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[2,3]. 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[9]. 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, glyoxylic acid, 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 macromolecules 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
Hyperoxaluria

CaOx

Renal injury

Species

Kidney dilatation, read out after 4 wk (HyP CaOx tubules, interstitium, ND)

Tubular injury, Hyperoxaluria

Ethylene glycol (0.75%)

1-6 d Hyperoxaluria

Hypercalciuria, CaOx (COM + COD) crystals in tubules (cortex, medulla), Papilla

Hyperoxaluria

Hypercalciuria, Hyperoxaluria

60%-70% of filtered phosphate reabsorption

60%-70% of filtered phosphate reabsorption

GRHPR KO mice: Primary hyperoxaluria is a monogenic disease resulting from a liver enzyme deficiency. In type 1 primary hyperoxaluria, alanine glyoxylate aminotransferase, which catalyzes transamination of glyoxylate to glycine in physiological conditions is deficient. In type 2, two enzymes are dysfunctional (glyoxylate reductase and hydroxypyruvate reductase), which normally catalyse the reduction of glycine to glycolate and hydroxypyruvate to D-glycerate. Hence, increased glyoxylate which is finally oxidized to oxalate 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

and stones in papillary tips. 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.

Genetically modified animals

TH KO mice: Tamm Horsfall protein is synthesized by renal tubules and abundant in mammalian urine. TH is considered as a critical nephrolithiasis inhibitor, acting against crystal growth and aggregation. Indeed, TH KO mice between 2 and 4 mo old have crystal deposits located in medullar collecting ducts. 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.

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

Table 1  Rodent models of nephrocalcinosis

| Ref.          | Species | Crystal main compounds | Crystals location | Animal Model | Read out | Urinary phenotype | Renal injury          |
|---------------|---------|------------------------|-------------------|--------------|----------|-------------------|-----------------------|
| Tawashi et al. 1980 | Rats    | CaOx                   | Tubules           | HyP injection i.p. (10 mL/kg) | 1 d       | Hyperoxaluria     | Kidney dilatation, oedema |
| Khan et al. 1982 | Rats    | CaOx                   | Tubules, interstitium, papillary tips | Sodium oxalate Injection (7 mg/100 g body weight) | 1 h       | Hyperoxaluria     | Tubular obstruction and dilatation |
| Marengo et al. 2004 | Rats    | COM crystals           | Tubules (cortex, medulla) | Potassium oxalate SC (Minipump) | 14 d      | Hyperoxaluria     | Tubular injury, dilatation, regeneration, interstitial inflammation |
| Vervaet et al. 2009 | Rats    | COM crystals           | Tubules           | Ethylene glycol (0.75%) | 1-6 d     | Hyperoxaluria     | Tubular injury, dilatation and regeneration, interstitial inflammation |
| Khan et al. 2006 | Rats    | CaOx                   | Tubules (cortex, medulla), Papillary tips (plagues β stones) | 5% Hyp supplement | 28 d      | Hyperoxaluria     | Inflammation, tubular injury |
| Mo et al. 2004 | Mice    | CaOx                   | Collecting ducts (medulla, papilla) | Tamm-Horsfall KO mice | 2-4 mo    | ND                |                       |
| Chau et al. 2003 | Mice    | -CaP                   | Tubules (cortex, medulla), Papilla | Npt2 KO mice + HyP supplement (4 wk) | From birth | Hypercalciuria, Hyperphosphaturia | ND                   |
| Knight et al. 2012 | Mice    | CaOx (COM + COD)       | Tubules (Cortex, medulla) interstitium | GRHPR KO mice | After 4 wk (HyP supplements) | Hyperoxaluria | ND |
removal of glyoxylate\textsuperscript{[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\textsuperscript{[1,25]}. Genetic hypercalcemic 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\textsuperscript{[25]}. As a matter of fact, after 18 wk of age, all GHS rats develop kidney stones. Noteworthy, stone composition is mostly apatite (CaHPO\textsubscript{4}) when animals are fed with a standard 1.2% calcium diet, probably explained by urine CaHPO\textsubscript{4} supersaturation which increases faster than CaOx supersaturation\textsuperscript{[26]}. Conversely, an additional diet supplement of HyP 5% induces CaOx stones formation\textsuperscript{[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\textsuperscript{[28]}. This model thus appears very close 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).

#### 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\textsuperscript{[29]} (Table 3).

#### Small bowel resection

Ileal resection (IR) or bypass in humans may lead to massive hyperoxaluria and nephrolithiasis due to increased intestinal oxalate absorption\textsuperscript{[33,34]}. Indeed, CaOx nephrolithiasis has been estimated to occur in 15%-30% of patients after intestinal bypass surgery\textsuperscript{[30]}. 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\textsuperscript{[32]}. Moreover, these patients share a tendency to chronic volume contraction due to loss of water and

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**Table 2** Rodent models of nephrolithiasis

| Ref. | Species | Crystals main compound | Crystals location | Animal model | Read out | Urinary phenotype | Renal injury |
|------|---------|------------------------|------------------|--------------|----------|-------------------|-------------|
| Bushinsky et al\textsuperscript{[20]}, 2006 | Rats | CaP CaOx\textsuperscript{1} | Renal cavity (fornices) | Hypercalciuric rats (Genetic selection) under supplements calcium 1.2% + 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 | None |

\textsuperscript{1}Indicate the CaP or CaOx nature of crystal obtained either with \textsuperscript{2}calcium 1.2% or \textsuperscript{3}calcium 1.2% + HyP 5% as indicated column 5 above; \textsuperscript{3}Have been erased. CaP: Calcium phosphate; CaOx: Calcium oxalate; HyP: Hydroxyproline.
Table 3 Rodent models of nephrocalcinosis/nephrolithiasis

| Ref. | Species | Crystals main compound | Crystals location | Animal model | Read out | Urinary phenotype | Renal injury |
|------|---------|------------------------|------------------|-------------|----------|-------------------|-------------|
| O’Connor et al[29], 2003 | Rats | CaOx CaP | Collecting ducts in cortex, medulla and papillary tips, renal fornices, pelvis and bladder | Intestinal resection | 4 mo after surgery | Hyperoxaluria, Hypocitraturia | Interstitial inflammation |
| Ogawa et al[30], 1990 | Rats | CaOx | Cortex and medulla tubules | Glycolic acid supplements | 4 wk | Hyperoxaluria |
| Di Tommaso et al[31], 2002 | Rats | CaOx CaP | Tubules, plaques on papillary tips, renal fomrines, pelvis and bladder | Vitamin 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 ilium) 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 fornimce, 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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