Br. J. Pharmac. (1984), **83**, 363–371

Inhibition of vasoconstriction by frusemide in the rat

John F. Gerkens & Anthony J. Smith

Discipline of Clinical Pharmacology, Faculty of Medicine, University of Newcastle, Newcastle, Australia

1 Mesenteric blood flow was measured in anaesthetized rats with a non-cannulating electromagnetic flow probe around the superior mesenteric artery. Reductions in blood flow were produced by intravenous bolus injections of angiotensin II (1–300ng) and noradrenaline (3–300ng) before and after the administration of frusemide (5 mg kg^{-1}, i.v.). Loss of volume after frusemide was prevented by either a urinary bladder-intravenous shunt or replacement of urinary output by intravenous saline.

2 Frusemide administration caused a small increase in baseline blood pressure of 3.2 ±1.3 mmHg ($P<0.05$) but did not change mesenteric blood flow. This dose of frusemide inhibited the vasoconstrictor responses to both angiotensin II and noradrenaline ($P<0.01$, two way analysis of variance). Responses to angiotensin II were inhibited to a greater extent.

3 Acute bilateral nephrectomy or treatment with indomethacin (2 mg kg^{-1}, i.v.) completely prevented the inhibitory effect of frusemide on the responses to angiotensin II and noradrenaline.

4 To test whether frusemide-induced increased endogenous levels of angiotensin II may be responsible for the effects of frusemide on the vasoconstrictor responses, a separate group of rats were not given frusemide but were infused with exogenous angiotensin II (12.5–25 ng kg^{-1} min^{-1}). This produced a small increase in mean blood pressure (4.0± 1.4 mmHg, $P<0.05$) but did not change baseline mesenteric blood flow. Unlike frusemide, the responses to bolus injections of angiotensin II and noradrenaline were not changed by the infusion of angiotensin II.

5 It is suggested that frusemide may release directly or indirectly a prostanoid from the kidney (or a substance from the kidney which leads to the formation of a prostanoid) which inhibits constrictor responses in the peripheral vasculature.

Introduction

Although the diuretic action of frusemide has been well documented, there is evidence that frusemide can also have effects on the cardiovascular system unrelated to the diuresis. For example, in the treatment of pulmonary oedema, frusemide relieved the clinical symptoms before any diuretic effect was noticeable (Bourland *et al.*, 1977). These and other authors (Dikshit *et al.*, 1973; Bayne & Williamson, 1979) have attributed these effects to an action of frusemide on either precapillary resistance vessels or venous capacitance. Bourland *et al.* (1977) also found that these effects of frusemide in dogs were abolished by either nephrectomy or indomethacin-treatment and concluded that frusemide elicits the release of substances from the kidney which mediate the vascular actions of the drug.

In an earlier study, Lockett & Nicholas (1968) found that frusemide reduced the pressor effects of noradrenaline in hypertensive rats and that this inhibitory effect was also blocked by prior nephrectomy. They also concluded that this action of frusemide was not a result of the diuresis but did, nevertheless, require the presence of the kidneys.

There is considerable evidence that frusemide can increase the production or release of prostanoids in vascular structures. For example, the increase in renal blood flow produced by frusemide can be blocked by indomethacin (Williamson *et al.*, 1974) and aortae from rats injected intravenously with frusemide have an increased capacity to produce prostacyclin (PGI_2, Sullivan & Patrick, 1981). Since prostanoids can inhibit vasoconstrictor responses (Jackson & Campbell, 1980) we were interested to determine if frusemide would also inhibit such responses and to determine the effect of nephrectomy and inhibition of prostaglandin synthesis on the action of frusemide.

To prevent the possible interfering effects of volume and electrolyte loss resulting from frusemide-induced diuresis, one group of rats was prepared with

a urinary-bladder intravenous shunt. This manoeuvre also helped sustain frusemide plasma levels by circumventing losses due to urinary clearance of frusemide. In another group of rats the urinary volume loss after frusemide was not recycled but was quantitatively replaced by a concurrent intravenous infusion of saline. For comparative purposes another group of rats was also given frusemide but the urine produced was then allowed to escape with no replacement of volume losses.

Frusemide itself causes the release of renin (Hesse & Nielsen, 1976) and thereby increases circulating endogenous angiotensin II levels. This may possibly affect the vasoconstrictor responses to exogenous angiotensin II and noradrenaline. To investigate this, rats were infused continuously with levels of angiotensin II that produced effects similar to those produced after frusemide administration. Responses to bolus injections of angiotensin II and noradrenaline were then re-examined.

Methods

Surgical preparation

Male Sprague Dawley rats (250–350 g) were anaesthetized with sodium 5-ethyl-5 (1-methyl-propyl)-2-thiobarbiturate (Inactin) 100 mg kg^{-1} intraperitoneally. The trachea was cannulated and catheters inserted into a femoral vein and a carotid artery for drug and fluid administration and blood pressure recording. The blood pressure was measured with a Gould P23 pressure transducer and recorded on a Grass 79D recorder.

