Interaction between renal prostaglandins and angiotensin II in controlling glomerular filtration in the dog

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Summary

1. Although previous studies suggest that the renal vasoconstrictor effects of angiotensin II (ANG II) are normally confined to the efferent arterioles, the mechanisms that prevent ANG II from constricting preglomerular vessels are still unclear. In the present study, the role of prostaglandins (PG) in protecting preglomerular vessels from ANG II constriction was examined in dogs with normal or non-filtering kidneys in which ANG II formation was blocked with captopril and renal artery pressure was servo-controlled at 75–80 mmHg.

2. Before PG blockade (n = 6), ANG II infusion (20 ng min⁻¹ kg⁻¹) decreased renal blood flow (RBF) by 54 ± 4%, but did not change glomerular filtration rate (GFR) significantly. After PG blockade (n = 6), ANG II infusion decreased GFR by 37 ± 7% and RBF by 56 ± 6%, while increasing calculated preglomerular resistance much more than before PG blockade.

3. In another group of dogs, secondary changes in renal resistances, due to tubuloglomerular feedback, were prevented by occluding the ureter during mannitol diuresis until glomerular filtration ceased. After inhibition of tubuloglomerular feedback in non-filtering kidneys (n = 7), ANG II decreased RBF by 40 ± 3% and increased glomerular hydrostatic pressure, estimated from stop-flow ureteral pressure and plasma colloid osmotic pressure, by 8.7 ± 1.7 mmHg. Postglomerular resistance increased by 91 ± 12% while preglomerular resistance was unchanged. After PG blockade and inhibition of tubuloglomerular feedback (n = 7), ANG II decreased RBF by 43 ± 4%, but did not change glomerular hydrostatic pressure due to large increases in both preglomerular (125 ± 46%) and postglomerular (81 ± 19%) resistance.

4. These observations suggest that with physiological increases in ANG II levels, PG minimize reductions in GFR by preventing preglomerular constriction without interfering with the effect of ANG II on postglomerular vessels.

Key words: angiotensin II, autoregulation, glomerular filtration rate, prostaglandins, renal blood flow, tubuloglomerular feedback.

Abbreviations: ANG II, angiotensin II; GFR, glomerular filtration rate; PCV, packed cell volume; PG, prostaglandins; RBF, renal blood flow.

Introduction

Although the principal site at which angiotensin II (ANG II) regulates renal vascular resistance is still somewhat controversial [1], previous studies from our laboratory [2–5] and other laboratories [6–8] suggested that ANG II acts primarily on the efferent arterioles during physiological activation of the renin–angiotensin system. Infusion of exogenous ANG II may cause constriction of preglomerular vessels under certain experimental conditions [1, 9], but these changes appear to be due to activation of various autoregulatory mechanisms since they do not occur when renal perfusion pressure is held constant and changes in tubuloglomerular feedback are prevented [8, 10]. In addition, ANG II does not constrict isolated afferent arterioles or interlobular arteries [11]. Thus considerable evidence suggests...
that the direct renal vasoconstrictor effects of ANG II are localized mainly in the efferent arterioles [9, 10].

The selective constrictor action of ANG II on efferent arterioles is important, because it allows the renin–angiotensin system to help prevent reductions in glomerular hydrostatic pressure and glomerular filtration rate (GFR) in various physiological and pathophysiological conditions such as sodium deprivation, renal artery constriction or increased renal nerve activity [9, 12]. However, the exact mechanisms that protect preglomerular vessels from ANG II constriction are not well understood and could be related either to a relative paucity of receptors in these vessels or to release of local vasodilators that selectively protect the afferent arterioles from ANG II vasoconstriction. One possible protective mechanism is increased formation of renal prostaglandins (PG) since ANG II stimulates PG formation [13] and since several of the PG (particularly PGE₂, PGD₂ and PGL₂) cause renal vasodilatation [14]. However, the quantitative importance of the renal PG in protecting preglomerular vessels from ANG II constriction and in stabilizing GFR is still unclear. In many of the studies in which interactions between PG and ANG II have been examined, GFR has not been measured. Also, the direct renal effects of ANG II–PG interactions on the determinants of GFR have often not been separated from possible indirect effects due to changes in renal perfusion pressure and subsequent changes in myogenic activity, or alterations in tubuloglomerular feedback.

