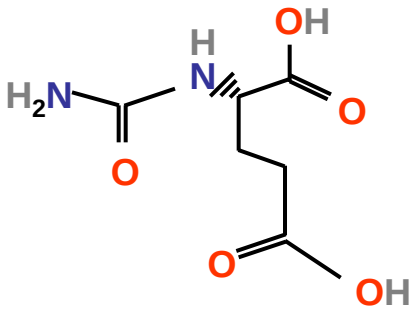
N-carbamylglutamate as Treatment of High Blood Ammonia levels in Propionic Acidemia

Renata C. Gallagher, MD, PhD
Assistant Professor
Clinical Genetics and Metabolism
University of Colorado School of Medicine
Children's Hospital Colorado
Renata.gallagher@childrenscolorado.org

Propionic Acidemia Family Foundation Meeting
June 29, 2013
Denver, CO



N-carbamylglutamate Consortium (NCGC)

NATIONAL INSTITUTES OF HEALTH

ORPHAN EUROPE
RECORDATI GROUP

RARE DISEASES CLINICAL RESEARCH NETWORK

UCDC

Urea Cycle Disorder Consortium

Consortium Sites

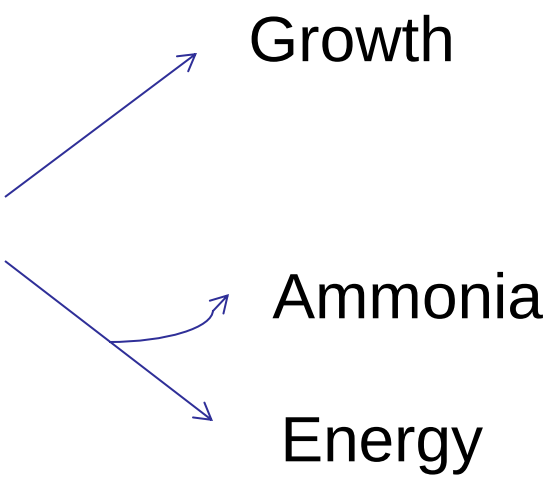
- **Children's National Medical Center, Washington, DC, Lead Site**
  - Children's Hospital of Philadelphia
  - Children's Hospital Boston
  - Rainbow Babies Children's Hospital, Cleveland
  - Children's Hospital Colorado
  - University of California, Los Angeles
  - Stanford University, Palo Alto, CA

Overview

- Background
  - What is ammonia?
  - Why is there high blood ammonia in PA?
  - What happens if blood ammonia is high?
  - How can ammonia be lowered?
- The Trials
- The Goals
- How to Participate

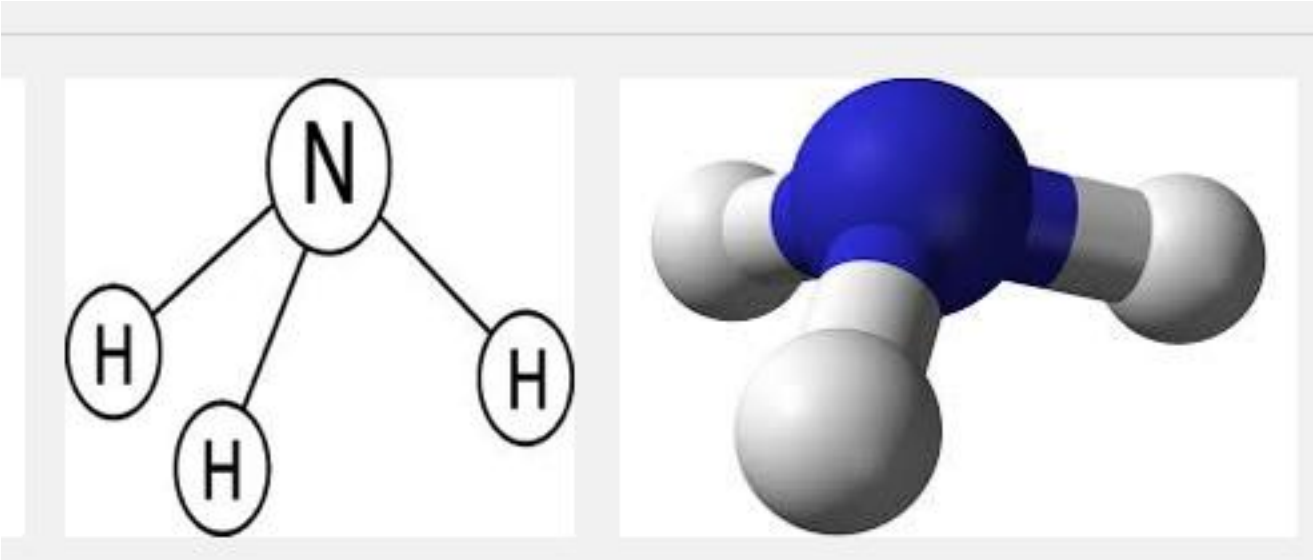
Background

- What is ammonia?
  - A chemical produced when protein is broken down for energy
  - Protein ----->Amino acids