In rats prepared with a urinary bladder-intravenous shunt, one arm of a 4-arm catheter was tied into the urinary bladder and a second arm inserted into a jugular vein. The urethra was then ligated so that urine flowed through the catheter and out through a third arm. The catheter was clamped between the bladder and the jugular vein and saline infused into the jugular vein at 2 ml h^{-1} through the fourth arm of the catheter. After frusemide was administered and a diuresis was noticeable, the clamp was shifted to the third arm so that the dilute urine then flowed into the jugular vein in addition to the saline infusion. In the rats to be given frusemide but without the urinary bladder-intravenous shunt, the urethra was tied and the bladder cannulated. The urine was then collected over timed periods and the rate of flow matched by an intravenous infusion of saline. In another group of rats, all urine was allowed to escape and was not replaced.

The superior mesenteric artery was cleared of surrounding tissue taking care to avoid cutting adjacent nerves and lymphatic vessels. A 1.0 mm or 1.5 mm diameter Statham SP7515 non-cannulating electromagnetic flow probe was placed around the artery and blood flow measured on a SP2202 flow meter and recorded on the Grass 79D recorder.

After the above surgical preparation, in the nephrectomized group of rats, ligatures were tied around the renal arteries, veins and ureters with care to avoid interference with the adrenal glands, and the kidneys removed. In these rats there was no urinary bladder-intravenous shunt.

All rats were kept at 37°C using a rectal temperature probe which controlled an overhead heating lamp. The animals were allowed at least 45 min to equilibrate after surgery before starting the experiment.

Experimental protocol

Dose-response curves to both angiotensin II and noradrenaline were constructed by repeatedly injecting doses in random order until the decreases in blood flow were reproducible with 5 min between injections. After frusemide or indomethacin administration 10 min was allowed before starting to repeat the dose-response procedure.

In another group of rats, after control vasoconstrictor responses to bolus injections of angiotensin II and noradrenaline had been obtained, angiotensin II was infused intravenously at a rate which produced effects which matched the effect of frusemide 5 mg kg^{-1} on mean blood pressure and baseline mesenteric blood flow in the group of rats with the urinary bladder-intravenous shunt. This infusion rate was found to range from 12.5 to 25 ng kg^{-1} min^{-1}. The bolus injections of angiotensin II and noradrenaline were then repeated during the angiotensin II infusion.

Solutions of angiotensin II and noradrenaline were freshly made in saline and kept on ice. All bolus intravenous injections of these were in volumes of 0.05 ml and were followed by 0.02 ml saline flush. Frusemide was injected intravenously slowly over 3 min as a 10 mg ml^{-1} solution. Indomethacin was dissolved in the minimal amount of 0.1 M sodium carbonate and injected slowly intravenously over 3 min.

Drugs

The following were used: noradrenaline bitartrate (Sterling), angiotensin II (Ciba), frusemide (Hoechst), sodium 5-ethyl-5 (1-methyl-propyl)-2-thio-barbiturate (Inactin) (Byk), indomethacin (Sigma).

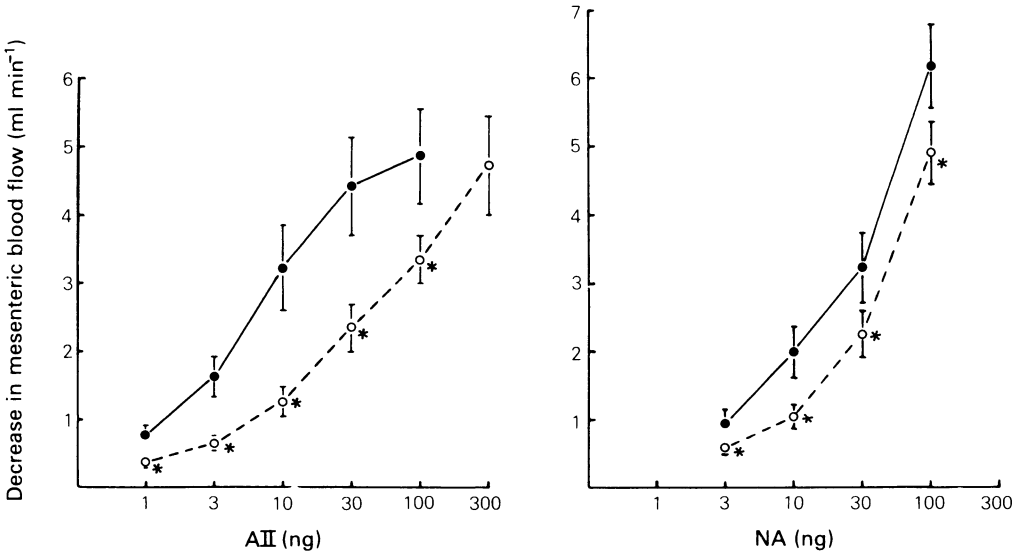

Figure 1 Decreases in mesenteric blood flow produced by intravenous bolus injections of angiotensin II (AII) and noradrenaline (NA) before (●) and after (○) the intravenous administration of frusemide 5 mg kg^{-1} in rats prepared with a urinary bladder-intravenous shunt. Each point is the mean of nine experiments and the bars represent s.e. mean. * $P<0.05$ for difference from corresponding value before frusemide.

