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Differential haemodynamic effects of endothelin receptor antagonist, SB 209670, in conscious hypertensive and normotensive rats

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Abstract

Endothelin has been implicated in the pathogenesis and/or maintenance of hypertension. Endothelin receptor antagonists lower blood pressure in the spontaneously hypertensive rat (SHR), but the regional haemodynamic effects of such drugs in the SHR remain unknown. The aim of this study was to examine the regional haemodynamic effects of the endothelin receptor antagonist, (±)-(1*S*,2*R*,3*S*)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid (SB 209670), in SHR and Wistar-Kyoto (WKY) rats. Rats underwent a two-stage operation for implantation of Doppler flow probes and intravascular catheters. Recordings were made of mean arterial pressure (MAP), heart rate (HR) and renal (Ren), mesenteric (Mes) and hindquarters (HQ) blood flows and conductances (Cond). SHR and WKY received 4.5 h infusions of saline or SB 209670 (5 mg/kg priming dose + 1 or 5 mg/kg/h, i.v.). SB 209670 lowered blood pressure in both SHR (−23 ± 2 mm Hg) and WKY rats (−13 ± 1 mm Hg). In addition, a lower dose infusion of SB 209670 also had an antihypertensive effect in SHR (−15 ± 5 mm Hg). In SHRs which received the higher dose of antagonist, Ren, Mes and HQ Cond were significantly increased as was the HQ Cond in a low-dose group. In WKY rats, SB 209670 decreased Ren blood flow whilst increasing Mes and HQ blood flows and Cond. SB 209670 also attenuated the regional vasoconstrictor effects of endothelin-1, except in the Mes circulation in SHR. This study illustrates that SB 209670 causes differential haemodynamic effects in SHR and WKY rats. In SHR, the antihypertensive effect of SB 209670 was accompanied by a generalised vasodilatation in the Ren, Mes and HQ vascular beds. In WKY rats, the hypotensive effect of SB 209670 was accompanied by Mes and HQ vasodilatation, but with Ren vasoconstriction. Thus, endothelin is involved in the maintenance of blood pressure and vascular tone in both SHR and WKY rats, but the haemodynamic profiles of these effects differ between the two strains.

Keywords: Endothelin; Hypertension; Blood flow, regional; Vasoconstriction; Dilatation; SB 209670

1. Introduction

Discovery of the potent vasoconstrictor peptide endothelin-1 has led to much speculation about its involvement in the pathogenesis and/or maintenance of various forms of hypertension (Yanagisawa et al., 1988). Endothelin is believed to cause its cardiovascular effects via stimulation of two receptor subtypes now designated endothelin ET_A and ET_B. It is generally considered that activation of endothelin ET_A and/or ET_B receptors on vascular smooth muscle results in vasoconstriction, while a vasodilator effect of endothelin is seen when endothelin ET_B receptors on the endothelium of resistance blood vessels are activated resulting in the release of vasorelaxing agents such as endothelium-derived nitric oxide and prostacyclin (Douglas et al., 1994b).

It has been well demonstrated that endothelin receptor antagonists inhibit the cardiovascular effects of endothelin in vivo (Gardiner et al., 1994a,b). In addition, endothelin antagonists such as the peptide endothelin ET_A-selective, c (D–Trp–D–Asp–Pro–D–Val–Leu) (BQ-123), and the nonpeptide, nonselective endothelin ET_A/ET_B compound (±)-(1*S*,2*R*,3*S*)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(prop-1-yloxy)-indane-2-carboxylic acid (SB 209670), have been shown to lower blood pressure in various experimental models of hypertension such as the spontaneously hypertensive rat (SHR), deoxycorticosterone acetate-salt, renal (Ren), and transgenic hypertensive rats (Ohlstein et al., 1993, 1994; Bird et al., 1995; Douglas et al., 1995a,b; Gardiner et al., 1995). However, to date, the regional haemodynamic effects of

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such antagonists in the SHR remain unknown, although BQ-123 and SB 209670 decreased total peripheral resistance in SHR (Ohlstein et al., 1993; Douglas et al., 1995b). Therefore, the aim of this study was to examine the effect of various infusion regimens of the nonselective endothelin antagonist SB 209670 on regional haemodynamics in conscious SHR.

