Role of COX-1 and -2 in prostanoid generation and modulation of angiotensin II responses

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Baber, Syed R., Albert L. Hyman, and Philip J. Kadowitz. Role of COX-1 and -2 in prostanoid generation and modulation of angiotensin II responses. Am J Physiol Heart Circ Physiol 285: H2399–H2410, 2003; 10.1152/ajpheart.00294.2003.—The role of cyclooxygenase (COX)-1 and -2 in prostanoid formation and modulation of pressor responses to ANG II was investigated in the pulmonary and systemic vascular beds in the rat. In the present study, selective COX-1 and -2 inhibitors attenuated increases in pulmonary arterial pressure and decreases in systemic arterial pressure in response to arachidonic acid but did not alter responses to PGE1 or U-46619. The selective COX-1 and -2 inhibitors did not modify systemic pressor responses to injections or infusions of ANG II or pulmonary pressor responses to injections of the peptide. COX-2 inhibitors did not alter, whereas a COX-1 inhibitor depressed, arachidonic acid-induced platelet aggregation. These data provide evidence in support of the hypothesis that prostanoid synthesis occurs by way of the COX-1 and -2 pathways in the pulmonary and systemic vascular beds but that pressor responses to ANG II are not mediated or modulated by these pathways in the rat.

cyclooxygenase; prostanoid synthesis; pulmonary and systemic pressor responses; vasoconstrictor peptide; NS-398; SC-560; SC-236

CYCLOOXYGENASE (COX) is the rate-limiting step in the formation of prostanoids from their essential fatty acid precursor arachidonic acid (26, 31, 35). Two COX isoforms have been described. COX-1 is constitutively expressed and involved in physiological processes, whereas COX-2 is an inducible enzyme upregulated by inflammatory cytokines (14, 18, 24, 29, 35). Recent studies (1, 3, 6, 7, 12, 17, 18) in the literature have shown that both COX isoforms are expressed in many organs, including the lung, kidney, and heart. In the coronary vascular bed of the dog and in the isolated rat lung, responses to the prostanoid precursor arachidonic acid are mediated by COX-2, whereas in the cerebral vascular bed of the mouse, COX-1 is the dominant isoform (11, 19, 28). Although it has been reported that ANG II increases prostanoid formation, the role of COX products in modulating vascular responses to this vasoconstrictor hormone is complex (5, 15, 32, 37). Because most previous studies (4, 8, 9, 13, 23, 32, 37) were carried out using nonselective COX inhibitors, the possibility that prostanoids formed by the COX-1 and -2 isoforms may have different effects on cardiovascular responses could not be evaluated. In a recent study (30), it has been reported that COX-1 and -2 exert opposite effects on renal function and that a COX-2 inhibitor or gene knockout enhances the pressor response to ANG II, whereas a COX-1 inhibitor or gene knockout blunts the response to the peptide. The present study was undertaken to investigate the role of COX-1 and -2 in the generation of vasoactive prostanoids and to test the hypothesis that prostanoids in the COX-1 and -2 pathways have differential effects on pressor responses to ANG II in the rat. In these experiments, the effects of selective COX-1 and -2 inhibitors on changes in pulmonary and systemic arterial pressure in response to the prostanoid precursor arachidonic acid and to the peptide hormone ANG II were investigated in the intact-chest rat using a recently developed right heart catheterization procedure.

METHODS

Prior approval for this study was obtained from the animal care committee of Tulane University Medical Center, and all procedures were conducted in accordance with the guidelines of the Institutional Animal Care and Use Committee. For hemodynamic studies, pulmonary arterial pressure, pulmonary arterial wedge pressure, cardiac output, and systemic arterial pressure were measured using a right heart catheterization procedure. Sprague-Dawley rats weighing 260–390 g were anesthetized with Inactin (140 mg/kg ip) with supplemental doses given intravenously as needed to maintain a uniform level of anesthesia. The animals were strapped to a fluoroscopic table, and body temperature was monitored with a rectal probe (Yellow Springs Instruments) and maintained at 37°C with the help of a warming lamp. The trachea was cannulated to maintain a patent airway, and the rats spontaneously breathed room air enriched with 100% O2 or were ventilated with a Harvard model 683 rodent respirator. A femoral artery was catheterized with polyethylene (PE)-90 tubing, and systemic arterial pressure was measured with a Statham P23 transducer. Heart rate was determined with a Grass model 7P44 tachygraph. The right external jugular was catheterized with PE-90 tubing, and the catheter tip was positioned at the confluence of the superior vena cava and right atrium. This catheter was used for the intravenous injection of drugs and for the saline indicator for cardiac output measurements.

