British Journal of Pharmacology (1996) 118, 325-334 

# Regional haemodynamic effects of antagonists of angiotensin II, endothelin and adrenoceptors in conscious, vasopressin-deficient, genetically hypertensive rats

[1]S.M. Gardiner, J.E. March, P.A. Kemp & T. Bennett

Department of Physiology & Pharmacology, University of Nottingham Medical School, Queen's Medical Centre, Nottingham NG7 2UH

**1** Male, vasopressin-deficient, normotensive (DI/N) and hypertensive (DI/H) rats were chronically instrumented (all surgery under sodium methohexitone anaesthesia) to allow assessment of resting haemodynamic status and responses to antagonism of $AT_1$-receptors (Experiment 1), $ET_A$- and $ET_B$-receptors (Experiment 2) or adrenoceptors (Experiment 3).

**2** Before any treatment, mean arterial blood pressure (MAP) was higher, and hindquarters vascular conductance was consistently lower in all groups of DI/H rats than in DI/N rats.

**3** In Experiment 1, losartan (10 mg $kg^{-1}$ i.v.), an $AT_1$-receptor antagonist, was given 5 h after s.c. injection of saline, (DI/N, $n=8$; DI/H, $n=8$) or hyperoncotic polyethylene glycol, (DI/N, $n=9$; DI/H, $n=9$) to induce isosmotic hypovolaemia. In the volume-replete state, losartan caused similar small falls in MAP in the two groups (maximum Δ MAP; DI/N, $-9\pm2$; DI/H, $-15\pm5$ mmHg), but the mesenteric and hindquarters vasodilatations were greater in DI/N rats. In the volume-depleted state the effects of losartan were augmented (Δ MAP; DI/N, $-32\pm3$; DI/H. $-31\pm3$ mmHg), but its vasodilator effects were still greater in DI/N than in DI/H rats.

**4** In Experiment 2, infusion of the $ET_A$-$ET_B$-receptor antagonist, SB 209670 (600 μg $kg^{-1}$ $h^{-1}$; DI/N, $n=8$; DI/H, $n=9$), had haemodynamic effects that were not different from those during saline infusion in DI/N ($n=7$) and DI/H rats ($n=8$).

**5** In Experiment 3, sequential administration of the $\beta_2$-adrenoceptor antagonist, ICI 118551 (0.2 mg $kg^{-1}$ bolus, 0.1 mg $kg^{-1}$ $h^{-1}$ infusion), the $\alpha_2$-adrenoceptor antagonist, idazoxan (0.75 mg $kg^{-1}$ bolus, 1 mg $kg^{-1}$ $h^{-1}$ infusion), and losartan (10 mg $kg^{-1}$ bolus) had only slight haemodynamic effects in DI/N ($n=8$) and DI/H ($n=9$) rats. Subsequent administration of the $\alpha_1$-adrenoceptor antagonist, prazosin (0.5 mg $kg^{-1}$ bolus, 0.8 mg $kg^{-1}$ $h^{-1}$ infusion) caused marked hypotension, although MAP was still higher in DI/H ($95\pm4$ mmHg) than in DI/N ($75\pm4$ mmHg) rats. However, in this circumstance there were no significant differences between renal, or mesenteric, or hindquarters vascular conductances in the two groups.

**6** The results indicate that the hypertension and hindquarters vasoconstriction in DI/H rats is not dependent on AII or endothelin. Moreover, the relative elevation in MAP in DI/H persists in the presence of antagonism of $\beta_2$, $\alpha_2$- and $\alpha_1$-adrenoceptors, in spite of no significant difference in regional vascular conductances.

**Keywords:** Vasopressin-deficient hypertensive rats; angiotensin II; endothelin; adrenoceptors

## Introduction

There has been much discussion about the possible involvement of vasopressin in the genesis and maintenance of hypertension (e.g., Share & Crofton, 1982; Sharabi & Schmid, 1983). Reports that vasopressin-deficient, Brattleboro rats did not show an increase in arterial blood pressure in response to deoxycorticosterone acetate and salt loading (Crofton *et al.*, 1979; Berecek *et al.*, 1982) were interpreted as evidence for an involvement of vasopressin in this model of experimental hypertension. However, the subsequent demonstration that hypertension occurred in the absence of vasopressin in animals obtained from cross-breeding Brattleboro and Okamoto hypertensive rats (Ganten *et al.*, 1983), or New Zealand hypertensive rats (Ashton & Balment, 1989), indicated that vasopressin was not indispensible to the development or maintenance of blood pressure in these animals, but the factors contributing to the hypertension are unknown.

Under water-replete conditions, vasopressin-deficient, homozygous Brattleboro rats maintain a normal cardiovascular status without reliance on the renin-angiotensin system (RAS) (Gardiner & Bennett, 1985; 1986; Gardiner *et al.*, 1989). However, following water deprivation, or hypovolaemia induced by subcutaneous injection of a hyperoncotic solution of polyethylene glycol (PEG), the maintenance of systemic arterial blood pressure becomes abnormally dependent on the RAS (Gardiner & Bennett, 1985; 1986; Gardiner *et al.*, 1989; Muller *et al.*, 1990; Batin *et al.*, 1991a,b). These observations, together with the finding that vasopressin-deficient, genetically hypertensive rats (DI/H; obtained by cross-breeding male New Zealand hypertensive rats with female Brattleboro rats (Ashton & Balment, 1989) have higher plasma angiotensin II (AII) levels than their normotensive controls (DI/N; Al-Barazanji & Balment, 1995), raise the possibility that the maintenance of hypertension in the DI/H rat is due to hyperactivation of the RAS. However, in such a case it does not follow that the elevation in blood pressure would be dependent, directly, on the vasoconstrictor action of angiotensin II. For example, recently we found that transgenic ((mRen-2)27) hypertensive rats, with increased expression of tissue RAS (Mullins *et al.*, 1990), showed marked hypotensive and vasodilator responses to the non-selective endothelin (ET) antagonist, SB 209670

[1] Author for correspondence.

(Gardiner *et al.*, 1995). These observations are consistent with the ability of AII to stimulate the synthesis and release of ET (Emori *et al.*, 1991; Imai *et al.*, 1992; Kohno *et al.*, 1991; 1992), and the synergism between the vascular actions of the two peptides (Yoshida *et al.*, 1992; Dohi *et al.*, 1992; Chen *et al.*, 1995).

Even in models of experimental hypertension in which important contributions from AII and ET can be demonstrated (Gardiner *et al.*, 1995), other factors may also be involved. In this respect it is notable that mesenteric microvessels, isolated from DI/H rats, and studied in a pressure myograph, showed increased sensitivity to noradrenaline, together with signs of vascular remodelling (Dunn & Gardiner, 1995).

Against this background, in the present work, we considered the possibility that the RAS, ET and adrenoceptor-mediated mechanisms might contribute to the maintenance of hypertension in DI/H rats. Some of the results have been reported to the British Pharmacological Society (March *et al.*, 1995).

## Methods

All experiments were carried out on male, DI/N and DI/H rats (350–500 g) raised in the Biomedical Services Unit in Nottingham, and produced, originally, by breeding pairs of DI/N and DI/H rats supplied by Professor R.J. Balment (University of Manchester) (see Ashton & Balment, 1989). Procedures for implanting pulsed Doppler probes (to monitor changes in renal, mesenteric and hindquarters Doppler shifts) and catheters (in the abdominal aorta to monitor arterial blood pressure and heart rate, and in the jugular vein to administer drugs) have been described previously (Gardiner & Bennett, 1988c; Gardiner *et al.*, 1989). All surgery was carried out under sodium methohexitone anaesthesia (Brietal, Lilly; 40–60 mg $kg^{-1}$ i.p., supplemented as required), and experiments did not begin until at least 24 h after the final surgical intervention (catheter implantation), when animals were conscious and unrestrained.