2. Materials and methods

2.1. Surgery

All experiments were approved by the Monash University Animal Ethics Committee and were performed according to the National Health and Medical Research Council of Australia's guidelines for animal experimentation. Male SHR and Wistar-Kyoto (WKY) rats of approximately 15 weeks of age (250–350 g) were anaesthetized with sodium methohexitone (Brietal, Eli Lilly; 60 mg/kg, i.p., supplemented as required) and pulsed Doppler flow probes were implanted around the Ren and mesenteric (Mes) arteries and the abdominal aorta for measurement of Ren, Mes and hindquarters (HQ) blood flows respectively, as described previously (Li and Widdop, 1995). Following at least 7 days recovery, rats were again anaesthetized (as above) and catheters were inserted into the right jugular vein for drug administration and another into the abdominal aorta via the caudal artery for measurement of mean arterial blood pressure and heart rate (HR). Rats were allowed a further 24-h recovery before commencement of experiments. Continuous measurements were then made of phasic blood pressure, HR and mean and phasic Ren, Mes and HQ blood flows (i.e., Doppler shift signals) using pulsed Doppler flowmeters (Crystal Biotech, Massachusetts, USA and University of Iowa Bioengineering, Iowa, USA). All variables were displayed on MacLab-8 systems (ADInstruments, Australia) interfaced with Macintosh computers. The Doppler shift (DS) signal is used as a reliable index of regional blood flows (Haywood et al., 1981) and corre-

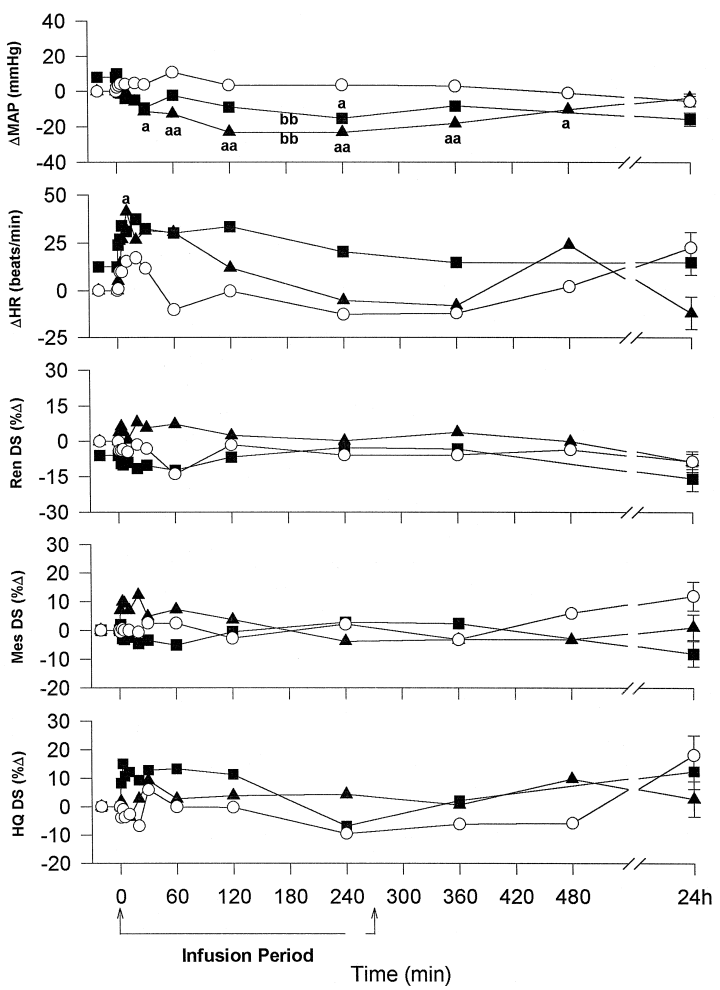

Fig. 1. Time course of changes in MAP, HR and DS (i.e., blood flow) in the Ren, Mes and HQ vascular beds following infusion of saline (1 ml/kg/h, i.v. for 4.5 h; open circles ($n = 8$)) or the endothelin ET_A/ET_B receptor antagonist, SB 209670 (5 mg/kg + 1 mg/kg/h, i.v. for 4.5 h; squares ($n = 8$) or 5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h; triangles ($n = 7$)), in conscious SHRs. Values are mean with group S.E.M. shown by vertical lines; $^{a}P < 0.05$, $^{aa}P < 0.01$ compared with respective baseline (ANOVA); $^{bb}P < 0.01$ compared with saline control (ANOVA).

sponding vascular conductances (Cond) were calculated as the DS divided by the corresponding mean arterial pressure (MAP).

2.2. Experimental protocol

Basal haemodynamic parameters were recorded prior to any experimental procedures. SHR received a 4.5-h infusion of saline (0.35 ml/h, i.v.) and SB 209670 (1 or 5 mg/kg/h, i.v.). However, each SHR received only one infusion regimen of SB 209670. WKY rats received a 4.5-h infusion of either SB 209670 (5 mg/kg/h, i.v.) or saline (0.35 ml/h, i.v.). Immediately prior to commencement of antagonist infusion, all three treatment groups received a bolus priming dose of 5 mg/kg, i.v. SB 209670. The effect of endothelin-1 was also examined during the antagonist infusions to test for a functional blockade of endothelin receptors. To this end, cardiovascular responses to endothelin-1 (300 ng/kg, i.v.) were recorded for 30 min, before and approximately 30 min, 2, 4 and 24 h after commencement of antagonist or saline infusion. The haemodynamic responses to endothelin-1 were expressed as area under and over the curve (AUC or AOC) over a 30-min period after injection. The changes in MAP, HR and HQ flow and Cond in response to endothelin-1 were, in general, biphasic with this dose of endothelin-1. The area of each phase was calculated separately and is expressed as such in Tables 2 and 3.

