Subpressor Infusions of Angiotensin II Alter Glomerular Binding, Prostaglandin E₂, and Cyclic AMP Production

JANICE GREEN DOUGLAS

SUMMARY Angiotensin II (ANG II) has been postulated to have a pathogenetic role in diminished glomerular function in a number of animal models of acute renal failure. The present studies were designed to test the hypothesis that modest elevations in circulating ANG II potentiate the ability of ANG II to reduce glomerular capillary surface area through an effect on ANG II binding to glomerular mesangial cells and/or influences on other modulators of function. Rat glomeruli isolated by a sieving technique were employed in vitro in an ANG II radioreceptor assay. Subpressor infusion of ANG II for 36 hours in rats increases the affinity and number of ANG II binding sites of isolated glomeruli. The ability of ANG II to influence function was tested by assessing its effect on glomerular surface area in vitro by image-analysis microscopy, a method of measuring mesangial cell contractility. The sensitivity and magnitude of ANG II-induced decrements in glomerular surface area were increased. ANG II infusion diminished glomerular prostaglandin E₂ (PGE₂) production, increased basal cyclic adenosine 3',5'-monophosphate (cAMP) production, and enhanced ANG II-induced decrements in cAMP production. In control glomeruli, only pharmacological concentrations of ANG II inhibited cAMP, but after ANG II infusion, physiological concentrations of ANG II were capable of inhibiting cAMP by as much as 57% (below basal values). In conclusion, continuous infusion of subpressor concentrations of ANG II in rats enhances the contractile response of the glomerular mesangial cell through effects on the cell's surface receptor for ANG II and on prostaglandin and cAMP production. These actions may be important mediators of the effects of ANG II on glomerular function associated with a number of experimental models of kidney disease.

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KEY WORDS receptors

ANGIOTENSIN II (ANG II) receptors have been identified on glomeruli and binding has been correlated with a sensitive contractile response in vitro.1-3 Mesangial cells (smooth muscle-like cells) represent one site where ANG II binds, induces contraction, and thereby decreases glomerular size, capillary patency, and surface area available for filtration.4,5 Systemic infusions of ANG II in the subpressor range cause reductions in glomerular capillary ultrafiltration coefficient (Kᵢ) through this action.6,7 In certain experimental models of kidney disease, the observed decreases in Kᵢ and nephron filtration rate have been postulated to occur in part secondary to increased circulating ANG II. A pathogenetic role for ANG II has been substantiated by the observation that a decrease in the intrarenal concentration of ANG II significantly minimizes the alterations in glomerular function.8-10 Although pharmacological concentrations of ANG II decrease glomerular ANG II receptor density, it is not clear whether there is an accompanying decrease in the Kᵢ-lowering effect of ANG II.11,12 It is also unclear whether a more modest elevation of ANG II has the same effect on binding or function. For example, mercuric chloride–induced renal failure associated with a twofold increase in circulating ANG II produces no decrement in glomerular ANG II receptor density.13 Thus it has been postulated that the failure to "down-
regulate” ANG II receptors potentiates the $K_f$-lowering ability of ANG II. In sodium depletion, for example, the $K_f$-lowering effects of ANG II are not diminished, despite a decrease in the number of glomerular ANG II receptors.14,15

As an outgrowth of these observations, the present studies were designed to test the hypothesis that increments in circulating ANG II may potentiate the $K_f$-lowering ability of ANG II through a receptor-mediated mechanism or other alterations in cellular function. Binding was determined in an ANG II radioreceptor assay employing isolated rat glomeruli. Functional responsiveness was assessed by determining ANG II-induced effects on glomerular surface area in vitro, a measure of mesangial contraction and the $K_f$-lowering ability of ANG II. Biochemical effects were also determined by measuring glomerular prostaglandin and cyclic adenosine 3',5'-monophosphate (cAMP) production, both known to be important modulators of mesangial cell function. These studies demonstrated increased ANG II binding and enhanced glomerular contractile responses to ANG II following infusion of a subpressor concentration of ANG II. Important observations were made regarding ANG II-induced changes in cAMP production as a potential regulator of glomerular function.