Although Doppler shift is not a direct measure of volume flow, it has been demonstrated that changes in Doppler shift are a reliable index of changes in flow (Haywood *et al.*, 1981). Moreover, although differences in crystal angle will influence the Doppler shift signal recorded (Gardiner *et al.*, 1990), we have never found consistent differences between different groups of normal rats using these techniques (see Gardiner *et al.*, 1994). In order to avoid confusion, all results for regional haemodynamics are presented as absolute Doppler shift (kHz).

To assess the effects of interventions on the behaviour of different vascular beds we calculated vascular conductance from the mean Doppler shift and the mean arterial blood

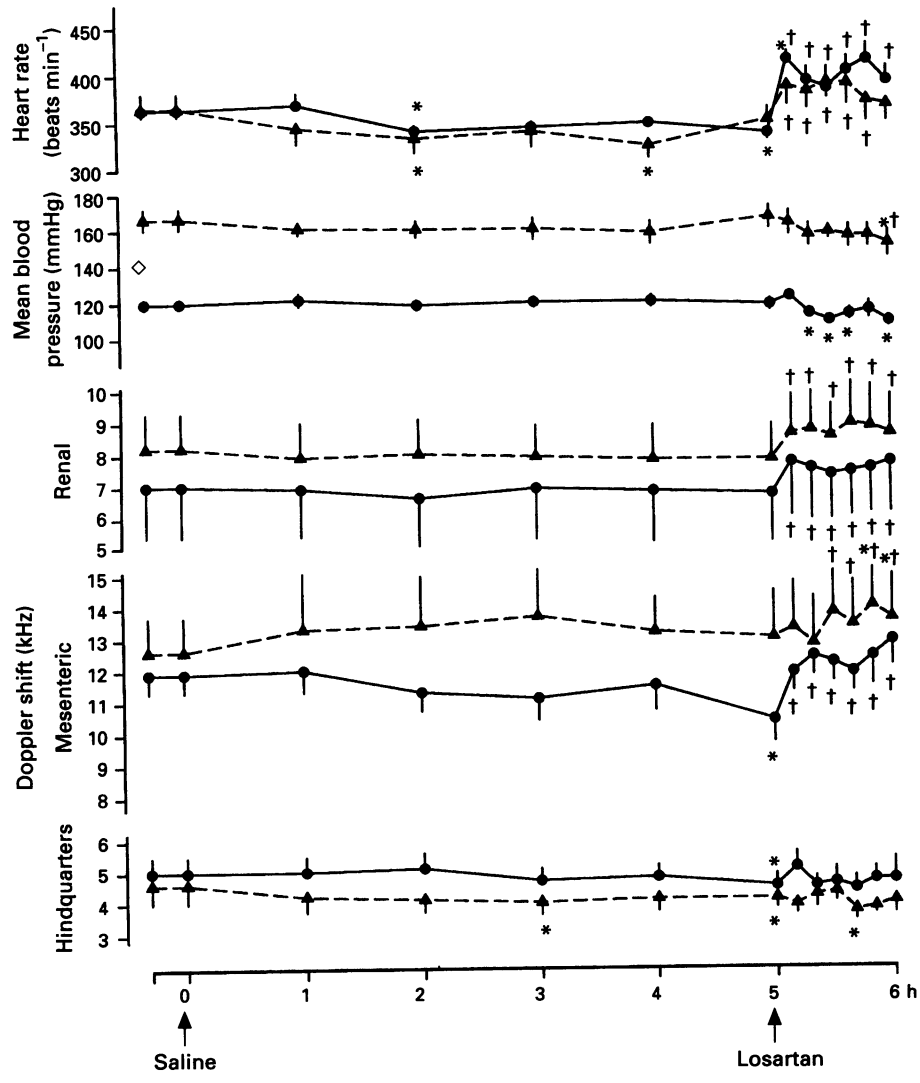


**Figure 1** Cardiovascular variables before and after s.c. injection of saline in conscious DI/N (●, $n=8$) and DI/H (▲, $n=8$) rats. At 5 h a bolus i.v. injection of losartan (10 mg $kg^{-1}$) was given. Values are mean with s.e.mean; ◇$P<0.05$ for difference between resting values, *$P<0.05$ versus original baseline, †$P<0.05$ versus pre-losartan (5 h) value).

pressure (kHz mmHg$^{-1}$). We elected to work with vascular conductance rather than vascular resistance because, on balance, the evidence indicates that the former better reflects vascular tone (e.g., Stark, 1968; Rodbard, 1971; Lautt, 1989; D'Almeida & Lautt, 1992; O'Leary, 1991). A rise in vascular conductance indicates vasodilatation, and a fall in vascular conductance vasoconstriction.

### *Haemodynamic responses to inhibition of the RAS in volume-replete and volume-deplete DI/N and DI/H rats*

DI/N and DI/H rats were given a subcutaneous injection of saline (5 ml, NaCl 154 mmol l$^{-1}$; $n=8$ in both groups) or hyperoncotic PEG (5 ml, 30% Carbowax 20 M in isotonic saline; $n=9$ in both groups) via a previously implanted catheter. In the latter experiment, rats were not allowed access to drinking water to ensure an isosmotic hypovolaemia was achieved (see Gardiner & Bennett, 1986). Five hours after the administration of saline or PEG, an i.v. injection of losartan (10 mg kg$^{-1}$) was given; elsewhere we have shown this dose of losartan inhibits pressor responses to exogenous AII for at least 9 h (Batin *et al.*, 1991a).

### *Haemodynamic responses to saline or SB 209670 in DI/N and DI/H rats*

DI/N ($n=7$) and DI/H ($n=8$) rats were given an i.v. infusion of saline (0.4 ml h$^{-1}$) for 8 h to act as a time control for an i.v. infusion of SB 209670 (600 $\mu$g kg$^{-1}$ h$^{-1}$; Douglas *et al.*, 1995; Gardiner *et al.*, 1995) given to DI/N ($n=7$) and DI/H ($n=8$) rats. Of the animals receiving SB 209670, 6 DI/N rats and 7 DI/H rats were those given saline (on the previous day). The dose of SB 209670 used completely reverses the haemodynamic effects of an infusion of endothelin-1 (120 pmol h$^{-1}$) which increased mean arterial blood pressure by 30–40 mmHg (Gardiner *et al.*, 1995; see also Douglas *et al.*, 1995).

### *Haemodynamic responses to adrenoceptor antagonism in DI/N and DI/H rats*

DI/N ($n=8$) and DI/H ($n=8$) rats were given a primed infusion of ICI 118551 (0.2 mg kg$^{-1}$, 0.1 mg kg$^{-1}$ h$^{-1}$; Gardiner & Bennett, 1988c) for 1 h before the onset of a primed infusion of idazoxan (0.75 mg kg$^{-1}$, 1 mg kg$^{-1}$ h$^{-1}$; Gardiner & Bennett, 1988c). One hour after the onset of idazoxan infusion, a bolus dose (10 mg kg$^{-1}$) of losartan was administered; a primed infusion of prazosin (0.5 mg kg$^{-1}$, 0.8 mg kg$^{-1}$ h$^{-1}$; Gardiner & Bennett, 1988c) was begun 1 h later, and recordings were continued for the subsequent 1 h. This protocol was based on our previous studies showing that $\beta_2$-adrenoceptors and the RAS can contribute to the haemodynamic effects of $\alpha$-adrenoceptor antagonism (Gardiner & Bennett, 1988a,b,c).

