Introduction to Organic Acidemias

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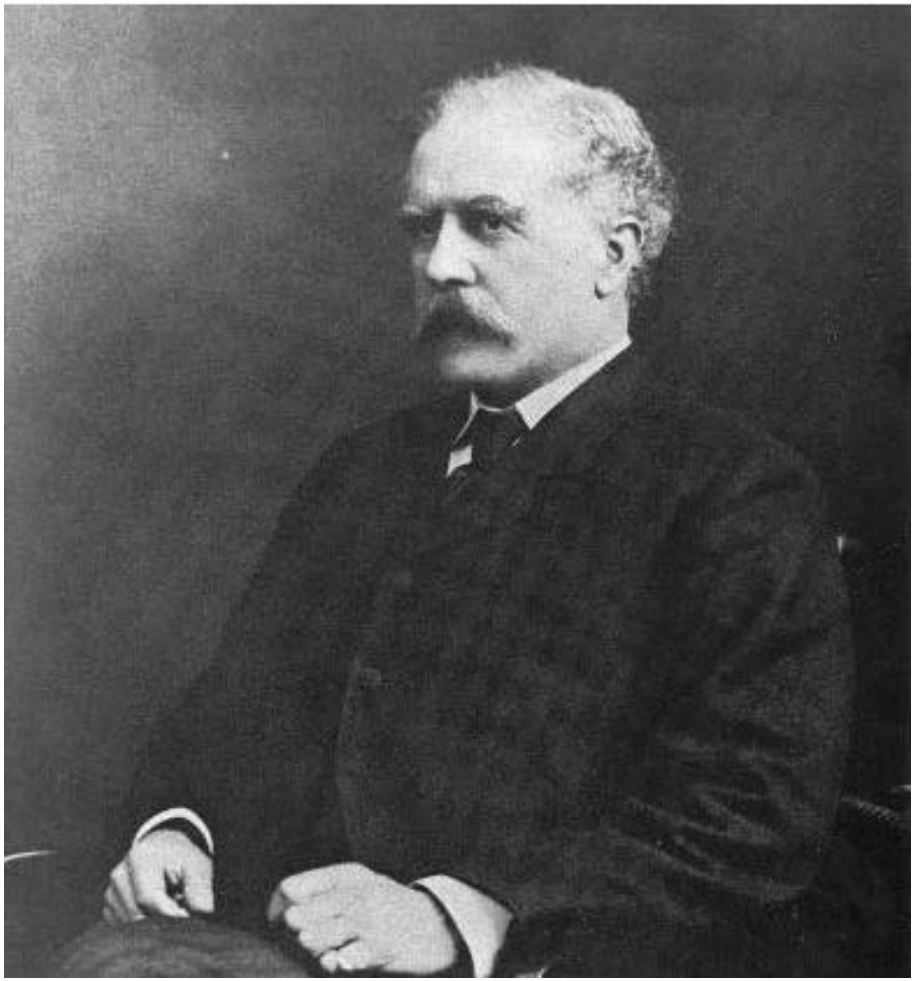
A Brief Historical Overview

Sir Archibald Garrod



THE INCIDENCE OF ALKAPTONURIA:

A STUDY IN CHEMICAL INDIVIDUALITY

ARCHIBALD E. GARROD

Physician to the Hospital for Sick Children,

Great Ormond Street,

Demonstrator of Chemical Pathology at St. Bartholemew's Hospital

Garrod, Archibald E. 1902. The Incidence of Alkaptonuria: A Study in Chemical Individuality. *Lancet, vol. ii, pp. 1616-1620.*

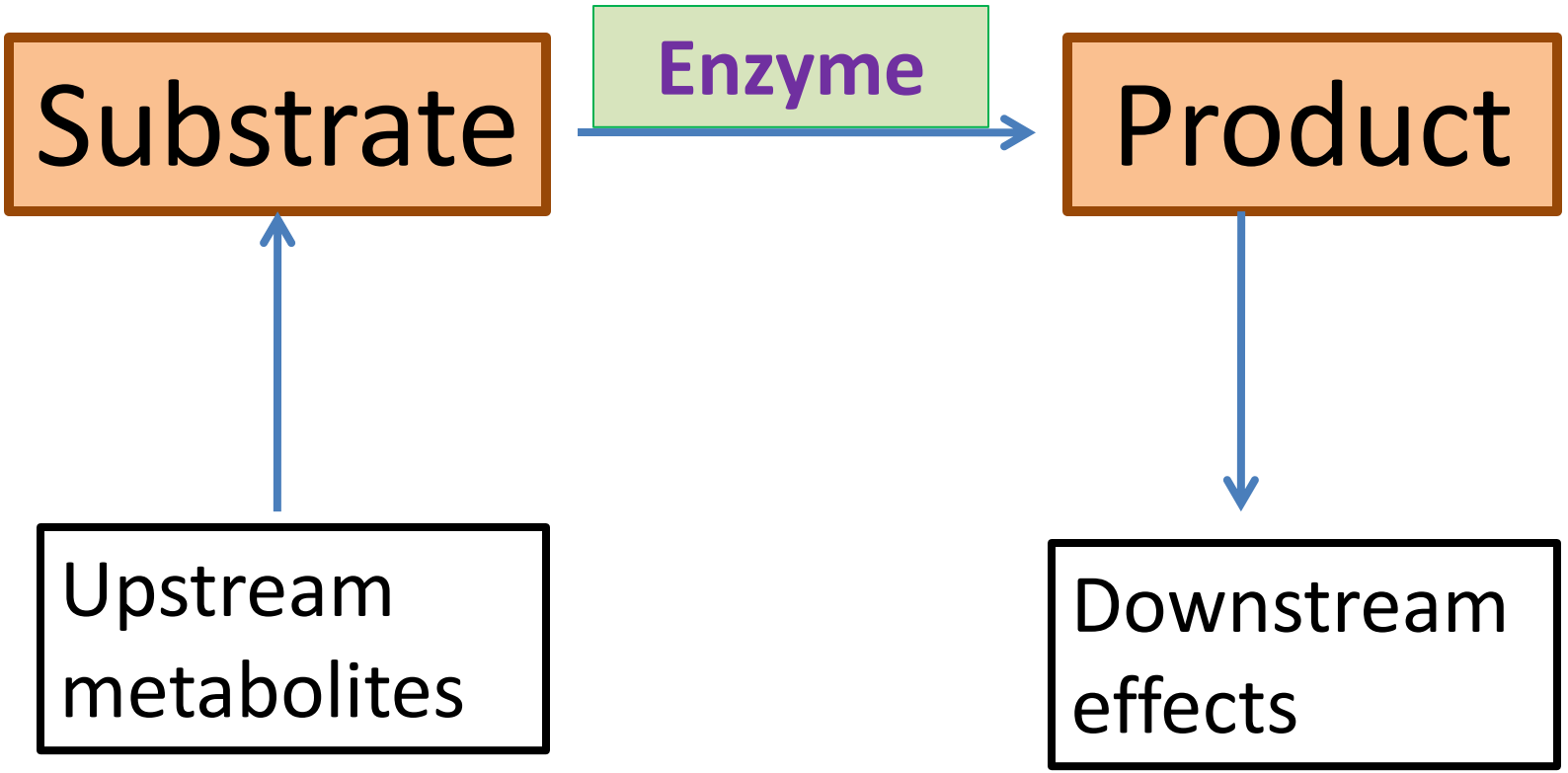
Sir Archibald Garrod

- Alkaptonuria followed autosomal inheritance
- hypothesized that it was caused by a mutation in a gene encoding an enzyme involved in the metabolism of ‘alkaptans’
- *The Incidence of Alkaptonuria: a Study in Chemical Individuality* in 1902
- formulated the "one gene, one enzyme" hypothesis and described recessive inheritance in enzyme defects
- presented this work to the Royal College of Physicians in a lecture entitled *Inborn Errors of Metabolism* in 1908.