2.3. Statistics

Basal haemodynamic parameters were compared between SHR and WKY using an unpaired Student's *t*-test. The effects of SB 209670 relative to pre-antagonist baseline and saline infusion, were analysed using one- and two-way analysis of variance (ANOVA) with repeated measures, respectively. Post hoc analysis was performed using the Newman–Keuls test. In addition, the effect of SB 209670 on haemodynamic responses to endothelin-1 (i.e., AUC or AOC) was analysed using a one-way ANOVA with repeated measures. Post hoc analysis was done using a Dunnett's test. For clarity, all data presented in Figs. 1–4

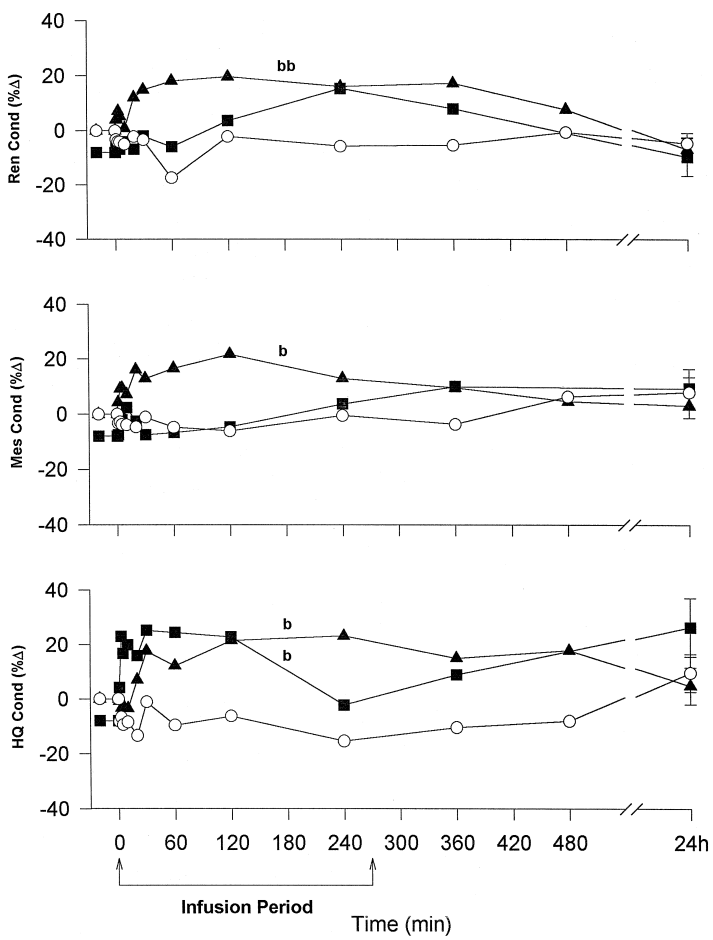

Fig. 2. Time course of changes in Ren, Mes and HQ vascular Cond following infusion of saline (1 ml/kg/h, i.v. for 4.5 h; open circles ($n = 8$)) or the endothelin ET_A/ET_B receptor antagonist, SB 209670 (5 mg/kg + 1 mg/kg/h, i.v. for 4.5 h; squares ($n = 8$) or 5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h; triangles ($n = 7$)), in conscious SHRs. Values are mean with group S.E.M. shown by vertical lines; $^{b}P < 0.05$, $^{bb}P < 0.01$ compared with saline control (ANOVA).