Materials and Methods

Male Sprague-Dawley rats (225–250 g) obtained from Zivic Miller (Pittsburgh, PA, USA) were maintained on a diet with normal sodium and potassium content for 2 days before implantation of miniosmotic pumps (Alza, Palo Alto, CA, USA). Synthetic [Asp$^1$, Ile$^4$] ANG II (US Biochem, Cleveland, OH, USA) was infused at a rate of 33 ng/kg/min employing mini-pumps implanted intraperitoneally under ether anesthesia. Controls received vehicle (0.1 N acetic acid) pumps implanted intraperitoneally under ether anesthesia. 14

Preparation of Isolated Glomeruli and Receptor Binding Procedures

The details of glomerular isolation techniques and ANG II receptor binding assay have been described elsewhere.2 Briefly, glomeruli were isolated by the sieving technique of Misra,22 with purity greater than 95%. Assay buffer was phosphate-buffered saline, pH 7.4, with 10 mM glucose. The assay buffer also contained 5 mM MgCl$_2$, 125 /ng/ml adrenocorticotropic hormone, and 1% bovine serum albumin in a final volume of 400 μl. Reported data on ANG II were derived from full binding inhibition studies using 5 to 10 fmol of 125I-labeled ANG II, 0.1 to 2 pmol of unlabeled ANG II, and 10 to 20 μg of protein. Nonspecific binding was determined in the presence of 1 nmol of unlabeled ANG II. Incubations for all groups were conducted for 2 hours at 22°C. Bound ANG II and free ANG II were separated by filtration through nitrocellulose filters (HAWP 0.45 μm; Millipore, Bedford, MA, USA). Filtrates were dried and counted in a Searle gamma spectrometer (Des Plaines, IL, USA), and data were analyzed by Scatchard analysis following correction for nonspecific binding. A linear regression analysis was employed in that a single class of receptors was present under all conditions. Proteins were determined by the method of Lowry et al.24 following precipitation with 8% TCA.

Glomerular Surface Area Determinations

Glomeruli were isolated in tissue culture medium (Medium 199 with 25 mM HEPES; Gibco Laboratories, New York, NY, USA), and incubated at 22°C for 15 to 30 minutes after the addition of diluent or ANG II in siliconized 12 x 75 mm borosilicate glass tubes in a final volume of 1 ml. The reaction was stopped by addition of an equal volume of 2.5% glutaraldehyde (Kodak, Rochester, NY, USA), 4% sucrose, and 50
mM cacodylate-buffer solution, as previously described. Surface area was determined using an inverted Nikon microscope (Chiyoda-Ku, Japan) attached to a digitizing screen, as described in detail elsewhere. Surface areas were determined for 30 to 50 glomeruli at each dose level of ANG II by a person other than the one who conducted the experiment. All samples were coded and measured blind to remove observer bias. Only intact decapsulated glomeruli were measured in each sample. Results are presented as a percent change from the control surface area in dose-response curves for ANG II and as absolute values.

Glomerular Incubations for PGE₂ and cAMP Determinations

Incubations were conducted at 22°C as described for surface area determinations, except that reactions were stopped by pouring samples into microfuge tubes and spinning for 20 seconds. PGE₂ was assayed on the supernate (unextracted), and cAMP was assayed on 0.1 N HCl or 5% TCA extracts of intact glomeruli. cAMP was determined routinely on the intracellular compartment only, since we found that differences were not observed in the corresponding media samples. For example, intracellular cAMP was 6.4 ± 0.5 pmol/min/mg of protein (n = 12) in control glomeruli and 8.1 ± 0.4 (n = 12, p < 0.02) in glomeruli from the group treated with ANG II in vivo. However, the corresponding values in the media did not differ (1.8 ± 0.07, n = 12 for controls and 1.8 ± 0.1, n = 12, after ANG II infusion). Therefore, all reported values are for intracellular cAMP. Protein was determined on NaOH extract of the pellet after removal of 0.1N HCl or TCA.

Statistical Analysis

Results are reported as means ± SEM. Statistical significance was determined using paired and unpaired Student's t tests.