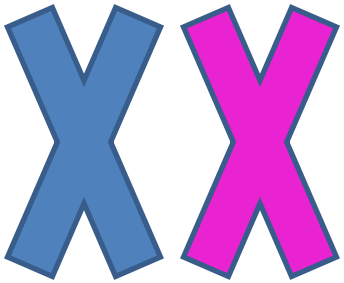
Inborn Errors of Metabolism

- Genetic disorders involving disorders of metabolism.
- Most are enzyme defects disrupt conversion of substrates into products.
- In most of the disorders, problems arise due to accumulation of toxic upstream substances, or to the effects of reduced downstream essential compounds.

Inborn Errors of Metabolism



One gene, One enzyme

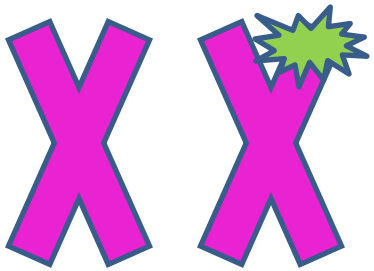


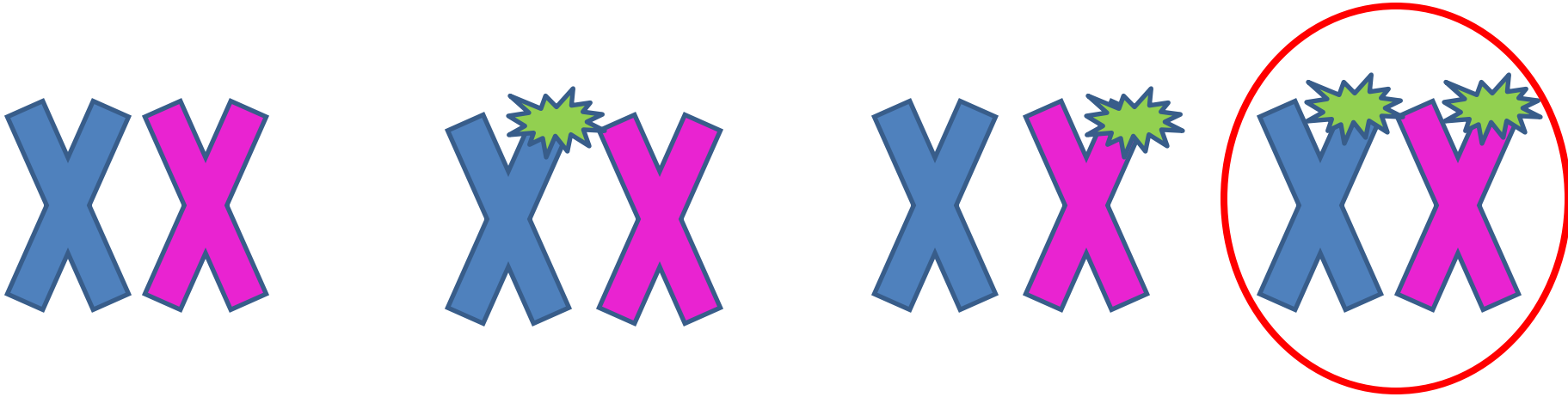
Gene

Enzyme

Substrate  Product

Autosomal Recessive Inheritance

Father   Mother



Children

Definition: Organic Acidemia

- Organic acidemias are characterized by abnormal amounts or types of organic acids in the urine and other body fluids
- The diagnosis is made by detecting an abnormal pattern of organic acids in a urine sample
  - via GC/MS
- In some conditions, the urine is always abnormal, in others the diagnostic organic acids are present (or at high levels) only intermittently

Diagnosis and treatment overview

Examples of Organic Acidemias (OAs)

- Disorders of Branch Chain amino acid metabolism
- Cerebral organic acidemias
- Ketogenesis/Ketolysis disorders
- and other disorders

3 different clinical presentations

- Most characteristic of disorders of branch chain amino acid metabolism
- Severe, neonatal-onset form
- Acute, intermittent, late-onset form
- Chronic, progressive form

Severe, neonatal-onset form

- Symptoms begin after a brief symptom-free period (hours or weeks)
- Drowsiness progresses to poor feeding, lethargy, possibly coma
- Abnormal laboratory values
  - Acidosis
  - Elevated ammonia
  - Elevated lactate
  - Hyper or hypoglycemia
  - Pancytopenia

Acute, intermittent, late-onset form

- 25% of cases
- present after symptom-free period
  - After 1 year of age
- Recurrent crises
- Onset of crises may be precipitated by catabolic stress
  - i.e. illness, high protein intake.