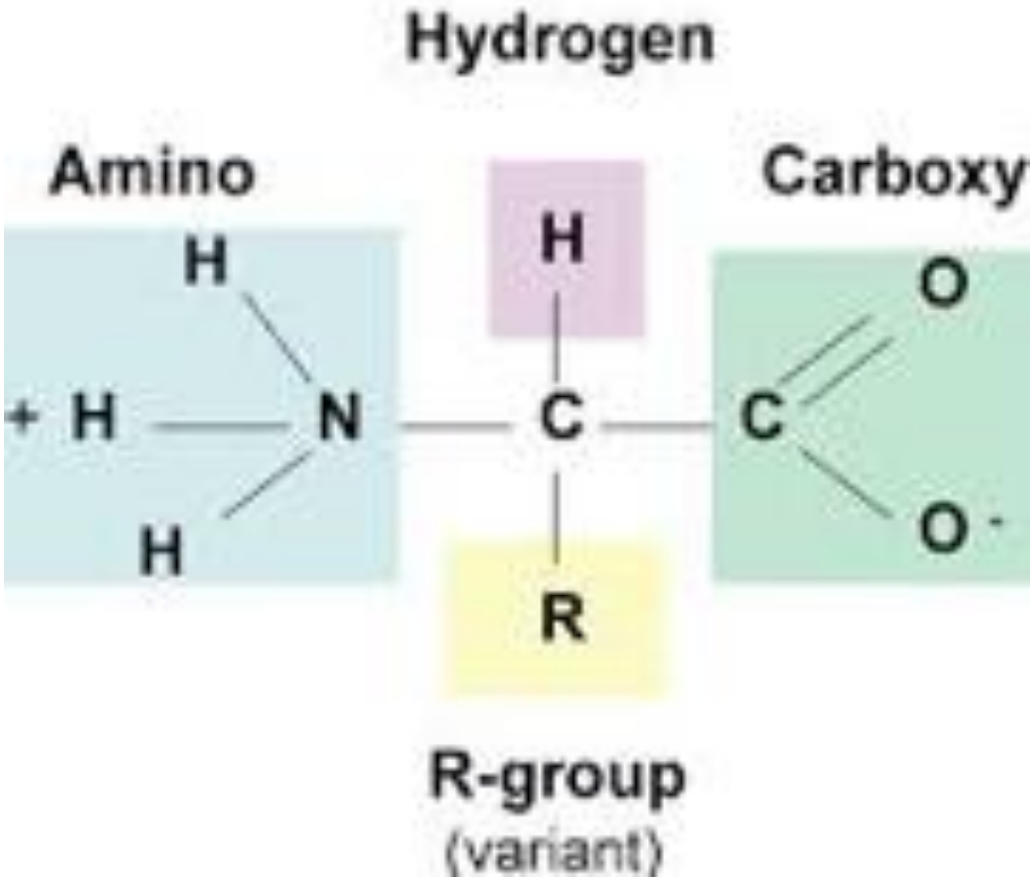


- Ammonia is made when amino acids -- > Energy

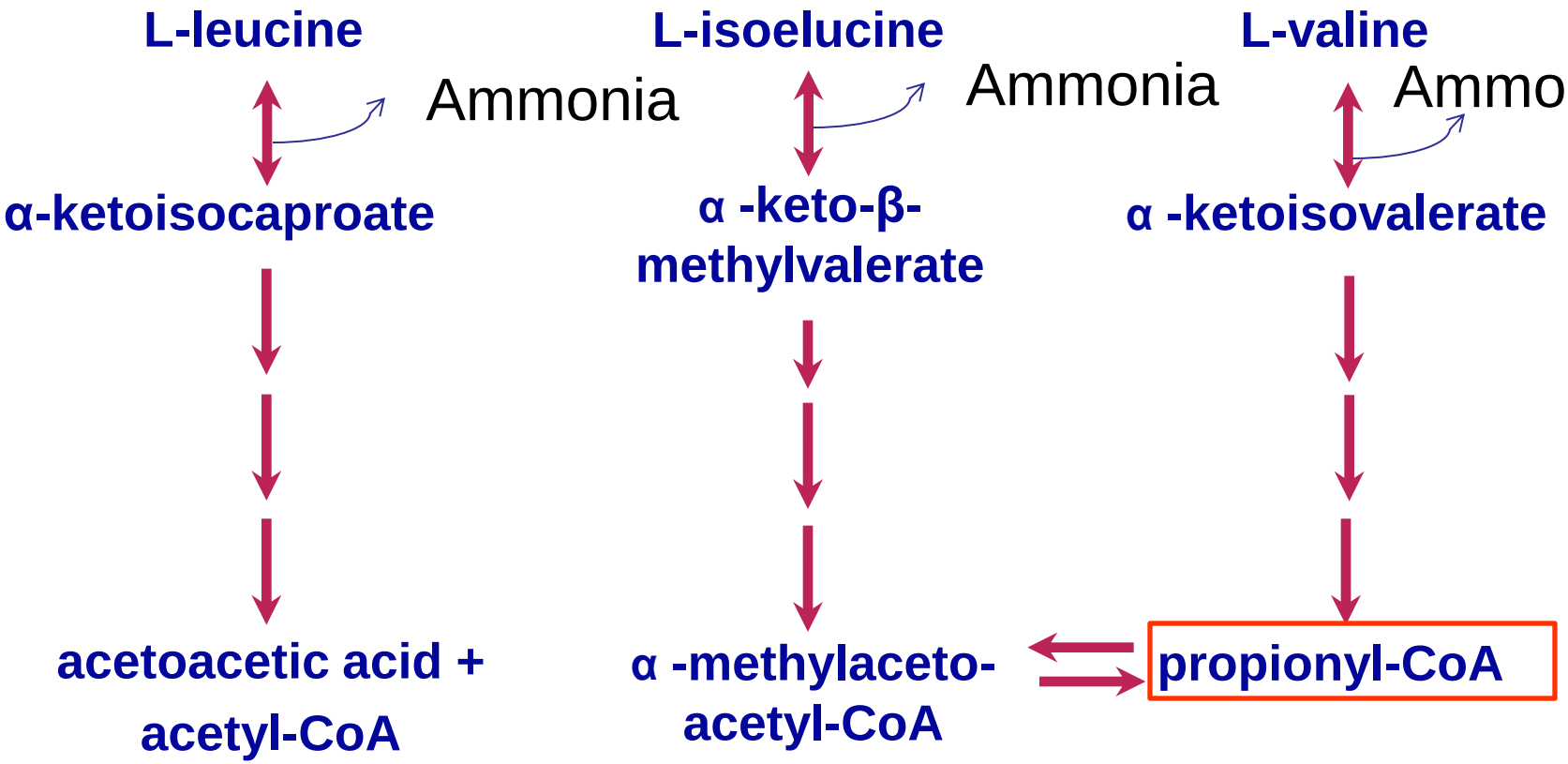
Ammonia



Amino acid



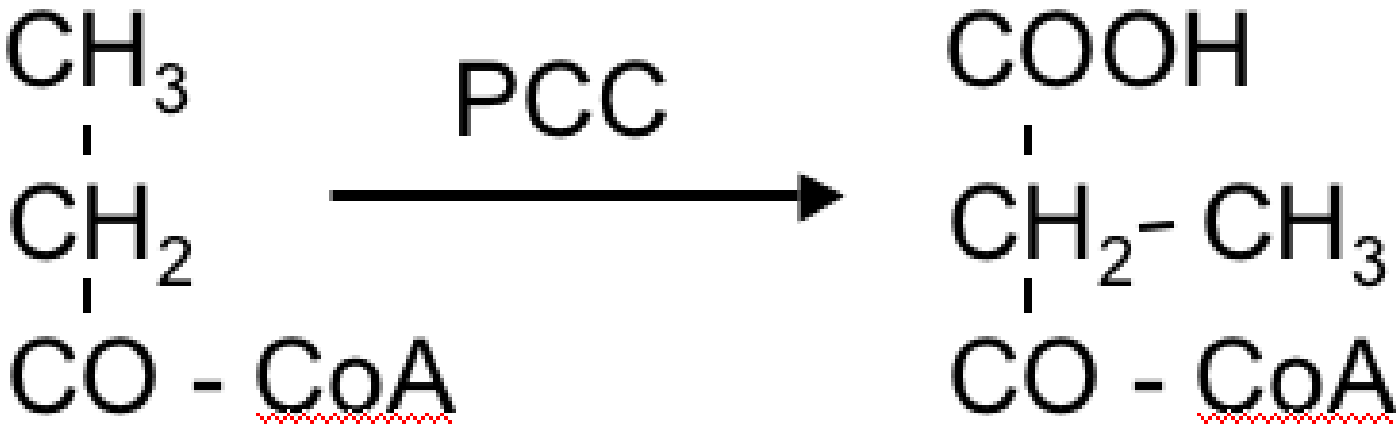
Branched-Chain Amino Acid Metabolism



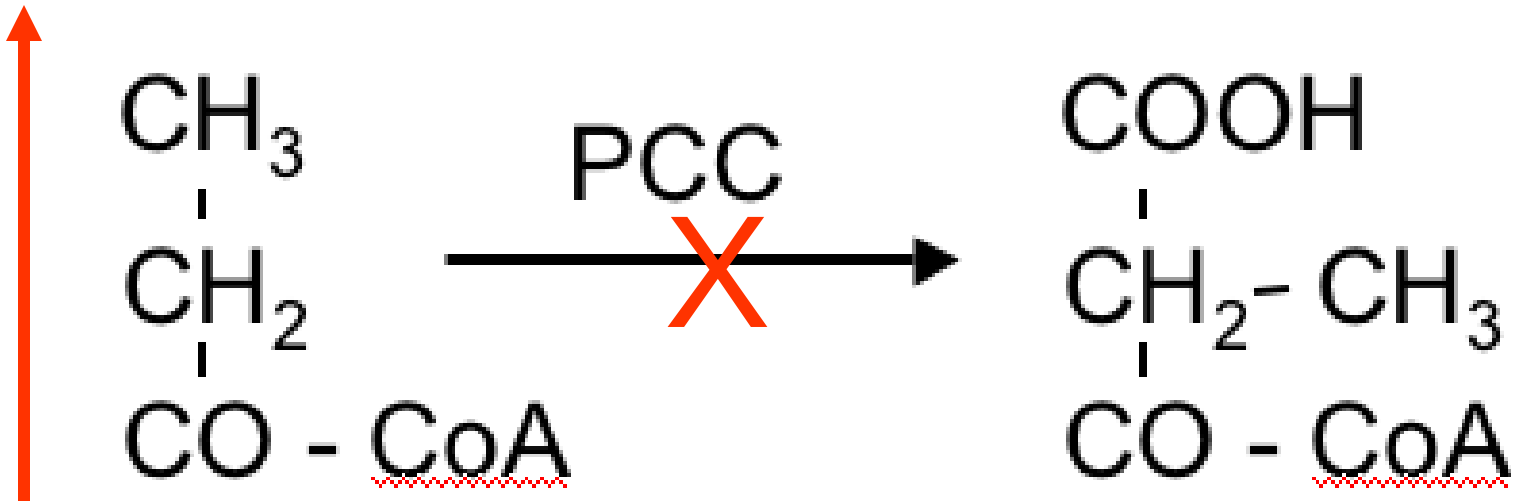
Background

- Why is there high blood ammonia in PA?
  - Propionyl-CoA resembles acetyl-CoA
  - Lots of propionyl-CoA prevents the body from making acetyl-CoA into acetyl-glutamate
  - Acetyl-glutamate is needed to turn ammonia into the non-toxic chemical urea that is excreted (peed out)

