Increased Vasodilator Responsiveness to BRL 34915 in Spontaneously Hypertensive versus Normotensive Rats: Contrast with Nifedipine (42847)

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Abstract. **The blood pressure-lowering potency and activity of BRL 34915, a new vasodilator and putative stimulator of potassium efflux from vascular smooth muscle, was investigated in conscious spontaneously hypertensive rats (SHR) and normotensive rats (NTR) after intravenous administration and compared with that of the calcium channel blocker, nifedipine. In SHR, BRL 34915 (3–100 μg/kg) or nifedipine (10–3000 μg/kg) produced similar reductions in mean arterial pressure of 58 ± 3% and 55 ± 3%, respectively. BRL 34915 ($ED_{30\%}$ = 13.8 μg/kg) was 15.3 times more potent than nifedipine ($ED_{30\%}$ = 207 μg/kg) in SHR. In contrast, only a 1.7-fold difference in potency was observed in NTR between BRL 34915 ($ED_{30\%}$ = 123 μg/kg) and nifedipine ($ED_{30\%}$ = 182 μg/kg). The potency ratio ($ED_{30\%}$ NTR/$ED_{30\%}$ SHR) for BRL 34915 was 8.83 whereas nifedipine had a ratio of 0.88, reflecting the greater responsiveness of the SHR to BRL 34915. Systemic hemodynamics were monitored in anesthetized SHR and NTR to determine the basis for the reductions in blood pressure. BRL 34915 (3–100 μg/kg iv) lowered mean arterial pressure in both groups solely by decreasing total peripheral vascular resistance, since no changes in cardiac output were observed. Relaxation responses were also obtained in phenylephrine-contracted isolated aortic strips from both strains of rat to ascertain whether differences in responsiveness existed at this level of the vasculature. No significant difference in the potency of BRL 34915 (3–10 μM) as a vasodilator was found in aortas from SHR or NTR. These results indicate that, unlike nifedipine, BRL 34915 is a more potent vasodepressor agent in SHR than in NTR and suggests that the potassium efflux stimulator may preferentially relax resistance vessels in the hypertensive rat.** [P.S.E.B.M. 1989, Vol 190]

BRL 34915 is a potent, long-acting vasodilator currently undergoing clinical investigation as an antihypertensive agent (1, 2). Hamilton *et al.* (3) first proposed that BRL 34915 relaxes smooth muscle by a novel mechanism involving the stimulation of potassium efflux from intracellular sites. The extrusion of potassium produces membrane hyperpolarization which, in turn, functionally antagonizes calcium influx through voltage-sensitive calcium channels. In addition to a calcium entry blocking effect, this mechanism can also inhibit the activity of pacemaker cells that influence smooth muscle tone (4). Hemodynamic differences between the activity of BRL 34915 and the calcium slow channel blocker, nifedipine, have been described *in vivo* that may reflect their distinct modes of action. For example, BRL 34915 has been shown to alter regional blood flow distribution in anesthetized cats in a manner different from nifedipine (1). Similarly, BRL 34915 causes less tachycardia in spontaneously hypertensive rats and renal hypertensive cats than does the calcium channel blocker (1). In view of the reported differences that exist between these two vasodilators, the present study compared the potency and activity for lowering blood pressure of BRL 34915 to nifedipine in normotensive rats (NTR) and spontaneously hypertensive rats (SHR). To characterize further the peripheral vascular responsiveness to BRL 34915 in both rat strains, hemodynamic studies were conducted in anesthetized, open-chest rats and relaxation responses were obtained from isolated aortic strips contracted with phenylephrine.

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Materials and Methods

Conscious Rats. Male spontaneously hypertensive rats (SHR) were obtained from Charles River (Kingston), housed in temperature and humidity controlled quarters on a fixed light cycle, and allowed free access to both tap water and standard laboratory rat chow. The animals ranged in weight from 294 to 386 g. Male normotensive rats (NTR) were obtained from Charles River (CD rat; Kingston) and housed and fed in the same manner. These rats ranged in weight from 295 to 480 g.

