Roles of vasoconstrictor prostaglandins, COX-1 and -2, AT-1, -2 and TP receptors in a rat model of early 2K,1C hypertension

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Abstract

Angiotensin II (Ang II) activating AT₁ receptors (Rs) enhances superoxide anion (O₂⁻) and arachidonate (AA) formation. AA is metabolism by cyclooxygenases (COXs) to PGH₂ which is metabolized by thromboxane A₂ synthase (TxA₂-S) to TxA₂ or is oxidized to 8-isoprostane PGF₂ₐ (8-Iso) by O₂⁻. PGH₂, TxA₂ and 8-Iso activate thromboxane-prostanoid receptors (TP-Rs). We investigated the hypothesis that BP in a rat model of early (3 week) 2K,1C Goldblatt hypertension is maintained by AT₁- or AT₂-Rs, driving COX-1 or -2-dependent products that activate TP-Rs. Compared to sham, 2K,1C Goldblatt rats had increased MAP (120±4 vs. 155±3 mmHg; p<0.001), plasma renin activity (22±7 vs. 48±5 ng·ml⁻¹·hr⁻¹; p<0.01), plasma malondialdehyde (1.07±0.05 vs. 1.58±0.16 nmol·L⁻¹; p<0.01) and TxB₂ excretion (26±4 vs. 51±7 ng·24h⁻¹; p<0.01). Acute iv graded doses of benazeprilat (angiotensin converting enzyme inhibitor) reduced MAP at 20 min (-36±5 mmHg; p<0.001) and the excretion of TxA₂ metabolites. Indomethacin (non-selective COX antagonist) or SC-560 (COX-1 antagonist) reduced MAP at 20 min (-25±5 and -28±7 mmHg; p<0.001), whereas valdecoxib (COX-2 antagonist) was ineffective (-9±5 mmHg; ns). Losartan (AT₁-R antagonist) or SQ -29,548 (TP-R antagonist) reduced MAP at 150 min (-24±6 and -22±3 mmHg; p<0.001), whereas PD-123,319 (AT₂-R antagonist) was ineffective. Neither acute blockade of TP-Rs, COX-1 or -2 changed PRA but TxB₂ generation by the clipped kidney was reduced by blockade of COX-1 and increased by blockade of COX-2. 2K,1C hypertension in rats activates renin, O₂⁻ and vasoconstrictor PGs. Hypertension is maintained by AT₁- Rs and by COX-1, but not -2 products that activate TP-Rs.
Key Words: Renovascular hypertension; angiotensin receptor blocker; thromboxane A₂; isoprostane; angiotensin converting enzyme inhibition
Introduction

Angiotensin II (Ang II) activates phospholipase A2 (PLA2) to release arachidonate (AA) whose metabolism by cyclooxygenases (COXs) generates prostaglandins (PGs). PGs normally have an antihypertensive action (12). Thus, non-steroidal anti-inflammatory drugs (NSAIDs) exacerbate human hypertension (4). However, PGH$_2$ (prostaglandin endoperoxide), thromboxane A$_2$ (TxA$_2$) generated by thromboxane A$_2$ synthase (TxA$_2$-S) and isoprostanes (Iso) generated by the interaction of superoxide ion ($O_2^-$) with AA (29), act on TP-Rs that can vasoconstrict blood vessels and the kidney (21, 44), activate the renal tubuloglomerular feedback (TGF) responses (39, 40), potentiate central actions of Ang II on the sympathetic nervous system (SNS), vasopressin release and drinking (5, 18, 45) and enhance renal NaCl reabsorption (41). Activation of TP-Rs has salt retaining and other pro-hypertensive actions (37). Unlike in essential hypertension, NSAIDs such as aspirin or indomethacin reduce BP in human renovascular hypertension (10) and 2K,1C hypertension in the rat (32), suggesting a potentially important role for vasoconstrictor PGs in these conditions.