### *Drugs*

Losartan potassium was a gift from Dr R. D. Smith (Du Pont, U.S.A.), and SB 209670 ([(±)-(1S,2R,3S)-3-(2-carboxymethoxy-4-methoxyphenyl)-1-(3,4-methylenedioxyphenyl)-5-(-prop-1-yloxy)indane-2-carboxylic acid]) was a gift from Dr E. Ohlstein (SmithKline Beecham, U.S.A.). Prazosin, idazoxan and ICI 118551 were gifts from Pfizer, Reckitt & Colman, and ICI plc, respectively. All drugs were dissolved in saline (ICI 118551 required gentle warming), except for prazosin which was dissolved in lactic acid (0.04 M in dextrose).

### *Data analysis*

Within group analysis was by Friedman's test (Theodorsson-Norheim 1987); between group analyses were by the Mann-Whitney U test or Kruskal-Wallis test as appropriate. A $P$ value $<0.05$ was taken as significant.

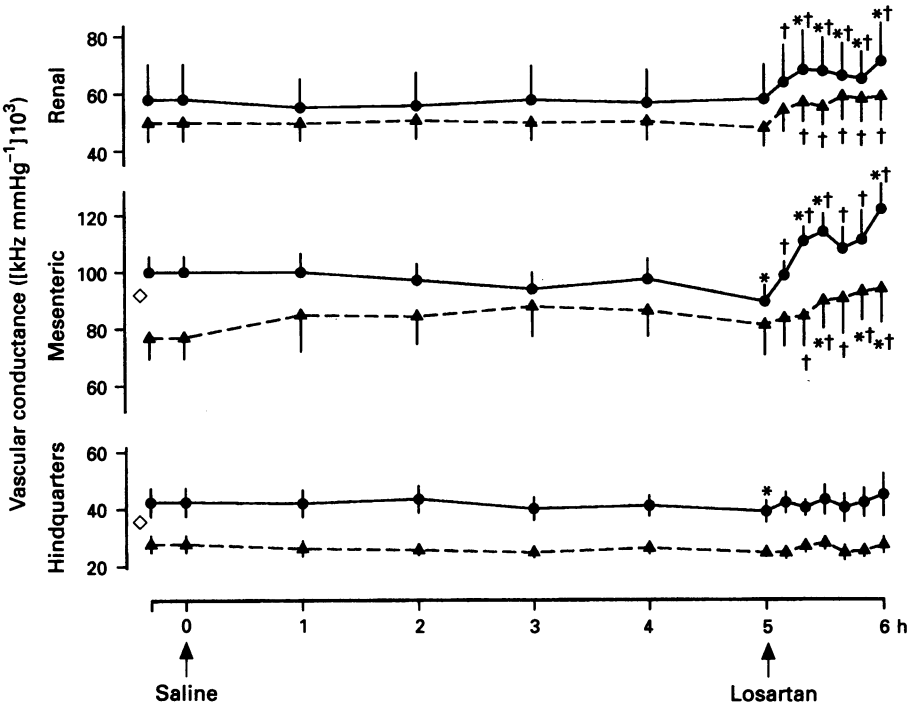


**Figure 2** Cardiovascular variables before and after s.c. injection of saline in conscious DI/N (●, $n=8$) and DI/H (▲, $n=8$) rats. At 5 h a bolus i.v. injection of losartan (10 mg kg$^{-1}$) was given. Values are mean with s.e.mean; ◇$P<0.05$ for difference between resting values, *$P<0.05$ versus original baseline, †$P<0.05$ versus pre-losartan (5 h) value).

## Results

### *Haemodynamic responses to inhibition of the RAS in volume-replete DI/N and DI/H rats*

Prior to the s.c. injection of saline, DI/H rats had a higher mean arterial blood pressure (MAP), and lower mesenteric and hindquarters vascular conductances than DI/N rats (Figures 1 and 2).

Over the 5 h following s.c. injection of saline, there were slight falls in heart rate in both groups, but neither showed a significant change in MAP (Figure 1). Renal haemodynamics did not change in either group, and the slight changes in hindquarters haemodynamics were similar in DI/N and DI/H rats (Figures 1 and 2). However, there was a significant difference between the changes in mesenteric haemodynamics in the two groups, with decreases in flow and conductance in DI/N rats, but a slight increase in mesenteric flow in DI/H rats (Figures 1 and 2).

Five hours after s.c. injection of saline, i.v. administration of losartan caused slight, and similar, reductions in MAP in DI/N and DI/H rats, although the accompanying tachycardia was significantly greater in the former (Figure 1). There were similar increases in renal flow and in vascular conductance in DI/N and DI/H rats, and in both strains, the hindquarters haemodynamics changed little (Figures 1 and 2). However, losartan caused significantly greater increases in mesenteric flow and vascular conductance in DI/N than in DI/H rats (Figures 1 and 2).

### *Haemodynamic responses to inhibition of the RAS in volume-deplete, DI/N and DI/H rats*

Prior to s.c. injection of PEG, DI/H rats had a higher MAP than DI/N rats, and lower conductances in renal, mesenteric and hindquarters vascular beds (Figures 3 and 4).

Over the 5 h following PEG administration, there was a significant fall in MAP in DI/H, but not in DI/N rats; there was little change in heart rate in either group (Figures 3 and 4). Although there were no significant changes in renal flow in either group, there was a significant renal vasoconstriction in DI/N, but not in DI/H, rats (Figure 4). There were significant, and similar, reductions in mesenteric flow in both groups, but the mesenteric vasoconstriction was greater in DI/N, than in DI/H rats (Figures 3 and 4). The reductions in hindquarters flow and in vascular conductance were similar in both groups (Figures 3 and 4).

Five hours after s.c. injection of PEG, administration of losartan caused similar, substantial reductions in MAP in DI/N and DI/H rats; there was marked tachycardia in both