The effects of BRL 34915 or nifedipine on mean arterial pressure (MAP) and heart rate (HR) were measured via direct cannulation. On the day of the experiment, catheters were implanted into the left carotid artery (PE 50) and the left jugular vein (tygon 0.02 in, inside diameter) of rats under light ether anesthesia. The catheters were exteriorized at the nape of the neck and secured with an adhesive wrap. Animals were then placed in stainless steel restraint cages in a quiet room and allowed at least 90 min of postsurgical recovery before control recordings were collected. Recordings of arterial pressure were obtained using a Statham pressure transducer connected to a Gould 2800 chart recorder and a Buxco Cardiovascular Analyzer. HR was obtained from a rate meter triggered by the arterial pulse wave. MAP and HR were monitored continuously throughout the protocol. A dose-response relationship was obtained by the cumulative administration of increasing quantities of drug in half-log increments to the same animal at 10-min intervals. Drugs were administered as an iv bolus in a volume of 0.1 ml/kg body wt followed by a 0.1 ml flush of 0.9% saline. Stock solutions (10 mg/ml) of BRL 34915 or nifedipine were prepared by solubilizing the drugs in dimethylformamide (10%) and diluting with 5% dextrose in distilled water. Individual doses were then prepared by further dilution of the stock solution with 5% dextrose in water. All drug solutions were prepared fresh daily and used immediately. Nifedipine was routinely shielded from light.

BRL 34915 was administered in cumulative doses of 3, 10, 30, 100, 300, and 1000 μg/kg iv to SHR (n = 5) and NTR (n = 6). In a separate group of rats, nifedipine was administered in cumulative doses of 10, 30, 100, 300, 1000, and 3000 μg/kg iv to SHR (n = 5) and NTR (n = 6). An equivalent volume of vehicle was found to exert negligible effects on MAP and HR. Absolute values for MAP (mm Hg) and HR (beats/min) were determined during the control period and the peak change (absolute units) and percentage of change from the predrug baseline were determined after each cumulative dose. Using the log dose-response curves, the $ED_{30\%}$ (dose of drug that produces a 30% reduction in control arterial blood pressure) was calculated for BRL 34915 or nifedipine in SHR and NTR. Statistical analysis of the data was performed using either Student's t test or an analysis of variance for multiple comparisons. Linear regression analysis was performed by the method of least squares. Effective dose calculations and 95% fiducial limits were determined from the regression analyses. All data are expressed as mean ± SEM.

Hemodynamics in Anesthetized SHR and NTR. The effects of BRL 34915 on ascending aortic flow (an estimate of cardiac output) and total peripheral resistance were measured in open-chest anesthetized SHR and NTR. Rats were anesthetized with sodium pentobarbital (50 mg/kg ip), placed on a prewarmed surgical table, and instrumented with arterial and venous catheters as described previously. A tracheostomy was performed and the rat was connected to a Harvard rodent respirator and ventilated with room air. A midsternal incision (2.5 cm) was made and a rib spreader was inserted. An electromagnetic flow probe (6.0 mm; Carolina Medical Electronics) was placed on the ascending aorta and attached to a square wave electromagnetic flowmeter. Zero flow was ascertained from the pulsatile flow tracing. SHR (n = 6) and NTR (n = 7) were treated with BRL 34915 at 0, 3, 10, 30, 50, 100 μg/kg iv, in a cumulative dosing sequence at 10-min intervals. Changes in MAP, HR, ascending aortic flow (AF), and calculated total peripheral resistance (TPR) were determined. Total peripheral resistance was derived from the quotient of mean arterial pressure and aortic flow. Data are expressed as absolute values and as percentage of change from control.