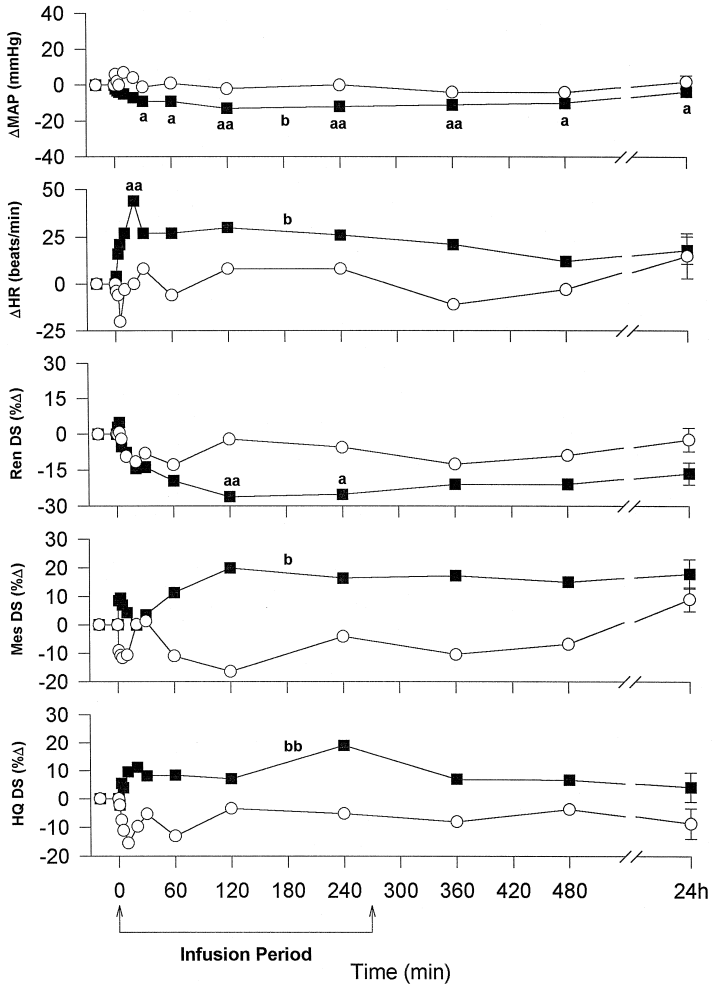

Fig. 3. Time course of changes in MAP, HR and DS (i.e., blood flow) in the Ren, Mes and HQ vascular beds following infusion of saline (1 ml/kg/h, i.v. for 4.5 h; open circles ($n = 4$)) or the endothelin ET_A/ET_B receptor antagonist, SB 209670 (5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h; triangles ($n = 6$)), in conscious WKY rats. Values are mean with group S.E.M. shown by vertical lines; $^{a}P < 0.05$, $^{aa}P < 0.01$ compared with respective baseline (ANOVA); $^{b}P < 0.05$, $^{bb}P < 0.01$ compared with saline control (ANOVA).

were expressed as mean ± group standard error, which was calculated as the $\sqrt{EMS/n}$, where EMS was the error mean square from the ANOVA, and n was the number of rats per group. Data presented in Tables 1–3 were expressed as mean ± S.E.M. $P < 0.05$ was accepted as significant.

3. Results

SHR had significantly higher basal MAP and lower Ren, Mes and HQ vascular Cond compared to WKY rats (Table 1). Resting values for each group of SHR given infusions of saline or SB209670 (1 or 5 mg/kg/h, i.v.) did not differ from the pooled means in Table 1.

3.1. Haemodynamic effect of SB 209670 infusion

Figs. 1 and 2 show the effect of saline or SB 209670 infusion on regional haemodynamics in SHRs. The high-dose regimen of SB 209670 significantly lowered MAP from 30 min to 8 h after commencement of the infusion (max: -23 ± 2 mm Hg at 4 h, $P < 0.01$), which was accompanied by a transient tachycardia. Similarly, low-dose SB 209670 also had a significant antihypertensive effect (max: -15 ± 5 mm Hg at 4 h, $P < 0.01$). Saline infusion had no significant effect on MAP per se, hence the depressor effects of both doses of SB 209670 were significantly different from those of saline infusion. Ren, Mes and HQ blood flows were largely unaffected by SB 209670 infusion. Therefore, Ren, Mes and HQ vascular Cond were all significantly increased by approximately 20% ($P < 0.01$) in SHRs receiving the high dose of SB 209670 compared with the saline-treated group. However, only the HQ Cond was increased in the low-dose group. Saline infusion had virtually no effect on Ren, Mes and HQ flows and Cond.

In WKY, SB 209670 (5 mg/kg/h) caused a significant hypotensive effect (max: -13 ± 1 mm Hg at 2 h) accom-