Statistical analysis

All values are expressed as the mean ± s.e. mean. The linear part of the control and post-frusemide dose-response curves for angiotensin II and noradrenaline were analysed by a model III 2-factor analysis of variance without replication in which the random factor was the presence of frusemide and the fixed factor the dose of angiotensin II or noradrenaline. If this showed statistical significance, a Student's paired *t* test was used to determine which doses of agonist produced changes in blood flow that were significantly different after frusemide. A *P* value of <0.05 was used as the criterion of significance. The resting or baseline values for mesenteric blood flow and mean blood pressure before and after frusemide, indomethacin or angiotensin II infusion were compared using Student's paired *t* test.

Results

Effect of frusemide on angiotensin II and noradrenaline dose-response in rats with a urinary bladder-intravenous shunt

The intravenous bolus injection of angiotensin II and noradrenaline at 5 min intervals produced transient and dose-dependent decreases in mesenteric blood flow (Figure 1). The administration of frusemide (5 mg kg^{-1}) intravenously over 3 min produced a

Table 1 Effect of frusemide (5 mg kg^{-1} in each case) on baseline mesenteric blood flow (ml min^{-1}) and mean blood pressure (mm Hg) in the different groups of rats measured before and 20 min after the frusemide administration (mean ± s.e.mean)

	Mesenteric blood flow		*Mean blood pressure*	
	Control	*After frusemide*	*Control*	*After frusemide*
Frusemide, bladder-intravenous shunt. $n=9$	9.0 ± 0.8	9.0 ± 0.8	117.2 ± 9.1	120.4 ± 9.9*
Frusemide, volume replacement. $n=9$	7.2 ± 1.1	6.8 ± 1.0*	108.3 ± 9.1	107.4 ± 3.3
Frusemide + nephrectomy. $n=6$	10.1 ± 1.3	9.9 ± 1.3	131.5 ± 6.9	131.7 ± 6.6
Frusemide-indomethacin-treated. $n=6$	7.7 ± 0.6	8.9 ± 0.9	94.3 ± 7.6[a]	100.3 ± 8.7
Frusemide, no urine replacement. $n=6$	7.9 ± 1.4	5.8 ± 1.0*	114.8 ± 6.4	104.8 ± 6.3*

* $P<0.05$; [a] value after indomethacin-treatment.

noticeable diuresis within 5 min. The concentrated urine in the urinary bladder catheter was allowed to escape and the intravenous shunt was not opened until dilute post-frusemide urine was being produced. It was found in preliminary experiments that if urine formed before the administration of frusemide was allowed to progress through the shunt into the circulation it produced transient increases in mesenteric flow and decreases in blood pressure. When only post-frusemide urine was recirculated through the shunt there were no changes in blood flow or mean blood pressure associated with the opening of the shunt and the recirculation of the dilute urine. Although baseline mesenteric blood flow did not change after frusemide 5 mg kg^{-1} administration, there was a small but significant increase in mean blood pressure of 3.2 ± 1.2 mmHg, ($n = 9$) measured 20 min after the frusemide injection (Table 1).

The responses to angiotensin II after the administration of frusemide 5 mg kg^{-1} were significantly less than control ($P < 0.01$, Figure 1). The dose-response curve was shifted 6.1 fold to the right at half-maximal response. Frusemide 5 mg kg^{-1} also significantly reduced the vasoconstrictor effect of noradrenaline but the degree of shift of the dose-response curve (1.8 fold) was not as great as for the angiotensin II responses (Figure 1).

Effect of frusemide on angiotensin II and noradrenaline dose-responses in nephrectomized rats

In rats which were acutely nephrectomized ($n = 6$) angiotensin II and noradrenaline produced dose-dependent decreases in mesenteric blood flow similar to the non-nephrectomized rats. However, in contrast to the previous group the administration of frusemide 5 mg kg^{-1} did not have any effect on the responses to either angiotensin II or noradrenaline (Figure 2). Frusemide did not change baseline mesenteric blood flow or mean blood pressure in this group (Table 1).

Effect of frusemide on angiotensin II and noradrenaline dose-responses in rats pretreated with indomethacin

Vasoconstrictor responses to angiotensin II and noradrenaline were obtained before and after the administration of indomethacin 2 mg kg^{-1} intravenously ($n = 6$). The responses after indomethacin were greater and the dose-response curves shifted to the left but these changes did not reach statistical significance (Figure 3). Indomethacin itself did not change baseline blood flow or mean blood pressure.

