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Circ Res. 2004;95:1118-1124; originally published online November 4, 2004;
doi: 10.1161/01.RES.0000149571.96304.36
Circulation Research is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7330. Online ISSN: 1524-4571

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Abstract—Xanthine oxidoreductase (XOR) is the enzyme responsible for the final step in purine degradation resulting in the generation of uric acid. Here we have generated mice deficient in XOR. As expected, these animals lack tissue XOR activity and have low to undetectable serum levels of uric acid. Although normal at birth, XOR−/− mice fail to thrive after 10 to 14 days, and most die within the first month. The cause of death appears to be a form of severe renal dysplasia, a phenotype that closely resembles what has been observed previously in cyclooxygenase-2 (COX-2)−/− deficient mice. We further demonstrate that in the first month of life, a period in which the mouse kidney is undergoing rapid maturation and remodeling, wild-type mice exhibit an ∼30-fold increase in renal XOR activity, with a corresponding induction of COX-2 expression. In contrast, during this same period, XOR−/− animals fail to augment renal COX-2 expression. Finally, we show that in vitro and in vivo, uric acid can stimulate basal COX-2 expression. These results demonstrate that XOR activity is an endogenous physiological regulator of COX-2 expression and thereby provide insight into previous epidemiological evidence linking elevated serum uric levels with systemic hypertension and increased mortality from cardiovascular diseases. In addition, these results suggest a novel molecular link between cellular injury and the inflammatory response. (Circ Res. 2004;95:1118-1124.)

Key Words: kidney ■ cyclooxygenase

Initially identified as the substance in milk that was capable of decolorizing methylene blue, the enzyme xanthine oxidoreductase (XOR) has been the subject of biochemical investigation for >100 years.1 These studies have established the enzyme to be a 145-kDa protein that functions as a homodimer and possesses an iron-sulfur, flavin adenine dinucleotide as well as a C-terminal molybdopterin-binding domain.2–4 The enzyme can exist in two forms. Xanthine dehydrogenase (XDH) preferentially uses nicotinamide adenine dinucleotide as an electron acceptor, whereas xanthine oxidase (XO) uses molecular oxygen as the acceptor. When grouped together, these two enzymatic forms are termed “xanthine oxidoreductase.” XDH and XO are capable of catalyzing the final two steps in purine catabolism by converting hypoxanthine to xanthine and xanthine to urate/urate acid.

XOR activity has been classically linked to conditions of cellular injury. Previous studies have demonstrated that pharmacological inhibition of XOR limits the degree of tissue injury that occurs with ischemia and subsequent reperfusion.3–5 These studies have also demonstrated that tissue hypoxia and injury results in the enhanced conversion of XDH to XO. In addition to conditions of ischemia reperfusion, a number of other reports have demonstrated that XOR activity increases dramatically in the setting of hepatitis, hemorrhagic shock, acute viral infection, and thermal injury.1,3–5 One common feature of these disparate pathologies is that they are all accompanied by cell injury and turnover, circumstances in which the substrates of XOR are known to increase. Consistent with these laboratory studies, uric acid, the product of XOR activity, is often used clinically as a surrogate marker for tissue injury and damage.6

In many pathological conditions, cellular injury and inflammation are often associated with one another. Prostaglandins, synthesized as a result of the enzymatic activity of cyclooxygenases, function as the classic mediator of inflammation. Although cyclooxygenase-1 (COX-1) is usually expressed constitutively, COX-2 expression is induced by a wide range of inflammatory stimuli.7 Here we demonstrate that XOR activity can regulate the level of COX-2. Although we demonstrate the importance of this regulation in the context of the developing kidney, these results also extend a growing body of evidence suggesting that the product of XOR activity, uric acid, may have important roles in immune regulation and the inflammatory response.8–10 In addition, our observation may shed light on a number of epidemiological studies that have implicated elevated serum levels of uric acid as a risk factor for subsequent mortality in patients with...
underlying heart failure, diabetes, or coronary artery disease, as well as a potential risk factor for development of systemic hypertension.\textsuperscript{11–13}