Results

Effects on Blood Pressure, Hormones, and Receptor Measurements

The infusion rate for ANG II at 33 ng/kg/min was chosen because it has been demonstrated to have no acute effect on blood pressure or glomerular hemodynamics. This was borne out at least in part in the present studies by the fact that there was no significant difference in the systolic blood pressures of conscious animals on the 2 days of ANG II infusion (Table 1). Both groups displayed a transient elevation in blood pressure on the first postsurgical day, but by the second postsurgical day blood pressures had returned to normal. The plasma ANG II concentration increased 3.5-fold above the control value of 5.5 ± 0.9 pg/ml (Table 2), and was associated with a twofold stimulation of plasma aldosterone. ANG II is known to inhibit renin release, but acute infusion fails to decrease kidney renin content. This was assessed in the present study to substantiate ANG II delivery to relevant receptors in the kidney. The ANG II-infused rats had 25% lower kidney renin content than the control animals (see Table 2). This suggests that an additional action of ANG II is to inhibit renin synthesis at the infusion rate employed.

Despite the fact that infusions of pharmacological concentrations of ANG II have been reported to decrease glomerular ANG II receptor density, in the present study, infusion in the physiological range increased the affinity and density of glomerular receptors. A typical Scatchard plot illustrating this is shown in Figure 1. Table 3 lists the binding constants from all experiments. There was a 19% decrease in Kᵣ following ANG II infusion and a 33% increase in receptor density. Such changes in binding would be expected to enhance ANG II's effects on glomerular function.

Glomerular Surface Area Determinations

Assessment of glomerular size in vitro has frequently been employed as a qualitative measure of mesangial contractile responses to vasoactive agents, including ANG II. In the present studies, measurements of the effects of ANG II on glomerular surface area (GSA) represented an important adjunct to binding. The surface area of control glomeruli was 11,335 ± 619 µm² (Table 4), while that from the group infused with ANG II was 9797 ± 725 µm² (n = 6, p < 0.05). The change in GSA of isolated glomeruli was also more sensitive to ANG II following ANG II treatment in vivo. Typical dose-response curves are presented in Figure 2. Values are presented as a percent change from basal values, and 30 to 40

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**Table 1. Systolic Blood Pressures in Conscious Rats**

<table>
<thead>
<tr>
<th>Time</th>
<th>Control</th>
<th>ANG II infusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Before surgery</td>
<td>105 ± 1.3 (35)</td>
<td>105 ± 2.8 (29)</td>
</tr>
<tr>
<td>After minipump implantation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Day 1</td>
<td>123 ± 3 (9)</td>
<td>130 ± 3.8 (10)</td>
</tr>
<tr>
<td>Day 2</td>
<td>108 ± 5.9 (7)</td>
<td>108 ± 8.5 (5)</td>
</tr>
</tbody>
</table>

Values shown are means ± SE. Values in parentheses indicate number of rats measured. Before surgery refers to the measurements done during the 7 days preceding osmotic minipump implantation intraperitoneally.

**Table 2. Results of Angiotensin II Infusion in Normal Rats**

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Control</th>
<th>ANG II</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma ANG II (pg/ml)</td>
<td>5.5 ± 0.9 (9)</td>
<td>19 ± 4.4 (14)</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Plasma aldosterone (ng/dl)</td>
<td>10 ± 0.7 (18)</td>
<td>20 ± 2.4 (18)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Kidney renin content (µg ANG I/hr/mg protein)</td>
<td>2 ± 0.2 (4)</td>
<td>1.5 ± 0.1 (4)</td>
<td>= 0.034</td>
</tr>
</tbody>
</table>

Values shown are means ± SE. Values in parentheses indicate number of rats.
glomeruli were measured at each dose level of ANG II in each experiment. The ANG II concentration that induced a maximum decrease in surface area was 100-fold lower in the ANG II-infused group (0.08 ± 0.02 pM, n = 4 experiments) as compared to 78 ± 2.3 pM (p < 0.05) for controls. The maximum response was a 6.7 ± 1.4% decrease for the control group, which was significantly lower than the maximum response for the ANG II group (11.5 ± 1.5%, p < 0.01). Enhanced in vitro responsiveness to ANG II has been reported by others and attributed to diminished in vitro eicosanoid biosynthesis, which would oppose mesangial cell contraction.3

