Amino Acid Disorders 1: Urea Cycle Disorders & Maple Syrup Urine Disease

Medical Biochemical Genetics

Clinical Core Seminar Series

Nicholas Ah Mew, MD

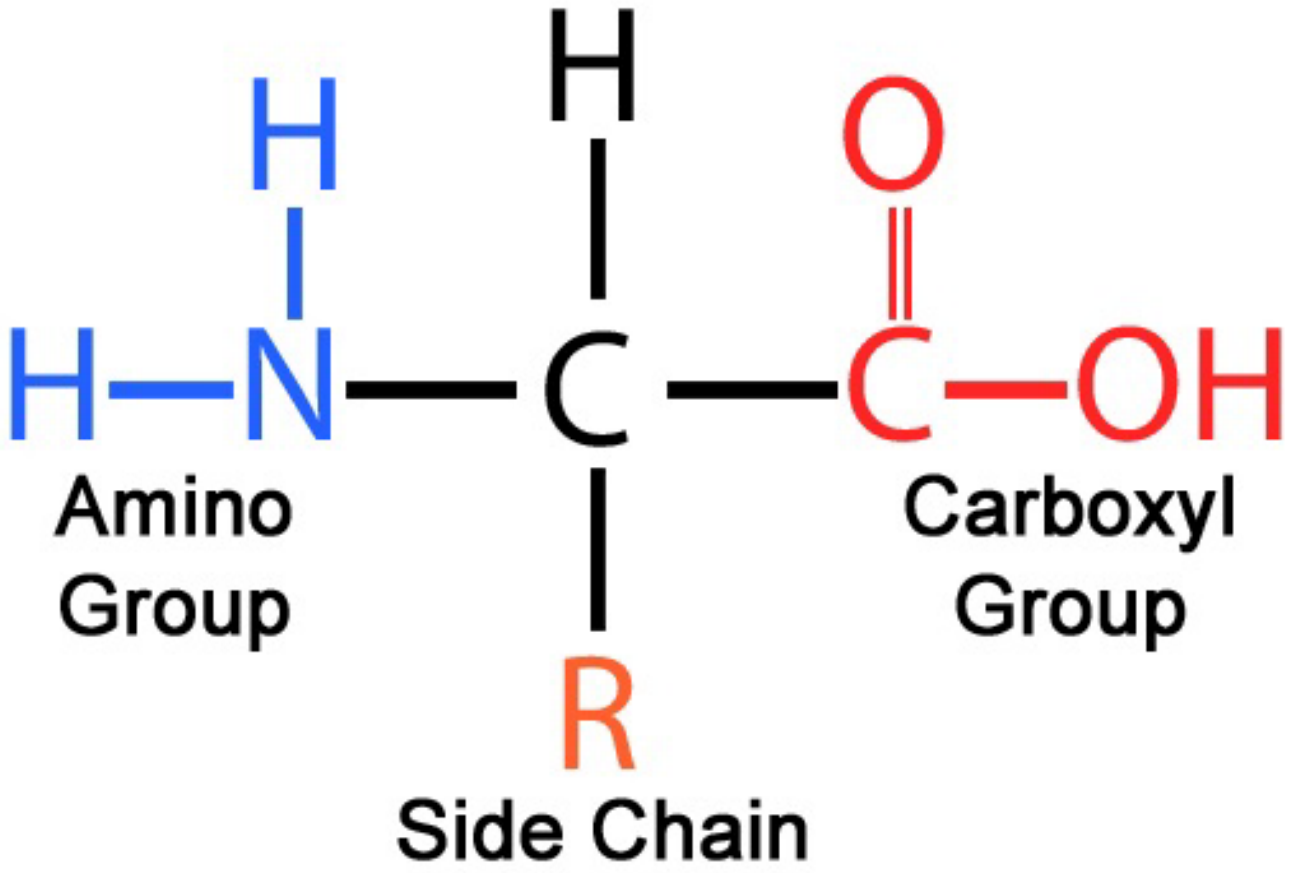
July 29, 2022

Children's National

Disclosures

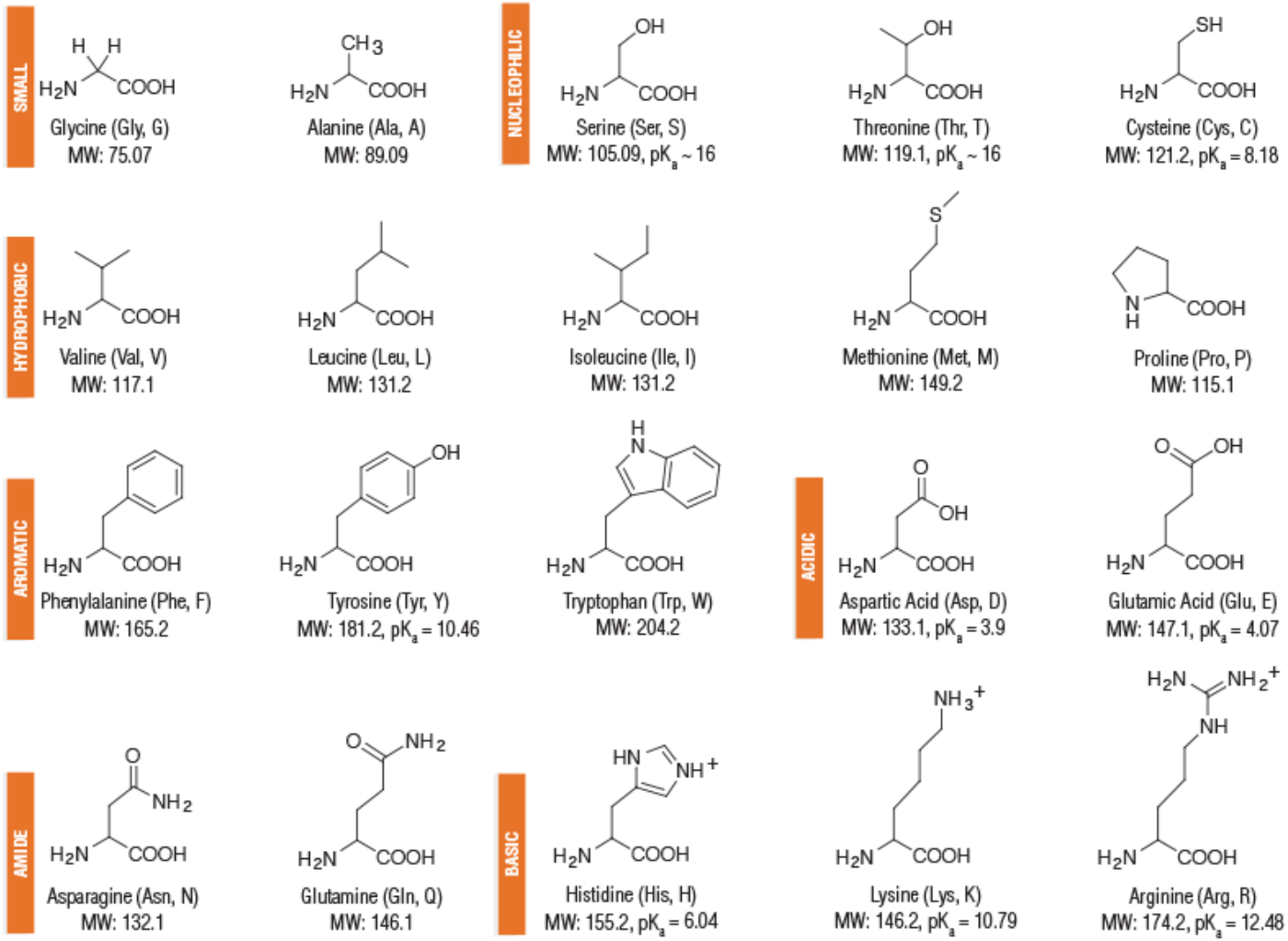
- Clinical trial/study support from Recordati Rare Diseases and Aeglea Biotherapeutics

Basic amino acid structure

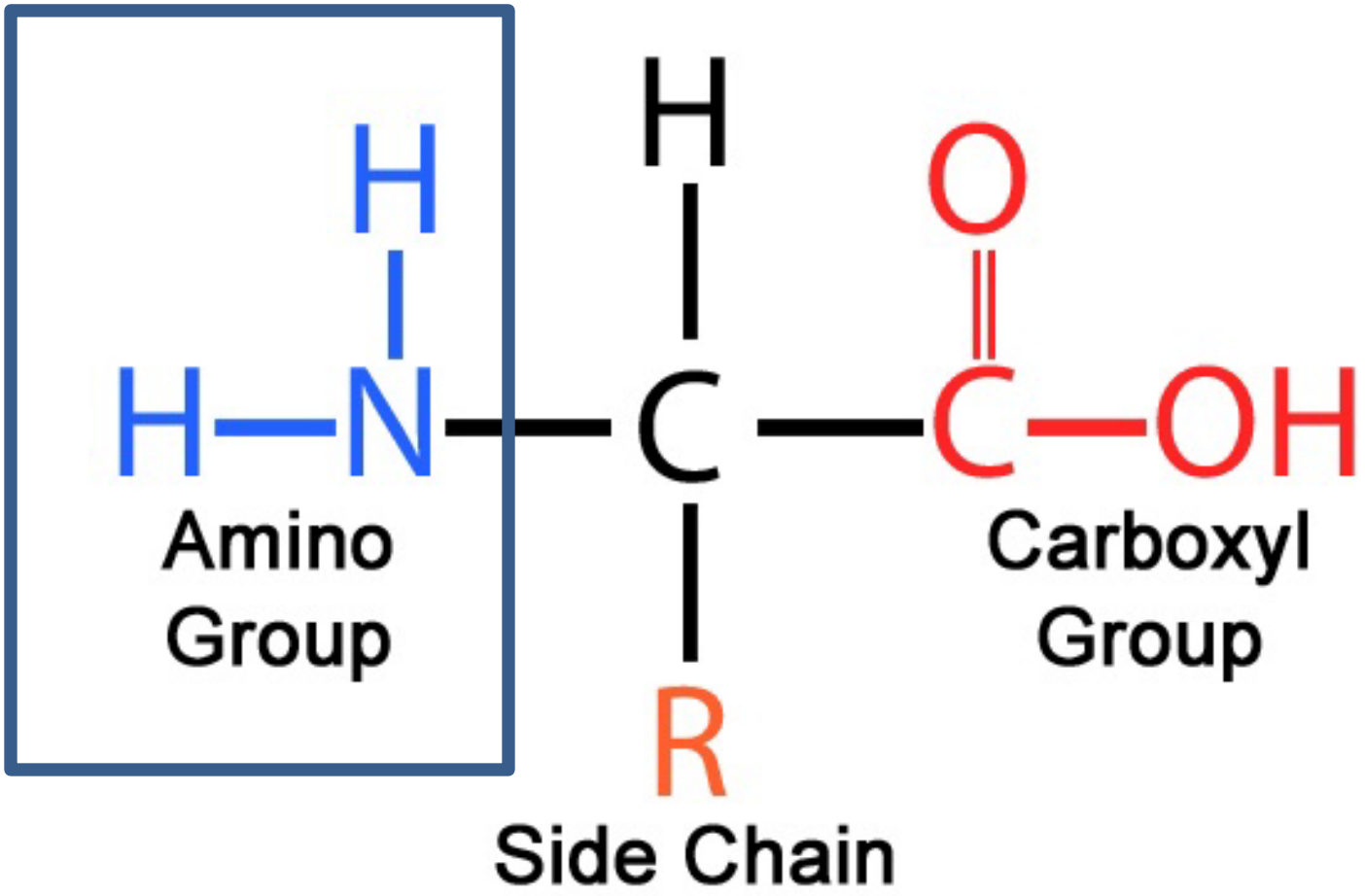


http://www.astrochem.org/sci/Amino_Acids.php

Protein amino acids



Amino acid fates



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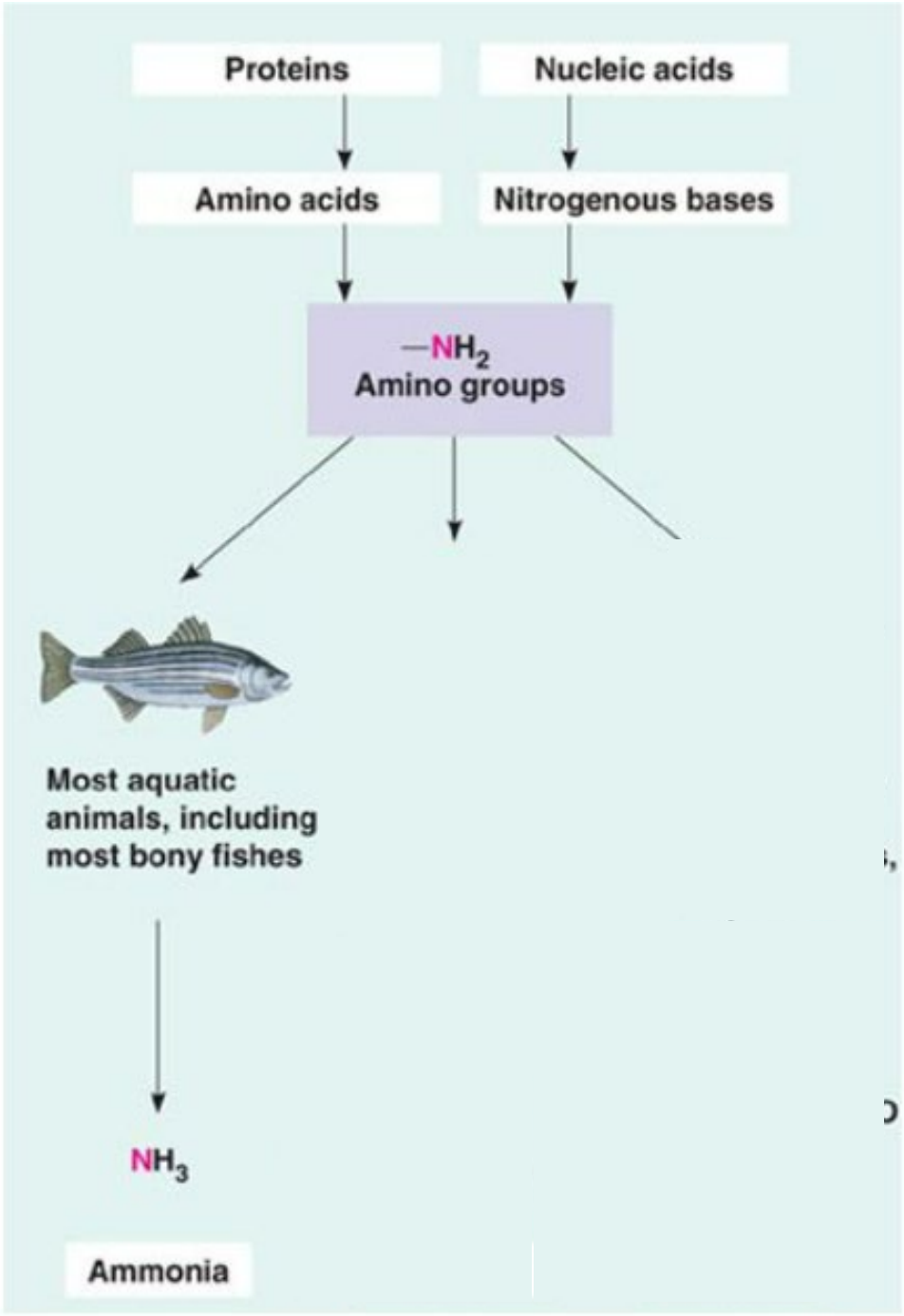

Proteins
Nucleic acids
Amino acids
Nitrogenous bases
—NH2
Amino groups
Most aquatic animals, including most bony fishes
NH3
Ammonia

Early “Ornithine” Cycle - 1931

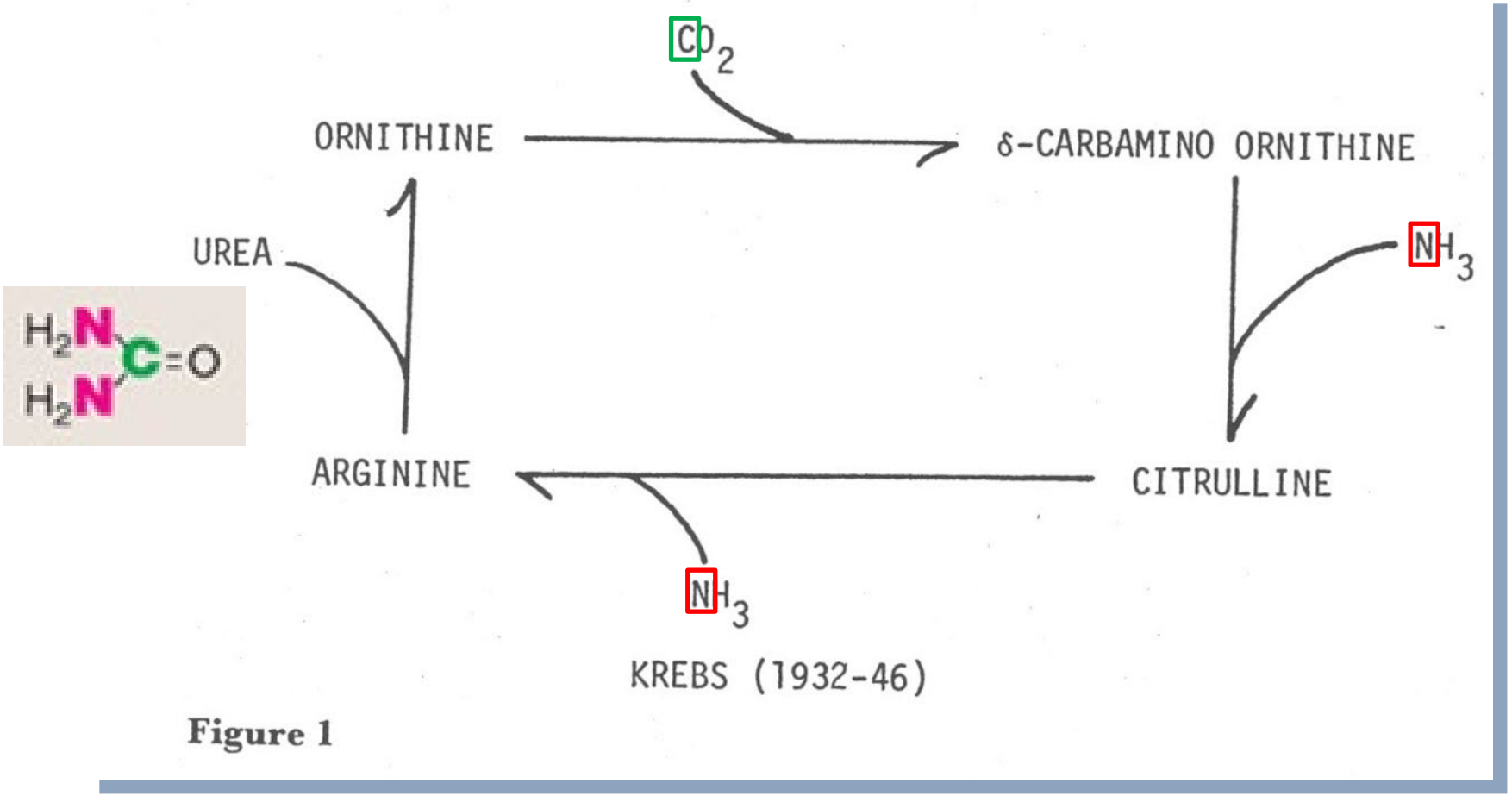


Figure 1

The Urea cycle – 1976 Eds Grisolia, Baguena, Mayor

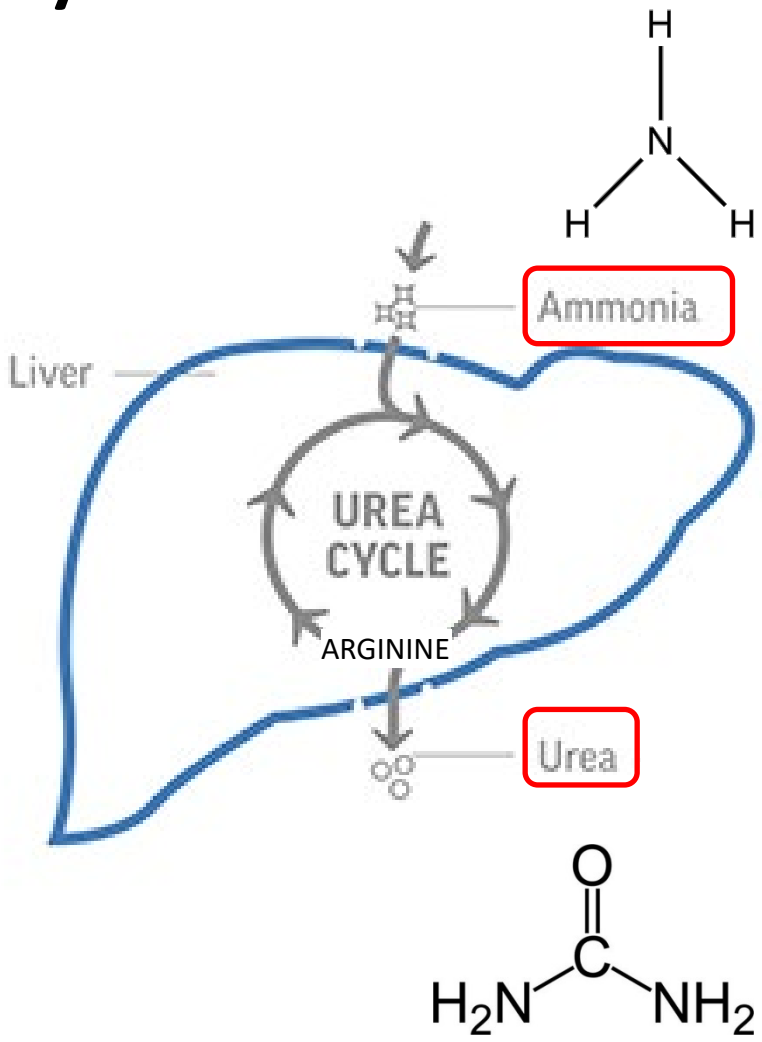
The urea cycle

- Has two roles:

  1) Convert ammonia into urea

  2) Make arginine

     (an amino acid)

