Abstract

To determine whether the amount of cyclooxygenase metabolites correlates with the development of lupus nephritis, intrarenal eicosanoid production was measured in autoimmune mice. Disease progression was related to the renal biosynthesis of prostaglandin (PGE2), prostacyclin (6 keto PGF1α), and thromboxane (TXB2) using the MRL-lpr and NZB×NZW F1 hybrid mouse strains with predictably progressive forms of renal disease that mimic the human illness. Mice were evaluated for renal disease by measuring urinary protein excretion and renal immunopathological conditions and these features were related to renal eicosanoid production. These studies show that: (a) intrarenal synthesis of TXB2 increased incrementally in MRL-lpr and NZB×NZW F1 mice as renal function deteriorated and renal pathologic events progressed; (b) there were no consistent increases in the levels of two other cyclooxygenase metabolites, PGE2 or 6 keto PGF1α; and (c) intrarenal protection occurred in the renal medulla, cortex, and within enriched preparations of cortical glomeruli; (d) when renal disease was prevented by pharmacologic doses of PGE2, intrarenal TXB2 did not increase; (e) administration of a dose of ibuprofen (9 mg/kg), a cyclooxygenase inhibitor capable of reducing 90% of platelet TXB2 without affecting intrarenal levels, did not retard the progression of renal damage. Taken together, these data indicate that the intrarenal level of TXB2 rises in relation to the severity of murine lupus nephritis. Furthermore, because of the potential deleterious effects of TXA2, enhanced production of this eicosanoid may be an important mediator of renal injury.

Introduction

Autoimmune lupus mice are uniquely valuable for studies of chronic progressive renal injury because their disease is spontaneous and remarkably similar to the human condition. By using both the MRL/Mp-lpr (MRL-lpr)1 and NZB×NZW F1 hybrid (NZB×W) mice with autoimmune lupus nephritis, it is possible to eliminate unimportant peculiar features unique to a strain and identify common denominators with potential pathogenic relevance.

Arachidonic acid metabolites, most notably prostaglandin E2 (PGE2), thromboxane A2 (TXA2), and prostacyclin (6 keto PGF1α), are potent mediators generated during immunologic inflammatory events and are capable of profoundly changing renal hemodynamics (reviewed in References 1–3). Recently, increased renal synthesis of thromboxane has been demonstrated during the inexorable progression of immune-mediated and nonimmunologic induced models of renal injury (4–8). Previous studies demonstrate that supplementing the diet of autoimmune mice with fish oil delays the onset of nephritis (9, 10), and that there is a concurrent reduction of endogenous renal cyclooxygenase metabolites during this dietary therapy (9). To assess whether this diet initiated a reduction in one or more renal cyclooxygenase products that might be related to the beneficial effect of a fish oil enriched diet, thromboxane B2 (TXB2), PGE2, and 6 keto PGF1α, the stable hydrolysis product of prostacyclin, were measured from renal tissue of NZB×W and MRL-lpr mice, which share features of the renal disease, but which differ in their time course and immunologic disturbances (11, 12).

Methods

Mice. Male and female MRL-lpr as well as MRL/Mp−− (MRL−−) mice originally obtained from the Jackson Laboratory (Bar Harbor, ME) were bred in our own facility. Female and male MRL-lpr mice were used because disease expression is similar in both sexes. Mating of NZB and NZW in our laboratory produced NZB×W F1 hybrids. In that disease is more predictable and rapidly progressive in female NZB×W mice, studies were limited to this sex. All animals were kept under standard laboratory conditions.

Extraction of cyclooxygenase metabolites. Mice were killed by rapid cervical dislocation, kidneys were excised, and the capsule was gently removed. The kidney was then bisected and the medulla and cortex were rapidly separated by fine dissection. Tissues were immediately moistened with Krebs–Ringer bicarbonate buffer, 22.5 meq, containing KCl, NaHCO3, NaH2PO4, and CaCl2 (KRB) at pH 7.2, and 10–30 mg of tissues were finely, uniformly minced with a razor blade and incubated in 2 ml of KRB in a 25-ml flask on a shaker platform in a 5% CO2 incubator at 37°C for 15 min or 30 min. All supernatants were immediately stored at −20°C for PGE2, 6 keto PGF1α, and/or TXB2 analysis. It was not necessary to extract PGE2, TXB2, or 6 keto PGF1α from tissues, because cyclooxygenase metabolites accumulate in the medium rather than in the tissues (13).