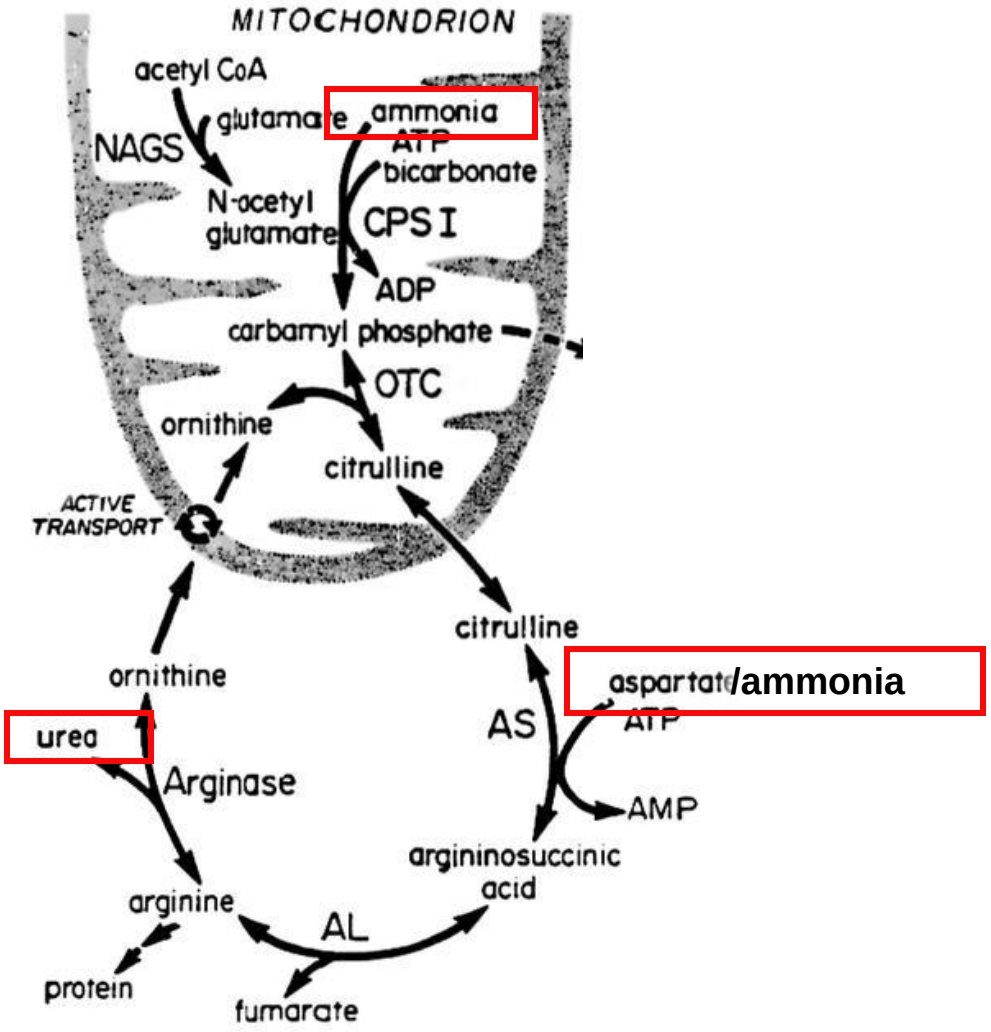
Propionyl-CoA Carboxylase



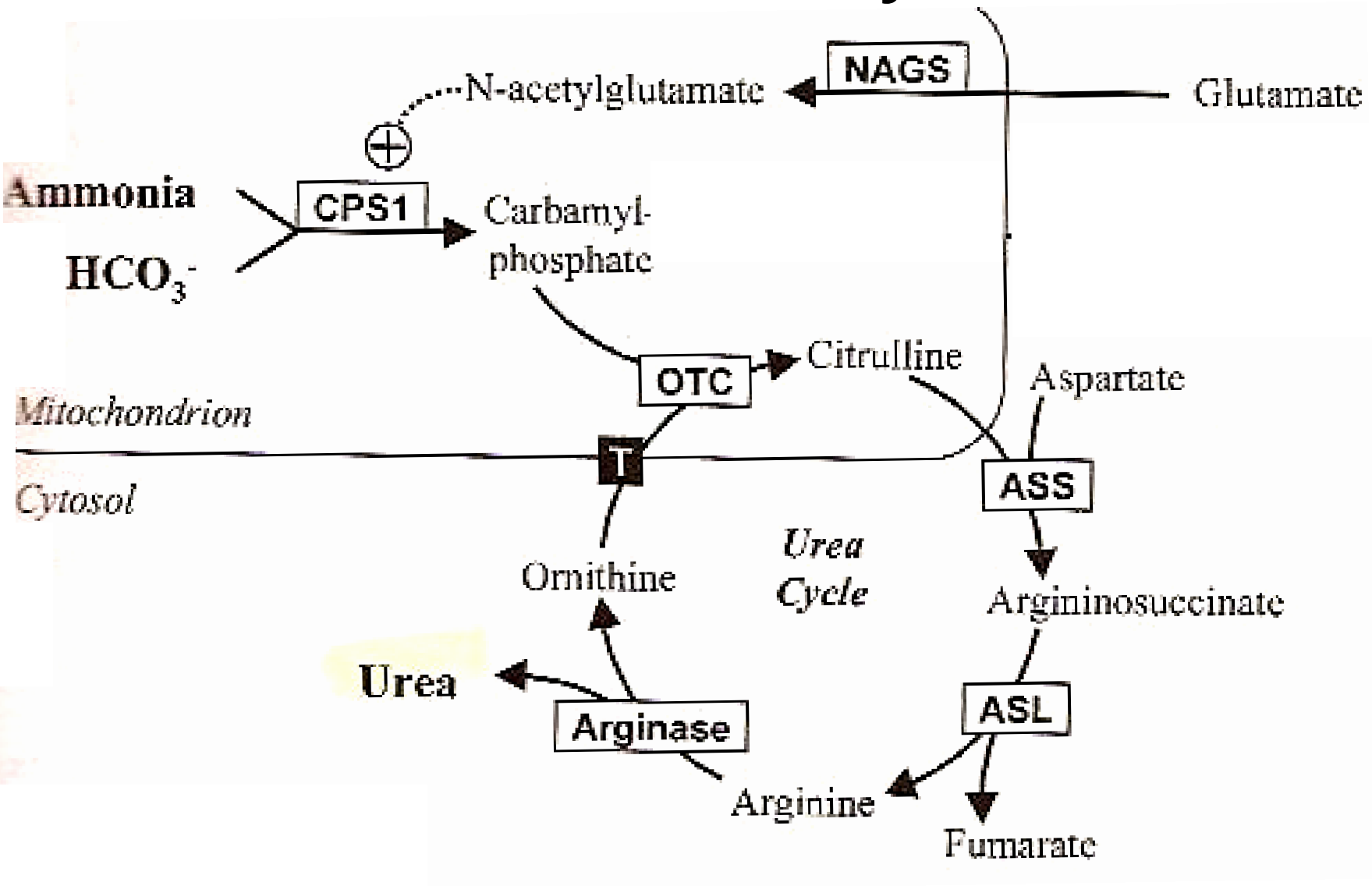
Propionyl-CoA Carboxylase



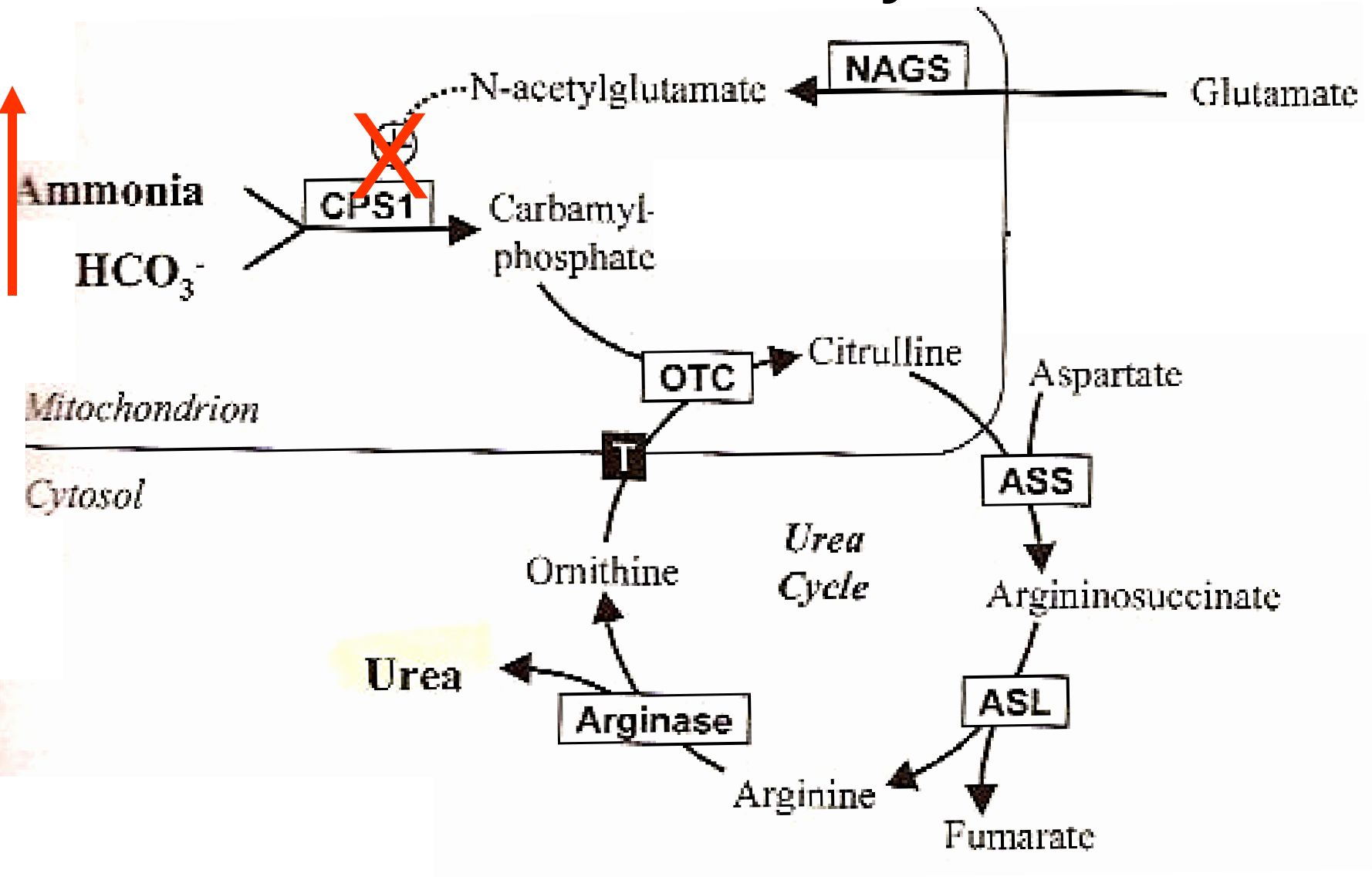
The Urea Cycle



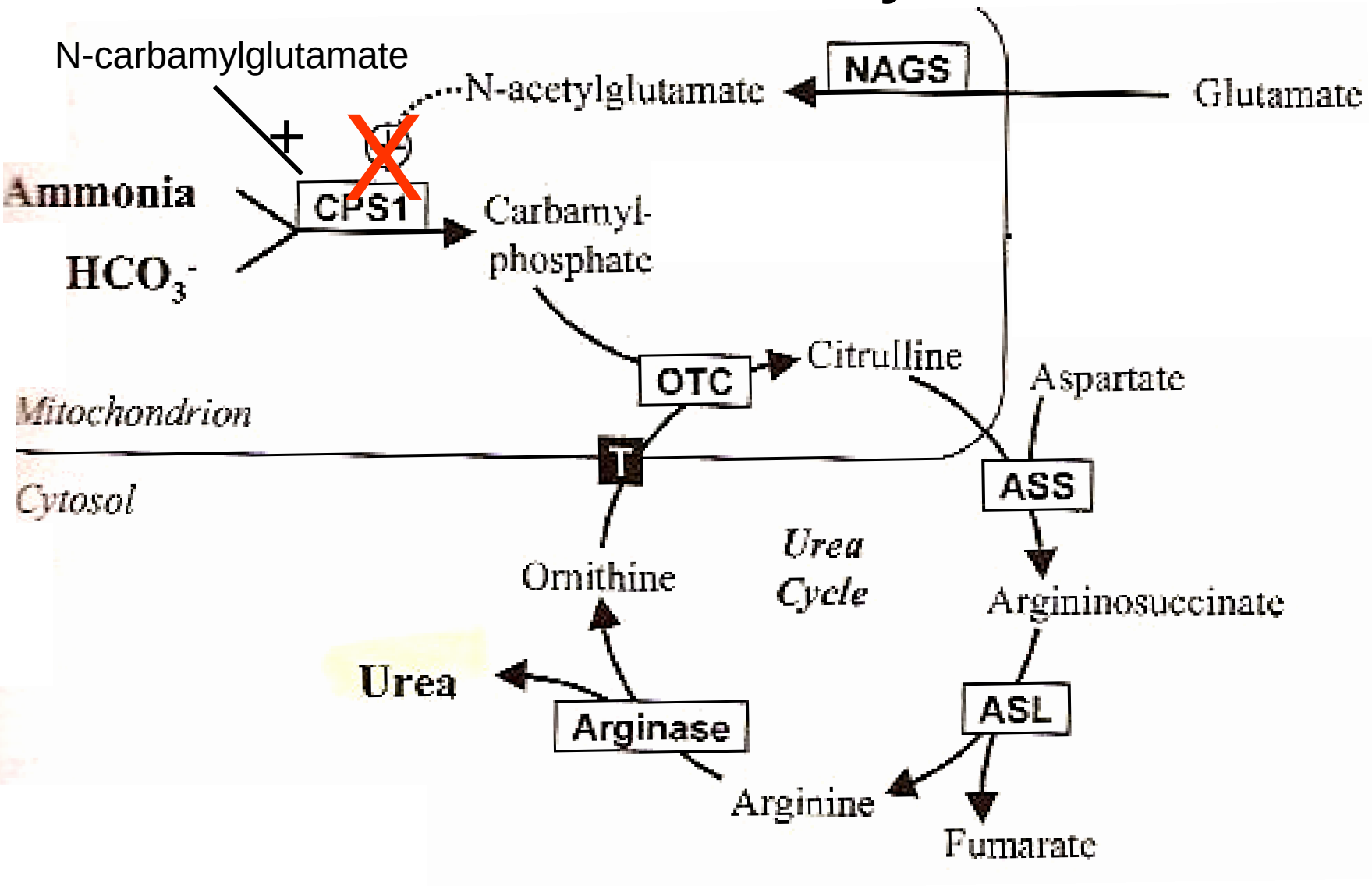
The Urea Cycle

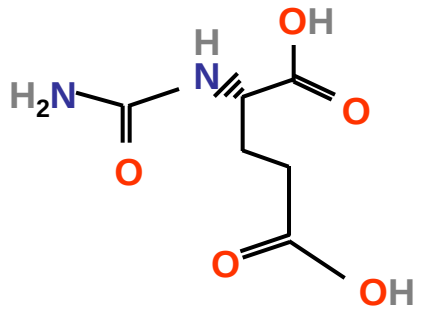


The Urea Cycle

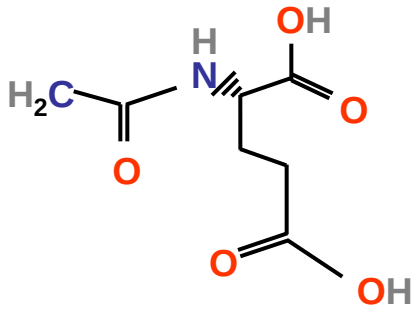


The Urea Cycle