The aim of the present study was to examine the possible role of renal PG in preventing reductions in GFR and in protecting preglomerular vessels from ANG II vasoconstriction. This was done by comparing the renal haemodynamic and GFR responses to ANG II in control dogs with the responses observed after injection of meclofenamate, an inhibitor of PG synthesis. To examine the role of intrinsic autoregulatory mechanisms in modifying the renal haemodynamic responses to ANG II and PG inhibition, experiments were also conducted in non-filtering kidneys in which changes in tubuloglomerular feedback were blocked before and after meclofenamate infusion. Changes in endogenous ANG II formation during ANG II infusion were also prevented by blocking ANG II formation with the converting enzyme inhibitor SQ-14225 (captopril) and renal perfusion pressure was held constant throughout the experiments.

Methods

Experiments were conducted in male or female greyhounds maintained on a normal sodium diet. The dogs were anaesthetized with an initial dose of 30 mg of sodium pentobarbital/kg and approximately 5 mg of pentobarbital h⁻¹ kg⁻¹ was infused intravenously to maintain a relatively constant level of anaesthesia throughout the experiment. Rectal temperature was maintained constant by warming the table on which the dog rested.

The left kidney was exposed through a retroperitoneal flank incision and small sections of the abdominal aorta, renal artery, gonadal vein and ureter were isolated. A catheter was advanced into the renal vein via the gonadal vein for collection of renal venous blood samples. The ureter was cannulated with polyvinyl chloride tubing connected to a T-tube, with one end of the tube attached to a Statham pressure transducer and the other end passing through a photoelectric drop counter for continuous measurement of urine flow rate. Renal blood flow (RBF) was measured using an electromagnetic flow transducer connected to a square-wave flowmeter (Carolina Medical Electronics). Renal artery pressure was measured from the catheter inserted into the femoral artery and advanced into the abdominal aorta just below the left renal artery. Mean systemic arterial pressure was measured and systemic arterial blood samples were collected from a catheter inserted into the femoral artery and advanced into the upper aorta above the renal arteries. Mean systemic and renal artery pressures, RBF, urine flow rate and ureteral pressure were recorded continuously on a Grass polygraph (model 7D).

GFR was determined from the renal arteriovenous extraction of [¹²⁵I]iothalamate (Glofil, Isotex Diagnostics, Friendwood, Texas, U.S.A.) and calculated as: 

\[
\text{GFR} = \frac{(1 - \text{PCV} \times \text{RBF}) \times (A - V)}{A},
\]

where PCV is the systemic arterial packed cell volume measured by the microcapillary method and A and V are the systemic arterial and renal venous ¹²⁵I radioactivities, respectively. Plasma protein concentration was measured with a refractometer (American Optical).

Experimental protocol

ANG II infusion before and after meclofenamate with constant renal artery pressure in normal kidneys. After recovery from surgery, the angiotensin converting enzyme inhibitor SQ-14225 (captopril) was infused intravenously at a rate of 20 µg min⁻¹ kg⁻¹ after a bolus intravenous injection of 1 mg/kg in order to block endogenous ANG II formation throughout the experiment. Previous studies in our laboratory have shown that captopril infusion at a rate of 14 µg min⁻¹ kg⁻¹ effectively blocks the renal haemodynamic and blood pressure responses to injections of angiotensin I [15]. Sodium
chloride solution (154 mmol/l NaCl:saline) was infused intravenously at a rate of 2.0 ml/min throughout the experiment to replace urinary losses. Renal artery pressure was reduced to and maintained at 75–80 mmHg with a servo-controlled silastic occluder [16] and 30–60 min was allowed to stabilize all variables. Renal artery pressure was maintained at the lower limits of autoregulation in order to minimize potential secondary autoregulatory changes in renal resistances that could occur during ANG II infusion. Then control measurements were made over the next 10–15 min and renal venous and arterial blood samples were obtained for measurements of $^{125}$I radioactivity as well as for plasma protein concentration and PCV. Intravenous ANG II infusion was then begun at a rate of 10 ng min$^{-1}$ kg$^{-1}$ and continued for 20 min while renal perfusion pressure was maintained constant. Renal venous and systemic arterial blood samples were obtained after 10 and 20 min of ANG II infusion for measurements of $^{125}$I radioactivities, plasma protein concentration and PCV. Then the rate of ANG II infusion was increased to 20 ng min$^{-1}$ kg$^{-1}$ and continued for 20 min while renal artery pressure was held constant and renal venous and systemic arterial blood samples were obtained after 10 and 20 min of infusion.

