ELSEVIER
SAUNDERS

Urol Clin N Am 34 (2007) 347–362

UROLOGIC
CLINICS
of North America

Management of Cystinuria

Alexandra Rogers, MD[a], Samer Kalakish, MD[b],
Rahul A. Desai, MD[b], Dean G. Assimos, MD[b,*]

[a]*Department of Urology, Mayo Clinic, Jacksonville, FL, USA*
[b]*Wake Forest University School of Medicine, Department of Urology, Medical Center Boulevard, Winston Salem, NC 27157-1094, USA*

The initial description of cystinuria is credited to Wollaston [1], who reported on bladder calculi composed of cystic oxide in 1810. Two decades later, Berzelius [2] noted that such calculi lacked oxide. At the turn of the nineteenth century, Friedman [3] defined the chemical structure of cystine, the true composition of the aforementioned stones. In 1908, Garrod [4] incorrectly characterized cystinuria as an inborn error of metabolism, but correctly noted that it was an inherited disorder. In 1955, Harris and colleagues [5,6] reported the inheritance as autosomal recessive.

Cystinuria is a monogenic disorder in which there is a transepithelial transport defect of dibasic amino acids, including cystine, ornithine, lysine, and arginine (COLA). This results in diminished reabsorption of these amino acids in both the intestine and renal proximal tubule. The defect in renal reabsorption occurs at the apical membrane of proximal tubular cells. This increases excretion of these amino acids and promotes cystine supersaturation and crystal formation in urine, which can eventuate in cystine stone formation. The other amino acids are soluble at normal urinary pH and do not become stone components. The gastrointestinal defect is not pathologic because these are not essential amino acids and their di-peptide forms are still transported [7,8].

* Corresponding author. Bowman Gray Campus, Department of Urology, Wake Forest University School of Medicine, Medical Center Boulevard, Winston Salem, NC 27157-1094.

E-mail address: dassimos@wfubmc.edu (D.G. Assimos).

Epidemiology

The estimated prevalence of cystine stones varies. The overall prevalence of the disease is 1 out of 7000 in neonates, but is influenced by ethnicity. One out of 2,500 neonates among Libyan Jews versus 1 out of 100,000 Swedes have the disease [9]. Homozygous prevalence is 1 in 20,000 while heterozygous expression is 1 in 20 to 1 in 200. Some have estimated that cystine stones account for as many as 1% to 2% of all urinary stone, but other studies report that the percentage is much lower [10,11]. A study by Mandel and colleagues [12] determined the prevalence to be 0.6% among United States veterans. Cystine stones comprise 6% to 8% of the stones reported in pediatric series [13,14]. Much like patients with other monogenic disorders associated with stone formation, these patients manifest their stone-forming condition at a younger age.

The International Cystinuria Consortium (ICC) has compiled demographic data on cystinuric patients [15]. The age of onset ranges between 2 to 40 years, but the median is 12 years for males and 15 years for females. Males are more likely to be affected before the age of 3 years. Similarly, men have 0.42 stone events per year while women have 0.21. Ten of the 224 patients in the ICC data did not develop stone disease, but only 2 of these patients were over 40 years of age. The ICC found that regardless of phenotype or genotype the clinical manifestations were the same. There are gender differences amongst siblings that have same mutations [16]. These differences have been attributed to other stone risk factors, which can be influenced by environment and genetics.

0094-0143/07/$ - see front matter
doi:10.1016/j.ucl.2007.04.006

Normal COLA renal transport

A review of the mechanisms of normal COLA renal transport is subsequently provided as a platform to understanding this disease process. The transporters involved in di-basic amino acid transport are known as heteromeric amino acid transporters. They consist of an amino glycosylated heavy subunit and an unglycosylated light subunit [17–20]. Different genes encode for these two subunits. The heavy subunit is derived from the SLC3 family while the light subunit is from the SLC7 family. The two chains, linked by a disulfide bridge, course through the cell membrane as well as inside and outside of the membrane [20]. The amino group of the heavy chains is within the cell and the carboxyl moiety is outside the cell. Both such light chain components are within the cell.