N-carbamylglutamate



N-acetylglutamate

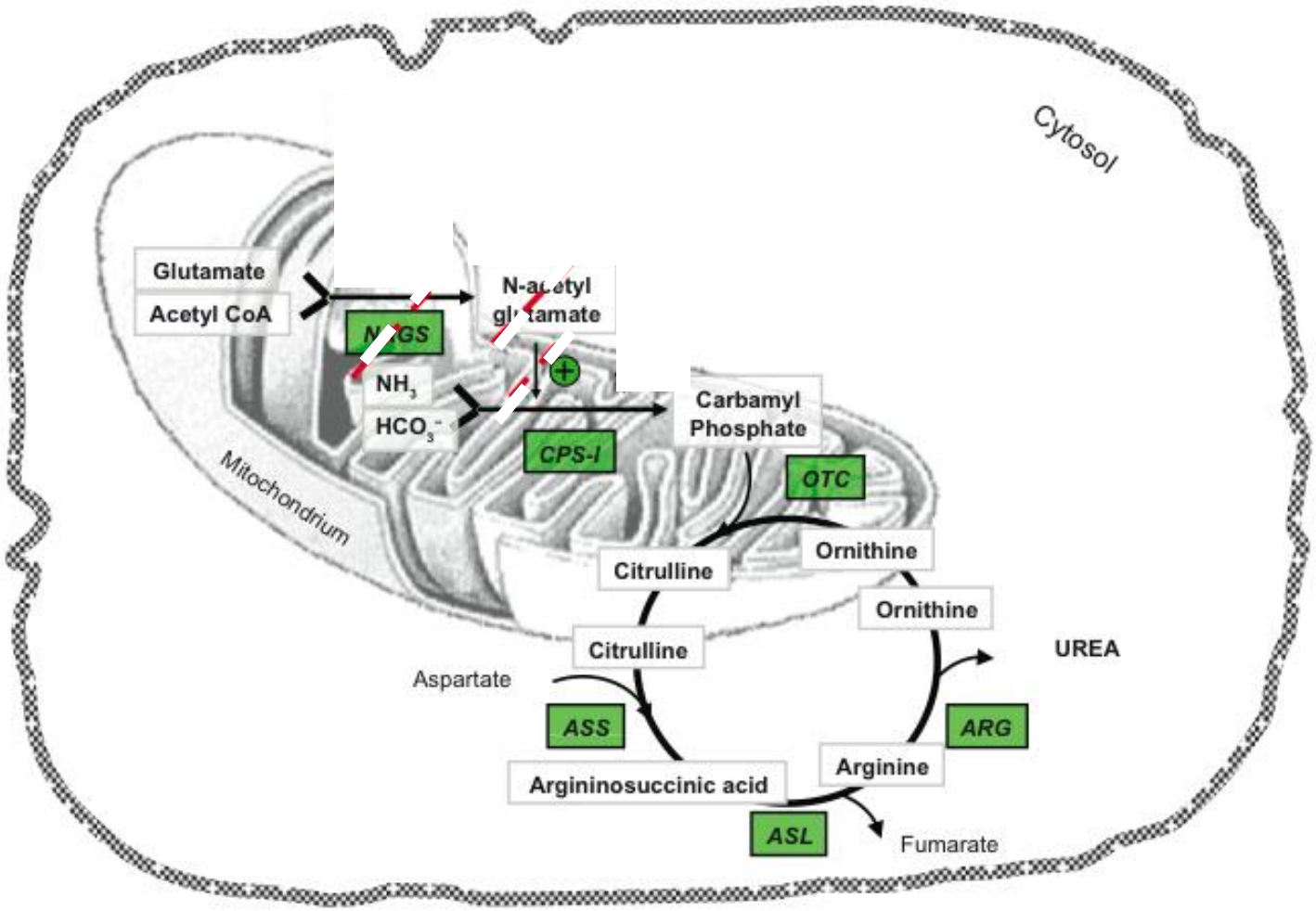


Figure 1 Schematic representation of the urea cycle and related pathways.
Abbreviations: ASS, argininosuccinate synthase; ASL, argininosuccinate lyase; ARG, arginase; CPS-I, carbamoyl-phosphate synthase I; MMA, methylmalonic acidemia; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PA, propionic acidemia.