PGE2, TXB2, and 6 keto PGF1α assays. PGE2, TXB2, and 6 keto PGF1α content in supernatant was determined by direct competitive binding radioimmunoassays. Anti-PGE2 serum, kindly provided by Dr. Lawrence Levine (Brandeis University, Waltham, MA) has a 100% cross-reactivity with PGE1 but only 2.7% with prostaglandin F2 (PGF2) and was used at a final dilution of 1:6,000. Therefore, our results cannot differentiate PGE1 and PGE2. However, because PGE2 was used as a standard, we have expressed our results as PGE2 equivalents. Antisera to TXB2, a generous gift of Dr. Perry V. Halushka (Medical University of South Carolina, Charleston, SC), did not cross-react (0.04%) with other arachidonic acid metabolites and was used at a final dilution of 1:50,000 (14). 6 Keto PGF1α antisera was provided by Dr. Michael Dunn (Case Western Reserve Medical School, Cleveland, OH) and has a cross-reactivity as previously described and was used at a 1:15,000 dilution.

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1. Abbreviations used in this paper: KRB, Krebs-Ringer buffer; MRL-lpr, MRL/Mp-lpr (MRL-lpr) and NZB×NZW F1 hybrid (NZB×W); PGE1, PGE2, and PGE3, prostaglandins E1, E2, and F2; 6 keto PGF1α, prostacyclin; TXA2 and TXB2, thromboxanes A2 and B2.

and 37°C min in 12 consisting 60-90% of tissue). The mesangium of the mesangial cells and perivascular lymphocytic infiltration in the cortex and medulla; 3, lobular formation of the glomerulus, thickness of basement membrane, and prominent numbers of lymphocytes surrounding vessels; 4, glomerular crescent formation, some sclerotic glomeruli, tubular atrophy, and casts and/or vasculitis.

Glomerular preparation. Glomerular enriched fractions were prepared by a modification of the method of Barcelli et al. (18). Kidneys were removed from mice and placed in phosphate-buffered saline (PBS) (pH 7.4) on ice. After bisecting each kidney, the capsule was removed and the cortex was separated from papilla and medulla. A total of 8–10 kidneys was pooled for each experiment. Cortical pieces were gently pressed through a #200 mesh stainless steel sieve (75-μm pore diameter) into 10 ml of PBS. This suspension was filtered through a 25-gauge needle and then centrifuged at 1,500 rpm for 5 min and the supernatant was discarded. The pellet was resuspended in 8 ml of PBS and allowed to settle for 30 min. Three quarters of the supernatant was aspirated and replaced with fresh PBS. This resuspension and settling step was repeated five to six times. The purity of glomerular preparations was assessed microscopically. Preparations consisted of 60–90% glomeruli with contamination consisting of tubular fragments. Glomerular enriched preparations were suspended in 2 ml of Krebs (pH 7.4) at 37°C and incubated for 45 min in 12 × 75-mm siliconized glass tubes with constant agitation at 37°C in a 5% CO2 environment. At the end of the incubation, glomeruli were centrifuged at 1,500 rpm for 5 min and the supernatant was removed and stored at −20°C for PGE2 and TXB2 analysis. Glomerular enriched pellets were resuspended in 2 ml and stored at −20°C until the total protein content was determined by the method of Lowry et al. (19).

In vivo treatments. Groups of MRL-lpr female mice (2 mo of age) were injected subcutaneously with 5 μg of a stable PGE2 analogue, 15(6)-15-methyl PGE2 (a gift of Dr. John Pike, The Upjohn Co.), twice daily on 5 days of the week and once on Saturday and Sunday. Because previous studies indicated that injecting the vehicle control was similar to uninjected mice, our controls were not injected (16). Mice were treated for 2 mo and sacrificed at 4 mo of age.

Groups of MRL-lpr (2 mo of age) female and male and NZB×XW (3 mo of age) female mice were injected daily for 1 wk with ibuprofen (generously supplied by The Upjohn Co.) 8–9 mg/kg, diluted with PBS as previously described (20). Controls consisted of littermates receiving the vehicle alone.

Statistical analysis of data. The Student's t test, Mann–Whitney U test, and linear regression analysis were used to determine significant differences in the data.