The two heavy subunits cloned thus far are rBAT and 4F2hc. The rBAT that heterodimerizes with a light chain is called b0,+AT and the whole unit is referred to as B0,+. It is located on the apical surfaces of the renal proximal tubule and the intestinal mucosa, where it promotes reabsorption of COLA amino acids. The protein 4F2hc, also known as CD98 or fusion regulatory protein 1 (FRP1), heterodimerizes with a light chain called y^+LAT1, which is located on the basolateral membrane of these cells. This complex facilitates COLA amino acid transport from the cell into the blood compartment. These two complexes have low capacity and high affinity for the COLA amino acids and are sodium independent. Sodium-dependent neutral amino acid transporters are present at the apical and basolateral membranes and maintain a high intracellular level of neutral amino acids. This maintains a membrane potential that facilitates COLA amino acid transport. The intracellular metabolism of cystine to cysteine further drives this process by maintaining a favorable cystine concentration gradient for reabsorption (Fig. 1).

There is evidence that the aforementioned heavy and light chain proteins involved in COLA amino acid transport may be dimerized to other protein subunits in the renal proximal tubule [21]. For example, there is a gradient for rBAT expression along the proximal tubule (S3 straight segment > S2 lower convoluted segment > S1 upper convoluted segment) that is opposite to that for b0,+AT [22,23]. However, there is sound experimental evidence that b0,+AT and rBAT form the main transporter involved in COLA amino acid transport [24].

Phenotypic characterization

A phenotypic classification of cystinuria was established before the responsible genes were

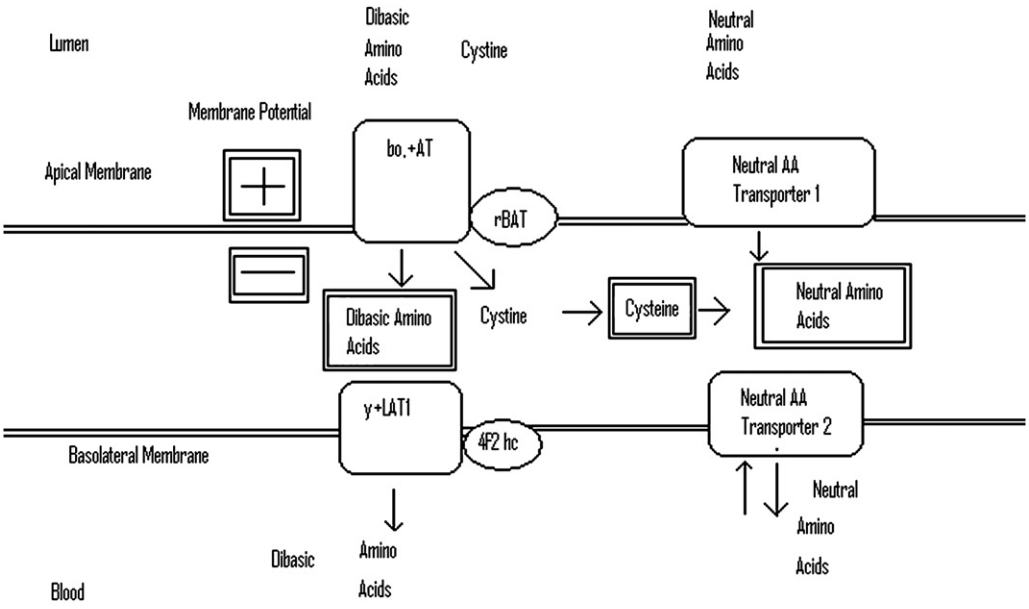

Fig. 1. Normal di-basic amino acid transport. AA, amino acid.