"Genética e Hígado: Cómo contribuye la genética en el algoritmo diagnóstico de la enfermedad hepática pediátrica?"

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'Genetic disorders are rare – why do I need to consider them?'

- 30-50% of liver disease in children < 5y were due to a genetic etiology
- The younger the patient, the more likely a genetic etiology
- Focus on metabolic disorders for which treatments are available
  - Disorders of intermediary metabolism
  - All are autosomal recessive disorders

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Categories of metabolic liver disease

- Hepatocellular dysfunction
- Hepatosplenomegaly
- Cholestasis
- Recurrent Hypoglycemia

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Hepatocellular dysfunction

- Galactosemia
- Tyrosinemia
- Urea cycle disorders
- Mitochondrial DNA depletion syndromes
- Valproate induced liver disease
- Bile acid synthetic disorders
- Mevalonic aciduria
- Wilson's disease

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King's college study (2005-2015)

36 of 127 with acute liver failure had metabolic cause:

- Galactosemia: 17
- Mitochondrial disorder: 7
- Urea cycle disorder: 4
- Tyrosinemia type I: 4
- Niemann-Pick disease type C: 3
- Disorder of glycosylation: 1

Eur J Pediatr. 2015 Oct;174(10):1387-92

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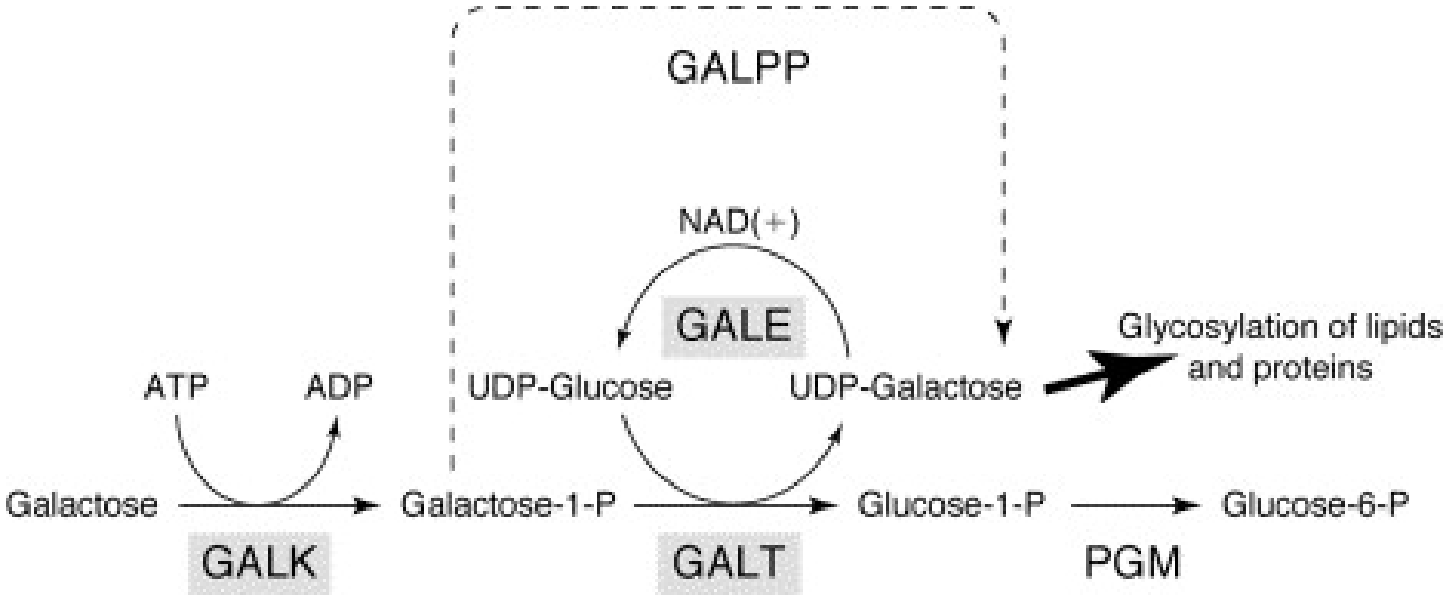
Galactose metabolism – the Leloir pathway



Galactose-1-Phosphate UridylTransferase

Trends Genet. 1998 Mar;14(3):98-102.

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Galactosemia - Clinical features

- Failure to thrive
- Liver dysfunction
- Jaundice (unconjugated → conjugated)
- E-coli sepsis

- Learning difficulties
- Primary ovarian insufficiency

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Galactosemia - Diagnosis

- Urine reducing substances
  - Identifies excess sugars in urine
  - If no glycosuria, suggestive of Galactosemia
- Diagnostic testing:
  - ↓ Erythrocyte GALT enzyme activity <10-15% activity
  - ↑ Erythrocyte Galactose-1-Phosphate
- DNA sequencing
- Pitfalls of newborn screening:
  - False positives in summer: GALT is a heat-sensitive enzyme
  - Duarte variant: ~25% of enzyme activity

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Galactosemia - Case presentation

- 1 month-old boy, missed newborn screen
  - AST: 292 U/L (3-34)
  - ALT: 115 U/L (15-41)
  - INR: 2.8 (0.8-1.2)
  - PTT: 55 (23-36)
  - Total Bilirubin: 9 mg/dl (0.2-1.3)
  - Direct Bilirubin: 5 mg/dl(<0.3)

- Liver transplant
  - Does not completely correct blood galactose levels

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Galactosemia - Management

- Avoidance of dietary galactose
  - Avoid lactose
  - Avoid breastmilk AND milk-based formulas
- Annual ophthalmologic exam