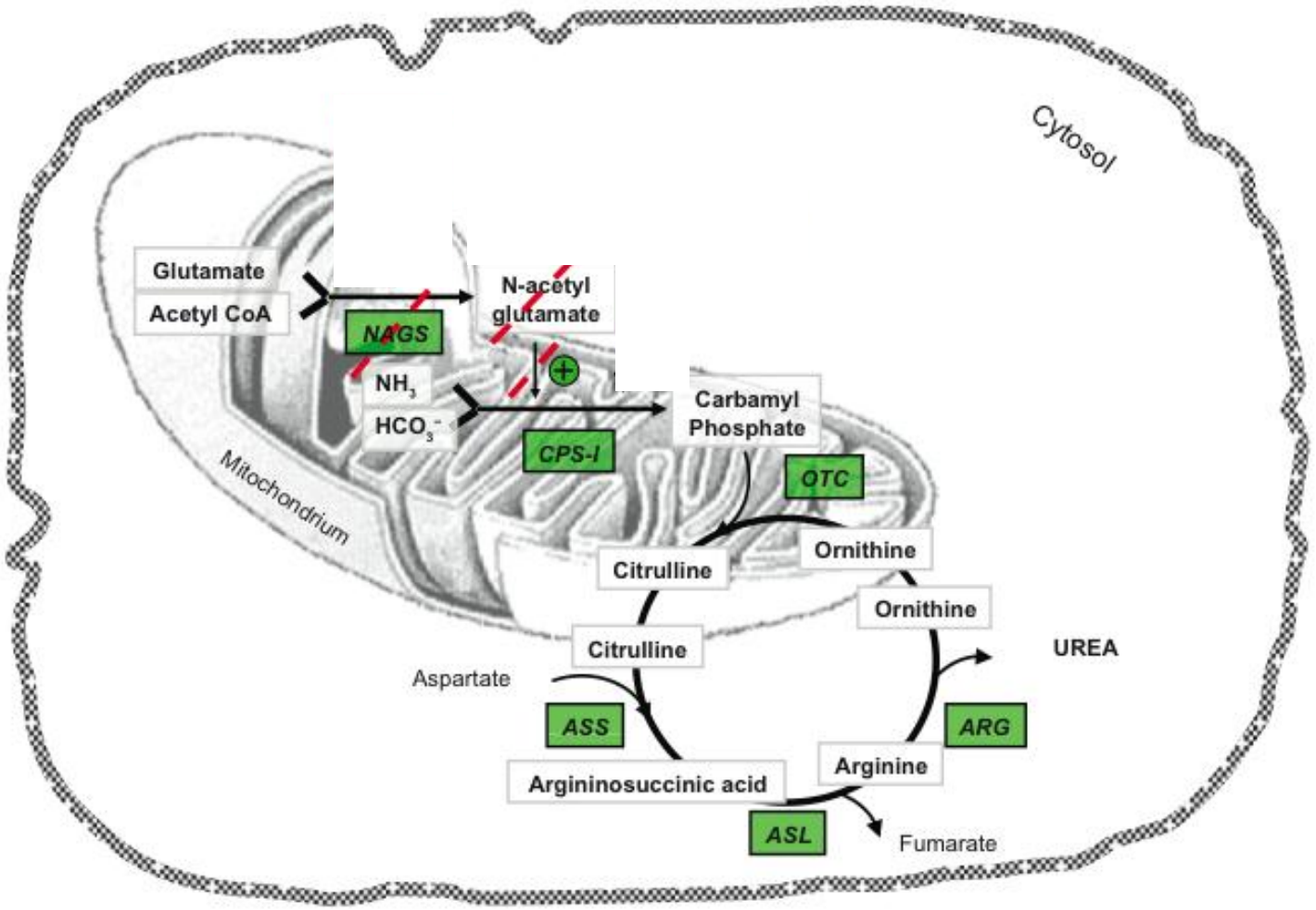


Figure 1 Schematic representation of the urea cycle and related pathways.
Abbreviations: ASS, argininosuccinate synthase; ASL, argininosuccinate lyase; ARG, arginase; CPS-I, carbamoyl-phosphate synthase I; MMA, methylmalonic acidemia; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PA, propionic acidemia.

