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Thromboxane mediates renal hemodynamic response to infused angiotensin II

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Thromboxane mediates renal hemodynamic response to infused angiotensin II. Since we had found that angiotensin II (Ang II), but not phenylephrine (PE), increased the excretion of thromboxane (Tx) and raised mean arterial pressure (MAP) by a Tx-dependent mechanism, we tested the role of TxA_2 in mediating Ang II-induced changes in renal hemodynamics. For series 1, groups of anesthetized rats received an i.v. infusion of Ang II (50 ng · kg^{-1} · min^{-1}). When infused with a vehicle, Ang II increased MAP, renal vascular resistance (RVR) and the excretion of TxB_2 factored by GFR. A PGH_2-TxA_2 receptor antagonist, SQ-29,548, or three days of pretreatment with a TxA_2 synthase inhibitor UK-38,485, which reduced excretion of TxB_2 by 80%, blunted the rise in MAP and RVR induced by Ang II. In contrast, three days of pretreatment with indomethacin did not alter the renal vascular response to Ang II. For series 2, groups of rats received Ang II at a higher rate (500 ng · kg^{-1} · min^{-1}) while the RPP was stabilized at +11 to +15 mm Hg with a suprarenal aortic clamp. SQ-29,548 and UK-38,485 both prevented Ang II-induced reductions in GFR and blocked 80% of the increase in RVR. For series 3, infusions of phenylephrine at an equipressor dose to series 2 of 30 μg · kg^{-1} · min^{-1} with control of RPP at +14 mm Hg also increased RVR but this was not blunted by SQ-29,548. In conclusion: 1.) infusion of Ang II increases excretion of filtered TxB_2, causes dose-dependent increases in RVR and, at high doses, reduces GFR. 2.) Inhibition of TxA_2 synthesis or blockade of PGH_2-TxA_2 receptors prevents the fall in GFR and blunts 70 to 90% of the increase in RVR. 3.) These effects are independent of RPP, appear to be specific for Ang II, and are counteracted by release of vasodilator cyclooxygenase products.

Angiotensin II (Ang II) is a powerful renal vasoconstrictor which, when infused in high doses, can reduce the glomerular filtration rate (GFR). There is evidence in a number of animal models of Ang II-related hypertension of increased thromboxane A_2 (TxA_2) generation by the tissues and/or the kidneys and a reduction in blood pressure (BP), or renal vascular resistance (RVR), with drugs which blunt TxA_2 generation or which block prostaglandin (PG) H_2-TxA_2 receptors. These models include the 2-kidney, 1-clip (2K,1C) renovascular rat [1–3], the spontaneously hypertensive rat (SHR) [4–6], the Dahl salt-sensitive rat [7], the Lyon genetically hypertensive rat [8] and the rat model of reduced renal mass [9–11]. Short- or long-term infusions of Ang II into anesthetized or conscious rats increases the renal excretion of TxB_2 [12, 13]. Therefore, the present studies were designed to investigate the hypothesis that TxA_2 mediates the renal vascular actions of infused Ang II. We contrasted the effect of Ang II infusion at two rates on renal hemodynamics in groups of rats administered a vehicle (Veh), a TxA_2 synthesis inhibitor or a PGH_2-TxA_2 receptor antagonist. Since indomethacin has been shown to potentiate the effects of infused Ang II on renal vasoconstriction in dogs [14–16] and salt-depleted rats [17], we tested also the effects of indomethacin pretreatment on the renal hemodynamic response to an Ang II infusion. During infusion of Ang II at the higher rate, the renal perfusion pressure (RPP) was controlled to the same level as at the lower rate to allow a comparison of the dose-response relationships without the confounding effects of large differences in the RPP. Since we found that the infusion of the α-adrenoreceptor agonist phenylephrine (PE) did not increase the excretion of TxB_2 and the pressor response to PE was unaffected by a PGH_2-TxA_2 receptor antagonist [12], we also assessed the effects of the PGH_2-TxA_2 receptor antagonist on the renal vasoconstrictor response to PE. Preliminary accounts of some of this work have been published [18, 19].

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Methods

Animal preparation

Male Sprague-Dawley rats (175 to 250 g) were maintained on standard rat chow (Rodent Laboratory Chow 5001, Ralston, Purina, Co., St. Louis, Missouri, USA) and prepared for renal clearance measurements [20]. Albumin (3 g · dl^{-1}; Sigma Chemical Co.) was dissolved in 0.154 M NaCl solution and infused throughout at 0.5 ml · 100 g body wt^{-1} · hr^{-1} following a priming dose of 0.5 ml to maintain a euvolemic state [21]. One femoral artery was cannulated to measure the mean arterial pressure (MAP) or the renal perfusion pressure (RPP). Both jugular veins were cannulated; one transmitted an infusion of [^{3}H]-inulin (In; 0.1 μCi · kg^{-1} · hr^{-1}) and [^{14}C]-paraaminohippurate (PAH; 0.05 μCi · kg^{-1} · hr^{-1}; both supplied by New England Nuclear, Boston, Massachusetts, USA) which were added to the maintenance infusion of albumin in saline. The other was maintained patent with heparin saline and used to infuse vehicle or drugs. The GFR was taken as the clearance of In and the renal plasma flow (RPF) as the clearance of PAH; renal extraction of PAH was not assessed.

Forty-five minutes elapsed following completion of surgery before any measurements were made. Thereafter, there was a basal urine collection period of 30 minutes; blood was sampled

Table 1. Summary of the experimental groups

Group	Number of rats studied	Three-day pre-tx	Gavage 15 & 1 hr before	Infusion throughout study	Control of RPP	Period 1 infusion	Period 2 infusion
Series 1							
1	16	Veh	None	Veh	No	Veh	Veh
2	8	Veh	None	Veh	No	Veh	Ang II (LD)
3	9	UK	None	Veh	No	Veh	Ang II (LD)
4	8	Veh	None	SQ	No	Veh	Ang II (LD)
5	8	Veh	Indo	Veh	No	Veh	Ang II (LD)
Series 2							
6	8	Veh	None	Veh	Yes	Veh	Ang II (HD)
7	9	Veh	None	SQ	Yes	Veh	Ang II (HD)
8	8	UK	None	Veh	Yes	Veh	Ang II (HD)
Series 3							
9	8	None	None	Veh	Yes	Veh	PE
10	8	None	None	SQ	Yes	Veh	PE

Abbreviations are: RPP, renal perfusion pressure; Veh, vehicle; Ang II, angiotensin II; LD, lower dose (50 ng · kg^{-1} · min^{-1}); HD, higher dose (500 ng · kg^{-1} · min^{-1}); SQ, SQ-29,548 (8 mg · kg^{-1} and 8 mg · kg^{-1} · hr^{-1}); UK, UK-38,485 (100 mg · kg^{-1} · day^{-1} i.p. ×3); Indo, indomethacin (5 mg · kg × 2 p.o.); PE, phenylephrine (30 μg · kg^{-1} · min^{-1}).

at the mid-point and replaced with an equal volume of albumin-saline solution. This was followed by a 15-minute equilibration period and a second experimental period of 30 minutes with blood sampled at the mid-point, during which vehicle (Veh), Ang II or PE were infused. Ten groups of rats were studied. The numbers of animals in each group, and a summary of their preparation are contained in Table 1.

