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Oxalate, inflammasome, and progression of kidney disease

Theresa Ermer¹, Kai-Uwe Eckardt¹, Peter S. Aronson², and Felix Knauf^{1,2}

¹Department of Nephrology und Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Erlangen, Germany

²Department of Internal Medicine, Yale University School of Medicine, New Haven, Connecticut, U.S.A

Abstract

Purpose of review—Oxalate is an end product of metabolism excreted via the kidney. Excess urinary oxalate, whether from primary or enteric hyperoxaluria, can lead to oxalate deposition in the kidney. Oxalate crystals are associated with renal inflammation, fibrosis and progressive renal failure. It has long been known that as glomerular filtration rate (GFR) becomes reduced in chronic kidney disease (CKD), there is striking elevation of plasma oxalate. Taken together, these findings raise the possibility that elevation of plasma oxalate in CKD may promote renal inflammation and more rapid progression of CKD independent of primary etiology.

Recent findings—The inflammasome has recently been identified to play a critical role in oxalate-induced renal inflammation. Oxalate crystals have been shown to activate the nucleotide-binding domain, leucine-rich repeat inflammasome 3 (also known as NALP3, NLRP3 or cryopyrin), resulting in release of Interleukin-1 β and macrophage infiltration. Deletion of inflammasome proteins in mice protects from oxalate-induced renal inflammation and progressive renal failure.

Summary—The findings reviewed in this article expand our understanding of the relevance of elevated plasma oxalate levels leading to inflammasome activation. We propose that inhibiting oxalate-induced inflammasome activation, or lowering plasma oxalate, may prevent or mitigate progressive renal damage in CKD, and warrants clinical trials.

Keywords

Oxalate; innate immune system; inflammasome; chronic kidney disease

Introduction

Oxalic acid is a potentially toxic dicarboxylic acid that is not further metabolized by mammals [1, 2, 3, 4, 5]. In its ionized form – oxalate – it forms highly insoluble complexes with calcium [1, 2]. When oxalate homeostasis is disturbed, oxalate accumulates in various body tissues and damages primarily the kidney, which serves as its main excretory organ.

Address for correspondence: Felix Knauf, M.D., Department of Nephrology and Hypertension, Friedrich-Alexander-Universität Erlangen-Nürnberg (FAU), Schwabachanlage 12, 91054 Erlangen, Germany, Tel.: +49-9131-85-39002, FAX.: +49-9131-85-39209, ; Email: Felix.Knauf@uk-erlangen.de

This in turn leads to further elevations of plasma oxalate levels. Recent studies have directed the focus to oxalate as an activator of inflammatory pathways. Thus, this review aims to provide an impulse to further investigate the prominent role of oxalate in inflammasome activation and the progression of kidney disease.

Oxalate – endogenous production

The liver has been identified as major site for the biosynthesis of oxalate as shown in Figure 1A. Endogenous oxalate production is thought to be fairly constant, attributing for up to 60–80% of total plasma oxalate and urinary oxalate excretion [6, 7]. Oxalate biosynthesis evolves from glyoxylate [8, 9, 10, 11] as central precursor molecule. Glyoxylate originates from the oxidation of glycolate by glycolate oxidase (GO) or from the catabolism of hydroxyproline, derived from collagen [12, 13]. Glyoxylate can be eliminated by conversion to glycine (alanine-glyoxylate aminotransferase: AGT) [10] or glycolate (glyoxylate reductase – hydroxypyruvate reductase: GRHPR) [9]. If, however, the glyoxylate supply overflows, oxalate is generated by the activity of either GO or lactate dehydrogenase (LDH). LDH is more likely to be responsible for the conversion *in vivo* as GO is strongly inhibited by physiological glycolate and lactate concentrations *in vitro* [10]. The glyoxylate cycle links various metabolic pathways for amino acids [10, 14, 15] and carbohydrates. In recent years glyoxal has been identified as another possible oxalate precursor. Glyoxal is a product of cellular peroxidation and protein glycation. Advanced glycation endproducts (AGEs) are associated with the progression of diabetic nephropathy and increased pro-inflammatory cytokines such as IL-1 β , which can both be ameliorated by methylglyoxal trapping [16, 17, 18, 19]. Also, diabetics tend to excrete more oxalate than healthy individuals [20, 21, 22]. In addition, experimental glutathione depletion increases oxalate formation from glyoxal [23, 24]. These findings may suggest links between sugar metabolism, peroxidation and oxalate generation that will require further investigation.