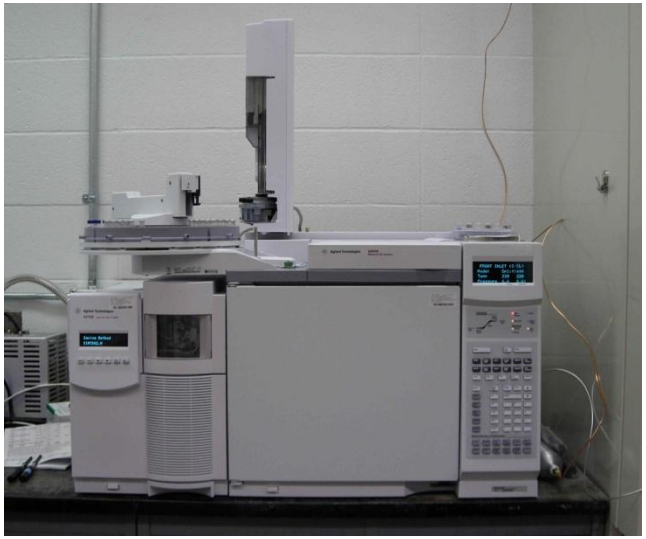
Chronic, progressive form

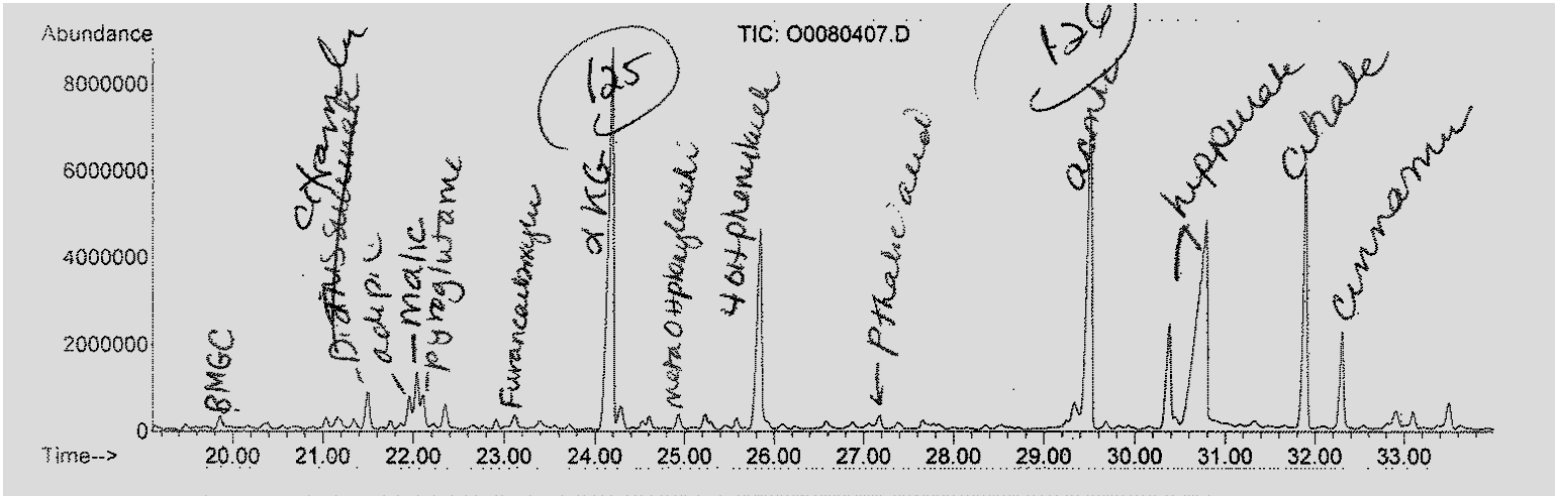
- Persistent poor feeding, chronic vomiting
- Low tone
- Failure to thrive
- Developmental delay
- May be misdiagnosed as milk-protein intolerance, celiac disease or other more common chronic illnesses

Diagnosis

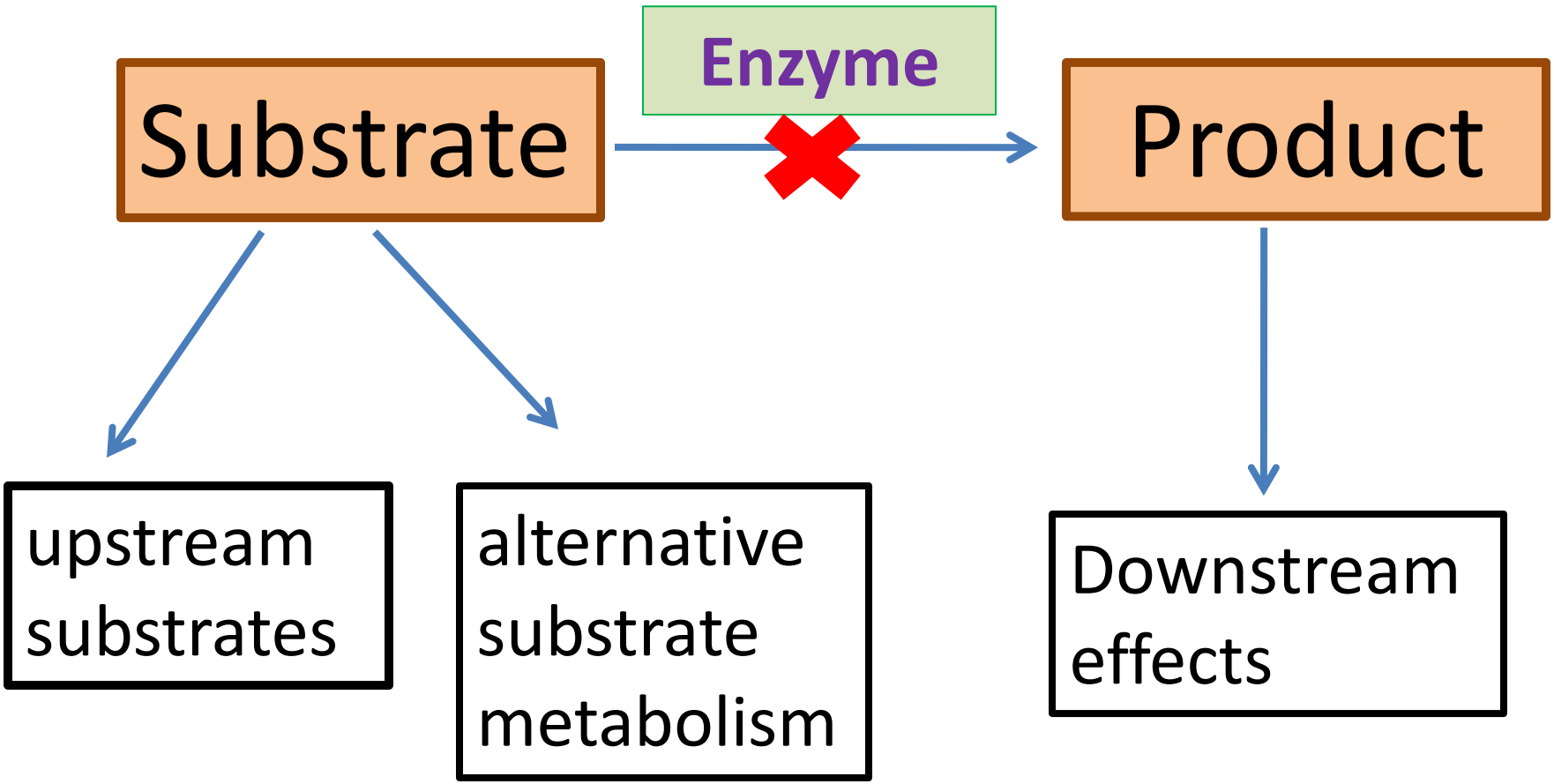
- Newborn Screen
  - Results must be confirmed by definitive testing
- Detection of organic acids in the urine
  - Urine organic acids
  - Acylglycines
- Detection of organic acid metabolites in the blood
  - acylcarnitines