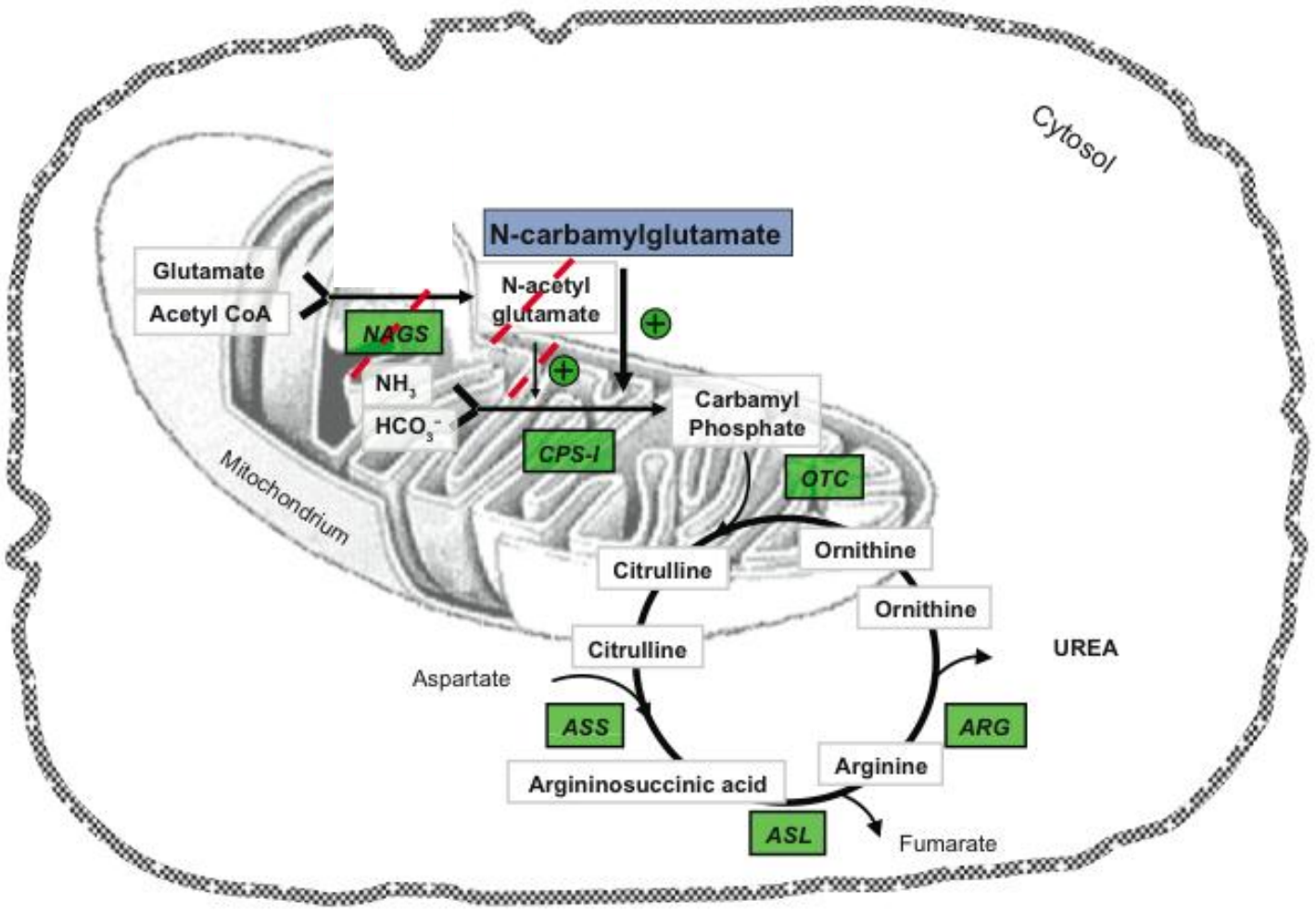


Figure 1 Schematic representation of the urea cycle and related pathways.

Abbreviations: ASS, argininosuccinate synthase; ASL, argininosuccinate lyase; ARG, arginase; CPS-I, carbamoyl-phosphate synthase I; MMA, methylmalonic acidemia; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PA, propionic acidemia.

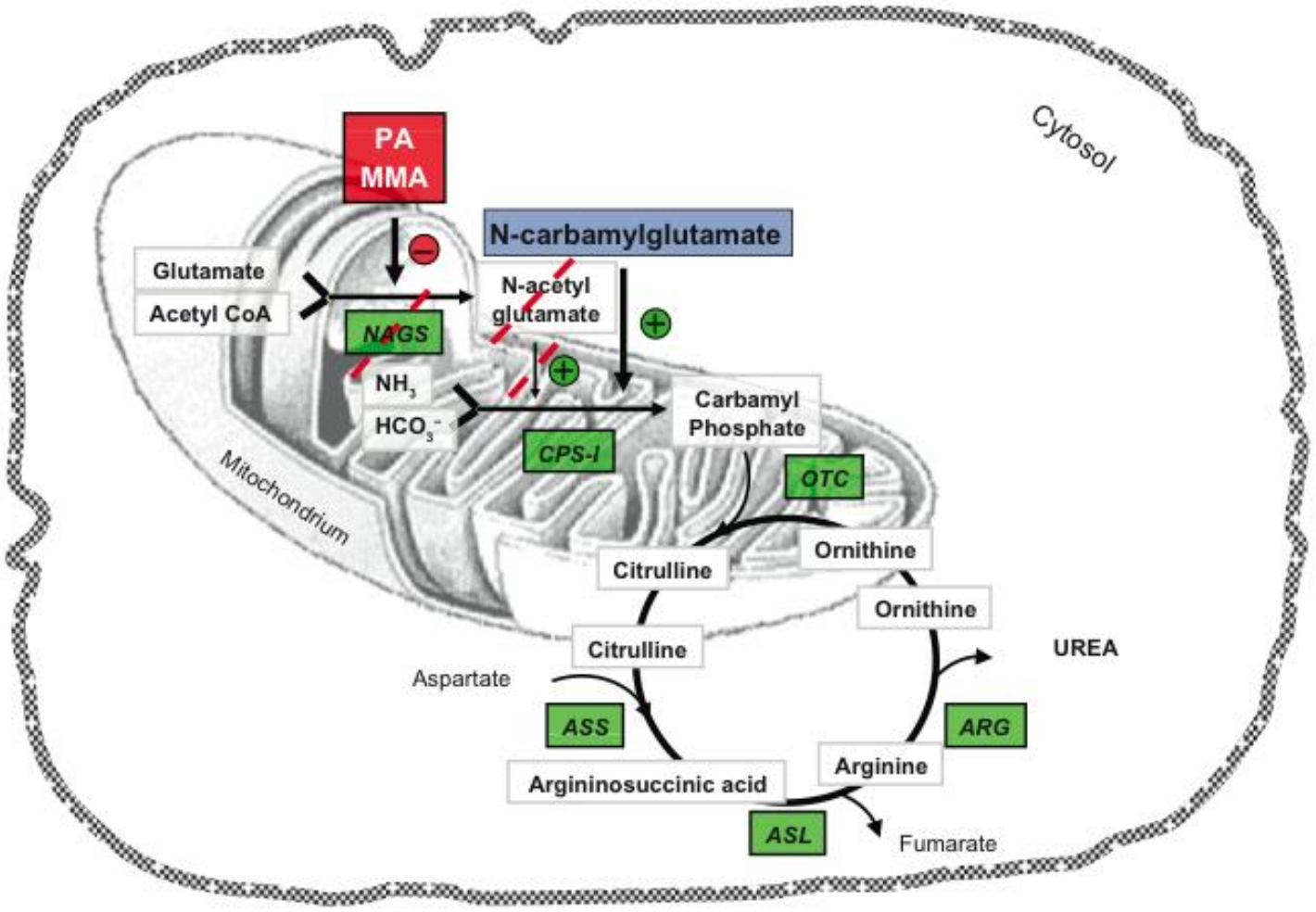


Figure 1 Schematic representation of the urea cycle and related pathways.