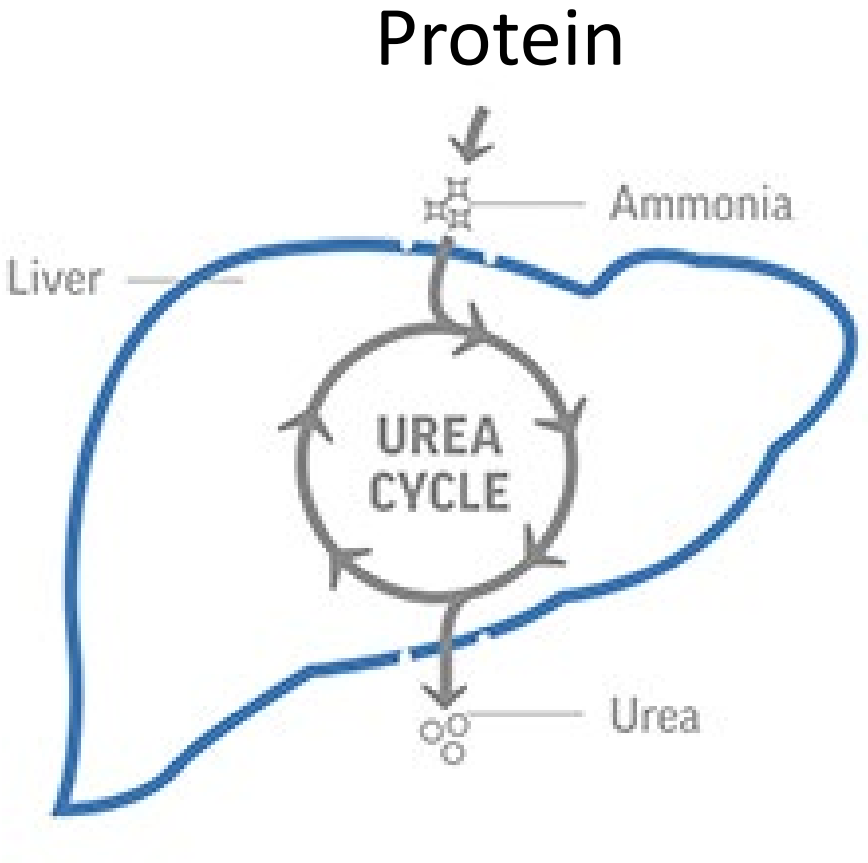


http://www.horizonpharma.com/wp-content/uploads/2015/04/UCD2.png

The urea cycle

- Ammonia (NH_3) is a form of waste nitrogen which comes protein degradation

- The urea cycle requires the coordinated function of 6 ENZYMES and 2 transporters



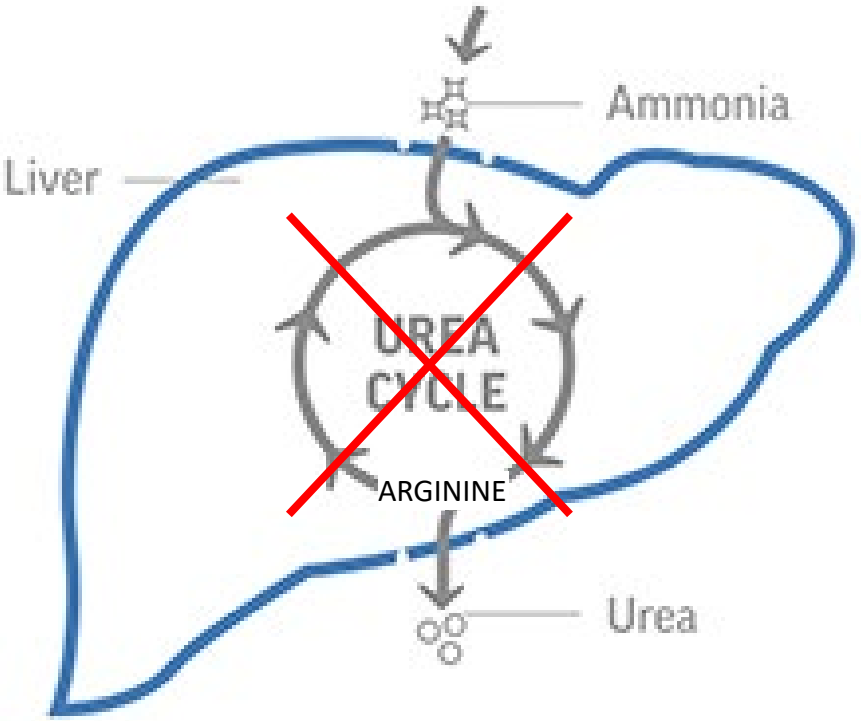
http://www.horizonpharma.com/wp-content/uploads/2015/04/UCD2.png

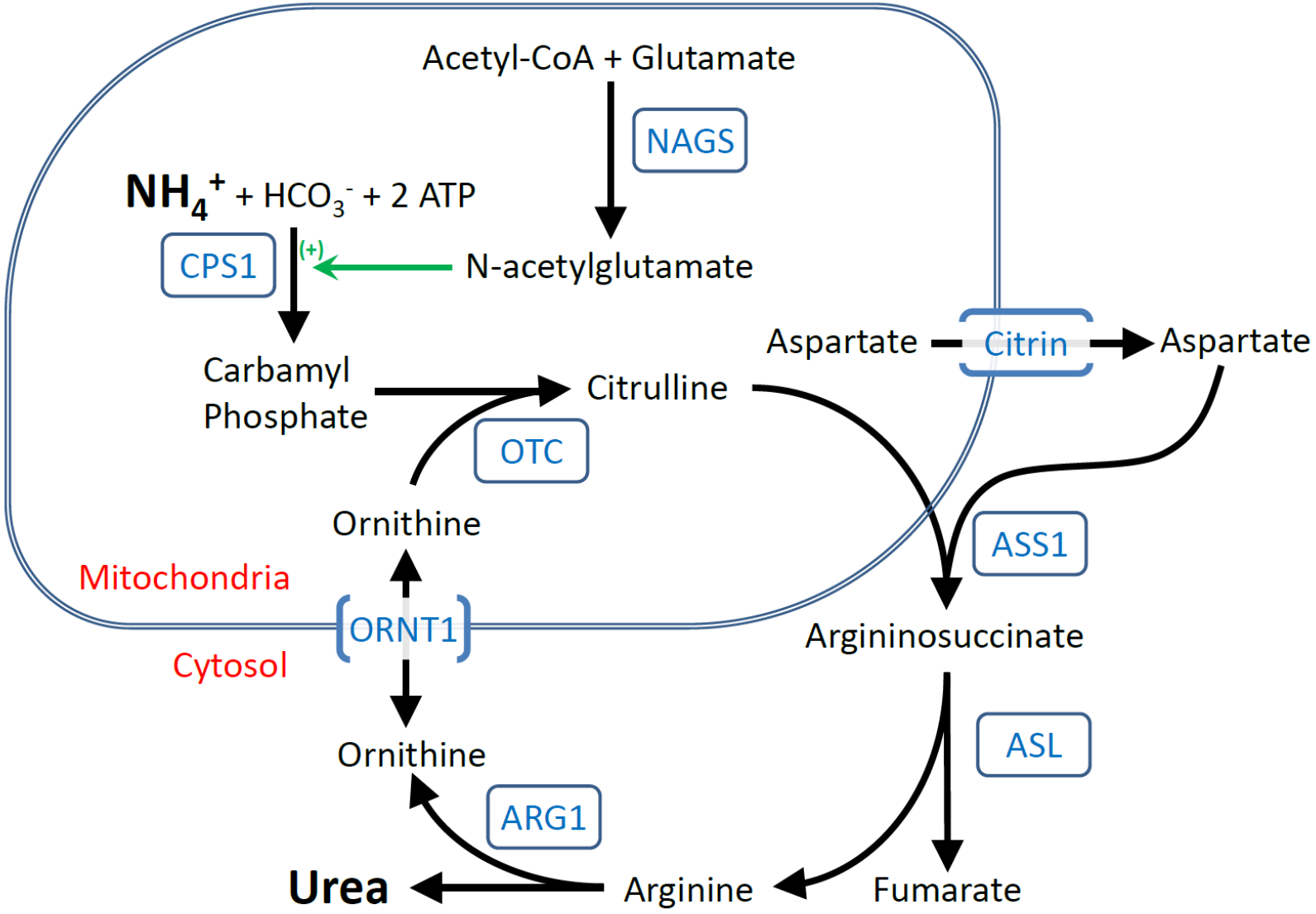
Urea cycle disorders

- A defect in one of these transporters or enzymes or may block urea cycle function

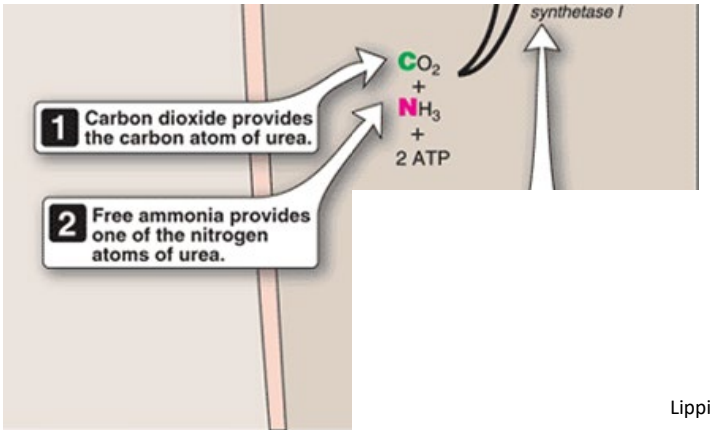
- This can result in

1) Build up of ammonia
2) Decreased arginine production



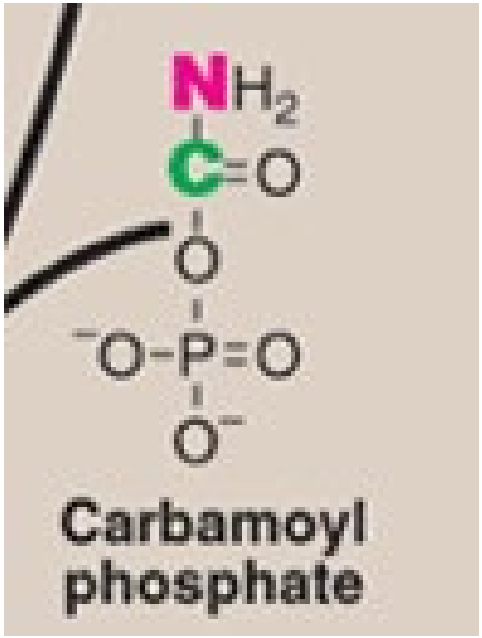

Acetyl-CoA + Glutamate
NAGS
NH_4^+ + HCO_3^- + 2 ATP
CPS1
(+)
N-acetylglutamate
Aspartate
Citrin
Aspartate
Carbamyl Phosphate
Citrulline
OTC
Ornithine
ASS1
Mitochondria
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

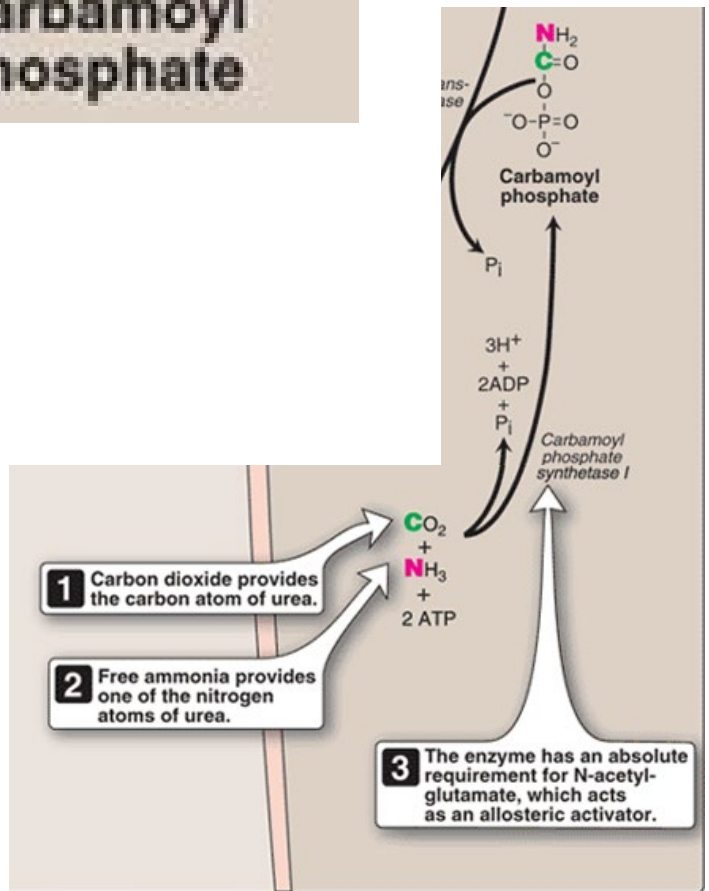
$CO_2 + NH_3 + 2ATP$

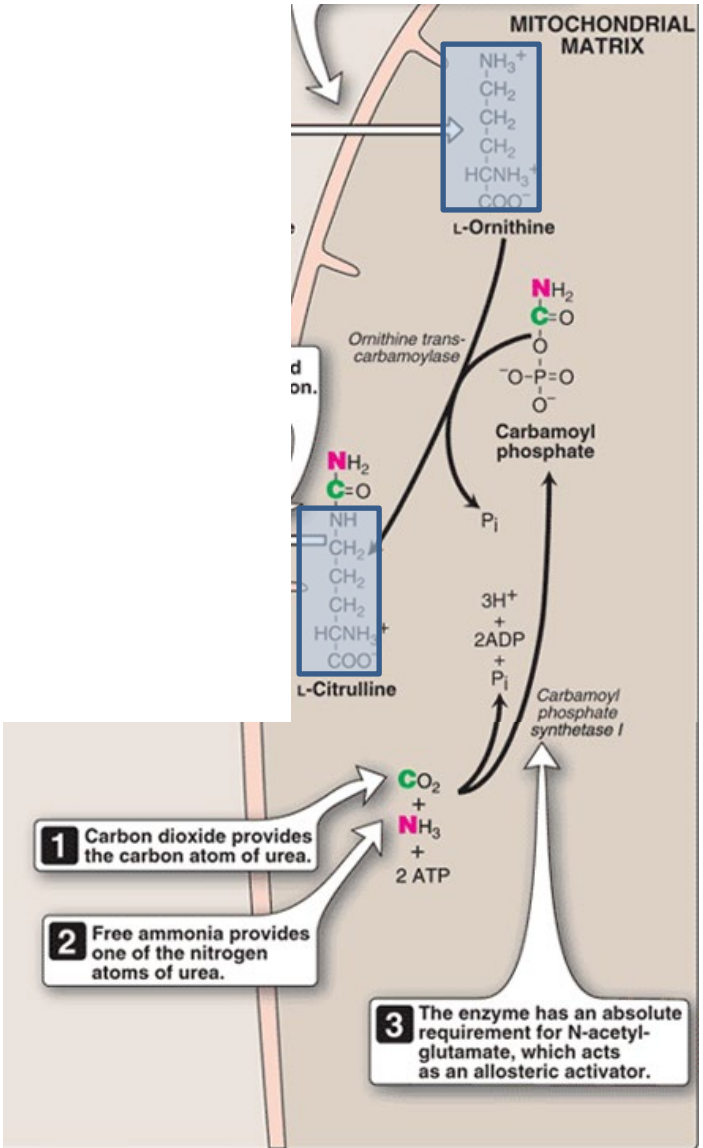


Lippincott, Biochemistry 7th ed, Chapter 19

$CO_2 + NH_3 + 2ATP =$


Carbamoyl phosphate


Carbamoyl phosphate
Pi
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
CO2 + NH3 + 2 ATP
1 Carbon dioxide provides the carbon atom of urea.
2 Free ammonia provides one of the nitrogen atoms of urea.
3 The enzyme has an absolute requirement for N-acetyl-glutamate, which acts as an allosteric activator.