Organic Acid Analysis





Principles of Treatment

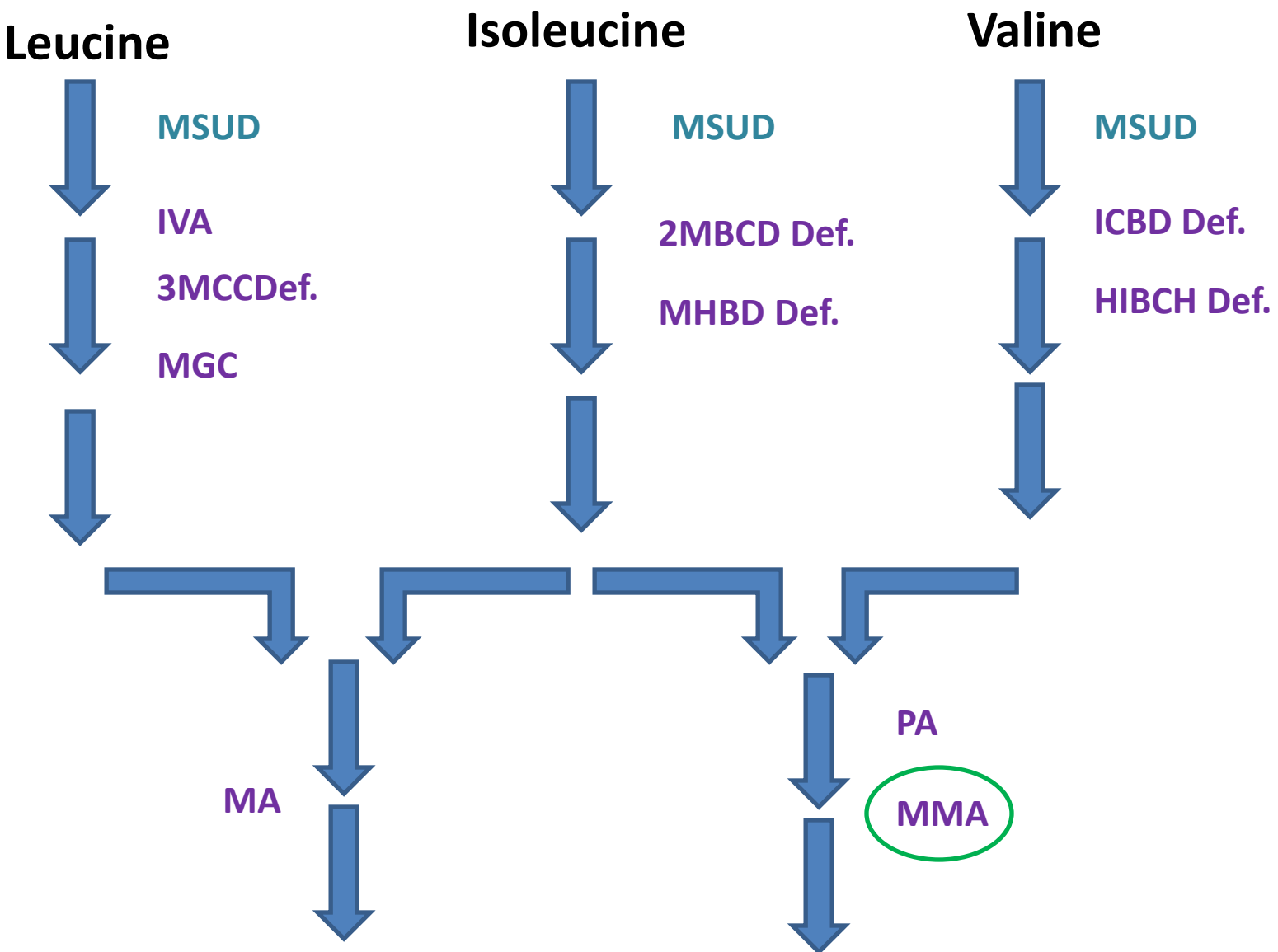


General Principles of Treatment

- Prevention of triggers for decompensation
  - Fever, illness, protein overload, dehydration
- Correct acute/sudden changes in body metabolism
  - Correct acidosis, hyperammonemia, glucose imbalance
- Reduce toxic substrates
  - Organic acids, etc.

