Selective Cyclooxygenase-2 Inhibition Impairs Glomerular Capillary Healing in Experimental Glomerulonephritis

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Abstract. Selective cyclooxygenase-2 (COX-2) inhibitors have anti-inflammatory activity and reduce proteinuria in experimental membranous glomerulonephritis. Antiangiogenic properties of COX-2 inhibitors were recently reported. Whether these properties are relevant to the glomerular healing process in inflammatory glomerular diseases was investigated. For evaluation of the effects of selective COX-2 inhibitors on the glomerular healing process in a rat model of mesangioproliferative glomerulonephritis (induced by anti-Thy 1.1 antibody), a selective COX-2 inhibitor (rofecoxib or celecoxib) or vehicle was administered daily from day 1 after disease induction until euthanasia on day 6. Additional nephritic rats were treated with rofecoxib or vehicle from day 1 to day 10 and were monitored until day 28. Selective COX-2 inhibition led to significant increases in mesangiolysis (up to +71%) on days 2 and 6 and in albuminuria (up to 3.1-fold) on day 6. This augmentation of glomerular capillary damage was associated with rarefaction of glomerular endothelial cells, whereas the proliferation and activation of mesangial cells were not affected. No significant effects on the glomerular influx of polymorphonuclear neutrophils or the infiltration and proliferation of monocytes/macrophages at day 2 were noted. These effects were independent of systemic hemodynamic features, because rofecoxib did not affect systolic BP on day 2 or 5. Nephritic rats treated with rofecoxib for 10 d demonstrated persistent glomerular injury at day 28, as indicated by increased albuminuria (10-fold) and mesangial type IV collagen deposition (+24%). In normal rats, 5-d administration of rofecoxib failed to induce albuminuria or morphologic renal damage. In conclusion, selective COX-2 inhibitors impair glomerular capillary repair after mesangiolysis in rats with anti-Thy 1.1 glomerulonephritis. These data suggest that selective COX-2 inhibitors should be used with caution among patients with inflammatory endocapillary glomerular disorders.

Cyclooxygenase (COX) is the key enzyme in the biosynthesis of prostaglandins. In physiologic states, prostaglandins are critically involved in the maintenance of gastric mucosal integrity and the regulation of renal vascular contractility, sodium and water balance, and BP (1). Therefore, the therapeutic use of nonselective COX inhibitors as analgesics is limited by their adverse effects, particularly gastrointestinal ulcers. COX-2 is normally undetectable in most tissues but is highly overexpressed at sites of inflammation (4,5). Selective COX-2 inhibitors have now reached the marketplace, and potent analgesic activity without serious gastrointestinal side effects has been reported (6).

Fetal and adult kidneys are among the few organs that constitutively express COX-2 (7–9), suggesting that expression of COX-2 is necessary for the maintenance of normal renal architecture and function and for postnatal renal development (10–12). Not surprisingly, COX-2 inhibitor-induced acute renal failure, similar to that observed with nonselective COX inhibitors, is being increasingly recognized (13). However, renoprotective and antiproteinuric effects of selective COX-2 inhibitors were observed in rodent models of renal injury (14,15).

A hitherto unrecognized activity of selective COX-2 inhibitors, namely antiangiogenic properties, was recently reported. Selective COX-2 inhibitors were demonstrated to suppress angiogenesis in tumors by inhibiting proangiogenic factor expression and endothelial cell growth (16,17). Another study demonstrated a delay in the healing of gastric ulcers in rats receiving a selective COX-2 inhibitor, which was linked to the antiangiogenic properties of the compound (18).

On the basis of these observations, we asked whether selective COX-2 inhibitors might also impair the capillary healing that occurs in the course of glomerulonephritis, such as anti-Thy 1.1 nephritis in rats (19,20). In this model, antibody- and complement-mediated acute mesangiolysis is followed by capillary repair, involving mesangial and glomerular endothelial cell proliferation as well as increased matrix synthesis (20–22). A unique feature of this model is that glomeruli spontaneously recover during a resolution phase (21).
Materials and Methods

Compounds

Rofecoxib (also known as MK-0966), a highly selective COX-2 inhibitor, was obtained from Merck Sharp & Dohme GmbH (Haar, Germany). Another selective COX-2 inhibitor, celecoxib (SC-58635), was obtained from Pfizer GmbH (Karlruhe, Germany).