Isolated Rat Aortic Strips. The smooth muscle relaxant effect of BRL 34915 was assessed in aortas from SHR and NTR contracted with phenylephrine. Male rats were sacrificed by ether asphyxiation. The thoracic aortas were rapidly excised and placed in ice-cold Krebs bicarbonate buffer of the following composition (mM): NaCl, 118.0; KCl, 4.75; $MgSO_4$, 1.18, KH_2PO_4, 1.18; glucose, 11.0; $NaHCO_3$, 25.0; $CaCl_2$, 2.5. Aortas were cut into spiral strips, mounted on glass support rods, and suspended in 10-ml tissue baths of Krebs bicarbonate buffer at 37°C, gassed with 95% O_2/5% CO_2. Tissues were attached to Grass (FT03) transducers and equilibrated under 1-g resting tension for 1 to 2 hr according to the method of Cohen and Berkowitz (5). A dose-response relationship to phenylephrine was established; the agonist was washed out and the tissues were allowed to reequilibrate to basal tension for approximately 1 hr. Tissues were then contracted with a dose of phenylephrine (1 μM) which gave approximately 90% of a maximal contraction and allowed to stabilize for 20 to 30 min. Concentration response curves were established for BRL 34915 using a cumulative dose technique. Data are reported as the percentage of relaxation of agonist-induced tension. The $ED_{50\%}$ (drug concentration causing 50% relaxation) was cal-

culated from the regression lines obtained by the method of least squares. All drugs were delivered to the bath using a Hamilton microliter syringe and recordings were made on a Beckman R612 dynograph. BRL 34915 was dissolved in dimethyl sulfoxide and serial dilutions were prepared with distilled water. Dimethyl sulfoxide was diluted in the same manner for the vehicle treatment.

Drugs. BRL 34915 was synthesized by the Medicinal Chemistry Division of Ortho Pharmaceutical Corporation. Nifedipine and phenylephrine were obtained commercially (Sigma). All other materials were of reagent grade. Doses used in these studies were calculated as the free base.

Results

Dose Response in Conscious Rats. Baseline parameters for MAP, HR, and body weight in conscious SHR and NTR are shown in Table I. Control MAP values were significantly higher in SHR than in NTR. No differences in control MAP were found within SHR receiving BRL 34915 or nifedipine. The same was true for NTR receiving either vasodilator. Control HR values tended to be greater in the SHR than in NTR, but this difference was not significant. Body weights were also similar between the two strains.

In SHR, BRL 34915 and nifedipine produced dose-related reductions in MAP (Fig. 1). These reductions ranged from 9 ± 2% at 3 μg/kg to 58 ± 3% at 100 μg/kg for BRL 34915. MAP declined by 5 ± 1% after 10 μg/kg of nifedipine to 55 ± 3% at 3000 μg/kg. Both vasodilators were equally efficacious in this dose range because no significant difference in their blood pressure-lowering activity was observed. Further administration of BRL 34915 (300–1000 μg/kg) caused additional decrements in MAP (70.1 ± 1.6%, peak effect). However, the limited solubility of nifedipine precluded administering higher doses of this compound to determine whether there were differences in the maximal efficacy of the two vasodilators.

In NTR (Fig. 2), BRL 34915 reduced MAP in a dose-related manner from 5 ± 1% at 3 μg/kg to 47 ± 2% at 1000 μg/kg. Nifedipine (10–3000 μg/kg) reduced MAP by 12 ± 3% to 48 ± 2% in this strain. The two vasodilators were identical in activity and their dose-response relationships were parallel.

The potencies of BRL 34915 and nifedipine as vasodilators, expressed as their $ED_{30\%}$ (iv dose causing a 30% fall in MAP), are shown for both rat strains in Table II. In the SHR, BRL 34915 ($ED_{30\%}$ = 13.8 μg/kg) was 15.3 times more potent than nifedipine ($ED_{30\%}$ = 206.9 μg/kg). In contrast, the values in NTR were similar for BRL 34915 ($ED_{30\%}$ = 121.8 μg/kg) and nifedipine ($ED_{30\%}$ = 181.9 μg/kg) such that the relative potency of BRL 34915 was only 1.7 times that of nifedipine in the normotensive strain. The disparity in potency for BRL 34915 between the SHR and NTR is reflected in its potency ratio ($ED_{30\%}$ NTR:$ED_{30\%}$ SHR). The ratio for BRL 34915 (8.83) is 10-fold higher than the ratio for nifedipine (0.88), emphasizing the difference in responsiveness to these vasodilators in SHR and NTR.