The relative roles of COX-1 versus -2 products in Ang II dependent hypertension is controversial. Thus, during short term Ang II infusion in the mouse, blockade, or genetic deletion, of COX-1, but not -2, moderates the hypertension and renal medullary vasoconstriction (28). In contrast, prolonged administration of a COX-2 antagonist moderates hypertension in a rat aortic coarctation model of renovascular hypertension (36) and in a prior study in early 2K,1C hypertension in the rat (26) whereas a COX-1 antagonist was not effective (19). This may relate to a reduction in plasma renin activity (PRA) accompanying prolonged COX-2 blockade reported in some (26, 36) but not all (6) studies on 2K,1C rats.
Ang II acting on type 1 receptors (AT\textsubscript{1}-R) activates nicotinamide dinucleotide phosphate (NADPH) oxidase (2) that generates O\textsubscript{2}^-\textsuperscript{.}. Metabolism of O\textsubscript{2}^-\textsuperscript{.} by superoxide dismutase (SOD) generates H\textsubscript{2}O\textsubscript{2} which activates PLA\textsubscript{2} (34) and COX (7) and enhances the membrane expression of TP-Rs (35). Therefore, Ang II may cause hypertension via generation of COX metabolites or by isoprostanes that activate TP-Rs. In contrast, activation of Ang II type 2 receptors (AT\textsubscript{2}-R) reduces hypertension in a renal wrap model (31).

There is increased renal generation of PGs including the prostacyclin (PGI\textsubscript{2}) metabolite 6 keto-PGF\textsubscript{1α} and the TxA\textsubscript{2} metabolite, TxB\textsubscript{2} in the clipped kidneys or glomeruli of rats with 2K,1C hypertension (8, 32). AT\textsubscript{1}-R and TP-R maintain hypertension throughout 2K, 1C hypertension (21, 22, 43). Studies implicate TxA\textsubscript{2} (8, 46, 48) and/or PGH\textsubscript{2} as the predominant vasoconstrictor PG in renovascular models (21, 22).

The present studies were undertaken in the early (3 weeks), Ang II-dependent phase of 2K,1C Goldblatt hypertension in the anesthetized rat. They were designed to test the hypothesis that Ang II acts on type 1 or 2 receptors to generate products of COX-1 or -2 or that activate TP-R to maintain hypertension. The first aim was to contrast the generation of renin, vasoconstrictor PGs, and markers of oxidative stress in sham-operated and 2K,1C hypertensive rats. The second aim was to test the acute BP responses to graded doses, or short infusions, of drugs that inhibit the generation of Ang II by the angiotensin converting enzyme (ACE), PGs by COX-1 or -2, or that block AT\textsubscript{1}-R, AT\textsubscript{2}-R or TP-R to assess the contributions of these pathways to the maintenance of hypertension. Studies were performed after acute drug administration to minimize the effects of renin secretion.
Methods

Male Sprague Dawley rats (4- to 6-wk old; 125-150g) were fed a standard rat chow (Na\(^+\) content of 0.35g·100g\(^{-1}\); Rodent Laboratory Chow 5001; Ralston Purina, St. Louis, MO). 2K,1C Goldblatt hypertension was induced under halothane anesthesia. The left renal artery was approached through a flank incision. It was cleared of supporting tissue. A 0.22-mm ID silver clip was placed around it (2K,1C hypertension) or the artery was prepared but not clipped (sham). The wound was closed with sutures, and the animal allowed to recover. Animals were house in individual cages for 3 weeks. Studies were undertaken in five series of rats.

All studies were undertaken under anesthesia with thiobutabarbital (Inactin; 100 mg·kg\(^{-1}\) ip). Rats received 0.5 ml·kg\(^{-1}\)·h\(^{-1}\) of maintenance fluid of 0.154M NaCl for 45 min before infusion of drugs, by which time the MAP had reached a stable value.