Glomerular PGE₂ Production
Recent studies document a decrease in basal surface area of glomeruli and enhanced contractile response to ANG II during cyclooxygenase inhibition in vitro.3 These effects are due to the loss of vasorelaxant eicosanoids and they parallel the decrease in basal surface area (see Table 4) and enhanced sensitivity and magnitude of the contractile response of isolated glomeruli following ANG II infusion (see Figure 2). Therefore, the effect of ANG II infusion on glomerular PGE₂ was evaluated. The time course of glomerular PGE₂ production under conditions identical to those for determinations of GSA demonstrated linear PGE₂ production for 30 minutes in controls, as reported elsewhere.27 A plateau was observed in the ANG II group after 15 minutes. Therefore, 15 minutes was chosen as the time point at which to compare production rates. Fifteen minutes was also the incubation period prior to surface area determinations. Control glomeruli produced 5.9 ± 1.5 ng/mg protein/15 min (see Table 4), while ANG II-pretreated glomeruli produced 4.0 ± 0.9 (p < 0.05). The lower glomerular PGE₂ production following ANG II infusion is identical to the changes accompanying sodium depletion in rats with similar increments in circulating ANG II.27 In rats with sodium depletion, decreased PGE₂ production was attributed to accelerated conversion to PGF₂α via 9-keto-PGE₂ reductase. Attempts to stimulate glomerular PGE₂ directly with ANG II (10⁻⁹–10⁻⁷ M) revealed only a 22 ± 9.6% (n = 11) increase in controls, and a 2.2 ±
4.1% (n = 11) increase following ANG II infusion in vivo.

Glomerular cAMP Production

Since the decrease in GSA following ANG II infusion exceeded the changes in either binding or basal PGE\(_2\) production, we were interested in whether glomerular cAMP serves as an additional modulator of the glomerular contractile response. cAMP is a vasodilator that relaxes mesangial cells and opposes the action of vasoconstrictors like ANG II. ANG II has been demonstrated to decrease glomerular cAMP production, albeit at pharmacological concentrations. Initial studies were designed to evaluate the effect of ANG II infusion in vivo on ANG II–induced changes in glomerular cAMP production. Knowing the effects of vasoactive agents, one could predict that decrements in mesangial or glomerular cAMP would enhance contraction, with the opposite change favoring relaxation. Basal cAMP values (see Table 4) were significantly increased after ANG II infusion when incubations were conducted in the presence of an inhibitor of cAMP-dependent phosphodiesterase (3-isobutyl-1-methylxanthine [IBMX]). Glomeruli from animals infused with ANG II (10\(^{-8}\) M) displayed a significant decrease in cAMP production that was sustained from 1 to 15 minutes. Basal production of cAMP for the control glomeruli was 4.7 ± 0.16 pmol/mg/5 min, compared to 6.7 ± 1.4 pmol/mg/5 min following ANG II infusion (p < 0.05). Figure 3 illustrates a typical dose-response curve demonstrating that after ANG II infusion in vivo, the ANG II concentration at ED\(_{50}\) was 15 nM, with a maximum response of 44% inhibition below basal values. Control glomeruli displayed no such inhibition.

Prostaglandins stimulate glomerular cAMP production. Therefore, if the contribution of PGE\(_2\) to cAMP is eliminated, ANG II's direct effect on cAMP production should be more pronounced. Figure 4 illustrates the dose-dependent effects of ANG II following 30 minutes of preincubation with 100 μM aspirin (cyclooxygenase inhibitor) and 250 μM of IBMX. The IBMX increased basal cAMP (see Table 4) and did not alter sensitivity or magnitude of ANG II–induced decrements in cAMP. The ED\(_{50}\) of the ANG II group decreased to 30 pM, and the maximum response to 1 nM (57% inhibition below the basal value of 8.6 ± 0.1 pmol/mg protein/5 min). The 23% inhibition of cAMP below the basal value of 5.5 ± 0.1 pmol/mg protein/min in control glomeruli at 10\(^{-4}\) M was of borderline statistical significance. However, a higher concentration of ANG II (10\(^{-7}\) M) induced significant inhibition of cAMP production to 54% below the basal value of 3.7 ± 0.4 pmol/mg protein/min for the control group in another experiment (not illustrated). These findings demonstrated that following ANG II infusion, the sensitivity and magnitude of ANG II–induced decrements in glomerular cAMP were markedly enhanced. This explains yet another mechanism for the enhanced contractile response to ANG II following ANG II infusion in vivo.