UK-38,485 is an imidazole-derived inhibitor of TxA_2 synthase [22]. At concentrations which produce considerable inhibition of TxA_2 synthase, it does not alter the activity of cyclooxygenase, lipoxygenase or angiotensin converting enzyme [22]. We found previously that although it did not produce reliable inhibition of TxB_2 excretion or blockade of Ang II pressor responses when given shortly before testing, when given for three days before testing it produced uniform suppression of TxB_2 and Ang II pressor responses. Moreover, this dosing schedule did not alter basal or Ang II-stimulated levels of excretion of PGE_2 or the prostacyclin metabolite $6kPGF_{1\alpha}$ [18]. Therefore, animals in the groups that required inhibition of TxA_2 synthase received three days of pre-treatment with UK-38,485 (100 mg · kg^{-1} · day^{-1} i.p.) while those in the remaining group received vehicle injections.

SQ-29,548 is a structural analogue of the PG endoperoxide, PGH_2 and of TxA_2 [23]. These two vasoconstrictor PG's share a common receptor which is inhibited reversibly by this drug [23]. SQ-29,548 does not inhibit cyclooxygenase or TxA_2 synthase in vitro [23]. However, this dose of SQ-29,548 totally blocks the renal vasoconstriction and reduction in GFR induced by an infusion of the TxA_2 mimetic, U-46,619 [24]. In contrast to the delayed effects of UK-38,485, we found that SQ-29,548 produced a powerful blockade of Ang II-induced pressor responses [18] or U-46,619-induced renal vasoconstriction [24] shortly after administration [18]. Therefore, SQ-29,548 was given as a bolus dose on completion of surgery followed by a maintenance infusion (8 mg · kg^{-1} and 8 mg · kg^{-1} · hr^{-1}). We have shown previously that the MAP and the renal hemodynamics remain stable during infusion of SQ-29,548 [24]. Indomethacin (Indo; Sigma Chemical Corp.) is a cyclooxygenase inhibitor. When given as two oral doses of 5 mg by gavage 15 and one hour before anesthesia, we have shown that it reduces the excretion of PGE_2, $6kPGF_{1\alpha}$, and TxB_2 by 80 to 95% [21]. Thus, rats of this group received indomethacin using this dosing schedule.

The results of the initial series indicated that UK-38,485 and SQ-29,548 moderated Ang II-induced pressor responses even at the lower rate of Ang II infusion of 50 ng · kg^{-1} · min^{-1}. Therefore, a second series was undertaken to test the effects of these drugs during a higher rate of Ang II infusion (500 mg · kg^{-1} · min^{-1}) and with regulation of renal perfusion pressure (RPP) at the same level as at the lower rate of Ang II infusion. Rats of series 3 received an infusion of phenylephrine at 30 μg · kg^{-1} · min^{-1} which we had found previously to increase MAP comparably to the higher dose of Ang II by 40 to 60 mm Hg [18]. To regulate RPP, a suprarenal aortic clamp was adjusted during the infusion of Ang II or phenylephrine in series 2 and 3 to limit the rise in RPP to the level produced by the lower rate of infusion of Ang II into vehicle-treated rats of series 1.

Chemical methods and calculations

Na was measured in a flame photometer (Instrumentation Laboratories, Lexington, Massachusetts, USA) and chloride (Cl) in a chloride meter (Corning Medical, Medfield, Massachusetts, USA). [^{3}H] and [^{14}C] were analyzed in a liquid scintillation counter (Beckman Instruments, Fullerton, California, USA) with correction for quenching and cross-counting. Since Ang II altered the GFR, data for Na and Cl excretion were transformed into fractional excretions (FE) by dividing the urine-to-plasma concentration ratios for these ions by the urine-to-plasma concentration ratio for In. The RPF was estimated in these studies from the clearance of PAH, assuming a constant renal extraction of PAH (E_{PAH}). Renal vasoconstrictor agents such as Ang II normally do not change E_{PAH} although, where RBF is greatly reduced, E_{PAH} may rise, leading to a small underestimation of the degree of renal vasoconstriction [25]. We found previously that neither hyperchloremia, which stimulated endogenous TxA_2 generation within the kidney, nor indomethacin, which blocked TxA_2 generation, altered E_{PAH} in the anesthetized rat [26]. Therefore,