Figure 3 shows the HR effects of BRL 34915 and nifedipine in SHR. Both vasodilators caused variable effects on HR in this strain, particularly at the higher doses. Thus, there were no significant changes in HR in response to increasing intravenous doses of BRL 34915 (3–1000 μg/kg) or nifedipine (10–3000 μg/kg). In the NTR (Fig. 4), small elevations in HR occurred in response to the higher doses of BRL 34915 (100–1000 μg/kg). Nifedipine tended to produce mild bradycardia in the NTR at doses ranging from 30–1000 μg/kg iv. This effect was not dose related. At the highest dose of nifedipine (3000 μg/kg), significant bradycardia was noted (48.8 ± 7.4%).

Effect of BRL 34915 on Hemodynamics in SHR and NTR. The effects of BRL 34915 (3–100 μg/kg iv) on MAP, HR, AF, and TPR in open-chest, anesthetized rats are presented in Table III. After surgery, the open-chest rats had lower baseline values for MAP than conscious rats (conscious SHR = 203 ± 6 mm Hg; anesthetized open-chest SHR = 160 ± 10 mm Hg). In the open-chest preparation, BRL 34915 was significantly more potent as a vasodilator in SHR ($ED_{20\%}$ = 16 (10–22) μg/kg iv) than in NTR ($ED_{20\%}$ = 50 (44–267) μg/kg iv). These findings are consistent with the potency differences found in conscious rats. In open-chest anesthetized SHR, BRL 34915 caused reductions in MAP ranging from 2.8 ± 2.1% at 3 μg/kg to 52.9 ±

Table I. Control Values for Body Weight, MAP, and HR in Conscious SHR and NTR[a]

Group	Treatment	N	Body weight (g)	MAP (mm Hg)	HR (beats/min)
NTR	BRL 34915	6	387 ± 31	117.7 ± 2.6	374.7 ± 13.6
	Nifedipine	6	366 ± 28	116.1 ± 3.8	383.0 ± 21.4
SHR	BRL 34915	5	353 ± 16	203.5 ± 6.4*	423.2 ± 17.7
	Nifedipine	5	372 ± 5	202.0 ± 5.5*	423.2 ± 12.0

[a] Data are expressed as mean ± SEM.
*$P < 0.05$ vs NTR.

2.3% at 100 μg/kg. In NTR, BRL 34915 reduced MAP from 5.3 ± 2.1% at 3 μg/kg to 21.4 ± 3.9% at 100 μg/kg. Heart rate was unaffected by BRL 34915 in the open-chest SHR. Significant tachycardia was apparent in NTR at a single dose of BRL 34915 (50 μg/kg iv). Baseline AF was similar in the two groups of rats (SHR = 64 ± 14 ml/min; NTR = 61 ± 7 ml/min) and BRL 34915 had no effect on AF in these rats at the doses tested. Control values for TPR were significantly higher in SHR vs NTR (3.0 ± 0.6 vs 1.7 ± 0.3 mm Hg/ml/min). TPR fell in both groups of rats in response to BRL 34915. However, the magnitude of the changes in TPR was greater in the SHR. Since AF, an estimate of cardiac output, did not change in response to BRL 34915, the reductions in MAP in both groups were solely attributable to the parallel decline in calculated TPR.