Protocols and Subgroups: Series I assessed the mean arterial pressure (MAP), plasma renin activity (PRA) and plasma malondialdehyde (MDA) in anesthetized rats and the excretion of TxB\(_2\) in conscious rats, 3 weeks after sham operations or clipping. One group was placed in metabolism cages for collection of 24 hour urine. Another group was anesthetized, and, after one hour, mean arterial pressure (MAP) was recorded and blood drawn for PRA and MDA.

Series II tested the hypothesis that maintenance of 2K,1C hypertension depends on the generation of Ang II. Groups of 2K,1C anesthetized rats received graded bolus intravenous (iv) injections of the following:

- Group 1: Vehicle (0.154M NaCl solution; n=12)
- Group 2: Benazeprilat (B; 0.01,0.1,1,10 and 100 mg·kg\(^{-1}\); ACE inhibitor; n=9).
The MAP was found to fall to a nadir within 20 min of the injection of the ACEI. Therefore, data are presented as changes in MAP at this time after which rats received the next bolus dose of the test agent.

Another two groups of rats were prepared as above and given a vehicle (n=9), or a supramaximal dose of benazeprilat (100 mg·kg\(^{-1}\) iv; n=8). Urine was collected from both kidneys via a cannula in the bladder for 45 minutes after the vehicle or ACEI was administered for analysis of TxB\(_2\).

Series III tested the hypothesis that the maintenance of hypertension depends on the generation of COX-1 or -2 products. Groups of 2K,1C anesthetized rats received graded iv injection of:

- **Group 7:** Vehicle (V: 0.154 M NaCl solution; n = 8)
- **Group 8:** SC-560 (SC: COX-1 inhibitor; 0.003; 0.01; 0.03; 0.1 and 0.3 mg·kg\(^{-1}\); n=8)
- **Groups 9:** Valdecoxib (V; COX-2 inhibitor; 0.1; 0.3; 1; 3 and 10 mg·kg\(^{-1}\); n=8)
- **Group 10:** Indomethacin (Indo; non-selective COX inhibitor; 0.03; 0.1; 0.3; 1; 3 and 10 mg·kg\(^{-1}\); n=8)

These doses of SC-560 and valdecoxib were selected to be equivalent to those of indomethacin when adjusted for relative blockade of COX-1 or COX-2 respectively, based on the molar IC\(_{50}\) value of each drug for inhibition of each COX isoform (4, 24) Valdecoxib is the active principal of paracoxib (33).

Additional rats (n=3) were studied using the Na\(_2\)CO\(_3\) solution required to solubilize the indomethacin (42) as a further vehicle control group. This small quantity of Na\(_2\)CO\(_3\) did not produce different changes in BP than the saline vehicle (data not presented).
Series IV tested the hypothesis that hypertension is maintained by AT\(_1\)-R, AT\(_2\)-R or TP-R. Group of 2K,1C rats received a bolus followed by a constant iv infusion over 150 min of:

- **Group 11**: Vehicle (0.154 M NaCl at 1 ml·100g\(^{-1}\)·h\(^{-1}\); n=8)
- **Group 12**: Losartan (LOS; 10mg·kg\(^{-1}\) and 10mg·kg\(^{-1}\)·h\(^{-1}\); AT\(_1\) receptor antagonist; n=6)
- **Group 13**: PD-123,319 (PD: 3mg·kg\(^{-1}\) and 3mg·kg\(^{-1}\)·h\(^{-1}\); AT\(_2\)-receptor antagonist; n=5)
- **Group 14**: SQ -29,548 (SQ; 10mg·kg\(^{-1}\) and 10mg·kg\(^{-1}\)·h\(^{-1}\); TP-R antagonist; n=10)

This dose of SQ-28,545 was selected from pilot studies (n=6) which showed that 3 and 30 mg·kg\(^{-1}\) doses of SQ-28,545 produced equivalent and apparently maximal reductions in MAP. These doses of losartan and PD-123,319 were selected from studies of Ang II- infused rats (20, 40).