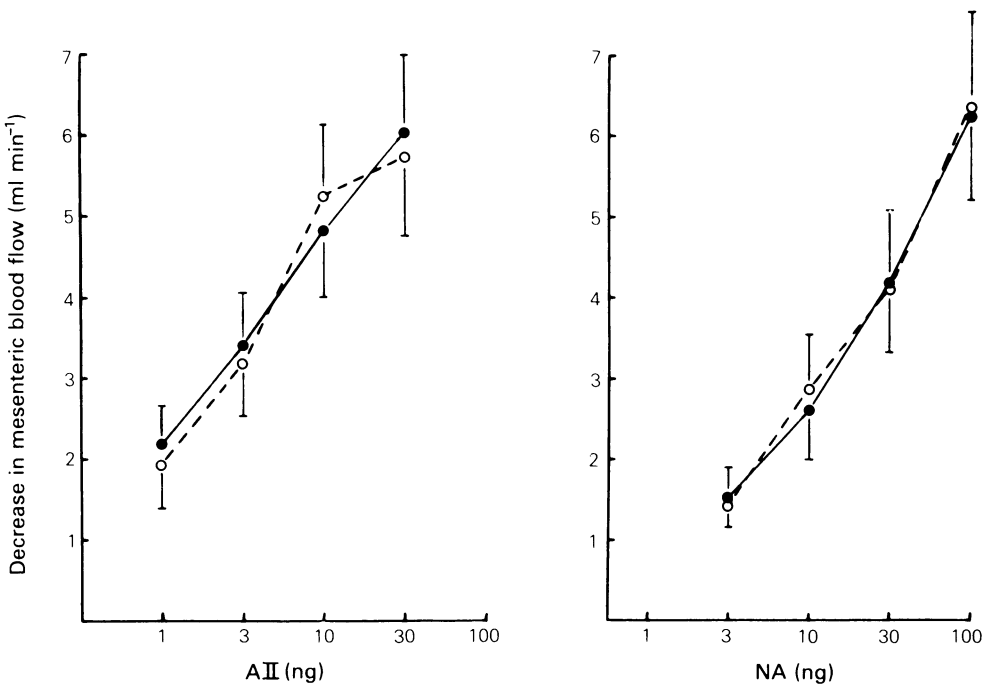

Figure 2 Decreases in mesenteric blood flow produced by intravenous bolus injections of angiotensin II (AII) and noradrenaline (NA) before (●) and after (○) the intravenous administration of frusemide 5 mg kg^{-1} in rats which had been bilaterally nephrectomized. Each point is the mean of five experiments and the bars represent s.e.mean.

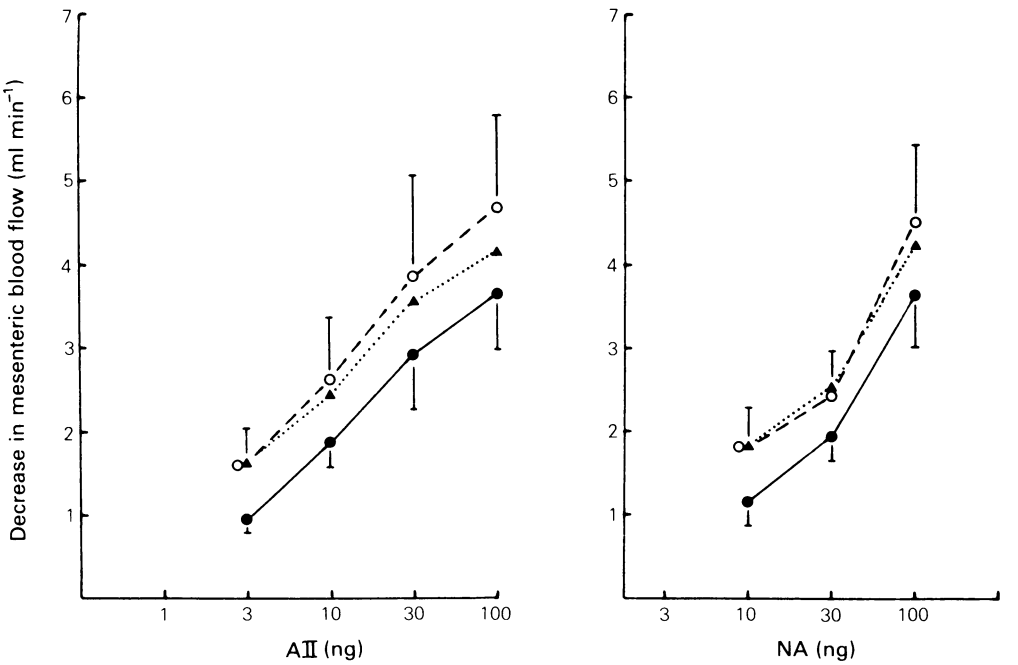

Figure 3 Decreases in mesenteric blood flow produced by intravenous bolus injections of angiotensin II (AII) and noradrenaline (NA) before (●) and after (▲) the intravenous administration of indomethacin 2 mg kg^{-1} and after the additional intravenous administration of frusemide 5 mg kg^{-1} (○) in rats prepared with a urinary bladder-intravenous shunt. Each point is the mean of six experiments and the bars represent s.e.mean.