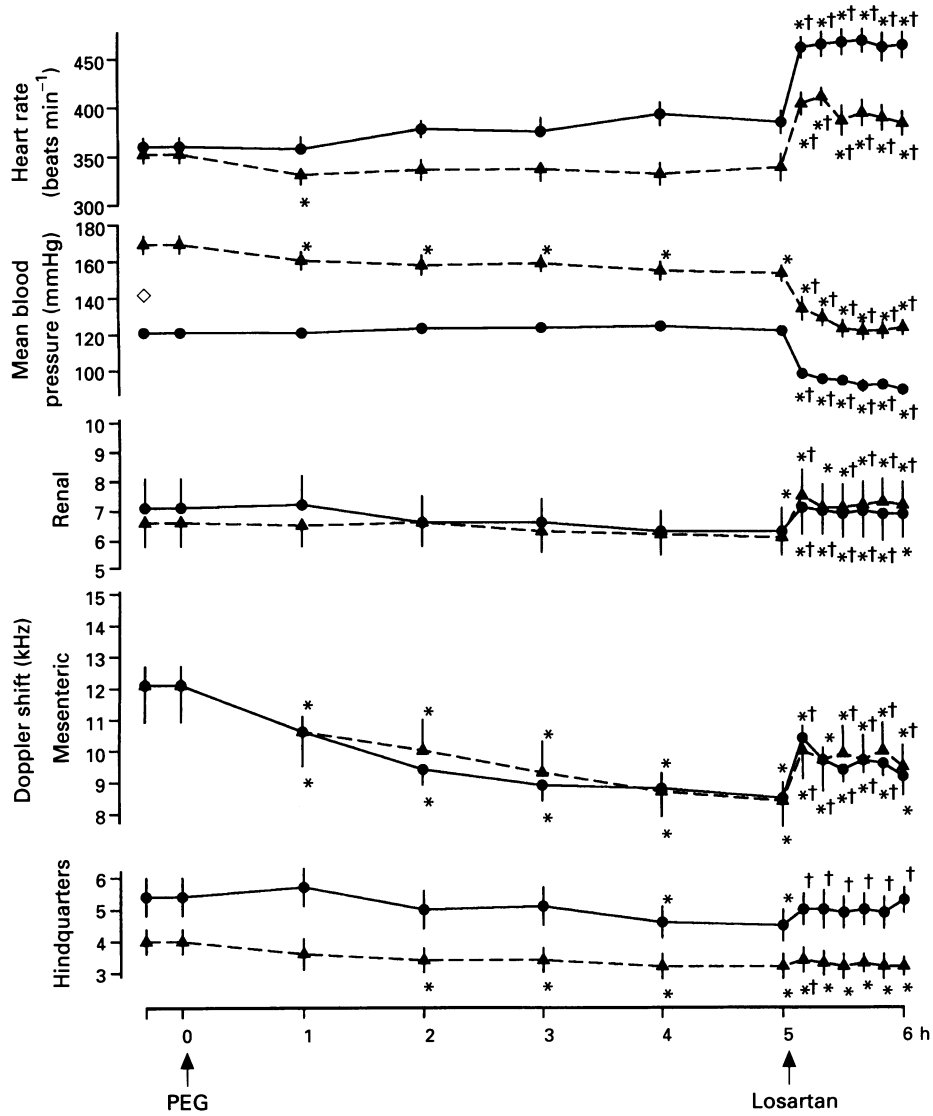


**Figure 3** Cardiovascular variables before and after s.c. injection of PEG in conscious DI/N (●, $n=9$) and DI/H (▲, $n=9$) rats. At 5 h a bolus i.v. injection of losartan (10 mg kg$^{-1}$) was given. Values are mean with s.e.mean; ◇$P<0.05$ for resting values, *$P<0.05$ versus original baseline, †$P<0.05$ versus pre-losartan (5 h) value).

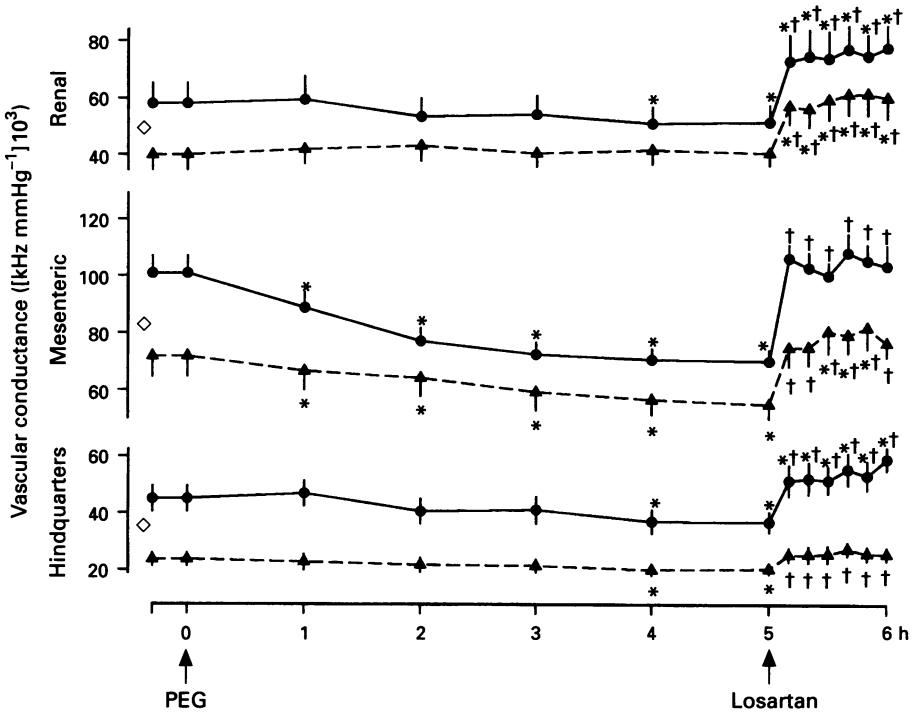


**Figure 4** Cardiovascular variables before and after s.c. injection of PEG in conscious DI/N (●, $n=9$) and DI/H (▲, $n=9$) rats. At 5 h a bolus i.v. injection of losartan (10 mg kg$^{-1}$) was given. Values are mean with s.e.mean; ◇$P<0.05$ for resting values, *$P<0.05$ versus original baseline, †$P<0.05$ versus pre-losartan (5 h) value).

groups, but it was significantly greater in DI/N rats (Figure 3). Losartan caused significant and similar increases in renal flow and in vascular conductance in both groups (Figures 3 and 4). Although the losartan-induced increase in mesenteric flow was similar in DI/N and DI/H rats, the increase in mesenteric vascular conductance was greatest in the former (Figures 3 and 4). There were only slight, similar increases in hindquarters flow in response to losartan in DI/N and DI/H rats, although the hindquarters vasodilatation was less in the latter (Figures 3 and 4).

### *Haemodynamic responses to saline or SB 209670 in DI/N and DI/H rats*

Prior to infusion of saline or SB 209670, MAP was higher and hindquarters vascular conductance was lower in DI/H than in DI/N rats (Figures 5 and 6).

In DI/N rats, during infusion of saline, there were slight falls in heart rate and in mesenteric and hindquarters flows and mesenteric vascular conductance (Figure 5). During infusion of SB 209670, there was a slight, significant fall in MAP, but it was not different from that during saline infusion. However, the change in heart rate in the two conditions was different because there was no bradycardia during infusion of SB 209670 (Figure 5). In addition, there were significant reductions in renal and mesenteric flows and conductances during infusion of SB 209670 that were significantly different from the changes seen during saline infusion (Figure 5).

In DI/H rats there were small falls in MAP, heart rate, mesenteric and hindquarters flows and hindquarters vascular conductance, together with a slight increase in renal vascular conductance during infusion of saline (Figure 6). There were no significant differences between these changes and those seen during infusion of SB 209670 (Figure 6).

### *Haemodynamic responses to adrenoceptor antagonism in DI/N and DI/H rats*

Before treatment, MAP was higher and hindquarters vascular conductance was lower in DI/H than in DI/N rats (Figures 7 and 8).

The selective $\beta_2$-adrenoceptor antagonist, ICI 118551, had little effect on heart rate or MAP in either DI/N or DI/H rats (Figure 7). In DI/N rats, there were slight reductions in hindquarters flow and renal and hindquarters vascular conductance, but more marked, and progressive falls in mesenteric flow and vascular conductance (Figures 7 and 8). In DI/H rats, there were marked, but transient, reductions in mesenteric flow and vascular conductance, whereas hindquarters haemodynamics changed little (Figures 7 and 8), and was still lower than in DI/N rats.

In DI/N rats, in the presence of ICI 118551, idazoxan caused a marked bradycardia and a fall in MAP, but not below baseline (Figure 7). There was a clear fall only in mesenteric flow and vascular conductance. The pattern of response to ICI 118551 was similar in DI/H rats, but the bradycardia was less (Figures 7 and 8). One hour after the onset of infusion of idazoxan, although MAP in DI/H rats was still higher than in DI/N rats, there was no longer any difference in hindquarters vascular conductance (Figures 7 and 8).

In the presence of ICI 118551 and idazoxan, losartan caused only a slight fall in MAP and an increase in heart rate in DI/N rats (Figure 7). There were rises in renal, mesenteric and hindquarters flows and vascular conductances, but only renal vascular conductance increased above baseline (Figures 7 and 8). Losartan caused similar cardiovascular changes in DI/H rats (Figures 7 and 8).