Experimental Design

All animal experiments were approved by the local review boards. Anti-Thy 1.1 glomerulonephritis was induced in male Wistar rats (160 to 180 g at the start of the experiments; Charles River, Sulzfeld, Germany) as described (23). The rats were treated by oral gavage, beginning 18 h after disease induction and continuing once daily up to day 5, with rofecoxib (1 mg/kg, n = 11; 10 mg/kg, n = 10), celecoxib (30 mg/kg, n = 9; 50 mg/kg, n = 8), or vehicle alone (n = 9). The choice of doses was based on various studies in rats that revealed significant anti-inflammatory effects in the dose ranges tested (24–29). Furthermore, COX-1 activity was not affected at the doses tested (30,31). The experimental doses reflected human clinical doses (up to 1 mg/kg) for rofecoxib, whereas higher doses were used for celecoxib, in comparison with human doses (up to 12 mg/kg).

Renal biopsies were obtained by intravital biopsy at day 2 and by post mortem biopsy at day 6 after disease induction. Twenty-four-hour urine collections were performed from day 5 to day 6. The rats received intraperitoneal injections of the thymidine analogue 5-bromo-2’-deoxyuridine (BrdU) (100 mg/kg; Sigma-Aldrich Chemie GmbH, Deisenhofen, Germany) 4 h before the day 2 intravital biopsy. BP was measured on day −1 before disease induction and on days 2 and 5 after disease induction.

Anti-Thy 1.1 glomerulonephritis was also induced in 10 rats that were treated with 10 mg/kg rofecoxib (n = 5) or vehicle alone (n = 5) from day 1 to day 10 and were then monitored until day 28. The rats underwent an intravital renal biopsy at day 6 after disease induction. BrdU was injected intraperitoneally 4 h before the intravital biopsy. In addition, normal rats were treated with rofecoxib at 1 or 10 mg/kg (n = 3 each) for 5 d, after which albuminuria was measured and renal tissue was obtained.

Renal Morphologic Assessments

Tissue for light microscopy and immunoperoxidase staining was fixed in methyl Carnoy’s solution and embedded in paraffin. In periodic acid-Schiff-stained sections, the numbers of mitoses and polymorphonuclear neutrophils (PMN) in 50 to 100 glomerular tufts were determined as described (19,23). By using a 1000-fold magnification, mitoses were differentiated into endothelial cells and nonendothelial cells, as described (19,23). By using a point-counting method. For this, a grid composed of 100 dots was superimposed on consecutive glomeruli (range, 25 to 30 glomeruli; magnification, ×1000) and the numbers of dots overlaying stained areas were counted (33). Sections immunostained for COX-2 were examined by using the same grid but at 400-fold magnification; the numbers of dots overlaying stained renal cortical areas were evaluated in at least 100 consecutive fields for each kidney.

Immunohistochemical Double-Staining

Double-immunostaining for identification of the type of proliferating cells was performed as reported previously (19,23). First, sections were stained for proliferating cells with a murine monoclonal antibody against BrdU-containing nuclease (clone BU-1; Amersham, Braunschweig, Germany), in Tris-buffered saline, using an immunoperoxidase procedure. 3,3’-diaminobenzidine was used as a substrate, resulting in a black product. Sections were then incubated with the IgGl monoclonal antibody ED-1 (directed against monocytes/macrophages) or the monoclonal antibody JG-12 (directed against rat endothelial cells). Aminothylcarbazole was used as a substrate, resulting in a red product. Cells were identified as proliferating monocytes/macrophages or proliferating glomerular endothelial cells if they demonstrated positive nuclear staining for BrdU and the nucleus was completely surrounded by cytoplasm positive for ED-1 or JG-12 antigen, respectively. Negative control assays included omission of either of the primary antibodies, in which cases no double-staining was noted.

Electron Microscopy

Kidneys were removed after in situ perfusion with Dulbecco’s modified Eagle’s medium/F-12 medium and 4% paraformaldehyde/phosphate buffer. Blocks of renal tissue were immersed in 4% formalin. The samples were then embedded in Epon and processed for transmission electron microscopy by using standard procedures.