In contrast to the first group of rats, in these indomethacin-treated animals the subsequent administration of frusemide 5 mg kg^{-1} did not change the responses to either angiotensin II or noradrenaline from their post-indomethacin values (Figure 3). The baseline values for blood flow and mean blood pressure also did not change (Table 1).

Effect of frusemide on angiotensin II and noradrenaline dose-responses in rats where urinary losses were replaced by intravenous saline infusion

These rats ($n = 9$) were prepared without a urinary bladder-intravenous shunt. The increased urine flow in response to frusemide 5 mg kg^{-1} was not recirculated but was collected and measured over timed periods. The calculated rate of fluid loss was then replaced quantitatively by increasing the rate of a continuous and concurrent intravenous infusion of normal saline. The rate of urine production increased from 0.008 ± 0.001 ml min^{-1} to a peak of 0.302 ± 0.065 ml min^{-1} 15 min after frusemide administration. The diuresis gradually declined but was still 0.201 ± 0.038 ml min^{-1} 45 min after the frusemide was given.

In these rats, as in the rats with the urinary bladder intravenous shunt, the responses to angiotensin II were significantly reduced after the administration of frusemide (Figure 4). The shift of the angiotensin II dose-response to the right at 3.2 fold was less than in the group with the shunt. The responses to noradrenaline were smaller after frusemide and the shift of the dose-response curve was not statistically significant.

In these rats, although frusemide did not change baseline blood pressure there was a small but statistically significant decrease in baseline mesenteric blood flow (Table 1).

Effect of continuous intravenous infusion of angiotensin II on vasoconstrictor responses to bolus injections of angiotensin II and noradrenaline

These rats ($n = 5$) were prepared without a urinary bladder-intravenous shunt since they did not receive frusemide. After control dose-responses to bolus injections of angiotensin II and noradrenaline had been obtained as before, a separate continuous intravenous infusion of angiotensin II was started. The rate of this infusion was gradually increased until there was a small change in baseline mean blood pressure comparable to the rise in mean blood pres-

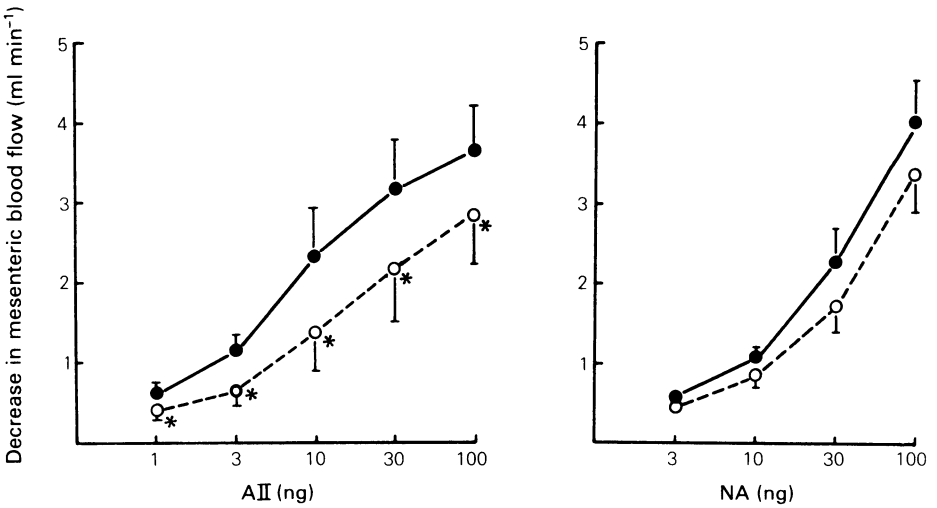

Figure 4 Decreases in mesenteric blood flow produced by intravenous bolus injections of angiotensin II (AII) and noradrenaline (NA) before (●) and after (○) the intravenous administration of frusemide 5 mg kg^{-1} in rats where urinary losses after frusemide were replaced by a concurrent intravenous infusion of saline. Each point is the mean of nine experiments and the bars represent s.e.mean.

sure found after frusemide 5 mg kg^{-1} in the first group of animals. The mean blood presssure rose by 4.0 ± 1.4 mmHg ($P < 0.05$) during the angiotensin II infusion. The rate of angiotensin II infusion ranged from 12.5 to 25 ng kg^{-1} min^{-1} and the baseline mesenteric blood flows were unchanged being 7.4 ± 1.1 ml min^{-1} and 7.5 ± 0.9 ml min^{-1} in the control and angiotensin II infusion periods respectively. The responses to bolus injections of angiotensin II and noradrenaline during this infusion of angiotensin II were not different from control responses (Figure 5).