Results

Cyclooxygenase metabolites in renal tissue

TXB2, PGE2, and 6 keto PGF1α in MRL-lpr mice. There was a dramatic increase in TXB2 levels in renal tissue of MRL-lpr mice during the course of autoimmune disease based on measurements before the onset of lymphadenopathy (2 mo) and after palpable nodes were apparent (4–6 mo). A significant increase in TXB2 synthesis occurred in both the cortex and medulla of older MRL-lpr mice with lymphoproliferation as compared with MRL−+++ and 2-mo MRL-lpr animals (P < 0.01, Fig. 1). Thus, the increase in TXB2 synthesis was limited to mice expressing products of the lpr gene. Cortical TXB2 levels in older MRL-lpr mice increased fivefold as compared to young mice of the same strain, whereas medullary TXB2 synthesis was at least three times greater in older MRL-lpr as compared with MRL—++ and young MRL-lpr mice. In fact, cortical TXB2 (pg/mg of tissue) in MRL-lpr mice increased progressively—38±2, 90±11, 100±20, and 326±37 at 6, 10, 13, and 20 wk of age, respectively. Similarly, medullary TXB2 (pg/mg of tissue) increased—90±2, 165±3, 280±10, and 415±35 at 6, 10, 13, and 20 wk of age, respectively. In striking contrast to the alteration in TXB2 synthesis in older MRL-lpr mice, PGE2 produc-
tion remained stable with increasing age for both the congenic strain and mice expressing the lpr gene (Fig. 1). When these renal tissues were further evaluated for their 6 keto PGF\textsubscript{1\alpha} synthesis, the values for this eicosanoid were also similar in young and old MRL-lpr mice and in congenic mice (Fig. 1).

**TXB\textsubscript{2}, PGE\textsubscript{2}, and 6 keto PGF\textsubscript{1\alpha} in NZB\texttimes W mice.** To eliminate the possibility that this increase in TXB\textsubscript{2} synthesis was an idiosyncratic feature peculiar to the MRL-lpr strain, we evaluated renal cortical and medullary tissues at several time points in another strain of mice prone to nephritis (Fig. 2). Increased TXB\textsubscript{2} synthesis occurred as mice aged from 2 to 4 mo (P < 0.01). An even greater increase in these mice was observed 4 mo later between 8 and 11 mo of age in both cortical and medullary tissue. In the NZB\texttimes W and MRL-lpr strain, the percentage incremental change in TXB\textsubscript{2} was greater in the cortex. Before the onset of renal disease (2 mo of age), cortical and medullary TXB\textsubscript{2} levels of the MRL-lpr and NZB\texttimes W mice were similar (Figs. 1 and 2). Although TXB\textsubscript{2} increased in both strains, MRL-lpr mice developed a two- to threefold greater increase in intrarenal TXB\textsubscript{2} with the development of renal disease as compared to NZB\texttimes W mice (Figs. 1 and 2). In sharp contrast to TXB\textsubscript{2}, renal PGE\textsubscript{2} synthesis did not vary with age in the NZB\texttimes W mice. There was a substantial rise in 6 keto PGF\textsubscript{1\alpha} in the cortex between 2 and 4 mo (Fig. 2). However, this increase did not appear to be related to disease in that the kidneys of these mice were normal between 2 and 4 mo and there was no further increase in this eicosanoid between 4 and 11 mo, when renal disease developed.

**Glomerular preparations**

In glomerular enriched preparations, the level of TXB\textsubscript{2} in MRL-lpr mice at 4 mo of age was increased by a factor two to three times above values in young MRL--++ mice and two to three times above MRL-lpr mice at only 2 mo of age (Table I). There was no consistent trend in PGE\textsubscript{2} synthesis in older MRL-lpr mice as compared with mice without lymphoproliferation. For example, in experiment 2 of Table I, PGE\textsubscript{2} values (in pg/mg of protein) were 33,768, 36,726, and 32,513 for MRL-lpr mice at 2 and 4 mo and MRL--++ mice 4 mo of age, respectively.

**Urinary protein and TXB\textsubscript{2}**

To determine whether there was a correlation between the amount of protein excreted and changes in TXB\textsubscript{2} in NZB\texttimes W mice of 2, 4, and 8-11 mo of age. These eicosanoid measurements (pg/mg of tissue) were analyzed by radioimmunoassays. Mean renal cortex (a) and medulla (b) values are indicated by bars±SEM.