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For measurement of pulmonary arterial and wedge pressures, a specially designed 3-Fr radiopaque catheter was passed from the left external jugular vein into the main pulmonary artery under fluoroscopic guidance. Pulmonary arterial pressure was measured from the port on the catheter tip, and wedge pressure was measured when the catheter was advanced into the left or right pulmonary artery into the wedge position with continuous pressure waveform monitoring. Pulmonary arterial and wedge pressure and systemic arterial pressure were recorded on a Grass model 7 polygraph, and mean pressures were derived by electronic integration. For cardiac output measurement, 200 μl of a 0.9% NaCl solution at 23°C were injected into the right jugular vein catheter with a Hamilton constant-rate syringe. Blood temperature changes were measured with a Columbus Instruments 3.5-F thermistor microprobe catheter positioned in the aortic arch. Cardiac output was determined with a Columbus Instruments Cardiotherm model 500 cardiac output computer with a small-animal interface. Arterial blood gases and pH were measured with a Corning model 178 analyzer with a 500-μl blood sample withdrawn from the femoral artery catheter. All catheter positions were verified at postmortem examination.

Arachidonic acid sodium salt (Sigma) was dissolved in 0.9% saline, U-46619 and PGE1 (Cayman Chemical) were dissolved in 95% ethanol (10 mg/ml), and dilutions were made in 0.9% saline solution. ANG II (Sigma), losartan (DuPont-Merck), and CGS-13080 (Ciba-Geigy/Novartis) were dissolved in 0.9% saline. Nimesulide, NS-398, and SC-560 (Cayman Chemical) were dissolved in 50 mM Na2CO3, and daltroban (Smith Kline Beecham) was dissolved in Tris buffer at pH 7.4. SC-236 (Cal Biochem or Searle) was dissolved in a saline-ethanol solution. Doses of nimesulide, NS-398, SC-236, and SC-560 were determined from studies in the literature and by pilot experiments (2, 7, 10, 22, 25, 28, 33). The doses for the COX-2 inhibitors NS-398 and nimesulide were 3 and 6 mg/kg iv, and the doses for SC-236 were 3, 6, and 10 mg/kg iv. The doses of the COX-1 inhibitor SC-560 were 10 and 20 mg/kg iv. A platelet aggregation assay was used to determine the selectivity of the COX-2 inhibitors and to determine the efficacy of the COX-1 enzyme blockade. Solutions were prepared daily, and working solutions of U-46619 and PGE1 were prepared on a frequent basis. ADP (Sigma) was dissolved in 0.9% saline. The vehicles for the drugs used in the studies had no significant effect on baseline pressures or on responses to the vasoactive agonists.

Fig. 1. A: effect of the cyclooxygenase (COX)-1 inhibitor SC-560 (10 mg/kg iv) on decreases in systemic arterial pressure and increases in pulmonary arterial pressure in response to intravenous injections of arachidonic acid. B: effect of SC-560 (10 mg/kg iv) on decreases in systemic and pulmonary arterial pressure in response to intravenous injections of PGE1. n, Number of experiments. *Response is significantly different from control.
Platelet aggregation was evaluated in platelet-rich plasma prepared from blood withdrawn from the femoral artery catheter of control rats and rats treated with nimesulide, NS-398 (3 mg/kg iv), or SC-560 (10 mg/kg iv). The blood was withdrawn into tubes and mixed with a 1/10 volume of 2.2% trisodium citrate and centrifuged at 500 rpm for 5 min. Platelet-rich plasma (0.5 ml) was placed in the cuvette of a Chrono-Log model 440-VS dual-channel aggregometer and stirred at 500 rpm, and aggregation was induced by the addition of arachidonic acid (0.5 mM) or ADP (10 μM).