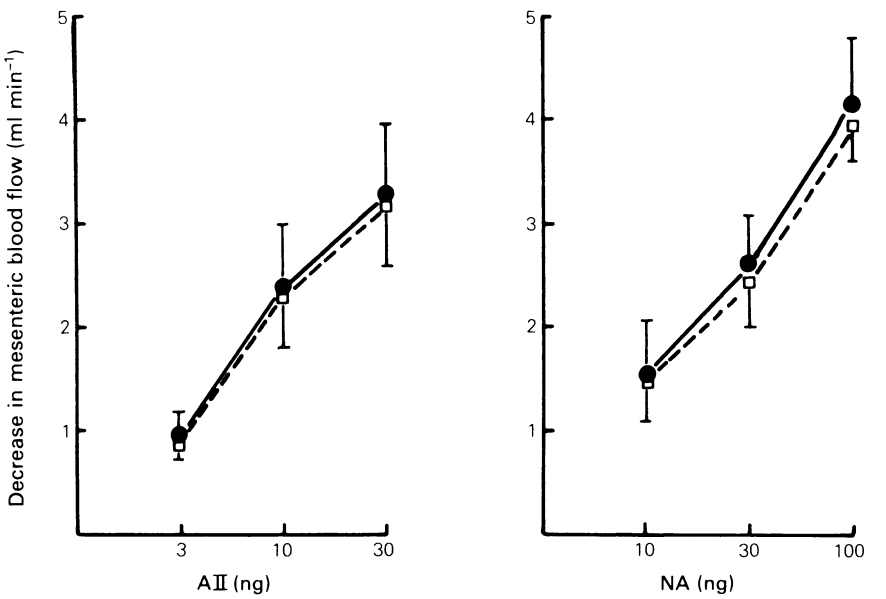

Figure 5 Decreases in mesenteric blood flow produced by intravenous bolus injections of angiotensin II (AII) and noradrenaline (NA) before (●) and during (□) the intravenous infusion of angiotensin II 12.5–25 ng kg^{-1} min^{-1}. Each point is the mean of five experiments and the bars represent s.e.mean.

Effect of frusemide on baseline mesenteric blood flow and mean blood pressure in rats where urinary losses were not replaced

These rats ($n=6$) were prepared without a urinary bladder-intravenous shunt and the urine produced after frusemide was not replaced. There was a marked decrease of 2.1 ± 0.5 ml min^{-1} in mesenteric blood flow ($P<0.01$) as well as a decrease in blood pressure of 10.0 ± 2.1 mmHg ($P<0.01$) after the administration of frusemide (Table 1).

Discussion

We have demonstrated that in rats prepared so that there is no loss of fluid from the circulation as a result of a diuresis, the administration of frusemide reduces the vasoconstrictor effects of angiotensin II and noradrenaline. This inhibition by frusemide is not seen if the animals are nephrectomized or treated with indomethacin. Although the data are presented as changes in blood flow the results and statistical analyses are the same when calculated as changes in resistance.

The loss of fluid as a result of the frusemide-induced diuresis was overcome by two separate techniques. In the first set of experiments the dilute urine produced after the administration of frusemide was allowed to recirculate back into the animal via a urinary bladder-intravenous shunt. In these experiments there was a small increase in blood pressure after frusemide, possibly caused by an increase in plasma renin activity (Arita *et al.*, 1983) but no change in baseline mesenteric blood flow. The fact that blood flow did not change is a good indication that there was no change in circulating fluid volume since we found that in rats where the urine is not recirculated nor replaced, there was a 27% decrease in mesenteric blood flow after frusemide as well as a 9% decrease in blood pressure. However since urine is known to contain substances that are possibly vasoactive, the experiments were also performed in rats where the rate of urine loss was replaced by a matching infusion of saline. In these animals there was no rise in blood pressure and a small but significant decrease in mesenteric blood flow. This probably indicates that there was in fact some net loss of circulating fluid volume. This may have been a consequence of the time lag inherent in collecting and measuring the rate of urine production and then matching that with the rate of saline infusion. In this group of rats the shift of dose-response curves to the right produced by frusemide was not as great as in the rats with the urinary bladder-intravenous shunt. This may reflect the loss of frusemide from the circulation as a result of urinary clearance. No attempt was made to compensate for the presumably more rapid decline in plasma frusemide levels in these animals.