Miscellaneous Measurements

Urinary albumin levels were determined on a 96-well enzyme-linked immunosorbent assay plate, using a peroxidase-conjugated anti-rat albumin antibody (ICN Biomedical, Eschwege, Germany), as described (34). All measurements were performed in duplicate. BP measurements were performed with the tail cuff method, using a programmed sphygmomanometer (BP-98A; Softron, Tokyo, Japan) (35).
Statistical Analyses
Values are expressed as mean ± SD unless otherwise noted. Statistical significance (defined as $P < 0.05$) was evaluated with Mann-Whitney $U$ tests or paired $t$ tests, where appropriate.

Results
Effects of Selective COX-2 Inhibitors on Mesangiolytic Injury and Albuminuria
Mesangiolytic changes were more pronounced at day 2 (i.e., 48 h) after disease induction in nephritic rats treated with rofecoxib or celecoxib, compared with rats treated with vehicle alone (Figure 1A). Furthermore, in rats treated with rofecoxib, a dose of 1 mg/kg led to a marked increase in the frequency of glomerular microaneurysms at day 2 (Figure 1B). The mesangiolytic changes and the frequency of glomerular microaneurysms were still more pronounced at day 6 for most groups that received selective COX-2 inhibitors, compared with control rats treated with vehicle alone. Apparent dose dependence in the degree of mesangiolysis and the frequency of glomerular microaneurysms at day 6 was noted for the celecoxib-treated animals (Figure 1, A and B). Rats treated with COX-2 inhibitors not only developed more severe glomerular pathologic conditions but also exhibited functional deterioration, as evidenced by an increase in urinary albumin excretion on day 6 (Figure 1C).

Effects of Selective COX-2 Inhibitors on Glomerular Endothelial Cell Behavior
Endothelial cell injury and repair are of importance in anti-Thy 1.1 glomerulonephritis. Selective COX-2 inhibition led to a significant rarefaction of glomerular endothelial cells at day 2, compared with rats treated with vehicle alone, as indicated by a rarefaction of glomerular JG-12 antigen expression (Figure 2). The proliferation of endothelial cells and nonendothelial cells was quantified by BrdU labeling and counting of mitotic figures. There was no significant difference in BrdU incorporation at day 2 between rats receiving selective COX-2 inhibitors and those receiving vehicle alone (data not shown). Similarly, the numbers of mitotic figures in glomerular endothelial cells and nonendothelial cells were not different between the groups. In an additional experiment, proliferating glomerular endothelial cells were also identified by double-immunostaining for BrdU and JG-12. This experiment also demonstrated no significant difference between rats treated with selective COX-2 inhibitors and those treated with vehicle alone (data not shown). Electron-microscopic evidence of glomerular endothelial damage was detected in nephritic rats at day 2 (Figure 3A) and seemed to be increased in rats receiving rofecoxib (Figure 3B).

Effects of Selective COX-2 Inhibitors on Glomerular Mesangial Cell Activation
We also investigated the effects of selective COX-2 inhibition on mesangial cell activation in anti-Thy 1.1 nephritis. Glomerular α-smooth muscle actin expression (a marker of mesangial cell activation) did not differ between rats receiving selective COX-2 inhibitors and those receiving vehicle alone at days 2 and 6 after disease induction (Figure 4).

Effects on Glomerular Leukocyte Influx and Activation
One of the early events in anti-Thy 1.1 nephritis is an influx of PMN into glomeruli, followed by monocytes/macrophages.
At 48 h after disease induction, glomerular accumulation of PMN (Figure 5A) and the numbers of monocytes/macrophages in glomeruli (Figure 5B) were not significantly affected in rats receiving COX-2 inhibitors. Selective COX-2 inhibitors also did not affect the intraglomerular proliferation of monocytes/macrophages, as determined by double-immunostaining for the ED-1 antigen and BrdU, at day 2 (Figure 5C). The glomerular influx of monocytes/macrophages at day 6 was significantly increased in rats treated with the low dose of rofecoxib (1 mg/kg) or the high dose of celecoxib (50 mg/kg) (Figure 5B).