MITOCHONDRIAL MATRIX
L-Ornithine
Ornithine trans-carbamoylase
Carbamoyl phosphate
Pi
L-Citrulline
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
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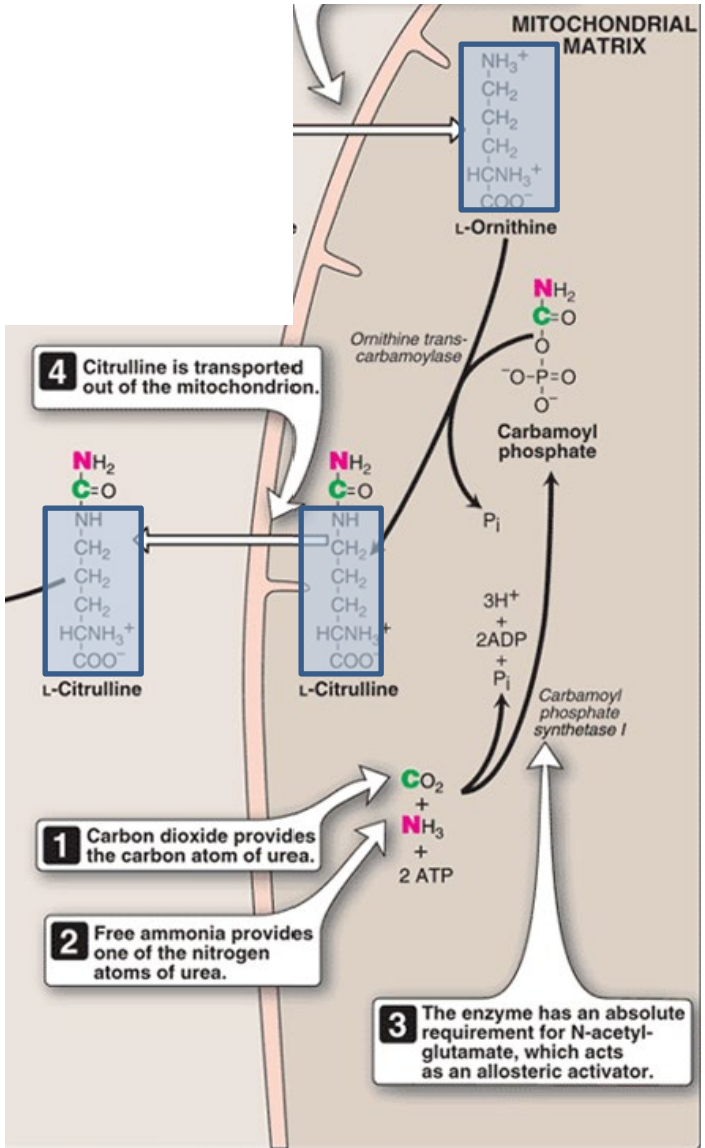
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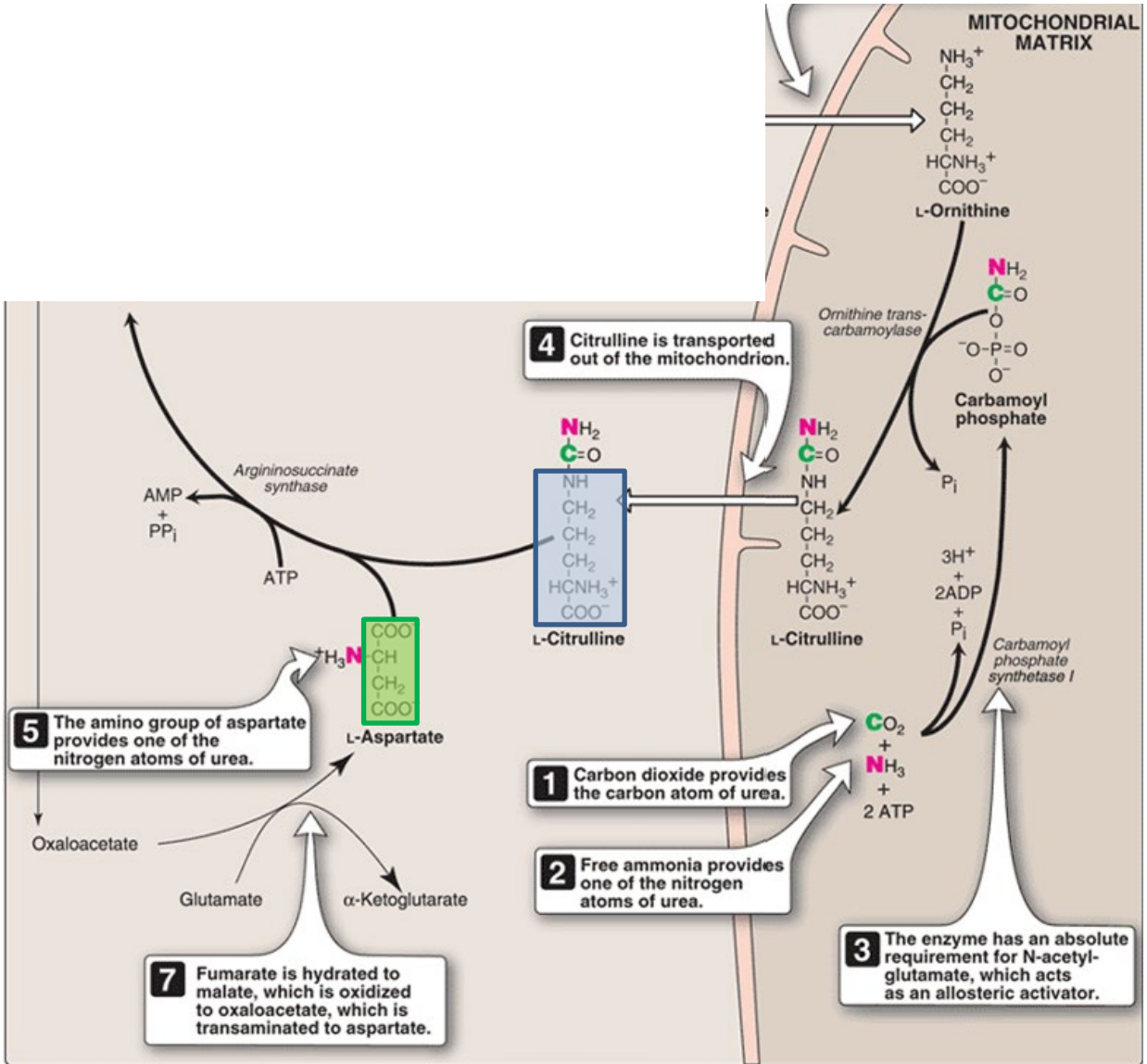
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Argininosuccinate synthase
AMP + PPi
ATP
3H+ + 2ADP + Pi
Carbamoyl phosphate synthetase I
L-Aspartate
5 The amino group of aspartate provides one of the nitrogen atoms of urea.
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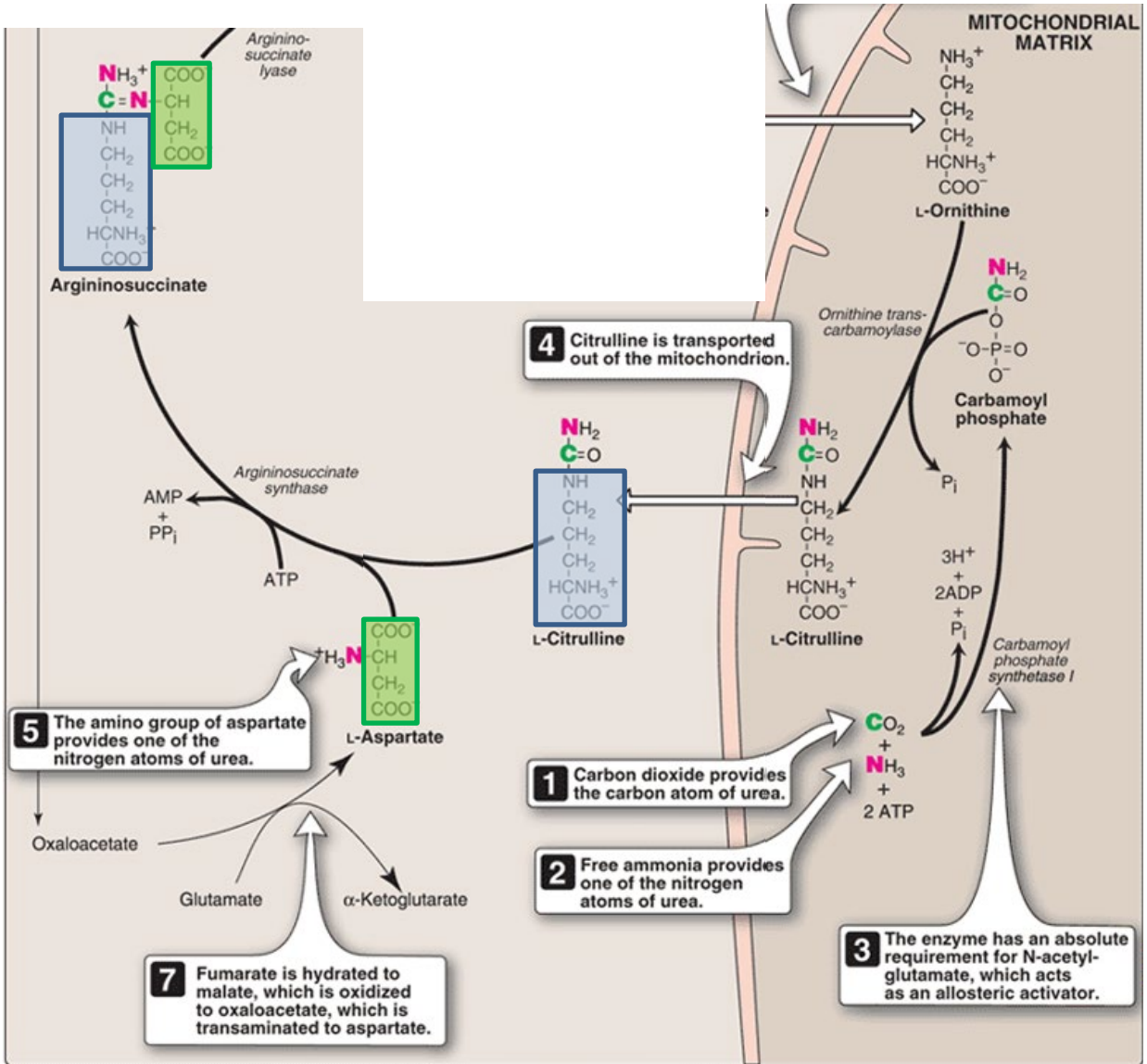
Oxaloacetate
Glutamate
α-Ketoglutarate
7 Fumarate is hydrated to malate, which is oxidized to oxaloacetate, which is transaminated to aspartate.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Argininosuccinate
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Ornithine trans-carbamoylase
Carbamoyl phosphate
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ATP
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L-Citrulline
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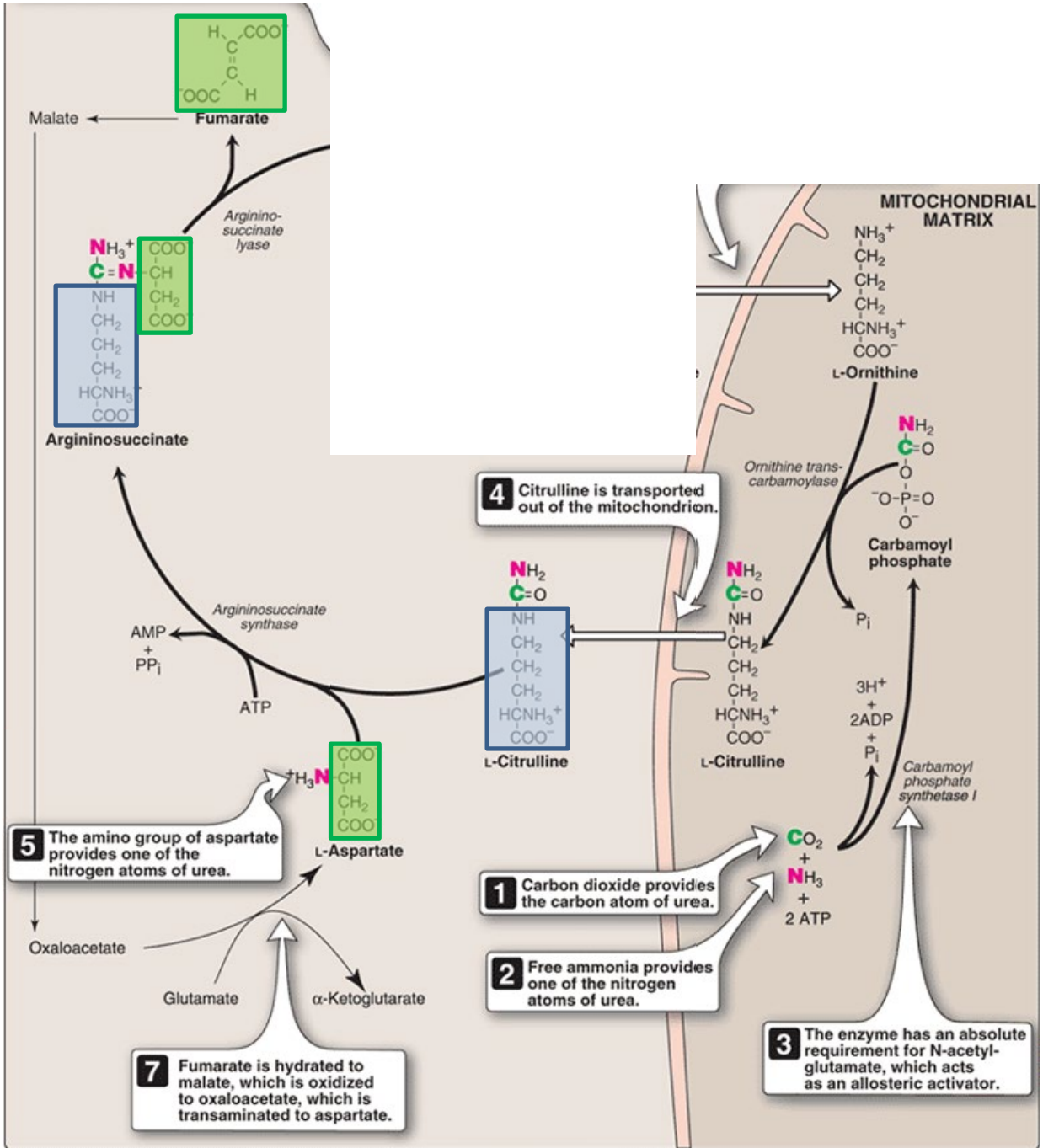
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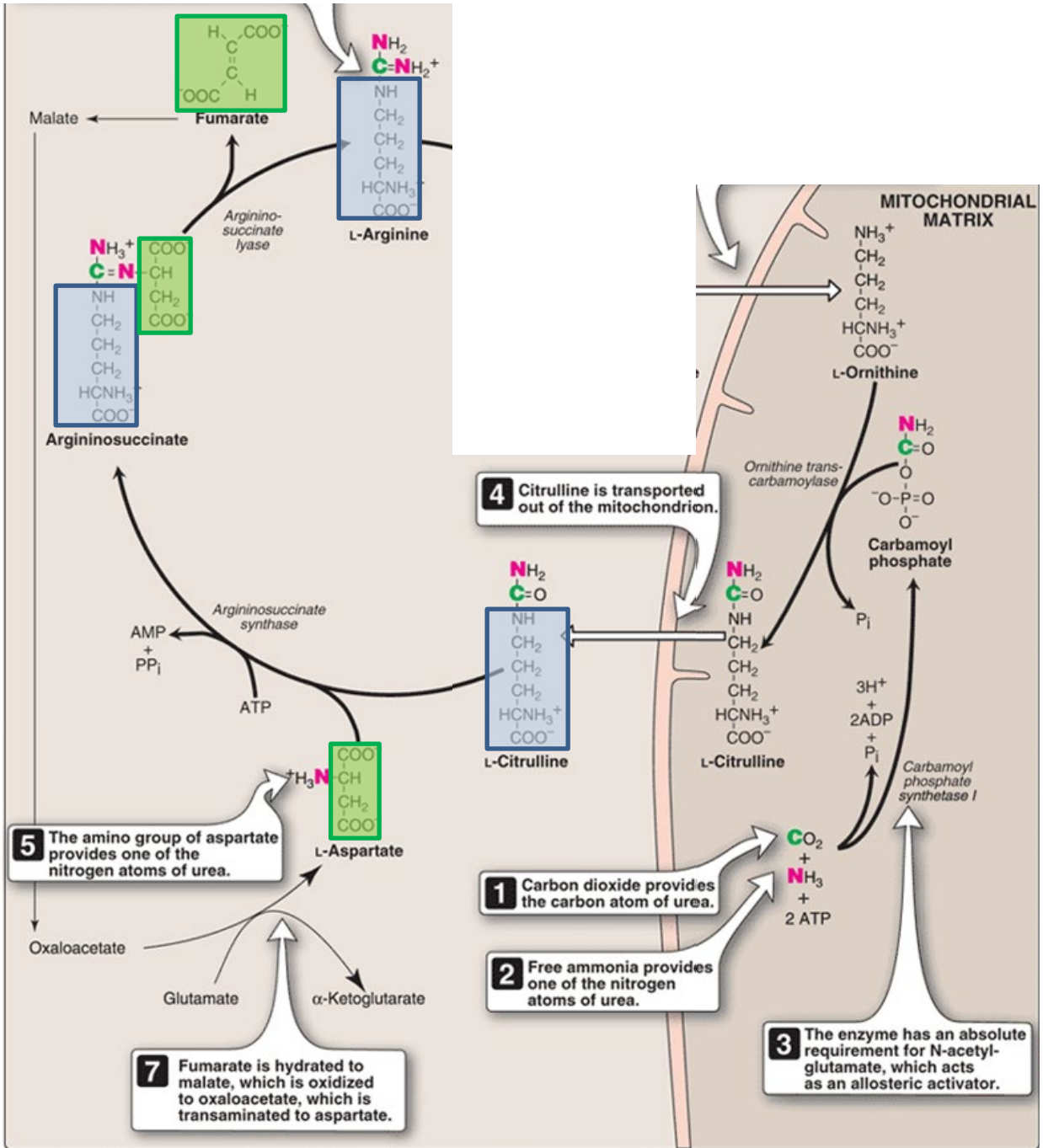
MITOCHONDRIAL MATRIX
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Malate
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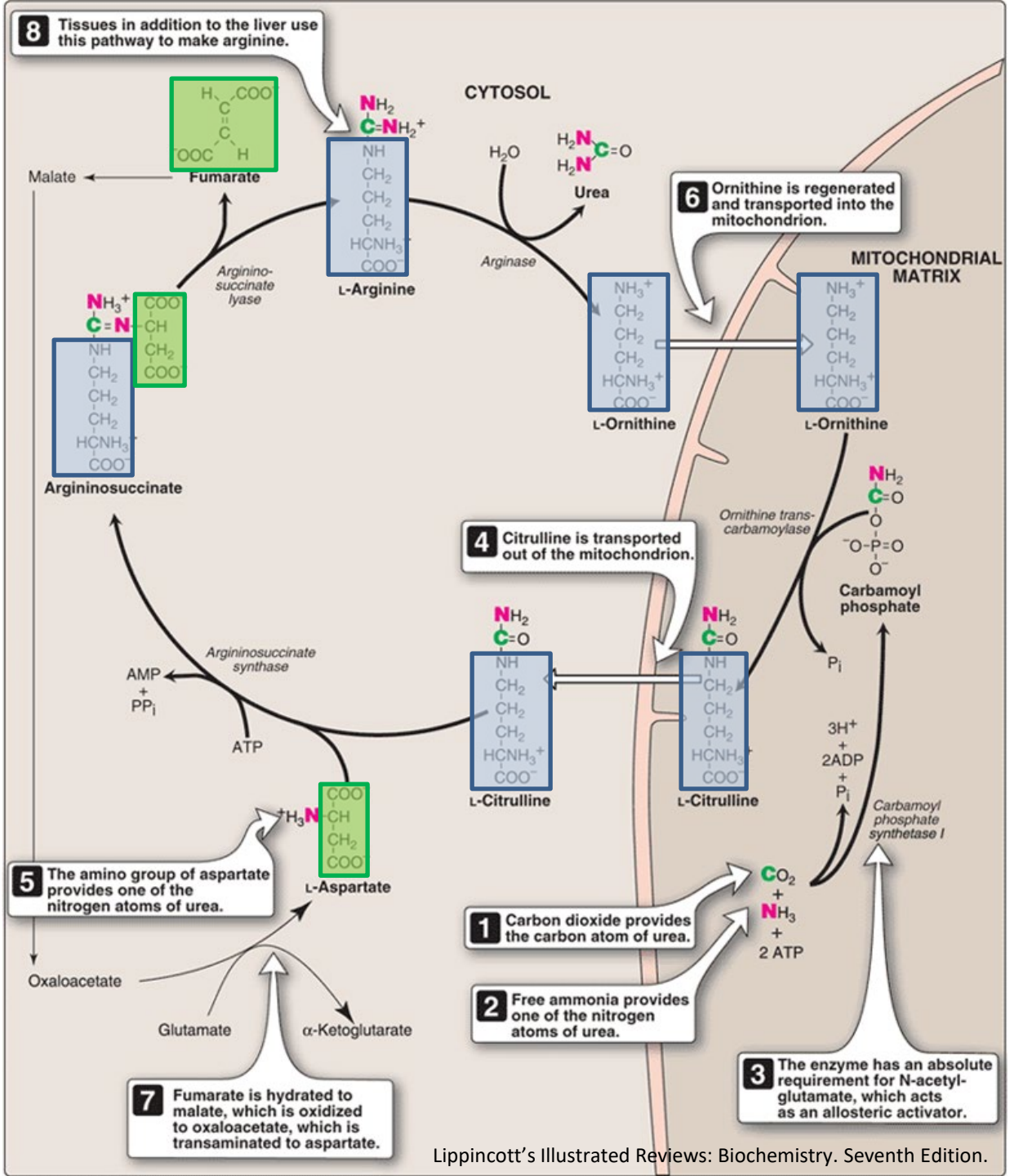
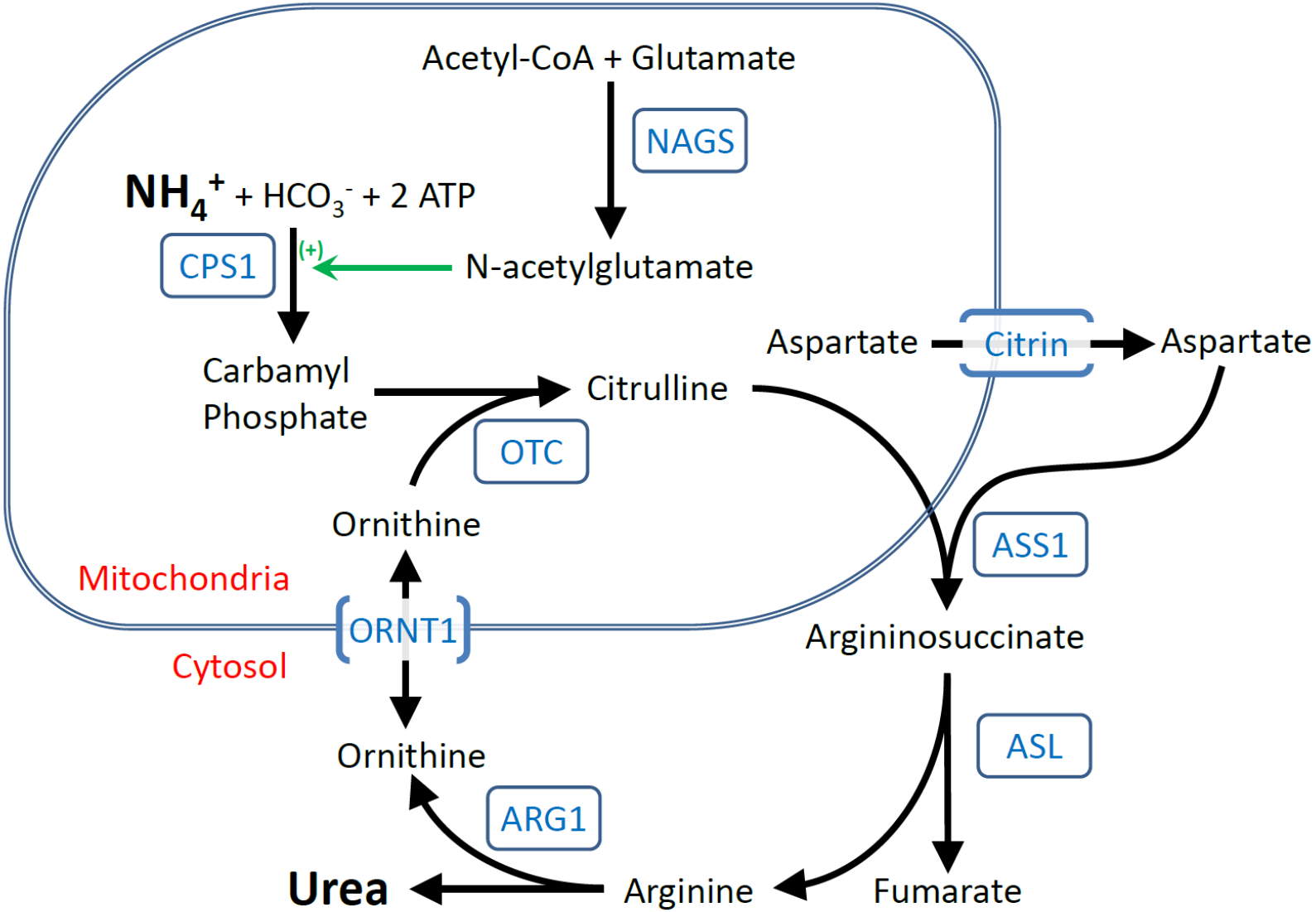


Lippincott's Illustrated Reviews: Biochemistry. Seventh Edition.

The hepatic urea cycle



Enzyme	Chromosomal location	Cellular location	Tissue expression
N-acetylglutamate synthetase E.C. 2.3.1.1; MIM 608300	17q21.31	Mitochondrial matrix	**Liver,** intestine, kidney (trace), spleen
Carbamyl phosphate synthetase 1 EC 6.3.4.16; MIM 608307	2q34	Mitochondrial matrix	**Liver,** intestine, kidney (trace)
Ornithine transcarbamylase E.C. 2.1.3.3; MIM 300461	Xp11.4	Mitochondrial matrix	**Liver,** intestine, kidney (trace)
Argininosuccinate synthetase 1 EC 6.3.4.5; MIM 603470	9q34.11	Cytosol	**Liver,** kidney, fibroblasts, brain (trace)
Argininosuccinate lyase EC 4.3.2.1; MIM 608310	7q11.21	Cytosol	**Liver,** kidney, fibroblasts, brain
Arginase 1 EC 3.5.3.1; MIM 608313	6q23.2	Cytosol	**Liver,** erythrocytes, kidney, lens, brain (trace)
Citrin (SLC25A13) MIM 603859	7q21.3	Inner mitochondrial membrane	**Liver,** kidney, heart
Ornithine transporter (SLC25A15) MIM 603861	13q14.11	Inner mitochondrial membrane	**Liver,** pancreas, intestine

Enzyme	Chromosomal location	Cellular location	Tissue expression
N-acetylglutamate synthetase E.C. 2.3.1.1; MIM 608300	17q21.31	Mitochondrial matrix	**Liver, intestine**, kidney (trace), spleen
Carbamyl phosphate synthetase 1 EC 6.3.4.16; MIM 608307	2q34	Mitochondrial matrix	**Liver, intestine**, kidney (trace)
Ornithine transcarbamylase E.C. 2.1.3.3; MIM 300461	Xp11.4	Mitochondrial matrix	**Liver, intestine**, kidney (trace)
Argininosuccinate synthetase 1 EC 6.3.4.5; MIM 603470	9q34.11	Cytosol	**Liver, kidney**, fibroblasts, brain (trace)
Argininosuccinate lyase EC 4.3.2.1; MIM 608310	7q11.21	Cytosol	**Liver, kidney**, fibroblasts, brain
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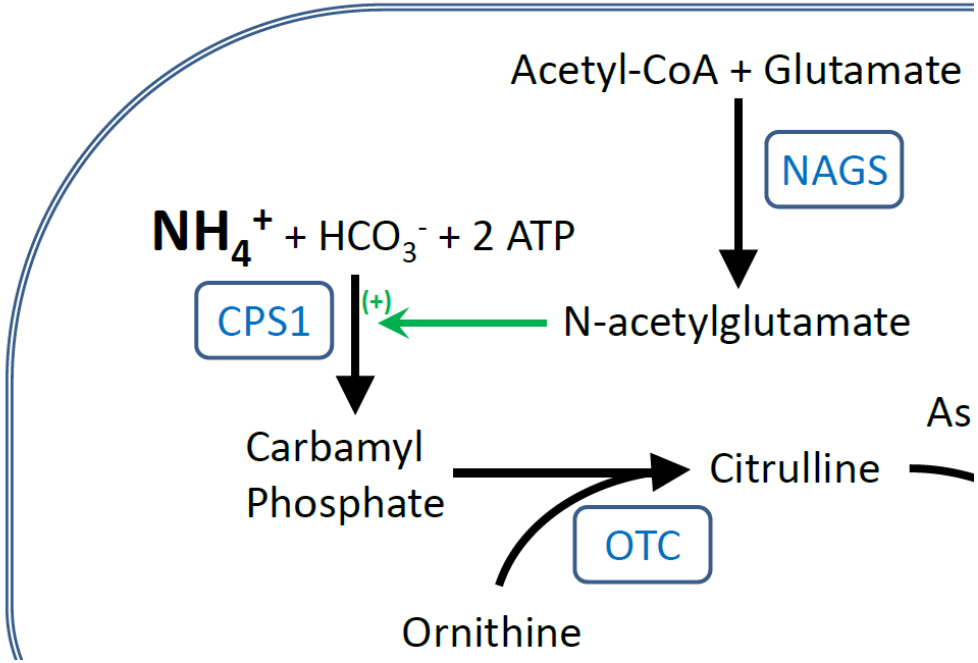
Ornithine transporter (SLC25A15) MIM 603861	13q14.11	Inner mitochondrial membrane	**Liver,** pancreas, intestine

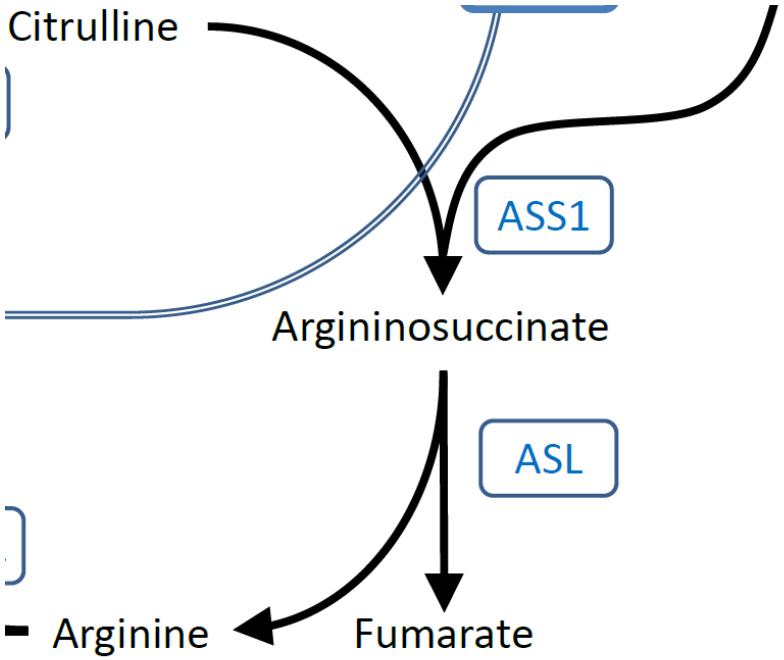
“Intestinal urea cycle”



- The small intestine exports citrulline to portal circulation
- Citrulline is not modified by the liver

“Kidney urea cycle”

- Kidney exports arginine



Incidence of Urea Cycle Disorders

Table 1
Distribution by group and estimated overall incidence.

