Role of cyclooxygenase-2-derived metabolites and nitric oxide in regulating renal function

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Llinás, María T., Francisca Rodríguez, Carol Moreno, and F. Javier Salazar. Role of cyclooxygenase-2-derived metabolites and nitric oxide in regulating renal function. Am J Physiol Regulatory Integrative Comp Physiol 279: R1641–R1646, 2000.—The aim of this study was to examine the relative contribution of NO and prostaglandins (PG) in the regulation of renal function when NO synthesis is reduced. In anesthetized dogs with reduced NO synthesis, the renal effects of nonisozyme-specific cyclooxygenase (COX) inhibitor (meclofenamate) were compared with those elicited by a selective COX-2 inhibitor (nimesulide) before and during an extracellular volume expansion (ECVE). Intrarenal Nω-nitro-l-arginine methyl ester (l-NAME) infusion (1 μg·kg⁻¹·min⁻¹; n = 6) did not elicit renal hemodynamic changes and reduced (P < 0.01) the renal excretory response to ECVE. Intravenous nimesulide (5 μg·kg⁻¹·min⁻¹; n = 6) did not modify renal hemodynamic and reduced (P < 0.05) sodium excretion before ECVE. Simultaneous l-NAME and nimesulide infusion (n = 7) elicited an increment (37%; P < 0.05) in renal vascular resistance (RVR; P < 0.05) before ECVE and no hemodynamic changes during ECVE. The reduced excretory response elicited by l-NAME and nimesulide was similar to that found during l-NAME infusion. Finally, simultaneous l-NAME and meclofenamate infusion (10 μg·kg⁻¹·min⁻¹; n = 7) induced an increase in RVR (91%; P < 0.05), a decrease in glomerular filtration rate (35%; P < 0.05), and a reduction of the renal excretory response to ECVE that was greater (P < 0.05) than that elicited by l-NAME alone. The results obtained support the notion that PG involved in regulating renal hemodynamic and excretory function when NO synthesis is reduced are mainly dependent on COX-1 activity.

when NO synthesis is simultaneously reduced (10, 11, 19). These results suggest that endogenous PG has an important role in regulating renal hemodynamic and excretory function when NO production is diminished.

Both COX-1 and COX-2 are involved in producing renal PG (7, 8, 25) and their expression change in response to long-term increments in sodium intake (8, 25). However, no studies have evaluated whether the expression and/or activity of each COX isoform is modified in response to an acute ECVE. It is also unknown which COX isoform is responsible for producing those PG involved in the regulation of renal function, when NO synthesis is reduced.

The objective of the present study was to evaluate the relative contribution of both COX isoforms in producing the PG involved in regulating renal hemodynamic and excretory function, when NO synthesis is reduced. This objective was accomplished by comparing the renal effects of a nonisozyme-specific COX inhibitor (meclofenamate) and a selective COX-2 inhibitor (nimesulide) in dogs with a reduced intrarenal NO synthesis. The renal hemodynamic and excretory changes were examined before and during an ECVE. Nimesulide is an arylsulfonamide that has been shown to inhibit COX-2 with high selectivity (15, 22, 23). In support of the selectivity of nimesulide for COX-2, we have reported (17) that nimesulide reduces PGE₂ excretion to a lower extent than meclofenamate and that meclofenamate (but not nimesulide) prevents the platelet aggregation elicited by arachidonic acid.

METHODS

Experiments were performed in mongrel dogs of either sex (14–25 kg) with free access to tap water and a normal sodium intake. Protocols were designed according to the guiding principles approved by the Council of the American Physiological Society. Surgery was performed in dogs anesthetized with pentobarbital sodium (30 mg/kg iv) as described (1, 11, 16, 19). Catheters were placed in the femoral artery for measurement of mean arterial pressure (MAP) and in the femoral vein for infusion of inulin and additional anesthetic (0.7 ml/min) and the COX inhibitor or vehicle (0.35 ml/min). The renal arteries were fitted with noncannulating electromagnetic flow probes and connected to flowmeters. Distal to the flow probe, a curved 23-gauge needle attached to poly-
ethylene tubing was inserted into the right renal artery and connected to a peristaltic pump for infusion of saline or N^6-nitro-l-arginine methyl ester (l-NAME, 0.35 ml/min). Finally, a 45-min stabilization period was allowed before experimental maneuvers were begun.