Materials and Methods

Construction of XOR\textsuperscript{−/−} Mouse

The XOR locus was cloned by polymerase chain reaction using a bacterial artificial chromosome library as template (Incyte Genomics). In brief, a targeting vector was prepared by cloning the XOR genomic regions (~6.5 kb of DNA) corresponding to exon 2 to 5. The region corresponding to exon 2 to 3 was isolated using the primers 5’-TAAGTGTGGTGGAGAGAAAAATGC-3’ and 5’-CGGTACCATGTTGAGATCAT-3’, whereas the region corresponding to exon 4 to 5 used the primers 5’-TTTCCGCGGCCATCTGCTCCTTGCATCAT-3’ and 5’-TTTCCCGGGCACCCTTGGAAGGACATTCTCG-3’. The XOR genomic sequences were inserted into the pKO Scrambler vector (Stratagene) and the construct linearized by Snf1 restriction digest before electroporation into mouse embryonic stem (ES) cells (GSI-1; Genomesciences, Inc.). This ES cell line was derived from the 129Sv mouse strain and was always cocultured with feeder cells (Mitomycin C inactivated primary mouse embryonic fibroblasts). After electroporation, the ES cells were grown in medium containing G418 (400 μg/mL) and Gancyclovir (2 μmol/L) to select double-resistant colonies. Among the 192 picked ES cell clones, two were demonstrated to have the correctly targeted XOR gene as assessed by Southern blotting. These two clones were microinjected into blastocysts isolated from C57BL/6j mice (black color) to produce chimeric mice. Male chimeras with significant agouti color were mated with C57BL/6j females. Germline-transmitted progeny (agouti color) were screened by Southern blots to identify heterozygous mice. Homozygous mice. Male chimeras with significant agouti color were mated with C57BL/6j females. Germline-transmitted progeny (agouti color) were screened by Southern blots to identify heterozygous mice. Homozygous knockout mice were obtained by screening progeny born to a pair of heterozygous breeding pairs developed normally, and in only 100 litters did the progeny appear to experience a 50% reduction in transcript levels (Figure 1C). Direct measurement of tissue enzymatic activity confirmed that XOR activity was essentially absent in XOR\textsuperscript{−/−} animals and reduced to roughly half in heterozygote mice (Figure 1D).

Results

To characterize the physiological role of XOR and uric acid, we generated mice with a targeted disruption in the XOR locus. The mouse XOR locus contains 36 exons and homologous recombinants in ES cells were generated by replacing a portion of exon 2 and exon 3 of the XOR gene with a neomycin resistance marker using standard homologous recombination methods (Figure 1A). These ES cells were then used to generate XOR\textsuperscript{−/−} mice, and the targeting was confirmed by Southern blotting (Figure 1B). Analysis of XOR\textsuperscript{−/−} mice demonstrated the absence of XOR mRNA, whereas XOR\textsuperscript{+/−} animals had an ~50% reduction in mRNA levels (Figure 1C). Direct measurement of tissue enzymatic activity confirmed that XOR activity was essentially absent in XOR\textsuperscript{−/−} animals and reduced to roughly half in heterozygote mice (Figure 1D).

Mice containing the XOR disruption were born at the expected frequency. In observations during a one-year period, we observed 684 live births derived from heterozygous pairings and noted 157 (23%) XOR\textsuperscript{−/−} animals, 358 (52%) XOR\textsuperscript{+/−} mice, and 169 (25%) wild-type offspring. A previous report demonstrated that postpartum XOR\textsuperscript{+/−} mothers are unable to maintain lactation, resulting in the uniform death of their offspring from starvation.\textsuperscript{15} In contrast, in our colony, wild-type and heterozygous mice derived from heterozygous breeding pairs developed normally, and in only one of ~100 litters did the progeny appear to experience a milk deficit. We expect that the basis for the absence of a lactation phenotype may relate to targeting differences, strain variations, or potentially dietary influences. Although XOR\textsuperscript{−/−} mice were indistinguishable from other genotypes at birth, after the first week of life, we began to see a notable increase in mortality (Figure 2A). Those XOR\textsuperscript{−/−} mice that survived past two weeks failed to thrive, as evidenced by a lack of weight gain (Figure 2B). Although examination of XOR\textsuperscript{−/−} mice euthanized in the first week of life exhibited no significant abnormalities, XOR\textsuperscript{−/−} mice euthanized after two weeks were smaller overall than their wild-type counterparts. Further pathological examination of these older XOR\textsuperscript{−/−} demonstrated that all internal organs, with the exception of the kidneys, appeared grossly normal. However, we cannot exclude that XOR activity may be important for the development or function of other organs, including the heart, in the early postnatal period. However, as noted in Figure 2C, the gross appearance of the XOR\textsuperscript{−/−} kidneys...
were strikingly abnormal. In general, the kidneys were significantly smaller, paler, and malformed (Figure 2C). Histological examination revealed that the renal parenchyma was immature, lacking the postnatal developmental changes that normally occur in the mouse during the first month of life. These immature areas were multifocal but often coalesced to encompass the majority of the kidney. Pathologically, these areas were characterized by ectatic to cystic tubules (Figure 2D). In the immature and dysplastic areas, glomeruli tended to be hypoplastic and primordial in appearance (Figure 2E). Serum chemistries revealed the renal insufficiency was characterized by an elevated blood urea nitrogen (BUN) that was nearly three times higher than wild-type or heterozygous mice (Table). The creatinine of...
These results suggest that COX-2 is necessary for significant renal dysplasia beginning around postnatal day type after inactivation of COX-2 was the development of obvious organ defect. In contrast, the predominant mediators of platelet aggregation but no specific kidney or other increased platelet aggregation whereas COX-1 expression is readily detected in COX-2 expression can be induced by a wide range of inflammatory mediators that are important in diverse functions from the immune response to the regulation of salt and water balance. Two separate cyclooxygenase genes have been defined. COX-1 is ubiquitously expressed, whereas COX-2 expression can be induced by a wide range of mediators. Although COX-1 expression is readily detected in the kidney, genetic inactivation of COX-1 resulted in decreased platelet aggregation but no specific kidney or other obvious organ defect. In contrast, the predominant phenotype after inactivation of COX-2 was the development of significant renal dysplasia beginning around postnatal day 10. These results suggest that COX-2 is necessary for normal postnatal renal development.