Table 2. Data for series 1

Group	MAP *mm Hg*	GFR *ml·min⁻¹·100 g⁻¹*	RBF *ml·min⁻¹·100 g⁻¹*	FF %	RVR *mm Hg·ml⁻¹·min⁻¹·100 g⁻¹*	UV *μl·min⁻¹·100 g⁻¹*	FE_{Na} %	FE_{Cl} %	PRA *ng·ml⁻¹·hr⁻¹*
Group 1 (N = 16)									
1. Before	110 ± 3	0.75 ± 0.04	4.59 ± 0.37	29.6 ± 1.4	26.4 ± 2.3	2.0 ± 0.3	0.07 ± 0.02	0.11 ± 0.05	28.8 ± 2.2
2. Vehicle	108 ± 2	0.70 ± 0.03	4.41 ± 0.33	27.6 ± 1.5	26.2 ± 1.8	5.7 ± 1.5	0.20 ± 0.08	0.37 ± 0.15	29.6 ± 2.5
Δ	−2 ± 1	−0.05 ± 0.03	−0.18 ± 0.17	−2.1 ± 0.7	−0.2 ± 1.5	+3.7 ± 0.9	+0.13 ± 0.04	+0.26 ± 0.15	+0.8 ± 1.3
Group 2 (N = 8)									
1. Before	118 ± 2	0.79 ± 0.05	4.13 ± 0.29	35.1 ± 1.4	29.4 ± 2.1	1.1 ± 0.1	0.05 ± 0.01	0.16 ± 0.02	31.6 ± 3.4
2. Ang II	130 ± 4	0.63 ± 0.07	3.13 ± 0.42	38.8 ± 2.0	46.7 ± 6.1	10.2 ± 3.4	0.74 ± 0.27	2.20 ± 0.91	6.0 ± 1.0
Δ	+12 ± 2	−0.16 ± 0.05	−1.00 ± 0.26	+3.6 ± 1.1	+17.3 ± 5.2	+9.1 ± 1.8	+0.69 ± 0.26	+2.04 ± 0.89	−24.6 ± 3.2
Group 3 (N = 9)									
1. UK	111 ± 3	0.87 ± 0.07	5.06 ± 0.38	30.8 ± 0.7	23.2 ± 2.3	1.2 ± 0.2	0.07 ± 0.01	0.17 ± 0.03	35.3 ± 3.7
2. UK + Ang II	118 ± 3	0.79 ± 0.06	4.66 ± 0.52	32.0 ± 1.4	28.1 ± 3.5	7.4 ± 2.4	0.77 ± 0.26	1.98 ± 0.53	10.4 ± 2.1
Δ	+7 ± 2	−0.08 ± 0.05	−0.40 ± 0.40	+1.2 ± 1.0	+4.9 ± 2.0	+6.2 ± 1.5	+0.70 ± 0.25	+1.81 ± 0.49	−24.9 ± 2.9
Group 4 (N = 8)									
1. SQ	110 ± 2	0.73 ± 0.06	4.73 ± 0.74	31.1 ± 3.8	29.4 ± 6.1	1.2 ± 0.3	0.05 ± 0.01	0.15 ± 0.02	44.3 ± 3.4
2. SQ + Ang II	115 ± 3	0.76 ± 0.06	4.50 ± 0.68	33.6 ± 4.1	32.9 ± 1.2	3.9 ± 7.7	0.35 ± 0.17	0.79 ± 0.15	9.2 ± 0.8
Δ	+5 ± 2	+0.03 ± 0.05	−0.24 ± 0.18	+2.5 ± 0.9	+3.5 ± 2.2	+2.7 ± 0.7	+0.31 ± 0.17	+0.64 ± 0.14	−31.0 ± 7.0
Group 5 (N = 6)									
1. Indo	115 ± 4	0.65 ± 0.10	4.95 ± 1.14	26.5 ± 3.1	28.9 ± 5.1	0.7 ± 0.1	0.01 ± 0.00	0.01 ± 0.00	
2. Indo + Ang II	122 ± 4	0.54 ± 0.11	3.04 ± 0.42	31.3 ± 1.4	43.1 ± 5.2	1.1 ± 0.7	0.21 ± 0.16	0.37 ± 0.21	
Δ	+7 ± 3	−0.11 ± 0.05	−1.90 ± 0.85	+4.8 ± 2.0	+14.2 ± 3.6	+0.5 ± 0.3	+0.21 ± 0.15	+0.36 ± 0.21	
P value by ANOVA									
Effects of Ang II:	< 0.00001	NS	NS	< 0.0001	< 0.0001	< 0.05	< 0.005	< 0.005	< 0.0001
Effects of drugs on response to Ang II:									
• UK	< 0.05	NS	NS	NS	< 0.005	NS	NS	NS	NS
• SQ	< 0.02	NS	NS	NS	< 0.002	< 0.05	NS	< 0.05	NS
• Indo	NS	NS	NS	NS	NS	< 0.01	NS	< 0.01	—

Mean arterial pressure, renal hemodynamics, excretion of fluid and ions and plasma renin activity before and during Ang II infusion at 50 ng · kg^{-1} · min^{-1} and effects of a TxA_2 synthesis inhibitor and a PGH_2-TxA_2 receptor antagonist. Data are presented as mean ± SEM (N = number of rats studied). Abbreviations are: Ang II, angiotensin II infusion; SQ, SQ-29,548 (8 mg · kg^{-1} and 8 mg · kg^{-1} · hr^{-1}); UK, UK-38,485 (100 mg · kg^{-1} · day^{-1} ×3); Indo, indomethacin (5 mg · kg^{-1} × 2 p.o.).

since renal vein blood sampling itself perturbs renal hemodynamics, E_{PAH} was not measured in these experiments. Renal blood flow (RBF) was calculated from RPF and hematocrit and RVR from MAP factored by RBF.

Urine for TxB_2 analysis in series 1 was stored at −70°C. The details of the methods used to extract, purify and assay the samples, and to measure the individual sample recoveries, as well as the performance characteristics and validation of the assay have been published [21]. Since the infusion of Ang II altered GFR, data for TxB_2 excretion were factored by GFR.

Blood for plasma renin activity (PRA) was drawn into EDTA-containing tubes and the plasma separated and stored at −70°C. For assay, samples were thawed to 4°C and the rate of angiotensin I generated over a 90 minute incubation at 37°C assessed with a radioimmunoassay (Travenol, Genentech Diagnostics, Cambridge, Massachusetts, USA) [20].

Drugs used

Angiotensin II (Sigma Chemical Co.) and phenylephrine (Sigma) were dissolved in 0.15 M NaCl. SQ-29,548 (Squibb Institute for Medical Research, Summit, New Jersey, USA) was dissolved in ethanol with equimolar TRIS chloride salt, dried under nitrogen gas and diluted in 0.15 M NaCl. UK-38,485 (Pfizer Central Research, Groton, Connecticut, USA) was dissolved in 1 N NaOH at pH 12.5, titrated with 1 N HCl to pH 8.5 and diluted with 0.15 M NaCl.

Statistical methods

The three series of experiments were analyzed separately. A two-way analysis of variance (ANOVA) was used to assess the separate effects of drugs (Ang II, PE or Veh) and treatments (UK-38,485, SQ-29,548 or Veh). Where a statistically significant effect was found, a post-hoc unpaired t-test was applied to detect the group(s) which differed. Data are presented as mean ± SEM and statistical significance taken at $P < 0.05$.

Results

Table 2 shows data for animals of series 1 which received an infusion of Ang II at 50 ng · kg^{-1} · min^{-1}. In the basal state, animals which had received UK-38,485 for three days before study had rather higher values for GFR and RBF and lower values for RVR compared to the other groups which had received no pretreatment. Indomethacin pretreatment led to lower basal rates of FE_{Na} and FE_{Cl}. Otherwise, the parameters of renal function were similar between groups in the basal state. The vehicle infusion did not alter the MAP, GFR, RBF, RVR or FE_{Cl}. However, there was a small, but consistent, reduction in the FF and increase in the UV and FE_{Na}. The Ang II infusion at 50 ng · kg^{-1} · min^{-1} caused a pressor response of +12 ± 2 mm Hg. When analyzed by ANOVA, this dose of Ang II did not significantly alter the GFR or RBF, but lead to a modest increase in the FF and a more striking increase in RVR of 60%.