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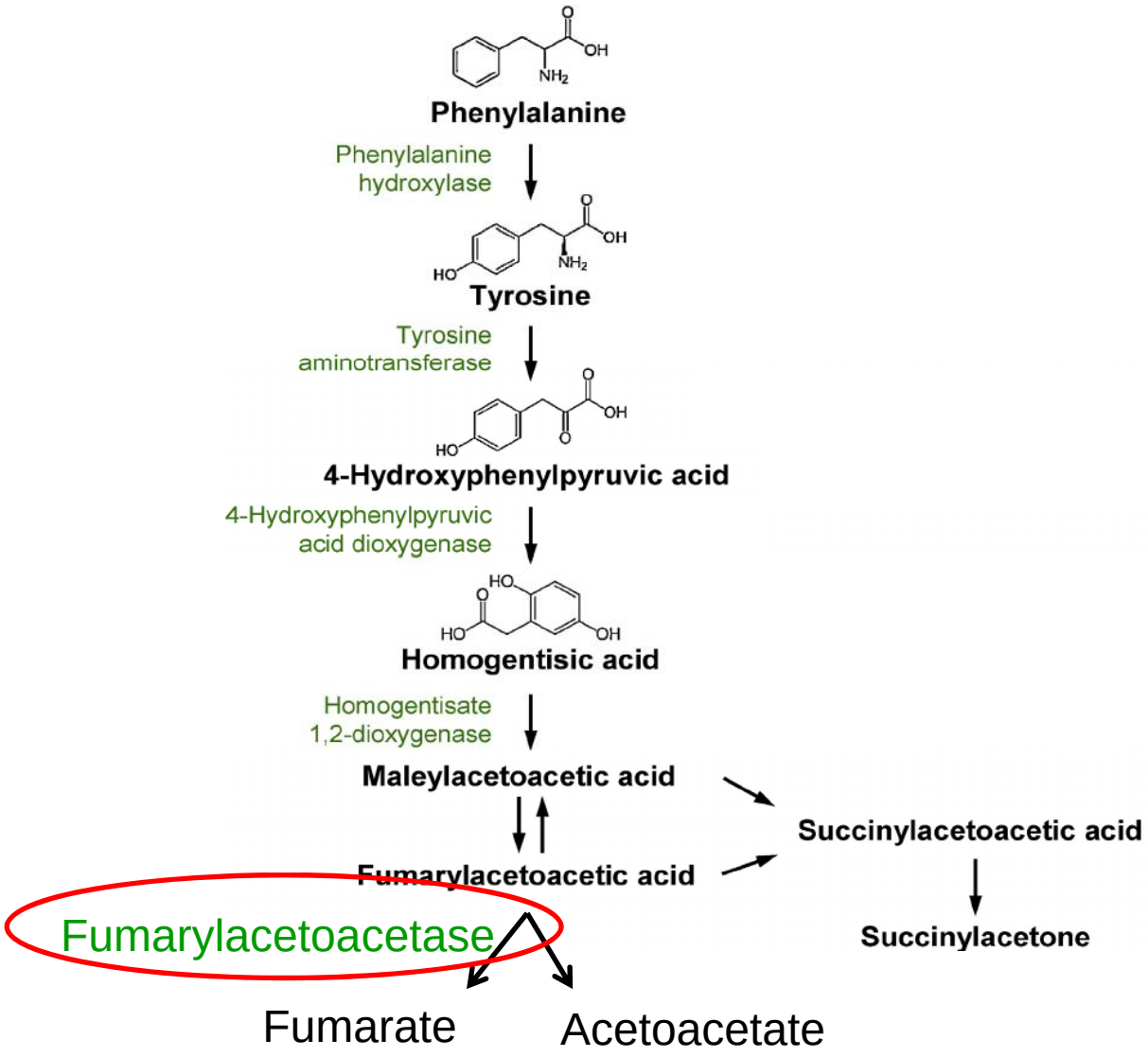
Tyrosinemia type I (Hepatorenal tyrosinemia)



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Tyrosinemia Type I - Pathophysiology

- Deficiency of Fumarylacetoacetase
- ↑ Fumarylacetoacetate (FAA), Maleylacetoacetate (MAA), Succinylacetone (SA)
  - Disrupt glutathione metabolism
  - Alkylating agents

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Tyrosinemia Type I – Clinical Features

- 'Hepatorenal tyrosinemia'
- Acute liver failure
  - Liver synthetic function first/most affected
- Cirrhosis, Hepatocellular Carcinoma
- Renal: Proximal Tubular Disease
  - Renal Tubular Acidosis, Fanconi, glycosuria
  - Hypophosphatemic rickets

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Tyrosinemia Type I Diagnostic tests

- Plasma amino acids
  - Marked and disproportionately elevated tyrosine
- Urine succinylacetone present
  - Differentiates from other tyrosinemias and transient newborn tyrosinemia
- DNA sequencing

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Tyrosinemia Type I - Case presentation

6 week-old girl, newborn screening for tyrosinemia I

- AST = 93 U/L(16-61)
- ALT = 41 U/L (23-61)
- Total bilirubin = 0.8 mg/dl (<0.8)
- INR = 3.74 (0.88-1.14)

- Urinalysis: 2+ glucose, 1+ protein
- Plasma tyrosine = 627 µmol/L (27-108)
- Positive urine succinylacetone

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Tyrosinemia Type I – Clinical Features

- Acute Neurological Crises
  - Results because succinylacetone inhibits 5-ALA dehydratase (heme synthesis)
  - Accumulation of neurotoxic 5-ALA
  - Painful paresthesias, autonomic signs (e.g., low blood pressure, difficulty urinating, sweating abnormalities)

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Tyrosinemia Type I - Treatment

- Dietary Protein (Tyrosine) restriction
- NTBC (Nitisinone, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione)

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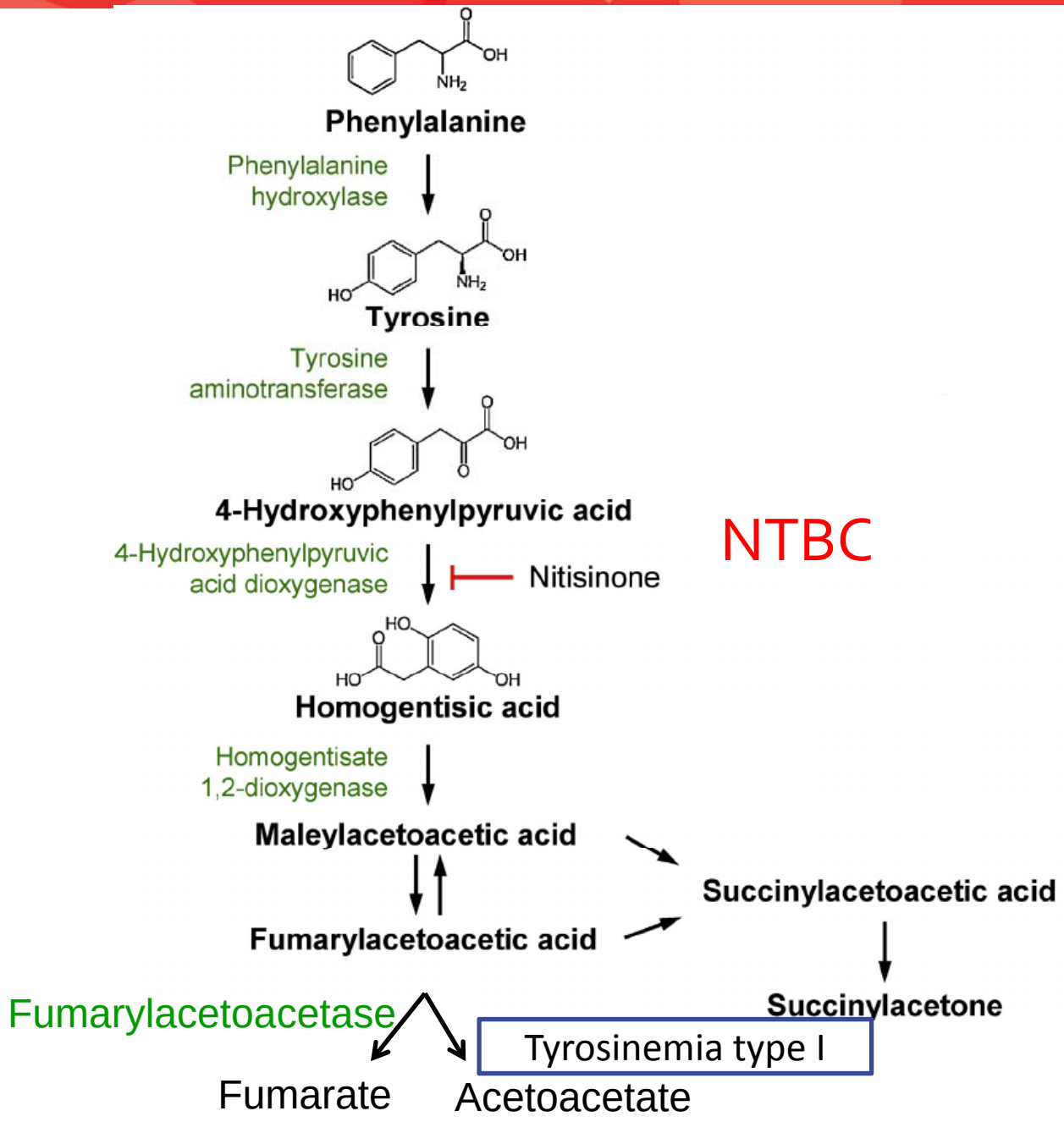