After stopping ANG II infusion, 60–90 min was allowed for all parameters to stabilize and then a bolus injection (5 mg/kg) of the prostaglandin synthetase inhibitor meclofenamate was administered intravenously. Studies by other investigators have demonstrated that doses of meclofenamate even lower than this effectively suppress PG synthesis [17]. Fifteen minutes were allowed and control measurements were made over the next 10–15 min. ANG II infusion was then begun at a rate of 10 ng min$^{-1}$ kg$^{-1}$ and continued for 20 min before the infusion rate was increased to 20 ng min$^{-1}$ kg$^{-1}$, according to the protocol described above. Measurements were made at the same time intervals as in the first part of the experiment.

Glomerular hydrostatic pressure, preglomerular resistance and efferent arteriolar resistance in normal kidneys were calculated according to methods previously described in detail [10].

**ANG II infusion before and after meclofenamate with constant renal artery pressure in non-filtering kidneys.** After recovery from surgery, seven dogs were infused with SQ-14225 (1 mg/kg as a bolus injection) followed by a constant infusion of 20 $\mu$g min$^{-1}$ kg$^{-1}$ in order to block endogenous ANG II formation. Then a priming dose of 200–300 ml of mannitol solution (5.4% in saline) was administered intravenously, followed by sustaining infusion of 2.0 ml/min. Renal artery perfusion pressure was reduced to and maintained at 75–80 mmHg with the servo-controlled silastic occluder and after 10–15 min of mannitol infusion and established diuresis, the ureteral outflow catheter was clamped and ureteral pressure was allowed to stabilize for at least 30 min. Renal artery pressure was lowered to 75–80 mmHg in these experiments, since previous studies suggest that glomerular hydrostatic pressure is maintained near normal levels during ureteral occlusion only when renal artery pressure is reduced to the lower limits of renal autoregulation.

After ureteral pressure had stabilized, blood samples for measurements of renal arterial and venous $^{125}$Iiothalamate radioactivities and for measurements of PCV and protein concentrations were obtained. Previous studies have demonstrated that renal arteriovenous extraction of $^{125}$Iiothalamate is essentially zero in this preparation after ureteral pressure stabilizes [10]. Then ANG II was infused intravenously at a rate of 10 ng min$^{-1}$ kg$^{-1}$ while renal perfusion was maintained constant with the servo-controlled silastic occluder. Arterial blood samples for measurements of plasma protein concentration and PCV were obtained at 5, 10, 15 and 20 min after beginning ANG II infusion. The rate of ANG II infusion was then increased to 20 ng min$^{-1}$ kg$^{-1}$ while renal artery pressure was maintained constant and RBF, ureteral pressure and mean arterial pressure was measured continuously for 20 min with arterial blood samples taken at 5, 10, 15 and 20 min of ANG II infusion at 20 ng min$^{-1}$ kg$^{-1}$. Then ANG II infusion was terminated and a 30–60 min recovery period was allowed before post-control measurements were obtained. After post-control measurements, the ureteral clamp was released in order to reduce any build up of pressure in the kidney caused by ANG II infusion and to wash out possible accumulated metabolites. Another new bolus infusion of 200 ml of mannitol was given along with a continuous infusion as described above. The ureter was again clamped and 30 min was allowed for stabilization. Then a bolus of meclofenamate (5 mg/kg) was injected intravenously and 15 min was allowed before control measurements were made 5–10 min apart. ANG II was infused at 10 and 20 ng min$^{-1}$ kg$^{-1}$ and the same protocol as described above was followed.

Glomerular hydrostatic and renal segmental resistances in non-filtering kidneys were calculated as previously described [10].

**Statistical analysis**

Data were converted to percentage change from control and analysed via a randomized block factorial analysis of variance. Presence or absence of meclofenamate, ANG II dose level and time served
as the independent variables in the analysis. In cases where the assumption of homogeneity among variances in the variance–covariance matrix were violated, a three-step testing strategy recommended by Kirk [18] was used. The $F$ values were then evaluated under both the Geisser–Greenhouse and Huynh–Feldt adjustments for degrees of freedom [18]. All analyses of variance and tests of simple main effects were analysed via the BMDP-4V general univariate and multivariate analysis of variance program [19]. Scheffe's procedure was used to evaluate multiple comparisons among treatment means [19]. Observed $F$ values and $t$ values were considered statistically significant only if $P < 0.05$. Results are expressed as means ± SE.