Table 3. Data from series 1

Group	Excretion of TxB_2 $pg \cdot min^{-1}$	Excretion of TxB_2/GFR $pg \cdot ml^{-1}$
Group 1 control ($N = 16$)		
1. Before	45 ± 6	22.6 ± 3.3
2. Vehicle	58 ± 10	29.8 ± 9.6
Δ	+12 ± 7	+7.0 ± 4.8
Group 2 ($N = 8$)		
1. Before	62 ± 7	30.6 ± 3.9
2. Ang II	76 ± 12	48.1 ± 8.1
Δ	+14 ± 15	+17.9 ± 9.9
Group 3 ($N = 9$)		
1. UK	7 ± 1[b]	2.9 ± 0.2[b]
2. UK + Ang II	33 ± 9[a]	15.8 ± 4.5[b]
Δ	+27 ± 9	+12.9 ± 4.5
P value by ANOVA		
Effects of Ang II:	NS	< 0.05
Effects of UK on response to Ang II:	NS	NS

Data are presented as means ± SEM (N = number of rats studied).
[a] $P < 0.05$, [b] $P < 0.005$ compared to group 2

There was an accompanying diuresis and increase in the fractional excretions of Na and Cl. UK-38,485 pretreatment blunted the Ang II-induced pressor response by 41% and the increase in RVR by 72%, while SQ-29,548 blunted the pressor response by 58% and the increase in RVR by 80%. Indomethacin did not alter the renal hemodynamic responses to Ang II. Both SQ-29,548 and indomethacin significantly blunted the Ang II-induced diuresis and increase in FE_{Cl}. In contrast, UK-38,485 did not modify Ang II-induced diuresis or increases in fractional excretion of Na or Cl. The PRA was profoundly suppressed during infusion of Ang II in all groups studied.

Compared to the vehicle-infused control animals, the infusion of Ang II at 50 ng $\cdot$ kg^{-1} $\cdot$ min^{-1} did not significantly increase the absolute rate of excretion of TxB_2 but it did increase the excretion of TxB_2 factored by GFR (Table 3). Pre-treatment with the TxA_2 synthase inhibitor, UK-38,485 reduced the basal rate of TxB_2 excretion by greater than 90% and, although infusion of Ang II still increased TxB_2 excretion, it remained suppressed in this group compared to animals receiving Ang II during a vehicle infusion.

Table 4 shows data for the RPP and the renal function of animals of series 2 which received an infusion of Ang II at 500 ng $\cdot$ kg^{-1} $\cdot$ min^{-1} during control of RPP. The rise in RPP was limited to a mean value of 15 mm Hg in the animals that received Ang II alone. At this higher rate of infusion, Ang II caused significant reductions in GFR and RBF, a striking rise in FF and a tripling of RVR. Compared to the controls in group 1, animals that had received UK-38,485 pretreatment or an infusion of SQ-29,548, had no significant differences in the baseline parameters. At this higher rate of Ang II infusion, both pretreatment with UK-38,485 and infusion with SQ-29,548 prevented the Ang II-induced fall in GFR, and blunted the rises in FF and RVR. In contrast to the results in animals which had received the lower rate of infusion, Ang II did not increase UV or FE_{Na}; however, both UK-38,485 and SQ-29,548 caused marked increases in diuresis and fractional excretion of Na during Ang II infusion.

To determine whether the blunting of the RVR response by the PGH_2-TxA_2 receptor antagonist was specific for Ang II, the effects of SQ-29,548 on the renal vascular response to PE was studied during control of RPP at the level of animals in series 2. Table 5 shows that, compared to controls, the basal levels of RPP and RVR were not altered in those that had received an infusion of SQ-29,548. The rise in RPP with PE was regulated in each group to 14 to 15 mm Hg by adjustment of the suprarenal aortic clamp. The increase in RVR of 78% in animals receiving the PE infusion alone was not significantly different from the increase of 65% in those that were also receiving an infusion of SQ-29,548.

Figure 1 shows the percentage changes in RVR and GFR from basal values during infusion of Ang II at the two different rates, and the effects of UK-38,485 or SQ-29,548. Ang II led to a steep dose-dependent increase in RVR and a fall in GFR at the higher dose. There was a profound, and very comparable, degree of inhibition of renal vasoconstriction at both doses of Ang II by UK-38,485 and SQ-29,548. Moreover, the fall in GFR at the higher dose of Ang II infusion was effectively prevented by both drugs.

Discussion

These studies have provided further evidence for an important interaction between the renal TxA_2 and Ang II systems. The first indication that TxA_2 might mediate some of the renal actions of Ang II derived from studies by Stahl and colleagues [1], who demonstrated increased renal TxB_2 excretion and increased TxB_2 release from isolated glomeruli of kidneys taken from rats with the 2K,1C model of renovascular hypertension. These authors showed further that, in this model, reduction of PG and TxA_2 synthesis with indomethacin reduced the BP. This finding was surprising since indomethacin administration to dogs has been shown to potentiate the renal vasoconstriction produced by infusion of Ang II [14–16]. Subsequently, further evidence that vasoconstrictor metabolites of cyclooxygenase, such as TxA_2, are of particular importance in the 2K,1C model was provided by Himmelstein and Klotman [2] who showed that a drug which inhibited PGH_2-TxA_2 receptors (GR-32,191) or one which inhibited TxA_2 synthesis (UK-38,485) both increased the GFR in the contralateral kidney and lowered the BP. Our own results using the 2K,1C model show that indomethacin produces dose-dependent reductions in BP and that infusion of SQ-29,548 reduces BP to normal levels [3]. An interaction between TxA_2 and Ang II had been demonstrated also in the hydronephrotic, ureter-obstructed kidney. In this model, there is increased renin secretion, increased TxB_2 excretion and renal vasoconstriction. Inhibition of angiotensin coverting enzyme (ACE) or TxA_2 synthase increases RBF and GFR suggesting that both Ang II and TxA_2 contribute to renal vasoconstriction [27, 28]. Although a part of the increased renal TxA_2 generation was ascribed to resident inflammatory cells, a second component was dependent on increased Ang II production [27]. Thus, as in the present study, TxA_2 may be mediating some of the renal vasoconstrictor actions of Ang II in this model. The details of the interaction between Ang II and TxA_2 in other models of hypertension have not yet been so completely elucidated. However, the findings of our previous study [18], and those of the present series, raises the possibility that Ang II-induced TxA_2 generation could mediate some of the systemic and renal vasoconstriction assigned to Ang II in these