It has been suggested over the years that diuretics may produce some of their effects on the circulation by the production of endogenous vasodilator substances (Struyker-Boudier *et al.*, 1983). Such explanations have been offered for the rapid and beneficial effects of frusemide in the relief of pulmonary oedema and Bourland *et al.* (1977) further concluded that frusemide exerted its vascular effects in the hypervolemic anuric dog by the release of substances from the kidney. These may be prostanoids since the effects were blocked by indomethacin treatment.

Our results do not produce any direct evidence on the nature of the final mediating mechanism for the reduction in vasoconstrictor responses. Frusemide has been shown to cause an increase in peripheral plasma concentration of free arachidonic acid in man (Weber *et al.*, 1977) and to increase the urinary excretion of prostaglandins (Scherer & Weber, 1979). Interestingly Sullivan & Patrick (1981) found that aortae from rats given intravenous frusemide had an increased capacity to produce PGI_2. This was an indirect effect since incubation of aortae with frusemide *ex vivo* had no effect. Gerber & Nies (1981) also showed that, after radioactive labelling of arachidonic acid within the kidney, frusemide given intravenously released arachidonic acid from the kidney. These findings taken together with our results suggest that frusemide acts *in vivo* to stimulate directly or indirectly prostaglandin production and that the presence of the kidney is essential. It is possible that the stimulation by frusemide of renin and angiotensin II within the kidney is a necessary intermediate step since Attallah *et al.* (1982) found that saralasin pretreatment abolished frusemide-stimulated prostaglandin E_2 (PGE_2) biosynthesis in conscious rabbits. Intra-renal angiotensin II may then mediate the prostaglandin production as it is known that angiotensin II can release arachidonic acid and prostaglandins (Gryglewski *et al.*, 1980). Recently the increase in venous capacitance seen in man after frusemide has been suggested to be prostaglandin-mediated but secondary to the production of renin and angiotensin II from the kidney by frusemide (Johnston *et al.*, 1983).

If, by whatever mechanism, the amount of vasodilatory prostaglandins were increased in the peripheral vasculature, this could account for the inhibition of the vasoconstrictor responses we found. The greater degree of inhibition of responses to angiotensin II than to noradrenaline suggests some additional effect. This is not likely to be a result of angiotensin II receptor blockade after frusemide since nephrectomy or indomethacin would be unlikely to influence any such effect. However, part of the vasoconstrictor effect of angiotensin II is a result of

its potentiation of the effect of sympathetic nerve stimulation (Hughes & Roth, 1971). Since the sympathetic innervation to the mesenteric vasculature in these rats was intact, such an effect may contribute to our angiotensin II responses. Such a facilitatory effect of angiotensin can be inhibited by prostaglandins or arachidonic acid. Recently Jackson & Campbell (1981) found, in the *in situ* blood perfused rat mesentery, that PGE_2 at a dose that does not itself affect basal vasoconstrictor responses to sympathetic nerve stimulation, does inhibit the angiotensin II-induced potentiation of those responses. This would indicate that low levels of arachidonic acid or prostaglandins that may result from frusemide administration, can interfere with the facilitatory effects of angiotensin II on sympathetic transmission and yet have no direct vasodilator effect themselves. This would fit with our findings of an inhibition of the responses to angiotensin II after frusemide with no change in baseline mesenteric blood flow.

Frusemide is well known to release renin from the kidney and the release seems to be prostaglandin-mediated (Bailie *et al.*, 1976). Thus this release of renin and increase in circulating endogenous angiotensin II levels would be prevented by either nephrectomy or indomethacin treatment. This raises the possibility that the effects of frusemide we found to reduce vasoconstrictor responses to exogenous angiotensin II and noradrenaline may be a more direct consequence of the increased endogenous angiotensin II levels. Although chronic increased levels of renin and angioteinsin II can reduce responses to pressor stimuli (Reid & Laragh, 1965) this seems an unlikely explanation for our results. We infused exogenous angiotensin II so that its vascular effects matched those produced by frusemide (i.e. a small rise in mean blood pressure with no change in mesenteric blood flow) and this infusion did not change the vasoconstrictor responses to angiotensin II and noradrenaline. Furthermore it has also recently been shown in anaesthetized rats that increased levels of endogenous angiotensin II produced in renal hypertensive rats, were in fact associated with an increased vasoconstrictor response to exogenous noradrenaline and that these increased responses returned to normal after angiotensin II blockade (Zimmerman *et al.*, 1983).

We wish to thank Peter J. Dosen for his excellent technical assistance. This work was supported by a grant from the National Health and Medical Research Council. Mrs M. Bond prepared the manuscript.

References

ARITA, M., UENO, Y., SURUDA, H., MOHARA, O., NISHIO, I. & MASUYAMA, Y. (1983). Changes in plasma norepinephrine after intravertebral artery infusion of saralasin in sodium depleted dogs. *Jap. Circ. J.*, **47**, 336–341.