Oxalate – exogenous supply

Dietary sources of oxalate include e.g. green leafy vegetables, different seeds and roots, cocoa and tea [2, 25]. Reports from different countries average daily oxalate intake to 100–200 mg/d (1.14–2.28 mmol/d) in healthy subjects [5, 7, 26]. Following dietary oxalate loads plasma levels peak at 2–4 hours. At 6 hours post-ingestion more than 75% of the ingested oxalate is excreted. This time course implicates the small intestine as the primary location for oxalate absorption [27, 28, 29]. Additional evidence suggests a role for the stomach and large intestine in physiological oxalate absorption [30, 31, 32]. The amount of oxalate that is absorbed from a dietary load can be extrapolated from an increase in urinary oxalate excretion as indicated, for example, by a ¹³C–oxalate absorption test. 5–15% of the ingested oxalate load reaches the systemic circulation in healthy children and adults [27, 28, 33, 34, 35, 36]. In total, exogenous oxalate is estimated to account for approximately 20–40% of urinary oxalate as shown in Figure 1A [7, 37, 38]. However, both oxalate intake and intestinal absorption are subject to a significant intra- and inter-individual variability: in some regional and seasonal diets oxalate ingestion may be considerably higher [25, 39]. In addition, oxalate bioavailability is an important factor [40] as dietary components such as Ca²⁺ or Mg²⁺ can reduce the amount of soluble oxalate in the intestinal lumen by complex

formation and precipitation, impede its intestinal absorption and thereby reduce its urinary excretion. Conversely, reduced availability of Ca^{2+} enhances oxalate absorption (see below). Additional factors influencing oxalate absorption such as fiber have been discussed but their relevance remains controversial [7, 29, 35, 41, 42, 43]. While oxalate absorption is largely passive and paracellular across the tight junction [44], studies using knockout mice suggest that apical transporter SLC26A3 (DRA) may also play a role in oxalate absorption [45]. Knockout mice studies suggest a pivotal role of apical transporter SLC26A6 in back-secretion of oxalate that limits its net intestinal absorption, as gene deletion of SLC26A6 results in significant hyperoxaluria [46, 47]. Likewise, knockout of the basolateral transporter SLC26A1 also results in hyperoxaluria [48]. However, the contribution of these oxalate transporters to oxalate homeostasis and risk for hyperoxaluria in humans needs to be further defined [49].

Hyperoxaluria – disturbed oxalate homeostasis

Oxalate is mainly excreted by the kidney [3, 50]. Several studies have demonstrated almost complete recovery of radiolabeled oxalate in urine following infusion into healthy subjects or given as dietary load [3, 28]. In addition to glomerular filtration, there is net tubular secretion of oxalate [51, 52, 53], mainly in the proximal tubule, although there is also evidence for oxalate transport in collecting duct and papillary cells [54, 55]. Total daily oxalate excretion by the kidney is estimated at 10–40 mg per 24 h (0.1–0.45 mmol per 24 h) in healthy children and adults, with the average excretion being slightly higher in males than in females [34, 37, 56, 57, 58]. Only a minor part is eliminated through the gastrointestinal tract [6]. Marengo et al. reported fecal oxalate excretion to account for only 5–7% of the oxalate administered in rats treated with subcutaneously implanted minipumps [37].

When oxalate homeostasis is disturbed (Figure 1B), hyperoxaluria ensues defined by a urinary excretion > 40–45 mg per 24 h (0.45–0.5 mmol per 24 h) [37, 56]. Primary hyperoxalurias (PH) are caused by mutations in the genes encoding key enzymes of hepatic oxalate biosynthesis with many of these patients presenting with end-stage renal disease (ESRD) already at time of diagnosis [59, 60, 61, 62]. Secondary or enteric hyperoxalurias are characterized by a pathological hyperabsorption of dietary oxalate that in turn increases plasma and urine oxalate (Figure 1B) [7, 63]. Secondary hyperoxalurias can have a broad range of etiologies. Fat malabsorption is a very common side effect following small bowel resection or bariatric surgery. Enteric hyperoxaluria is thought to be mediated by two mechanisms: 1) by increasing the permeability of the colonic mucosa for oxalate 2) by complexation of luminal calcium with fatty acids, increasing the amount of soluble oxalate available for absorption [64, 65, 66]. Humans are not able to degrade oxalate. In contrast, the bacterial species *Oxalobacter*, a gram-negative obligate anaerobic bacterium that colonizes the colon, takes up oxalate through an oxalate-formate-antiport carrier and metabolizes it to formate and CO_2 for exclusive energy supply [67]. Several human and animal studies hypothesize that a lack of colonic *Oxalobacter formigenes* favors enteric hyperoxaluria, kidney disease and adverse cardiovascular outcomes [7, 63, 68, 69, 70, 71].