In DI/N rats, in the presence of ICI 118551, idazoxan and losartan, prazosin caused marked hypotension and tachycardia; renal and hindquarters flows fell, but mesenteric flow increased, and there was significant renal, mesenteric and hindquarters vasodilatation (Figures 7 and 8). Prazosin caused a similar pattern of haemodynamic changes in DI/H rats, but 1 h after the onset of prazosin infusion, MAP was still significantly higher in DI/H than in DI/N rats (Figure 7).

## Discussion

In the present work we confirmed that the elevation in MAP in DI/H rats was, as in all experiments to date, accompanied by a relative reduction in hindquarters vascular conductance

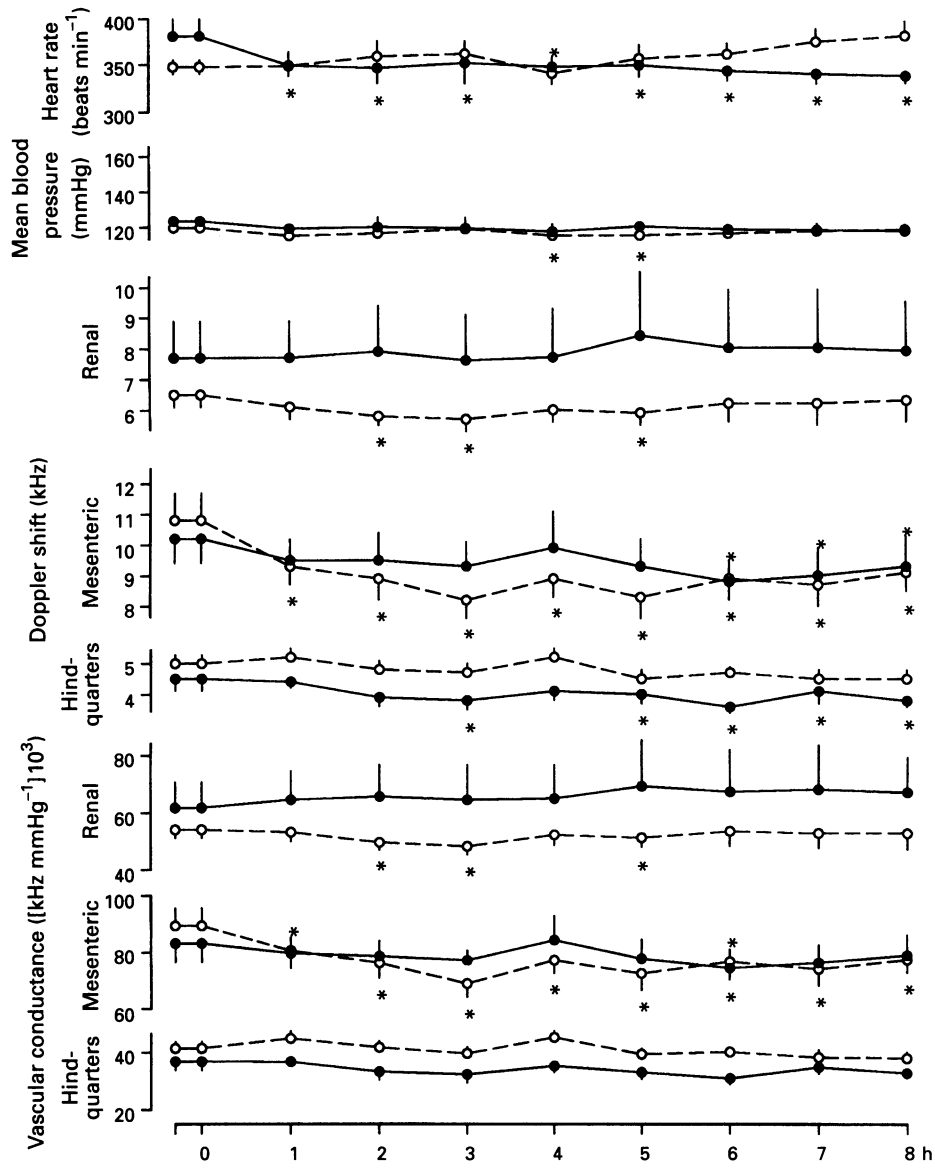


**Figure 5** Cardiovascular variables in DI/N rats before and during an 8 h i.v. infusion of saline (●, $n=7$) or SB 209670 (○, $n=8$). Values are mean with s.e.mean; $^*P<0.05$ versus original baseline.

(Gardiner *et al.*, 1994), with a variable difference in mesenteric and renal haemodynamics in the two strains.

From previous studies (Gardiner *et al.*, 1994: Dunn & Gardiner, 1995) there is evidence that the elevation in MAP in DI/H rats is not associated with impaired vasodilator function, hence other factors must be responsible for the hypertension. In the present work, for the reasons outlined in the Introduction, we assessed the possibility that AII, or ET, or adrenoceptor-mediated mechanisms contributed to the maintenance of the elevated MAP in DI/H rats.

During infusion of saline for 5 h, the difference in MAP and in hindquarters vascular conductance in DI/N and DI/H rats was well maintained, although mesenteric vascular conductance converged, due to a fall in the DI/N and a rise in the DI/H rats. At this juncture, the $AT_1$-receptor antagonist, losartan, caused significant and similar falls in MAP and increases in renal and hindquarters vascular conductance in DI/N and DI/H rats although the mesenteric vasodilatation and the tachycardia were significantly less in the latter. Hence these findings provide no evidence that the elevation in MAP, or the hindquarters vasoconstriction in DI/H rats, are due to AII. Indeed, it appears that AII is relatively less involved in cardiovascular control in DI/H than in DI/N rats in volume-replete conditions, in spite of the former having higher plasma AII levels (Al-Barazanji & Balment, 1995). The relatively small hindquarters vasodilator effect of losartan, compared to its clear renal and mesenteric vasodilator action is consistent with the haemodynamic profile of exogenous AII (Gardiner *et al.*, 1988).

Over the 5 h following s.c. injection of PEG to induce isosmotic hypovolaemia (Gardiner & Bennett, 1986), DI/N rats maintained their MAP, with little change in renal or hindquarters haemodynamics, but marked reductions in mesenteric flow and vascular conductance. This pattern of haemodynamic adaptation to hypovolaemia is as described previously in homozygous Brattleboro rats (see Introduction), but is nonetheless remarkable, considering it is achieved in spite of the total absence of circulating vasopressin. Interestingly, DI/H rats defended their MAP less well than DI/N rats, possibly because they showed less marked mesenteric vasoconstriction following s.c. injection of PEG. This finding is consistent with the proposition that, in hypertension, there is more effective defence against rises than against falls in MAP (Mancia *et al.*, 1979).