	UCDC	E-IMD*	NUCDF	Incidence based on UCDC and newborn screening
All UCDs	590	224	661	1:/35,000
NAGS	3 (0.5%)	2 (1%)	6 (1%)	<1:2,000,000
CPSI	16 (2.7%)	10 (4.5%)	53 (8%)	1:1,300,000
OTC	363 (62%)	133 (59%)	377 (57%)	1:56,500
ASS	83 (14%)	43 (19%)	86 (13%)	1:/250,000
ASL	93 (16%)	26 (11.5%)	119 (18%)	1:218,750
ARG	22 (3%)	4 (2%)	14 (2%)	1:950,000
Citrin	2 (<1%)	n/a	0	<1:2,000,000
HHH	8 (1%)	6 (3%)	6 (1%)	<1:2,000,000

Molecular Genetics and Metabolism 110 (2013) 179–180

Clinical presentation of Urea Cycle Disorders

Children's National

Symptoms of acute hyperammonemia

Brain Edema

- Poor feeding, vomiting
- Drowsiness → Lethargy → Coma
- Altered tone, opisthotonus
- Seizures
- Ataxia
- Hyper- or hypoventilation
- Hypothermia
- Bradycardia
- Delusions, hallucinations, and psychosis

Clinical presentation in UCD

- Neonatal (near absent enzyme activity)
  - Not all UCDs are identified via newborn metabolic screen
- ‘Late-Onset’ (residual enzyme activity)
  - Childhood & Adult
    - May present with acute liver failure or psychiatric symptoms
- Asymptomatic
- Pauci-symptomatic OTCD

Recommended Uniform Screening Panel
Core Conditions
(As of July 2018)

Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
	Organic acid condition	Fatty acid oxidation disorder	Amino acid disorder			
Propionic Acidemia	X					
Methylmalonic Acidemia (methylmalonyl-CoA mutase)	X					
Methylmalonic Acidemia (Cobalamin disorders)	X					
Isovaleric Acidemia	X					
3-Methylcrotonyl-CoA Carboxylase Deficiency	X					
3-Hydroxy-3-Methyglutaric Aciduria	X					
Holocarboxylase Synthase Deficiency	X					
ß-Ketothiolase Deficiency	X					
Glutaric Acidemia Type I	X					
Carnitine Uptake Defect/Carnitine Transport Defect		X				
Medium-chain Acyl-CoA Dehydrogenase Deficiency		X				
Very Long-chain Acyl-CoA Dehydrogenase Deficiency		X				
Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency		X				
Trifunctional Protein Deficiency		X				
Argininosuccinic Aciduria			X			
Citrullinemia, Type I			X			
Maple Syrup Urine Disease			X			
Homocystinuria			X			
Classic Phenylketonuria			X			

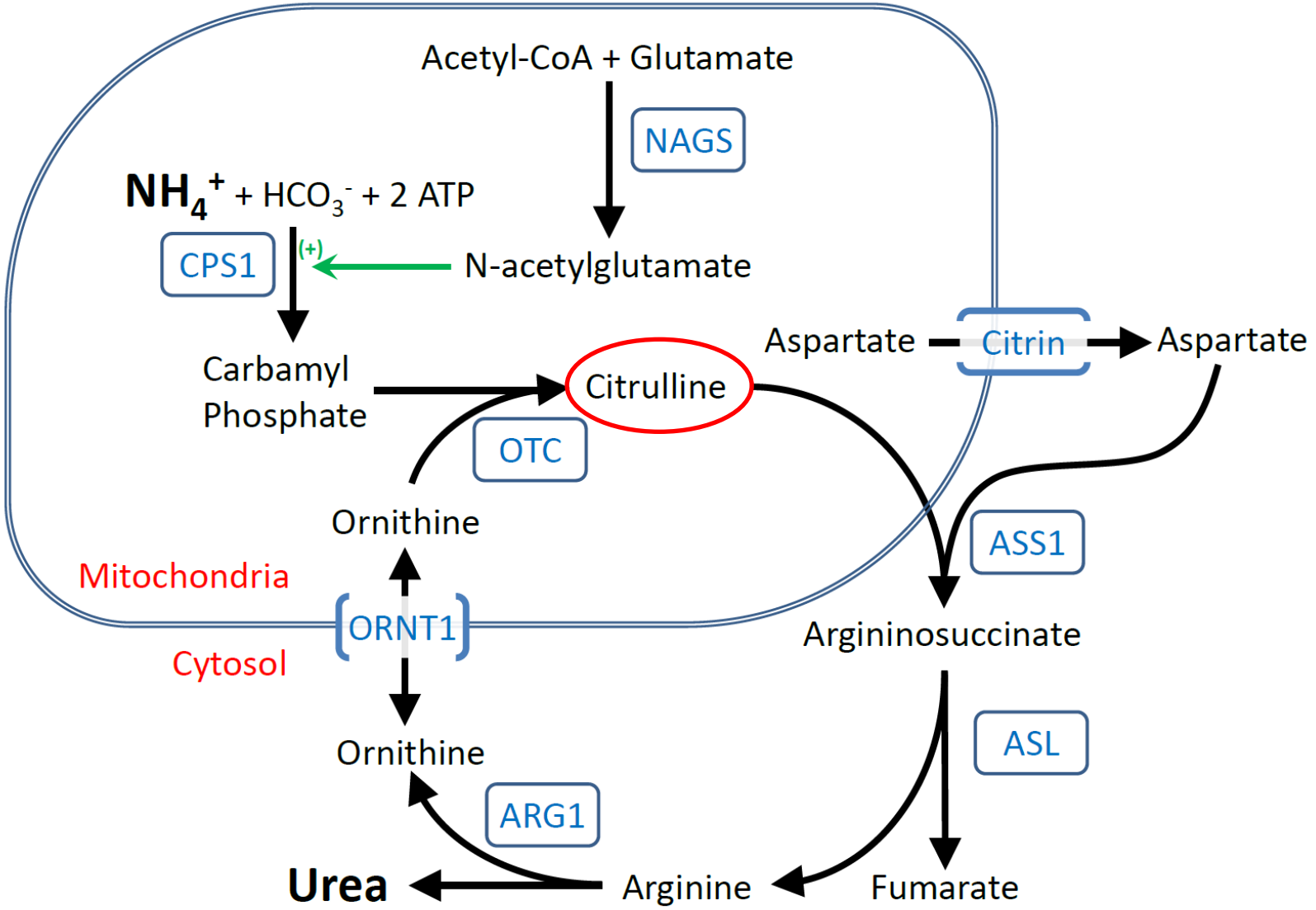
https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/rusp-uniform-screening-panel.pdf

Diagnosis of Urea Cycle Disorders

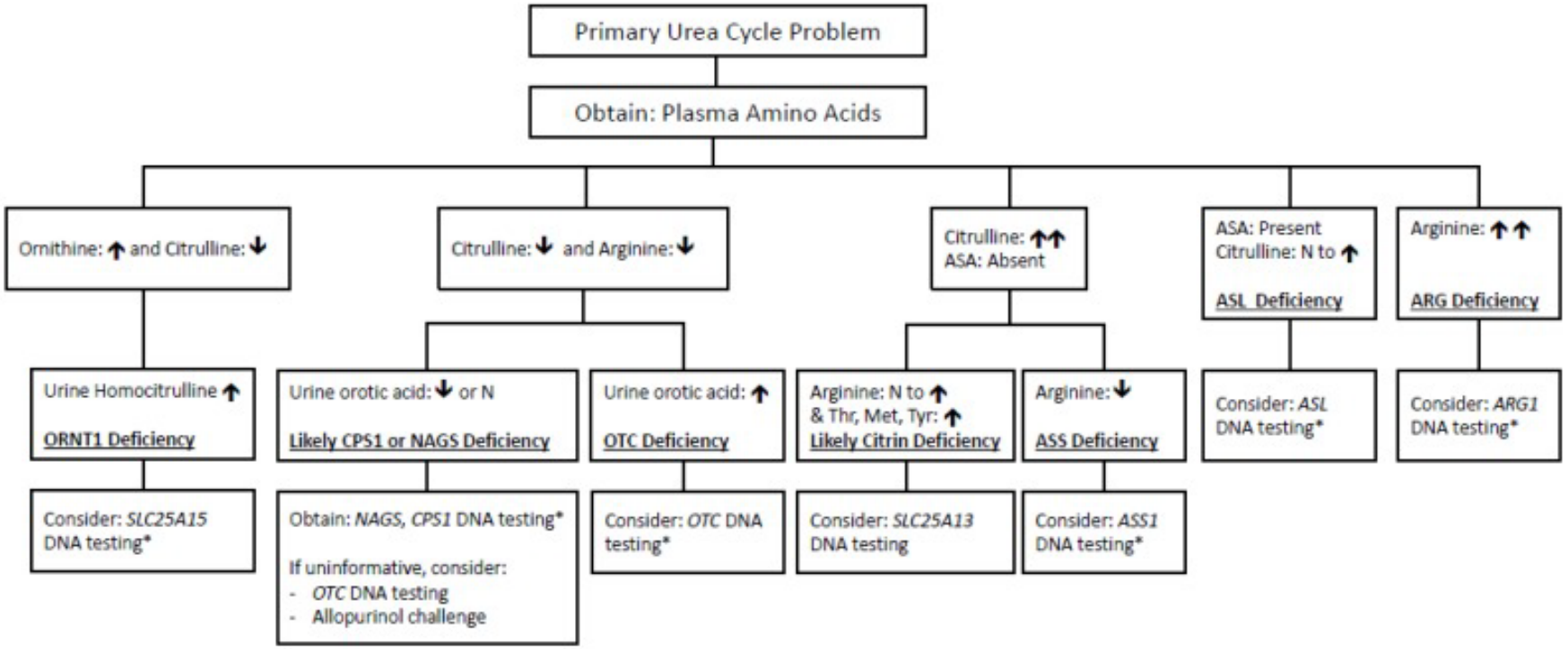
Laboratory Investigations

- Ammonia
- Blood gas (Respiratory alkalosis)
- Blood Urea Nitrogen (Disproportionally low)
- Liver enzyme (↑ PTT/INR, ↑AST/ALT)
- Plasma amino acid profile
- (Urine organic acid profile)
- (Orotic acid)
- DNA-based testing
- Enzymatic testing (Liver Biopsy)

Citrulline can help differentiate between “proximal” and “distal” UCD



https://www.ncbi.nlm.nih.gov/books/NBK1217/



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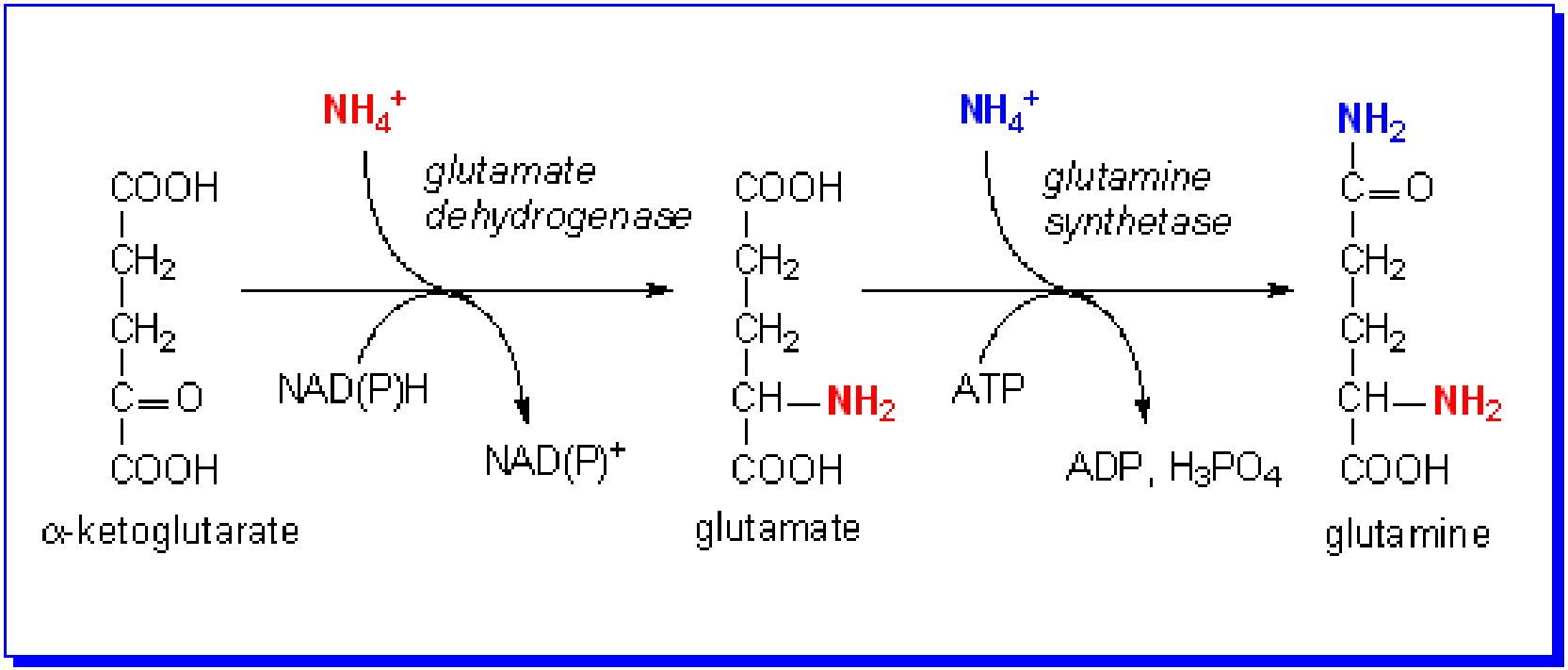
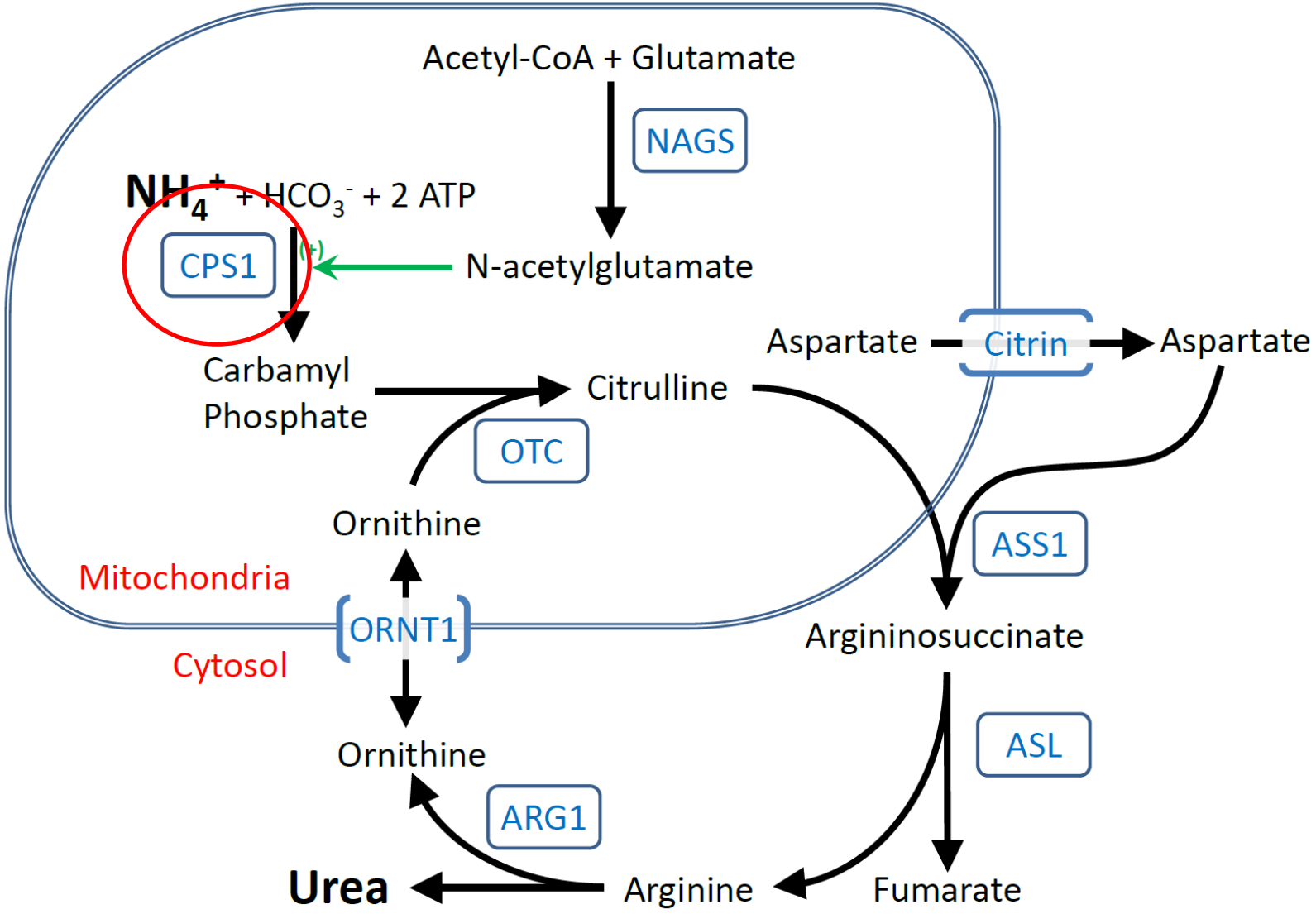
Elevated glutamine in hyperammonemia



Individual Urea Cycle Disorders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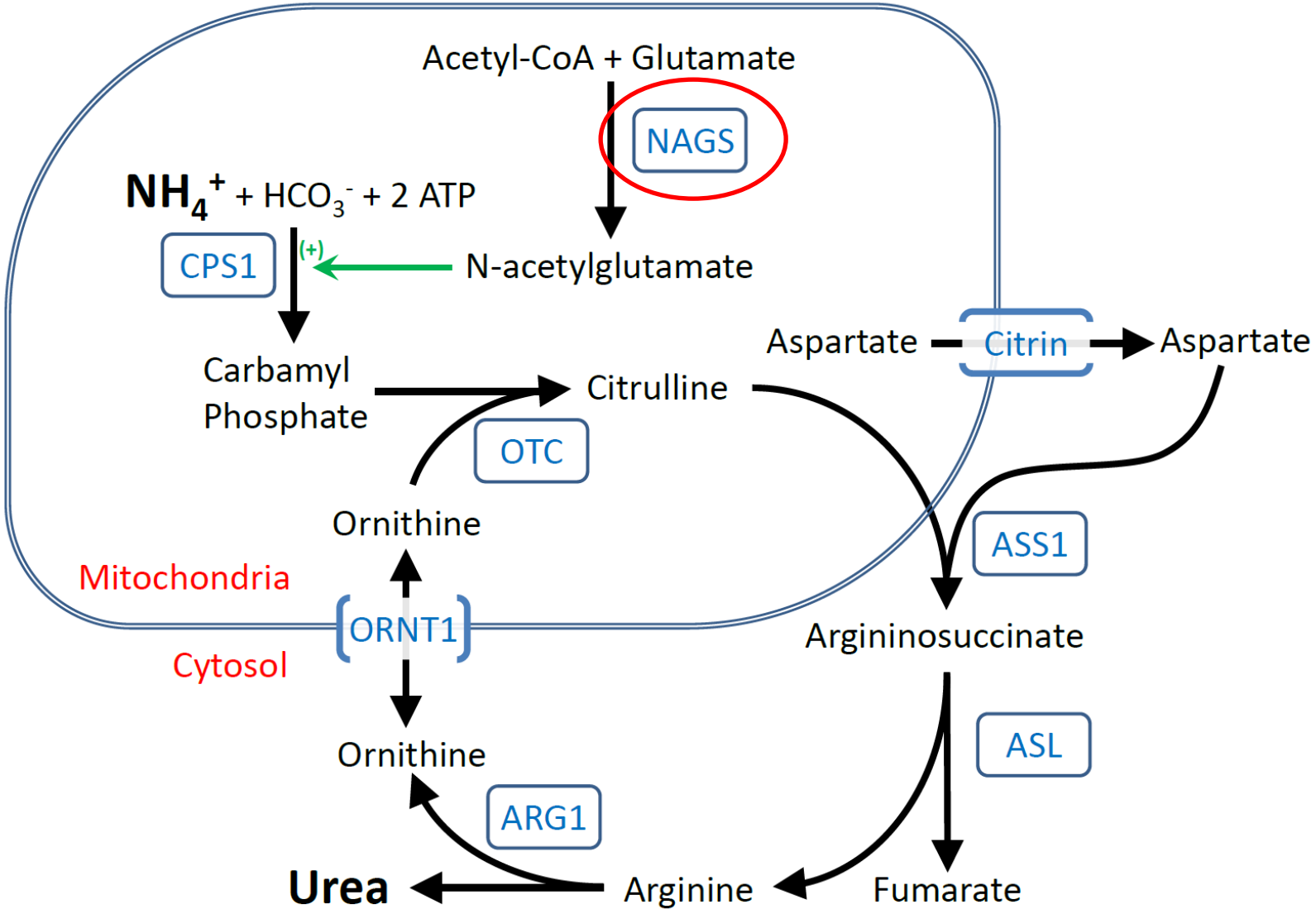
NH_4^+ + HCO_3^- + 2 ATP
CPS1
(+)
N-acetylglutamate
Aspartate
Citrin
Aspartate
Carbamyl Phosphate
Citrulline
OTC
Ornithine
ASS1
Mitochondria
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

Carbamyl Phosphate Synthetase 1

- Most abundant mitochondrial protein
- Rate limiting step of the urea cycle
- Has essential allosteric activator
  - N-acetyl-L-glutamic acid (NAG)
- 35-65% of CPS1 is bound to NAG at baseline

CPS1 deficiency

- No nitrogen intermediates produced
  - One of the most severe UCD
- Results in:
  - Hyperammonemia and Hyperglutaminemia
  - Low citrulline
- Some patients with CPS1 deficiency might be responsive to cofactor supplmentation


Acetyl-CoA + Glutamate
NAGS
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CPS1
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OTC
Aspartate
Citrin
Aspartate
Ornithine
ASS1
Mitochondria
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