NTBC

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Tyrosinemia Type I - Treatment

- Dietary Protein (Tyrosine) restriction
- NTBC (Nitisinone, 2-(2-nitro-4-trifluoromethylbenzoyl)-1,3-cyclohexanedione)
  - Titrate until plasma succinylacetone is absent

- Even on treatment: Risk of hepatocellular carcinoma
  - AFP - every 3 months
  - Liver sonogram - yearly
  - Liver transplantation

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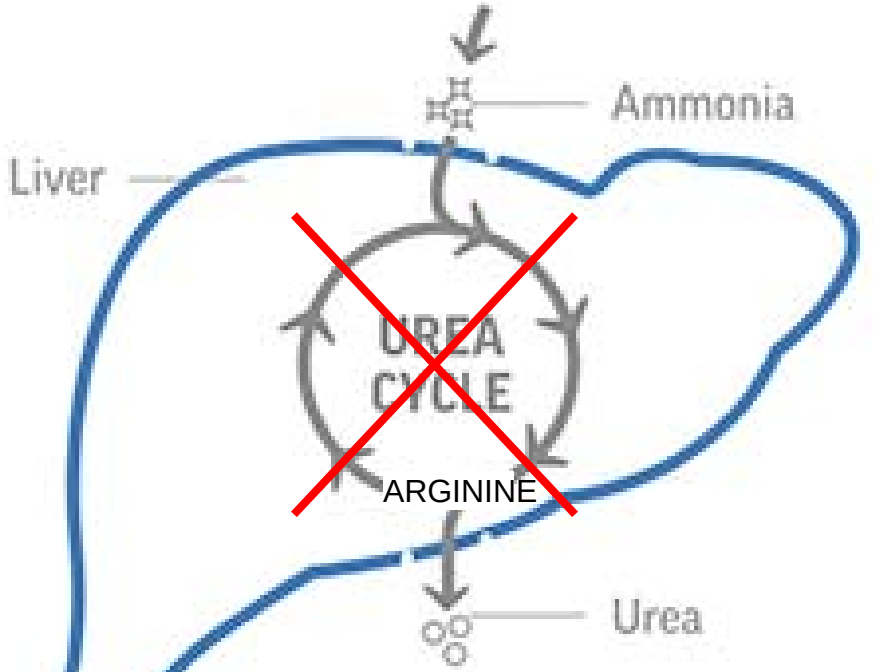
Urea cycle disorders

- Results from defect in one of 6 enzymes or 2 transporter needed for conversion of ammonia into urea

- This can result in

1) Build up of ammonia
2) Accumulation of intermediates



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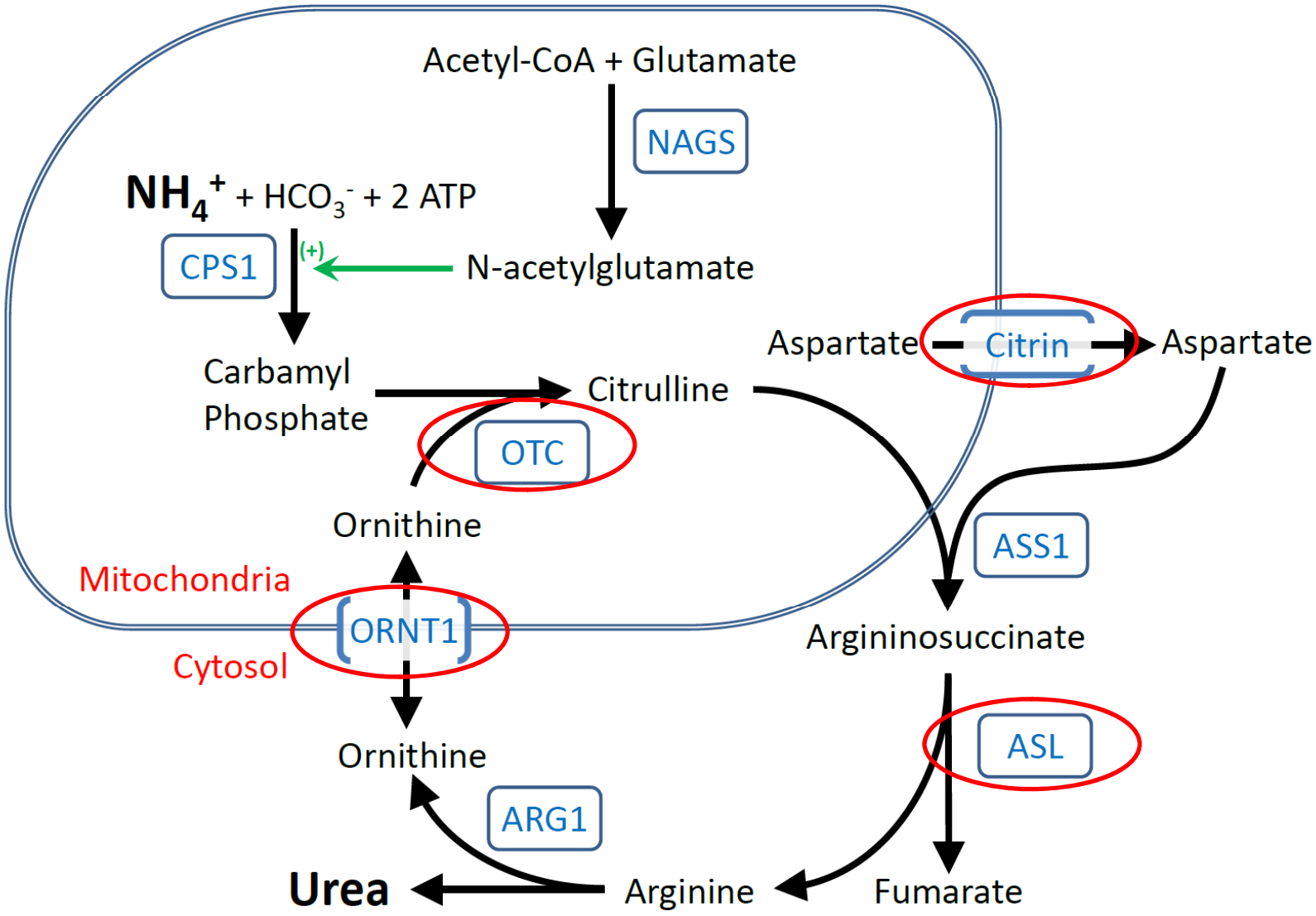
The hepatic urea cycle