Abbreviations: ASS, argininosuccinate synthase; ASL, argininosuccinate lyase; ARG, arginase; CPS-I, carbamoyl-phosphate synthase I; MMA, methylmalonic acidemia; NAGS, N-acetylglutamate synthase; OTC, ornithine transcarbamylase; PA, propionic acidemia.

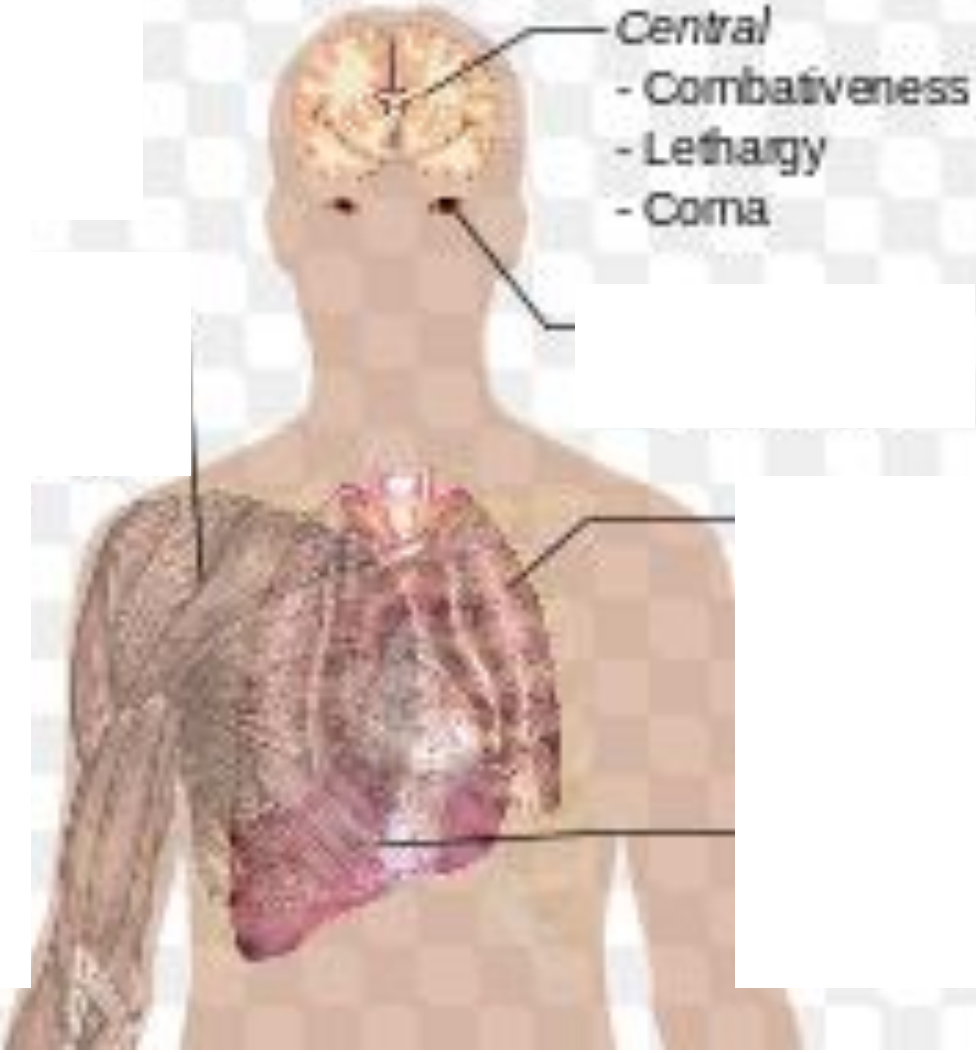
Background

- What happens if blood ammonia is high?
  - High ammonia is bad for the brain
  - Very high ammonia levels (levels in the thousands) can cause irreversible brain damage

Ammonia

Symptoms of

Hyperammonemia



Background

- How can blood ammonia be lowered?
  - Calories (sugar and fat) to prevent protein breakdown for energy
  - Sodium benzoate and phenylacetate to help the body excrete waste nitrogen
  - Arginine (for some disorders)
  - N-carbamylglutamate (for some disorders)