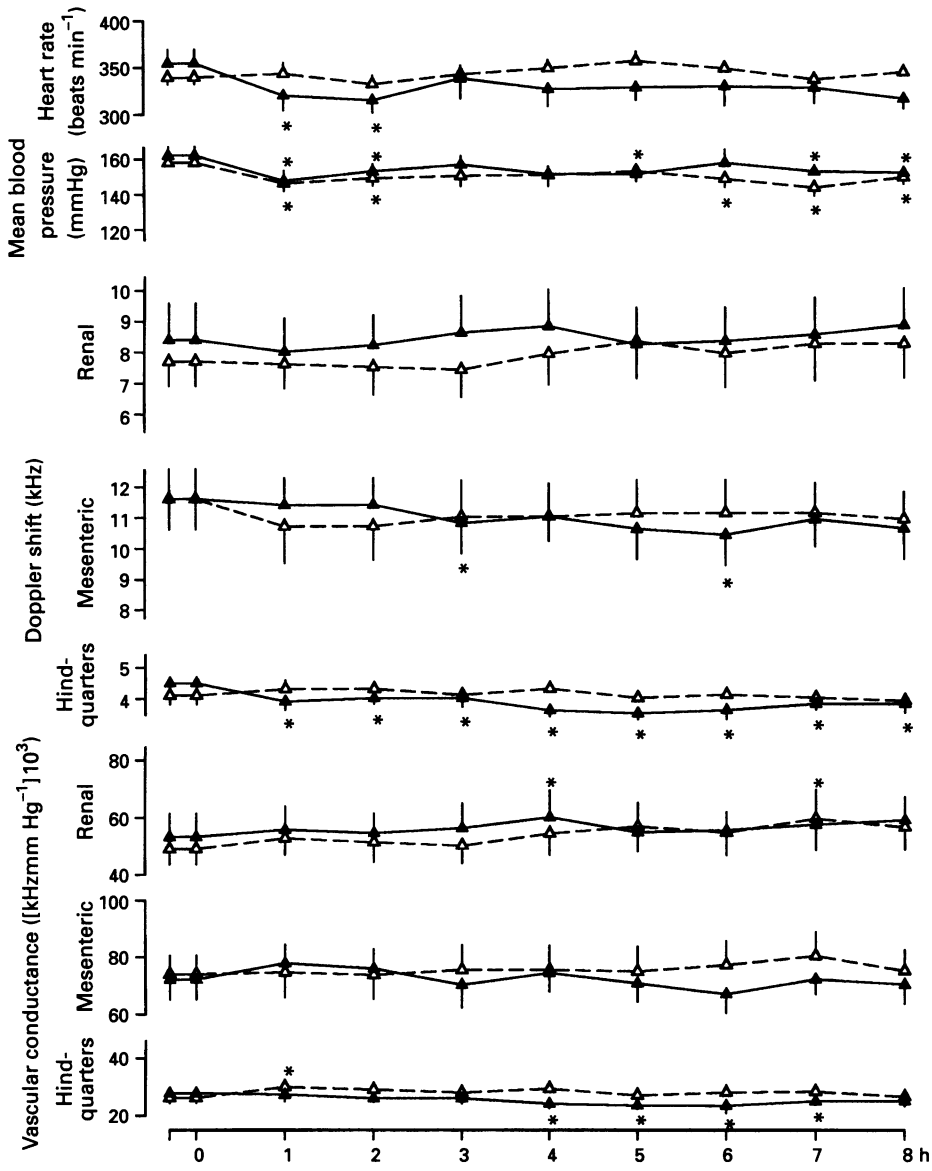


**Figure 6** Cardiovascular variables in DI/H rats before and during an 8 h i.v. infusion of saline (▲, $n=8$), or SB 209670 (△, $n=9$). Values are mean with s.e.mean; $*P<0.05$ versus original baseline.

In the hypovolaemic state, the hypotensive and vasodilator effects of losartan were augmented in both strains, but, although the falls in MAP were similar, the mesenteric and hindquarters vasodilator responses were more marked in DI/N than in DI/H rats. Hence, it is likely that losartan-induced increases in cardiac output (Batin *et al.*, 1991b) were greater in the former than in the latter group. This is not likely to have been due to the greater tachycardia in DI/N rats, because there was probably a concurrent reduction in cardiac index (Batin *et al.*, 1991b). Since, in the volume-deplete state, and in the presence of losartan, MAP was higher and renal, mesenteric and hindquarters vascular conductances were lower in DI/H than in DI/N rats, it appears that a direct vasoconstrictor effect of AII makes no contribution to the abnormal cardiovascular status of DI/H rats.

Likewise, it seems that ET is not involved in the elevation of MAP or the relative hindquarters vasoconstriction in DI/H rats, since the non-selective ET-receptor antagonist, SB 209670 had haemodynamic effects that were indistinguishable from those of saline. In DI/N rats, SB 209670 tended to cause relative dilatation in renal and mesenteric vascular beds, but these effects were slight. At the outset of this work we considered it possible that hyperactivation of the RAS might account for the maintenance of hypertension in the DI/H rat, possibly through an interaction with ET, as seen in the transgenic (mRen-2(27)) hypertensive rat (Gardiner *et al.*, 1995). The failure of losartan or SB 209670 to influence the hypertension or vasoconstriction in DI/H rats indicates that enhanced effects of losartan or SB 209670 are not inevitable consequences of an elevation in MAP. The corollary of this is that neither losartan nor SB 209670 possess non-specific vasodilator effects.

In previous studies we have found that $\beta_2$-adrenoceptor-mediated vasodilator effects contribute significantly to the responses evoked by $\alpha$-adrenoceptor antagonists in conscious Brattleboro rats (Gardiner & Bennett, 1988a,b,c), and that the RAS can contribute to haemodynamic status under these conditions (Gardiner & Bennett, 1988c). Therefore, in the present work we assessed the haemodynamic responses to prazosin having first antagonized $\beta_2$-adrenoceptors, $\alpha_2$-adrenoceptors and $AT_1$-receptors. Clearly, this approach does not permit an assessment of the extent to which $\alpha_1$-adrenoceptor

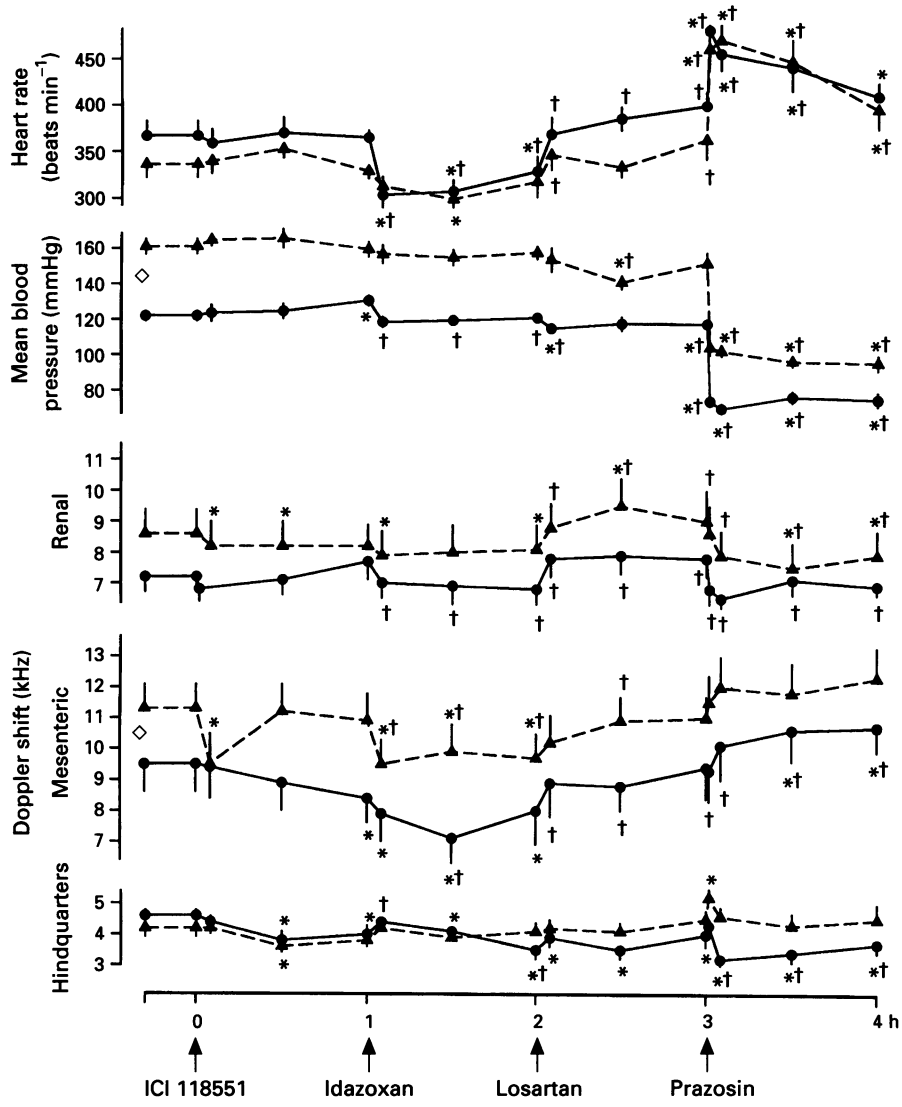


**Figure 7** Cardiovascular variables in DI/N (●, $n=8$) and DI/H (▲, $n=9$) rats, before and during sequential administration of ICI 118551, idazoxan, losartan and prazosin. Values are mean with s.e.mean; $\diamond P<0.05$ for difference between resting values, $*P<0.05$ versus original baseline, $\dagger P<0.05$ versus the value immediately preceding that intervention.