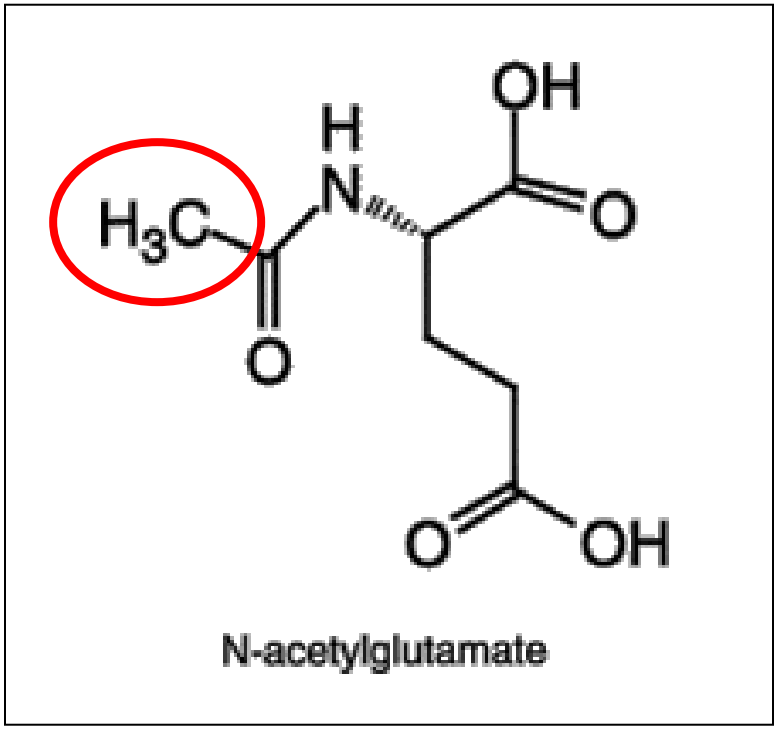
NAGS & NAGS Deficiency

- NAGS deficiency results in absence of

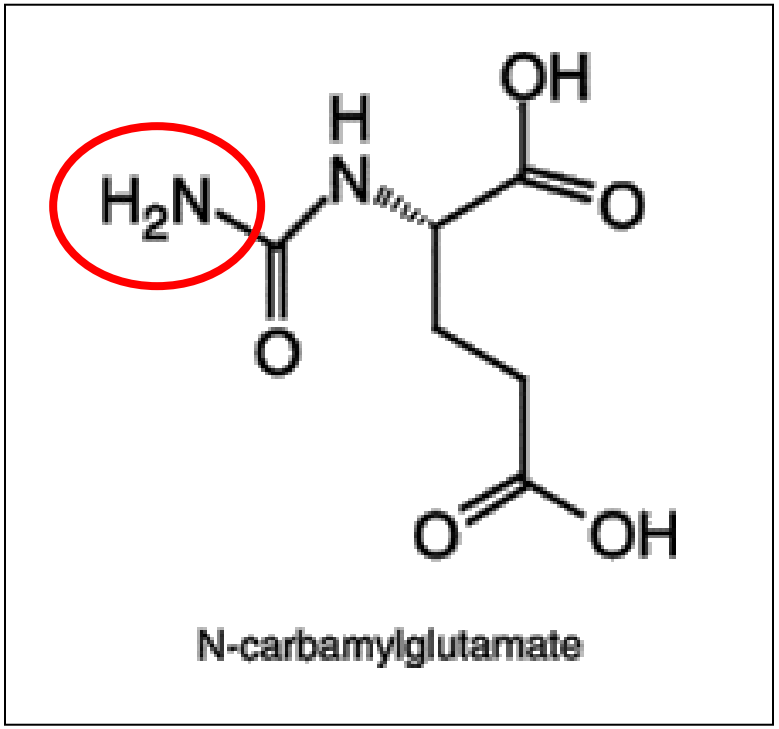
N-acetyglutamate

- Results in functional CPS1 deficiency
- Biochemical phenotype identical to CPS1-D
- NAGS also secondarily inhibited by organic acidemias (e.g., propionic acidemia)
- Treatable with N-carbamyl-L-glutamic acid

NCG is a stable analog of N-acetylglutamate



N-acetylglutamate



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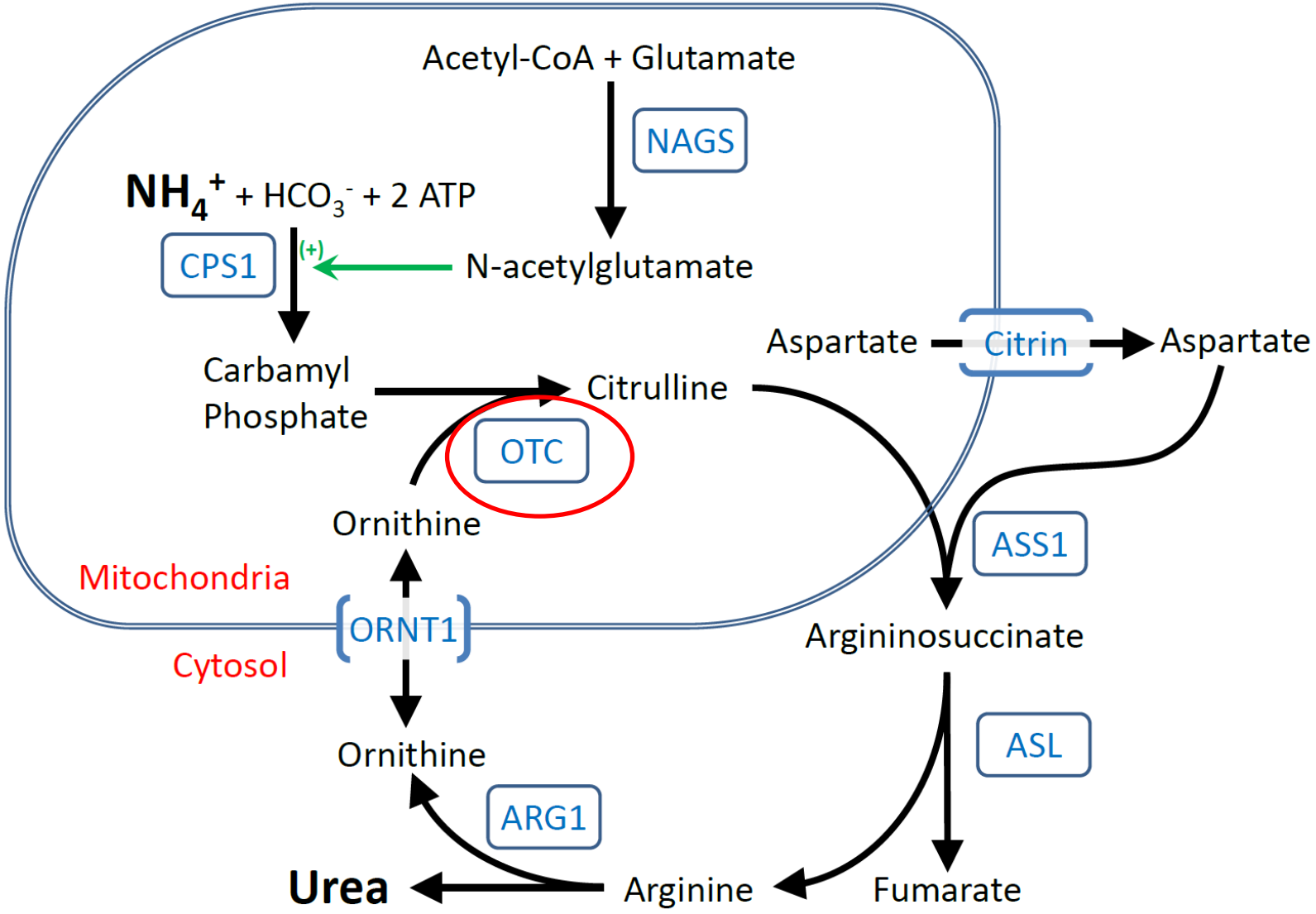
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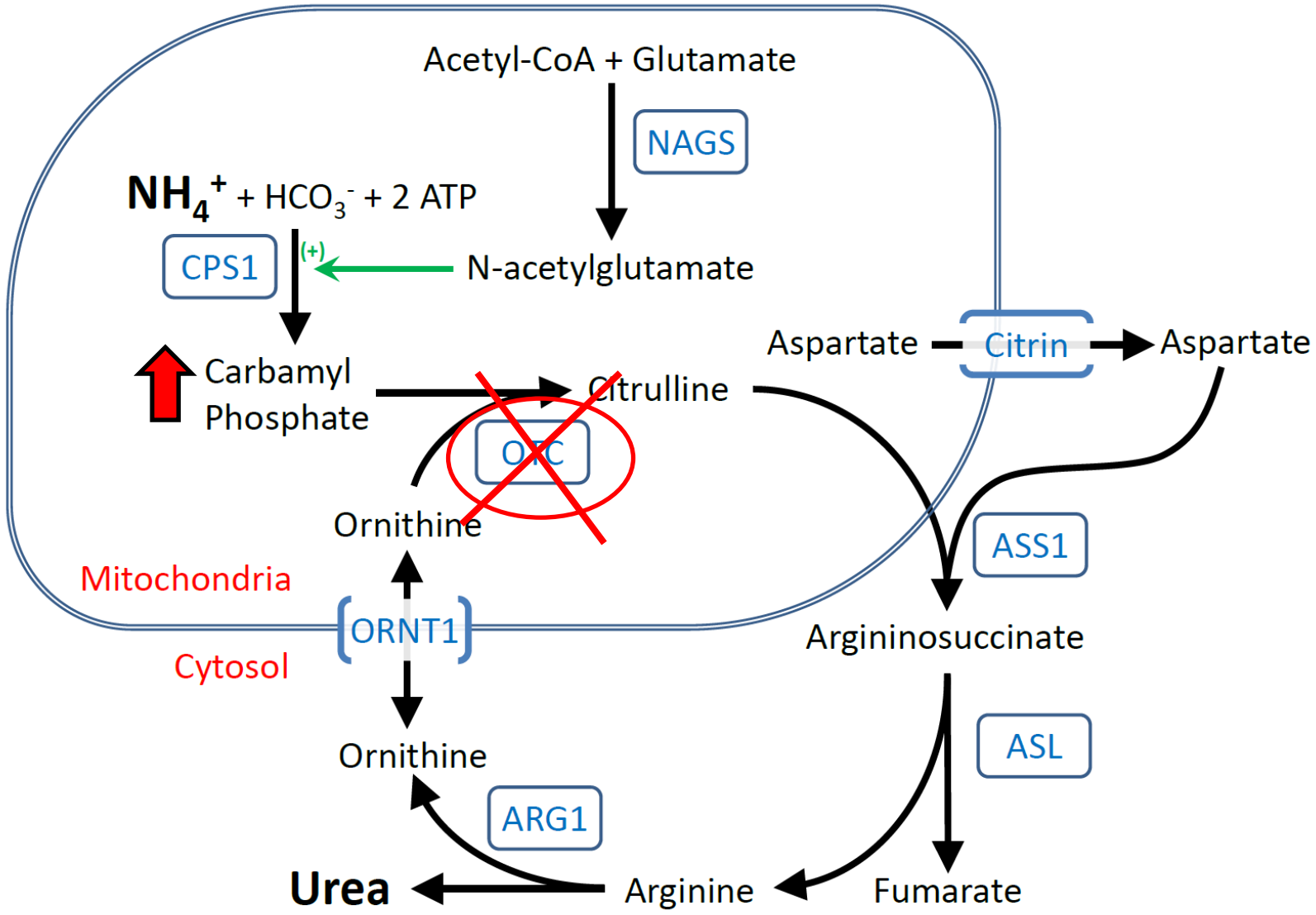
NAGS
NH_4^+ + HCO_3^- + 2 ATP
CPS1
(+)
N-acetylglutamate
Aspartate
Citrin
Aspartate
Carbamyl Phosphate
Citrulline
OTC
Ornithine
ASS1
Mitochondria
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

Ornithine Transcarbamylase Deficiency

- X-linked disorder
  - Males more commonly symptomatic
  - Females symptomatic with skewed lyonization
  - Paucisymptomatic females: Deficits in executive functioning without elevated ammonia
- Zinc required for OTC function
  - Some reported cases of acrodermatitis enteropathica with hyperammonemia

- Biochemical features:
  - Hyperammonemia and Hyperglutaminemia
  - Low citrulline
  - Elevated orotic acid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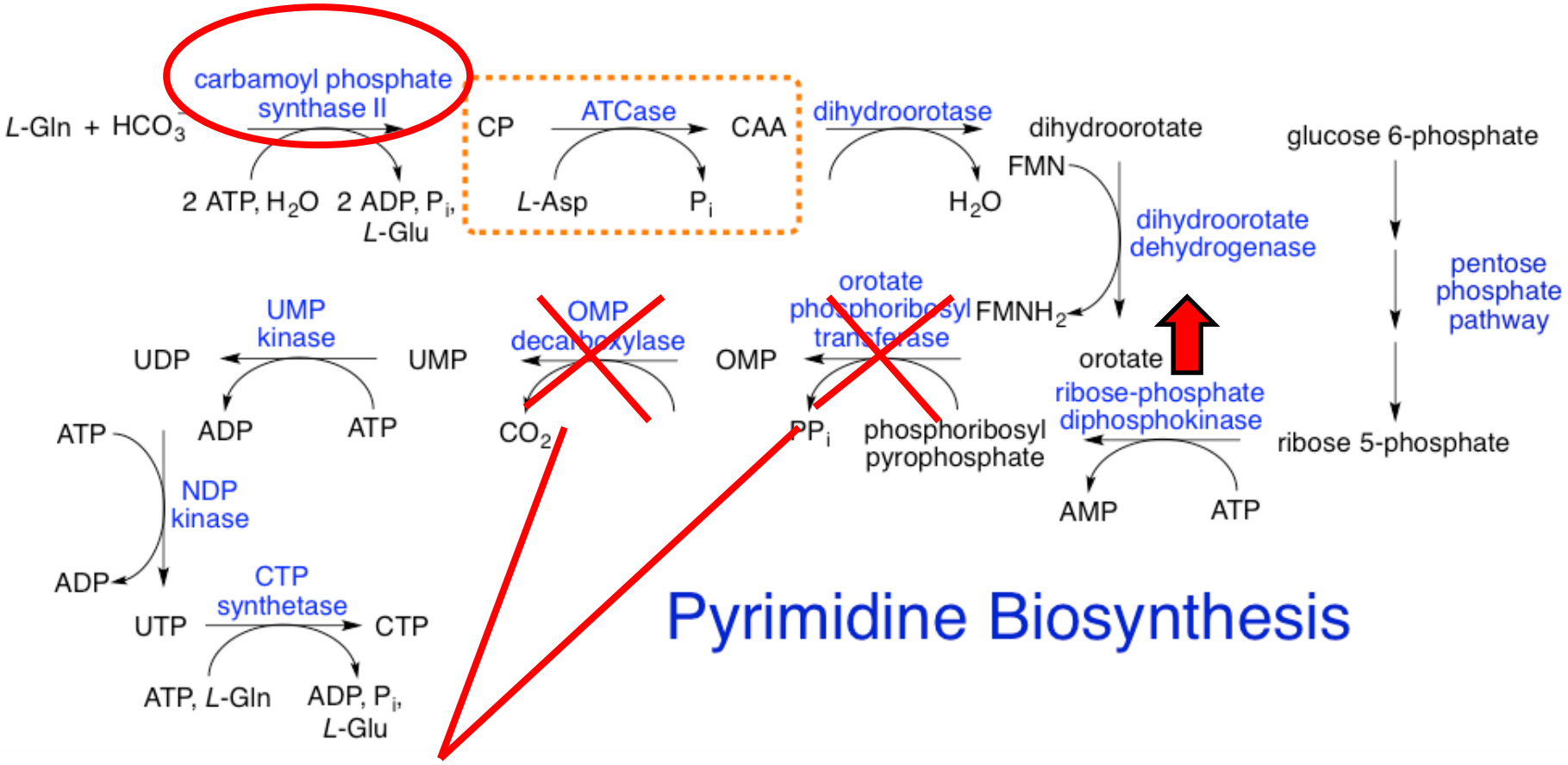
Fumarate

Orotic aciduria in OTCD



Allopurinol challenge

Enzyme	Chromosomal location	Cellular location	Tissue expression
N-acetylglutamate synthetase E.C. 2.3.1.1; MIM 608300	17q21.31	Mitochondrial matrix	**Liver, intestine**, kidney (trace), spleen
Carbamyl phosphate synthetase 1 EC 6.3.4.16; MIM 608307	2q34	Mitochondrial matrix	**Liver, intestine**, kidney (trace)
Ornithine transcarbamylase E.C. 2.1.3.3; MIM 300461	**X**p11.4	Mitochondrial matrix	**Liver, intestine**, kidney (trace)
Argininosuccinate synthetase 1 EC 6.3.4.5; MIM 603470	9q34.11	Cytosol	**Liver, kidney**, fibroblasts, brain (trace)
Argininosuccinate lyase EC 4.3.2.1; MIM 608310	7q11.21	Cytosol	**Liver, kidney**, fibroblasts, brain
Arginase 1 EC 3.5.3.1; MIM 608313	6q23.2	Cytosol	**Liver,** erythrocytes, kidney, lens, brain (trace)
Citrin (SLC25A13) MIM 603859	7q21.3	Inner mitochondrial membrane	**Liver,** kidney, heart
Ornithine transporter (SLC25A15) MIM 603861	13q14.11	Inner mitochondrial membrane	**Liver,** pancreas, intestine

Inherited vs *de novo* OTCD

Proportions of Spontaneous Mutations in Males and Females With Ornithine Transcarbamylase Deficiency

Mendel Tuchman, Ichiro Matsuda, Arnold Munnich, Sue Malcolm, Sandra Strautnieks, and Trevor Briede

Departments of Pediatrics (M.T., T.B.), and Laboratory Medicine and Pathology (M.T.), University of Minnesota, Minneapolis, Minnesota; Department of Pediatrics, Kumamoto University, Kumamoto, Japan (I.M.); Unité de Recherches sur les Handicaps Génétiques de l'Enfant, Hôpital des Enfants-Malades, Paris, France (A.M.); and Mothercare Unit of Paediatric Genetics, Institute of Child Health, London, England (S.M., S.S.)

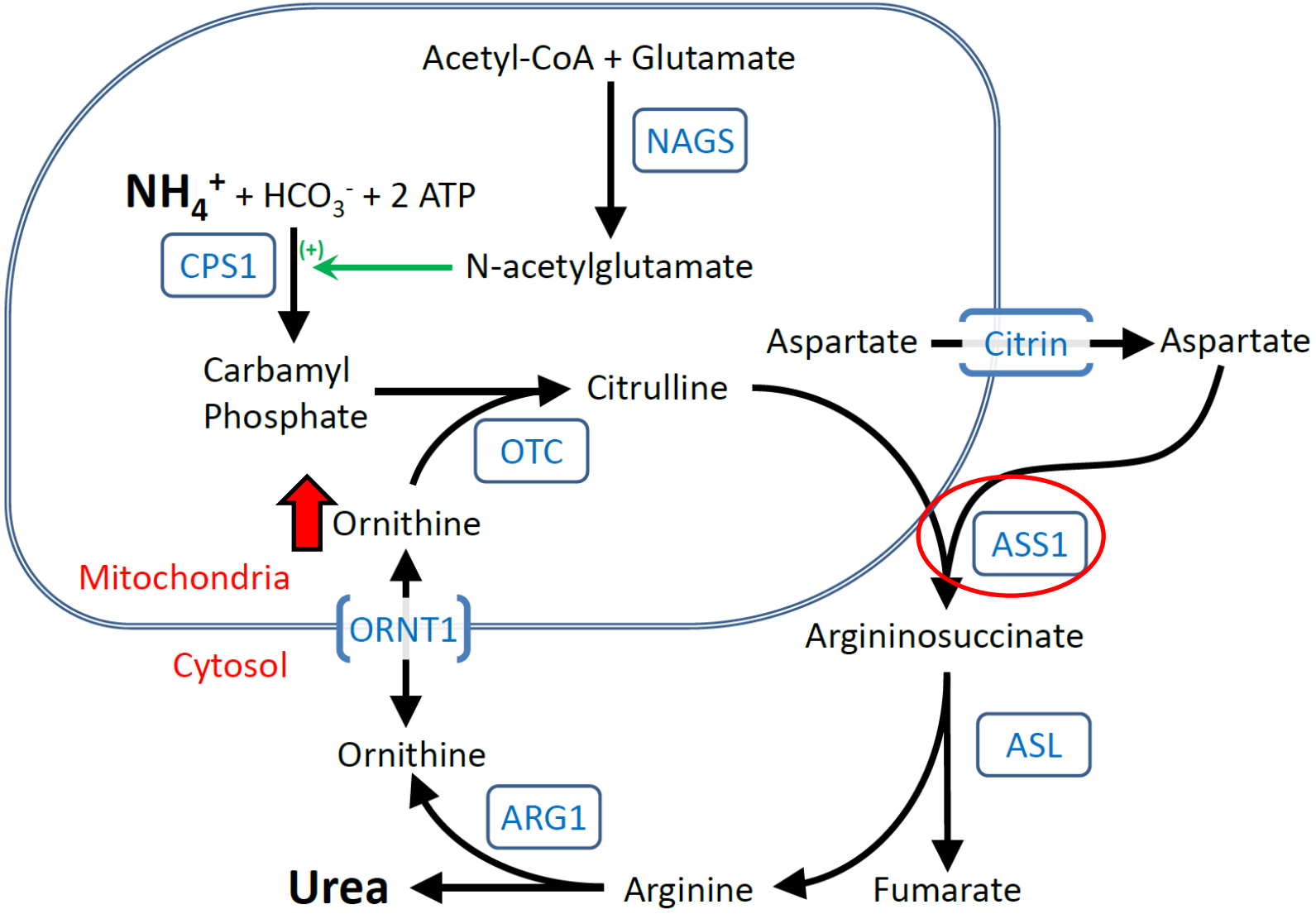
We used specific mutation analysis to estimate the proportions of males and females with ornithine transcarbamylase (OTC) deficiency whose mutations occurred in the germ cells of one of the parents. The mutations were identified in the probands, and subsequently carrier testing was performed on their mothers and some of the grandmothers. Of 28 OTC deficient males, only 2 (7%) had sporadic mutations (95% CI, 0.6–18.5%), whereas of 15 OTC deficient females, 12 (80%) had sporadic mutations (95% CI, 63–99%) ($P < 0.001$). Based on these results we estimated the male/female mutation rate ratio (ν/μ) in the OTC gene to be approximately 52. Assuming a fitness for males with OTC deficiency of 0 and the proportion of new female mutants at 0.80, the estimated fitness of heterozygous females is 0.4. Because of the difference in mutation rates between male and female germ cells, we suggest that 9/10 or higher, rather than the conventional 2/3 proportion, be applied when estimating prior risk of carrier status in a mother of one affected male. The prior risk of a mother of an affected female is much lower, approximately 2/10.

