

Experimental models of renal calcium stones in rodents

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Abstract

In human nephrolithiasis, most stones are containing calcium and are located within urinary cavities; they may contain monohydrate calcium oxalate, dihydrate calcium oxalate and/or calcium phosphates in various proportion. Nephrolithiasis may also be associated with nephrocalcinosis, *i.e.*, crystal depositions in tubular lumen and/or interstitium, an entity which suggests specific pathological processes. Several rodents models have been developed in order to study the pathophysiology of intrarenal crystal formation. We review here calcium rodent models classified upon the presence of nephrolithiasis and/or nephrocalcinosis. As rodents are not prone to nephrolithiasis, models require the induction of a long standing hypercalciuria or hyperoxaluria (thus explaining the very few studies reported), conversely to nephrocalcinosis which may occur within hours or days. Whereas a nephrotoxicity leading to tubular injury and regeneration appears as a critical event for crystal retention in nephrocalcinosis models, surprisingly very little is known about the physiopathology of crystal attachment to urothelium in nephrolithiasis. Creating new models of nephrolithiasis especially in different genetic mice strains appears an important challenge in order to unravel the early mechanisms of urinary stone formation in papilla and fornices.

Key words: Nephrolithiasis; Nephrocalcinosis; Oxalate; Crystal; Urothelium

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Core tip: We review here calcium rodent models classified upon the presence of nephrolithiasis or nephrocalcinosis which appear as two different entities. Nephrocalcinosis appears related to tubular cell injuries in the setting of urinary supersaturation whereas the pathophysiology of nephrolithiasis is mostly unraveled. Though few models are available, attachment of crystals in the fornix or in the

papilla appear as a striking feature. Creating mice models of nephrolithiasis are thus required to understand the interaction between crystals and urothelium.

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INTRODUCTION

Renal stone is a common disease, occurring in 8% of the population. This disease is multifactorial and mainly considered related to environmental factors, especially western diet^[1]. Calcium stones are encountered in 80% of cases and contain calcium oxalate (72%), phosphate oxalate (14.7%) and often a mixture of the two^[1,2]. Among calcium oxalate crystals, calcium oxalate monohydrate crystalline form is oxalate dependent, whereas calcium oxalate dihydrate crystalline form is calcium dependent. Calcium deposits can be located within urinary cavities, in papilla and also in medullar collecting ducts as described in Cacchi-Ricci disease^[3]. Thus, though urine supersaturation is a prerequisite and accounts for crystal composition, it does not explain the diversity of calcium stone localization^[4]. Several animal models have been developed to investigate the pathophysiology of calcium oxalate nephrolithiasis, in rodent but also in larger animals such as porcine model^[5]. However, a majority of studies were performed in rodents due to an ease of access though most models lead to nephrocalcinosis instead of nephrolithiasis. Surprisingly, very few studies were performed in mice despite the possibility to create transgenic animals in order to study the early mechanisms of urinary stone formation in papilla and fornices.

We review here rodent models of calcium renal stone according to the presence of nephrocalcinosis, nephrolithiasis or the presence of the two features.

MODELS OF NEPHROCALCINOSIS

Oxalate minipumps

Administration of potassium oxalate (1.5 mol/L) by subcutaneous osmotic minipumps induces nephrocalcinosis in male Harlan-Sprague Dawley rats^[6,7]. Hyperoxaluria is detected as soon as day 1 and intrarenal deposits of COM crystals (birefringent crystals) are present mostly in tubules by day 14 with no reported renal failure. Interestingly, renal morphology of kidneys is normal although localized regions of inflammation are present. In some focal sites, tubular debris with cytoplasm vacuolization and also some regenerating tubules are present. At the time of crystal retention osteopontin (OPN), tumor necrosis factor (TNF) and kidney injury molecules (KIM) synthesis are significantly increased as assessed by northern blot^[6]

further assessing tubular injuries. No crystal retention within urinary cavities is reported (Table 1).