OA of Branch Chain Amino Acid (BCAA) Metabolism: Methylmalonic Acidemia

Disorders BCAA Metabolism

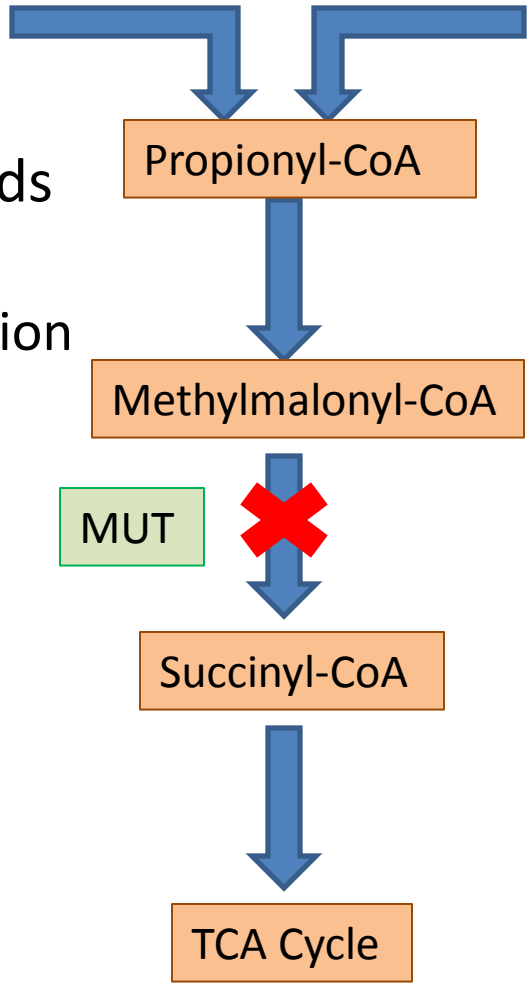


First OA of BCAA reported: Propionic Acidemia

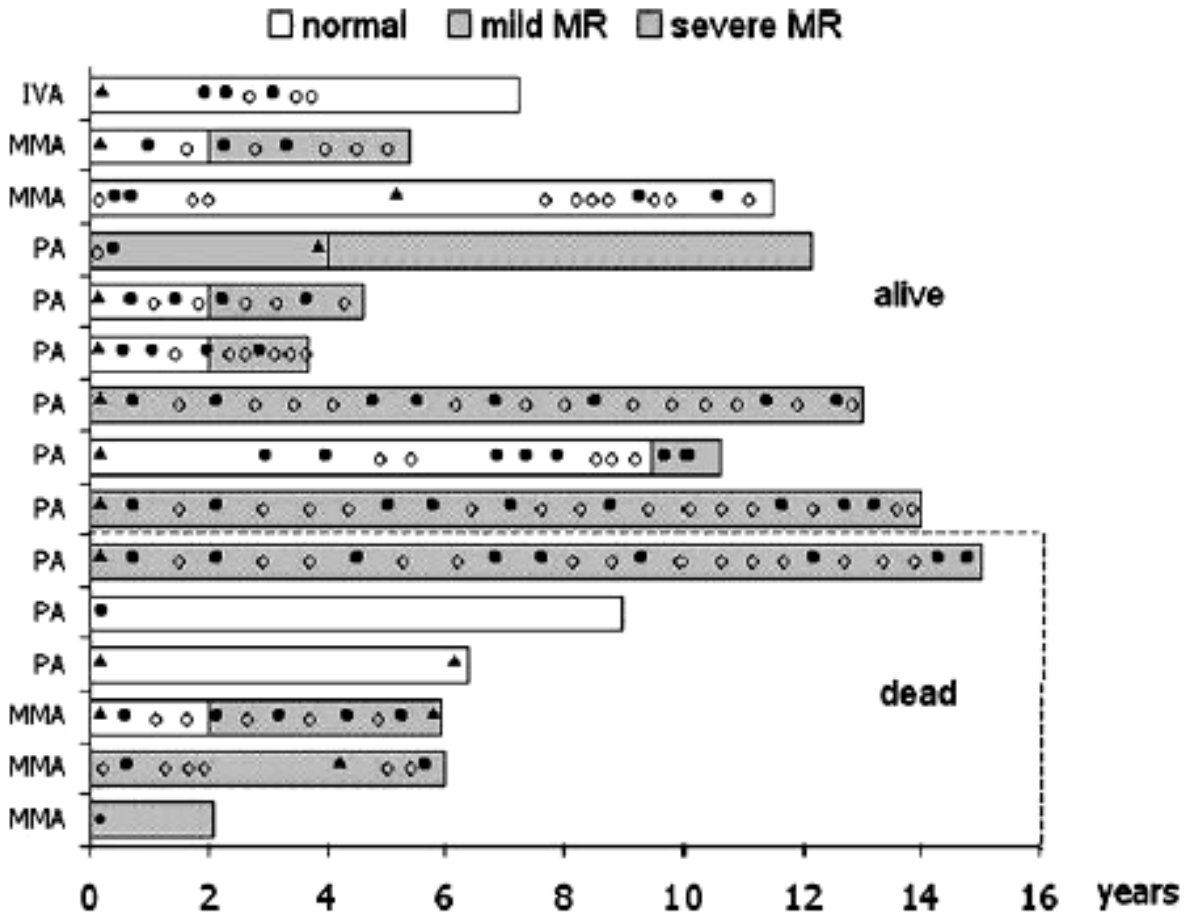
- First reported in 1961
  - Ketones, hyperglycinemia
  - Developmental delay
  - Neutropenia
- Primary biochemical abnormality described later
  - Propionic Acidemia

Methylmalonic Acidemia

- 1/50,000
  - defect in MUT
  - vitamin B12 metabolism
- Massive elevation of MMA in all body fluids
- Acute Crises
  - episodic metabolic acidosis/decompensation
  - metabolic stroke
  - pancreatitis
- Chronic Medical Conditions
  - kidney failure,
  - failure to thrive,
  - intellectual disability
  - cardiomyopathy
  - optic nerve atrophy