The apparent similarity between the COX-2−/− phenotype and XOR−/− phenotype suggested that the two knockouts might share a similar pathophysiology. To address this possibility, we first measured XOR activity in the developing kidney. As noted in Figure 3A, in wild-type mice, renal XOR activity increased >30-fold within the first month of life. Thereafter, levels of XOR activity were relatively unchanged. Examination of renal COX-2 expression in wild-type animals confirmed that, as observed previously in other rodent species, levels of the inducible enzyme increased ≈3-fold from week one to week three (Figure 3B). In contrast, levels of COX-1 revealed only minor variation over this time. Examination of the XOR−/− mice that lacked any detectable renal XOR activity (data not shown) demonstrated that these animals failed to induce COX-2 expression within the kidney over the same time period (Figure 3B). This difference in COX-2 expression could not be explained by differences in overall vascularity because levels of the endothelial marker, eNOS, were similar in the wild-type and XOR−/− mice (Figure 3B). As noted in Figure 3B, absolute eNOS expression appeared to decline over the first 23 days, although this decline was similar in wild-type and XOR−/− mice. A quantification from six wild-type and a similar number of XOR−/− mice revealed that COX-2 expression was reduced ≈70% in XOR−/− mice (Figure 3C).

These results suggest that the increase in XOR activity seen in the developing kidney may be required for the subsequent induction of COX-2 and suggest XOR activity or its products are upstream of the cyclooxygenase. Interestingly, some recent reports have suggested that in certain cells, uric acid may indeed directly regulate COX-2 expression, and this might have physiological consequences in conditions such as gout and hypertension. To further pursue these observations, we treated NIH 3T3 cells with exogenous levels of uric acid that approximate the known serum concentration of this metabolite. As demonstrated in Figure 4A, uric acid treatment of cultured cells results in an increase in COX-2 protein, whereas COX-1 levels are unaffected. A similar increase in basal COX-2 expression could also be observed in these cells when the growth medium was supplemented with the XOR substrate hypoxanthine (Figure 4B). These results suggest that COX-2 levels can be increased in certain cells by exposure to uric acid or by increasing overall XOR activity. In contrast to these stimulatory effects, treatment of NIH 3T3 cells with the XOR inhibitor allopurinol did not alter the basal expression of COX-2 (Figure 4C). This difference between basal and stimulated levels of COX-2 was also evident from the analysis of COX-2 levels in primary fibroblasts isolated from either XOR+/+ or XOR−/− animals. As demonstrated in Figure 4D, levels of COX-2 were indistinguishable in these two primary cell lines. Therefore, although increased XOR activity is associated with increased COX-2 levels, XOR activity does not appear to be an important regulator of constitutive levels of COX-2 expression.

### Relevant Serum Chemistries in Wild-Type, Heterozygote, and XOR−/− Mice

<table>
<thead>
<tr>
<th></th>
<th>XOR+/+</th>
<th>XOR−/+</th>
<th>XOR−/−</th>
</tr>
</thead>
<tbody>
<tr>
<td>BUN, mg/dL</td>
<td>21±6</td>
<td>19±6</td>
<td>59±18*</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>0.3±0.1</td>
<td>0.2±0.1</td>
<td>0.2±0.1</td>
</tr>
<tr>
<td>Uric acid, mg/dL</td>
<td>2±1</td>
<td>1.1±0.4</td>
<td>0.18±0.08*</td>
</tr>
</tbody>
</table>

*P<0.001; n=7.