Effects of Rofecoxib on Systemic Hemodynamics

To exclude the possibility that differences between COX-2 inhibitor- and vehicle-treated animals were attributable to effects on BP, we determined the effects of rofecoxib on systemic hemodynamics. No significant effect of rofecoxib on
systolic BP was noted on days 2 and 5 after disease induction, compared with rats treated with vehicle alone (Table 1). COX-2 inhibitor treatment also did not affect the rate of body weight gain or food or water intake (data not shown).

**Chronic Effects of Rofecoxib on the Resolution of Renal Functional and Pathologic Damage**

The anti-Thy 1.1 glomerulonephritis model used is characterized by complete resolution of the injury within 4 to 8 wk after antibody injection. When nephritic rats were monitored for 28 d after disease induction, marked glomerular accumulation of type IV collagen persisted only in rats treated transiently with rofecoxib and not in the vehicle-treated control group (Table 2). This increased type IV collagen deposition was associated with an increase in albuminuria for the rats treated with rofecoxib (Table 2).

**Expression of COX-2 Immunoreactive Protein**

COX-2 expression in the renal cortex of normal and vehicle-treated nephritic rats was restricted to epithelial cells in a small number of tubular segments. According to anatomic criteria, these segments were the macula densa and cortical thick ascending limb of Henle’s loop, in agreement with previous descriptions of COX-2-immunoreactive cells within renal tissues (7). Tubular expression of COX-2 was dose-dependently increased on days 2 and 6 in the nephritic rats treated with rofecoxib. Treatment with celecoxib also increased COX-2 expression, but the effects did not demonstrate dose dependence at the doses tested (Figure 6). In glomeruli, there were few cells with COX-2 immunoreactivity at day 6 in nephritic rats treated with COX-2 inhibitors, whereas we failed to observe COX-2-positive cells at day 6 in glomeruli of nephritic rats treated with vehicle alone or at day 2 in any group (data not shown).

**Effects of Selective COX-2 Inhibition in Normal Rats**

For normal rats, 5 d of treatment with 1 or 10 mg/kg rofecoxib failed to induce albuminuria (Table 3). Furthermore, glomerular endothelial expression of the JG-12 antigen did not change. As expected, rofecoxib dose-dependently increased the intrarenal expression of COX-2 (Table 3).

**Discussion**

In this study, we investigated the effects of specific COX-2 inhibition in the anti-Thy 1.1 model of mesangioproliferative glomerulonephritis. In this model, glomerular disease is initiated by selective immune-mediated mesangial cell damage, resulting in mesangiolysis, but secondary damage to the glomerular capillaries, with the formation of microaneurysms and endothelial damage, is also well recognized (20). This initial phase of the disease is quickly followed by overshooting mesangial cell proliferation, which leads to a histologic pattern that resembles human mesangioproliferative glomerulonephritis. Finally, at least for anti-Thy 1.1 nephritis induced by the monoclonal antibody OX-7, spontaneous restoration of the normal glomerular architecture ensues.

The major finding of this study was that the administration of different COX-2 inhibitors significantly aggravated early glomerular capillary injury in anti-Thy 1.1 nephritis, as evidenced by increased mesangiolysis, microaneurysm formation, and albuminuria. The pathophysiologic relevance of this early augmentation of glomerular damage by COX-2 inhibitors was
emphasized by our findings in the long-term study, in which transient COX-2 inhibition resulted in persistent glomerular damage at 4 wk after disease induction, i.e., at a time when most glomerular changes have usually resolved.