stimulation is normally involved in the maintenance of cardiovascular status, because each sequential intervention prior to the administration of prazosin is likely to have elicited neuronal and hormonal compensatory responses. However, following administration of prazosin under these circumstances it is reasonable to assume that any persisting differences between DI/N and DI/H rats were due to mechanisms other than those that had been antagonized.

Administration of ICI 118551 caused a marked, but transient, reduction in mesenteric vascular conductance in DI/H, but not DI/N rats. However, there was a hindquarters vasoconstrictor response to ICI 118551 in DI/N, but not DI/H rats. But, since DI/H rats show normal hindquarters vasodilator responses to salbutamol (Gardiner *et al.*, 1994), it appears that any abnormality in hindquarters $\beta_2$-adrenoceptor-mediated vasodilator processes is subtle, and not likely to contribute to the hypertension in DI/H rats, since ICI 118551 caused little change in MAP.

The overall effects of sequential administration of idazoxan and losartan were little different in DI/N and DI/H rats. However, prior to administration of losartan, and subsequently prazosin, there were no significant differences between regional vascular conductances in the two groups, although MAP was still elevated in DI/H rats. Hence, the hypertension was not associated with a relative constriction in any of the vascular beds monitored. Following additional administration of prazosin, MAP fell markedly in DI/N and DI/H rats, but it was still significantly higher in the latter. Under these conditions renal and mesenteric vascular conductances were numerically lower in DI/H than in DI/N rats, but the differences were not significant. Hence it appears that any vascular remodelling in, for example, the mesenteric vascular bed in DI/H rats (Dunn & Gardiner, 1995), does not result in a clear difference between the vascular conductance in this bed in DI/N and DI/H rats in the presence of adrenoceptor antagonists. However, it is feasible that small differences between vascular conductances in all vascular beds in the two groups contribute collectively to the difference in MAP.

This work was supported by a project grant from the M.R.C.

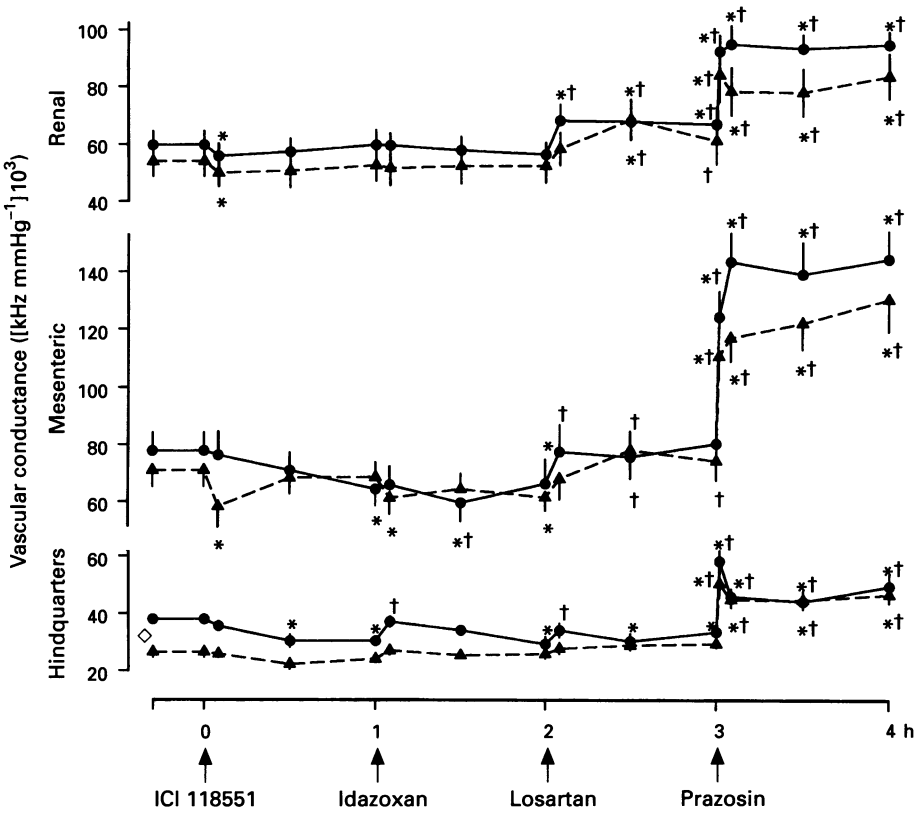


**Figure 8** Cardiovascular variables in DI/N (●, $n=8$) and DI/H (▲, $n=9$) rats, before and during sequential administration of ICI 118551, idazoxan, losartan and prazosin. Values are mean with s.e.mean; ◇$P<0.05$ for difference between resting values, *$P<0.05$ versus original baseline, †$P<0.05$ versus the value immediately preceding that intervention.

## References


AL-BARAZANJI, K.A. & BALMENT, R.J. (1995). Renal, endocrine and vascular effects of atrial natriuretic peptide in a novel vasopressin-deficient genetically hypertensive strain of rat. *Exp. Physiol.*, **80**, 275–284.

ASHTON, N. & BALMENT, R.J. (1989). Blood pressure and renal function in a novel vasopressin-deficient, genetically hypertensive rat strain. *J. Physiol.*, **410**, 21–34.

BATIN, P., GARDINER, S.M., COMPTON, A.M. & BENNETT, T. (1991a). Differential regional haemodynamic effects of the non-peptide angiotensin II antagonist, DuP 753, in water-replete and water-deprived Brattleboro rats. *Life Sci.*, **48**, 733–739.

BATIN, P., GARDINER, S.M., COMPTON, A.M., KEMP, P.A. & BENNETT, T. (1991b). Cardiac haemodynamic effects of the non-peptide, angiotensin II-receptor antagonist, DuP 753, in conscious Long Evans and Brattleboro rats. *Br. J. Pharmacol.*, **103**, 1585–1591.

BERECEK, K.H., MURRAY, R.D., GROSS, F. & BRODY, M.J. (1982). Vasopressin and vascular reactivity in the development of DOCA hypertension in rats with hereditary diabetes insipidus. *Hypertension*, **4**, 3–12.

CHEN, L., MCNEILL, J.R., WILSON, T.W. & GOPALAKRISHNAN, V. (1995). Differential effects of phosphoramidon on contractile responses to angiotensin II in rat blood vessels. *Br. J. Pharmacol.*, **114**, 1599–1604.

CROFTON, J.T., SHARE, L., SHADE, R.E., LEE-KWON, W.J., MANNING, M. & SAWYER, W.H. (1979). The importance of vasopressin in the development and maintenance of DOC-salt hypertension in the rat. *Hypertension*, **1**, 31–38.