**Experimental Groups**

*Group 1 (n = 6).* After two 15-min control clearances, l-NAME was infused into the right renal artery (1 μg·kg^-1·min^-1) for the duration of the experiment. Forty-five minutes after initiating l-NAME infusion, two 15-min clearances were obtained and a 5% ECVE with isotonic saline was then performed for 45 min. Two clearances were taken during the last 10 min of saline infusion and 10 min after cessation of this infusion. Finally, 30 min after the end of saline infusion, two 15-min clearances were obtained.

*Group 2 (n = 6).* A similar protocol to that of group 1 was performed, with the difference being that after the two control clearances nimesulide was infused intravenously as a bolus (0.75 mg/kg) and continuously (5 μg·kg^-1·min^-1) through the experiment. Forty-five minutes after initiating nimesulide infusion, two more 15-min clearances were obtained and a 5% ECVE with isotonic saline was then performed for 45 min. Clearances during and after ECVE were similar to those described for groups 1 and 2. Forty-five minutes after starting both infusions, two 15-min clearances were taken and the 5% ECVE was performed. Clearances during and after ECVE were similar to those obtained in groups 1 and 2.

*Group 3 (n = 7).* After two 15-min control clearances, l-NAME and nimesulide were infused simultaneously, as previously described for groups 1 and 2. Forty-five minutes after starting both infusions, two 15-min clearances were taken and the 5% ECVE was performed. Clearances during and after ECVE were similar to those described for groups 1, 2, and 3.

**Analytic Methods**

Renal clearances were taken during each experimental period to determine glomerular filtration rate (GFR), sodium, and potassium excretion, and urine flow rate (UV). Blood samples for hematocrit, plasma sodium, potassium, and insulin concentrations were also obtained. GFR was measured by the clearance of inulin. Inulin concentrations were analyzed by the anthrone method. Concentrations of sodium and potassium were measured by flame photometry.

**Statistical Analysis**

The data for the two clearance periods for each condition were averaged for statistical comparisons because the fluid and solute excretions were in steady-state conditions. There were no differences between the results obtained during both renal clearances of each period. Data are expressed as means ± SE. Significance of differences in values of each period in the same group and kidney was evaluated using an ANOVA for repeated measures and the Fisher test. Significant differences between both kidneys during one experimental period in the same group were also calculated with an ANOVA for repeated measures and the Fisher test.

**RESULTS**

*Group 1*

As shown in Table 1 and Figs. 1 and 2, MAP, GFR, and renal blood flow (RBF) did not change throughout the experiment in response to the intrarenal L-NAME infusion. Figure 1 shows that RVR also did not change as a consequence of intrarenal NO synthesis inhibition. As in previous studies (1, 19), the intrarenal infusion of l-NAME at a dose of 1 μg·kg^-1·min^-1 did not modify urinary sodium excretion (UNaV) and UV (Table 1). However, the renal excretory response to ECVE was significantly reduced in the right kidney where l-NAME was infused, with respect to the contralateral kidney.
kidney. It can be observed in Table 1 that the increments of $U_{NaV}$ and UV in the right kidney in response to ECVE were lower ($P < 0.01$) than those found in the contralateral kidney. During the recovery period of ECVE $U_{NaV}$ (150 ± 13 μeq/min) and UV (0.9 ± 0.1 ml/min) in the kidney where NO synthesis was reduced remained lower ($P < 0.01$) than in the contralateral kidney (232 ± 25 μeq/min and 1.6 ± 0.2 ml/min, respectively). As expected, plasma sodium and potassium concentration did not change throughout the experiment and hematocrit decreased during ECVE (45 ± 2 to 33 ± 1%, $P < 0.05$).