The aggravation of early glomerular injury in anti-Thy 1.1 nephritis by COX-2 inhibitors is in accordance with our underlying hypothesis, namely that COX-2 inhibitors may affect glomerular capillary healing via their antiangiogenic properties (16,17). As described earlier, glomerular capillary healing in anti-Thy 1.1 nephritis exhibits features of angiogenesis, such as glomerular endothelial cell proliferation and elongation and mesangial cell proliferation (20). In this study, increased mesangiolysis and microaneurysm formation in rats treated with COX-2 inhibitors represent indirect evidence of augmented intracapillary damage. More important is the rarefaction of staining with the JG-12 antibody. This monoclonal antibody, which recognizes a currently unknown antigen, was recently demonstrated to allow the sensitive detection of endothelial cells in normal and diseased rat glomeruli (33). Rarefaction of the JG-12 staining pattern thus provides more-direct evidence for increased damage to endothelial cells in the COX-2 inhibitor-treated rats. Of note, we were unable to document reduced proliferation of glomerular endothelial cells in these experimental groups, suggesting that mechanisms other than antiinfectious actions of the COX-2 inhibitors were underlying the increased endothelial damage. In this respect, Iruela-Arispe et al. (20) observed that, in anti-Thy 1.1 nephritis, glomerular endothelial cells often appeared elongated, with extended processes, during the course of capillary (in particular, microaneurysm) repair and endothelial cells encircled areas of mesangial cellularity. Therefore, one mechanism by which COX-2 inhibitors might have reduced the JG-12 staining pattern could be related to inhibition of endothelial cell migration and shape changes. This idea is supported by data obtained with cultured umbilical cord venous endothelial cells, as well as human renal microvascular endothelial cells; COX-2 inhibition reduced endothelial cell migration (36,37), possibly by preventing the integrin-dependent activation of small GTPases (38). This may also explain why inhibition of COX-2 from day 1 to day 10 in our long-term study resulted in persistent glomerular damage, because increased proliferation and migration of glomerular endothelial cells have been documented until day 14 of anti-Thy 1.1 nephritis (20).

Could mechanisms other than the actions of COX-2 inhibitors on glomerular endothelial cells underlie our observations? It seems unlikely that COX-2 inhibitors altered the extent of immunologic mesangial damage, because oral treatment was initiated 18 h after disease induction (a time at which anti-Thy 1.1 antibody binding in the glomeruli has already reached its maximum). A second possibility is that COX-2 inhibition altered systemic BP and thus hypertension was superimposed on immunologic injury. We failed to demonstrate any effect of COX-2 inhibition on systemic BP, either in the very early phase or during the peak of mesangial cell proliferation on day 6. This finding is in agreement with data obtained by Wang et al. (14) in rats with renal ablation and by Komers et al. (39) in streptozotocin-diabetic rats. Importantly, in the latter study,

**Figure 5.** Effects of selective COX-2 inhibitors on glomerular leukocyte accumulation and activation. (A) Numbers of infiltrating glomerular polymorphonuclear neutrophils (PMN) on days 2 and 6 after disease induction (n = 8 to 11 for each group). (B) Numbers of infiltrating ED-1-positive monocytes/macrophages on days 2 and 6 after disease induction (n = 8 to 11 for each group). (C) Numbers of proliferating glomerular ED-1-positive monocytes/macrophages on days 2 and 6 after disease induction (n = 5 to 9 for each group). BrdU, 5-bromo-2-deoxyuridine.
renal plasma flow was also not affected by acute COX-2 inhibition (39). In rats with renovascular hypertension, COX-2 inhibition even decreased BP and plasma renin activity (40). However, at least some instances in which selective COX-2 inhibitors elevated BP have been documented (41). A third possibility is related to the effects of COX-2 inhibition on intrinsic glomerular cells other than endothelial cells, particularly mesangial cells. This possibility also is unlikely, because the glomerular expression of \(\alpha\)-smooth muscle actin, which is a very sensitive marker of mesangial damage (42), was not affected in the studies presented here. Finally, COX-2 inhibitors might have affected glomerular leukocyte influx and thus influenced the course of the disease. Indeed, we noted a non-significant trend toward increases in glomerular PMN counts on day 2 for the low-dose rofecoxib-treated group. Although we cannot formally exclude the possibility that this was a direct effect of COX-2 inhibition, a more likely explanation for this observation is that increased PMN numbers in this group were the result, rather than the cause, of increased capillary damage. In contrast to PMN, early monocyte/macrophage counts were not affected by COX-2 inhibition. The enhancement of glomerular monocyte/macrophage counts for the two COX-2 inhibitor-treated groups on day 6 after disease induction may be accounted for by the finding that selective COX-2 inhibitors can increase glomerular monocyte chemoattractant protein-1 mRNA expression in anti-Thy 1.1 nephritis on day 5 (43).

To demonstrate that COX-2 inhibition indeed affected COX-2 \textit{in vivo}, we also investigated the renal expression of COX-2 in the various groups. The COX-2 expression pattern in our untreated nephritic rats corresponded well to that observed in normal and diabetic rats (7,39), as well as that observed in anti-Thy 1.1 nephritis (44). Our data are at variance with those of Hirose et al. (45), who, using a different antibody and technique, demonstrated strong COX-2 expression in glomerular epithelial cells of rats with anti-Thy 1.1 nephritis. Our data also indicate the existence of a feedback mechanism \textit{in vivo}, because COX-2 inhibition uniformly led to upregulated (but not redistributed) expression of the enzyme within the kidney.