Intraperitoneal administration of oxalate

A single injection of sodium oxalate solution (7 mg/100 g body weight) in male Sprague Dawley rats is responsible for hyperoxaluria and CaOx crystals within tubules^[8]. Some small crystal aggregates are indeed present by 1 h in the loop of Henle, by 3 h in collecting ducts and by 6 h on papillary tips. Interestingly, crystals are initially intraluminal and later are located in tubular cells and also in the interstitium. CaOx crystals aggregate into tubular lumen leading to obstruction and lumen dilatation, with tubular cells necrosis, luminal cellular debris and exposure of basal lamina^[8]. The authors suggest that calcium oxalate crystals would appear in the lumen within proximal tubular segment and would coat cellular debris and urinary macromolecules, thus enhancing self aggregation and finally leading to tubular obstruction. Simultaneously, at the papillary tip, urothelial cells are injured with crystal deposits forming lesions suggestive of Randall Plaques^[8].

Ethylene glycol administration

Ethylene glycol (EG) administration is a well-known model of nephrocalcinosis: EG metabolizes into glycolate, glyoxylate, and oxalate leading to COM crystals in both urine and kidneys^[9]. Rats receiving EG-supplemented drinking water (0.75% vol/vol) develop hyperoxaluria and hypercalciuria one day after initiation^[10]. Moreover, intra tubular crystal deposits are detected as soon as day 1 both in medulla and cortex altogether with tubular injury, dilatation, regeneration and interstitial inflammation. Several macromolecule such as OPN, bikunin or Tamm-Horsfall (TH) protein that could either inhibit or promote calcification are also induced^[11]. Of notice, glycolate and glyoxylate metabolites seem to modify normal tubular epithelium into a crystal-binding epithelium^[10]. This EG model is currently used to study crystal binding molecules, crystal clearance and the relevance of several macromolecular inhibitors such as OPN in crystal retention^[10,12,13].

Hydroxyproline administration

The amino acid hydroxyproline (HyP) is a precursor of oxalate. In physiological conditions, HyP is first metabolized in mitochondria into glyoxylate and further metabolized to glycine by alanine glyoxylate aminotransferase (AGT) or to glycolate by glycolate reductase. Finally, glycolate is oxidized to oxalate by lactate dehydrogenase (LDH)^[14,15].

Diet supplements: After 7 d of exposure, Sprague-Dawley rats supplemented with HyP 5% in diet, develop a hyperoxaluria and many urinary crystals (a mixture of COD, COM, struvite and CaP crystals)^[16]. Noteworthy, after 28 d of supplements, all rats develop CaOx deposits in both medulla and cortex tubules, with some plaques

Table 1 Rodent models of nephrocalcinosis

Ref.	Species	Crystal main compounds	Crystals location	Animal Model	Read out	Urinary phenotype	Renal injury
Tawashi <i>et al</i> ^[17] , 1980	Rats	CaOx	Tubules	HyP injection <i>i.p.</i> (10 mL/kg),	1 d	Hyperoxaluria	Kidney dilatation, oedema
Khan <i>et al</i> ^[8] , 1982	Rats	CaOx	Tubules, interstitium, papillary tips	Sodium oxalate Injection (7 mg/100 g body weight)	1 h	Hyperoxaluria	Tubular obstruction and dilatation
Marengo <i>et al</i> ^[6] , 2004	Rats	COM crystals	Tubules (cortex, medulla)	potassium oxalate SC (Minipump)	14 d	Hyperoxaluria	Tubular injury, dilatation, regeneration, interstitial inflammation
Vervaet <i>et al</i> ^[10] , 2009	Rats	COM crystals	Tubules	Ethylene glycol (0.75%)	1-6 d	Hyperoxaluria	Tubular injury, dilatation and regeneration, interstitial inflammation
Khan <i>et al</i> ^[16] , 2006	Rats	CaOx	Tubules (cortex, medulla), Papillary tips (plaques & stones)	5% Hyp supplement	28 d	Hyperoxaluria	Inflammation, tubular injury
Mo <i>et al</i> ^[20] , 2004	Mice	CaOx	Collecting ducts (medulla, papilla)	Tamm-Horsfall KO mice	2-4 mo		ND
Chau <i>et al</i> ^[23] , 2003	Mice	-CaP	Tubules (cortex, medulla), Papilla	Npt2 KO mice + HyP supplement (4 wk)	From birth	Hypercalciuria, Hyperphosphaturia	ND
Knight <i>et al</i> ^[24] , 2012	Mice	CaOx (COM + COD)	Tubules (Cortex, medulla) interstitium	GRHPR KO mice	After 4 wk (HyP supplements)	Hyperoxaluria	ND