Bolus injections were given over one minute. The mean arterial pressure (MAP) was recorded as a maximum reduction within 20 min which encompassed the full early effects for bolus injections when assessed in pilot studies over 30 min periods. All groups had similar starting values for MAP. Therefore, data are presented as changes in MAP from baseline.

Series V tested the hypothesis that the reductions in MAP seen with SQ-29,548 and SC-560 (but not with valdecoxib) could be ascribed to reductions in plasma renin activity (PRA) or TxA\(_2\) generation in the post-clipped kidneys. Groups of 2K,1C rats were prepared as in series III and IV and given vehicle, SQ-29,548, SC-560 or valdecoxib. Thereafter, blood was drawn for PRA, and the post-clipped kidney was removed and frozen at -80°C prior to extraction and assay for TxB\(_2\) (39).

**24-hour urine collections**: A 24-hour urine was collected from rats of series I into containers with indomethacin and antibiotics to prevent \textit{ex vivo} COX metabolism or bacterial overgrowth (2, 39). It was filtered, centrifuged and the supernatant frozen at -70°C until analyzed.
Chemical Methods: For assay of TxB₂, each sample was spiked with [³H]-TxB₂ to assess individual recovery. Samples were purified, extracted using organic extraction, thin-layer chromatography and C-18 column separation prior to analysis with a radioimmunoassay for TxB₂. The details of the method, together with normal values, recovery, intra- and inter-assay coefficients of variation and validation against GCMS have been published (39).

Plasma for malondialdehyde (MDA) was measured as described previously (2) (Oxi-Tek, Zeptometrix Corp., Buffalo, NY).

Blood for plasma renin activity (PRA) was taken into cooled, EDTA-containing tubes and the plasma frozen at –70°C. PRA was assayed from the generation of Ang I (42).

Statistical analysis

Data are presented as mean ± standard error (SEM). Within each series, data were analyzed at each time point for changes in MAP relative to baseline using analysis of variance (ANOVA) for repeat observations. Where appropriate, a post-hoc Dunnett’s t test was used to assess differences from vehicle between groups. Statistical significance is taken at p < 0.05.

Results

Data are shown in figure 1 for sham operated control and 2K,1C rats 2-3 weeks after clipping. Compared to controls, anesthetized 2K,1C rats had significant elevations of MAP that averaged +35 mmHg and 2-fold elevations of PRA and plasma MDA. TxB₂ excretion by conscious 2K,1C rats during a 24 hour urine collection from both kidneys also was increased two-fold.
Changes in MAP at 20 min after administration of vehicle or drugs in rats of series II are shown in figure 2. There was a small reduction in MAP with vehicle. Administration of benazeprilat (ACEI) produced graded reductions of MAP with a maximal effect of −36±5 mmHg (p<0.001). Renal excretion of TxB2 from both kidneys was significantly lower over 45 minutes following administration of benazeprilat than after vehicle (26±4 vs 40±5 pg·min⁻¹; p<0.05).

The results of Series III are shown in figure 3. The COX-1 antagonist SC-560 (panel A) reduced the MAP significantly with a maximum effect at 20 minutes of -28±7 mmHg (p<0.001 vs. vehicle). In contrast, (Panel B) administration of the COX-2 antagonist valdecoxib produced no significant changes in MAP (-9±7 mmHg; ns vs. vehicle). The non-selective COX inhibitor, indomethacin reduced MAP by -25±5 mmHg; p<0.001 vs. vehicle). When plotted at equivalent doses based on relative ID₅₀ values for inhibition of COX-1 (panel A), the responses to indomethacin were closely similar to those of SC-560. In contrast, for equivalent COX-2 inhibitory doses, the responses to indomethacin were quite distinct from those of valdecoxib (panel B).