Oxalate-induced inflammasome activation

The inflammasome is a cytosolic multiprotein complex that assembles to promote Caspase-1 and thus IL-1 β and IL-18 activation [72, 73]. A wide variety of immune cells, such as dendritic cells (DCs) and macrophages, have been shown to use the inflammasome machinery to release cytokines [74]. Several studies suggest an additional role in tubular epithelial cells (TECs) [75, 76, 77] and podocytes [78, 79]. The NLRP3 inflammasome is the most extensively studied so far. As shown in Figure 2, it consists of three subunits: 1) a *sensor protein* (Nod-like receptor pyrin-domain containing protein 3), 2) an *adaptor protein* (apoptosis-associated speck-like protein (ASC)) and 3) pro-inflammatory *Caspase-1* [80]. For inflammasome activation, first a priming signal is required to induce transcription of NLRP3, pro IL-1 β , and pro IL-18. *In vitro* experiments have primarily shown TOLL-like receptor (TLR) ligands to provide signal 1. A broad spectrum of pathogen-associated molecular patterns (PAMPs) and damage-associated molecular patterns (DAMPs), likely released secondary to oxalate crystals, can then serve as signal 2 which eventually triggers the formation of the inflammasome complex and secretion of IL-1 β , IL-18 and pyroptosis [74, 81, 82]. The importance of oxalate-induced inflammasome activation in nephropathy has been shown in murine models of acute [74] and chronic kidney injury [81]. Calcium-oxalate (CaOx) treatment leads to a NLRP3-activation in DCs by either 1) CaOx-phagocytosis or 2) CaOx-induced K⁺-efflux or 3) CaOx-induced ATP-release from necrotic TECs in co-culture with DCs [74]. *In vitro* DCs responded with a marked IL-1 β -release [74] and *in vivo* plasma BUN and creatinine indicated prominent renal failure [74, 81]. A recent study found that ROS might trigger oxalate-induced NLRP3-activation, as an inhibition of the former decreased renal oxalate deposition and injury [83]. Moreover, a cornucopia of experimental models has illustrated the protective effect of NLRP3 gene deletion in different types of renal disease, such as necrotic cell induced sterile inflammation, diabetic nephropathy, renal ischemia-reperfusion-injury (IRI), unilateral ureteral obstruction and glomerular disease [76, 77, 78, 84, 85].

Current treatment options for auto-inflammatory diseases (Figure 2) targeting inflammasome activation are directed against IL-1, principally through their central agent IL-1 receptor antagonist (IL-1ra) Anakinra. Administration of IL-1ra protects rats from renal IRI [86] and reduces plasma levels of inflammatory biomarkers in HD patients [87]. In addition, it has been demonstrated to attenuate oxalate-induced AKI [74]. Two newcomers among the IL-1-blockers were first approved for the treatment of cryopyrin-associated periodic syndrome (CAPS): the neutralizing IL-1 β antibody canakinumab and the soluble decoy IL-1 receptor rilonacept. They are now reported to remarkably reduce symptoms also in other rare autoinflammatory syndromes and widespread diseases such as gout and diabetes [88, 89, 90, 91, 92]. Presently the multinational phase III CANTOS study is evaluating treatment benefits of canakinumab in cardiovascular disease, which is the No. 1 cause of death in advanced CKD [93, 94, 95]. In a preliminary phase IIb trial enrolling well controlled diabetic patients with high cardiovascular risk, canakinumab significantly reduced CRP, IL-6 and fibrinogen [96]. Pharmacokinetically, canakinumab and rilonacept bear advantages over anakinra: 1) Their long half-life allows for less frequent applications (anakinra: daily, rilonacept: weekly, canakinumab: once every 8 weeks) and 2) due to their

large molecular size elimination is mainly non-renal, which makes dosage adjustments in kidney disease as required with anakinra treatment unnecessary [91, 97, 98]. As a result of their favorable pharmacologic profile in ESRD and promising effects in autoinflammatory diseases, canakinumab and rilonacept might have the potential to emerge as future therapeutic drugs in CKD as well.