INTRODUCTION

Ornithine transcarbamylase (OTC; E.C. 2.1.3.3) deficiency [McKusick 311250], the most common inherited defect of the urea cycle, exhibits X-linked partially dominant inheritance [Brusilow and Horwich, 1989]. Most of the mutations reported to cause OTC deficiency in males may be considered genetically lethal as they result either in neonatal death or severe mental retardation with a marked reproductive disadvantage. According to Haldane's rule [Haldane, 1935], the proportion of patients with X-linked recessive, genetically lethal disease, who are new mutants in a population at equilibrium is 1/3 providing the mutation rates in male and female germ cells are identical. Although one would expect mutation rates in ova and sperm to be different because of discordant developmental biology of the 2 gametes, recent data from X-linked disorders suggest that genes at different positions on the X-chromosome may behave differently with respect to spontaneous mutations. For example, the mutation rate in the Duchenne muscular dystrophy gene seems to be equivalent in male and female germ cells according to some studies [Caskey et al., 1980; Williams et al., 1983; Moser, 1984], whereas in other X-linked disorders, such as hemophilia [Bröcker-Vriends et al., 1991] and Lesch-Nyhan disease [Francke et al., 1976], the mutation rate seems higher in male germ cells. Moreover, OTC is

(But for your exam… stick with

Mendelian 2/3 inherited -1/3 *de novo)*


Acetyl-CoA + Glutamate
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Aspartate
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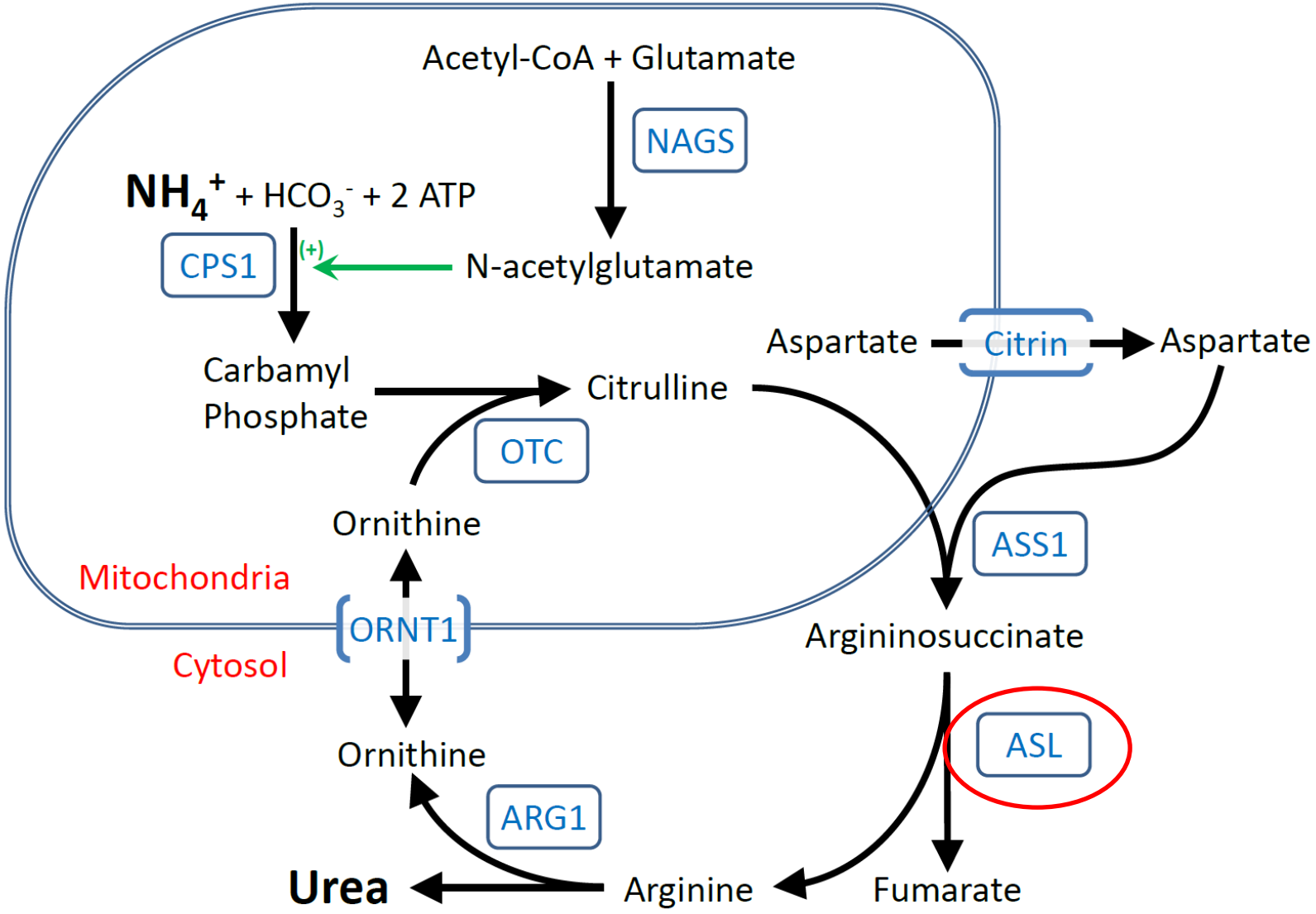
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

Argininosuccinate synthetase deficiency

- ‘Citrullinemia’ type I
- Results in:
  - Hyperammonemia and Hyperglutaminemia
  - Markedly elevated citrulline

The word ‘citrulline’ comes from…

- Citrullus – latin for watermelon (Citrullus Lanatus)
- Citrulline first isolated from watermelon (1914)
- Watermelon has high concentration of citrulline in all parts
- Watermelon consumption can result in temporary elevations plasma citrulline and arginine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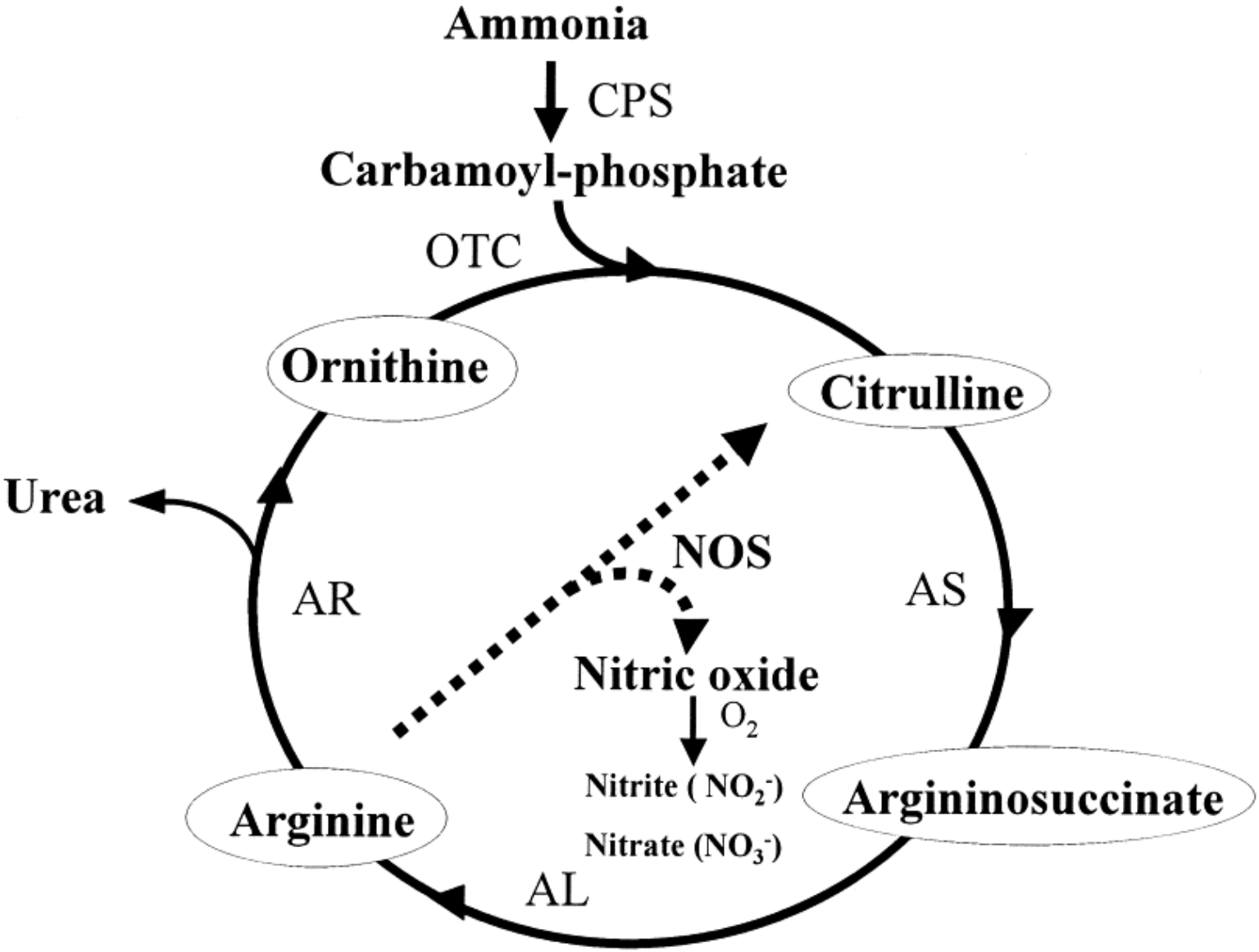
ORNT1
Argininosuccinate
Cytosol
Ornithine
ASL
ARG1
Urea
Arginine
Fumarate

Argininosuccinate Lyase deficiency

- Clinical features:
  - Trichorexis Nodosa (hair 10-20% arginine by weight)
  - Hypertension (impaired nitric oxide metabolism)
- Results in:
  - Hyperammonemia
  - Elevated argininosuccinate (ASA) and anhydrides
  - Mildly elevated citrulline
- ASA is not reabsorbed by kidneys
  - Urine concentration of ASA is more abnormal than in plasma

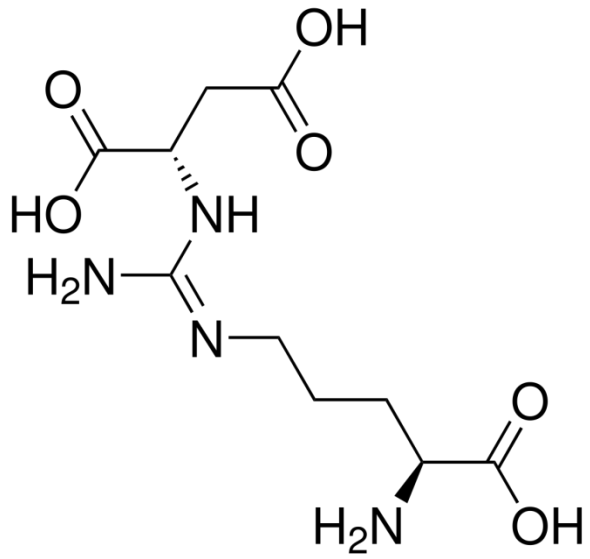
Nitric Oxide and the Urea Cycle



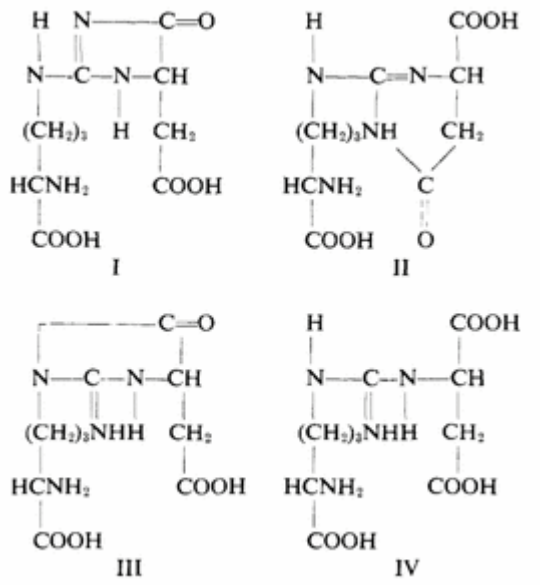
Argininosuccinate Lyase deficiency

- Clinical features:
  - Trichorexis Nodosa (hair 10-20% arginine by weight)
  - Hypertension (impaired nitric oxide metabolism)
  - Chronic liver involvement
- Results in:
  - Hyperammonemia
  - Elevated argininosuccinate (ASA) and anhydrides
  - Mildly elevated citrulline
- ASA is not reabsorbed by kidneys
  - Urine concentration of ASA is more abnormal than in plasma

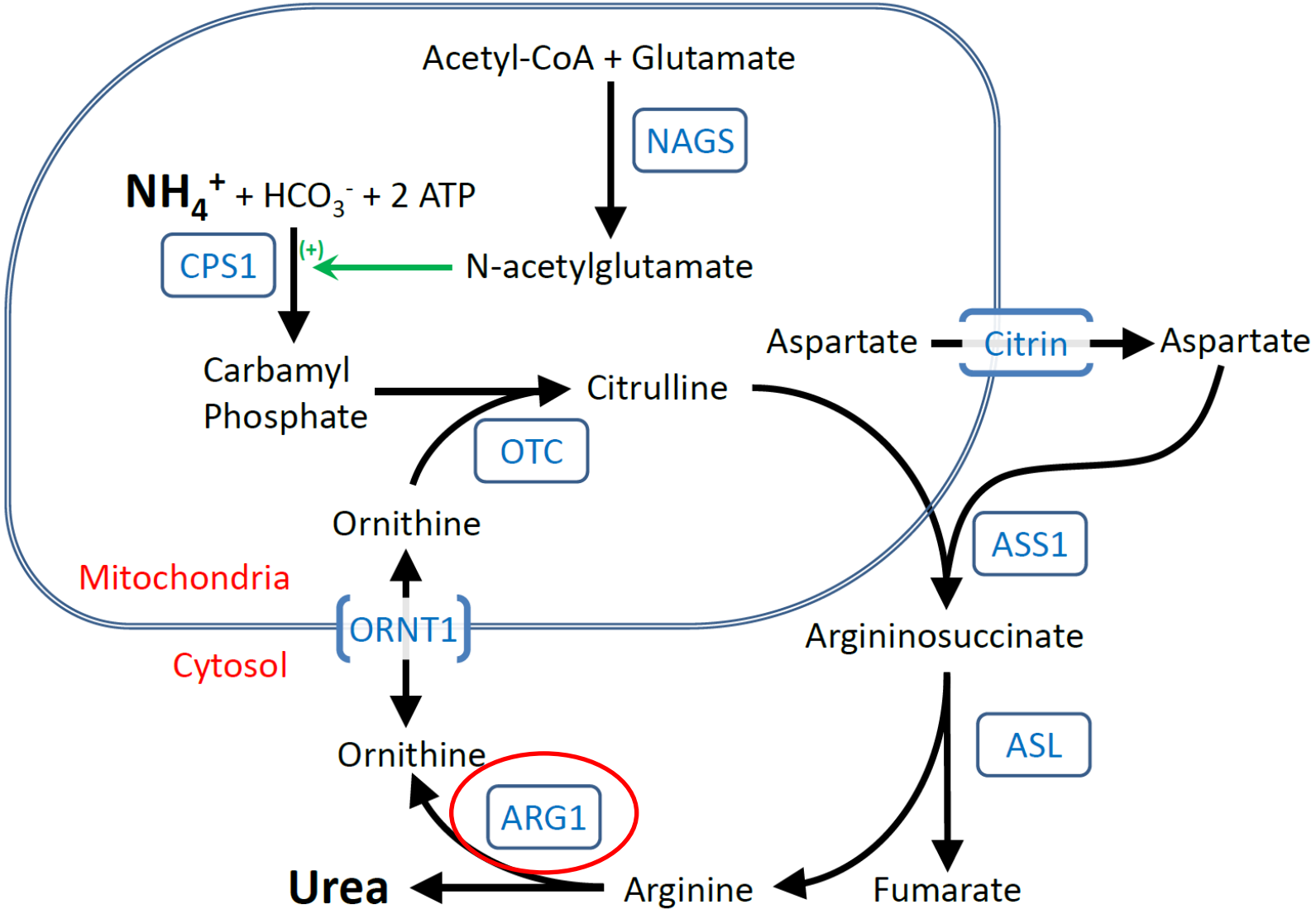
ASA and anhydrides



ASA co-elutes with leucine



Anhydrides Co-elute with Beta-alanine and GABA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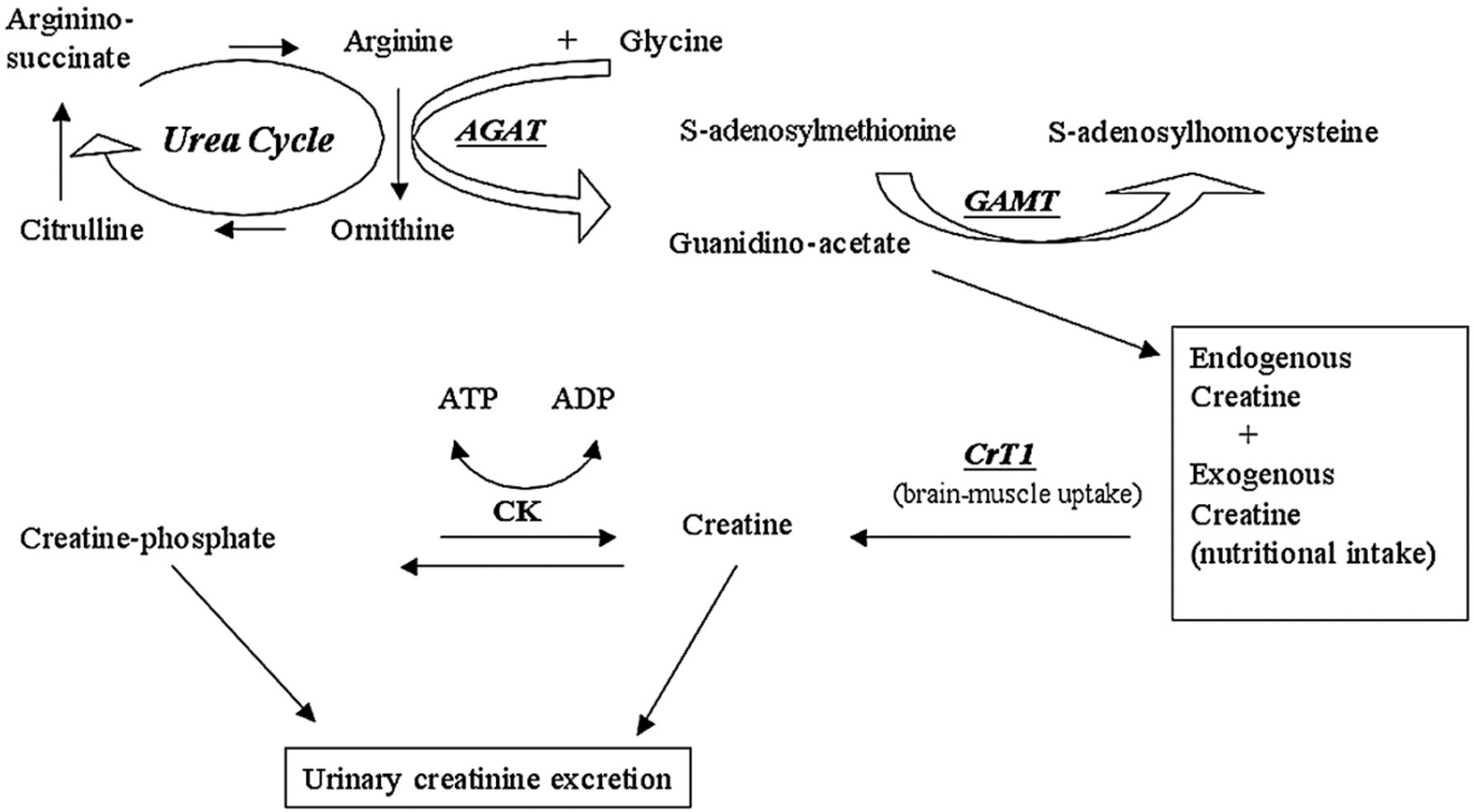
Arginine
Fumarate

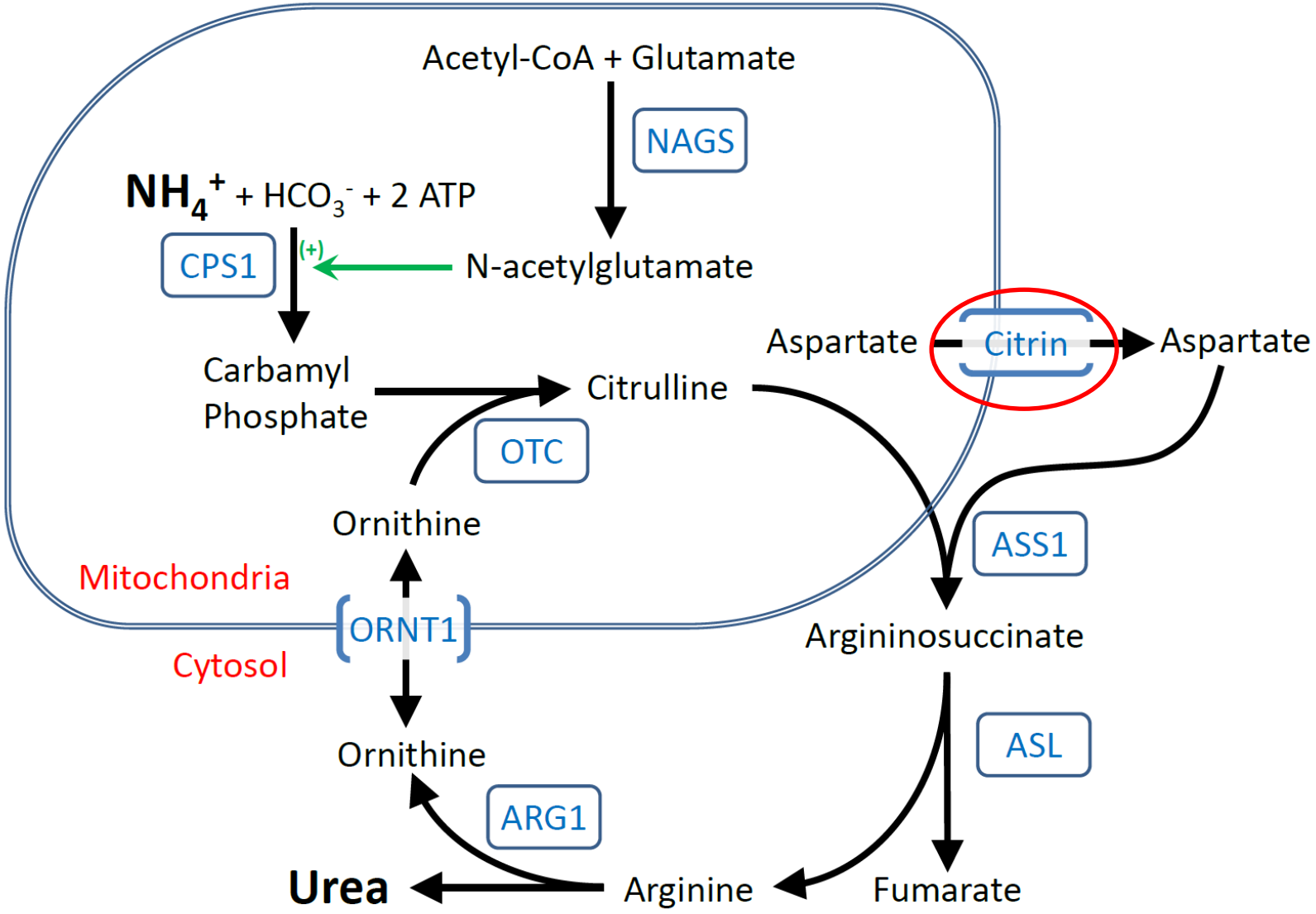
Arginase deficiency

- Hyperammonemia is an uncommon feature
- Markedly elevated arginine
- Peripheral neuropathy
- Intellectual disability, seizures
- Elevated arginine increases production of guanidinoacetate
  - May contribute to intellectual disability, epilepsy,

Arginine and *de novo* Creatine Biosynthesis



American Journal of Neuroradiology March 2007, 28 (3) 548-554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ASL
ARG1
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Arginine
Fumarate