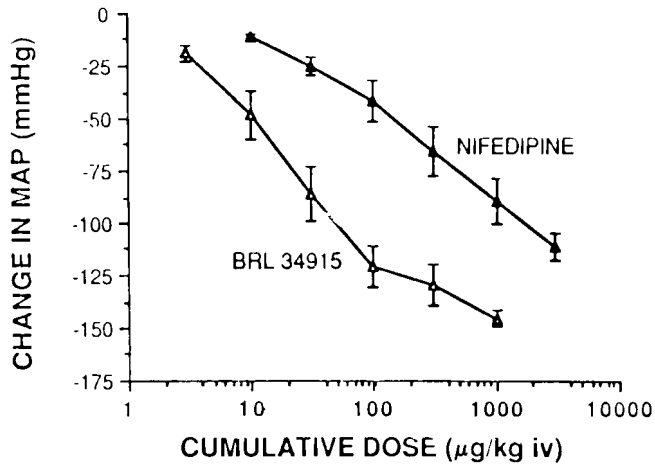

Figure 1. Log dose-response curve for changes in MAP in conscious SHR treated with cumulative doses of BRL 34915 (3–1000 μg/kg iv) (Δ, $n = 5$) or nifedipine (10–3000 μg/kg iv) (▲, $n = 5$).

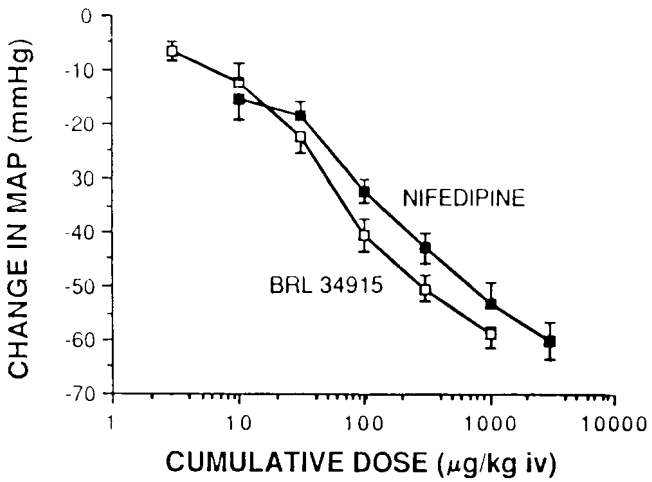

Figure 2. Log dose-response curve for changes in MAP in conscious NTR treated with cumulative doses of BRL 34915 (3–1000 μg/kg iv) (□, $n = 6$) or nifedipine (10–3000 μg/kg iv) (■, $n = 6$).

Isolated Rat Aortic Strips. Comparable submaximal increases in tension were elicited with 1 μ*M* phenylephrine in strips from SHR and NTR (Table IV). BRL 34915 (0.003–10 μ*M*) produced concentration-dependent relaxation of contracted tissues (Fig. 5). No significant difference in the potency ($ED_{50\%}$) of BRL 34915 was discernible in aortic strips from SHR and NTR (Table IV). Thus, at this level of the vasculature, the sensitivity to BRL 34915 was similar between the two strains. Interestingly, BRL 34915 tended to produce slightly greater than 100% relaxation of aortas from SHR, suggesting a greater propensity for the compound to influence basal tone in vessels from this strain.

Discussion

This study has shown that the potassium efflux stimulator, BRL 34915, is a potent blood pressure-lowering agent by the iv route in conscious SHR, in which it is approximately 15 times more potent than the calcium channel blocker, nifedipine. Interestingly, a much smaller difference in potency is observed between these two vasodilators in conscious NTR. Thus, BRL 34915 is only 1.7 times more potent than nifedipine in the normotensive strain. The ratio of doses causing a 30% reduction in MAP in both strains (i.e., $ED_{30\%}$ NTR:$ED_{30\%}$ SHR) is 8.83 for BRL 34915 and 0.88 for nifedipine, which reflects a 10-fold greater responsiveness to the BRL compound in SHR relative to NTR. Other investigators have previously shown that BRL 34915 is 10–30 times more potent than nifedipine in lowering arterial blood pressure after oral administration in SHR and other hypertensive models (1, 6), with which our findings are consistent. In addi-

Table II. Comparative Potencies of BRL 34915 and Nifedipine in Conscious SHR and NTR