**Group 2**

Table 2 shows that MAP, GFR, and RBF were not significantly modified by the infusion of the COX-2 inhibitor. Figures 1 and 2 represent the renal hemodynamic data in the right kidney. Similarly to the results obtained previously (17), nimesulide induced a decrease ($P < 0.05$) in $U_{NaV}$ and UV before ECVE (Table 2). The ECVE elicited a similar and significant elevation in $U_{NaV}$ and UV in both kidneys (Table 2). The natriuretic and diuretic response to ECVE in these dogs treated with a COX-2 inhibitor were similar to those reported by Krier and Romero (10) and by our group (19) in vehicle-treated dogs and in dogs treated with a non-enzyme-specific COX inhibitor. Both excretory parameters also were similar during the recovery period of ECVE in the right (184 ± 15 μeq/min and 0.8 ± 0.1 ml/min) and left (202 ± 20 μeq/min and 1.0 ± 0.1 ml/min) kidney. Plasma sodium and potassium levels did not change during the experiment and hematocrit decreased during ECVE (47 ± 1 to 39 ± 1%, $P < 0.05$).

**Table 2. Effects of a 5% ECVE during intravenous infusion of nimesulide to reduce COX-2 activity**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>Nimesulide</th>
<th>ECVE</th>
</tr>
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<tbody>
<tr>
<td>MAP, mmHg</td>
<td>135 ± 5</td>
<td>138 ± 4</td>
<td>142 ± 4</td>
</tr>
<tr>
<td>Right kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>42 ± 1</td>
<td>43 ± 1</td>
<td>40 ± 1</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>196 ± 18</td>
<td>180 ± 17</td>
<td>184 ± 18</td>
</tr>
<tr>
<td>$U_{NaV}$, μeq/min</td>
<td>70 ± 25</td>
<td>29 ± 5*</td>
<td>581 ± 57*</td>
</tr>
<tr>
<td>UV, ml/min</td>
<td>0.39 ± 0.09</td>
<td>0.15 ± 0.01*</td>
<td>6.10 ± 0.82†</td>
</tr>
<tr>
<td>Left kidney</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>GFR, ml/min</td>
<td>40 ± 1</td>
<td>44 ± 1</td>
<td>42 ± 2</td>
</tr>
<tr>
<td>RBF, ml/min</td>
<td>200 ± 20</td>
<td>188 ± 16</td>
<td>196 ± 19</td>
</tr>
<tr>
<td>$U_{NaV}$, μeq/min</td>
<td>70 ± 23</td>
<td>30 ± 5*</td>
<td>606 ± 45†</td>
</tr>
<tr>
<td>UV, ml/min</td>
<td>0.38 ± 0.08</td>
<td>0.15 ± 0.01*</td>
<td>6.31 ± 0.70†</td>
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</tbody>
</table>

Values are mean ± SE; n = 6 dogs studied. COX, cyclooxygenase. *P < 0.05 vs. control period. †P < 0.01 vs. control period.

**Group 3**

The intravenous infusion of the COX-2 inhibitor in dogs in which NO synthesis was reduced in the right kidney did not induce significant changes in MAP (Table 3). However, RBF decreased ($P < 0.01$) in the right kidney before ECVE as a consequence of the simultaneous L-NAME and nimesulide infusion (Table 3). During ECVE RBF in the right kidney returned to levels not significantly different from those found during the basal period. RVR only increased in the right kidney before ECVE as a consequence of infusing nimesulide (0.72 ± 0.01 vs. control period). RVR in the same kidney was similar during basal period (0.72 ± 0.01 vs. control period) and ECVE (0.79 ± 0.06 mmHg·ml⁻¹·min⁻¹; Fig. 1). No significant changes in GFR were found in both kidneys before and during the ECVE (Table 3 and Fig. 2).