Discussion

The present study provides direct evidence that alterations in the glomerular ANG II receptor can modulate ANG II–induced changes in glomerular function. This model, which employed subpressor infusion of
ANG II, demonstrated enhanced ANG II-induced changes in GSA that reflected mesangial cell contractility and correlated with the increased number and affinity of ANG II receptors. In a number of studies demonstrating modulation of glomerular ANG II receptors, it has been assumed that the observed changes would alter function. Glomerular ANG II receptors reportedly are modulated following altered electrolyte composition in vitro, changes in sodium balance in vivo, infusion of pharmacological doses of ANG II, and diabetes in rat models.8-10 Until the present study, observations that changes in binding modulated functional responses to ANG II were derived from other ANG II target tissues, primarily the adrenal glomerulosa. In the adrenal, changes in sodium and potassium balance and ANG II infusion reportedly are associated with parallel changes in ANG II binding and ANG II–induced aldosterone secretion.16,33,34

In the present study, the contractile response to ANG II of the isolated glomerulus was enhanced to a much greater degree than was binding, thereby prompting us to evaluate other known modulators of mesangial cell function. cAMP is a vasodilator that relaxes mesangial cells and opposes the action of vasoconstrictors like ANG II.28 We confirmed the observation that pharmacological concentrations of ANG II are required to decrease cAMP production by glomeruli from normal rats.29 However, subpressor infusions of ANG II that have no acute effect on glomerular receptors, it has been assumed that the observed changes would alter function. Glomerular ANG II receptors reportedly are modulated following altered electrolyte composition in vitro, changes in sodium balance in vivo, infusion of pharmacological doses of ANG II, and diabetes in rat models.8-10 Until the present study, observations that changes in binding modulated functional responses to ANG II were derived from other ANG II target tissues, primarily the adrenal glomerulosa. In the adrenal, changes in sodium and potassium balance and ANG II infusion reportedly are associated with parallel changes in ANG II binding and ANG II–induced aldosterone secretion.16,33,34

In vivo, however, ANG II regulation of cAMP production mediated through N1 has not been previously shown.33 Inhibition of cAMP production may be an important contributor to the amplification of the contractile response of the whole glomerulus beyond what can be explained by an increase in the number and affinity of ANG II binding sites. In several models of acute renal injury in which intrarenal ANG II is increased slightly, the enhanced ability of ANG II to decrease cAMP may be an important modulator of function. There are no changes in ANG II receptors that provide an alternative explanation for the observed actions of ANG II.13 Therefore, decreased cAMP production may be a previously unrecognized mechanism that amplifies the ability of ANG II or other vasoactive agents to contract glomerular mesangial cells and decrease the capillary ultrafiltration coefficient ($K_f$).6,7 Consistent with this hypothesis is the observation by others that decreasing circulating ANG II has a beneficial effect in several models of acute renal injury.8-10