CaP: Calcium phosphate; CaOx: Calcium oxalate; COM: Calcium oxalate monohydrate; COD: Calcium oxalate dihydrate.

and stones in papillary tips^[16]. In this model, crystal deposits are also associated with inflammation and damaged tubules; OPN is also up-regulated in tubules surrounding crystals; and hypercalciuria does not seem mandatory for renal CaOx deposits.

Intraperitoneal administration: In Sprague-Dawley rats *i.p.* administration of high dose of HyP (2, 5 g/kg), is followed by a massive deposition of calcium oxalate in renal parenchyma within 24 h with presumably an acute renal failure: Increased kidney volume and weight kidney, inflammation and oedema^[17].

Genetically modified animals

TH KO mice: Tamm Horsfall protein is synthesized by renal tubules and abundant in mammalian urine^[18,19]. TH is considered as a critical nephrolithiasis inhibitor, acting against crystal growth and aggregation^[1]. Indeed, TH KO mice between 2 and 4 mo old have crystal deposits located in medullar collecting ducts^[20]. Additional treatment with vitamin D and EG (1% in drinking water) for one month is responsible for a significant increase of crystal deposits especially in ascending limb of Henle loop (outer medulla), where TH is normally expressed. This model demonstrates the physiological relevance of TH protein in nephrocalcinosis prevention. Some studies suggest that the presence of Ca²⁺-binding domains and negatively charged sialylated residues would explain TH crystal inhibiting property^[21].

Npt2 KO mice: Co-transporters sodium/inorganic phosphate (Na/Pi) located in proximal tubules mediate 60%-70% of filtered phosphate reabsorption^[22]. In this

nephron segment, Na/Pi Type II a (Npt2) represents 80% of Na/Pi cotransporter mRNA and plays a major role in the maintenance of Pi homeostasis^[23]. Npt2^{-/-} mice are hypophosphatemic due to a renal Pi leak which in turn increases calcitriol synthesis resulting in the occurrence of hypercalciuria. Renal sections of Npt2^{-/-} pups mice display crystal deposits within tubules both in cortex, medulla and papilla. Interestingly, renal calcifications are increased in newborns and weaning pups and decrease thereafter in adult mice suggesting that the magnitude of urinary calcium and phosphate would be critical factors in this model. Accordingly, crystal deposits are mainly composed of hydroxyapatite (a calcium phosphate species) which is consistent with both a renal phosphate wasting and hypercalciuria. In this model, OPN is also up-regulated and expressed in tubules in the vicinity of apatite crystals. The reversal of crystal deposits appears also here as a remarkable feature.

GRHPR KO mice: Primary hyperoxaluria is a monogenic disease resulting from a liver enzyme deficiency. In type 1 primary hyperoxaluria, alanine glyoxylate aminotransferase, which catalyze transamination of glyoxylate to glycine in physiological conditions is deficient. In type 2, two enzymes are dysfunctional (glyoxylate reductase and hydroxypyruvate reductase), which normally catalyze the reduction of glyoxylate to glycolate and hydroxypyruvate to D-glycerate^[14]. Hence, increased glyoxylate which is finally oxidized to oxalate^[24] is responsible for a massive hyperoxaluria leading to nephrocalcinosis in human. Mice deficient in glyoxylate reductase (GR)/hydroxypyruvate reductase (GRHPR) or in alanine glyoxylate aminotransferase (AGT KO) develop as expected an inadequate