Group	Treatment	Potency $ED_{30\%}$[a] (μg/kg)	Relative potency[b]	Ratio[c]
SHR	BRL 34915	13.8 (6.4–22.4)[d]	15.3 (5.9–40.8)	8.83
	Nifedipine	206.9 (136.6–318.5)	1	0.88
NTR	BRL 34915	121.8 (83.5–203.5)	1.7 (1.1–2.9)	
	Nifedipine	181.9 (138.7–239.1)	1	

[a] Dose lowering MAP by 30%.
[b] Nifedipine assigned a relative potency of 1.
[c] $ED_{30\%}$ NTR/$ED_{30\%}$ SHR.
[d] Numbers in parentheses denote 95% fiducial limits.

tion, Cook *et al.* (7) reported similar intravenous blood pressure-lowering doses for BRL 34915 in NTR as confirmed in our study.

No differences in peak blood pressure-lowering activity were discerned between BRL 34915 and nifedipine in either strain of rat within the limits of solubility of nifedipine. The effects of both vasodilators on HR were highly variable in our studies, but no significant differences in HR were noted between BRL 34915 and nifedipine in the SHR. Buckingham *et al.* (1) observed that BRL 34915 produced transient, dose-related tachycardia in conscious SHR after oral administration. In conscious renal hypertensive cats, an equiactive dose of BRL 34915 tended to produce less tachycardia than nifedipine, although similar increases in rate were observed with either vasodilator in renal hypertensive dogs (1). The increase in HR evoked by BRL 34915 appears to be mediated by the activation of baroreceptor reflexes since it can be abolished by pretreatment with a β receptor antagonist (1).

Results from hemodynamic studies conducted in anesthetized, open-chest SHR and NTR show that the reductions in MAP produced by BRL 34915 are the results of parallel decrements in total peripheral vascular resistance, since no significant changes in cardiac output (measured as ascending aortic blood flow) are observed. This finding suggests that the basis for the differential effect of BRL 34915 may reside in greater responsiveness of the resistance vessels of the SHR vs the NTR. Whether there is a uniform increase in the responsiveness of all vascular beds of the SHR or a preferential effect of the BRL compound on selected vascular beds (i.e., a redistribution of cardiac output) remains to be elucidated in this model. No evidence for

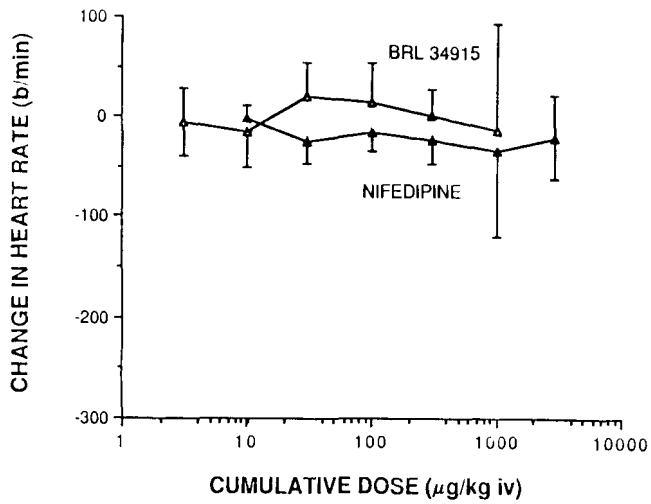

Figure 3. Log dose-response curve for changes in HR in conscious SHR treated with cumulative doses of BRL 34915 (3–1000 μg/kg iv) (Δ, $n = 5$) or nifedipine (10–3000 μg/kg iv) (▲, $n = 5$).