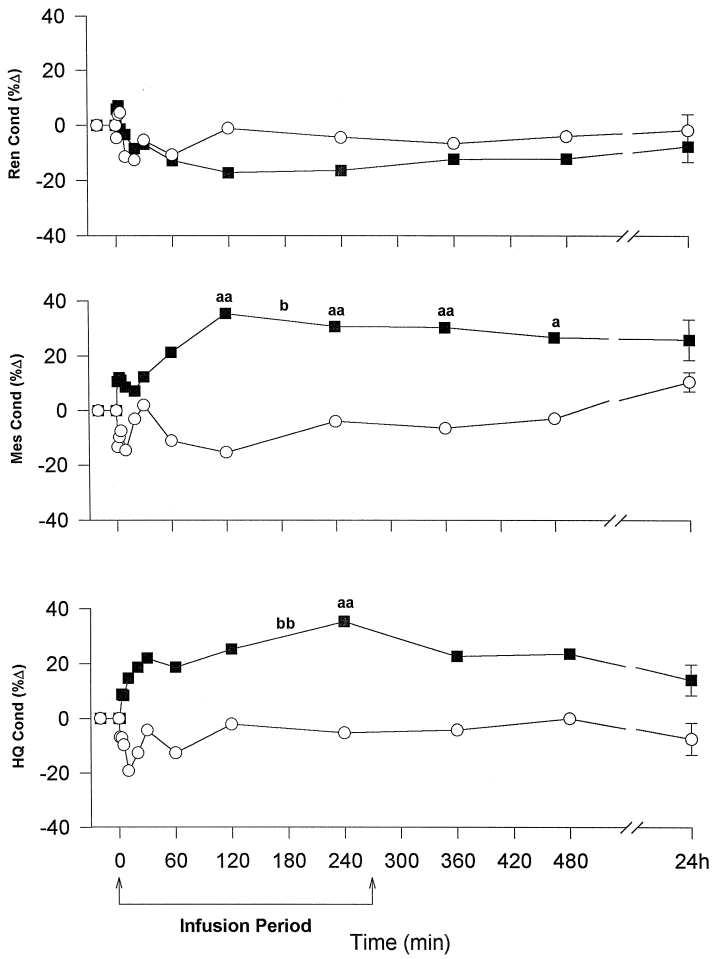

Fig. 4. Time course of changes in Ren, Mes and HQ vascular Cond following infusion of saline (1 ml/kg/h, i.v. for 4.5 h; open circles ($n = 4$)) or the endothelin ET_A/ET_B receptor antagonist, SB 209670 (5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h; triangles ($n = 6$)), in conscious WKY rats. Values are mean with group S.E.M. shown by vertical lines; $^{a}P < 0.05$, $^{aa}P < 0.01$ compared with respective baseline (ANOVA); $^{b}P < 0.05$, $^{bb}P < 0.01$ compared with saline control (ANOVA).

panied by an initial significant tachycardia. Unlike in SHR, however, SB209670 caused a significant decrease in Ren blood flow compared with baseline (max: $-26 \pm 6\%$ at 2 h, $P < 0.01$) (Fig. 3). In addition, there was a significant increase in Mes (max: $+35 \pm 6\%$ at 2 h, $P < 0.01$) and HQ (max: $+35 \pm 3\%$ at 4 h, $P < 0.01$) vascular Cond compared with baseline. Ren Cond tended to decrease, but this effect was on the borderline of significance ($P = 0.06$)

Table 1
Baseline cardiovascular variables for SHR and WKY rat groups prior to infusion of SB 209670

Variable	SHR (high dose infusion) ($n = 7$)	SHR (low dose infusion) ($n = 8$)	SHR (saline infusion) ($n = 8$)	SHR (total) ($n = 17$)	WKY (total) ($n = 6$)
MAP (mm Hg)	159 ± 4	160 ± 7	164 ± 6	162 ± 3^{aa}	111 ± 5
HR (beats/min)	335 ± 6	376 ± 13	331 ± 12	357 ± 8	340 ± 17
Ren DS (kHz)	4.4 ± 0.8	6.2 ± 0.8	4.3 ± 0.6	5.3 ± 0.5	7.6 ± 1.3
Mes DS (kHz)	6.4 ± 0.8	6.3 ± 0.8	5.9 ± 0.7	6.1 ± 0.5	7.2 ± 0.5
HQ DS (kHz)	2.9 ± 0.5	2.4 ± 04	2.7 ± 0.5	2.5 ± 0.3	2.7 ± 0.3
Ren Cond ((kHz/mm Hg) $\times 10^3$)	27 ± 5	39 ± 4	26 ± 4	33 ± 3^{aa}	72 ± 15
Mes Cond ((kHz/mm Hg) $\times 10^3$)	40 ± 5	40 ± 6	36 ± 4	38 ± 3^{aa}	65 ± 6
HQ Cond ((kHz/mm Hg) $\times 10^3$)	18 ± 3	16 ± 3	17 ± 4	16 ± 2^{aa}	25 ± 3

$^{aa}P < 0.01$ for pooled SHR vs. WKY group (Student's unpaired t-test).