Table 2 Rodent models of nephrolithiasis

Ref.	Species	Crystals main compound	Crystals location	Animal model	Read out	Urinary phenotype	Renal injury
Bushinsky <i>et al</i> ^[25] , 2006	Rats	CaP ² CaOx ¹	Renal cavity (fornices) Papilla	Hypercalciuric rats (Genetic selection) under supplements ³ calcium 1.2% ⁴ calcium 1.2% + HyP 5%	18 wk after birth	Hypercalciuria Hyperoxaluria	None
Unpublished personal data	Mice	CaOx	Renal cavity (fornices)	Water supplement: HyP 4% + vitamin D (1000 UI) + ammonium chloride (0.28 mol/L) + calcium (0.25%)	15 d	Hypercalciuria Hyperoxaluria Hypocitraturia	None

¹Indicate the CaP or CaOx nature of crystal obtained either with ³calcium 1.2% or ⁴calcium 1.2% + HyP 5% as indicated column 5 above; ²Have been erased. CaP: Calcium phosphate; CaOx: Calcium oxalate; HyP: Hydroxyproline.

removal of glyoxylate^[24], with nephrocalcinosis occurring only in 25% of untreated GRHPR mice (crystal deposits are mostly intraluminal and few are located in the interstitium). However, after Hyp administration (1% in the diet) for one month, all GRHPR KO mice develop severe nephrocalcinosis, but only 20% for AGT KO mice. These data further strengthen the remarkable resistance of mice to renal crystal retention.

MODELS OF NEPHROLITHIASIS

Genetic hypercalciuric stone forming rats

Hypercalciuria is present in many patients with kidney stones (40%) and is often considered idiopathic. Hypercalciuria leads to urine supersaturation and thus increases calcium renal stone risk factors^[1,25]. Genetic hypercalciuric stone forming rats (GHS) (selected for 70 generations) have urine calcium excretion 8 to 10 fold above normal values. The authors demonstrated that hypercalciuria stems from 3 mechanisms: (1) an increased calcium intestinal absorption; (2) an decreased (Calcium sensor dependent) calcium tubular reabsorption; and (3) an increased bone resorption^[25]. As a matter of fact, after 18 wk of age, all GHS rats develop kidney stones. Noteworthy, stone composition is mostly apatite (CaHPO₄) when animals are fed with a standard 1.2% calcium diet, probably explained by urine CaHPO₄ supersaturation which increases faster than CaOx supersaturation^[26]. Conversely, an additional diet supplement of HyP 5% induces CaOx stones formation^[27] with crystal deposits mainly in contact with urothelial cells lining the papilla and in the fornix areas. Interestingly, similarly to tubular cells surrounding crystals, some urothelial cells in contact with crystals are indeed proliferating and also expressing high levels of OPN^[28]. This model thus appears very close to human renal stone disease as no nephrocalcinosis is observed though very rare and scattered crystal deposits may be detected within renal parenchyma (Table 2).

Hydroxyproline supplement in drinking water

Whereas Hyp administration in the diet induces nephrocalcinosis, Khan *et al*^[16] reported crystal deposits in renal pelvis and fornices after rat exposure to Hyp in drinking water for 28 d. A very few crystals are also seen in the tubules and in the papillary base. This model, thus also

looks very similar to human nephrolithiasis disease since most crystals are located within urinary cavities. Conversely to rats, mice develop mainly nephrocalcinosis after Hyp administration in drinking water (see below).

MODELS OF NEPHROCALCINOSIS ASSOCIATED WITH NEPHROLITHIASIS

Glycolic acid administration

Administration in male Wistar-strain rats of a glycolic acid diet during 4 wk leads to hyperoxaluria and CaOx tubular crystals both within cortex and medulla but also in pelvic cavities^[29] (Table 3).

Vitamin B-6 deficient diet

The liver enzyme alanine/glyoxylate amino-transferase which plays a key role in the conversion of glyoxylate (oxalate precursor) to glycine is vitamin B6 dependent; thus, vitamin B6 deficiency causes its dysfunction^[30]. Indeed, vitamin B6 deficient diet induces hyperoxaluria and hypocitraturia. Urinary oxalate excretion increases within 2 h after an intravenous hydroxypyruvate load in vitamin B6 deficient rats. These rats develop both calcium oxalate deposits in tubules, plaques on papillary tips and stones in renal fornices, pelvis and bladder^[31]. Another study slightly differs and shows only nephrocalcinosis with CaOx and CaP crystals in the papillary and parenchyma, tubular atrophy, interstitial fibrosis and chronic inflammatory infiltration^[32].