All mice were less than 25 days.

XOR−/− mice was not significantly different from levels seen in either wild-type or heterozygous animals. Levels of serum uric acid in XOR−/− mice were generally below detection (<0.2 mg/dL), whereas heterozygote mice had serum uric acid levels that were intermediate between wild-type and XOR−/− animals. The other serum chemistries in the XOR−/− and XOR+/− animals were unremarkable except for a mildly elevated serum amylase (presumably because of decreased renal clearance) in the null animals.

The pathological phenotype and the BUN/creatinine ratios observed in the XDH−/− mice are remarkably similar to what has been observed previously in mice deficient in COX-2. Cyclooxygenases function to generate a wide range of inflammatory mediators that are important in diverse functions from the immune response to the regulation of salt and water balance. Two separate cyclooxygenase genes have been defined. COX-1 is ubiquitously expressed, whereas COX-2 expression can be induced by a wide range of mediators. Although COX-1 expression is readily detected in the kidney, genetic inactivation of COX-1 resulted in decreased platelet aggregation but no specific kidney or other obvious organ defect. In contrast, the predominant phenotype after inactivation of COX-2 was the development of significant renal dysplasia beginning around postnatal day 10. These results suggest that COX-2 is necessary for normal postnatal renal development.

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### Figure 3

XOR activity is required for renal COX-2 induction. A, Time-dependent increase in the level of renal XOR activity in wild-type mice. Values represent the mean±SD activity from three animals at each time point. B, Western blot analysis of COX-2, COX-1, and eNOS protein levels in renal tissue of either wild-type (+/+ ) or XOR−/− animals euthanized at various time points after birth. C, Quantification of renal COX-2 expression in wild-type or XOR−/− mice. Animals were euthanized ~3 to 5 weeks after birth and the ratio of COX-2 to actin protein expression determined for the two genotypes (n=6 animals per genotype). *P<0.005.
To further pursue this XOR-dependent stimulation of COX-2 expression, we isolated an approximate 2-kb fragment corresponding to the most proximal element of the mouse COX-2 promoter. When this construct was used to regulate the luciferase reporter gene, we noted a modest but dose-dependent increase when cells were subsequently treated with uric acid (Figure 4E). Finally, to further confirm that serum levels of uric acid can regulate tissue levels of COX-2, we treated adult wild-type animals with a special diet containing elevated uric acid as well as the uricase inhibitor oxonic acid. This diet resulted in a rise in serum uric acid from a baseline of 3.7 ± 0.7 to 5.7 ± 0.3 mg/dL (n = 4). Western blot analysis of animals after either two or four weeks on this diet revealed that elevated serum uric acid levels resulted in increased renal COX-2 protein of ~25% and 40%, respectively (Figure 4F).

**Discussion**

Our results demonstrate a linkage between XOR activity and COX-2 expression. Although XOR activity does not appear to be an important regulator of basal COX-2 expression, it does appear to regulate the induction of COX-2 in vitro and in vivo. As mentioned previously, in mice, COX-2 deletion results in a dramatic effect on kidney development first observed ~10 days after birth. In normal rodents, the first week or two after birth is a period of rapid extrauterine renal development. This period is also accompanied by an induction of COX-2 protein. Analysis of COX-2−/− mice demonstrated that this COX-2 induction was indeed required for postnatal renal development. However, these previous studies have not discerned the physiological stimulus for COX-2 induction. Our results demonstrate that in the absence of XOR, levels of COX-2 remain static in the developing kidney because XOR−/− mice appear to maintain their initial basal levels of COX-2 without the subsequent postnatal induction of the cyclooxygenase. These results provide an explanation as to why the XOR−/− mice phenocopy the COX-2−/− mice. To date, we have been unable to rescue XOR−/− pups by administering uric acid injections (T.O. and T.F., unpublished data). This may relate to a number of factors including the difficulty in XOR−/− pups of obtaining sustained normal serum levels of uric acid by intraperitoneal injections. Similarly, it remains possible that within the renal parenchyma, levels of uric acid are significantly higher than serum levels might suggest. Finally, we cannot exclude that XOR may stimulate COX-2 expression via additional uric acid–independent mechanisms, including perhaps the local generation of reactive oxygen species. Indeed, previous evidence supports a redox-dependent induction of COX-2.

