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Urinary kidney stone inhibitors. Where are we?

B. Dussol and Y. Berland
Service de Néphrologie et Hémodialyse, Hopital Sainte Marguerite, Marseille, France

Introduction

There is no doubt that during water conservation, kidneys supersaturate urine, especially with respect to calcium salts, and that protein inhibitors of stone formation play the major role in the natural defence against nephrocalcinosis. This editorial will first focus on the recent advances concerning the protein inhibitors of calcium oxalate (CaOx) crystallization and then on some unsolved problems.

Glycosaminoglycans (GAGs)

Urinary GAGs are enzymatic products of proteoglycans. They are excreted in urine and present in the stone matrix. Their concentration in urine is too low to decrease calcium supersaturation significantly. In the crystal growth model and by zeta-potential measurements, GAGs have been shown to act as inhibitors of CaOx crystal growth and aggregation by blocking the growth sites. GAGs prevent crystal adhesion to renal cells, which is likely to be an important step in urolithiasis. Exogenous GAGs can restore the anti-adhesion properties of an injured urothelium, thereby preventing crystal adhesion [1].

Oral administration of GAG to a group of stone formers (SF) led to a significant decrease in oxalate self exchange, which is abnormal in the majority of SF. Many investigators have studied urinary GAGs but it remains unclear whether there are qualitative and/or quantitative differences between SF and normal individuals (N).

From urine, kidney tissue, and CaOx stones, Coe et al. isolated a glycoprotein inhibiting CaOx crystal growth by absorption to crystal surfaces [2]. Nephrocalcin inhibits CaOx nucleation and aggregation, and crystal adhesion to renal cells. One mole of NC binds 4 moles of Ca²⁺ and its binding sites differ completely from those in other Ca²⁺-binding proteins [3]. Nephrocalcin is produced in human kidney by proximal tubule and the thick ascending limb of Henle’s loop. It contains 2–3 residues of γ-carboxyglutamic acid (Gla) per molecule, therefore NC is a vitamin-K-dependent protein. Abnormal forms of NC, lacking Gla, seem to occur in SF.

In a cloning study of the mouse osteocalcin gene, Desbois et al. found a cluster of three genes. Two of them are expressed only in bone. The third one, named ORG, is expressed in kidney but not in bone. Several lines of evidence suggest that ORG encodes nephrocalcin [4].

Nephrocalcin has never been sequenced; thus its role in kidney stone disease is unclear.

Uropontin

Uropontin is very closely related, if not identical, to osteopontin, the bone phosphoprotein that binds to the bone matrix. There may be differences between the two molecules with respect to post-translational modifications such as phosphorylation, glycosylation and sulphation, which are tissue specific. Uropontin is rich in non γ-carboxylated aspartic residues, and thus distinct from NC. At concentrations that normally prevail in urine, the urinary form of osteopontin is a potent inhibitor of CaOx nucleation, growth and aggregation.
It also inhibits the crystal adhesion to renal cells. Osteopontin is upregulated by 1,25-(OH)_{2}-vitamin D, and a vitamin D response element has been found in the promoter region of the osteopontin gene, but regulation in kidney has not yet been elucidated. Uroponitin is an abundant component of the organic matrix of CaOx stones [5].

The kidney distribution of uroponitin is controversial: it has been detected either in the thick ascending limb of Henle's loop and in the distal convoluted tubule [5], or in the descending thin limb of Henle's loop and in the papillary surface epithelium [6].

**Crystal matrix protein (CMP)**

Described in 1991 by Ryall et al., the formerly called CMP is actually a urinary form of F1, a degradation product of prothrombin, the serum zymogen involved in the coagulation. The protein, which is present in CaOx crystals has been localized in the thick ascending Henle's loop and in the distal convoluted tubule. This glycoprotein possesses the domain rich in Gla of the native protein which confers the ability to bind calcium ions, thus explaining its inhibitory effect on CaOx crystal aggregation.

It is not known whether F1 may have undergone some molecular modification before or after its release in urines. Furthermore it remains to be determined whether F1 is simply a catabolic by-product of normal prothrombin turnover or whether its rate of excretion is influenced by urinary conditions [7].

**Light chain of inter-α-trypsin inhibitor (ITI) or bikunin**

Described in 1993 by Atmani et al., the formerly called uronic-acid rich protein (UAP) is a urinary glycoprotein inhibiting CaOx growth. The amino-acid sequence of UAP is similar to bikunin, the light chain of ITI, a big plasma protein member of the Kunitz type protease inhibitor superfamily [8]. The same protein had been isolated by Sorensen et al. [9]. Atmani recently demonstrated that bikunin is present in the kidney and in the kidney stone matrix and that bikunin from SF urine inhibits CaOx crystallization less potently than does that from N.

**Tamm–Horsfall protein (THP)**

THP is a glycoprotein produced by the thick ascending loop of Henle. It is present in large amount in urine. THP may be either a promoter or an inhibitor of crystallization depending on its physicochemical properties.