Small bowel resection

Ileal resection (IR) or bypass in humans may lead to massive hyperoxaluria and nephrolithiasis due to increased intestinal oxalate absorption^[33,34]. Indeed, CaOx nephrolithiasis has been estimated to occur in 15%-30% of patients after intestinal bypass surgery^[35]. The surgery decreases bile and pancreatic actions which trigger a poor fat absorption resulting into decreased calcium oxalate complexes and increased free oxalate (and oxalate salts which are efficiently absorbed in the colon segment) in intestinal lumen. Thus, dietary oxalates absorption increases leading to increased oxalate urine excretion^[35]. Moreover, these patients share a tendency to chronic volume contraction due to loss of water and

Table 3 Rodent models of nephrocalcinosis/nephrolithiasis

Ref.	Species	Crystals main compound	Crystals location	Animal model	Read out	Urinary phenotype	Renal injury
O'Connor <i>et al</i> ^[35] , 2003	Rats	CaOx CaP	Collecting ducts in cortex, medulla and papillary tips Urinary pelvis	Intestinal resection (40-45 cm)	4 mo after surgery	Hyperoxaluria, Hypocitraturia	Interstitial inflammation
Ogawa <i>et al</i> ^[29] , 1990	Rats	CaOx	Cortex and medulla tubules	Glycolic acid supplements	4 wk	Hyperoxaluria	
Di Tommaso <i>et al</i> ^[32] , 2002	Rats	CaOx CaP	Tubules, plaques on papillary tips, renal fornices, pelvis and bladder	Vitamine B6 deficient diet	12 wk	Hyperoxaluria, hypocitraturia	Tubules, inflammation

CaP: Calcium phosphate; CaOx: Calcium oxalate.

salt in diarrheal stool, which leads to decreased urine volumes. They also have decreased absorption, and therefore diminished urinary excretion, of citrate and magnesium, which normally act as inhibitors of CaOx crystallization^[34].

Intestinal resection (distal ileum) performed on male Sprague-Dawley rats fed individually with a low calcium and high oxalate diet (0.02% calcium, 18% lipid, 1% sodium oxalate) reproduces hyperoxaluria, hypocitraturia and nephrocalcinosis (by 4 mo). Calcium deposits are located in the cortex, medulla and papillary tip and contain CaOx, apatite and calcium carbonate^[35]. Of notice, crystal deposits are present in several collecting ducts associated with interstitial inflammation; crystal aggregates are detected near the fornix and 87% of kidneys display some calculi within pelvic lumen, measuring 0.5-2 mm^[35]. This model thus appears very similar to human enteric hyperoxaluria with both nephrocalcinosis and nephrolithiasis.

CONCLUSION

Concerning renal calcium stones, the most striking difference between rodents and humans lies in a special resistance of rodents to crystal retention noteworthy in female mice^[36]. Among all models, a hydroxyproline enriched diet responsible for both nephrocalcinosis and nephrolithiasis appears close to conditions encountered in a clinical setting when patient intakes of proteins are high. Nephrocalcinosis appears in several models due to the severity of oxalate burden but focusing data also epithelial phenotypical changes following injuries and/or crystal exposure would be a requirement for the onset of crystal adhesion and intratubular nephrocalcinosis, a mechanism called "fixed particle theory". *In situ* macromolecular inhibitors would in supersaturating condition unexpectedly promote crystal aggregation. The models associating nephrolithiasis and mild nephrocalcinosis suggest that such processes may be, at various degrees, more frequent in humans than expected. To date, no reliable models for Randall plaques are available with only two nephrolithiasis models but all in rats. Despite the differences between humans and rodents mentioned above, creating a nephrolithiasis model in mice appears indeed an important challenge

in order to better understand the early of urinary stone formation in papilla and fornices, the weight of calcium intake or absorption, enhanced bone resorption, and relevant macromolecules at play. It should also allow to test whether the "fixed particle theory" also applies to urothelium. Studying a nephrolithiasis model in specific genetically modified mice could also provide a deep insight into the very efficient rodent crystal clearance processes with potential translational applications.

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