Sodium depletion in the presence or absence of prostaglandin synthesis inhibition represents another situation in which ANG II contributes to the degree of impairment of $K_f$.14,16,37 During chronic sodium depletion associated with high levels of circulating ANG II, ANG II has $K_f$-lowering abilities similar to those observed during sodium loading, despite markedly different glomerular receptor densities.13,27 Sodium loading increases the number of glomerular ANG II receptors, and sodium depletion has the opposite effect.33 One mechanism postulated for enhanced $K_f$ lowering due to ANG II is the contributory effect of lower levels of glomerular PGE$_2$.36 A similar observation was noted in the present study following ANG II infusion. A decrease in glomerular PGE$_2$ has been documented previously to enhance ANG II–induced decrements in GSA, effects that are reversed by addition of exogenous PGE$_2$. Therefore, a decrease in glomerular PGE$_2$ could contribute to the pathophysiology. These findings seem at variance with reports that ANG II increases PGE$_2$ production by mesangial cells.4 Several reports reveal that continuous ANG II administration causes no sustained elevation in renal PGE$_2$ production.37-39 Therefore, the hypothesis seems well founded that decreased glomerular PGE$_2$ may contribute to 1) enhanced $K_f$ lowering by ANG II in states of sodium depletion and 2) surface area change with sodium depletion. The observation that ANG II–induced inhibition of cAMP production was enhanced to a greater degree in the presence of a cyclooxygenase inhibitor provides an explanation for the potentiation of ANG II–induced decrements in GSA and $K_f$ during cyclooxygenase inhibition. It suggests that prostaglandins contribute to maintenance of GSA through stimulation of cAMP production.29

Observations in the present study about the ability of ANG II to enhance binding and contractile responses of the isolated glomerulus differ from those of Bellucci and Wilkes.11 They demonstrated a decrement in glomerular ANG II receptor density following infusion of ANG II and reported no change in binding affinity. Similar down-regulation was observed by Kitamura et al.15 despite the fact that higher affinity binding was noted after prolonged ANG II infusion. Several important differences in experimental design could account for the lack of agreement. The concentration of ANG II employed in this study was physiological and subpressor, decreased renal renin content, and stimulated aldosterone twofold (see Table 1). Bellucci and Wilkes and Kitamura et al. employed a pharmacological infusion rate that was pressor and 7- to 15-fold greater than that reported here. It is not surprising that such marked increments in circulating ANG II down-regulate glomerular ANG II receptors. An analogous observation has been made following pharmacological ANG II infusion in adrenal glomerulosa, a tissue that ordinarily up-regulates with modest elevations in circulating ANG II.40 A second major difference in experimental design is the incubation conditions for the ANG II radioreceptor assay employed by Bellucci and Wilkes.11 Their ligand and glomerular protein concentrations were much higher and their time course much shorter, yielding lower affinity binding in controls.
A similar relationship between opiate agonist receptor number and ADP-ribosylated N\textsubscript{i} has been demonstrated with cultured Ng-108-15 cells.\textsuperscript{41} The opposite was observed in the present study, in which enhanced binding was correlated with greater inhibition of cAMP production.

In summary, ANG II infusion markedly enhances the sensitivity and magnitude of the contractile response of the isolated glomerulus, an action that seems to predict a greater $K_{D}$-lowering ability in vivo. A number of biochemical effects could account for the observed potentiation in function, namely, 1) an increase in the binding affinity and number of ANG II receptors, 2) an enhanced ability of ANG II to decrease cAMP production, and 3) diminished PGE\textsubscript{2} production. Similar changes in the biochemistry of the glomerulus might mediate glomerular pathophysiology during renal injury, sodium depletion, and cyclooxygenase inhibition. These observations emphasize the complex interrelationships between ANG II and glomerular function.

Acknowledgments

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(40 \times 10^{-10} \text{M}).\textsuperscript{3} In contrast, the sensitivity of the present radioreceptor assay is close to one order of magnitude higher, and for this reason is more likely to detect any changes in affinity that are present. If one takes these differences in study design into account, it is not surprising to find that study conclusions are diametrically opposed. It is possible that the observed changes in number of ANG II receptors in the present study were indirect and mediated through changes in the intracellular regulator $N\text{i}$. A progressive decrease in the number of ANG II receptors on hepatocytes was correlated with increasing adenosine 5'-diphosphate (ADP) ribosylation of $N\text{i}$ with pertussis toxin and loss of ANG II inhibition of cAMP production.\textsuperscript{35} A similar relationship between opiate agonist receptor number and ADP-ribosylated $N\text{i}$ has been demonstrated with cultured Ng-108-15 cells.\textsuperscript{41} The opposite was observed in the present study, in which enhanced binding was correlated with greater inhibition of cAMP production.

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