Diagnosis of urea cycle disorders

- Hyperammonemia
- Plasma amino acid abnormalities
- ↑ Urine orotic acid

- DNA sequencing
- Hepatic (or erythrocyte) enzyme testing

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Urea cycle disorder – Case Presentation

- 1 ½ year-old girl, 1 month history of emesis and changes in sleep pattern

- Laboratory investigations:
  - ALT=1797 U/L
  - AST=784 U/L
  - INR = 4.0
  - Total bilirubin = 0.5 mg/dL
  - Ammonia = 225 µmol/L
  - Abnormal plasma amino acid profile
  - Elevated urine orotic acid

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Urea cycle disorders - Management

- Protein-restricted diet
- Alternative pathway medications
- Avoidance of prolonged fasting

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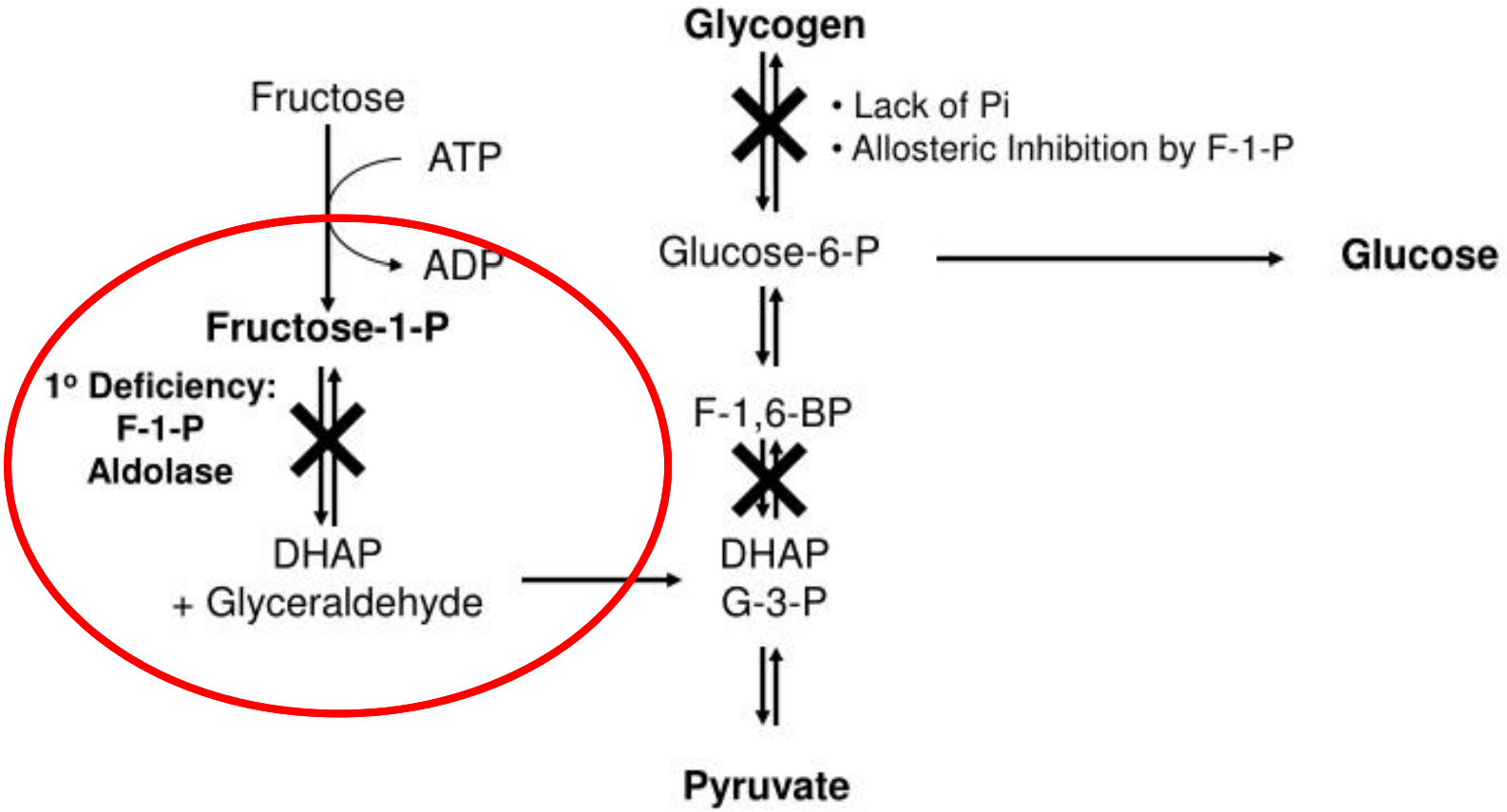
Hereditary fructose intolerance – inhibition of glycolysis and gluconeogenesis



Hereditary Fructose Intolerance – Diagnostic features

- Nausea
- Vomiting
- Abdominal distress
- Failure to thrive
- Dietary avoidance of fructose

- Hypoglycemia
- Hyperlactatemia
- Hyperuricemia
- Renal tubular dysfunction

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Hereditary Fructose Intolerance - Diagnosis and management

Diagnosis:

- Medical History
- Fructose challenge
- DNA sequencing
- Hepatic enzyme analysis

Management: avoidance of fructose, sucrose, sorbitol

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Hepatocellular dysfunction – Diagnostic investigations

- Plasma amino acid profile
- Urine organic acid profile
  - (succinylacetone, orotic acid)
- Urine reducing substances
- Galactose-1-Phosphate and GALT enzyme level

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Categories of metabolic liver disease

- Hepatocellular dysfunction
- Hepatosplenomegaly
- Cholestasis
- Recurrent Hypoglycemia

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Hepatosplenomegaly

Lysosomal storage disorders:

- Gaucher
- Niemann-Pick type A/C
- GM1 gangliosidosis
- Sialidosis type II
- I-cell
- Galactosialidosis

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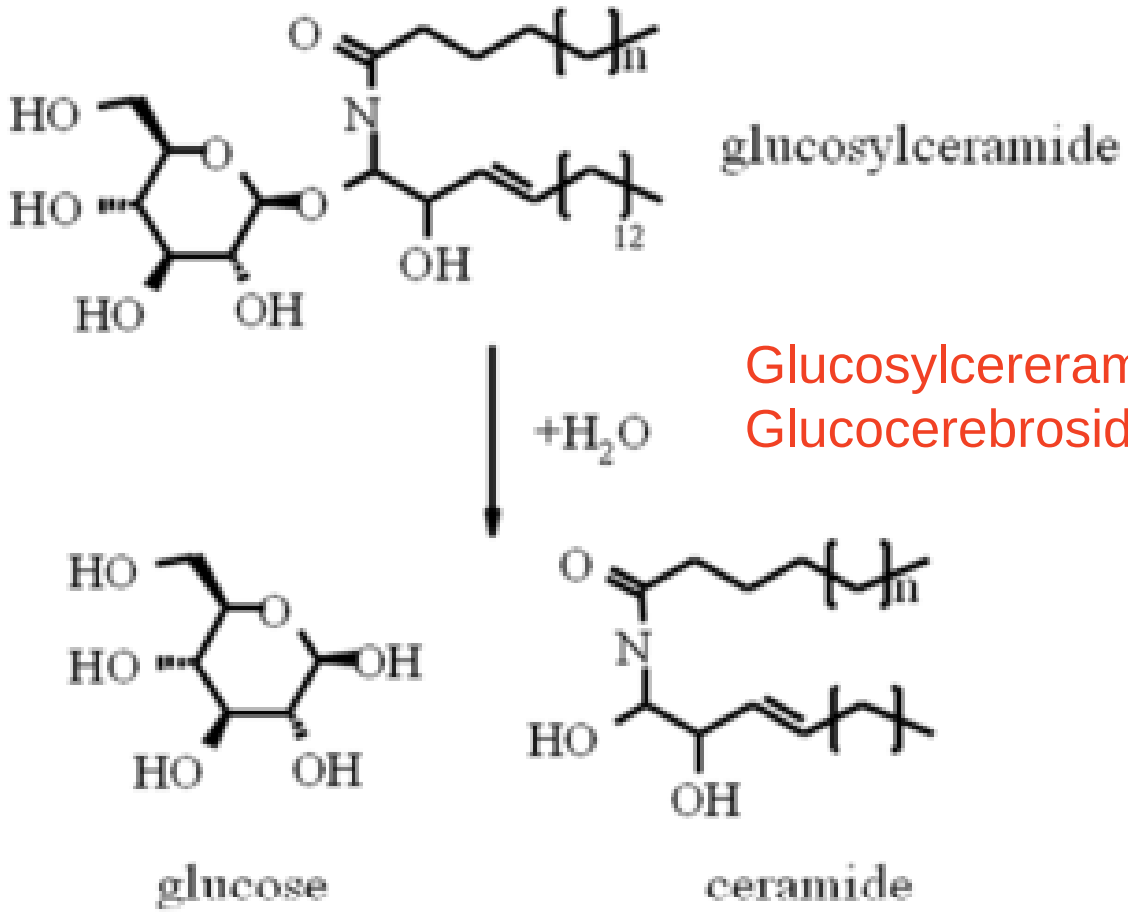
Gaucher Disease - Pathophysiology



Gaucher Disease – Clinical Manifestations

- Hepatosplenomegaly
  - Cytopenias
  - Coagulation disorder
- Bone disease (type I)
  - Focal lytic or sclerotic lesions
  - Acute bone pain ('bone crises')
- Neurological disease (type II, III)
  - Deteriorating neurological disease

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Gaucher Disease – Diagnosis

- Bone marrow exam: lipid-engorged macrophages (non-specific)
- DNA sequencing
- Enzymatic testing of leukocyte glucocerebrosidase

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Gaucher Disease - Management

- Symptomatic treatments
- Bone Marrow Transplantation
- Enzyme Replacement Therapy
- Substrate Reduction Therapy

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Categories of metabolic liver disease

- Hepatocellular dysfunction
- Hepatosplenomegaly
- Cholestasis
- Recurrent Hypoglycemia

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Cholestasis

- Galactosemia
- Tyrosinemia
- Citrin deficiency
- Alpha-1-Antitrypsin
- Progressive Familial Intrahepatic Cholestasis
- Bile acid synthetic disorders
- Wolman
- Dubin Johnson
- Rotor

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Categories of metabolic liver disease

- Hepatocellular dysfunction
- Hepatosplenomegaly
- Cholestasis
- Recurrent Hypoglycemia