$U_{NaV}$ and UV decreased similarly in both kidneys before ECVE as a consequence of the simultaneous L-NAME and nimesulide infusion (Table 3). These decrements in $U_{NaV}$ and UV were not significantly different from those found after nimesulide infusion of nimesulide and L-NAME into the right renal artery (Table 3).
only PG synthesis was inhibited before (0.91 ± 0.06 mmHg·ml⁻¹·min⁻¹) and during the ECVE (0.80 ± 0.07 mmHg·ml⁻¹·min⁻¹). In contrast to the absence of changes in GFR during the simultaneous nimesulide and l-NAME infusion (group 3), GFR decreased before ECVE (P < 0.01) when meclofenamate and l-NAME were infused and returned to basal levels during ECVE (Table 4, Fig. 2). GFR did not change throughout the experiment in the contralateral kidney (Table 4). U NaV and UV decreased (P < 0.05) in the right and left kidney before ECVE. The fall in UV was greater (P < 0.01) in the right than in the left kidney (Table 4). ECVE-induced increments in U NaV and UV were significantly lower in the right kidney, in which NO synthesis inhibition was reduced, than in the contralateral kidney (Table 4 and Fig. 3). The reduced excretory response to ECVE, induced by simultaneous infusion of l-NAME and meclofenamate was greater (P < 0.05) than that elicited by l-NAME and meclofenamate was greater (P < 0.05) than that elicited by l-NAME alone and than that secondary to the simultaneous infusion of l-NAME and nimesulide (Fig. 3).

**DISCUSSION**

The results obtained in this study suggest that PG involved in modulating the effects induced by NO synthesis inhibition on renal hemodynamic and excretory function are mainly dependent on COX-1 activity. This suggestion is based on results showing that 1) l-NAME infusion only reduces the renal excretory response to an acute ECVE; 2) simultaneous reduction of NO and PG synthesis with l-NAME and a nonisoenzyme-specific COX inhibitor induce a 91% elevation in RVR, a 35% decrease in GFR, and a decrease of the renal excretory response to an acute ECVE that is greater than that elicited by NO synthesis inhibition alone; and finally 3) simultaneous administration of a selective COX-2 inhibitor and l-NAME only induces a transitory increment in RVR (37%) and reduces the excretory response increments in U NaV and UV were lower in the right kidney (P < 0.05) than in the left kidney (Fig. 3). The reduced natriuretic response to ECVE in this group, during simultaneous infusion of l-NAME and nimesulide, was not greater than that observed during infusion of l-NAME alone in group 1 (Tables 1 and 3). During recovery of ECVE in this group, U NaV and UV were lower (P < 0.05) in the right (147 ± 27 μeq/min and 0.9 ± 0.2 ml/min, respectively) than in the left (227 ± 24 μeq/min and 1.4 ± 0.1 ml/min, respectively) kidney (Fig. 3). Plasma sodium and potassium concentrations did not change throughout the experiment but hematocrit decreased during ECVE (46 ± 1 to 36 ± 1%, P < 0.05).

**Group 4**

As in previous studies (11, 19) the intrarenal l-NAME infusion in meclofenamate-treated dogs elicited a mean increment in MAP of 16 ± 2 mmHg (P < 0.01) that remained significant through the experiment (Table 4). RBF decreased (P < 0.05) before ECVE and during ECVE in the right kidney, in which NO synthesis and both COX isoforms were inhibited and only decreased (P < 0.05) before ECVE in the left kidney (Table 4). RBF was greater (P < 0.01) in the left than in the right kidney after the infusions of l-NAME and meclofenamate were started (Table 4). Figure 1 shows that RVR increased (P < 0.01) from 0.69 ± 0.04 to 1.32 ± 0.12 mmHg·ml⁻¹·min⁻¹ before ECVE and remained elevated during ECVE (1.07 ± 0.17 mmHg·ml⁻¹·min⁻¹, P < 0.05), when NO and PG synthesis were simultaneously reduced in the right kidney. These increments in RVR were greater (P < 0.05) than those found in group 3, where NO synthesis was reduced in dogs in which synthesis of COX-2-derived metabolites was blocked (Fig. 1). RVR was also greater (P < 0.05) in the right than in the left kidney, in which

**Table 4. Effects of 5% ECVE during intravenous infusion of meclofenamate to reduce both COX isoforms activity and infusion of l-NAME into the right renal artery to reduce NO synthesis in the right kidney**