Data are expressed as means ± SE and were analyzed using a paired t-test or one-way ANOVA with repeated measures and Scheffé’s F-test. The duration of the response to ANG II (in min) was measured from the start of pressure change to the time when pressure returned to the baseline value. The area under the pressure-response curve (in cm²) was measured with a Bruning area graph chart no. 4849. A P value of <0.05 was used as the criterion for statistical significance.

RESULTS

Role of COX-1. The role of COX-1 in the generation of vasoactive prostanoids and in the regulation of pressor responses to intravenous injections of ANG II was investigated in the rat, and these data are summarized in Figs. 1–3. The intravenous administration of the prostanoid precursor arachidonic acid caused dose-related increases in pulmonary arterial pressure and decreases in systemic arterial pressure (Fig. 1A). After administration of the COX-1 inhibitor SC-560 (10 mg/kg iv), the increases in pulmonary arterial pressure and the decrease in systemic arterial pressure in response to arachidonic acid were reduced significantly (Fig. 1A). The effect of SC-560 on responses to injected prostanooids was investigated to determine whether the COX-1 inhibitor altered responses to preformed prostanooids, and the administration of SC-560 (10 mg/kg iv) did not change the decreases in systemic and pulmonary arterial pressure in response to intravenous injections of PGE1 (Fig. 1B). After administration of SC-560, increases in pulmonary and systemic arterial pressure in response to intravenous injections of the thromboxane mimic U-46619 were not altered, whereas pressor responses to U-46619 in the pulmonary and systemic vascular bed were significantly attenuated by the thromboxane receptor antagonist daltroban (5 mg/kg iv; Fig. 2, A and B).

The results of experiments with arachidonic acid and SC-560 suggest that vasoactive prostanoids are generated from the prostanoid precursor via the COX-1 pathway and that the COX-1 inhibitor does not alter responses to injected prostanooids. The role of prostanooid precursor arachidonic acid caused dose-related increases in pulmonary arterial pressure and decreases in systemic arterial pressure (Fig. 1A). After administration of the COX-1 inhibitor SC-560 (10 mg/kg iv), the increases in pulmonary arterial pressure and the decrease in systemic arterial pressure in response to arachidonic acid were reduced significantly (Fig. 1A). The effect of SC-560 on responses to injected prostanooids was investigated to determine whether the COX-1 inhibitor altered responses to preformed prostanooids, and the administration of SC-560 (10 mg/kg iv) did not change the decreases in systemic and pulmonary arterial pressure in response to intravenous injections of PGE1 (Fig. 1B). After administration of SC-560, increases in pulmonary and systemic arterial pressure in response to intravenous injections of the thromboxane mimic U-46619 were not altered, whereas pressor responses to U-46619 in the pulmonary and systemic vascular bed were significantly attenuated by the thromboxane receptor antagonist daltroban (5 mg/kg iv; Fig. 2, A and B).

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noids in the COX-1 pathway in modulating responses to ANG II injections was investigated, and these data are summarized in Fig. 3. After administration of SC-560 (10 mg/kg iv), the increases in pulmonary arterial and systemic arterial pressure in response to ANG II injections were not significantly changed (Fig. 3, A and B). Increases in pulmonary and systemic vascular resistance in response to ANG II were not altered by SC-560, whereas the COX-1 inhibitor attenuated increases in pulmonary and decreases in systemic vascular resistance in response to arachidonic acid (Fig. 4, A and B). In addition to not changing the magnitude of the pressor response to ANG II injections in the pulmonary and systemic vascular beds, the duration of the response and the area under the pressor response curve were not changed (Fig. 3, A and B). The increases in pulmonary and systemic arterial pressure in response to ANG II were reduced significantly after administration of the AT1 receptor antagonist losartan (1 mg/kg iv), whereas the thromboxane receptor antagonist daltroban (5 mg/kg iv) had no significant effect on the pressor response to ANG II (Fig. 5, A and B). The administration of SC-560, daltroban, or losartan caused small insignificant changes in baseline pulmonary and systemic arterial pressure.