The findings of this study are at variance with conclusions derived from other rodent models of renal disease. In the renal ablation model, COX-2 inhibition reduced proteinuria and glomerulosclerosis (14). In the passive Heymann nephritis model of human membranous nephropathy, COX-2 inhibition with the relatively selective inhibitor flosulide also resulted in a decrease in proteinuria (15). The major difference between those two models and the anti-Thy 1.1 nephritis model is the

### Table 1. Effects of rofecoxib on systemic BP$^a$

<table>
<thead>
<tr>
<th>Group</th>
<th>Systolic BP (mmHg)</th>
<th>Day -1</th>
<th>Day +2</th>
<th>Day +5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib (10 mg/kg)</td>
<td>112 ± 7</td>
<td>109 ± 7</td>
<td>121 ± 10</td>
<td></td>
</tr>
<tr>
<td>Rofecoxib (1 mg/kg)</td>
<td>116 ± 10</td>
<td>119 ± 7</td>
<td>114 ± 5</td>
<td></td>
</tr>
<tr>
<td>Vehicle alone</td>
<td>109 ± 4</td>
<td>108 ± 4</td>
<td>114 ± 5</td>
<td></td>
</tr>
</tbody>
</table>

$^a$ Data are presented as means ± SD (\(n = 5\) in each group). All differences are nonsignificant (paired t test).

### Table 2. Effects of rofecoxib on the resolution of renal functional and pathologic changes on day 28$^a$

<table>
<thead>
<tr>
<th>Group</th>
<th>Albuminuria (mg/d)</th>
<th>Glomerular Type IV Collagen Staining (% stained area)</th>
<th>Glomerular (\alpha)-Smooth Muscle Actin Staining (% stained area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib (10 mg/kg)</td>
<td>6.7 ± 3.8$^b$</td>
<td>57 ± 2$^b$</td>
<td>11 ± 6</td>
</tr>
<tr>
<td>Vehicle alone</td>
<td>0.6 ± 0.2</td>
<td>45 ± 2</td>
<td>10 ± 4</td>
</tr>
</tbody>
</table>

$^a$ Data are presented as means ± SD (\(n = 5\) in each group).

$^b$ \(P < 0.05\) versus vehicle alone.

### Table 3. Effects of rofecoxib in normal rats$^a$

<table>
<thead>
<tr>
<th>Group</th>
<th>Albuminuria (mg/d)</th>
<th>Glomerular JG-12 Staining (% stained area)</th>
<th>COX-2 Expression in Renal Cortex (positive points/field)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rofecoxib (10 mg/kg)</td>
<td>0.5 ± 0.4</td>
<td>61 ± 2</td>
<td>0.53 ± 0.15$^b$</td>
</tr>
<tr>
<td>Rofecoxib (1 mg/kg)</td>
<td>0.8 ± 0.5</td>
<td>62 ± 4</td>
<td>0.34 ± 0.16</td>
</tr>
<tr>
<td>Vehicle alone</td>
<td>0.7 ± 0.1</td>
<td>59 ± 2</td>
<td>0.13 ± 0.08</td>
</tr>
</tbody>
</table>

$^a$ Data are presented as means ± SD (\(n = 3\) in each group).

$^b$ \(P < 0.05\) versus vehicle alone.
extent of early intracapillary damage, particularly the extent of damage to glomerular endothelial and mesangial cells. Although some endothelial cell damage and early mesangial cell activation have been documented (particularly in the renal ablation model) (46,47), both are minor in comparison with those in the anti-Thy 1.1 model. These considerations lead us to conclude that COX-2 inhibition may be harmful in instances of pronounced glomerular capillary damage, such as endocapillary or mesangiocapillary glomerulonephritis, transplant glomerulopathy, or thrombotic microangiopathies.

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References


with celecoxib elevates blood pressure and promotes leukocyte adherence. *Br J Pharmacol* 129: 1423–1430, 2000