**Renal pathology**

**MRL-lpr mice.** The earliest features of renal disease in MRL-lpr mice included proliferation of glomerular mesangial cells,

<table>
<thead>
<tr>
<th>Experiment</th>
<th>Strain</th>
<th>Age</th>
<th>n</th>
<th>TXB\textsubscript{2}</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>pg/mg of protein</td>
</tr>
<tr>
<td>1</td>
<td>lpr</td>
<td>2</td>
<td>10</td>
<td>5,988</td>
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<tr>
<td></td>
<td>lpr</td>
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<td>8</td>
<td>13,301</td>
</tr>
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<td></td>
<td>++</td>
<td>4</td>
<td>8</td>
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</tr>
<tr>
<td>2</td>
<td>lpr</td>
<td>2</td>
<td>6</td>
<td>2,752</td>
</tr>
<tr>
<td></td>
<td>lpr</td>
<td>4</td>
<td>6</td>
<td>5,269</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>4</td>
<td>6</td>
<td>2,246</td>
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<tr>
<td>3</td>
<td>lpr</td>
<td>2</td>
<td>10</td>
<td>3,800</td>
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<td>lpr</td>
<td>4</td>
<td>10</td>
<td>8,511</td>
</tr>
<tr>
<td>4</td>
<td>++</td>
<td>2</td>
<td>8</td>
<td>2,677</td>
</tr>
<tr>
<td></td>
<td>++</td>
<td>4</td>
<td>8</td>
<td>3,219</td>
</tr>
</tbody>
</table>

\(n\), number of kidneys pooled.

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1.2 TXB2 vs. 3. x 3C were slower significantly. Accompanied by the intima mononuclear disease cells and immune complexes and crescent areas (grade 4). As the progression of chronic glomerulonephritis, there was a pronounced increase of mesangial area (grade 3). These glomerular changes were accompanied by a lymphoctic infiltration in the cortex and medulla (predominantly perivascular), and thickening of the intima and/or media of renal arteries. In the final stage of disease (grade 4), mononuclear cells, lymphocytes, macrophages, and plasma cells were in the cortical and medullary interstitium accompanied by tubular atrophy and casts, and crescent formation and sclerosis of glomeruli (Fig. 4 A and B). The time course of these renal changes began at 3 mo with mild proteinuria at 3–4 mos, and a 50% mortality between 5 and 6 mo of age.

NZBXW mice. Renal disease in NZBXW mice was a considerably slower illness than in the MRL-lpr mice. Glomerular changes were similar to those described for MRL-lpr mice; however, vasculitis was rare. Renal disease consisted of a modest increase in glomerular mesangial cells beginning at 4 mo of age, followed by immune complexes in the peripheral capillary walls and proteinuria at 6 mo, and a 50% mortality by 10 mo of age with only 10% surviving beyond 1 yr.

Renal pathology and TXB2
TXB2 synthesis increased with the severity of renal pathology in autoimmune mice. A linear regression analysis plotting the degree of renal pathology in MRL-lpr mice vs. the level of cortical TXB2 showed a high degree of correlation (r = 0.87, n = 22, P < 0.01) between these variables (Fig. 5 a). Similarly, TXB2 levels in the medulla of this strain also increased with the degree of renal pathology (r = 0.78, n = 22, P < 0.01) (Fig. 5 b). A similar trend occurred in NZBXW mice. There was good correlation of an increase in TXB2 and the severity of pathology in the cortex (r = 0.80, n = 9, P < 0.01) and medulla (r = 0.82, n = 9, P < 0.01) (Fig. 6).

Treatments
A series of treatment protocols was investigated to determine the relation between renal damage and TXB2 production.

Prostaglandin therapy with pharmacologic doses of PGE. In previous studies, twice-daily injections of pharmacologic doses of PGE1 or PGE2 protected MRL-lpr and NZBXW mice from developing renal disease (16, 21). As indicated in Table III, treatment of MRL-lpr mice with PGE1 modestly reduced TXB2 in the cortex but markedly suppressed production in the medulla as compared with the control group. Treated mice did not become proteinuric nor did they develop renal disease.