Role of COX-2. The role of COX-2 in the generation of vasoactive prostanoids and in modulating responses to ANG II was investigated, and these data are summarized in Figs. 6 and 7. The effects of the COX-2 inhibitors NS-398 and nimesulide were examined, and, after administration of NS-398 or nimesulide (3 mg/kg), increases in pulmonary arterial pressure and decreases in systemic arterial pressure in response to arachidonic acid were significantly decreased (Fig. 6A). NS-398 at the dose that attenuated pulmonary pressor and systemic vasodepressor responses to the prostanoid precursor arachidonic acid had no significant effect on changes in systemic and pulmonary arterial pressure in response to PGE1 or U-46619 (Fig. 6, A–C). NS-398 at the dose that attenuated responses to arachidonic acid.
acid had no significant effect on the increases in pulmonary and systemic arterial pressure in response to ANG II injections and did not change the duration of the pressor response or the area under the pressor-response curve (Fig. 7, A and B). The increases in pulmonary and systemic vascular resistance in response to ANG II were not altered by NS-398, whereas the COX-2 inhibitor attenuated increases in pulmonary vascular resistance and decreases in systemic vascular resistance in response to arachidonic acid (Fig. 4, A and B). Nimesulide (3 mg/kg iv) had no significant effect on changes in pulmonary and systemic arterial pressure in response to ANG II, PGE1, or U-46619 injections (data not shown). The administration of NS-398 or nimesulide did not produce significant changes in baseline pulmonary and systemic arterial pressure.

Role of thromboxane A2. The role of thromboxane A2 (TXA2) formation in mediating or modulating the increase in pulmonary vascular resistance and the decrease in systemic vascular resistance in response to arachidonic acid was examined, and these data are summarized in Fig. 8. After treatment with the thromboxane synthetase inhibitor GS-13080 (10 mg/kg iv), the increase in pulmonary vascular resistance was significantly attenuated, whereas the decrease in systemic vascular resistance in response to arachidonic acid was not altered (Fig. 8). These data suggest that the pulmonary vasoconstrictor response to arachidonic acid is mediated by the formation of TXA2, whereas the systemic vasodilator response is not modulated by the formation of TXA2.

ANG II infusions. To determine whether products in the COX-1 and -2 pathways play a role in modulating the sustained pressor response to ANG II, the effects of the selective COX inhibitors on the response to an intravenous ANG II infusion were investigated. Infusion of ANG II at rates of 100 ng·kg⁻¹·min⁻¹ and 1 μg·kg⁻¹·min⁻¹ iv increased systemic arterial pressure and, at the higher infusion rate, produced a decrease in
cardiac output (Figs. 9 and 10). The increase in systemic arterial pressure in response to ANG II infusion at 100 ng·kg⁻¹·min⁻¹ or 1 μg·kg⁻¹·min⁻¹ was not altered by SC-560 at doses of 10 and 20 mg/kg iv or by nimesulide at doses of 3 and 6 mg/kg iv (Figs. 9 and 10, A and B).

The effect of SC-236, another selective COX-2 inhibitor, was investigated, and the increase in systemic arterial pressure in response to ANG II infusion (100 ng·kg⁻¹·min⁻¹ or 1 μg·kg⁻¹·min⁻¹) was not altered by SC-236 at rates of 3, 6, and 10 mg/kg iv (Figs. 9C and 10C).

Platelet aggregation. The effects of the COX inhibitors on ex vivo platelet aggregation were investigated, and these data are summarized in Table 1. Arachidonic acid-induced platelet aggregation was significantly decreased in platelet-rich plasma from rats treated with SC-560 (10 mg/kg iv; Table 1). Arachidonic acid-induced platelet aggregation was not significantly changed in platelet-rich plasma from rats treated with NS-398, nimesulide, and SC-236 (3 mg/kg iv; Table 1).

