcutaneous injection of morphine produced greater hypotension and bradycardia, as well as a greater antinociceptive effect, in SHR compared with normotensive controls. Opioid binding sites are upregulated in the spinal cord and in different areas of the brain of SHR;[21] this may contribute to the enhanced analgesia and hypotension induced by morphine. Spontaneously hypertensive rats exhibit an increased nociceptive threshold in many tests in which the endogenous opioid system is the main system involved in the hypoalgesia.[22] Despite this, pretreatment of endothelium-denuded aortic rings from WKY rats and SHR with naloxone did not interfere with the relaxation induced by tramadol.

In addition to binding to opioid receptors and inhibition of monoamine reuptake, blockade of potassium and sodium channels may also be involved in the analgesic effects of tramadol.[23] Yalcin and Aksu[24] reported that a non-specific voltage-dependent potassium channel could participate in the antinociceptive effect of tramadol in mice. Because the activation of K^+ channels results in hyperpolarization of cell membranes and consequent relaxation of vascular smooth muscle, we investigated the participation of different type of K^+ channels in the vasorelaxant effect of tramadol. However, pretreatment of aortic rings from WKY rats and SHR with glybenclamide, 4-AP and TEA did not inhibit the vasodilation induced by tramadol. Similarly, Kaya *et al*.[25] showed that ATP-sensitive and Ca^{2+}-activated K^+ channels are not involved in the vasodilator action of tramadol in rabbit isolated aorta. Conversely, Cho *et al*.[26] demonstrated that tramadol attenuates vasorelaxant responses to ATP-sensitive K^+ channel activation in normotensive rat aorta.

Intravenous injection of tramadol (10 mg/kg) produced a significant reduction in BP of conscious SHR, which was not observed in WKY rats. This effect may be explained by the intense vasodilation produced in aortic rings isolated from SHR. Lack of significant changes in BP after intravenous injection of tramadol in WKY rats confirmed previous results observed in normotensive Wistar rats.[13] Differences in the vascular actions of tramadol between WKY rats and SHR may be due to the structural and functional modifications present in hypertension, such as changes in intracellular Ca^{2+} levels, augmented Ca^{2+} efflux[27] and increased protein kinase C activity.[28] However, those effects were only observed at supraclinical concentrations, indicating the safety of tramadol use even in conditions associated with arterial hypertension.

ACKNOWLEDGEMENTS

This work was supported by Conselho Nacional de Desenvolvimento Cientifico e Tecnológico (CNPq), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES), Fundação Universitária Jose Bonifácio (FUJB), Pronex, Fundação Carlos Chagas Filho de Amparo à Pesquisa do Estado do Rio de Janeiro (FAPERJ). In addition, this work was supported, in part, by fellowships from CAPES (to JMR, LBP) and from CNPq (to G2S, RTS). Tramadol was kindly donated by Cristália Produtos Químicos e Farmacêuticos (Itapira, SP, Brazil). The authors thank Dr Thomas Nelson (Department of Anesthesiology, Wake Forest University, Winston Salem, NC, USA) for his positive critical analysis of the manuscript.

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