Results

Effects of ANG II on renal haemodynamics in normal kidneys maintained at constant perfusion pressure

ANG II raised mean arterial pressure by 22 and 32 mmHg at infusion rates of 10 and 20 ng min$^{-1}$ kg$^{-1}$, respectively. However, renal artery pressure was held constant at 77 ± 1 mmHg with the servocontroller. RBF decreased from 333 ± 53 to 202 ± 32 and 147 ± 18 ml/min after ANG II infusion for 20 min at 10 and 20 ng min$^{-1}$ kg$^{-1}$, respectively (Fig. 1). GFR did not change significantly during ANG II infusion, averaging 36.1 ± 7.4 ml/min during the control period and 35.3 ± 5.9 and 28.2 ± 3.8 ml/min after 20 min of ANG II infusion at 10 and 20 ng min$^{-1}$ kg$^{-1}$. Therefore, filtration fraction increased markedly from 0.207 ± 0.015 to 0.330 ± 0.007 and 0.367 ± 0.021 during ANG II infusion at 10 and 20 ng min$^{-1}$ kg$^{-1}$. Calculated preglomerular resistance increased slightly, from 0.085 ± 0.019 to 0.121 ± 0.029 and 0.184 ± 0.036 mmHg/(ml/min), during ANG II infusion at 10 and 20 ng min$^{-1}$ kg$^{-1}$ for 20 min, respectively, while efferent arteriolar resistance increased from 0.162 ± 0.021 to 0.278 ± 0.044 and 0.364 ± 0.064 mmHg/(ml/min) (Fig. 2). Calculated glomerular hydrostatic pressure did not change significantly during ANG II infusion.

Effects of ANG II on renal haemodynamics after meclofenamate treatment in normal kidneys maintained at constant perfusion pressure

After injection of meclofenamate, ANG II infusion for 20 min at 10 and 20 ng min$^{-1}$ kg$^{-1}$ raised mean arterial blood pressure by 19 and 27 mmHg, respectively, while renal artery pressure was maintained constant at 77 ± 1 mmHg. RBF decreased from 284 ± 37 to 141 ± 23 and 123 ± 24 ml/min and GFR decreased from 39.9 ± 3.8 ml/min to 29.2 ± 3.9 and 25.3 ± 4.0 ml/min after 20 min of ANG II infusion at 10 and 20 ng min$^{-1}$ kg$^{-1}$, respectively (Fig. 1). Filtration fraction increased from 0.277 ± 0.037 to 0.40 ± 0.033 and 0.395 ± 0.024 during ANG II infusion of 10 and 20 ng min$^{-1}$ kg$^{-1}$.

Calculated preglomerular resistance increased from 0.060 ± 0.010 to 0.198 ± 0.051 and 0.292 ± 0.075 mmHg/(ml/min) while efferent arteriolar resistance increased from 0.204 ± 0.036 to 0.413 ± 0.074 and 0.461 ± 0.091 mmHg/(ml/min) after 20 min of ANG II at 10 and 20 ng min$^{-1}$ kg$^{-1}$, respectively (Fig. 2). Calculated glomerular hydrostatic pressure decreased from 58.3 ± 2.9 to 53.3 ± 3.4 and 49.0 ± 1.4 mmHg during ANG II infusion at 10 and 20 ng min$^{-1}$ kg$^{-1}$. The decreases in GFR and glomerular hydrostatic pressure and the increases in preglomerular resistance during ANG II infusion were significantly greater after meclofenamate than under control conditions.

Effects of ANG II on renal haemodynamics in nonfiltering kidneys maintained at constant perfusion pressure

Infusion of ANG II at 10 and 20 ng min$^{-1}$ kg$^{-1}$ raised mean arterial blood pressure by 15 and 20
Prostaglandin–angiotensin II interactions

Fig. 2. Effect of ANG II infusion on renal segmental vascular resistances in normal kidneys during infusion of captopril (n = 6, ■) or captopril plus meclofenamate (n = 6, ○). C, Control; PC, post-control.

Fig. 3. Effect of ANG II infusion on renal hemodynamics in non-filtering kidneys during infusion of captopril (n = 7, ■) or captopril plus meclofenamate (n = 7, ○). C, Control; PC, post-control.

mmHg, respectively. Renal artery pressure, however, was maintained constant at 78 ± 1 mmHg. RBF decreased from 216 ± 17 to 153 ± 13 and 129 ± 9 ml/min, respectively, at 10 and 20 ng of ANG II min⁻¹ kg⁻¹ (Fig. 3). Urinary stop-flow pressure increased by 5.9 ± 1.4 and 8.8 ± 1.8 mmHg during ANG II infusion at 10 and 20 ng min⁻¹ kg⁻¹, respectively.