ATTALLAH, A.A., STAHL, R.A., BLOCH, D.L., AMBRUS, J.L., & LEE J.B. (1982). Renal prostaglandin E_2 biosynthesis dependence on angiotensin II. *Am. J. Cardiol.*, **49**, 1521–1523.

BAILIE, M.D., CROSSLAN, K. & HOOK, J.B. (1976). Natriuretic effect of furosemide after inhibition of prostaglandin synthetase. *J. Pharmac. exp. Ther.*, **199**, 469–576.

BAYNE, E.J. & WILLIAMSON, H.E. (1979). Effect of furosemide on peripheral venous compliance following ureteral ligation in the adult dog. *Res. Comm. Chem. Path. Pharmac.*, **25**, 399–402.

BOURLAND, W.A., DAY, D.K. & WILLIAMSON, H.E. (1977). The role of the kidney in the early nondiuretic action of furosemide to reduce elevated left atrial pressure in the hypervolemic dog. *J. Pharmac. exp. Ther.*, **202**, 221–229.

DIKSHIT, K., VYDEN, J.K., FORRESTER, J.S., CHATTERJEE, K., PRAKASH, R. & SWAN, H.J.C. (1973). Renal and extrarenal hemodynamic effects of furosemide in congestive heart failure after acute myocardial infarction. *N. Engl. J. Med.*, **288**, 1087–1090.

GERBER, J.G. & NIES, A.S. (1981). Interaction between furosemide-induced renal vasodilation and the prostaglandin system. *Prost. Med.*, **6**, 135–145.

GRYGLEWSKI, R.J., SPLAWINSKI, J. & KORBUT, R. (1980). Endogenous mechanisms that regulate prostacyclin release. In *Advances in Prostaglandin and Thromboxane Research*, Vol. 7, pp. 177–287. ed. Samuelsson, B., Ramwell, P. & Paoletti, R. New York: Raven Press.

HESSE, B. & NIELSEN, I. (1976). Unimpeded plasma renin increase after intravenous furosemide during saline replacement. *Scand J. Clin. Lab. Invest.*, **36**, 23–30.

HUGHES, J. & ROTH, R.H. (1971). Evidence that angiotensin enhances transmitter release during sympathetic nerve stimulation. *Br. J. Pharmac.*, **41**, 239–255.

JACKSON, E.K. & CAMPBELL, W.G. (1980). The *in situ* blood perfused rat mesentery, a model for assessing modulation of adrenergic neuro-transmission. *Eur. J. Pharmac.*, **66**, 217–224.

JACKSON, E.K. & CAMPBELL, W.B. (1981). A possible antihypertensive mechanism of propranolol: antagonism of angiotensin II enhancement of sympathetic nerve transmission through prostaglandins. *Hypertension*, **3**, 23–33.

JOHNSTON, G.D., NICHOLLS, D.P., LEAKEY, W.J. & FINCH, M.B. (1983). The effects of captopril on the acute vascular responses to frusemide in man. *Clin. Sci.*, **65**, 359–363.

LOCKETT, M.F. & NICHOLAS, T.E. (1968). The effect of hydroclorothiazide and frusemide on noradrenaline sensitivity and blood pressure of salt-loaded rats before and after nephrectomy. *Br. J. Pharmac.*, **33**, 136–144.

REID, W.D. & LARAGH, J.H. (1965). Sodium and potassium intake, blood pressure and pressor response to angioten-

sin. *Proc. Soc. exp. Biol. Med.*, **120,** 26–29.

SCHERER, B. & WEBER, P.C. (1979). Time-dependent changes in prostaglandin excretion in response to frusemide in man. *Clin. Sci.*, **56,** 77–81.

STRUYKER-BOUDIER, H.A.J., SMITS, J.F.M., KLEINJANS, J.C.S. & VAN ESSEN, H. (1983). Hemodynamic actions of diuretic agents. *Clin. Exp. Hyper.*, **A5,** 209–223.

SULLIVAN, J.S. & PATRICK, D.R. (1981). Release of prostaglandin I_2-like activity from the rat aorta: effect of captopril, furosemide and sodium. *Prostaglandins*, **22,** 575–585.

WEBER, P.C., SCHERER, B. & LARSSON, C. (1977). Increase of free arachidonic acid by furosemide in man as the cause of prostaglandin and renin release. *Eur. J. Pharmac.*, **41,** 329–332.

WILLIAMSON, H.E., BOURLAND, W.A. & MARCHAND, G.R. (1974). Inhibition of furosemide induced increase in renal blood flow by indomethacin. *Proc. Soc. exp. Biol. Med.*, **148,** 164–165.

ZIMMERMAN, J.B., BRANCH, R.A. & JACKSON, E.K. (1983). Chronic renal artery constriction potentiates noradrenergic nerve transmission *in vivo* via an angiotensin II mechanism. *Clin. Res.*, **4,** 337A.

(*Received December 8, 1983.*
Revised May 22, 1984.)