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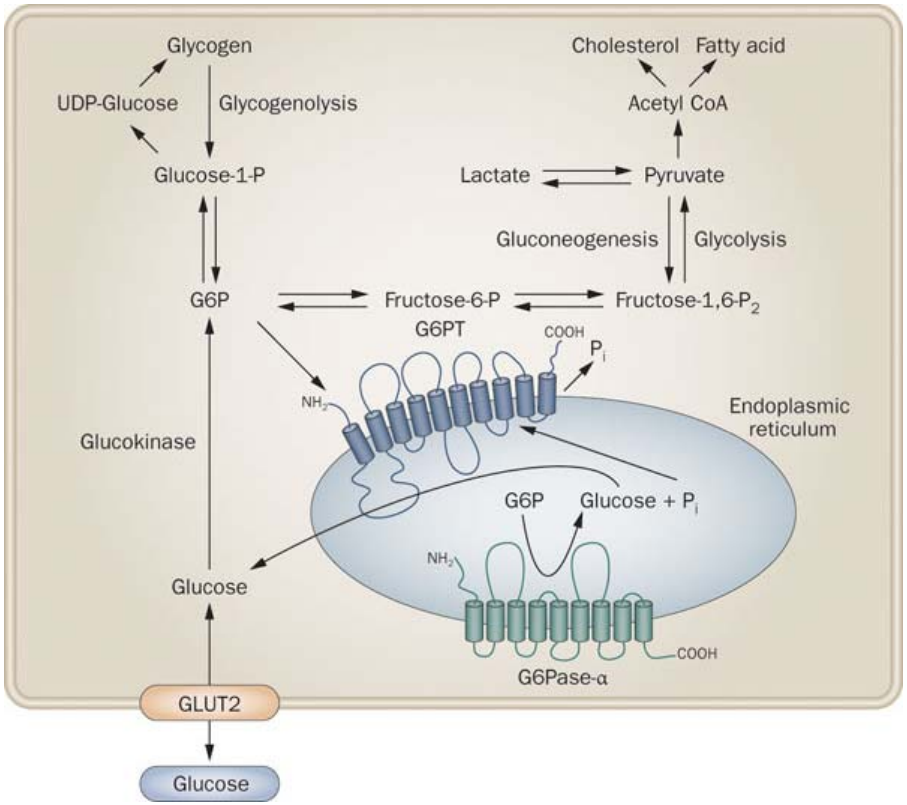
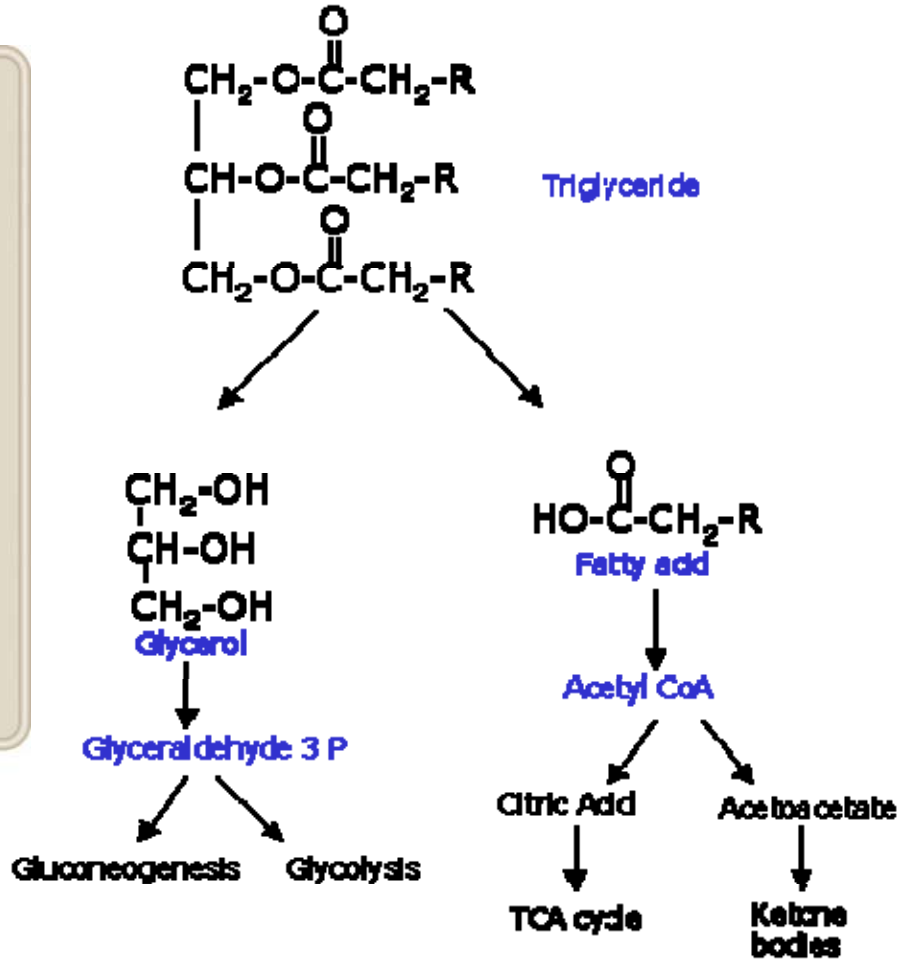
Recurrent Hypoglycemia: Disorders of energy metabolism





Nature Reviews Endocrinology 6, 676-688 (December 2010)

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Recurrent Hypoglycemia – categories of disorders

- Glycogen storage disorders
- Gluconeogenesis disorders
- Fatty acid oxidation disorders

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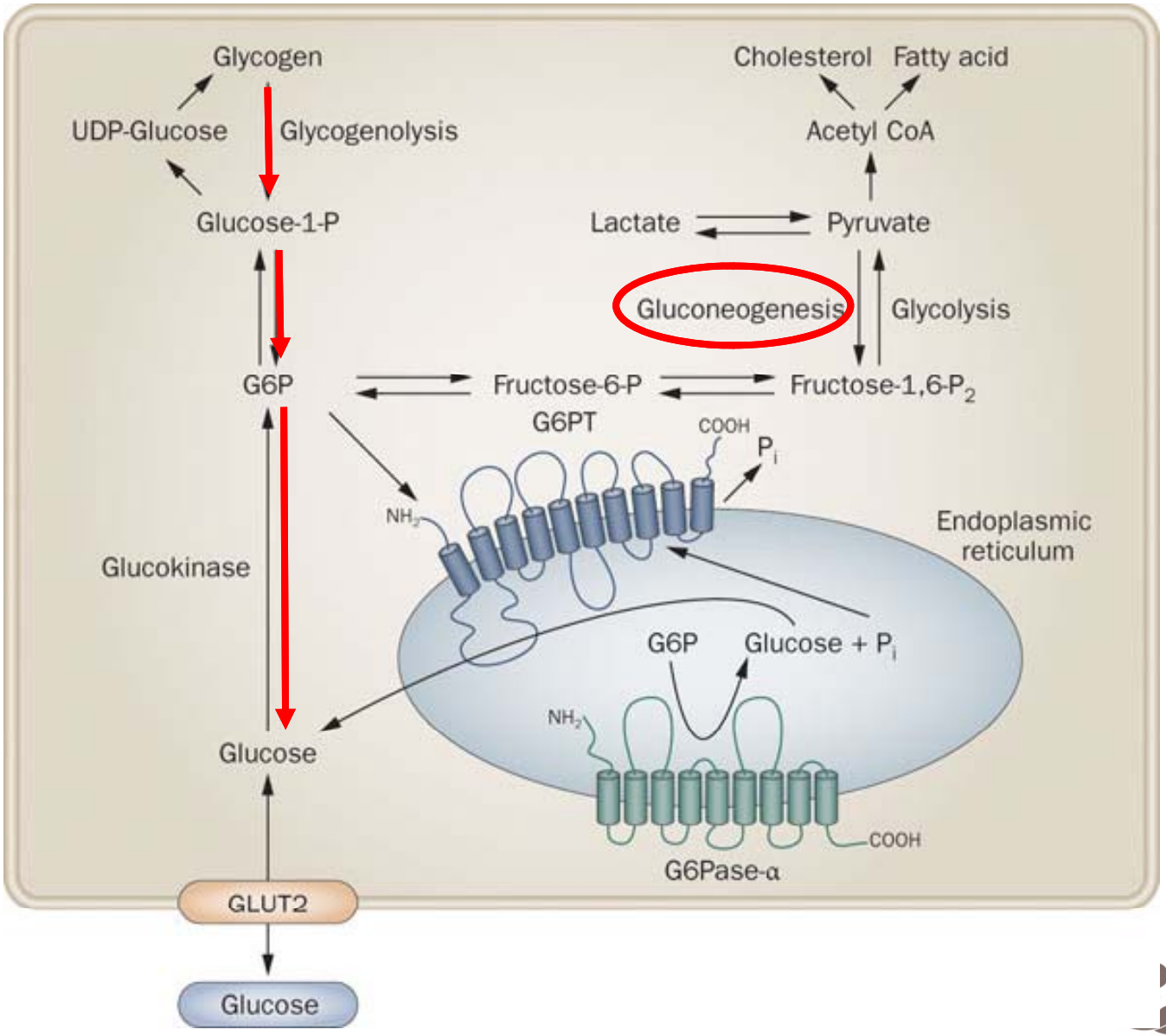
Disorders of glycogen metabolism / gluconeogenesis