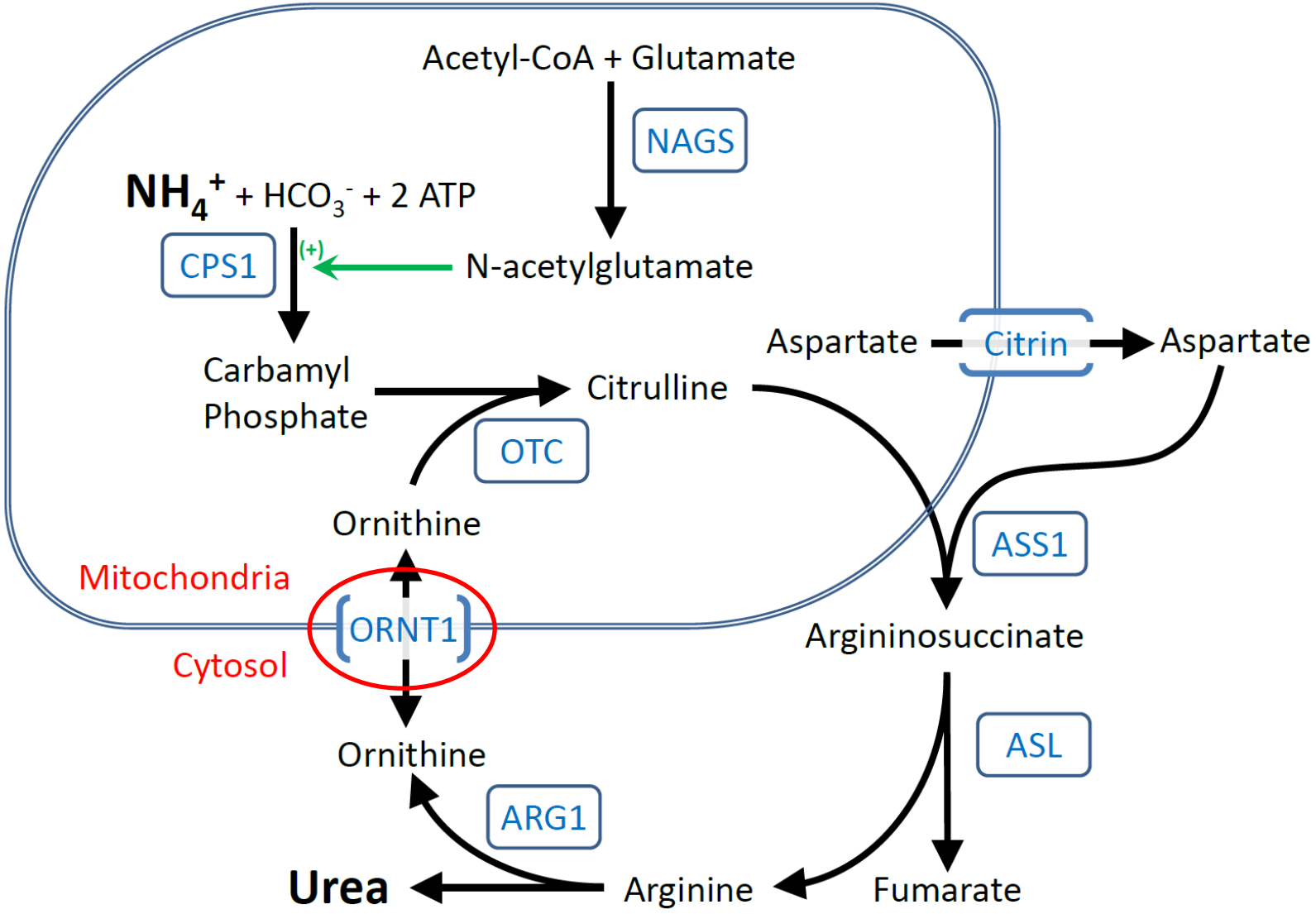
Citrin Deficiency

- Deficiency of SLC25A13
  - Aspartate - Glutamate counter-transport
- Elevated citrulline

- Neonates: Intrahepatic Cholestasis
- Juvenile: Failure to Thrive, dyslipidemia
- Adolescent or adulthood: Recurrent hyperammonemia (“Citrullinemia type II”)

Citrin Deficiency

- Common in Asian populations
  - Carrier rate: 1:50-100
- Treatment
  - Unlike UCDs: High protein, High fat, low carbohydrate diet
  - Patients self-select this diet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Mitochondria
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Ornithine
ASL
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Urea
Arginine
Fumarate

Hyperornithinemia-Hyperammonemia-Homocitrullinuria

- Ornithine levels ~ 300-500 µmol/L
- No ocular abnormalities
- In some early-childhood onset: gait abnormalities and spasticity

- Founder mutation in French-Canadian population (F188del)

J Inherit Metab Dis. 2019 Nov;42(6):1118-1127. doi: 10.1002/jimd.12144. Epub 2019 Aug 25.

Chronic liver involvement in urea cycle disorders

Giusy Ranucci [1], Miriam Rigoldi [2], Giovanna Cotugno [1], Silvia Maria Bernabei [3], Alessandra Liguori [1], Serena Gasperini [4], Bianca Maria Goffredo [1], Diego Martinelli [1], Lidia Monti [5], Paola Francalanci [6], Manila Candusso [7], Rossella Parini [4], Carlo Dionisi-Vici [1]

Affiliations + expand

PMID: 31260111 DOI: 10.1002/jimd.12144

Management of Urea Cycle Disorders

Children's National

Management principles: (applies to both acute and chronic)

1) Reduce or stop influx of excess nitrogen
   (Stop production of ammonia)
2) Alternative pathways of nitrogen removal
3) Arginine/Citrulline supplementation
4) Improve enzymatic function
   (Carbamylglutamate, Liver Transplant)
5) Treatment of intercurrent illness

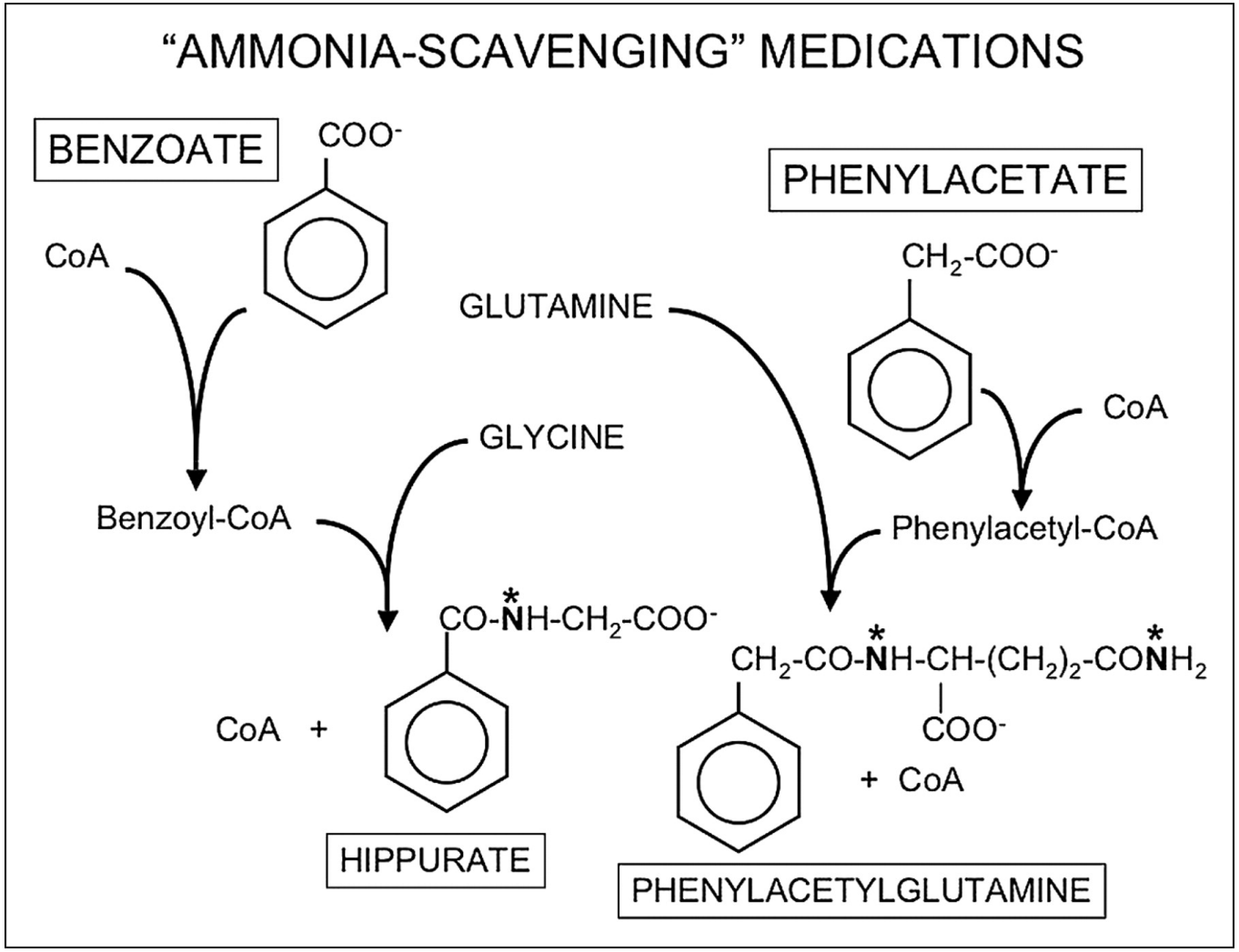
Reduce or eliminate influx of excess nitrogen

- Two sources of nitrogen:
  - Exogenous (i.e., dietary)
  - Endogenous (e.g., body proteins)
    - Reduce/Reverse catabolism by providing sufficient/excess non-protein calories
    - (Insulin drip may be started if patient hyperglycemic)

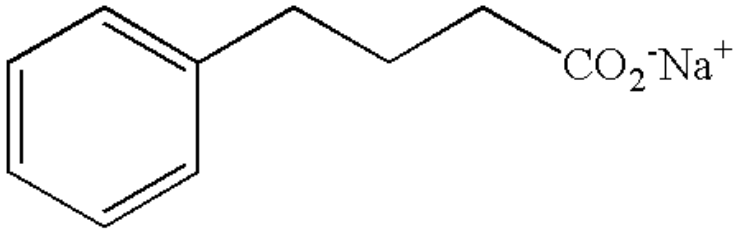
Alternative pathways of nitrogen removal

- Extracorporeal removal
  - Continuous or intermittent hemodialysis/filtration
- ‘Ammonia scavenger’ medications
  - Removal of non-essential amino acids
  - Work stoichiometrically

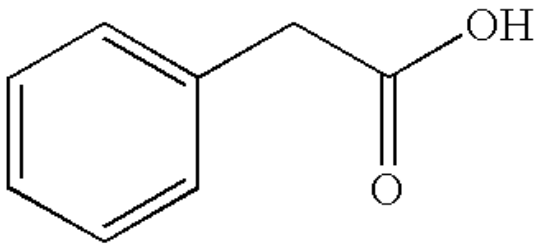
Alternative Pathway Medications



Phenylbutyrate metabolism

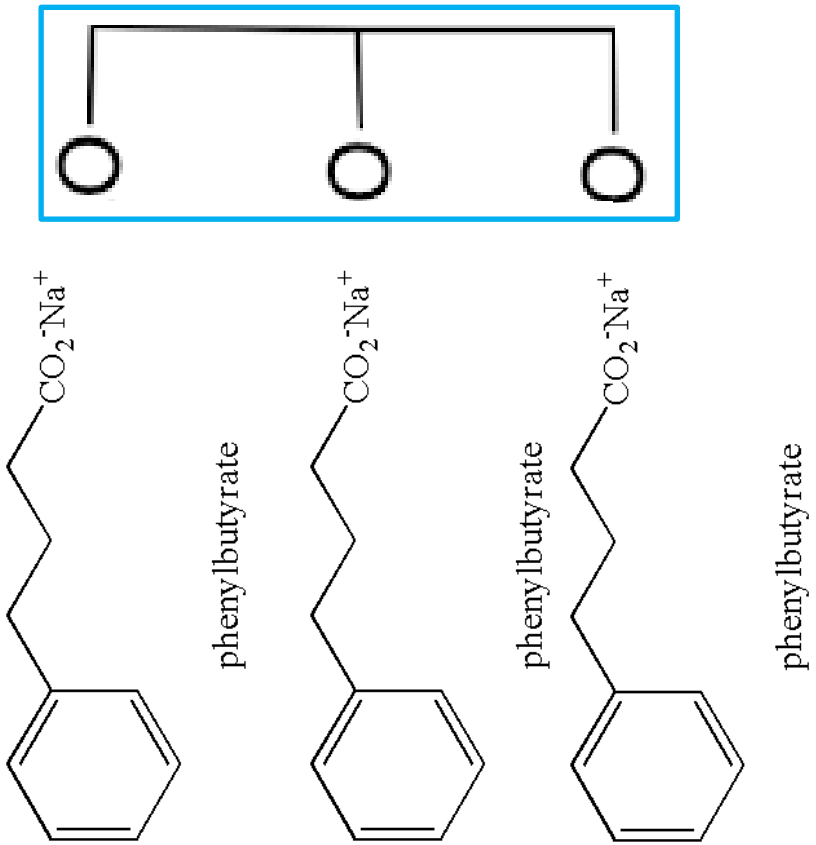


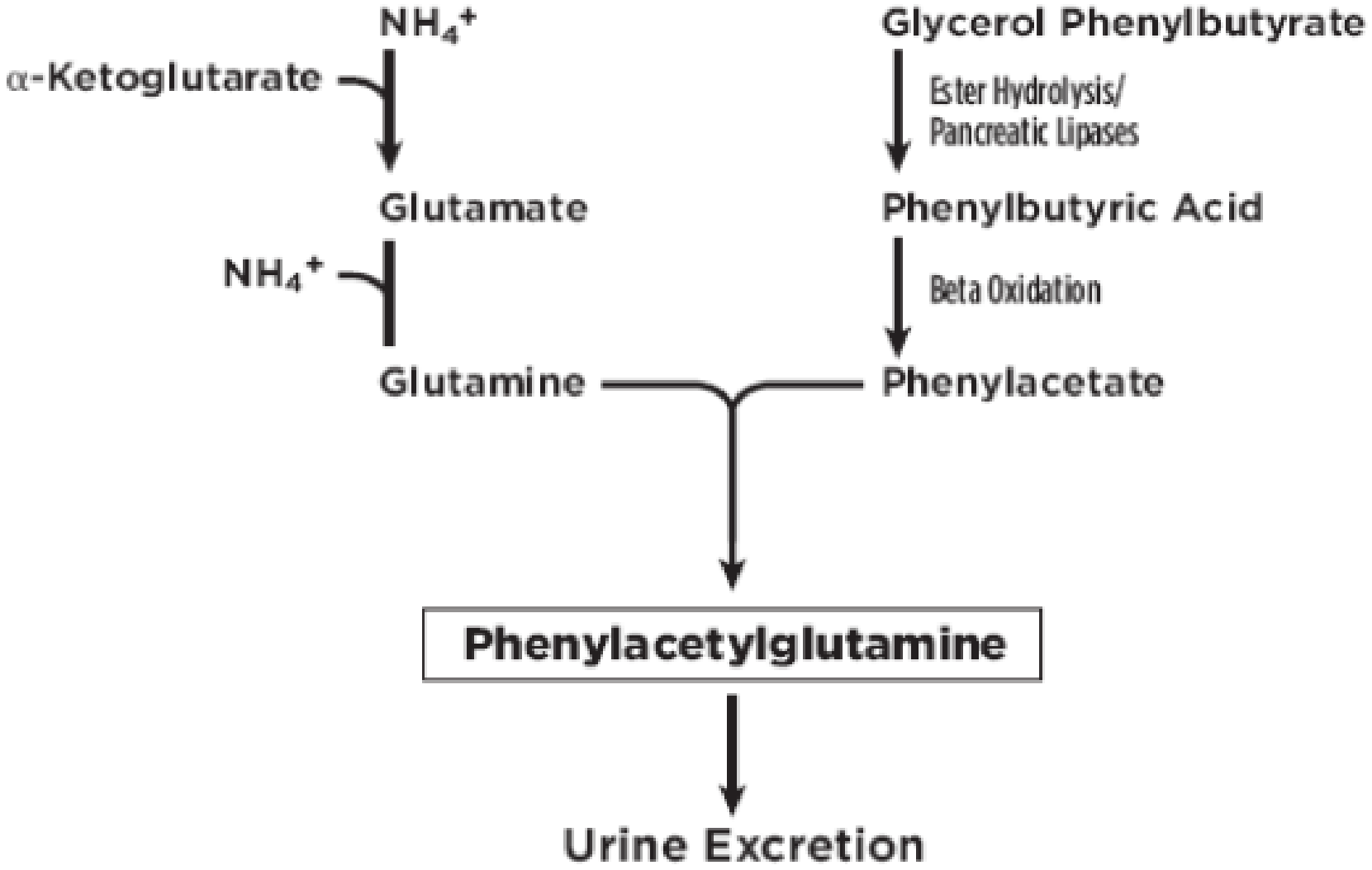
phenylbutyrate



Phenylacetic acid

Glycerol Phenylbutyrate




NH_4^+
α-Ketoglutarate
Glutamate
NH_4^+
Glutamine
Glycerol Phenylbutyrate
Ester Hydrolysis/
Pancreatic Lipases
Phenylbutyric Acid
Beta Oxidation
Phenylacetate
Phenylacetylglutamine
Urine Excretion

Alternative pathway medications

- May be administered together (e.g., Ammonul)
- No head-to-head comparisons in UCD patients

Published in final edited form as:
Genet Med. 2018 July ; 20(7): 708–716. doi:10.1038/gim.2017.167.

A randomized trial to study the comparative efficacy of phenylbutyrate and benzoate on nitrogen excretion and ureagenesis in healthy volunteers

Sandesh C.S. Nagamani, MD[1,2], Umang Agarwal, PhD[3], Allison Tam, MD[1], Mahshid Azamian, MD, MPH[1], Ann McMeans, MS, RD[2,3], Inka C. Didelija, MS[3], Mahmoud A. Mohammad, MD[3], and Juan C. Marini, DVM, PhD[3,4,*]

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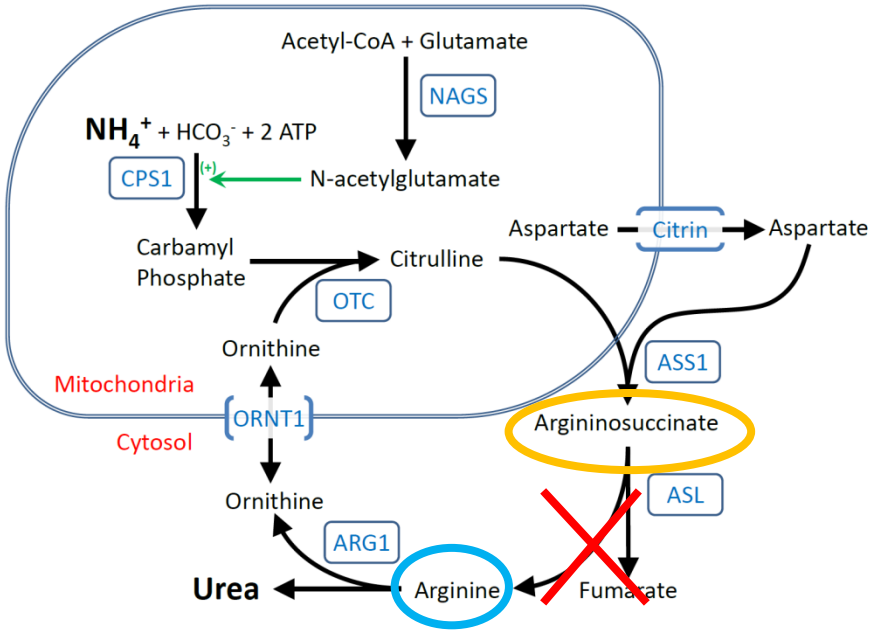
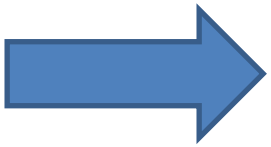
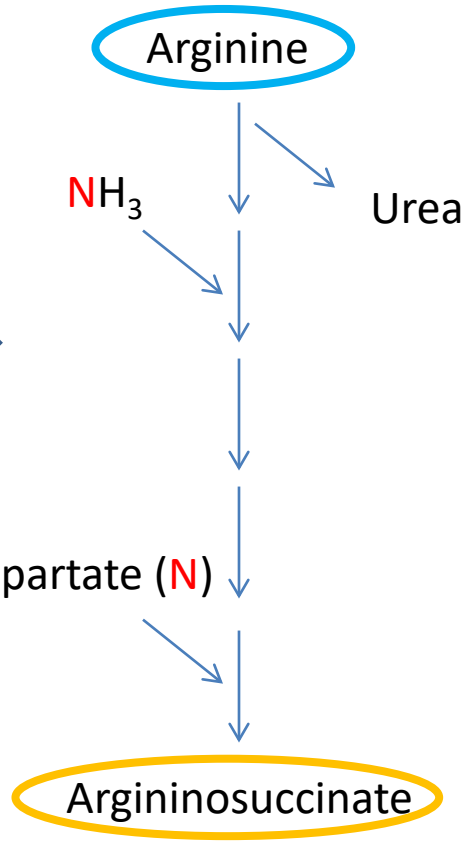
Arginine Supplementation - ASLD

- Urea cycle becomes a linear pathway







Arginine use in ASLD

Molecular Genetics and Metabolism 107 (2012) 315–321

Contents lists available at SciVerse ScienceDirect

Molecular Genetics and Metabolism

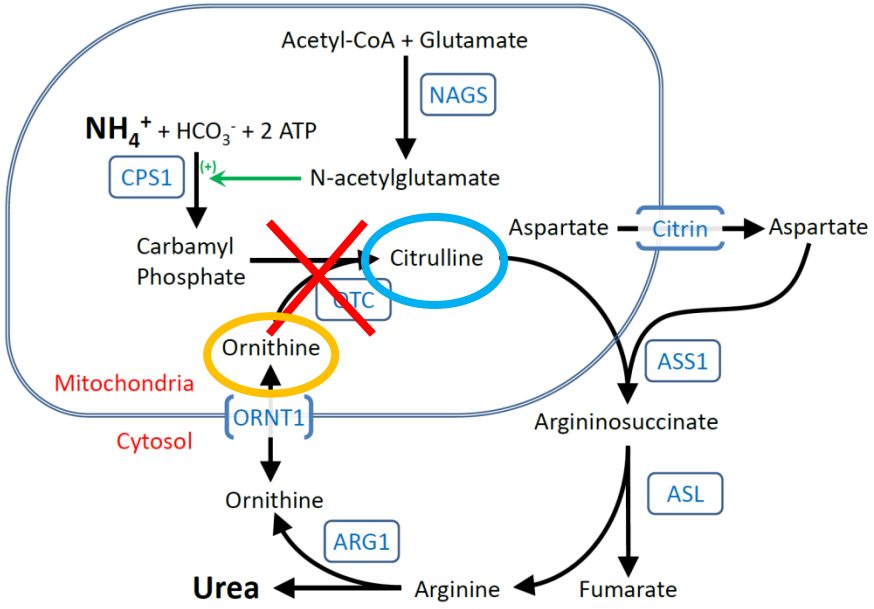
journal homepage: www.elsevier.com/locate/ymgme

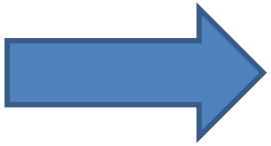
A randomized controlled trial to evaluate the effects of high-dose versus low-dose of arginine therapy on hepatic function tests in argininosuccinic aciduria