Table 4. Data for series 1

Group	RPP *mm Hg*	GFR *ml·min⁻¹· 100 g⁻¹*	RBF *ml·min⁻¹· 100 g⁻¹*	FF %	RVR *mm Hg· ml⁻¹·min⁻¹· 100 g⁻¹*	UV *μl·min⁻¹· 100 g⁻¹*	FE_{Na} %
Group 1 (N = 16)							
1. Before	110 ± 2	0.75 ± 0.04	4.6 ± 0.4	30.0 ± 1.4	26.4 ± 2.3	2.0 ± 0.3	0.09 ± 0.03
2. Vehicle	108 ± 2	0.70 ± 0.03	4.4 ± 0.3	27.5 ± 1.5	26.2 ± 1.8	4.4 ± 1.4	0.25 ± 0.14
Δ	−2 ± 1	−0.05 ± 0.02	−0.2 ± 0.2	−2.1 ± 0.7	−0.2 ± 1.5	+2.4 ± 0.9	+0.16 ± 0.10
Group 5 (N = 8)							
1. Before	123 ± 5	0.69 ± 0.08	4.2 ± 0.5	32.1 ± 1.7	31.5 ± 2.8	1.5 ± 0.3	0.06 ± 0.01
2. Ang II	138 ± 5	0.43 ± 0.04	1.6 ± 0.2	50.1 ± 1.6	92.4 ± 10.6	2.1 ± 0.5	0.24 ± 0.06
Δ	+15 ± 2	−0.26 ± 0.10	−2.5 ± 0.6	+19.8 ± 2.2	+60.9 ± 22.4	+0.6 ± 0.7	+0.18 ± 0.05
Group 6 (N = 8)							
1. UK	117 ± 5	0.96 ± 0.08	5.4 ± 0.8	30.4 ± 2.5	29.4 ± 8.0	1.6 ± 0.2	0.09 ± 0.02
2. UK + Ang II	128 ± 4	0.96 ± 0.06	3.9 ± 0.3	40.1 ± 3.3	34.9 ± 4.2	13.2 ± 1.8	1.46 ± 0.27
Δ	+11 ± 2	0.00 ± 0.06	−1.5 ± 0.6	+9.8 ± 2.2	+5.5 ± 4.5	+11.6 ± 1.7	+1.37 ± 0.25
Group 7 (N = 9)							
1. SQ	114 ± 2	0.87 ± 0.09	4.4 ± 0.6	27.4 ± 1.4	21.5 ± 3.5	1.6 ± 0.1	0.03 ± 0.01
2. SQ + Ang II	127 ± 5	0.80 ± 0.05	3.0 ± 0.4	38.9 ± 3.2	34.1 ± 4.7	6.6 ± 1.2	0.79 ± 0.29
Δ	+13 ± 1	−0.07 ± 0.06	−1.4 ± 0.5	+11.4 ± 2.8	+12.6 ± 3.6	+5.0 ± 1.2	+0.76 ± 0.29
P value by ANOVA							
Effects of Ang II:	< 0.0001	< 0.02	< 0.0002	< 0.00001	< 0.00001	NS	NS
Effects of drugs on response to Ang II:							
• UK	NS	< 0.01	NS	< 0.005	< 0.0001	< 0.001	< 0.005
• SQ	NS	< 0.05	NS	< 0.02	< 0.0001	< 0.02	< 0.0002

Renal perfusion pressure, renal hemodynamics and excretion of fluid and ions before and during vehicle or Ang II infusion at 500 ng · kg^{-1} · min^{-1} and effects of a TxA_2 synthetase inhibitor and PGH^2-TxA_2 receptor antagonist. Data are presented as mean ± SEM (N = number of rats studied). Abbreviations are: Ang II, angiotensin II infusion; SQ, SQ-29,548 (8 mg · kg^{-1} and 8 mg · kg^{-1} · hr^{-1}); UK, UK-38,485 (100 mg · kg^{-1} · day^{-1} ×3).

models. This is of interest because TxA_2 is not only a vasoconstrictor and platelet aggregating agent, but also promotes growth in vascular smooth muscle or mesangial cells [6, 29] and might therefore provide an important link between Ang II, intraglomerular coagulation and structural changes in the blood vessels and kidneys in hypertension. Indeed, in the rat model of reduced renal mass, not only Ang II converting enzyme inhibitors, but also TxA_2 synthase inhibitors can produce striking amelioration of glomerular sclerosis, improvement of renal function and reduction in proteinuria, hypertension and cardiac hypertrophy [9–11].

Evidence for an interaction between TxA_2 and Ang II has derived both from experiments involving in vitro studies of isolated glomeruli and in vivo infusion of Ang II. In studies of isolated glomeruli, Ang II can activate phospholipases, release arachidonate and cause dose-dependent stimulation of TxB_2 release [4, 30–32]. In contrast, the effects of norepinephrine on glomerular TxB_2 release are limited to potentiating the role of other agonists [30]. The renal excretion of both the prostacyclin derivative, $6kPGF_{1\alpha}$ and TxB_2 are increased during short-term infusions of Ang II into anesthetized rats [18] and during prolonged infusions of Ang II into conscious rats [13, 33]. In a previous study, infusion of Ang II at the dose equivalent to the high dose used in these protocols was shown to increase the excretion of TxB_2 [18], whereas in the present study, infusion of Ang II at the lower dose led to a more modest increase in TxB_2 excretion which was apparent only when factored by GFR. This suggests that there may be dose-dependent effects of Ang II on renal TxA_2 generation. The present finding that a TxA_2 synthesis inhibitor prevented renal vasoconstriction with infused Ang II confirms a previous finding in which furegrelate was used to inhibit TxA_2 generation [34].

Prolonged infusion of Ang II into conscious rats receiving saline to drink causes severe renal and vascular damage characteristic of malignant hypertension and nephrosclerosis. In this model, there is increased production of $6kPGF_{1\alpha}$, PGE_2 and TxB_2 by renal and vascular tissues [33, 35, 36]. Although the severe hypertension of this model is ameliorated by a PGH_2-TxA_2 receptor antagonist, a TxA_2 synthase inhibitor is without effect [35, 36]. However, neither drug altered GFR and the effect of the PGH_2-TxA_2 antagonist was limited to maintaining RBF during a fall in BP [36]. Presumably, in this much more severe model, there are fixed vascular and glomerular lesions which prevent the major reversal of renal vasoconstriction and the elevation of GFR that were found in the present study after TxA_2 synthesis inhibition or PGH_2-TxA_2 receptor blockade. Since Mistry et al [35, 36] found that a PGH_2-TxA_2 receptor antagonist, but not a TxA_2 synthesis inhibitor, lowered BP and RVR in their model, they concluded that pressor prostanoids such as PGH_2 were of particular importance in causing the hypertension and renal vasoconstriction. In contrast, we observed that a TxA_2 synthase inhibitor produced a substantial blockade of Ang II-induced pressor responses [18] or renal hemodynamic changes which were strictly comparable to those produced by a PGH_2-TxA_2 receptor antagonist. It is possible that a component of the response to the TxA_2 synthesis inhibitor might be mediated by increased PGI_2 synthesis since PGI_2 infusion in the rat can reduce RVR [37]. However, we have found that a similar three-day pretreatment regimen with UK-38,485 does not increase the release of the PGI_2 metabolite, $6kPGF_{1\alpha}$ or PGE_2 from isolated rat aortic strips studied ex vivo (unpublished observation), nor does it increase the basal or the Ang II- or PE-stimulated rates of excretion of these PG's [18]. At the same level of RPP, SQ-29,548 and UK-38,485 produced