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Glycogen storage disorders

- Liver specific isoforms
  - 0, I, III, IV, VI, IX, XI

- Typically present at age 3-4 months:
  - Fasting hypoglycemia
  - Hepatomegaly (except GSD 0)
  - Ketosis (except GSD 1)
  - Fasting lactic acidosis (except GSD 0)
  - Hyperlipidemia (except GSD 0, IV)
  - Hyperuricemia (GSD I)

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Glycogen Storage Disorders - Treatment

- Avoidance of fasting
- Soy-based formula without fructose, sucrose, lactose
- Frequent overnight feeds or continuous feeds
- Uncooked corn starch or glytactin

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Glycogen Storage Disorders - Diagnosis

- Liver biopsy: Histology shows fat and glycogen without fibrosis
- Enzyme assay on snap-frozen liver tissue
- DNA sequencing

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Disorders of gluconeogenesis

- Fructose 1,6-bisphosphatase
- Phosphenolpyruvate Carboxykinase
- Pyruvate Carboxylase
- (Glucose-6-phosphatase)

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Fructose 1,6-bisphosphatase deficiency

- Presents nearly identically to GSD I
  - Hepatomegaly
  - Elevated transaminases
  - Fasting hypoglycemia and hyperlactatemia
  - Hyperuricemia
  - Preserved response to glucagon

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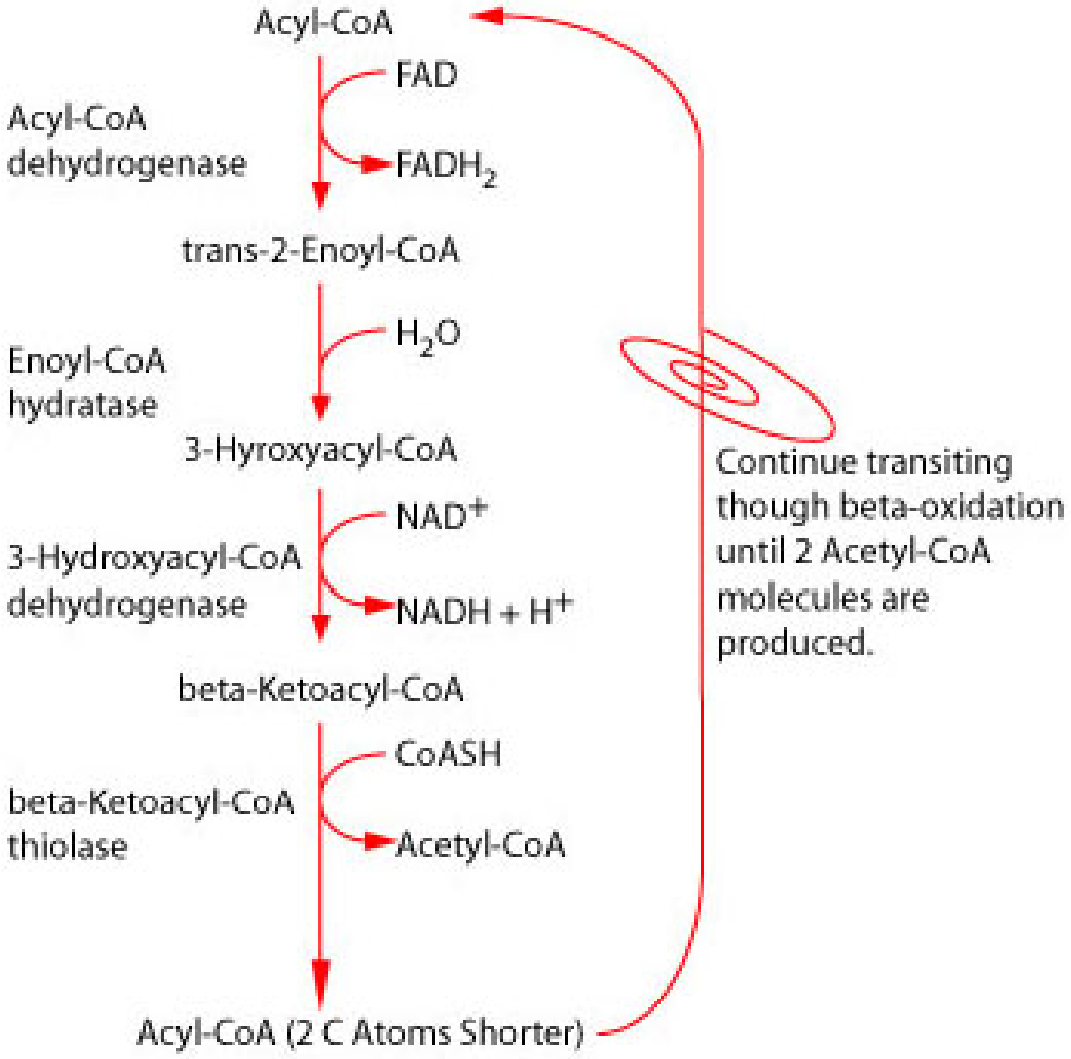
Fatty acid oxidation - pathophysiology