Results of series IV are shown in figure 4. There were no significant changes with vehicle. Infusion of the AT₁-R antagonist losartan reduced MAP by −24±6 mmHg (p<0.001) at 150 minutes. This was similar to the reduction achieved with the TP-R antagonist SQ-29,548 of −22±3 mmHg (p<0.001). In contrast, the AT₂-R antagonist PD-123,319 failed to the change the MAP.

Results of series V are shown in figure 5. At the time that MAP was reduced by SQ-29,548 or SC-560 (but not by valdecoxib) in series III and IV, there were no significant changes in PRA (Panel A). However, the generation of TxB₂ by the post-clipped kidney was reduced by SC-560, and was increased by valdecoxib (Panel B). We conclude that the falls in MAP cannot be ascribed to reductions in PRA, and that the doses of SC-560 and valdecoxib are effective in changing renal TxA₂ generation.
Discussion

This study was undertaken during the early phase of 2K,1C hypertension in the rat, characterized by a doubling of PRA, lipid peroxidation products and renal excretion of TxB2 and a 35 mmHg increase in MAP when assessed under anesthesia. We confirm that blockade of the generation of Ang II reduces MAP substantially, and report that this is accompanied by a 35% reduction in renal excretion of TxB2. The acute administration of a COX-1 antagonist in this model reduces the BP similarly to an NSAID and reduces renal TxB2 generation whereas a COX-2 antagonist does not change MAP and increases renal TxB2 generation. The role of vasoconstrictor PGs was shown further by the similar reductions in MAP following inhibition of COX-1 or blockade of TP or AT1 receptors. At the time that these measurements of BP were undertaken, there were no significant effects of the COX-1 or -2 antagonists or the TP-R antagonist on plasma renin activity.

One limitation is that rats were studied under anesthesia. However prior studies in conscious 2K,1C rats studied 3 weeks after clipping have shown similar increases in BP and PRA and similar reductions in MAP with AT1-R or TP-R antagonists (43). A second limitation is that urine was collected from the clipped and non-clipped kidneys together. However, enhanced TxB2 release has been shown directly in studies of isolated glomeruli from the post-clipped kidneys of 2K,1C rats (32).

We confirm that an ACEI or AT1-R antagonist reverses hypertension in early 2K,1C hypertension (43). The AT2-R apparently is not implicated since PD-123,319 failed to moderate hypertension, consistent with the failure of an AT2-R antagonist to change the BP in Ang II-infused rats (20) or the 2K,1C hypertensive mouse (9). In contrast, blockade of AT2-Rs enhances
hypertension in renal wrap hypertension (31). The pro-hypertensive actions of Ang II in early 2K,1C hypertension apparently are expressed predominantly via AT1-Rs.

Stahl et al (32) demonstrated that the clipped kidneys of 2K,1C hypertensive rats releases excessive thromboxane, similar to the findings from excised kidney of patients with renovascular hypertension (1). Himmelstein and Klottman (8) demonstrated that infusion of a TxA2 synthase inhibitor or a TP-R antagonist reduces the BP in the 2K,1C rat model. The present study, which also was at an early phase of 2K,1C hypertension, confirms a substantial increase in the excretion of TxB2, and a substantial fall in MAP with a TP-R antagonist.

NSAIDs normally increase the BP in human hypertensives, indicating a net antihypertensive effect of COX products (4). In contrast, indomethacin given to animal models of the late phase of renovascular hypertension reduces the MAP (13, 32). Acute aspirin administration to patients with renovascular hypertension reduces their blood pressure, PRA and the release of PGE2 from the post-stenotic kidney (10, 11). Renin release in the rat is inhibited by indomethacin (13, 42) and by prolonged COX-2 blockade in the aortic coarctation model (3) or in two reports in the early 2K,1C rat model (26, 36) of renovascular hypertension in which the COX-2 blocker also reduced the MAP. However, a third study of prolonged COX-2 blockade did not detect a reduction in PRA or BP in this model (6). COX-1 blockade is reported not to modulate renin release (3). Blockade of TP receptors increases PRA (42). Thus studies were undertaken with acute dosing of drugs to obviate the effects of large changes in renin secretion seen during prolonged administration in rat models of renovascular hypertension (3, 13, 26, 32, 36). The role of PRA in the changes in BP reported in this study was examined in a further series of 2K,1C rats dosed as in the MAP studies. At the time corresponding to the changes in MAP, there were no significant changes in PRA in 2K,1C rats after SC-560, SQ-29,548 or valdecoxib,
consistent with the half life of renin in the rat of 65 minutes (17). We conclude that the reductions in MAP produced by SQ-29,548 and SC-560 in this protocol occur without reductions in PRA.

