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Minireview

Contrasting features of urea cycle disorders in human patients and knockout mouse models

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Abstract

The urea cycle exists for the removal of excess nitrogen from the body. Six separate enzymes comprise the urea cycle, and a deficiency in any one of them causes a urea cycle disorder (UCD) in humans. Arginase is the only urea cycle enzyme with an alternate isoform, though no known human disorder currently exists due to a deficiency in the second isoform. While all of the UCDs usually present with hyperammonemia in the first few days to months of life, most disorders are distinguished by a characteristic profile of plasma amino acid alterations that can be utilized for diagnosis. While enzyme assay is possible, an analysis of the underlying mutation is preferable for an accurate diagnosis. Mouse models for each of the urea cycle disorders exist (with the exception of NAGS deficiency), and for almost all of them, their clinical and biochemical phenotypes rather closely resemble the phenotypes seen in human patients. Consequently, all of the current mouse models are highly useful for future research into novel pharmacological and dietary treatments and gene therapy protocols for the management of urea cycle disorders.

Keywords: Urea; Hyperammonemia; Knockout; *N*-Acetylglutamate synthase; Carbamyl phosphate synthetase I; Ornithine transcarbamylase; Argininosuccinate synthetase; Argininosuccinate lyase; Arginase

Introduction

The urea cycle

The urea cycle is the only metabolic pathway capable of removing excess nitrogen from the body [1]. Occurring in the liver, ammonium nitrogen from dietary protein sources and from the breakdown of endogenous protein is converted into urea, which unlike ammonia is nontoxic, water-soluble, and is easily excreted from the body through the kidneys as a component of urine. The urea cycle is originally thought to have evolved in amphibians through adaptation to an air-breathing terrestrial lifestyle, necessitating a novel method whereby ammonia could be efficiently expelled [2]. While fish are able to passively excrete ammonia across their gills, terrestrial animals are not able to excrete enough water to dilute ammonia to a nontoxic level without becoming dehydrated [3]. Six separate enzymes comprise the urea cycle, namely *N*-acetylglutamate synthase (NAGS), carbamyl phosphate synthetase I (CPS-I), ornithine transcarbamylase (OTC), argininosuccinate synthetase (AS), argininosuccinate lyase (AL), and arginase (ARG), and a deficiency in any one of the enzymes causes a urea cycle disorder (UCD) in humans [4]. NAGS, CPS-I, and OTC function in the mitochondria, while AS, AL, and ARG exist in the cytosol (Fig. 1). Except for OTC deficiency, which is X-linked, all of the UCDs are

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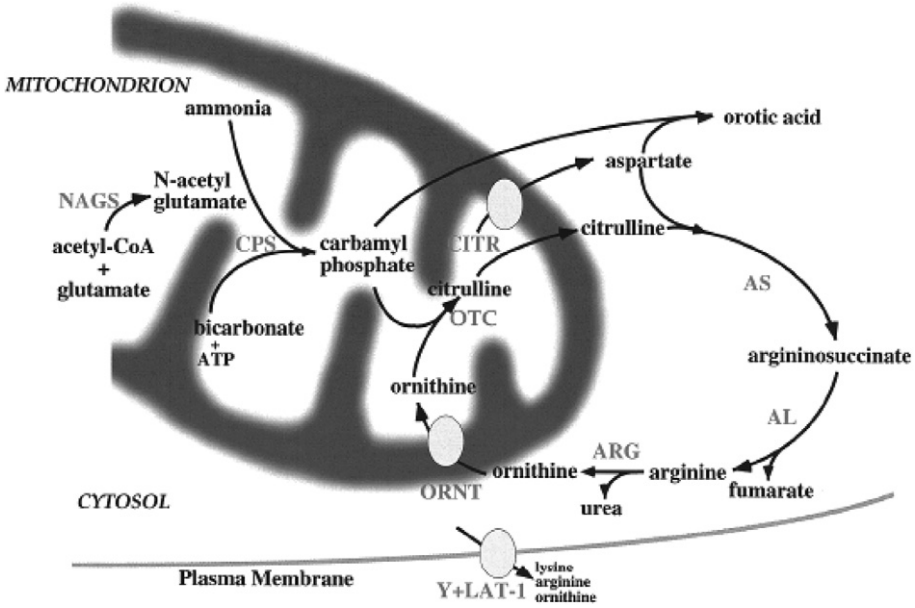

Fig. 1. Enzymes of the urea cycle, reproduced with permission from [93]. Ammonia in the mitochondria is converted to urea in the cytosol, and ornithine is transported back into the mitochondria to continue the cycle.

Table 1
Human and mouse homologs of urea cycle enzymes

Enzyme	Disorder	Human gene	Mouse gene	Mouse model?
N-Acetylglutamate synthase	NAGS deficiency	Chr. 17	Chr. 11	No
Carbamyl phosphate synthetase I	CPS-I deficiency	Chr. 2	Chr. 1	Yes
Ornithine transcarbamylase	OTC deficiency	Chr. X	Chr. X	Yes
Argininosuccinate synthetase	Citrullinemia type I	Chr. 9	Chr. 2	Yes
Argininosuccinate lyase	Argininosuccinic aciduria	Chr. 7	Chr. 5	Yes
Arginase	Hyperargininemia	Chr. 6	Chr. 10	Yes

Note. The CPS-I knockout mouse model is no longer available.

inherited in an autosomal recessive pattern, and their overall frequency is approximately 1 in 30,000 live births [5] (Table 1).

Diagnosis and treatment of urea cycle disorders

Hyperammonemia, or high plasma ammonia, is the primary diagnostic finding associated with all of the urea cycle disorders, and patients with UCDs usually present as neonates. They are born normally but often reveal initial symptoms within the first few days to weeks of life. Generally, the most severe course of disease is associated with the most proximal blockage in the cycle. For example, patients with complete CPS-I or OTC deficiency frequently present during the first few days of life, patients with AS or AL deficiency tend to present during the first month, and patients with ARG deficiency usually present later in childhood [6]. Urea cycle disorders are generally severe, and if left untreated for too long, the resulting hyperammonemia can cause mental retardation, seizures, and early morbidity [1]. Therefore, the initial focus for patients with UCDs is centered on lowering ammonia levels in the plasma.

Since hyperammonemia originally results from protein breakdown, the first step in the treatment of UCDs is to stop all protein intake and substitute an oral or intravenous high energy source such as glucose [7]. If the plasma ammonia is extremely high and stopping protein intake does not sufficiently normalize ammonia levels, hemodialysis or hemofiltration are used. Other oral and intravenous compounds also exist that can assist in the removal of excess nitrogen without the need to produce urea. Sodium benzoate was the first compound introduced; benzoate conjugates with glycine to form hippurate which can be easily excreted in the urine, and for every mole of benzoate administered, one mole of nitrogen is removed [8]. Sodium phenylacetate was introduced next; however, sodium phenylbutyrate is more commonly used today for the treatment of UCDs due to the unpleasant odor of phenylacetate. Phenylbutyrate is converted to phenylacetate which conjugates with glutamine, and the resulting compound is easily excreted in the urine [1,5]. In contrast to benzoate, two moles of nitrogen are eliminated for every mole of phenylbutyrate administered.