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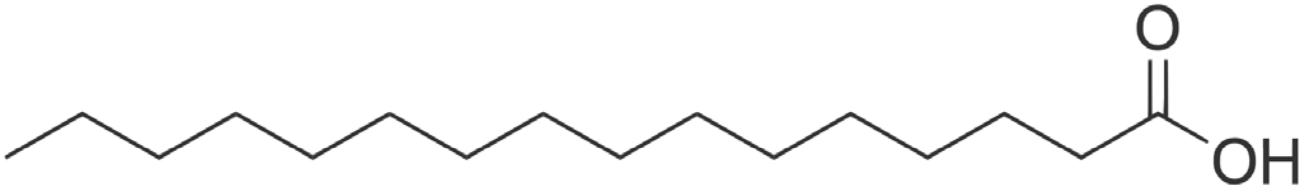
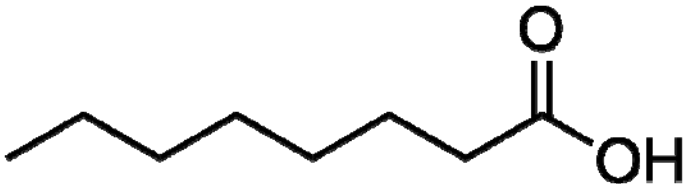
Different length fatty-acids require different enzymes



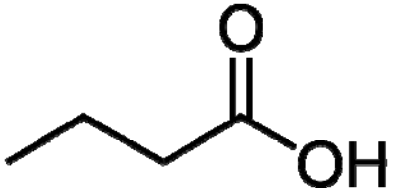
VLCAD

Long Chain Fatty Acid



MCAD

Medium Chain Fatty Acid



SCAD

Short Chain Fatty Acid

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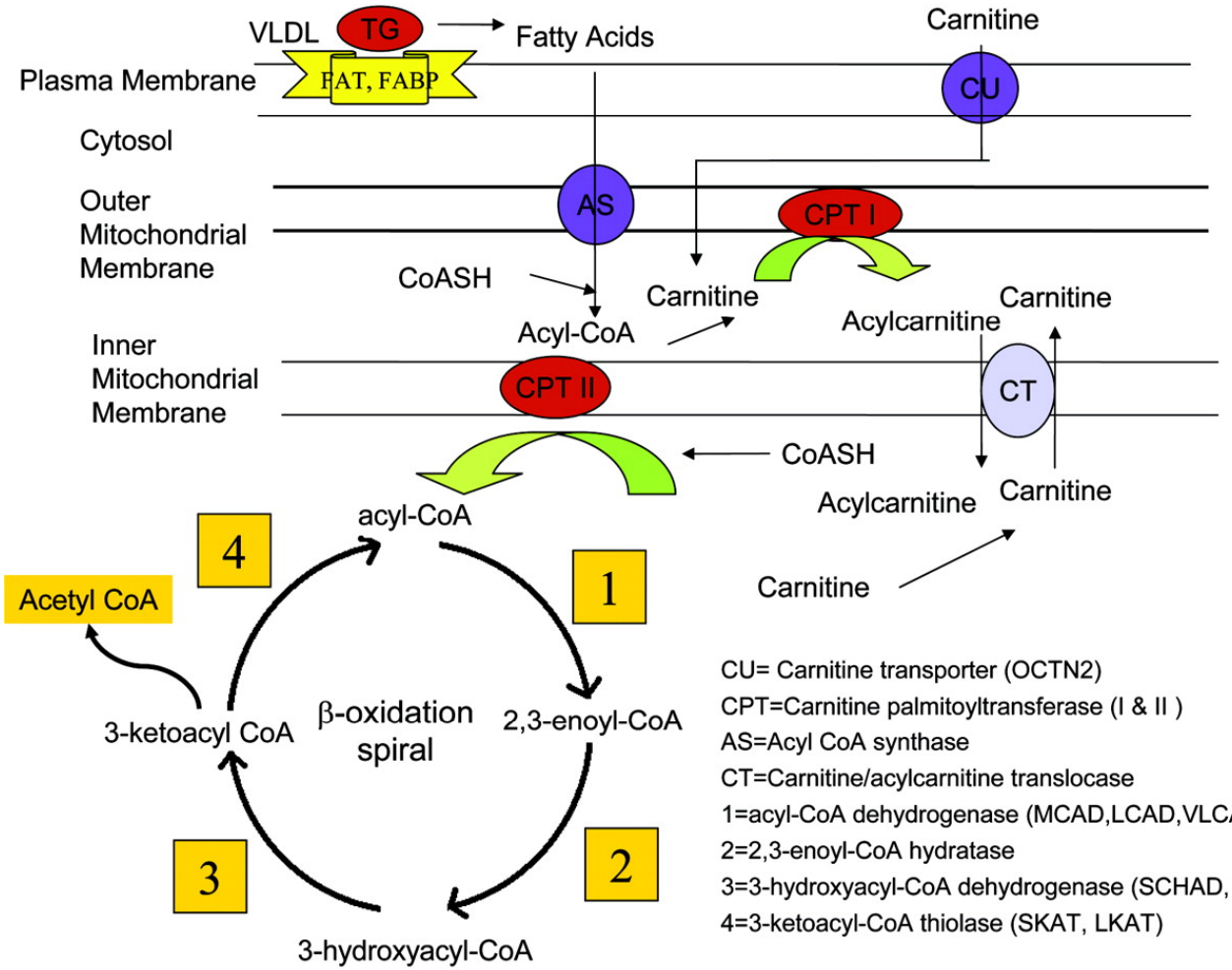
Fatty acids require carnitine and carnitine transport



AJP- Endocrinology and Metabolism; June 2003 284; 6; E1098-E1105

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Fatty acid oxidation disorders – Clinical presentation

- Fasting hypoglycemia
  - Reduced or absent ketones
- Elevated transaminases
- LCHAD: maternal presentation of acute fatty liver of pregnancy or hemolysis, elevated platelets and liver failure (HELLP syndrome)
- Cardiomyopathy or arrhythmias

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Fatty acid oxidation disorders - Diagnosis

- Urine ketones (during hypoglycemia)
- Acylcarnitine profile
- Free / Total carnitine

- DNA sequencing
- Enzymatic testing (hepatocytes, leukocytes)

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Fatty acid oxidation disorders - Management

- Fasting avoidance (not as severe as GSDs)
  - Dextrose Infusion if NPO
- Replacement of Carnitine
- Echocardiogram (yearly)

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Summary: Recurrent Hypoglycemia +/- elevated transaminases +/- hepatomegaly

Disorders:

- Glycogen storage disorders
- Gluconeogenesis disorders
- Fatty acid oxidation disorders

Investigations:

- Lactate
- Triglycerides
- Uric acid
- Acylcarnitine profile
- Free/total carnitine

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Thank you!

Questions?

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