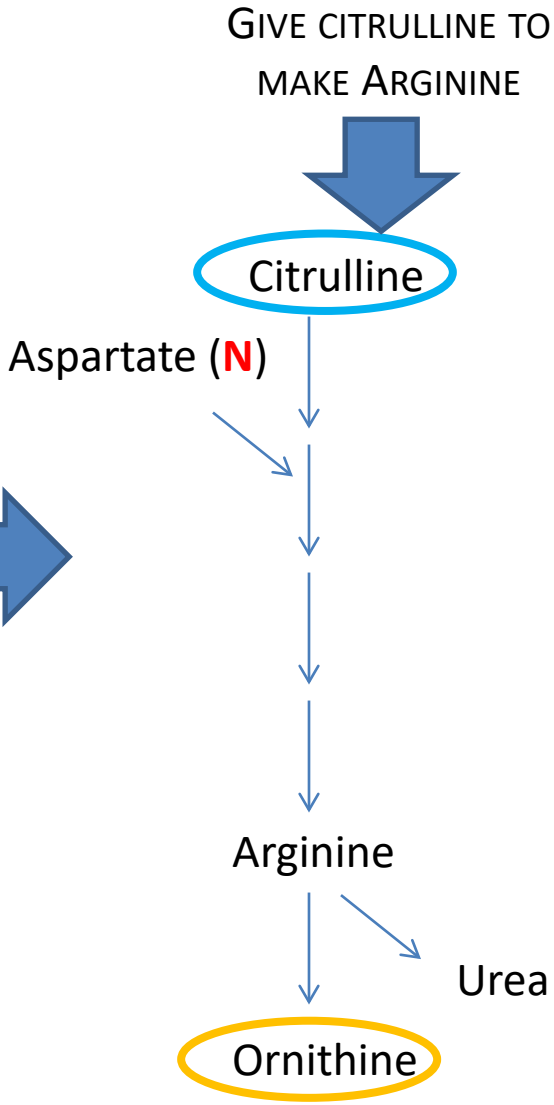
Sandesh C.S. Nagamani [a,*,1], Oleg A. Shchelochkov [a,1], Mary A. Mullins [a], Susan Carter [a,c], Brendan C. Lanpher [a,2], Qin Sun [a], Soledad Kleppe [a,3], Ayelet Erez [a], E. O'Brian Smith [b], Juan C. Marini [b]
Members of the Urea Cycle Disorders Consortium, Brendan Lee [a,c]

[a] *Department of Molecular and Human Genetics, Baylor College of Medicine, Houston, TX, USA*
[b] *Department of Pediatrics/Nutrition, USDA/ARS Children's Nutrition Research Center, Baylor College of Medicine, USA*
[c] *Howard Hughes Medical Institute, Houston, TX, USA*

Arginine supplementation - OTCD







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5) Treatment of intercurrent illness

Maple Syrup Urine Disease

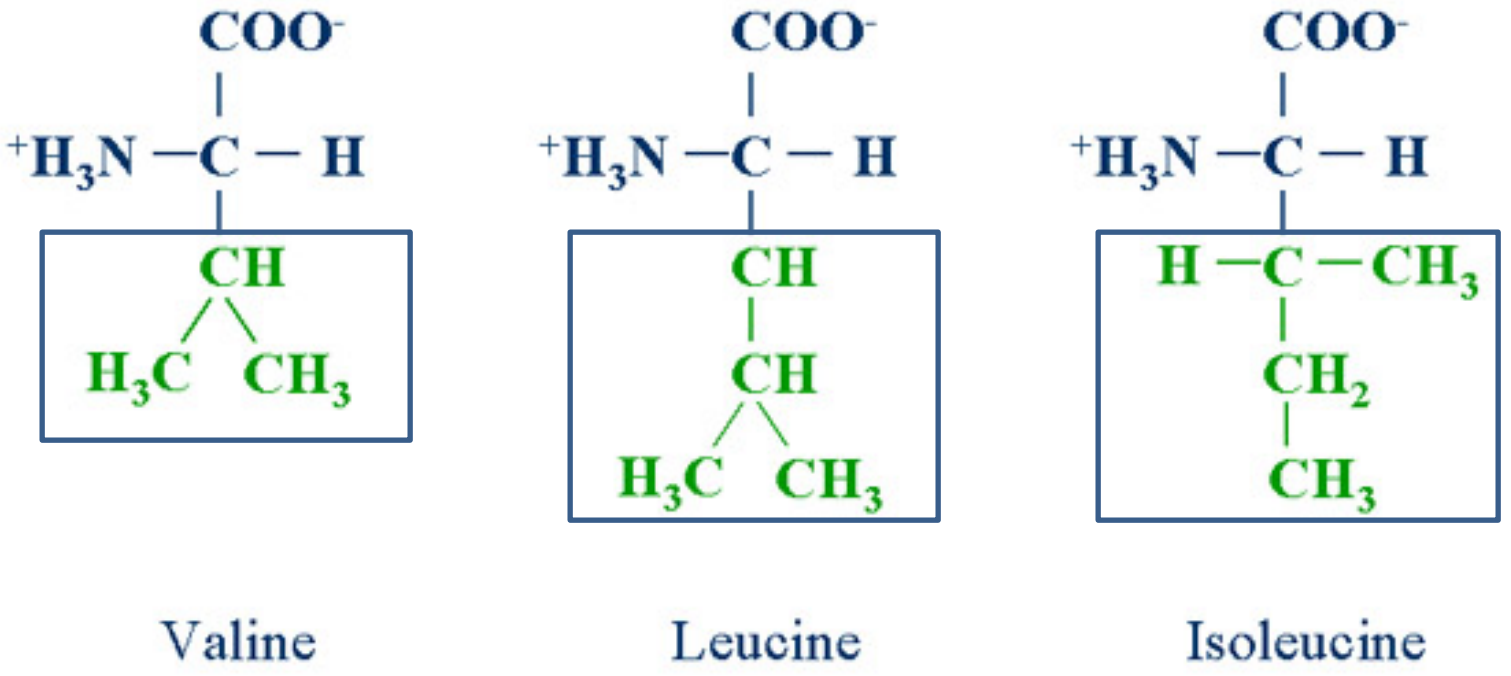
Children's National™

What is MSUD?

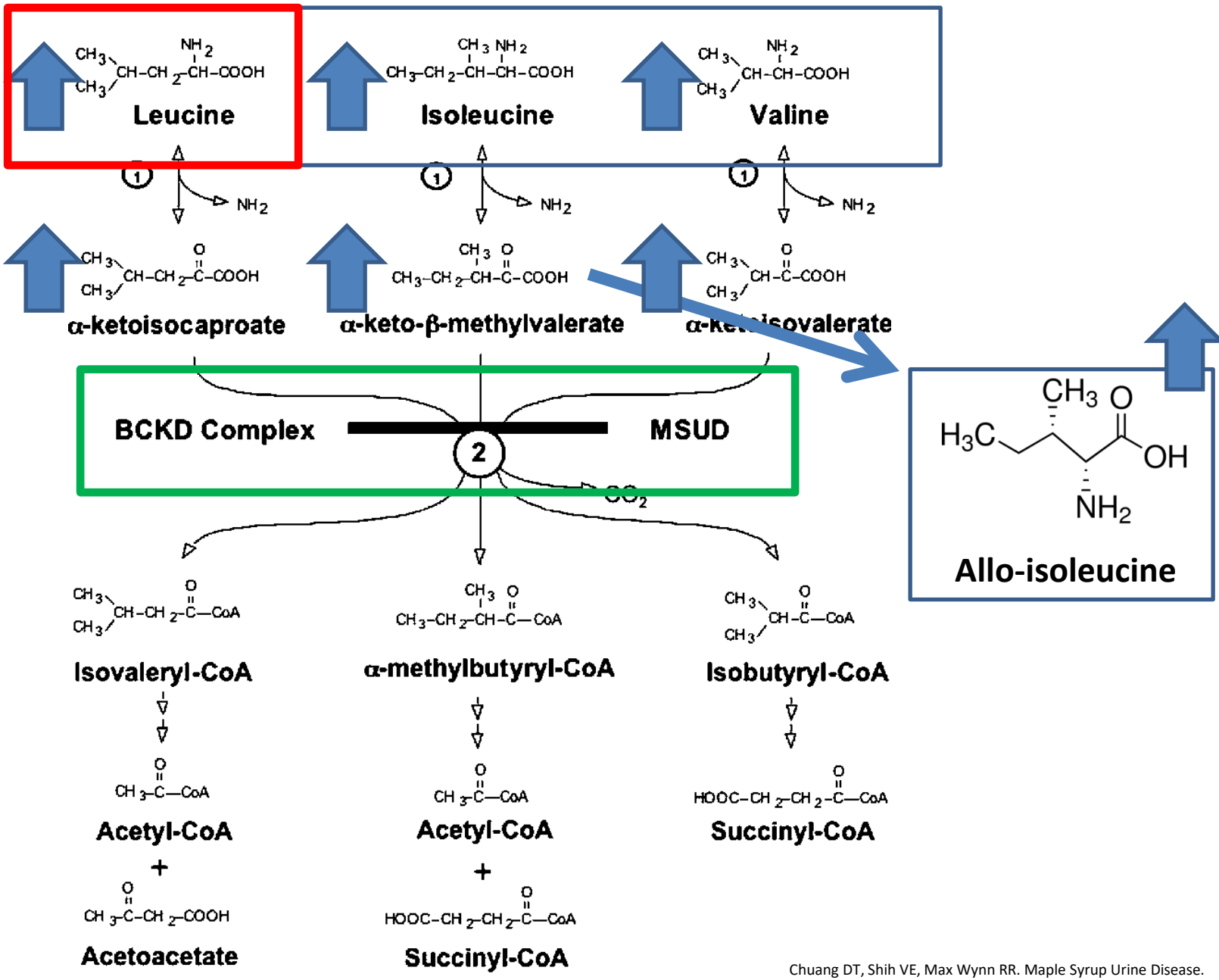
- Maple Syrup Urine Disease
- Caused by a partial or complete lack of Branched-Chain Keto-Acid Dehydrogenase (**BCKD**) complex
- This enzyme is needed in the breakdown of **branched-chain amino acids** (**BCAA**)

What are branched-chain amino acids?

Essential amino acids with branched side chain



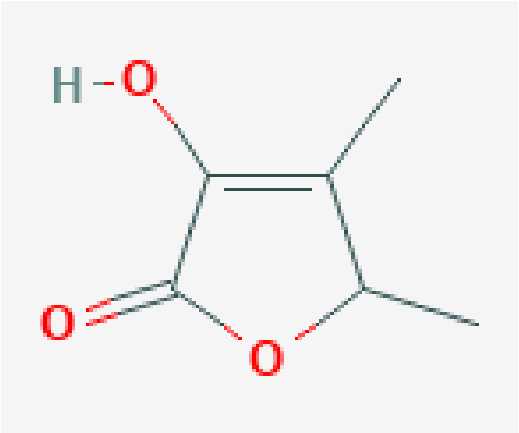
https://www.creative-proteomics.com/images/Branched-chain-amino-acids-1.jpg



Chuang DT, Shih VE, Max Wynn RR. Maple Syrup Urine Disease. In OMMBID – The Online Metabolic and Molecular Bases of Inherited Diseases; 2018

Why is it called Maple Syrup Urine Disease?

- Characteristic “sweet” “burnt sugar” odor
- Comes from a by-product of isoleucine (sotalone)



- Present in urine, ear wax

Snyderman et al. Pediatrics 1964: 34;454

Podebrad et al. JIMD 1999:22(2)

J. Paediatr. Child Health (2001) **37**, 403–404

Pseudo-maple syrup urine disease due to maternal prenatal ingestion of fenugreek

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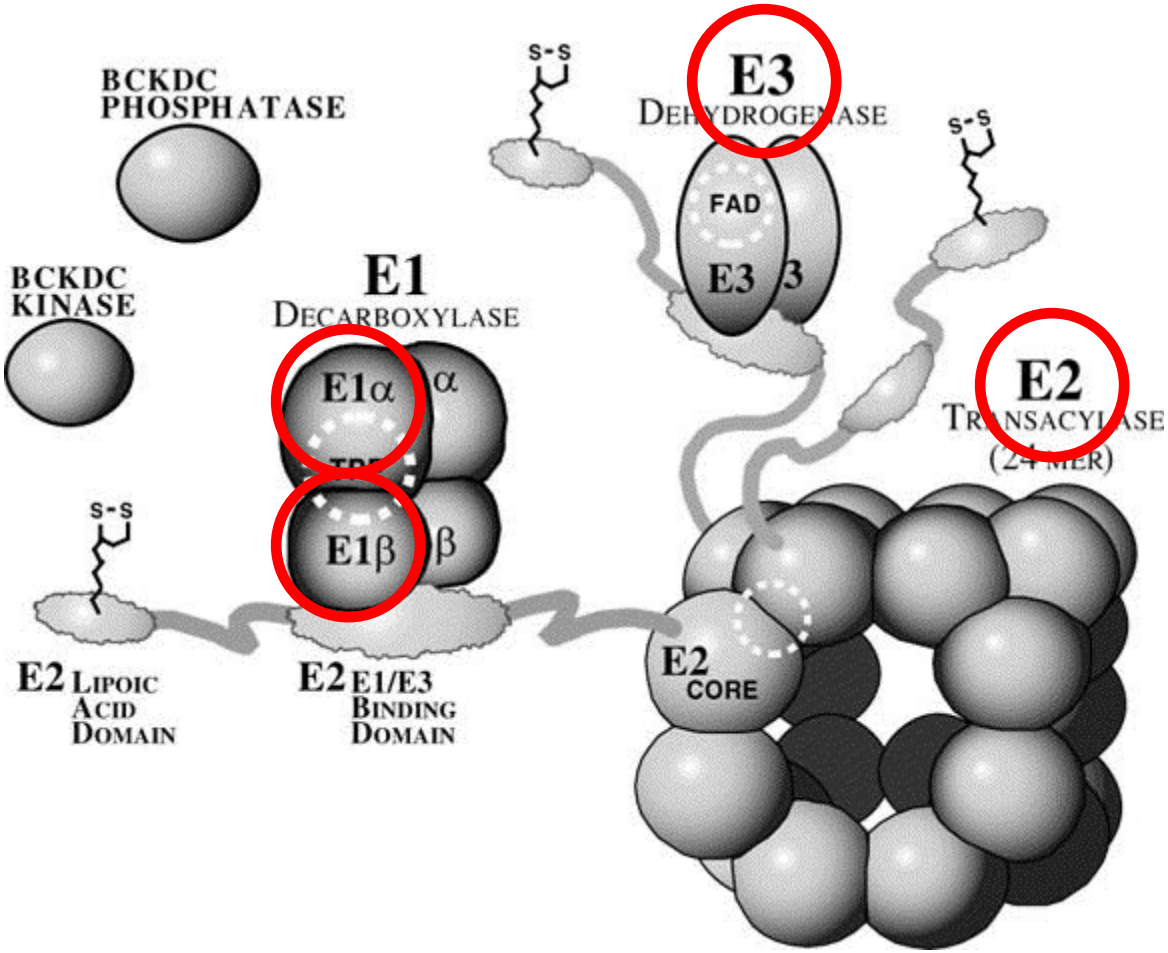
Abstract: Fenugreek, maple syrup and the urine of maple syrup urine disease (MSUD) patients all share a characteristic odour originating from a common component, sotolone. Ingestion of fenugreek by mothers during labour resulted in a maple syrup-like odour in their newborn infants, leading to a false suspicion of MSUD.

The different subunits of BCKD



Chuang DT; J Pediatr. 1998 Mar;132(3 Pt 2):S17-23.

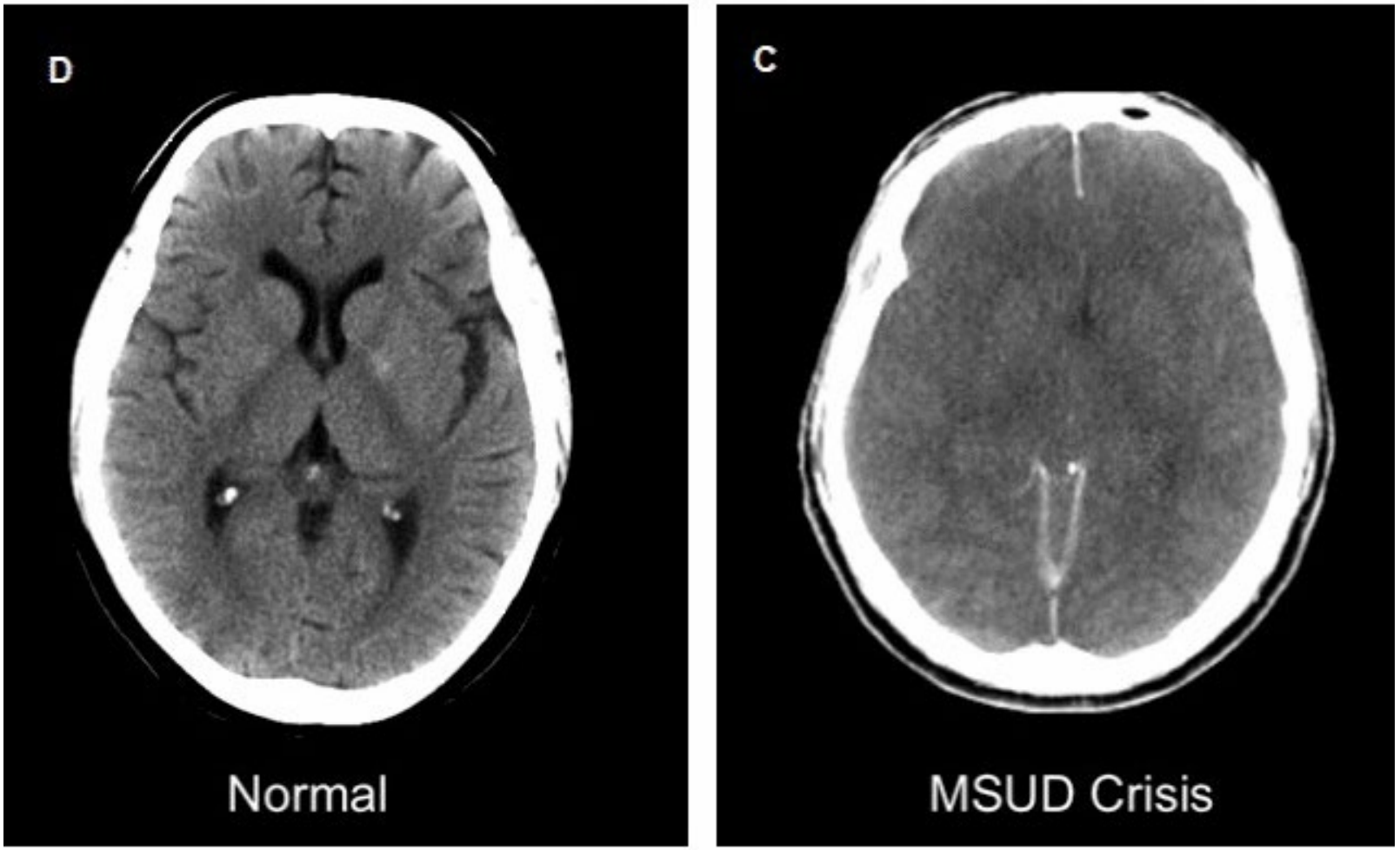
Genetics of MSUD

- Autosomal Recessive
- Incidence ~ 1:185,000
- E1α (gene: *BCKDHA)* (45%)
  - Founder mutation in Mennonite population (T391N)
- E1β (gene: *BCKDHB)* (35%)
  - Founder mutation in Ashkenazi population (R183P)
- E2 (gene: *DBT)* (20%)
  - Some variants are thiamine (vitamin B1) responsive
- E3 (gene: *DLD)*

Types of MSUD

- Classic/Severe
  - Most common and most severe form
  - Neonatal presentation
- Acute Intermittent
  - Non-neonatal, but acute presentation
  - Amino and keto acids may be normal between episodes
- Intermediate / subacute
  - Developmental Delay, Hypotonia, Failure to thrive
- (E3 or DLD deficiency)

Why is a high blood leucine toxic?



Strauss KA, Puffenberger EG, Morton DH. Maple Syrup Urine Disease. 2006 Jan 30 [Updated 2013 May 9]. In: Adam MP, Ardinger HH, Pagon RA, et al., editors. GeneReviews® [Internet]. Seattle (WA): University of Washington, Seattle; 1993-2018. Available from: https://www.ncbi.nlm.nih.gov/books/NBK1319/

Symptoms of acute crisis in MSUD

Symptoms of Acute Intoxication:

- Poor feeding, vomiting
- Irritability, Fatigue
- Neuropsychiatric symptoms
- Lethargy (severe drowsiness) → Coma
- Abnormal tone or movements
- Seizures
- Ataxia

Recommended Uniform Screening Panel
Core Conditions
(As of July 2018)

Core Condition	Metabolic Disorder			Endocrine Disorder	Hemoglobin Disorder	Other Disorder
	Organic acid condition	Fatty acid oxidation disorder	Amino acid disorder			
Propionic Acidemia	X					
Methylmalonic Acidemia (methylmalonyl-CoA mutase)	X					
Methylmalonic Acidemia (Cobalamin disorders)	X					
Isovaleric Acidemia	X					
3-Methylcrotonyl-CoA Carboxylase Deficiency	X					
3-Hydroxy-3-Methyglutaric Aciduria	X					
Holocarboxylase Synthase Deficiency	X					
ß-Ketothiolase Deficiency	X					
Glutaric Acidemia Type I	X					
Carnitine Uptake Defect/Carnitine Transport Defect		X				
Medium-chain Acyl-CoA Dehydrogenase Deficiency		X				
Very Long-chain Acyl-CoA Dehydrogenase Deficiency		X				
Long-chain L-3 Hydroxyacyl-CoA Dehydrogenase Deficiency		X				
Trifunctional Protein Deficiency		X				
Argininosuccinic Aciduria			X			
Citrullinemia, Type I			X			
Maple Syrup Urine Disease			X			
Homocystinuria			X			
Classic Phenylketonuria			X			

https://www.hrsa.gov/sites/default/files/hrsa/advisory-committees/heritable-disorders/rusp/rusp-uniform-screening-panel.pdf

Diagnosis of MSUD

- Confirmation with plasma amino acid profile
  - High leucine, isoleucine, valine and **allo-isoleucine**
  - (Hyponatremia)
- DNA sequencing of BCKD genes
  - *BCKDHA, BCKDHB, DBT, (DLD)*

Thiamine (Vitamin B1) Challenge

- High-dose thiamine (100mg daily) for 30 days
- Periodic measurements of BCAA with diet record to assess leucine tolerance
- Positive response: lower BCAA and/or increased leucine intake
- Changes in diet during the challenge can make results difficult to interpret

Management of acute crises

Promote protein synthesis

- Provide all amino acids *except* leucine
  - BCAA-free formula (by mouth or tube)
  - May give BCAA-free IV solution (parenteral nutrition)
  - Supplement isoleucine and valine

- Reverse catabolism: Give lots of calories
  - BCAA-free formula (by mouth or tube)
  - If not tolerating formula
    - IV calories (typically dextrose at high concentration)
    - May start insulin drip if hyperglycemic

Acute management (con't)

- Use of Normal or Hypertonic Saline
  - (Avoid hypotonic solutions)
- (Mannitol)
- (Diuretics)
- Hemodialysis/filtration

Chronic dietary management

- Exact amount of regular protein (“natural”, “intact”, “complete”)
  - Some teams may measure exact amount of BCAA
- Synthetic formula with everything except leucine, isoleucine, valine
  - Provides calories, essential fats, vitamins, minerals
- Valine and isoleucine supplementation
- Protein-free foods

What are the target BCAA ranges?

- Leucine 75-200 µmol/L
- Isoleucine 200-400 µmol/L
- Valine 200-400 µmol/L

From Genetic Metabolic Dietitians International (GMDI): https://southeastgenetics.org/ngp/guidelines.php/107/nr/43/summary/MSUD%20Nutrition%20Guidelines/Version%201.55/%3Cspan%20class=%22bold%22%3ENutrition%20Recommendations%3C/span%3E

Liver transplantation

- Liver transplant from unrelated donor can restore ~9-13% of whole-body BCKA metabolism
  - Enough to allow less restrictive diet and prevent acute crisis
  - BCAA tend to be ~2x normal, but in normal ratios
- Domino liver transplants have been successful

Thank you!

Questions?