Most authors agree that THP is a weak inhibitor of CaOx crystal nucleation and growth. THP has a dual role as a modifier of crystal aggregation: in solutions with high pH, low ionic strength, and low concentrations of divalent ions and THP itself, the glycoprotein is in its monomeric form and acts as a powerful inhibitor of CaOx crystal aggregation. Conversely, low pH, high ionic strength and high concentrations of divalent ions and THP all favour self-aggregation of THP molecules, leading to reversible gel formation, which lowers its inhibitory activity against crystal aggregation. THP, even in its monomeric form, has no effect on crystal adhesion to renal cells but rather blocks crystal uptake by the same cells.

Some SF excrete abnormal THPs which self-aggregate at concentrations of calcium at which normal THP remains in monomeric form [10].

**Renal lithostathine (RL)**

Renal lithostathine, the urinary inhibitor of calcium carbonate (CaCO3) crystal growth has been purified by Tatemichi et al. [11]. They showed that RL has the same amino-acid composition as pancreatic lithostathine S2_5. The small difference in molecular weight between the two proteins is due to variations in the carbohydrate side chain. It is not known whether RL is really synthesized in the kidney or only filtered and/or taken up from tubular fluid or blood by renal cells. The demonstration that RL urine levels are increased in certain renal diseases suggests that the kidney is another source of the protein [11].

RL is involved in the control of CaCO3 crystal growth but its inhibitory activity in urolithiasis is likely to be more important since CaCO3 is a promoter of CaOx crystallization [12].

**Conclusion**

The process of kidney stone formation results from supersaturation with respect to urinary salts and from crystal retention in the urinary tract. Urinary inhibitors are involved in the control of these phenomena [13].

It is impossible to know the exact composition of urine and hence the supersaturation with respect to the different urinary salts in the different parts of the nephron. Thus the exact role of the protein inhibitors detected all along the nephron in the control of urinary stone formation and especially calcium stone formation must be specified. Moreover some urinary proteins may be involved in the promotion of stone formation. Recently we demonstrated that albumin, the most abundant protein found in the stone matrix [14] can induce CaOx nucleation (not published).

Understanding the role of inhibitors in the process of urinary stone formation is complicated by the fact that the activities of inhibitors were studied in vitro where conditions may not be as in vivo. Urine composition, as evidenced for the THP ability to inhibit CaOx aggregation, and the interactions between the different inhibitors in urine and upon the crystals are not considered. Furthermore there is no universally accepted model for measuring inhibition, nor is there...
agreement on what stage of crystal growth might be the critical point for inhibitory activity. Proteins may be inhibitors at one step of crystallization and inactive or promoters at another step. Finally there are no comparative studies of the ability of each inhibitor to act at each step of crystallization.

The renal involvement of protein inhibitors will probably be established when the genes encoding these proteins are identified and transgenic animal model studies are done.

References


Does it make sense to administer albumin to the patient with nephrotic oedema?

E. J. Dorhout Mees

Nephrology Department, Ege University Medical School, Bornova, Izmir, Turkey

Introduction

The notion that fluid retention in the nephrotic syndrome is caused by a decreased circulating blood volume (hypovolaemia concept) has dominated medical thinking and practice for decades. During recent years evidence has accumulated that this concept, logical as it may seem, does not reflect reality in most patients [1]. Yet these new insights have only slowly entered into textbooks and even slower in the minds of many clinicians. Thus albumin infusions (the supposed beneficial effects of these follow logically from the hypovolaemia concept) are still administered on a large scale. Surprisingly few adequate investigations have been dedicated to this theoretically and practically important subject.

Plasma volume expansion by intravenous human albumin

It is amazing that albumin infusion became so popular at all, since the first reports on patients with NS were not very encouraging. Janaway et al. [2] remarked that large amounts of albumin had to be given over long periods before improvement of oedema occurred. Eder et al. [3] reported a good response in one of two patients.

More systematic studies were even less positive. Brown et al. [4] reported no effect of albumin infusion in three patients. Koomans et al. [5] studied 10 patients with minimal lesions or focal sclerosis with severe Na retention. Mean Na excretion increased from 9 to only 43 μmol/min, while some patients did not show any response at all. Similar results were recently reported by other investigators [6,7].

Because an increase in plasma albumin after hyporonic infusions might have a Na-retaining effect [8], the Utrecht group [9] investigated the effect of sustained plasma volume expansion with iso-oncotic albumin for 68 h. Mean Na excretion rose from 56 to 98 μmol/min but all patients excreted less than the amount administered with the infusions, and gained some weight. Remarkably, mean arterial pressure gradually rose from 99 to 110 mmHg, and plasma natriuretic peptide increased from 31 to 81 pmol/L.

Against these more or less discouraging results Usberti et al. [10] reported on an increase of Na

Correspondence and reprint requests to: Prof. Dr E. J. Dorhout Mees, E. U. Lojmanlar 1 A 12, 35050 Bornova, Izmir, Turkey.