**DISCUSSION**

The results of the present study provide evidence in support of the hypothesis that prostanoid synthesis proceeds by way of COX-1 and -2 pathways in the pulmonary and systemic vascular beds of the rat but suggest that neither pathway plays a significant role in mediating or modulating systemic or pulmonarypressor responses to ANG II in this species. It is generally believed that COX-1 is constitutively expressed, whereas COX-2 is an inducible isoform upregulated by inflammatory stimuli (14, 18, 24, 29, 35). There are reports in the literature (1, 3, 6, 7, 12, 17, 36) demonstrating that COX-2 is constitutively expressed in a number of organ systems and that prostanoid synthesis proceeds by way of the COX-2 pathway. The expression and cellular localization of COX-1 and -2 have been examined in the rat lung, and the presence of both isoforms has been detected with intense COX-2 staining in smooth muscle cells of arteries and veins (12). It has been reported that prostanoid synthesis occurs by
way of the COX-2 pathway in the isolated buffer-perfused rat lung, and it has been suggested that this pathway may dominate in the rat lung (11). The present results are in agreement with the hypothesis that prostanoid synthesis occurs by way of the COX-2 pathway in the pulmonary vascular bed of the rat but also demonstrate that both COX-1 and -2 pathways are constitutively active in generating vasoactive prostanoids in the pulmonary and systemic vascular beds of the rat.

Intravenous injections of arachidonic acid produce opposite changes in pulmonary and systemic arterial pressure, suggesting that different patterns of prostanoids are formed in the pulmonary and systemic vascular beds (21). In a previous study (21), responses to arachidonic acid were attenuated by non-selective COX inhibitors and were not dependent on the presence of platelets or other formed elements in blood in that the pulmonary pressor response was not attenuated when the lung was perfused with a cell-free perfusate. Thromboxane synthesis inhibitors or receptor antagonists attenuate pulmonary vasoconstrictor responses to arachidonic acid without altering decreases in systemic arterial pressure or increases in coronary blood flow (19, 20). These data, along with the present observation that the pulmonary pressor response to arachidonic acid is attenuated by COX-1 and -2 inhibitors and a thromboxane synthetase inhibitor, suggest that TXA$_2$ is formed by both COX pathways in the lung and that significant amounts of TXA$_2$ are not formed in the peripheral vascular bed, because systemic and coronary vasodilator responses to arachidonic acid were not modified by thromboxane synthesis inhibitors (19–21).

COX-1 and -2 have similar biochemical activity in converting arachidonic acid to PGH$_2$ in tissue or recombinant enzyme systems and, in the present study, mediate pulmonary pressor and systemic vasodepressor responses to injections of the prostanoid precursor.

**Fig. 6.** A: effect of the COX-2 inhibitors NS-398 and nimesulide (3 mg/kg iv) on decreases in systemic arterial pressure and increases in pulmonary arterial pressure in response to arachidonic acid. B: effect of NS-398 (3 mg/kg iv) on decreases in systemic and pulmonary arterial pressure in response to PGE$_1$. C: effect of NS-398 (3 mg/kg iv) on increases in systemic and pulmonary arterial pressure in response to U-46619. n, Number of experiments. *Response is significantly different from control.
arachidonic acid (26, 31, 35). An infusion of ANG II increases prostanoid formation, which can modulate the pressor effects of the vasoconstrictor hormone (5). However, the role of increased prostanoid formation in modulating pressor responses is complex, and prostanoids can subserve both pro- and antihypertensive actions, depending on species, vascular bed, and experimental conditions (5, 15, 32). Moreover, in some studies (4, 8, 9, 13, 23) in different vascular beds in several species, nonselective COX inhibitors had no consistent effect on vasoconstrictor responses to ANG II, whereas in the rat vasa recta, ANG II-induced vasoconstriction is partially dependent on thromboxane formation (32). Although COX-1 and -2 exhibit similar biochemical activities, different patterns of prostanoid formation could occur if the isoforms were differentially regulated or if different downstream prostaglandin synthases are activated (15, 16, 30, 34). In this regard, selective COX inhibitors or COX gene knockouts had differential ef-