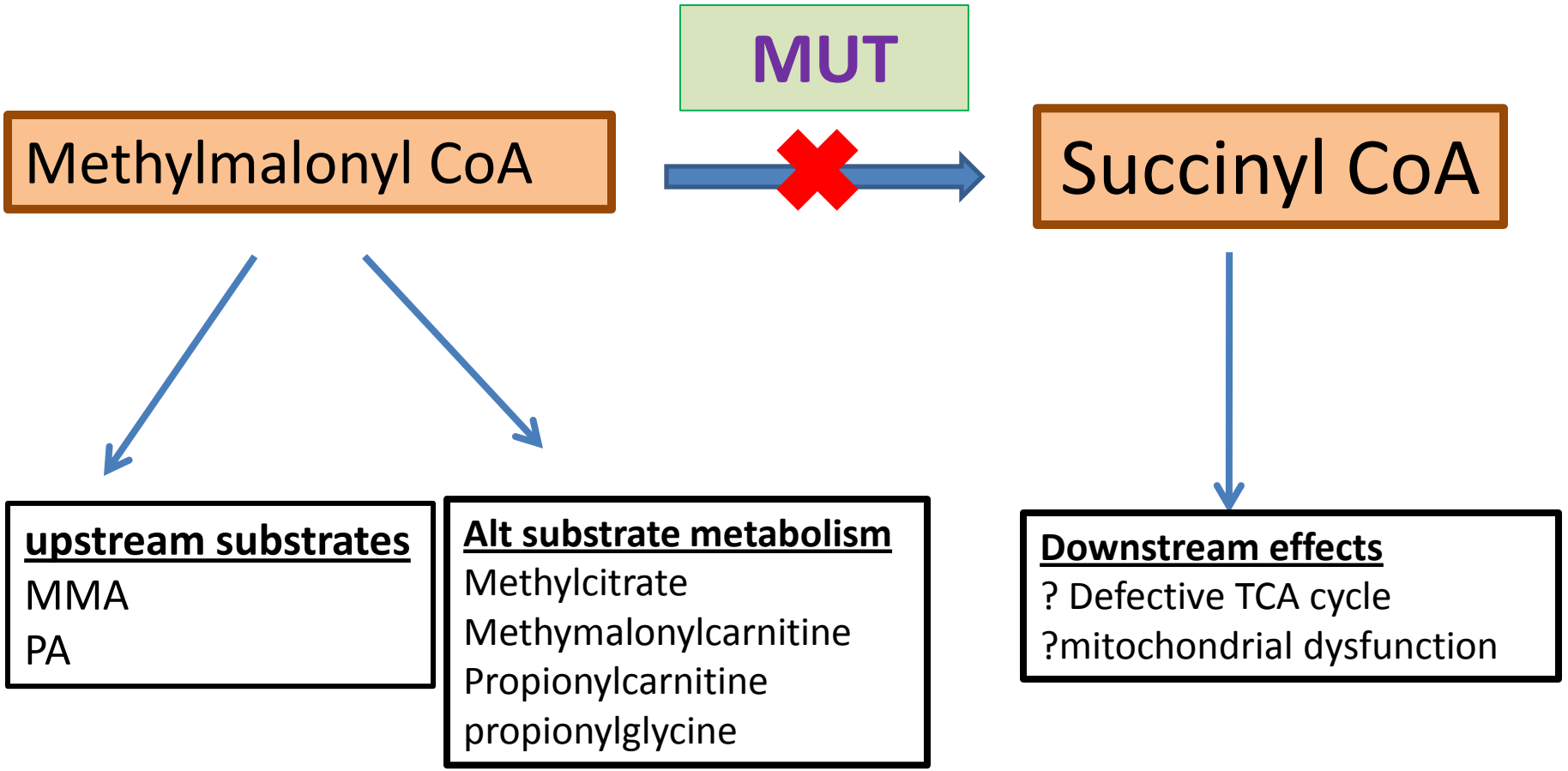


Morbidity in MMA/PA/IVA

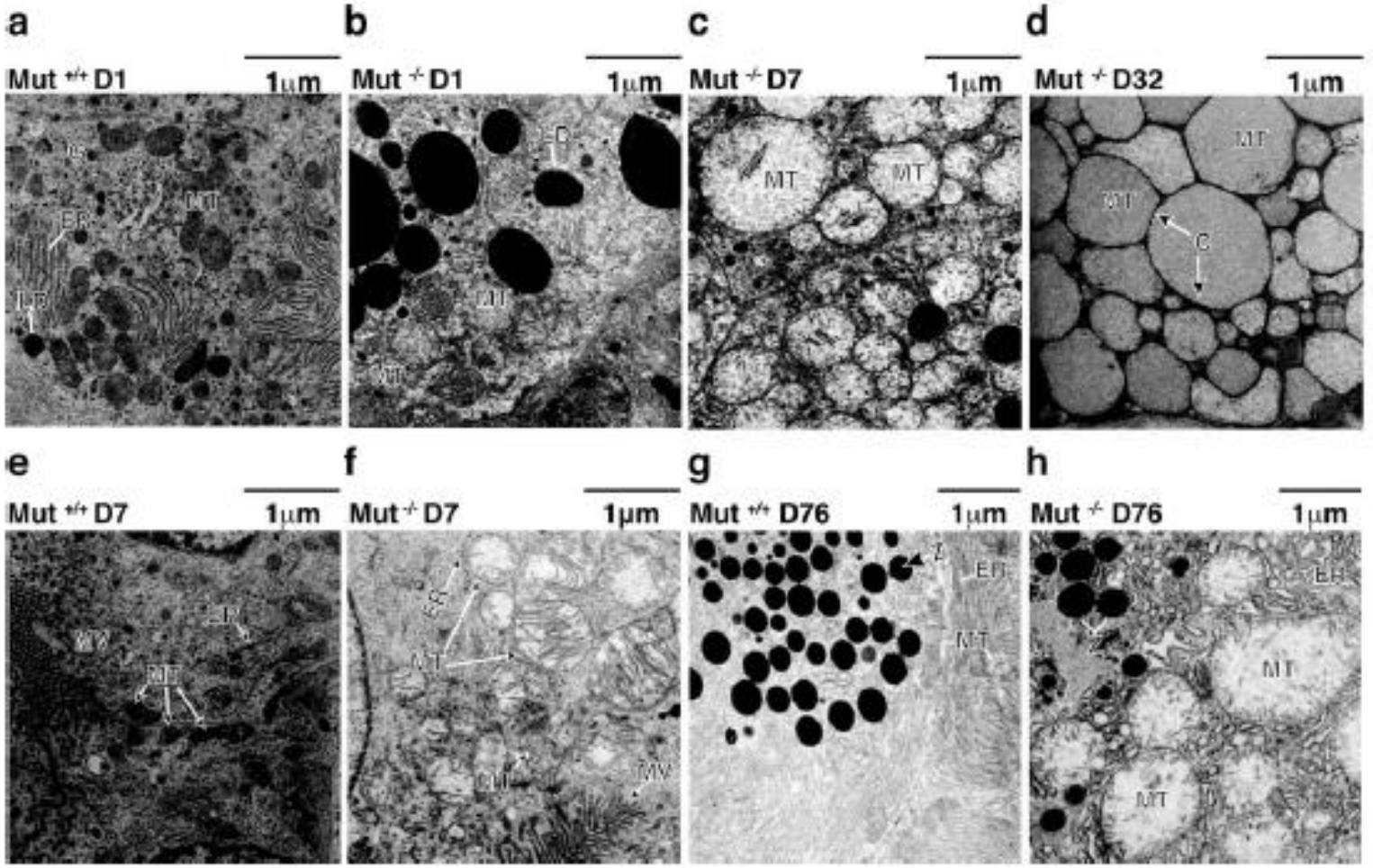


Dionisi-Visi et al. J Inherited Metab Dis (2006) 29: 383-389.

Targets for Treatment



Further downstream disturbance: Mitochondrial Dysfunction



Chandler et al. FASEB (2009) 23, 1254.

Principles of Therapy: MMA

- Chronic management
  - Prevention of triggers for decompensation
    - Fever, illness, protein overload, dehydration
  - Dietary management
    - Protein, fat, carbohydrate balance
- Acute management
  - Correct acute/sudden changes in body metabolism
    - Acidosis, hyperammonemia, glucose
- Mitochondrial protection?
  - antioxidants

Cerebral OA:
Glutaric Acidemia, Type I

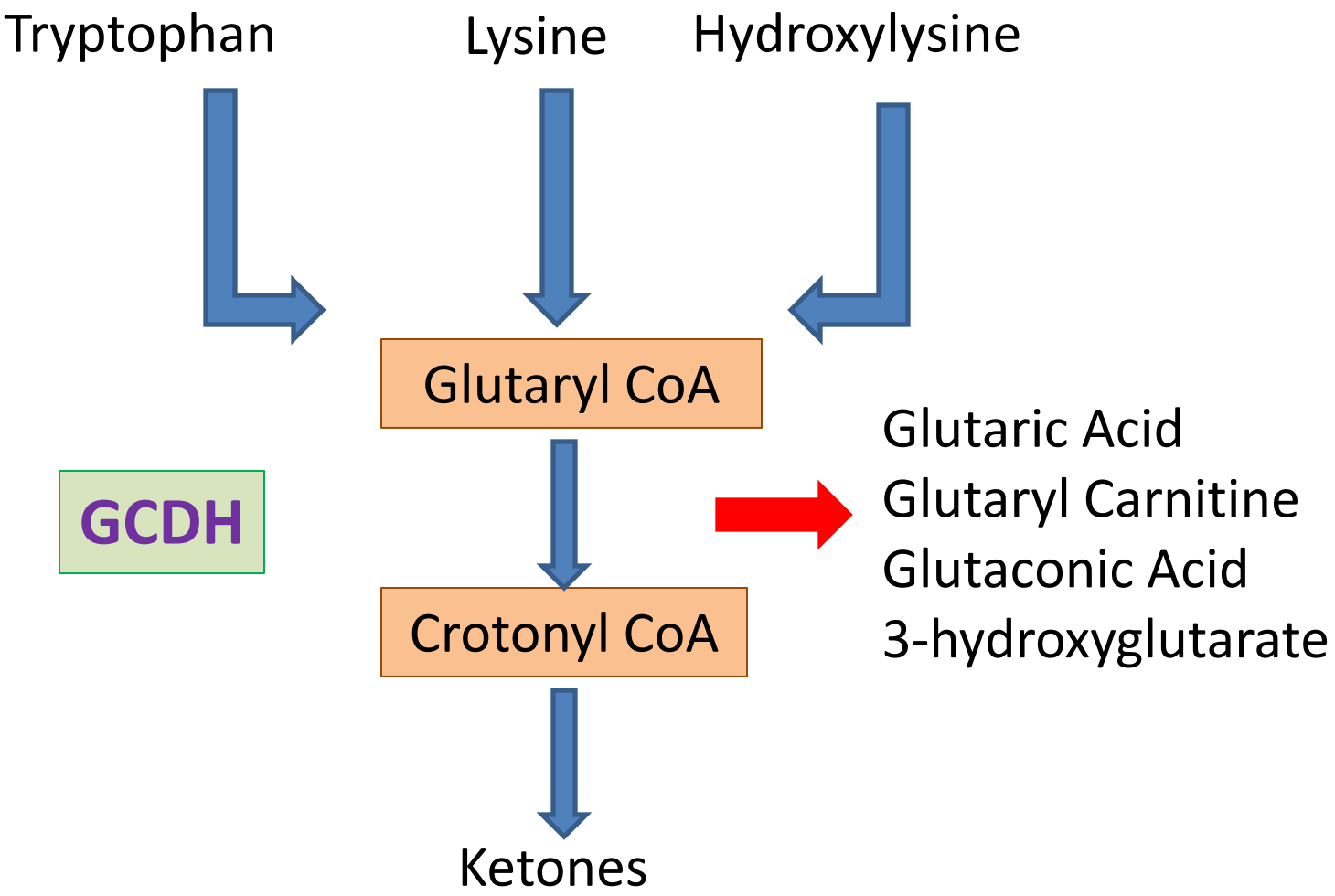
Glutaric Acidemia Type I

- Deficient function of GCDH
- Inability to metabolize lysine, hydroxylysine, and tryptophan
- The products of alternative metabolism of this defect are neurotoxic
  - Glutaric Acid
  - Glutaryl-CoA
  - Glutaconic acid
  - 3-hydroxyglutarate