Most recently, investigations have shifted towards specific NLRP3 inhibitors (Figure 2). Glyburide, a sulfonylurea-containing diabetic drug known to inhibit ATP-sensitive K^+ - channels in the pancreas, also impedes NLRP3-activation and IL-1 β production at micromolar concentrations upstream of inflammasome assembly and independent of effects on K^+ channels [99]. Parthenolide, an herbal compound, and Bay 11-7082, a synthetic molecule, target ATP-mediated NLRP3-activation downstream of the P_2X_7 receptor. Parthenolide has also been shown to directly inhibit caspase-1 by alkylation of the enzyme's p20 subunit [100]. Ahn et al. revealed two new selective NLRP3 inhibitors targeting multiple steps during inflammasome activation in the past two years: dimethyl sulfoxide (DMSO) [101] and its oxidized metabolite methylsulfonylmethane (MSM) [102]. Both substances 1) restrain NLRP3 activation through blockage of mitochondrial ROS generation, and 2) dose-dependently attenuate IL-1 β -release in models of LPS-primed bone marrow-derived macrophages (BMDMs). MSM also interferes with the priming step (Signal 1) by downregulating NLRP3 and pro-inflammatory cytokines [101, 102]. 3,4-methylenedioxy- β -nitrostyrene (MNS) [103] and MCC950, also known as CRID3 (cytokine release inhibitory drug CP-456,773) [104], interfere primarily with ASC oligomerization at micromolar levels [103]. MCC950 is a small synthetic diarylsulfonylurea antagonizing the cysteinyl leukotriene-receptor that has been known to block IL-1 β for over a decade [105, 106]. Only very recently it has been demonstrated that MCC950 specifically inhibits NLRP3-dependent pyroptotic cell death *in vivo*, beginning at concentrations as low as 10 nM in human cells *ex vivo* [88]. While MCC950 blocks ASC oligomerization and inhibits both canonical and noncanonical inflammasome pathways, β -hydroxybutyrate (BHB) additionally hinders intracellular K^+ -depletion and specifically obstructs the canonical route [107]. BHB is a ketone body used as alternative energy source in metabolic states of energy depletion, such as those simulated by the experimental concentrations starting at 1 mM BHB [107]. This discovery proposes an interesting link between metabolism and the regulation of systemic inflammation. Given the profound protection against oxalate-induced progressive renal insufficiency in mice deficient for NLRP3, future studies should examine these compounds in the established murine models of oxalate-induced CKD and crystal-induced progressive renal failure [81, 108].

Oxalate and CKD

In primary hyperoxalurias the unbounded oxalate overproduction causes sheer CaOx supersaturation in plasma by exceeding the oxalosis cut-off $> 30 \mu\text{mol/L} (\beta_{\text{CaOx}} > 1)$ [109, 110, 111] and extreme urinary excretion ranging between 1–2 mmol/1.73 m² in 24 hours [112]. In enteric hyperoxaluria the high oxalate absorption is often associated with diarrhea-induced volume depletion, metabolic acidosis and hypocitraturia, providing favorable conditions for oxalate accumulation and precipitation in renal tissue [5, 7, 65]. PH patients usually progress to CKD rapidly: mean age at ESRD onset in PH1 patients is 24–27 years.

70% of adults and 29% of kids are in renal failure already at time of diagnosis [62, 112]. In secondary hyperoxaluria progression to acute or chronic kidney disease is less frequently reported – possibly in part because it is under recognized. Glew et al. recently provided an extensive review of nephropathy resulting from enteric hyperoxaluria [5]. Hence, both primary and secondary hyperoxaluria provide the “proof of principle” that increased plasma oxalate can lead to progressive CKD in humans.