Blocking cyclooxygenase metabolites with ibuprofen. As previously reported by our laboratory, daily injections of ibuprofen (8–9 mg/kg) in NZBXW mice did not modify development of renal disease or survival (20). Although, as previously reported, this dose inhibits 90% of platelet TXB2 production (20), it did not alter the level of TXB2 in the kidney (Table IV). There was no substantial decrease in either TXB2 or PGE2 levels in the renal cortex or medulla in the NZBXW or MRL-lpr mice injected with this agent.

Discussion
The present experiments indicate that (a) renal biosynthesis of the specific cyclooxygenase metabolite TXB2 increased in the MRL-lpr and NZBXW mice with spontaneous lupus nephritis; (b) as renal function deteriorated and renal pathologic events progressed, TXB2 increased in the renal medulla, cortex, and cortical glomeruli (60–90% pure); (c) drug therapy and dietary manipulation that prevented renal disease correlated with no elevation in renal TXB2; (d) conversely, a dose of the cyclooxygenase inhibitor, ibuprofen, capable of decreasing platelet but not TXB2 intrarenal synthesis, did not prevent an increase in renal TXB2 or retard the progression of chronic renal injury. Together, these data indicate that increased intrarenal TXB2 synthesis accompanies renal disease in murine lupus nephritis.

Increased intrarenal TXB2 levels have been directly implicated in the relentless progression of immune-mediated and nonimmunologically induced forms of renal injury (4–8). The present study is the first report showing the increase of thromboxane in the progression of spontaneous, chronic renal disease in animal models with a human counterpart. Preliminary reports from other laboratories in several experimental rat models in-

Table II. Intrarenal TXB2 and Urinary Protein in MRL-lpr Mice

<table>
<thead>
<tr>
<th>TXB2</th>
<th>Medulla</th>
<th>Urinary protein</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cortex</td>
<td>Medulla</td>
<td>Urinary protein</td>
</tr>
<tr>
<td>µg/mg of tissue</td>
<td>µg/mg of tissue</td>
<td>mg/24 h</td>
</tr>
<tr>
<td>107</td>
<td>206</td>
<td>4.4</td>
</tr>
<tr>
<td>60</td>
<td>99</td>
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<td>36</td>
<td>62</td>
<td>1.7</td>
</tr>
<tr>
<td>19</td>
<td>51</td>
<td>0.6</td>
</tr>
<tr>
<td>19</td>
<td>41</td>
<td>0.6</td>
</tr>
</tbody>
</table>

MRL-lpr mice were females 4–5 mo of age.
* r = 0.99, P < 0.01.
† r = 0.97, P < 0.01.
§ Amounts > 1.2 are pathologic.

Figure 3. A linear regression analysis of (a) cortical and (b) medullary TXB2 vs. urinary protein in NZBXW female mice. Protein values >1.2 mg/24 h are considered to be pathologic.
Figure 4. A paraffin section (a and b) of the cortex of the kidney of a female MRL-lpr mouse 6 mo of age scored as a grade 4. The prominent pathologic changes include sclerotic glomerulus (arrow), tubular casts (*), and a mononuclear cellular infiltrate (arrow head) in the interstitium and surrounding vessels. grade 0, normal and 4. most severe. Periodic acid-Schiff strain.
 dictate that augmentation of renal thromboxane biosynthesis is linked to the formation of proteinuria and/or impaired renal hemodynamics. For example, inhibiting renal thromboxane production prevents progressive renal disease with partial renal ablation (6), reduces proteinuria in adriamycin nephrosis (7), and prevents the decrements in the glomerular filtration rate in immunologically induced nephrotoxic serum nephritis (anti-glomerular basement membrane disease) (4). Thus, it is apparent that intrarenal TXA₂ levels can modulate renal hemodynamic forces and influence the course of renal damage.

What causes the intrarenal increase in thromboxane and which cells are producing this metabolite? Several candidates emerge as the cellular source responsible for increasing renal TXB₂. Broadly, these cells could either be a component of the renal tissue, or alternatively, circulate into the kidney via the blood. Glomerular epithelial and mesangial cells, and collecting tubules are the intrinsic elements capable of synthesizing TXB₂ (22–24). In murine lupus nephritis, there is an increase in mesangial cells, and a broadening of the glomerular epithelial foot processes. In that these cell types are capable of synthesizing TXB₂, intrarenal accumulation may be contributed to by these intrinsic renal components. However, because there is increased elaboration of TXB₂ in the medulla, as well as the cortex, the glomerular changes cannot account exclusively for the total increase. This leaves the possibility of TXB₂ release by circulating cells including leukocytes, monocytes, and platelets. Leukocytes can be eliminated because they are rarely present in kidneys of either MRL-lpr or NZBXW mice. Similarly, although platelets secrete abundant amounts of TXB₂, it is unlikely that they are the source of increased intrarenal production because a dose of the cyclooxygenase inhibitor, ibuprofen, capable of blocking platelet TXB₂ formation, did not reduce renal levels or protect autoimmune mice from renal injury. Thus, it is probable that monocytes, abundant in these kidneys and instrumental in the pathogenesis of glomerulonephritis, are a major source of eicosanoids (25–28).