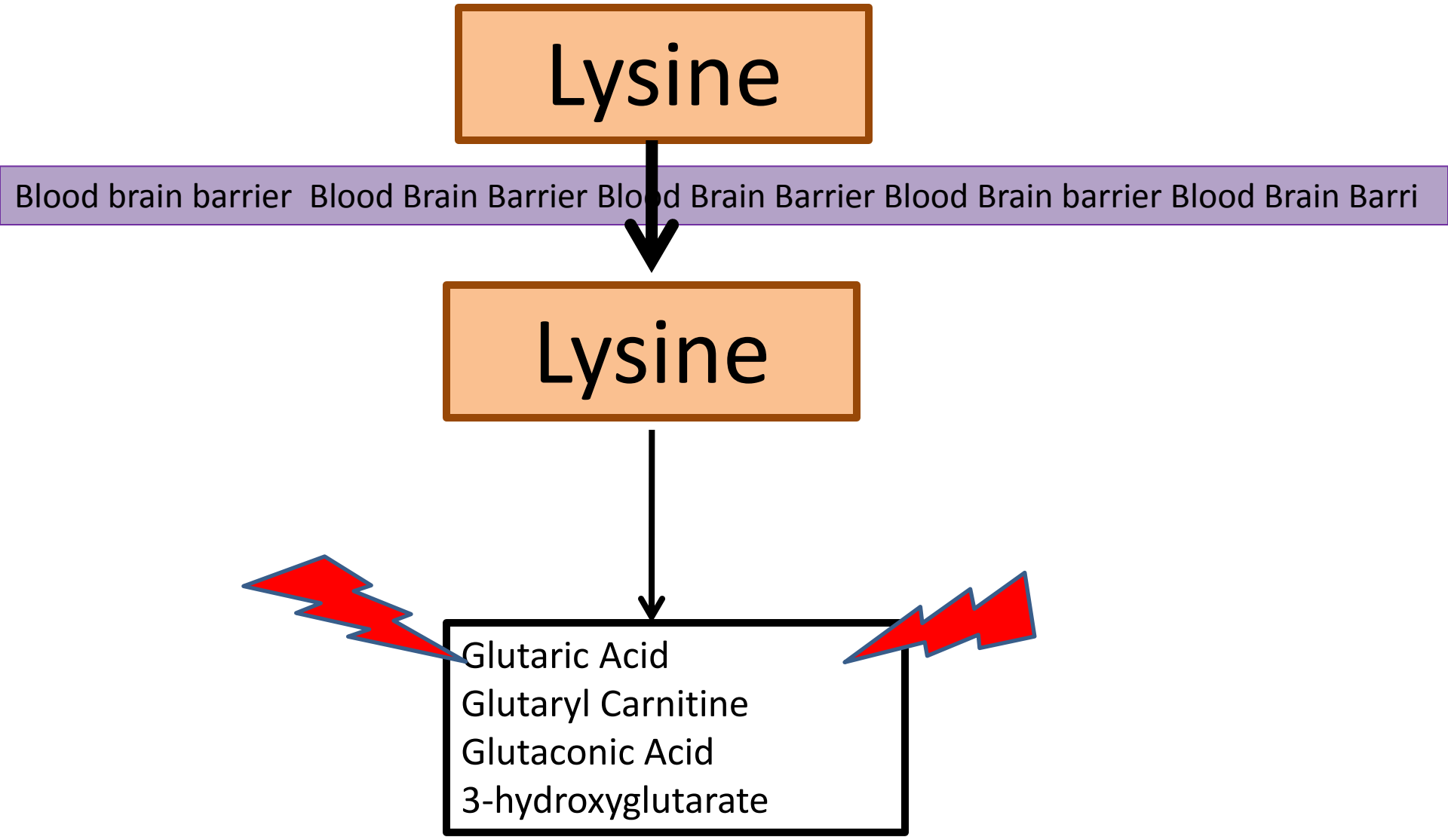
Cerebral Metabolic Crisis

- >90% of untreated patients will have an acute brain injury b/w 3-36 months
  - Typically bilateral striatal infarction
- Acute loss of physical abilities
  - Ability to sit, swallow, maintain head control
  - Profound hypotonia
- Leads to a permanent, often severe movement disorder