![Fig. 7. Effect of NS-398 (3 mg/kg iv) on increases in systemic arterial pressure, area under the pressor-response curve, and duration of the pressor response (A) and increases in pulmonary arterial pressure, area under the pressor-response curve, and response duration to intravenous injections of ANG II (B). n, Number of experiments.](image)

![Fig. 8. Effect of the thromboxane synthetase inhibitor CGS13080 (10 mg/kg iv) on the decrease in systemic vascular resistance (A) and the increase in pulmonary vascular resistance in response to the injection of arachidonic acid (1 mg/kg iv; B). n, Number of animals. *Response is significantly different from control.](image)
fected on the pressor response to ANG II in the mouse (30). In these studies, the sustained increase in systemic arterial pressure in response to infusion of the vasoconstrictor peptide was augmented by a COX-2 inhibitor or gene knockout, whereas the sustained pressor response was attenuated by a COX-1 inhibitor or gene knockout (30). These results have been interpreted to suggest that COX-1 and -2 have different vascular activities when prostanoid synthesis is stimulated by ANG II in the mouse (30).

The hypothesis that pressor responses to ANG II are differentially regulated by COX-1 and -2 in the systemic and pulmonary vascular bed was examined in the rat. The results of the present study indicate that vasoactive prostanoids can be synthesized by constitutively active COX-1 and -2 pathways but that increases in systemic and pulmonary arterial pressure and vascular resistance in response to intravenous injections of ANG II are not modified by COX-1 or -2 inhibitors in doses that attenuate responses to arachidonic acid. It is interesting to note that different downstream synthases are activated in the pulmonary and systemic vascular beds, in that arachidonic acid increases pulmonary vascular resistance by generating TXA2 and decreases systemic vascular resistance. The decrease in systemic vascular resistance in response to arachidonic acid is not dependent on the pulmonary pressor response, because the systemic vasodilator response is not changed after the pulmonary pressor response is blocked by a thromboxane synthetase inhibitor. Although different downstream synthases are activated in the pulmonary and systemic vascular beds when

A

B

C

Fig. 9. Effect of SC-560 (10 and 20 mg/kg iv; A), nimesulide (3 and 6 mg/kg iv; B), and SC-236 (3, 6, and 10 mg/kg iv; C) on the increase in systemic arterial pressure in response to an intravenous infusion of ANG II at 100 ng·kg⁻¹·min⁻¹. Cardiac output (in ml/min) measured at time = 0, 20, and 40 min is indicated by the numbers below the x-axes. n, Number of experiments.
Arachidonic acid is injected, pressor responses to ANG II injections were not altered by COX-1 or -2 inhibitors in the two circulations. In addition to not altering the magnitude of the pressor response to ANG II, the time course of the response to ANG II, an AT1 receptor-mediated event, also was not altered by the COX inhibitors. The results with ANG II injections suggest that the initial pressor response to the peptide is not modulated by the COX-1 or -2 pathway and are consistent with a study (30) in the mouse. To ascertain whether the sustained pressor response can be modulated, the effects of the COX inhibitors on the response to a continuous ANG II infusion were investigated. The results of these studies show that increases in systemic arterial pressure in response to ANG II were inhibited by the COX inhibitors.

Table 1. Effect of SC-560, NS-398, nimesulide, and SC-236 on arachidonic acid-induced platelet aggregation