Table 5. Data from series 3

Group	RPP *mm Hg*	RVR *mm Hg · ml^{-1} · min^{-1} · 100 g^{-1}*
Group 8 (N = 8)		
1. Before	90 ± 0	26.8 ± 3.5
2. PE	104 ± 0	47.8 ± 9.2
3. Δ	+14 ± 1	+21.0 ± 7.3
Group 9 (N = 8)		
1. SQ	90 ± 3	27.2 ± 2.7
2. SQ + PE	105 ± 3	45.0 ± 5.5
3. Δ	+15 ± 1	+17.8 ± 5.0
Effects of PE:	P <0.0001	P < 0.001
Effects of SQ on response to PE:	NS	NS

Renal perfusion pressure and renal vascular resistance shown during vehicle or phenylephrine infusion at 30 μg · kg^{-1} · min^{-1} and effects of a PGH_2-TxA_2 receptor antagonist. Data are presented as mean ± SEM (N = number of rats studied). Abbreviations are: PE, phenylephrine infusion; SQ, SQ-29,548 (8 mg · kg^{-1} and 8 mg · kg^{-1} · hr^{-1}).

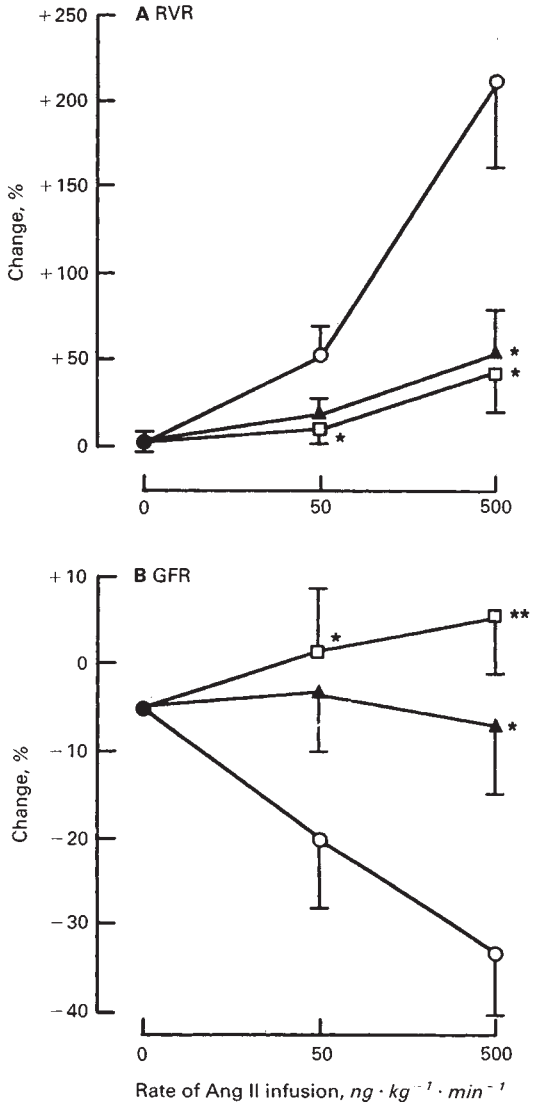

Fig. 1. *Mean ± SEM values for percentage changes in renal vascular resistance and glomerular filtration rate from baseline values as a function of the rate of infusion of angiotensin II in rats which had received no other drug treatments (vehicle, ○), pretreatment with a TxA_2 synthesis inhibitor (UK-38,485, □) or a PGH_2-TxA_2 receptor antagonist (SQ-29,548, ▲).* Compared to infusion of Ang II with vehicle: *, $P < 0.05$; **, $P < 0.01$.

a remarkably comparable and uniform blockade of Ang II-induced increases in RVR and decreases in GFR, both at the low and high pressor doses (Fig. 1). Therefore, the results of the present experiments implicate TxA_2, rather than PGH_2, as the predominant pressor prostanoid in the Ang II-induced increase in RVR and reduction in GFR in these anesthetized rats infused short-term with pressor doses of Ang II. The very large fraction of the Ang II-induced increase in renal vasoconstriction which these pharmacologic studies have assigned to TxA_2 is consistent with the findings that TxA_2 is a very potent and selective renal vasoconstrictor agent [38, 39].

There were some differences between the effects of the drugs on the Ang II responses at the two doses. At the lower dose, Ang II increased the FF modestly; this response was not blocked by either the TxA_2 synthesis inhibitor or the PGH_2-TxA_2 receptor antagonist or the cyclooxygenase inhibitor. At the high dose, Ang II produced a much more striking rise in FF despite a fall in GFR, and these actions were blunted by both UK-38,485 and SQ-29,548. The lower FF during Ang II infusion in rats receiving the blocking drugs might diminish the fraction of fluid reabsorbed in the proximal tubule [40] which could contribute to the diuresis and natriuresis that these drugs produced at the higher rate of infusion of Ang II. At the lower dose of Ang II, where there were no consistent effects of the drugs on the GFR or the FF, SQ-29,548 and indomethacin actually blunted the diuresis and chloriuresis. Whether this reflects a specific interference with the complex, biphasic effects of Ang II on proximal reabsorption [40, 41] cannot be answered with clearance methods. However, the effects of SQ-29,548 and indomethacin in blunting Ang II-induced diuresis and chloriuresis were not seen in UK-38,485-pretreated rats, which suggests that they might be due to blockade of PGH_2 synthesis or receptors. At the higher rates of Ang II infusion where RPP was controlled, both SQ-29,548 and UK-38,485 promoted a diuresis and natriuresis during Ang II infusion which is consistent with our preliminary findings which have implicated TxA_2 in enhancing Cl reabsorption in the loop of Henle [42].

Both TxA_2 synthesis inhibition and PGH_2-TxA_2 receptor blockade fully prevented the fall in GFR during high rates of Ang II infusion when RPP was controlled. Therefore, it is possible that these drugs may have some special value in certain Ang II-dependent states, such as the post-stenotic kidney in renovascular hypertension, where non-selective inhibition of angiotensin converting enzyme can lead to a sharp fall in GFR [43].

In the present series, the absence of a consistent change in the renal vasoconstrictor response to Ang II after indomethacin administration, when contrasted with the blunting of renal vasoconstriction with drugs which inhibit TxA_2 synthesis or receptors, may imply that Ang II induces a balanced release of vasodilator and vasoconstrictor cyclooxygenase products in this euvolemic model. Previous studies have shown that indomethacin can accentuate pressor and renal vasoconstrictor responses to Ang II which are pronounced in the dog [14–16].