Breyer et al (28) reported that genetic deletion or inhibition of COX-1, but not -2, moderates the rise in BP and renal medullary vasoconstriction during acute infusion of Ang II in mice. Our results in this Ang II dependent hypertensive model confirm the importance of COX-1 in maintaining MAP.

These studies have not identified the predominant PG activating TP-Rs in this model. Prolonged infusions of Ang II increase the excretion of PGs and TxB2 (23). Acute blockade of TxA2 synthase does not reduce the BP in angiotensin infused rats (25) but more prolonged blockade does lower the BP (47) and reduces the renal vasoconstriction (48). However, a TP-R antagonist is consistently effective in reversing hypertension and renal vasoconstriction in Ang II-infused rats (25, 47, 48) and in the early 2K,1C model in this, and a previous study (43). We now find that a COX-1 antagonist, given acutely to anesthetized 2K,1C rats, reduces their BP and TxB2 generation in the post-clip kidney whereas a COX-2 antagonist does not reduce the BP and actually increases renal TxB2 generation. The fall in MAP in response to the COX-1 antagonist of 28±7 mmHg was quite similar to the fall of 22±3 mmHg in response to the TP receptor antagonist or of 36±5 mmHg in response to the ACEI which was also shown to reduce renal TxB2 excretion. These results are consistent with the reduction in TxB2 excretion reported in the COX-1 knockout mouse (16) and the increase in TxB2 excretion reported after COX-2 inhibition (27) and confirm that the doses of these COX antagonists were effective at the time that the measurements of MAP were made. Since the antihypertensive response to blockade of COX-1 and TP receptors were quite similar in this study, it is not likely that isoprostanes (which
are generated by oxidative stress (29) but not by COX) are implicated. The results are consistent with the conclusion that hypertension is maintained in this model by activation of TP receptors by TxA2 or, as suggested by Nasjletti et al (25), by a prostaglandin endoperoxide which also activates TP receptors. The finding of increased plasma malondialdehyde in this study confirms our prior observation of increased renal excretion of 8-isoprostane PGF2α in early 2K,1C rats (38) which we found was normalized by prolonged administration of an AT1-R antagonist (38). AT1-R activation of oxidative stress in this model may contribute to COX-dependent hypertension since COX is activated by peroxides and H2O2 (7). Nasjletti et al (25) have proposed that PGH2 is the major COX-dependent TP-R ligand maintaining BP in Ang II-induced hypertension. Our data are consistent with their conclusion.

**Perspective:** Activation of TP-Rs leads to a “slow pressor” response that is broadly similar to that with Ang II (15, 37). Both responses generate O2− (2, 30), cause renal vasoconstriction (44, 48), enhance tubuloglomerular feedback (40, 41), activate the sympathetic nervous system (5, 23), release arginine vasopressin (45) and potentiate drinking (18). Therefore, the TP-R could mediate many of the prohypertensive actions of Ang II in this model of early, Ang II-dependent renovascular hypertension. Indeed, TP-R knockout mice have a blunted rise in BP and no increase in renal vascular resistance during a prolonged slow pressor infusion of angiotensin II (14). H2O2 stabilizes the TP-R in the cell membrane, effectively enhancing its action (35) which may help to explain why the TP receptor is so important in maintaining hypertension in this model in which oxidative stress is prominent (38).
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Disclosures

None.
Reference List


Figure Legends

Figure 1: Mean ± SEM values (number of rats) comparing sham-operated control (S; open boxes) with 2K,1C clipped rats (2K,1C; cross-hatched boxes). Panel A, mean arterial blood pressure, Panel B, plasma renin activity and Panel C, plasma malondialdehyde (all measured under anesthesia), and Panel D, renal excretion of thromboxane B₂ (measured in conscious rats).