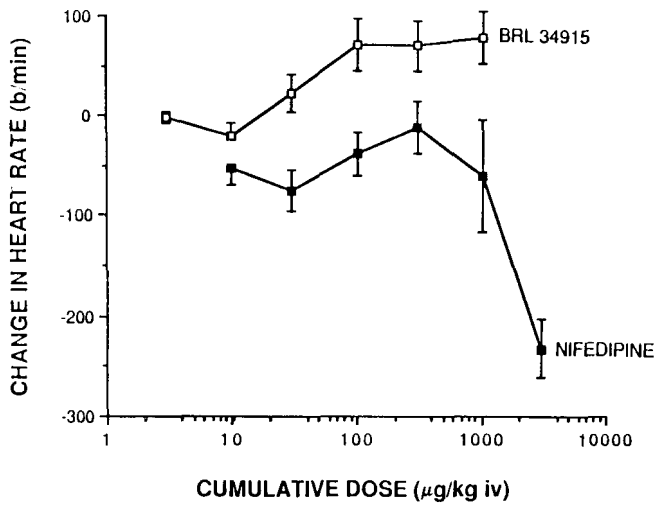

Figure 4. Log dose-response curve for changes in HR in conscious NTR treated with cumulative doses of BRL 34915 (3–1000 μg/kg iv) (□, $n = 6$) or nifedipine (10–3000 μg/kg iv) (■, $n = 6$).

Table III. Effect of BRL 34915 on MAP, HR, AF, and TPR in Anesthetized Open-Chest Rats[a]

BRL 34915 (μg/kg iv)	MAP (mm Hg)	HR (beats/min)	AF (ml/min)	TPR (mm Hg/ml/min)
SHR ($n = 6$)				
Control	159.5 ± 9.5	426 ± 15	63.7 ± 13.6	3.04 ± 0.56
3	155.5 ± 11.5	412 ± 15	64.7 ± 13.7	2.88 ± 0.51
10	136.8 ± 7.2	428 ± 15	65.5 ± 14.2	2.64 ± 0.53
30	132.2 ± 14.4*	430 ± 15	61.7 ± 12.1	2.38 ± 0.30
50	95.0 ± 3.8*	435 ± 18	63.3 ± 11.5	1.70 ± 0.23*
100	74.7 ± 4.3*	439 ± 20	61.0 ± 11.8	1.41 ± 0.21*
NTR ($n = 7$)				
Control	96.0 ± 2.4†	436 ± 21	60.7 ± 6.6	1.74 ± 0.25†
3	92.0 ± 2.5	444 ± 22	63.7 ± 6.7	1.58 ± 0.22
10	93.4 ± 3.7	454 ± 20	64.7 ± 6.9	1.60 ± 0.25
30	85.7 ± 2.5*	477 ± 25	64.1 ± 6.9	1.48 ± 0.23
50	86.8 ± 3.1	513 ± 17*	60.8 ± 8.9	1.53 ± 0.25
100	76.4 ± 4.2*	499 ± 27	60.6 ± 6.8	1.36 ± 0.16

[a] Data are expressed as mean ± SEM.
* $P < 0.05$ vs control.
† $P < 0.05$ vs SHR at baseline.

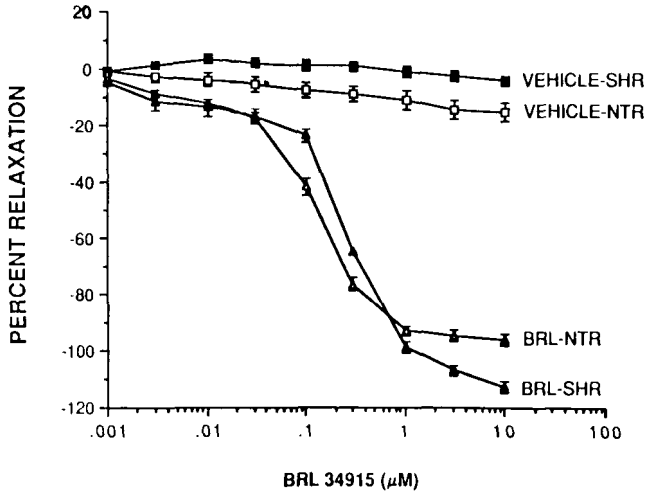

Figure 5. Effect of BRL 34915 on relaxation in phenylephrine-contracted rat aortic strips from SHR and NTR. Tissues were equilibrated at 1 g of basal tension and contracted with 1 μM phenylephrine. BRL 34915 (SHR, ▲; NTR, Δ) or equal volumes of vehicle (SHR, ■; NTR, □) were administered in cumulative doses of 0.003–10 μM.