Table 2
Effect of the endothelin ET_A/ET_B receptor antagonist, SB 209670, on regional haemodynamic responses to endothelin-1 in conscious SHRs

Variable[a]	SB 209670 (5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h ($n = 7$))				
	Pre	30 min	2 h	4 h	24 h
MAP — depressor (AOC)	7 ± 5	0 ± 0	0 ± 0	0 ± 0	13 ± 9
MAP — pressor (AUC)	463 ± 61	160 ± 68[b]	386 ± 111	546 ± 153	422 ± 104
HR — tachycardia (AUC)	290 ± 134	29 ± 26[b]	2 ± 1[b]	0 ± 0[b]	64 ± 51
HR — bradycardia (AOC)	198 ± 99	156 ± 60	252 ± 93	472 ± 178	475 ± 100
Ren DS (AOC)	649 ± 56	148 ± 66[c]	144 ± 32[c]	209 ± 101[c]	812 ± 104
Mes DS (AOC)	365 ± 71	273 ± 87	239 ± 93	349 ± 135	530 ± 134
HQ DS — dilatation (AUC)	178 ± 78	18 ± 8[b]	19 ± 8[b]	55 ± 41	274 ± 75
HQ DS — constriction (AOC)	164 ± 67	193 ± 97	232 ± 117	223 ± 89	124 ± 62
Ren Cond (AOC)	767 ± 104	192 ± 81[c]	271 ± 63[c]	390 ± 165[b]	949 ± 123
Mes Cond (AOC)	516 ± 69	334 ± 111	437 ± 135	585 ± 193	682 ± 155
HQ Cond — dilatation (AUC)	106 ± 30	20 ± 9[c]	13 ± 6[c]	10 ± 7[c]	155 ± 52
HQ Cond — constriction (AOC)	272 ± 90	220 ± 127	379 ± 158	436 ± 157	263 ± 122

[a]AUC/AOC units are defined as: MAP (mm Hg min), HR (beats), DS (kHz min) and Cond ((kHz min/mm Hg) × 10^3).
[b]$P < 0.05$ vs. the control response to endothelin-1 (ANOVA).
[c]$P < 0.01$ vs. the control response to endothelin-1 (ANOVA).

compared with its own baseline (Fig. 4). Saline infusion had virtually no effect on all haemodynamic variables and SB 209670-induced changes were significantly different from saline infusion for all variables except the Ren flow and Cond.

3.2. Effect of SB 209670 on endothelin-1

Endothelin-1 (300 ng/kg, i.v.) given prior to SB 209670 resulted in a characteristic depressor followed by significant pressor response in SHR, while there was minimal depressor response in WKY. In both strains, Ren and Mes blood flows and Cond were markedly decreased, while there was transient vasodilatation (measured as AUC) followed by vasoconstriction (measured as AOC) in the HQ. The cardiovascular effects of endothelin-1 were highly reproducible when tested over a 24-h period in SHR and WKY infused with saline (data not shown).

In SHR, SB 209670 (5 mg/kg/h) significantly blocked the pressor responses to endothelin-1 given 30 min after commencement of antagonist infusion. The depressor response to endothelin-1 was quite variable and was absent throughout the infusion period, but the AOC analysis did not reach statistical significance. The Ren and HQ (vasodilator component) flows and Cond as well as the tachycardic responses to endothelin-1 were significantly attenuated throughout the infusion period, but had returned to control levels by 24 h (Table 2). The haemodynamic responses to endothelin-1 were much less affected by the low-dose infusion regimen of SB 209670 (1 mg/kg/h), since regional vasoconstriction was only attenuated at 30 min and not thereafter (data not shown).

Table 3
Effect of the endothelin ET_A/ET_B receptor antagonist, SB 209670, on regional haemodynamic responses to endothelin-1 in conscious WKY rats

Variable[a]	SB 209670 (5 mg/kg + 5 mg/kg/h, i.v. for 4.5 h ($n = 6$))				
	Pre	30 min	2 h	4 h	24 h
MAP — depressor (AOC)	2 ± 2	2 ± 1	1 ± 0	0 ± 0	0 ± 0
MAP — pressor (AUC)	224 ± 36	72 ± 24[b]	81 ± 39[b]	164 ± 40	225 ± 58
HR — tachycardia (AUC)	18 ± 12	23 ± 15	31 ± 17	0 ± 0	12 ± 8
HR — bradycardia (AOC)	510 ± 153	9 ± 8[c]	148 ± 89[b]	199 ± 53	858 ± 150
Ren DS (AOC)	532 ± 120	252 ± 94[b]	105 ± 50[c]	262 ± 87[b]	428 ± 95
Mes DS (AOC)	287 ± 57	112 ± 47	160 ± 80	314 ± 80	393 ± 116
HQ DS — dilatation (AUC)	132 ± 71	78 ± 65	25 ± 15	23 ± 4	106 ± 43
HQ DS — constriction (AOC)	134 ± 63	180 ± 86	187 ± 83	226 ± 69	260 ± 120
Ren Cond (AOC)	636 ± 144	263 ± 86[b]	165 ± 85[c]	383 ± 69	523 ± 106
Mes Cond (AOC)	401 ± 70	134 ± 27[b]	126 ± 35[b]	406 ± 76	352 ± 74
HQ Cond — dilatation (AUC)	54 ± 15	14 ± 5[b]	5 ± 3[b]	8 ± 4[b]	25 ± 9
HQ Cond — constriction (AOC)	230 ± 89	187 ± 100	238 ± 92	332 ± 79	397 ± 119

[a]AUC/AOC units are defined as: MAP (mm Hg min), HR (beats), DS (kHz min) and Cond ((kHz min/mm Hg) × 10^3).
[b]$P < 0.05$ vs. the control response to endothelin-1 (ANOVA).
[c]$P < 0.01$ vs. the control response to endothelin-1 (ANOVA).