D'ALMEIDA, M.S. & LAUTT, W.W. (1992). Expression of vascular escape: conductance or resistance? *Am. J. Physiol.*, **262**, H1191–H1196.

DOHI, Y., HAHN, A.W.A., BOULANGER, C.M., BUHLER, F. & LUSCHER, T.F. (1992). Endothelin stimulated by angiotensin II augments contractility of hypertensive rat resistance arteries. *Hypertension*, **19**, 131–137.

DOUGLAS, S.A., GELLAI, M., EZEKIEL, M., FEUERSTEIN, G.Z., ELLIOTT, J.D. & OHLSTEIN, E.H. (1995). Antihypertensive actions of the novel nonpeptide endothelin receptor antagonist SB 209670. *Hypertension*, **25**, 818–822.

DUNN, W.R. & GARDINER, S.M. (1995). Structural and functional properties of isolated, pressurized, mesenteric resistance arteries from a vasopressin-deficient rat model of genetic hypertension. *Hypertension*, **26**, 390–396.

EMORI, T., HIRATA, Y., OHTA, K., KANNO, K., EGUCHI, S., IMAI, T., SHICHIRI, M. & MARUMO, F. (1991). Cellular mechanism of endothelin-1 release by angiotensin and vasopressin. *Hypertension*, **18**, 165–170.

GANTEN, U., RASCHER, W., LANG, R.E., DIETZ, R., RETTIG, R., UNGER, T., TAUGNER, R. & GANTEN, D. (1983). Development of a new strain of spontaneously hypertensive rats homozygous for hypothalamic diabetes insipidus. *Hypertension*, **5** (suppl I), I-119 I-128.

GARDINER, S.M. & BENNETT, T. (1985). Interactions between neural mechanisms, the renin-angiotensin system and vasopressin in the maintenance of blood pressure during water deprivation: studies in Long Evans and Brattleboro rats. *Clin. Sci.*, **68**, 647–657.

GARDINER, S.M. & BENNETT, T. (1986). Pressor contributions from angiotensin and vasopressin after polyethylene glycol. *Am. J. Physiol.*, **251**, R769–R774.

GARDINER, S.M. & BENNETT, T. (1988a). Involement of $\beta_2$-adrenoceptor-mediated mechanisms in the cardiovascular responses to $\alpha_1$- and $\alpha_2$-adrenoceptor antagonism in conscious, unrestrained, Long Evans and Brattleboro rats. *Br. J. Pharmacol.*, **93**, 9–22.

GARDINER, S.M. & BENNETT, T. (1988b). Adrenoceptors and cardiovascular regulation in conscious, unrestrained, Long Evans and Brattleboro rats. *J. Autonom. Nerv. Syst.*, **193–203.**

GARDINER, S.M. & BENNETT, T. (1988c). Regional hemodynamic responses to adrenoceptor antagonism in conscious rats. *Am. J. Physiol.*, **255**, H813–H824.

GARDINER, S.M., BENNETT, T. & COMPTON, A.M. (1988). Regional haemodynamic effects of neuropeptide Y, vasopressin and angiotensin II in conscious, unrestrained, Long Evans and Brattleboro rats. *J. Autonom. Nerv. Syst.*, **24**, 15–27.

GARDINER, S.M., COMPTON, A.M. & BENNETT, T. (1989). Regional hemodynamic changes following hypovolemia in conscious rats. *Am. J. Physiol.*, **256**, R1076–R1083.

GARDINER, S.M., COMPTON, A.M., BENNETT, T. & HARTLEY, C.J. (1990). Can pulsed Doppler technique measure changes in aortic blood flow in conscious rats? *Am. J, Physiol.*, **259**, H448–H456.

GARDINER, S.M., MARCH, J.E., KEMP, P.A., MULLINS, J.J. & BENNETT, T. (1995). Haemodynamic effects of losartan and the endothelin antagonist, SB 209670, in conscious, transgenic ((mRen-2)27), hypertensive rats. *Br. J. Pharmacol.*, **116** (in press).

GARDINER, S.M., MARCH, J.E., KEMP, P.A. & BENNETT, T. (1994). Resting cardiovascular status and vasodilator function in a vasopressin-deficient, hypertensive strain of rat. *J. Hypertens.*, **12**, 1217–1224.

HAYWOOD, J.R., SHAFFER, R.A., FASTENOW, C., FINK, G.D. & BRODY, M.J. (1981). Regional blood flow measurement with pulsed Doppler flowmeter in conscious rats. *Am. J. Physiol.*, **241**, H273–H278.

IMAI, T., HIRATA, Y., EMORI, T., YANAGISAWA, M., MASAKI, T. & MARUMO, F. (1992). Induction of endothelin-1 gene by angiotensin and vasopressin in endothelial cells. *Hypertension*, **19**, 753–757.

KOHNO, M., HORIO, T., IKEDA, M., YOKOKAWA, K., FUKUI, T., YASUNARI, K., KURIHARA, N. & TAKEDA, T. (1992). Angiotensin II stimulates endothelin-1 secretion in cultured rat mesangial cells. *Kid. Int.*, **42**, 860–866.

KOHNO, M., YASUNARI, K., YOKOKAWA, K., MURAKAWA, K., HORIO, T. & TAKEDA, T. (1991). Inhibition by atrial and brain natriuretic peptides of endothelin-1 secretion after stimulation with angiotensin II and thrombin of cultured human endothelial cells. *J. Clin. Invest.*, **87**, 1999–2004.

LAUTT, W.W. (1989). Resistance or conductance for expression of arterial vascular tone. *Microvasc. Res.*, **37**, 230–236.

MANCIA, G., FERRARI, A., GREGORINI, L., PARATI, G., POMIDOSSI, G. & ZANCHETTI, A. (1979). Control of blood pressure by carotid sinus baroreceptors in human beings. *Am. J. Cardiol.*, **44**, 895–902.

MARCH, J.E., GARDINER, S.M., KEMP, P.A. & BENNETT, T. (1995). Effects of losartan on haemodynamics in conscious, vasopressin-deficient hypertensive rats. *Br. J. Pharmacol.*, **115**, 58P.

MULLER, A.F., GARDINER, S.M., COMPTON, A.M. & BENNETT, T. (1990). Regional haemodynamic effects of captopril, enalaprilat and lisinopril in conscious water-replete and water-deprived Brattleboro rats. *Clin. Sci.*, **79**, 393–401.

MULLINS, J.J., PETERS, J. & GANTEN, D. (1990). Fulminant hypertension in transgenic rats harbouring the mouse Ren-2 gene. *Nature*, **344**, 541–544.

O'LEARY, D.S. (1991). Regional vascular resistance vs. conductance: which index for baroreflex responses? *Am. J. Physiol.*, **260**, H632–H637.

RODBARD, S. (1971). The burden of the resistance vessels. *Circ. Res.*, **28** (Suppl. 1), 1-2–1-8.

SHARABI, F.M. & SCHMID, P.G. (1983). Evidence for a role of vasopressin in hypertension. *Am. J. Nephrol.*, **3**, 164–171.

SHARE, L. & CROFTON, J.T. (1982). Contribution of vasopressin to hypertension. *Hypertension*, **4** (supp III), III-85–III-92.

STARK, R.D. (1968). Conductance or resistance? *Nature*, **217**, 779.

YOSHIDA, K., YASUJIMA, M., KOHZUKI, M., KANAZAWA, M., YOSHINAGA, K. & ABE, K. (1992). Endothelin-1 augments pressor response to angiotensin II infusion in rats. *Hypertension*, **20**, 292–297.

*(Received October 16, 1995*
*Revised January 15, 1996*
*Accepted February 7, 1996)*