In contrast to the effect of ANG II in the normal kidneys, preglomerular resistance did not change appreciably during ANG II infusion in non-filtering kidneys, averaging 0.083 ± 0.007 during the control period and 0.088 ± 0.005 and 0.078 ± 0.006 mmHg/(ml/min) after 20 min of ANG II infusion at 10 and 20 ng min⁻¹ kg⁻¹, respectively (Fig. 4). However, postglomerular resistance increased markedly during ANG II infusion in non-filtering kidneys; postglomerular resistance averaged 0.280 ± 0.028 mmHg/(ml/min) during the control period and 0.429 ± 0.038 and 0.522 ± 0.040 mmHg/(ml/min) after 20 min of ANG II infusion at 10 and 20 ng min⁻¹ kg⁻¹, respectively. Glomerular hydrostatic pressure, calculated from the sum of the stop-flow ureteral pressure and the plasma colloid osmotic pressure, increased from 59.6 ± 1.9 to 64.9 ± 1.2 and 67.8 ± 0.7 mmHg after 20 min infusion of ANG II at 10 and 20 ng min⁻¹ kg⁻¹, respectively.

Effects of ANG II on renal hemodynamics after meclofenamate treatment in non-filtering kidneys maintained at constant perfusion pressure

After meclofenamate treatment in non-filtering kidneys ANG II infusion at 10 and 20 ng min⁻¹ kg⁻¹ raised mean arterial blood pressure by 13 and 15 mmHg while decreasing RBF from 131 ± 8 ml/min to 95 ± 8 and 77 ± 7 ml/min, respectively (Fig. 3). In contrast to the effects of ANG II before meclofenamate treatment, urinary stop-flow pressure and calculated glomerular hydrostatic pressure did not change appreciably after 20 min infusion of ANG II at 10 and 20 ng min⁻¹ kg⁻¹ after injection of
meclomenamate. Preglomerular resistance increased from 0.107±0.015 to 0.146±0.024 and 0.214±0.034 mmHg/(ml/min) while postglomerular resistance increased from 0.491±0.034 to 0.687±0.062 and 0.896±0.107 mmHg/(ml/min) during ANG II infusion at 10 and 20 ng min⁻¹ kg⁻¹, respectively, after injection of meclomenamate (Fig. 4).

Discussion
The results from this study suggest that PG may play an important role in preventing reductions in GFR when circulating levels of ANG II are increased. This protective effect of PG appears to be due mainly to an interaction of PG and ANG II on pregglomerular vessels, since meclomenamate potentiated the vasoconstrictor effect of ANG II on pregglomerular vessels but did not substantially alter the constrictor action of ANG II on postglomerular vessels.

In normal filtering kidneys with intact PG synthesis and servo-controlled renal artery perfusion pressure, ANG II infusion caused marked decreases in RBF but no changes in efferent arterial resistance and small increases in pregglomerular resistance. Other investigators, using micropuncture methods, have also found small increases in pregglomerular resistance, as well as increases in efferent arteriolar resistance, during ANG II infusion in normal animals [1, 8] even when PG synthesis is intact. However, increases in pregglomerular resistance during ANG II infusion in normal kidneys are probably due either to a pressure-dependent myogenic response [8] or to activation of a tubuloglomerular feedback mechanism attempting to compensate for inappropriately high levels of ANG II [10]. In the present study, increases in pregglomerular resistance did not occur during ANG II infusion when tubuloglomerular feedback was blocked by occluding the ureter during mannitol diuresis. This observation also supports the view that increases in pregglomerular resistance during ANG II infusion are due to activation of secondary autoregulatory mechanisms, mediated by changes in tubuloglomerular feedback, and are not due to a direct action of ANG II. Also in agreement with this conclusion is the observation that ANG II has little or no direct effect on isolated perfused interlobular arteries or afferent arterioles of the kidney, but has a marked constrictor effect on efferent arterioles [11].

The inability of ANG II, at physiological concentrations, to directly increase pregglomerular resistance is apparently not due to a lack of receptors on pregglomerular vessels. After meclomenamate treatment, ANG II caused marked increases in pregglomerular resistance in normal as well as in non-filtering kidneys in which changes in renal perfusion pressure and tubuloglomerular feedback were blocked. This observation supports the concept that renal PG may play an important role in minimizing ANG II constriction of pregglomerular vessels. However, meclomenamate did not appear to markedly alter the response of efferent arterioles to ANG II, suggesting that the protective effect of PG is selective and confined mainly to pregglomerular vessels. This protective effect of PG may also explain why ANG II is ineffective in constricting isolated afferent arterioles and intralobular arteries [11] in which the ability to synthesize PG is presumably still intact.