Jones 2008 JIMD Infant with PA given NCG to Decrease Ammonia

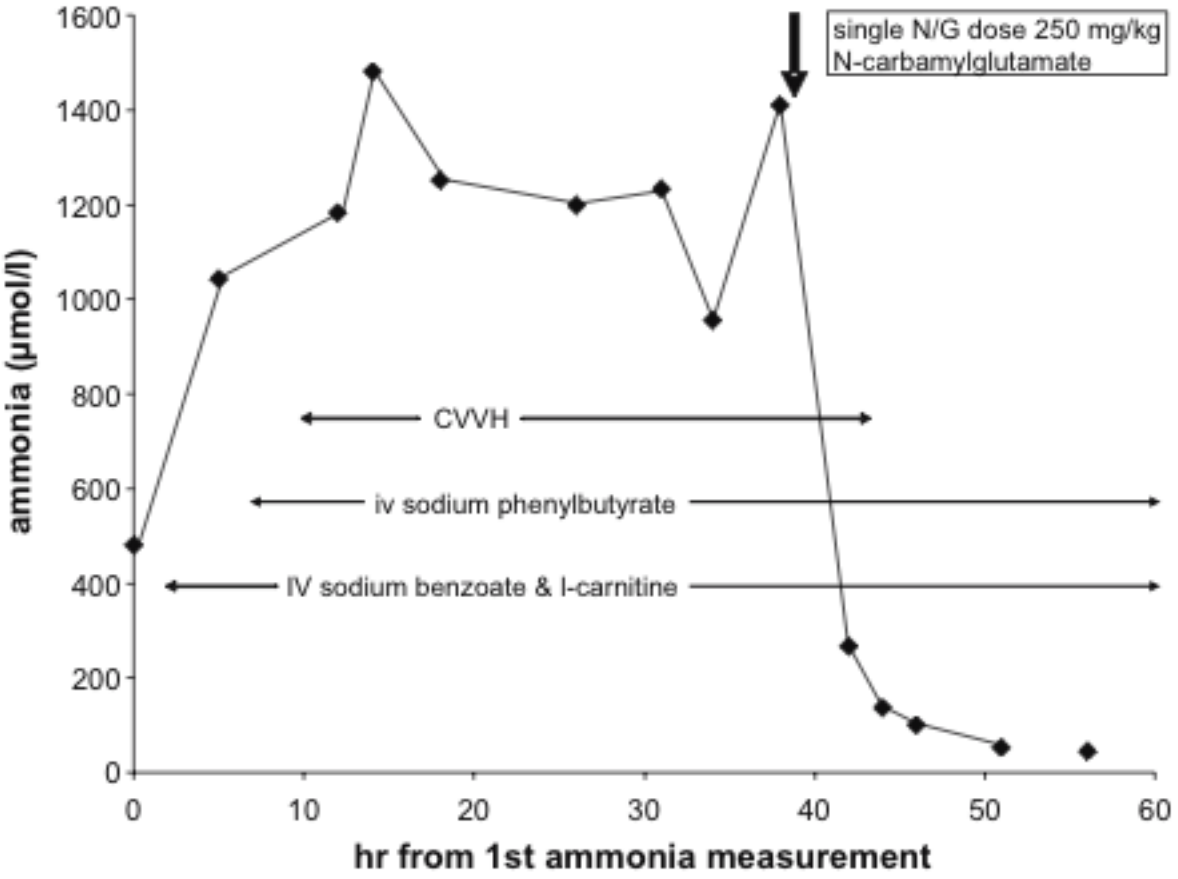


Fig. 1 Serial plasma ammonia measurements in patient 1

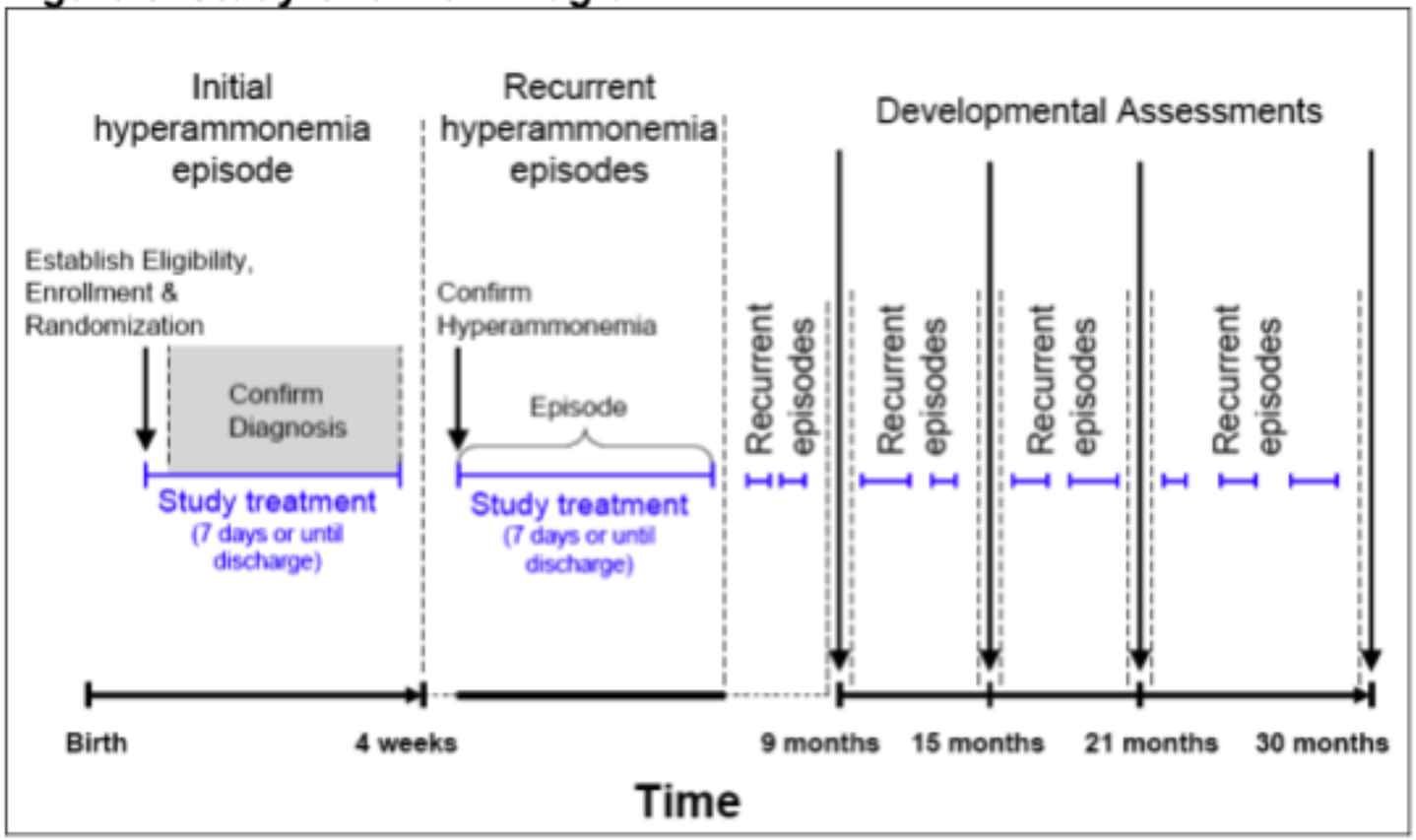
The Trials

- Two protocols
  - Long-term
    - Infants
    - Ammonia greater than 200 umol/L
    - Get standard therapy and NCG or placebo for 7 days, assigned randomly, blinded
    - Next admission, if ammonia greater than 100 umol/L get the same therapy for 7 days
    - Regular neurodevelopmental evaluations

3.1 Overview of Study Design

The study will be a double-blinded, placebo controlled, randomized clinical trial to evaluate the efficacy of NCG in the treatment of two organic acidemias (severe PA and MMA). Figure 3 summarizes the design of the proposed trial.

Figure 3. Study Overview Diagram



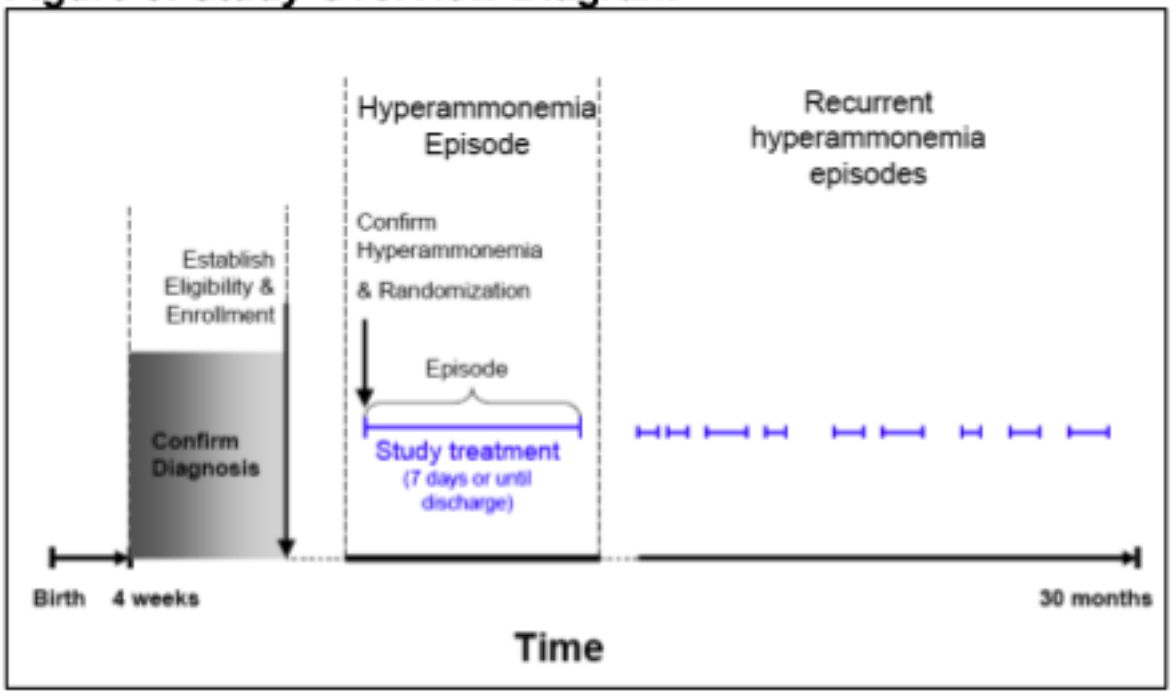
The Trials

- Two protocols
  - Short-term
    - Greater than 4 weeks
    - Ammonia greater than 100 umol/L
    - Get standard therapy and NCG or placebo for 7 days, assigned randomly, blinded
    - Next admission get NCG or placebo for 7 days, assigned randomly, blinded
    - Ammonia followed in the admission

3.1 Overview of Study Design

This will be a double-blinded, placebo controlled randomized clinical trial to evaluate the efficacy of NCG in the treatment of two organic acidemias (severe PA and MMA), and two urea-cycle disorders (late-onset CPSD and OTCD). Figure 3 summarizes the design of the proposed trial.

Figure 3. Study Overview Diagram



The Goals

- To determine if the use of NCG is associated with a difference in neurodevelopmental outcome
- To determine if the use of NCG has an effect on ammonia values
- To get approval of NCG for use in PA if it is safe and effective

Summary of NCGC Project

- N-carbamylglutamate in the treatment of hyperammonemia
- Investigator initiated efficacy/safety Phase II trial
- Blinded placebo controlled intervention for acute metabolic crisis
- Data to be used for new drug application to FDA
- Design and research plan model for other drugs/disorders

How to Participate

- If you are near a participating site contact that site

- If you have questions contact me, or the lead site Principal Investigators, Nicholas Ah Mew, and Mendel Tuchman, go to Clinicaltrials.gov

Thank you!

- Thanks to:
  - Curtis Coughlin, MBE, Assistant Professor, Clinical Genetics and Metabolism, Colorado Site Study Coordinator
  - Janet Thomas, MD, Associate Professor, Clinical Genetics and Metabolism, Co-Investigator