<table>
<thead>
<tr>
<th>Agent</th>
<th>n</th>
<th>Percent Aggregation</th>
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<tr>
<td>Vehicle control</td>
<td>10</td>
<td>77 ± 9</td>
</tr>
<tr>
<td>SC-560 (10 mg/kg iv)</td>
<td>9</td>
<td>10 ± 3 *</td>
</tr>
<tr>
<td>NS-398 (3 mg/kg iv)</td>
<td>6</td>
<td>74 ± 8</td>
</tr>
<tr>
<td>Nimesulide (3 mg/kg iv)</td>
<td>8</td>
<td>75 ± 6</td>
</tr>
<tr>
<td>SC-236 (3 mg/kg iv)</td>
<td>6</td>
<td>61 ± 7</td>
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Values are means ± SE; n, no. of animals. Platelet aggregation was induced by the addition of 0.5 mM arachidonic acid to the aggregometer cuvette. *P < 0.05 compared with vehicle control.
arterial pressure in response to a 40-min intravenous ANG II infusion at 100 ng·kg⁻¹·min⁻¹ and 1 μg·kg⁻¹·min⁻¹ are not altered by COX-1 or -2 inhibitors. The explanation for the difference in results in the present study and studies in the mouse may be due to differences in species, inhibitors and doses used, experimental conditions, or design employed. The present results do not provide evidence in support of the hypothesis that responses to ANG II are differentially regulated by COX-1 and -2 in the pulmonary and systemic vascular beds in the rat.

COX gene knockouts are not available in the rat, and the results of the present study are dependent on the selectivity of the COX inhibitor for the COX isoform and the premise that these agents do not interfere with prostanoid-mediated vascular responses. SC-560 is reported to be a highly selective COX-1 inhibitor, and NS-398 and nimesulide are reported to be highly selective COX-2 inhibitors (2, 10, 22, 25, 33). The selectivity of the inhibitors for COX-1 versus COX-2 in the present study was examined using a platelet aggregation assay. COX-1 is the only isoform in platelets, and COX-2 inhibitors should not alter arachidonic acid-induced platelet aggregation (10, 29). In the present study, when platelet-rich plasma was prepared from rats treated with NS-398, nimesulide (3 mg/kg iv), and SC-236 (3 mg/kg iv), arachidonic acid-induced platelet aggregation was not altered significantly. There was an inhibitory effect on arachidonic acid-induced aggregation in platelet-rich plasma rats treated with SC-236; however, this effect was not significant. In contrast, when rats were treated with SC-560 (10 mg/kg iv), arachidonic acid-induced platelet aggregation was significantly inhibited. These data provide support for the concept that nimesulide, NS-398, and SC-236 do not inhibit COX-1 under the conditions of the present experiments, whereas the platelet enzyme is inhibited by SC-560, a selective COX-1 inhibitor. The effects of the selective COX inhibitors on cardiovascular responses to vasoconstrictor and vasodilator prostanoids were assessed, and NS-398, nimesulide, or SC-560 had no significant effect on pressor responses to the thromboxane mimic U-46619 or depressor responses to PGE₁. These data suggest that the COX inhibitors are selective for the COX isoform and do not alter direct prostanoid-mediated responses in the pulmonary and systemic vascular beds in the rat.

In conclusion, the results of the present study show that increases in pulmonary arterial pressure and decreases in systemic arterial pressure in response to arachidonic acid are attenuated by selective COX-1 and -2 inhibitors, suggesting that vasoactive prostanoids are generated by a constitutively active COX-1 and -2 pathway in both vascular beds. However, the selective COX inhibitors had no significant effect on the magnitude or the time course of pressor responses to ANG II. These results provide support for the hypothesis that both COX pathways are constitutively active in generating vasoactive prostanoids in the rat but that prostanoids in the COX-1 or -2 pathway do not mediate or modulate pressor responses to ANG II in the pulmonary or systemic vascular bed in this species.

In regard to the issue of risk of cardiovascular events with COX-2 inhibitors, basic and clinical studies raise concerns about a prothrombotic effect of these agents (27). The present results, which show that vasodilator prostanoids can be generated by both COX-1 and -2 pathways in the peripheral vascular bed, can be interpreted to suggest that this pathway redundancy may provide a margin of safety in patients taking COX-2 inhibitors. Therefore, in patients taking selective COX-2 inhibitors, the formation of PGI₂ by COX-1 in the systemic vessels could oppose the actions of TXA₂ formed by COX-1 in the platelets.

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DISCLOSURES

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