The selective effect of renal PG to protect pregglomerular vessels from ANG II constriction may be important in allowing the renin-angiotensin system to act as an effective controller of GFR by preferential constriction of efferent arterioles. Previous studies have demonstrated that during various physiological and pathophysiological conditions, such as low sodium intake [16], decreased
renal perfusion pressure [3–5] or increased renal sympathetic nerve activity [12], increased ANG II formation helps to prevent reductions in GFR by preferential constriction of efferent arterioles. If ANG II did have a major constrictor effect on preglomerular vessels, activation of the renin–angiotensin system would tend to lower GFR and could initiate a vicious cycle leading to renal failure. For example, initial reductions in GFR would decrease sodium chloride delivery to the distal tubule and stimulate ANG II formation, via a macula densa mechanism. Increased levels of ANG II would then increase preglomerular resistance, causing greater reductions in GFR and further stimulation of ANG II formation, eventually leading to renal failure. Fortunately, this vicious cycle does not normally occur because ANG II does not appear to have a major constrictor action on preglomerular vessels. One could speculate from the results of the present study that renal PG may play a major role in preventing such a vicious cycle and renal failure.

A potential criticism of our calculations of renal segmental resistances in normal filtering kidneys is that ANG II or meclofenamate may have altered the glomerular capillary filtration coefficient ($K_f$), whereas we assumed $K_f$ to remain constant. Although some investigators have reported that ANG II decreases $K_f$ [20], other studies have failed to document a significant effect of ANG II, in physiological concentrations, on $K_f$ in the dog [21]. To the extent that ANG II decreases $K_f$, our calculations would tend to underestimate increases in efferent arteriolar resistance and overestimate increases in preglomerular resistance caused by ANG II in normal filtering kidneys. This would tend to bias the results against our hypothesis that ANG II normally has no significant effect on preglomerular resistance. However, in non-filtering kidneys, the calculations of renal segmental resistances are independent of $K_f$ since GFR is zero. The fact that similar results were obtained in non-filtering and filtering kidneys strengthens our conclusion that PG selectively protect preglomerular vessels from the constrictor effect of ANG II.

Another factor that must be considered in our experiments is that the contribution of renal PG in offsetting the constrictor effect of ANG II may have been magnified by the use of captopril to block endogenous ANG II formation. Captopril has been shown to increase PG synthesis in rat glomeruli [22], but the importance of this effect in altering overall renal haemodynamics is still unclear.

It is possible that some other effect of meclofenamate, besides blockade of PG synthesis, may have altered the constrictor response to ANG II in preglomerular vessels. For example, cyclo-oxygenase inhibitors could also decrease phosphodiesterase activity and cause accumulation of adenosine. We have previously shown that when renal adenosine levels are elevated, ANG II may have a marked constrictor action on preglomerular vessels as well as on efferent arterioles [23]. Therefore, we cannot completely rule out the possibility that part of the effect of meclofenamate on the renal vascular response to ANG II may be due to increased levels of adenosine rather than blockade of PG synthesis. It is also possible that meclofenamate may have some other non-specific action on preglomerular vessels that could alter their response to ANG II. Also, because meclofenamate blocks the entire PG cascade, it is not possible from the present studies to determine which of the renal PG may be most important in protecting against ANG II vasoconstriction of preglomerular vessels. Further studies are needed to determine the exact mechanism by which ANG II and PG interact on preglomerular vessels.

In summary, the results from the present study suggest that ANG II causes marked increases in efferent arteriolar resistance with little or no direct effect on preglomerular vessels. The small increase in preglomerular resistance that occurred during ANG II infusion in normal kidneys appears to be a secondary autoregulatory response due to increased renal perfusion pressure or changes in tubuloglomerular feedback activity. The lack of a direct effect of ANG II on preglomerular vessels is apparently due, in part, to a selective action of renal PG to protect these vessels from ANG II constriction. However, renal PG do not appear to interfere with the constrictor effect of ANG II on postglomerular vessels. This protective effect of renal PG on preglomerular vessels may play an important role in allowing the renin–angiotensin system to effectively control GFR through an efferent arteriolar mechanism and to prevent the development of a vicious cycle leading to renal failure.

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References