<table>
<thead>
<tr>
<th></th>
<th>Control</th>
<th>l-NAME + Meclofenamate</th>
<th>l-NAME + Meclofenamate</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAP, mmHg</td>
<td>Right kidney</td>
<td>122 ± 1</td>
<td>137 ± 3†</td>
</tr>
<tr>
<td></td>
<td>GFR, ml/min</td>
<td>34 ± 3</td>
<td>22 ± 4‡</td>
</tr>
<tr>
<td></td>
<td>RBF, ml/min</td>
<td>181 ± 10</td>
<td>109 ± 8*</td>
</tr>
<tr>
<td></td>
<td>U NaV, μeq/min</td>
<td>50 ± 13</td>
<td>7 ± 3*</td>
</tr>
<tr>
<td></td>
<td>UV, ml/min</td>
<td>0.48 ± 0.11</td>
<td>0.07 ± 0.02*</td>
</tr>
<tr>
<td>Left kidney</td>
<td>GFR, ml/min</td>
<td>34 ± 3</td>
<td>32 ± 3‡</td>
</tr>
<tr>
<td></td>
<td>RBF, ml/min</td>
<td>186 ± 12</td>
<td>153 ± 7‡</td>
</tr>
<tr>
<td></td>
<td>U NaV, μeq/min</td>
<td>62 ± 19</td>
<td>15 ± 7*</td>
</tr>
<tr>
<td></td>
<td>UV, ml/min</td>
<td>0.56 ± 0.13</td>
<td>0.26 ± 0.12*</td>
</tr>
</tbody>
</table>

Values are mean ± SE; n = 7 dogs studied. *P < 0.05 vs. control period. †P < 0.01 vs. control period. ‡P < 0.01 vs. contralateral kidney.
to ECVE to an extent that is similar to that elicited by the infusion of l-NAME alone.

The results obtained during intrarenal l-NAME infusion (group 1) are similar to those previously reported (1, 11, 19) and suggest that NO is involved in the regulation of the renal excretory response to an ECVE. The l-NAME infusion at the dose used in this study does not induce changes in arterial pressure and does not modify the hemodynamic and excretory function in the contralateral kidney (1, 19). In previous studies (4, 10, 11, 19) it was proposed that the renal effects of NO synthesis inhibition seem to be modulated by the endogenous levels of PG because the simultaneous administration of a nonisozyme-specific COX inhibitor significantly potentiates the renal hemodynamic and antinatriuretic effects elicited by acute and prolonged NO synthesis inhibition. However, no studies have examined the relative contribution of each COX isoform in producing the renal PG involved in modulating the effects induced by NO synthesis blockade.

The role of PG in the regulation of renal function has been evaluated extensively (10, 14, 16, 17, 19). It has been shown that infusion of a nonisozyme-specific COX inhibitor to dogs with normal sodium intake reduces sodium excretory ability and increases RVR. In this study we have evaluated the renal hemodynamic and excretory changes induced by a COX-2 inhibitor (nimesulide) before and during an acute ECVE but not the renal effects elicited by a nonisozyme-specific COX inhibitor because they have been examined previously by our group (16, 19) and other groups (10, 14). As in a previous study (17), nimesulide did not induce significant changes in RVR and reduced UNaV and UV. These results suggest that COX-2-derived metabolites are not involved in the regulation of renal hemodynamic but play an important role in regulating renal excretory function during normal sodium intake. This suggestion is supported by studies showing that COX-2 is constitutively expressed in medullary interstitial cells (6), vasa recta (9), and loop of Henle (24).

The role of COX-2-derived metabolites has been evaluated using an inhibitor with a high COX-2 selectivity (15, 22, 23). Nevertheless, the possibility that nimesulide effects are partly due to COX-1 inhibition cannot be totally ruled out. Supporting that the effects elicited by the dose used of nimesulide are not secondary to COX-1 inhibition, we have reported that platelets aggregation elicited by arachidonic acid is absent in plasma from dogs treated with meclofenamate and not altered in plasma from nimesulide-treated dogs (17). These results are relevant because the thromboxane A2 involved in platelet aggregation is COX-1 dependent (3). We also have found that 1) nimesulide reduces urinary PGE2 excretion to a lower extent (by 40%) (17) than meclofenamate does (by 90%) (14, 16) and 2) meclofenamate, but not nimesulide, prevents bradykinin-induced natriuresis in dogs pretreated with l-NAME (18). Finally, it is obvious in this study that nimesulide and meclofenamate have different renal effects in dogs with reduced NO synthesis.