It is interesting to note that the relationship between uric acid, XOR activity, and COX-2 has been explored in several other contexts. In particular, COX-2 inhibitors are an effective treatment for gouty arthritis, a condition precipitated by urate crystal deposition. Previous in vitro studies have demonstrated that monosodium urate crystals, but not, for instance, calcium pyrophosphate dihydrate crystals, can induce COX-2 expression in isolated mononuclear phagocytes. A similar in vitro effect of uric acid on COX-2 expression was noted in vascular smooth muscle cells. Given our results in...
NIH 3T3 cells, the stimulation of COX-2 by uric acid would therefore appear to be a general phenomenon. Other conditions in which XOR activity and COX-2 have been tentatively linked include patients with familial adenomatous polyposis. Polyposis lesions in this disease have been demonstrated to have elevations in XO activity as well as COX-2. Indeed, the COX-2 inhibitor Celecoxib has been approved for treatment of these individuals as a therapy for polyph regression. Similarly, in the case of pulmonary hypertension, it has been appreciated that serum uric acid represents a strong predictor for morbidity and mortality, and again, elevated COX-2 has been implicated in the pathogenesis of this condition.

There has been particular interest in the role of uric acid regulation of COX-2 levels in the kidney. This interest has been motivated by epidemiological studies demonstrating a consistent association between serum uric acid levels and systemic hypertension. It has been postulated that high uric acid levels may have provided an evolutionary survival advantage by inducing COX-2 in the kidney and thereby supporting basal blood pressure under conditions of low salt intake. Although the modern diet has an excess of salt intake, on the basis of fossil evidence, the early hominid diet may have contained <2 g of salt per day. Dietary differences may explain why, from an evolutionary perspective, high levels of uric acid were important to protect against hypotension, whereas today, these same factors may contribute to the high prevalence of hypertension.

Interestingly, serum levels of uric acid are significantly higher in great apes and humans than other mammals, including mice. This difference is attributed to two distinct mutations that are believed to have occurred in the Miocene epoch, leaving the primate uricase gene nonfunctional. For instance, in our animals, serum uric acid was ~2 mg/dL, whereas in humans, hyperuricemia is usually defined as serum levels >6 mg/dL in women and 6.5 to 7.0 mg/dL in men. The occurrence of two distinct mutations has led to speculation that, as suggested above, higher serum concentrations of urate/uric acid may have provided an evolutionary advantage. Besides the regulation of blood pressure, numerous studies have suggested that urate is a potent antioxidant capable of scavenging superoxide, hydroxyl radical, singlet oxygen, and peroxynitrite. In addition, recent evidence suggests that uric acid may also regulate antioxidant scavenger activity and, in particular, the levels of extracellular superoxide dismutase. In this regard, it is interesting to note that XOR enzymatic activity produces superoxide, whereas the enzymatic end-product, uric acid, functions as a free radical scavenger. The balance between oxidants and antioxidants is of considerable significance because there is a growing appreciation that oxidants can act as signaling molecules in cells potentially affecting a number of pathways involved in cell growth, apoptosis, and gene expression.

Although uric acid may act as a potent serum antioxidant, it is also important to note that a variety of experimental observations have demonstrated that persistent hyperuricemia can predispose to renal injury. In rats with elevated uric acid levels, a variety of renal pathologies are commonly seen including tubulointerstitial fibrosis, afferent vascular changes, as well as structural alterations within the glomerulus. Interestingly, in these animal models, COX-2 expression is also elevated within the kidney. Similarly, in patients with gout, there is a high prevalence of moderate renal dysfunction. At autopsy, histopathological changes that mimic what has been observed in animal experiments are observed in the majority of patients.

Together, these results suggest that uric acid has a complicated in vivo biology and has the potential to act in a positive and negative fashion. There is also a growing appreciation that XOR may provide functions beyond its basic housekeeping role in purine catabolism. Among these newly detected properties is a role for the enzyme in mucous and milk secretion, host defense and immunity, as well as oxidant signaling. Recently, uric acid, the product of XOR activity, has also been shown to potentiate T cell--dependent immune responses. This effect was suggested to provide a mechanism in which dying cells could alert the immune system. Our results suggest that the role for uric acid in regulating the inflammatory response may extend beyond T lymphocyte stimulation and also include COX-2 regulation. Together, these results suggest an expanded molecular framework to understand how injury and inflammation may be coordinately regulated. Further studies are needed to assess the potential therapeutic benefit of blocking XOR activity in conditions similar to those above, in which COX-2 plays a role in the underlying pathogenesis.

Acknowledgments

We acknowledge the National Institutes of Health intramural program. References