However, interpretation of these findings is complicated because aspirin is without effect [16] and indomethacin can potentiate mesenteric vascular resistance by an action independent of cyclooxygenase inhibition [44]. Moreover, in the rat or human, indomethacin can augment Ang II-induced systemic and renal vasoconstriction after dietary salt restriction but not after salt loading [45, 17] or administration or mineralocorticosteroids [46]. Indeed, in the rat PGI_2 does not constrict the juxtamedullary afferent arteriole when applied directly, and PGE_2 is a vasoconstrictor which *potentiates* the actions of Ang II in this preparation [47]. Indomethacin does not alter consistently the response of Ang II added to the bathing solution of isolated cortical afferent arterioles of the rat [48]. Moreover, in the context of a sustained increase in renin secretion and plasma Ang II levels in the 2K,1C rat model of renovascular hypertension, indomethacin causes dose-dependent reductions in blood pressure [1, 3]. Therefore, the absence of a consistent change in renal vascular responsiveness to Ang II after indomethacin administration in the present series of euvolemic rats may be explained by some other action of indomethacin that is distinct from effects on PG synthesis.

Phenylephrine was selected as a contrast agent for Ang II since we found previously that, at equipressor rates of infusion, it did not increase TxB_2 excretion nor was the rise in BP attenuated by SQ-29,548 [18]. Moreover, using the perfused mesentery preparation in the rat, Jackson [49] found that a TxA_2 synthesis inhibitor did not blunt the vasoconstrictor response to addition of norepinephrine to the perfusate. The present study shows that, in contrast to Ang II, the PE-induced rise in RVR was not moderated by SQ-29,548. This indicates that TxA_2 may have a specific role in mediating the pressor and renal vasoconstrictor actions of Ang II.

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References

1. Stahl RAK, Helmchen U, Paravicini M, Ritter LJ, Schollmeyer P: Glomerular prostaglandin formation in two-kidney, one-clip hypertensive rats. *Am J Physiol* 247 (Renal Fluid Electrol Physiol 16):F975–F981, 1984
2. Himmelstein SI, Klotman PE: The role of thromboxane in two-kidney, one-clip Goldblatt hypertension in rats. *Am J Physiol* 256 (Renal Fluid Electrol Physiol 26):F190–F196, 1989
3. Wilcox CS, Welch WJ, Folger WH, Snellen H: Renovascular hypertension: Roles of PG's, angiotensin II and thromboxane, in *Current Advances of ACE Inhibition* (vol. 2), edited by Mac Gregor GA, Sever PS, London, Churchill Livingstone (in press)
4. Shibouta Y, Inada Y, Terashita Z, Nishikawa K, Kikuchi S, Shimamoto K: Angiotensin-II-stimulated release of thromboxane A_2 and prostacyclin (PGI_2) in isolated, perfused kidneys of spontaneously hypertensive rats. *Biochem Pharmacol* 28:3601–3609, 1979
5. Purkerson ML, Martin KH, Yates J, Kissane JM, Klahr S: Thromboxane synthesis and blood pressure in spontaneously hypertensive rats. *Hypertens* 8:1113–1120, 1986
6. Ishimtsu T, Uehara Y, Ishii M, Ikeda T, Matsuoka H, Sugimoto T: Thromboxane and vascular smooth muscle cell growth in genetically hypertensive rats. *Hypertens* 12:46–51, 1988
7. Uehara Y, Tobian L, Iwai J, Ishii M, Sugimoto T: Alterations of vascular prostacyclin and thromboxane A_2 in Dahl genetical strain succeptible to salt-induced hypertension. *Prostaglandins* 33:727–738, 1987
8. Geoffroy J, Benzoni D, Sassard J: Antihypertensive effect of thromboxane A_2 receptor blockade in genetically hypertensive rats of the Lyon strain. *J Hypertens* 7 (Suppl 6):S272–S273, 1989
9. Purkerson ML, Joist JH, Yates J, Valdes A, Morrison A, Klahr S: Inhibition of thromboxane synthesis ameliorates the progressive kidney disease of rats with subtotal ablation. *Proc Natl Acad Sci USA* 82:193–197, 1985
10. Salvati P, Ferti C, Ferrario RG, Lamberti E, Duzzi L, Bianchi G, Remuzzi G, Perico N, Benigni A, Braidotti P, Coggi G, Publiese F, Patrono C: Role of enhanced glomerular synthesis of thromboxane A_2 in progressive kidney disease. *Kidney Int* 38:447–458, 1990
11. Zoja G, Perico N, Corna D, Benigni A, Gabanelli M, Morigi M, Bertani T, Remuzzi G: Thromboxane synthesis inhibition increases renal prostacyclin and prevents renal disease progression in rats with remnant kidneys. *J Am Soc Nephrol* 1:799–807, 1990
12. Wilcox CS, Welch WJ: Thromboxane mediation of the pressor response to infused angiotensin II. *Am J Hypertens* 2:242–249, 1990
13. Luft FC, Wilcox CS, Unger T, Kuhn R, Rohmeis P, Sterzel RB: Angiotensin-induced hypertension in the rat: Effects on sympathetic nerve activity and the renal excretion of prostaglandins. *Hypertens* 14:396–403, 1989
14. Aiken JW, Vane JR: Intrarenal prostaglandin release attenuates the renal vasoconstrictor activity of angiotensin. *J Pharmacol Exp Ther* 184:678–687, 1972
15. McGiff J, Crowshaw CK, Terragno NA, Lonigro AM: Release of a prostaglandin-like substance into renal venous blood in response to angiotensin II. *Circ Res* 26-27 (Suppl 1):I121–I130, 1970
16. Anderson WP, Selig SE, Woods RL, Gilchrist AI: Renal responses to angiotensin II in conscious dogs: Effects of aspirin and indomethacin. *Clin Exp Pharmacol Physiol* 14:641–647, 1987
17. Yasa S, Takamitsu Y, Miki S, Yura T, Sumikura T, Matsuo H: Angiotensin and prostaglandins in the pressor natriuretic response in rats. *Nippon Tinzo Gakkai Shi* 32:191–198, 1990
18. Welch WJ, Wilcox CS: Renal hemodynamic response to infusion of angiotensin II or phenylephrine in anesthetized rats: role of thromboxane. (abstract) *J Physiol* 407:111P, 1988
19. Wilcox CS, Welch WJ: Angiotensin II and thromboxane in the regulation of blood pressure and renal function. *Kidney Int* 38 (Suppl 30):S81–S83, 1990
20. Welch WJ, Wilcox CS, Dunbar KR: Modulation of plasma renin by thromboxane in anesthetized rats: Studies with thromboxane synthetase inhibitor, receptor antagonists and mimetic. *Am J Physiol* (Renal Fluid Electrol Physiol 26):F554–F560, 1989
21. Welch W, Wilcox CS: Modulating role for thromboxane in the tubuloglomerular feedback response in the rat. *J Clin Invest* 81: 1843–1849, 1988
22. Cross PE, Dickinson RP, Parry MJ, Randall MJ: Selective thromboxane synthesis inhibitors 2.2-(IH-imidazol-l-ylmethyl)-2-methyl-IH-indole-1-propanoric acid and analogues. *J Med Chem* 29:342–346, 1986
23. Ogletree ML, Harris DN, Greenberg R, Haslanger MF, Nakane M: Pharmacological actions of SQ-29,548, a novel selective thromboxane antagonist. *J Pharmacol Expl Ther* 234:435–441, 1985
24. Welch WJ, Wilcox CS: Feedback response during sequential inhibition of angiotensin and thromboxane. *Am J Physiol* 258 (Renal Fluid Electrol Physiol 27):F457–F466, 1990
25. Nissen OI: The extraction fraction of p-aminohippurate in the superficial and deep drainage areas of the cat kidney. *Acta Physiol Scand* 73:329–338, 1968