Despite the fact that several studies have evaluated the variations in renal COX-1 and COX-2 expression, in response to prolonged changes in sodium intake (8, 25), it has not been examined whether the expression and/or activity of each isoform is modified during an acute ECVE. As previously mentioned, several studies have demonstrated that infusion of a nonisozyme-specific COX inhibitor does not modify renal function during an acute ECVE (10, 14, 16, 19). With these antecedents, the results obtained during nimesulide infusion (group 2) were highly expected and support that COX-2-derived metabolites do not play an important role in regulating renal hemodynamic and excretory function during an acute ECVE. In contrast with the results found in our study during an acute ECVE, it can be expected that COX-2 inhibition would reduce renal excretory ability when sodium intake is chronically elevated because COX-2 expression is enhanced during prolonged increments in sodium intake (25). However, this hypothesis needs to be confirmed in future studies.

The results found during the simultaneous infusion of l-NAME and nimesulide (group 3) and in response to l-NAME and meclofenamate (group 4) suggest that the PG involved in modulating the renal vasoconstriction induced by NO synthesis inhibition are mainly dependent on COX-1 activity. This idea is supported by the fact that COX-1 expression in the renal cortex is significantly greater than that of COX-2 (8). Previous studies by our group have proposed that the important renal vasoconstriction elicited by simultaneous NO and PG synthesis inhibition is secondary not only to the decrease in these vasodilators but also to the effects induced by the endogenous ANG II levels (12). The increase in RVR induced by l-NAME and nimesulide before ECVE can be explained by studies showing that COX-2 is constitutively expressed in macula densa (7) and glomeruli (9). The COX-2-derived metabolites would have a more important role in regulating renal hemodynamic when NO synthesis is reduced. The importance of these metabolites is not evident during acute increments in extracellular volume because RVR returned to basal levels (Fig. 1).

The reduction in the renal excretory response to ECVE induced by NO synthesis inhibition was not modified by nimesulide and significantly potentiated by the simultaneous infusion of meclofenamate (Fig. 3). These results, together with those found during nimesulide administration (group 2) and those previously found during meclofenamate infusion alone (10, 11, 19), suggest that there is an important interaction between NO and COX-1-derived metabolites in regulating the renal response to an acute ECVE. The increased sodium reabsorption induced by l-NAME and meclofenamate is mainly secondary to a tubular effect (12). That inhibition of NO and PG increases tubular sodium reabsorption has been proposed in studies showing that NO regulates sodium reabsorption in proximal and distal tubules (1, 11, 21) and that showing that PG are involved in regulating sodium reabsorption in different tubular segments (14, 20). The
importance of COX-1-derived metabolites in regulating sodium excretion during an acute ECVE is supported by results suggesting that natriuresis secondary to increments in renal interstitial hydrostatic pressure is reduced by COX-1 inhibition and well preserved during COX-2 inhibition (5). The greater antinatriuretic effect induced by simultaneous L-NAME and meclofenamate infusion could also be secondary to an effect on medullary blood flow, because NO and PG are involved in regulating blood flow to the medulla (2, 14). In support of the hypothesis that L-NAME and meclofenamate reduce renal excretory ability, by decreasing medullary blood flow, it recently has been found by our group that the natriuresis elicited by infusing a medullary vasodilator (bradykinin) is only prevented when both inhibitors are simultaneously administered (18).

In summary, the results of this study suggest that PG involved in modulating the renal hemodynamic and excretory response to NO synthesis reduction are mainly dependent on COX-1 activity.

Perspectives

Considering that selective COX-2 inhibitors are increasingly used for treatment of inflammatory processes and that the renal effects of these nonsteroidal anti-inflammatory drugs is not well known, the results obtained in this study may have some clinical implications since the increase of arterial pressure in some hypertensive patients seems to be secondary to a decreased NO production (13). With our results, it could be proposed that the acute administration of a non-isoenzyme-specific COX inhibitor to these patients may have more deleterious effects on renal function than the acute administration of a selective COX-2 inhibitor. The latter is only a hypothesis that needs to be confirmed by future studies.

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