In WKY, SB 209670 infusion significantly inhibited the pressor response as well as the Ren flow and Ren, Mes and HQ (vasodilatation) Cond responses caused by endothelin-1, all of which had returned to control levels by 24 h (Table 3).

4. Discussion

In the present study, we have demonstrated that intravenous infusion of SB 209670 attenuated the haemodynamic responses to endothelin-1 and caused a significant decrease in blood pressure in both SHR and WKY rats, although this effect was more pronounced in the hypertensive animals. Moreover, there were differences in the regional haemodynamic profiles caused by SB 209670 in the two strains.

The regional haemodynamic changes associated with the cardiovascular effects of SB 209670 in SHR and WKY have not previously been determined, although Douglas et al. (1995b) showed that SB 209670 decreased total peripheral resistance in SHR. In this study, we have shown that in SHR, SB 209670 caused a marked generalised vasodilatation, i.e., increased Ren, Mes and HQ vascular Cond. However, it appears that the Ren and HQ vasculatures are particularly important as vasodilatation persisted up to 3.5 h after cessation of the high-dose infusion regimen, whereas Mes Cond had returned to relatively normal levels at this time. Moreover, the low-dose SB 209670 caused a relatively selective HQ vasodilatation. Thus, these results extend previous studies which have found that endothelin receptor antagonists lower blood pressure in both hypertensive and normotensive rats (Ohlstein et al., 1993; Douglas et al., 1994a, 1995b; Bird et al., 1995; Gardiner et al., 1995, 1996). While no other haemodynamic studies using SHR are available for comparison, similar effects of this endothelin receptor antagonist have been noted by Gardiner et al. (1995) in transgenic ((mRen-2)27) hypertensive rats.

By contrast, i.v. infusion of SB 209670 (5 mg/kg/h) in WKY rats caused a different haemodynamic profile compared with SHR. SB 209670 caused a small, but significant fall in blood pressure and a small tachycardia throughout the infusion period. Ren blood flow and Cond were decreased compared with baseline during the treatment, while Mes and HQ flows and Cond were increased compared to both baseline and saline infusion. This finding is similar to that seen in conscious, normotensive rats, in which SB 209670 caused a significant fall in blood pressure and Ren Cond, while Mes Cond was elevated (Gardiner et al., 1996). Moreover, we also found that the Mes vasodilatation was more prolonged in WKY rats compared with SHRs.

The reason for different Ren haemodynamic effects of SB 209670 in SHR and WKY rats may involve a balance between the various endothelin receptor subtypes. Given that SB 209670 caused Ren vasodilatation in SHR, it is reasonable to assume the overriding importance of vasoconstrictor effects of endothelin-1 in this strain. Endothelin ET_A and ET_B receptors mediating contraction of isolated Ren arteries obtained from SHR and WKY rats have been described (Seo and Luscher, 1995). However, a predominant role for endothelin ET_A receptors is implicated since the endothelin ET_A receptor antagonist BQ-123 increased Ren blood flow in conscious SHR, and this effect was similar in magnitude to that evoked by the endothelin ET_A/ET_B receptor antagonist bosentan (Hocher et al., 1996). Interestingly, in another haemodynamic study using anaesthetized rats, BQ-123 caused systemic vasodilatation which was more prolonged in the Ren and HQ, compared with Mes, vasculature beds (Bigaud and Pelton, 1992) — a situation analogous to the differential time-courses we observed in SHR with SB 209670.