26. BULLIVANT EMA, WILCOX CS, WELCH WJ: Intrarenal vasoconstriction during hyperchloremia: Role of thromboxane. *Am J Physiol* 256 (Renal Fluid Electrol Physiol 25):F152–F157, 1989
27. YANAGISAWA H, MORRISSEY J, MORRISON AR, PURKERSON ML, KLAHR S: Role of Ang II in eicosanoid production in isolated glomeruli from rats with bilateral ureteral obstruction. *Am J Physiol* 258 (Renal Electrol Physiol 27)F85–F93, 1990
28. PURKERSON ML, KLAHR S: Prior inhibition of vasoconstrictors normalizes GFR in postobstructed kidneys. *Kidney Int* 35:1306–1314, 1989
29. MENE P, ABBOUD HE, DUNN MJ: Regulation of human mesangial cell growth in culture by thromboxane A_2 and prostacyclin. *Kidney Int* 38:232–239, 1990
30. PODJARNY E, MAGEN H, SHAPIRA J, RATHAUS M, BERNHEIM J: Effect of vasoactive agents on prostanoid synthesis in isolated rat glomeruli. *Isr J Med Sci* 22:797–800, 1986
31. LEFKOWITH JB, SCHREINER G: Essential fatty acid deficiency depletes rat glomeruli of resident macrophages and inhibits angiotensin II-induced eicosanoid synthesis. *J Clin Invest* 80:947–956, 1987
32. MENE P, DUBYAK GR, ABBOUD HE, SCARPA A, DUNN MJ: Phospholipase C activation by prostaglandins and thromboxane A_2 in cultured mesangial cells. *Am J Physiol* 255 (Renal Fluid Electrol Physiol 24):F1059–F1069, 1988
33. MISTRY M, NASJLETTI A: Role of pressor prostanoids in rats with angiotensin II-salt-induced hypertension. *Hypertension* 11:758–762, 1988
34. KANUSHAL RD, WILSON TW: Effects of furegrelate on renal plasma flow after angiotensin II infusion. *Can J Physiol Pharmacol* 68:500–504, 1990
35. MISTRY M, NASJLETTI A: Contrasting effect of thromboxane synthase inhibitors and a thromboxane receptor antagonist on the development of angiotensin II-salt hypertension in rats. *J Pharmacol Expl Ther* 253:90–94, 1990
36. MISTRY M, MUIRHEAD EE, YAMAGUCHI Y, NASJLETTI A: Renal function in rats with angiotensin II salt-induced hypertension: Effect of thromboxane synthesis inhibition and receptor blockade. *J Hypertens* 8:75–83, 1990
37. BAER PG, MCGIFF JC: Comparison of effects of prostaglandin E_2 and I_2 on rat renal vascular resistance. *Eur J Pharmacol* 54:359–363, 1979
38. CIRINO M, MORTON H, MACDONALD C, HADDEN J, FORD-HUTCHINSON AW: Thromboxane A_2 and prostaglandin endoperoxide analogue effects on porcine renal blood flow. *Am J Physiol* 258 (Renal Fluid Electrol Physiol 27):F109–F114, 1990
39. FOLGER WH, WILCOX CS, WELCH WJ: Roles of eicosanoids and sympathetic nervous system in renal vasoconstriction with thromboxane. (abstract) *Clin Res* 38:348R, 1990
40. WILCOX CS, BAYLIS C: Glomerular-tubular balance and proximal regulations, in *The Kidney: Physiology and Pathophysiology*, edited by SELDIN DW, GIEBISCH G, New York, Raven Press, 1985, pp. 985–1012
41. HARRIS PJ, NAVAR LG: Tubular transport responses to angiotensin. *Am J Physiol* 248 (Renal Fluid Electrol Physiol 17):F621–F630, 1985
42. WELCH WJ, WILCOX CS: Action of thromboxane mimetic on tubuloglomerular feedback. (abstract) *Kidney Int* 37:557, 1990
43. WILCOX CS, SMITH TB, FREDERICKSON ED, WINGO CS, WILLIAMS CM, BUCCI CM: The captopril GFR renogram in renovascular hypertension. *Clin Nucl Med* 14:1–7, 1988
44. LIPPTON HL, ARMSTEAD WM, HYMAN AL, KADOWITZ PJ: Characterization of the vasoconstrictor activity of indomethacin in the mesenteric vascular bed of the cat. *Prostagland Leukot Med* 27:81–91, 1987
45. ASHIDA T, NISHIOEDA Y, KIMURA G, KOJIMA S, KAWAMURA M, IMANISHI M, ABE H, KAWANO Y, YOSHIMI H, YOSHIDA K: Effects of salt, prostaglandin, and captopril on vascular responsiveness in essential hypertension. *Am J Hypertens* 2:640–642, 1989
46. WHITWORTH JA, CONNELL JM, GORDON D, SCOGGINS BA: Effects on indomethacin-steroid-induced changes in pressor responsiveness in man. *Clin Exp Pharmacol Physiol* 15:305–310, 1988
47. INSCHO EW, CARMINES PK, NAVAR LG: Prostaglandins influence an affarent arteriolar response to vasoconstrictor agonists. *Am J Physiol* 259:F157–F163, 1990
48. YUAN BH, ROBINETTE JB, CONGER JD: Effects of angiotensin II and norepinephrine on isolated rat afferent and efferent arterioles. *Am J Physiol* 258:F741–F750, 1990
49. JACKSON EK: Effects of thromboxane synthase inhibition on vascular responsiveness in the in vivo rat mesentery. *J Clin Invest* 76:2286–2295, 1985