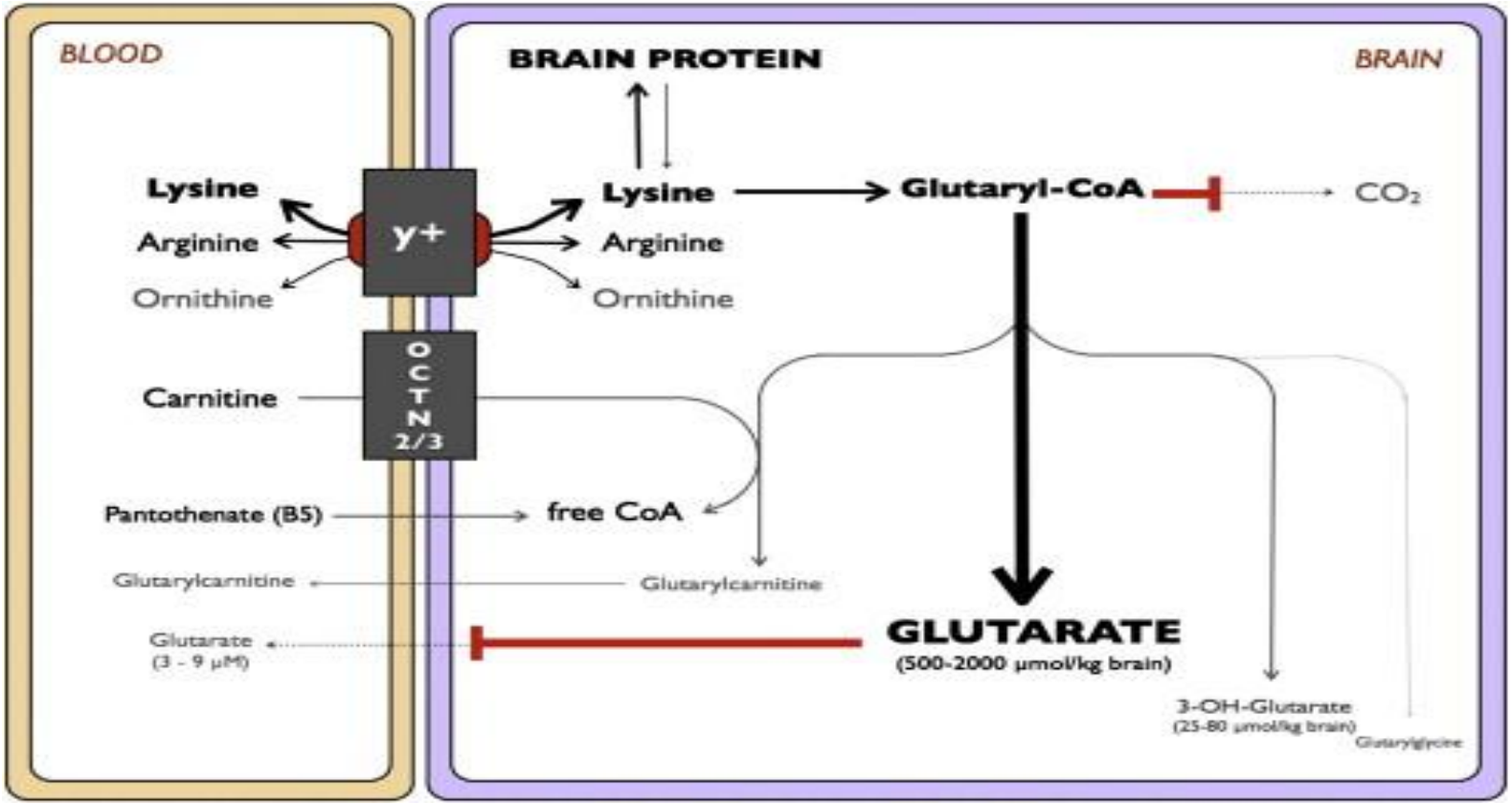
Lysine Metabolism



Principles of Treatment



Managing Blood Brain Barrier Transport



Kevin A. Strauss , Joan Brumbaugh , Alana Duffy , Bridget Wardley , Donna Robinson , Christine Hendrickson , Silvi...

Molecular Genetics and Metabolism Volume 104, Issues 1?2 2011 93 - 106

Treatment

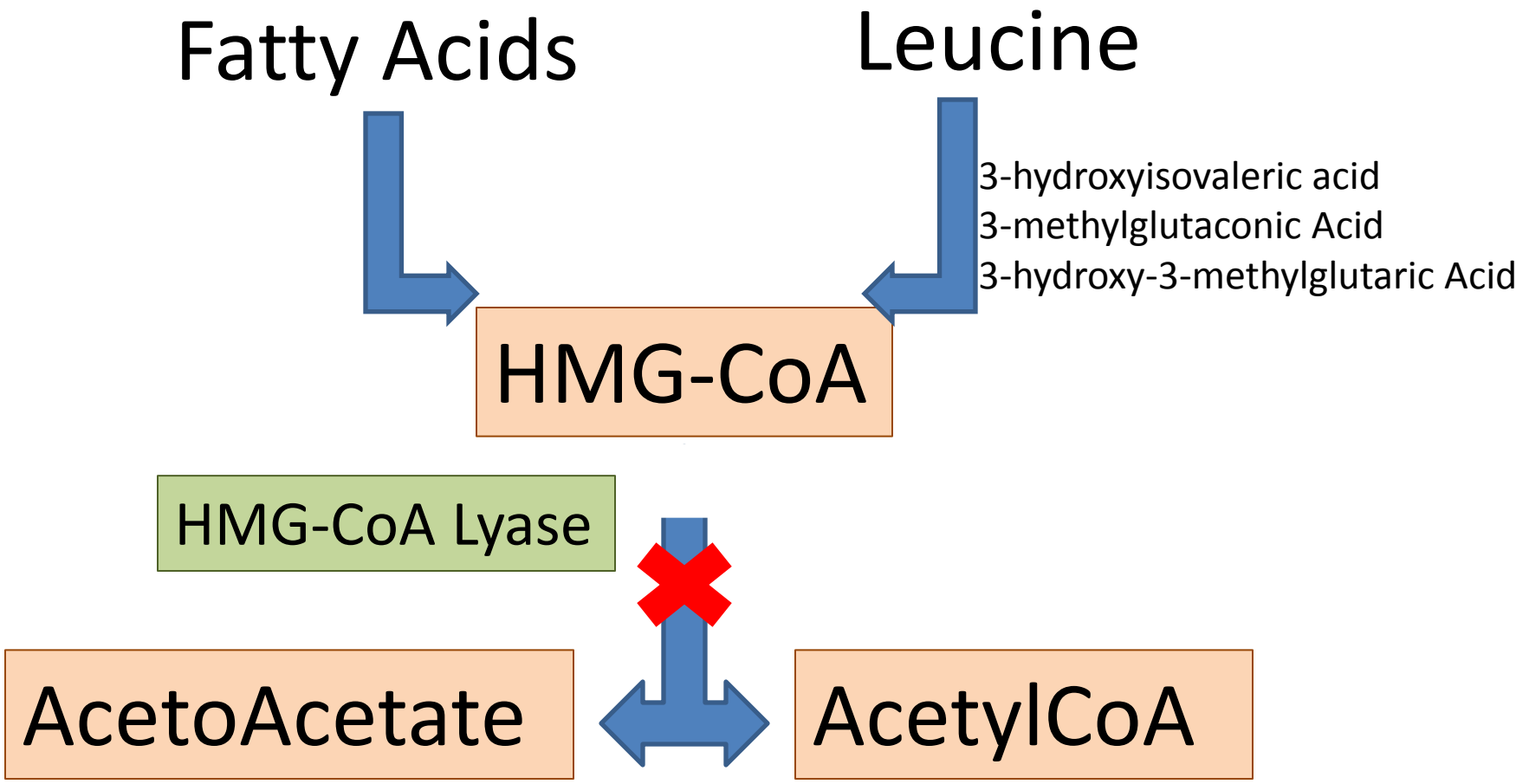
- Employ a formula to restrict cerebral lysine uptake
  - competition between lysine and arginine at the blood–brain barrier
- Lys and Arg share a common cerebrovascular cationic transporter (y + system)
- Highly successful in preventing cerebral crises

Disorder of Ketogenesis: HMG-CoA Lyase Deficiency

HMG CoA Lyase Deficiency

- Defective function of 3-Hydroxy-3-Methylglutaryl-CoA Lyase
  - crossover between ketogenesis and leucine metabolism
- Insufficient production of the ketones acetyl-CoA and acetoacetate
  - Leads to glucose overutilization
  - Hypoglycemia, lactic acidosis, liver dysfunction

HMG CoA Lyase Deficiency



Treatment: Avoid Need for Ketones

- High carbohydrate, moderate protein and low fat diet
- Prevention of triggers for decompensation
  - Fever, illness, fasting, dehydration
- Correct acute/sudden changes in body metabolism
  - Correct acidosis, hypoglycemia

Summary

- OAs are a heterogeneous group of inherited genetic conditions that result in accumulation of metabolites with similar chemical structures (“organic acids”)
- Treatment is centered around
  - Preservation of metabolic stability
  - Management of acute crises
- The upstream and downstream metabolic consequences are better understood and better controlled on some disorders more than others
- Advances in understanding many OAs is rapidly progressing

Thank you and Questions