On the other hand, tonic vasodilatation via endothelial ET_B receptors is thought to play a role in basal Ren vascular tone in normotensive rats, since the endothelin ET_B receptor antagonists, Gly–Asn–Trp–His–Gly–Thr–Ala–Pro–Asp–Trp–Phe–Phe–Asn–Tyr–Tyr–Trp (RES-701-1) (Gellai et al., 1996) and *N-cis*-2,6-Dimethylpiperidinocarbonyl-L-gamma-methylleucyl-D-1-methoxycarbonyltrptophanyl-D-Nle (BQ-788) (Matsuura et al., 1997), caused Ren vasoconstriction. Alternatively, blockade of endothelin ET_B receptors may unmask endothelin ET_A receptor-mediated Ren vasoconstriction (Matsuura et al., 1997). This possibility seems unlikely since, in the present study, SB 209670 also exerted a similar Ren effect to the endothelin ET_B antagonists, while endothelin ET_A receptor antagonists generally exerted negligible Ren effects in normotensive rats (Gellai et al., 1996; Matsuura et al., 1997). Therefore, it is feasible that a preferential effect of SB 209670 to block endothelial, as opposed to vascular, endothelin ET_B receptors, would favour a Ren vasoconstrictor effect of this antagonist in normotensive rats. This would require SB 209670 to have a greater affinity for endothelial ET_B receptors and endothelial ET_B receptors to be of greater importance than vascular smooth muscle endothelin ET_A/ET_B receptors in regulating Ren vascular tone in WKY rats. Importantly, we found that SB 209670 more readily attenuated the depressor and HQ vasodilator responses to exogenous endothelin-1 than the pressor and HQ vasoconstrictor responses and Douglas et al. (1995a) reported that SB 209670 attenuated endothelin-1-mediated carotid vasodilatation at 10-fold lower doses than carotid vasoconstriction; all of which suggests that this compound preferentially inhibited endothelin ET_B receptor-mediated vasodilatation. Furthermore, a greater role for vasodilator endothelin ET_B receptors in isolated arteries (e.g., Ren) from WKY rats compared with SHR has been identified (Seo and Luscher, 1995; Montagnani et al., 1999).

Therefore, it is likely that differences in receptor populations/density in the Ren vasculature between the two strains account for the differential haemodynamic effects

of SB 209670. It is also possible that differential tissue distribution of endothelin-1 may contribute to the observed effects. However, endothelin-1 is not overexpressed in the vasculature of SHR compared with WKY rats, although the local generation of endothelin-1 may differ between blood vessels (Haynes and Webb, 1998; Schiffrin, 1998).

In the present study, we also determined the degree of functional blockade of the responses to endothelin-1 in order to correlate functional endothelin-1 blockade with the haemodynamic effects of SB 209670. Infusion of SB 209670 blocked the endothelin-1-mediated pressor response in both SHRs and WKY rats. In addition, the Ren vasoconstrictor (flow/Cond) and HQ vasodilator (Cond) responses to endothelin-1 were markedly attenuated by SB 209670 in both SHRs and WKY rats, while the Mes vasoconstrictor (Cond) effect was blocked in only WKY rats. These data are consistent with the greater Mes vasodilatation in WKY rats evoked by SB 209670 per se and suggest that the Mes vasculature in WKY rats is more sensitive to blockade by SB 209670 of endothelin receptors. In this context, Gardiner et al. (1994a) reported that the endothelin receptor antagonist, bosentan, potentiated the initial vasoconstriction evoked by endothelin-1, but inhibited the delayed maximum response in the mesentery, suggesting complex interactions in this vascular bed. Alternatively, it is feasible that in the Mes vasculature of SHR, there is a third type of receptor which mediates vasoconstriction and is antagonised to a lesser extent by SB 209670. Whatever the explanation, these inhibitory effects of SB 209670 are consistent with the haemodynamic effects of SB 209670 in SHR, since the vasodilator response to SB 209670 appeared to be more prolonged in the Ren and HQ vasculatures than in the Mes circulation.

In summary, we have demonstrated that the infusion of the endothelin ET_A/ET_B endothelin receptor antagonist, SB 209670, exhibits a differential haemodynamic profile in SHR and WKY rats. It has a marked antihypertensive effect in conscious SHR which is in support of other studies; however, we have shown that this effect is mediated by a generalised vasodilatation in the Ren, Mes and HQ vasculatures in SHR. In addition, we have observed that in normotensive control WKY rats, SB 209670 also had a slight hypotensive effect which was accompanied by a different regional haemodynamic profile. In this case, there was significant vasodilatation in the mesentery and HQ as in SHR; however, in WKY rats, there was significant Ren vasoconstriction throughout the infusion period which may have served to offset the fall in blood pressure. SB 209670 inhibited haemodynamic responses to endothelin-1 recorded in both SHR and WKY, demonstrating a functional blockade of endothelin receptors by the antagonist, except for the response of the Mes vasculature in the hypertensive rats, suggesting a possible difference in sensitivity to antagonism of endothelin receptors in this particular vascular bed, or the possible existence of an as yet unidentified endothelin receptor mediating vasoconstriction in the Mes vasculature. Collectively, these results suggest that endothelin is intricately involved in the maintenance of hypertension in the SHR and the regulation of vascular tone in WKY rats. However, the vascular haemodynamic mechanisms contributing to cardiovascular homeostasis vary between these particular strains.

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