Do patients with chronic renal disease have an increased level of TXB₂? Elevated urinary TXB₂ excretion (29, 30) has been connected with the deterioration of renal function in lupus patients with chronic glomerulonephritis (29) and during renal allograft rejection (30). Furthermore, recently, administration of dipyridamole and aspirin slowed the deterioration of renal function and the development of end-stage renal disease in.

Table III. MRL-lpr Mice Treated with Pharmacologic Doses of 15-Methyl PGE₁

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Medulla</th>
<th>Cortex</th>
</tr>
</thead>
<tbody>
<tr>
<td>*PGE₁</td>
<td>134±26†</td>
<td>73±12§</td>
</tr>
<tr>
<td>Control</td>
<td>262±19</td>
<td>98±7</td>
</tr>
</tbody>
</table>

Values are means±SEM. 
* 15-methyl PGE₁ injected bid for 2.5 mo. 
† P < 0.01. 
§ P < 0.02.

Table IV. Ibuprofen-treated Mice

<table>
<thead>
<tr>
<th>Strain</th>
<th>TXB₂</th>
<th>PGE₂</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Medulla</td>
<td>Cortex</td>
</tr>
<tr>
<td>MRL-lpr</td>
<td>340±64</td>
<td>45±9</td>
</tr>
<tr>
<td>Control</td>
<td>362±65</td>
<td>68±14</td>
</tr>
<tr>
<td>NZB×W</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibuprofen*</td>
<td>92±20</td>
<td>23±4</td>
</tr>
<tr>
<td>Control</td>
<td>83±5</td>
<td>23±2</td>
</tr>
</tbody>
</table>

Values are mean±SEM. n = 4 at all points. MRL-lpr mice were 3 mo of age. NZB×W mice were 3 mo of age. 
* Dose that inhibit platelet TXB₂ 90% (20).

Renal Thromboxane in Murine Lupus Nephritis
membranoproliferative glomerulonephritis; a result that could be attributed to the inhibition of renal thromboxane (31). Thus, elevations in urinary TXB₂ are prominent in several forms of renal injury.

Our results, combined with human studies and data from diverse experimental models of nephritis (4, 7, 8) suggest that elevation of intrarenal TXB₂ is a mediator of impaired renal function and a useful indicator of renal injury. To support the role of thromboxane as a modulator of renal injury, studies from our laboratory, as well as other investigators, showed that restricting substrate by feeding a diet deficient in an essential fatty acid (32) or by exclusively limiting lipid to fish oil (9, 10, 33) prevented renal disease and increased survival in autoimmune mice. However, we cannot eliminate the possibility that this beneficial effect was promoted by a reduction in lipoxigenase metabolites. Because both diets reduced the amount of endogenous prostanoids (9) and are theoretically capable of also lowering the lipoxigenase metabolites (34), we cannot exclude the possibility that reductions in 12-hydroxy-5,8,11,13-eicosatetraenoic acid may influence the progression of renal injury. In fact, a recent study suggests that renal function is influenced by TXA₂ as well as the sulfidopeptide leukotrienes (35). At the present time, it is uncertain whether the excess of TXA₂ in lupus nephritis is a mediator of renal damage. Although treatment with pharmacologic doses of PGE₁ prevents increases in renal TXB₂ and renal injury, it is possible that the action of PGE₁ is operating independently of TXB₂ suppression. To clarify this point, studies in progress are investigating the effects of direct, specific in vivo inhibition of TXA₂ synthesis in autoimmune mice. Thus, the hemodynamic, immunologic, and inflammatory consequences of altered renal cyclooxygenase metabolism should offer insight into the pathogenesis of renal injury and may provide promising therapeutic possibilities.

Acknowledgments

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References