Table IV. Effect of BRL 34915 on Phenylephrine-Contracted Rat Aortic Strips

Group	*N*	Baseline tension (g)	Relaxant potency[a] $ED_{50\%}$ (μM)
NTR	6	0.79 ± 0.32	0.117 (0.091–0.157)
SHR	5	0.74 ± 0.28	0.213 (0.155–0.276)

[a] $ED_{50\%}$ = drug concentration producing 50% relaxation of active tension; numbers in parentheses are 95% fiducial limits.

a generalized increase in vasodilator responsiveness to BRL 34915 was found in vessels from SHR relative to NTR because no difference in the potency of BRL 34915 to induce relaxation was observed in isolated, phenylephrine-contracted aortic strips from either strain of rat. Buckingham *et al.* (1) found in the anesthetized cat that BRL 34915 produced a vasodilator profile unlike that of nifedipine by increasing blood flow to the renal and carotid vascular beds. Certain vascular beds of the SHR may be disproportionately more responsive to BRL 34915 as has been shown for nifedipine (8).

Both nifedipine and BRL 34915 are vasodilators with the ability to antagonize calcium entry into vascular smooth muscle through voltage-sensitive channels. This common action may be responsible for the coronary vasodilator and antihypertensive properties shared by both compounds. However, the mechanisms by which they antagonize calcium entry into smooth muscle are different. Nifedipine binds to sites at the calcium channel and blocks the movement of calcium ions into the cell when activated by changes in membrane potential (9). BRL 34915 is believed to selectively open potassium channels in smooth muscle causing the efflux of potassium ions from the intracellular space, leading to changes in membrane potential (i.e., hyperpolarization). This, in turn, reduces the open state of voltage-dependent calcium channels and antagonizes calcium entry. Increases in resting membrane potential, stimulation of ^{86}Rb efflux, inhibition of ^{45}Ca influx, and decreases in vascular smooth muscle tone have all been measured in the presence of BRL 34915 (4, 7, 10, 11). Differences in resting membrane potential or differences in ion channel characteristics between SHR and NTR might selectively predispose the SHR peripheral vasculature to the influence of BRL 34915 and preferentially reduce elevated myogenic tone. In support of this contention, it was found that resting membrane potential in the superior mesenteric artery of the SHR is decreased (i.e., more depolarized) relative to its normotensive counterpart, which could contribute to an increased sensitivity to agents affecting voltage-operated calcium channels (12).

It has recently been reported (13) that the vasodilators pinacidil (7), minoxidil sulfate (14, 15) and nicorandil (16) also possess the ability to stimulate potassium efflux from smooth muscle cells in a manner similar to that of BRL 34915. It remains to be determined whether they might also have a differential profile similar to that of BRL 34915 in SHR and NTR. Despite some similarities in their mechanisms of action, these vasodilators are known to have differences in potency, regional vascular selectivity, and duration of action, suggesting that potassium efflux stimulators are a heterogeneous class of vasodilators (17, 18). The basis for these differences is an area for further research.

We have found that the novel vasodilator BRL 34915 is a potent intravenous blood pressure-lowering agent in conscious SHR. Furthermore, it displays greater potency in SHR than NTR, in contrast to nifedipine which is approximately equipotent in both strains of rat. The vasodilator activity appears to be mediated by a reduction in total peripheral vascular resistance since the drug did not alter cardiac output. No difference in the potency of BRL 34915 as a vasodilator was discerned in aortic strips from SHR and NTR, which suggests that relaxation of larger vessels is not responsible for the increased potency of the compound in the SHR. These results raise the possibility that the smaller resistance vessels which maintain elevated blood pressure in SHR are more responsive to BRL 34915 than their counterparts in the NTR. Although the basis for this difference remains to be fully elucidated, fundamental differences in the mechanism of action of these two compounds (i.e., K^+ efflux stimulation vs calcium channel blockade) may be responsible.

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