Figure 2: Mean ± SEM values from rats of series II showing change in MAP in anesthetized 2K,1C rats 20 minutes after graded iv dose of vehicle (open circles and broken lines; n=9) or benazeprilat (ACEI; closed triangles and continuous lines; n=9). Comparing groups: *, p<0.05; ***, p<0.005.

Figure 3: Mean ± SEM values for rats of series III showing change in MAP in anesthetized 2K,1C rats. Panel A depicts responses 20 minutes after graded iv doses of vehicle (open circles and broken lines; n=12), indomethacin (non-selective COX inhibitor; open triangle and broken lines; n=12), and SC-560 (COX-1 inhibitor; solid circles and continuous lines; n=8). Panel B depicts responses to vehicle, indomethacin and valdecoxib (COX-2 antagonist; solid squares and continuous lines; n=8) Compared to vehicle: *, p<0.05; **, p<0.01; ***, p<0.005.

Figure 4: Mean ± SEM values from rats of series IV showing change in MAP in anesthetized 2K,1C rats infused with vehicle (open circles and broken lines; n=8), SQ-29,584 (10 mg·kg⁻¹ bolus and 10 mg·kg⁻¹·h⁻¹ by infusion; TP-R antagonist; open squares and broken lines; n=10) losartan (10 mg·kg⁻¹ bolus and 10 mg·kg⁻¹·h⁻¹ by infusion; AT₁-R antagonist; solid circles and continuous lines; n=6) or PD-123,329 (3 mg·kg⁻¹ bolus and 3 mg·kg⁻¹·h⁻¹ by infusion; AT₂-R
antagonist; closed squares and continuous lines; n=5) Compared to vehicle: *, p<0.05; **, p<0.01; ***, p<0.005.

Figure 5: Mean ± SEM values from rats of series V showing plasma renin activity (Panel A) and thromboxane B₂ in post-clipped kidneys (Panel B) of groups of rats given treatments as in series III and IV of vehicle (open boxes; n=6), the thromboxane prostanoid receptor antagonist, SQ-29,548 (10 mg·kg⁻¹ and 10 mg·kg⁻¹·h⁻¹; closed boxes; n=6); the COX-1 antagonist, SC-560 (1 mg·kg⁻¹ iv; hatched boxes; n=6); or the COX-2 antagonist, valdecoxib (10 mg·kg⁻¹ iv; cross hatched boxes; n=6). Compared to vehicle: *, p<0.05.
Figure 1
Figure 2

Δ MAP (mmHg) vs Dose of benazeprilat (mg · kg⁻¹) or equivalent vehicle

- Vehicle
- ACEI (Benazeprilat)

Significance levels:
- * p < 0.05
- *** p < 0.001
Figure 3A

A. Cox-1 inhibition

Change in MAP (mmHg)

Vehicle

Non-selective COX inhibitor (Indomethacin)

COX-1 selective inhibitor (SC-560)

SC-560 (mg · kg⁻¹)

Indomethacin (mg · kg⁻¹)

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Figure 3B

B. Cox-2 inhibition

Change in MAP (mmHg)

- Vehicle
- COX-2 selective inhibitor (Paracoxib)
- Non-selective COX inhibitor (Indomethacin)

Paracoxib (mg·kg⁻¹)

Indomethacin (mg·kg⁻¹)

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Figure 4
Figure 5

A. PRA

B. TxB₂ generation from post-clipped kidney

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