Plasma or serum oxalate levels in healthy children and adults are mainly reported to be in the range of 1–3 $\mu\text{mol/L}$ [57, 58, 113, 114, 115, 116]; depending on the method used, however, higher normal limits of up to 11 $\mu\text{mol/L}$ have been reported [117, 118]. As GFR declines, renal oxalate clearance is decreasing, which leads to increased plasma oxalate as depicted in Figure 1C [59, 119, 120, 121, 122, 123, 124, 125]. Mean plasma oxalate levels reported for different kinds of chronic renal disease are above normal limits and inversely correlate with GFR [123, 126]. Moreover, in patients on dialysis maximal oxalate elimination of 6–10 mmol/1.73 m² per week in routine HD or peritoneal dialysis (PD) is insufficient to address supersaturation. Consequently, ESRD patients on dialysis tend to have even higher plasma oxalate levels ranging around 45 $\mu\text{mol/l}$ [111, 119, 126, 127, 128]. These extreme plasma oxalate levels are only exceeded by those in PH patients with levels of 80–125 $\mu\text{mol/L}$ commonly found [110, 111]. In mouse models of oxalate-induced CKD, there is clear evidence for activation of inflammasome pathways by oxalate crystals. Translating this concept to a clinical setting, it becomes possible or even likely that high plasma oxalate levels as observed in advanced CKD patients launch a vicious cycle of inflammasome mediated systemic inflammation and kidney damage resulting in progressive renal disease. In particular, the cardiovascular implications of such high oxalate levels in the circulation are of great concern: in our murine model of dietary oxalate-induced CKD, mice develop a clear presentation of cardiovascular disease including cardiac fibrosis and profound arterial hypertension [108]. Whether these findings are solely related to reduced renal function or elevated plasma oxalate levels remains to be defined.

Conclusion

Progressive kidney failure and early mortality due to adverse cardiovascular outcomes make CKD a very serious disease. Oxalate is strongly involved in inflammatory pathways, which makes it a prime candidate to contribute to progression of CKD and systemic inflammation. In animal models, members of our and other research groups have uncovered part of the complex interplay between oxalate, inflammasome activation and the progression of kidney disease. Accordingly, inhibiting oxalate-induced inflammasome activation, or lowering plasma oxalate, may prevent or mitigate progressive renal damage in CKD, and also reduce morbidity and mortality due to systemic inflammation. Possibly some of the new anti-inflammatory drugs presented in this review might provide novel therapeutic options of tomorrow for patients with primary or secondary hyperoxaluria or CKD in general.

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Key points

- Oxalate can accumulate as a result of endogenous overproduction (primary hyperoxaluria), exogenous oversupply (secondary hyperoxaluria) or decreasing renal clearance (declining GFR in CKD).
- Primary hyperoxaluria proves the principle that excess plasma oxalate can lead to CKD.
- Oxalate is a potent activator of the NLRP3-inflammasome that mediates inflammation in murine models of oxalate-induced CKD.
- NLRP3-knockouts are protected from oxalate-induced progressive kidney disease.
- Novel NLRP3- and IL-1-inhibitors might be promising therapeutic options of tomorrow for primary or secondary hyperoxaluria or CKD in general to prevent progressive loss of kidney function and systemic inflammatory complications of CKD.

Figure 1A

Figure 1a

Figure 1B

Figure 1b

Figure 1C

Figure 1c

Figure 1. Oxalate homeostasis in health and disease

A: Oxalate homeostasis is determined by the contribution of dietary (20–40%) and endogenous oxalate (60–80%) to plasma oxalate concentration (normal: 1–3 $\mu\text{mol/L}$), which is maintained low by > 90% of plasma oxalate excreted by the kidney (normal: 0.1–0.45 mmol/d). **B: Hyperoxaluria** is defined by a urinary oxalate excretion of >0.45–0.5 mmol/d and may occur as a consequence of endogenous overproduction (primary) or exogenous oversupply (secondary). **C: Oxalate homeostasis in CKD** is impaired secondary to reduced renal clearance of oxalate leading to elevated plasma oxalate levels.

Figure 2. Model of the NLRP3-inflammasome with specific inhibitors targeting its activation

Two distinct signals (Signal 1 and Signal 2) are required for inflammasome and caspase-1 activation: Signal 1, a priming signal, is mainly provided by TLR ligands, such as LPS. Signal 2 is an activating signal. A variety of stimulating PAMPs or DAMPs, likely released secondary to oxalate crystals, can trigger Signal 2 by one of three mechanisms: 1) *ion flux*: potassium, calcium or protons 2) *ROS generation* 3) *lysosomal rupture* induced by uptake of crystalline or aggregated materials (**not shown**). NLRP3 inflammasome activation results in processing and release of IL-1 β and IL-18 which communicate mainly with inflammatory cells (*adjacent cell*) via the IL-1 receptor. Several pharmacological approaches have been developed targeting Signal 1, Signal 2, inflammasome assembly, cytokines, and their respective receptors as detailed in the main body of the text. * Exact target not identified. Glyburide acts downstream of the P₂X₇ ATP receptor and upstream of cryopyrin.