Fructose and Galactose Oxidation and Pentose Phosphate Pathway

Fructose Metabolism

- Fructokinase traps fructose as fructose 1-phosphate.
- Fructose metabolism occurs primarily in the liver and kidney
- Defects in fructose metabolism thus affect primarily liver and kidney
- Fructose channeled into glycolysis in the middle of the pathway
- The entry site is after the critical regulatory step in glycolysis, namely PFK-1
- Excess fructose leads to obesity because its metabolism bypasses the PFK-1 step

Enzymes of fructose metabolism

Fructokinase

Fructose + ATP ➔ Fructose-1-P + ADP

Fructose-1-P aldolase (Aldolase B)

F1P ➔ Dihydroxyacetone phosphate + Glyceraldehyde

Triose kinase

Glyceraldehyde + ATP ➔ Glyceraldehyde-3-P + ADP

DHAP and Glyceraldehyde-3-P are intermediates in glycolysis downstream of PFK-1

Essential Fructosuria

- Fructokinase deficiency
- No clinical presentation; elevated blood and urine fructose
- Tests for fructosuria: positive for reducing sugar (Fructose); Negative for glucose oxidase test because glucose (also a reducing sugar) is not present

Hereditary Fructose Intolerance

- Fructose-1-P aldolase deficiency
- Fructose-1P builds up; hepatotoxic and nephrotoxic
- Jaundice, cirrhosis, hypoglycemia, gout
- Fanconi syndrome (generalized renal defect resulting in amino aciduria)
- Limit fructose in diet (sucrose, honey, high-fructose corn syrup; sugary sodas)

Galactose Metabolism

Galactokinase

Galactose + ATP ➔ Gal-1-P + ADP

Gal-1-P uridyl transferase

Gal-1-P + UDP-Glucose ➔ Glucose-1-P + UDP-galactose

UDP-galactose 4-epimerase

UDP-galactose ➔ UDP-glucose

Phosphoglucomutase

Glucose-1-P ➔ Glucose-6-P (an intermediate in glycolysis)

Classical Galactosemia

- Deficiency in galactose-1P uridyl transferase
- Build up of galactose-1P is toxic
- Nausea, avoidance of feeding, mental retardation, cataracts (due to elevated galactitol in lens; sometime seen in even in early childhood)
- Galactitol produced by aldose reductase (polyol pathway)
- The polyol pathway also produces cataracts in diabetes by converting excess glucose into sorbitol)

Galactosemia From Galactokinase Deficiency

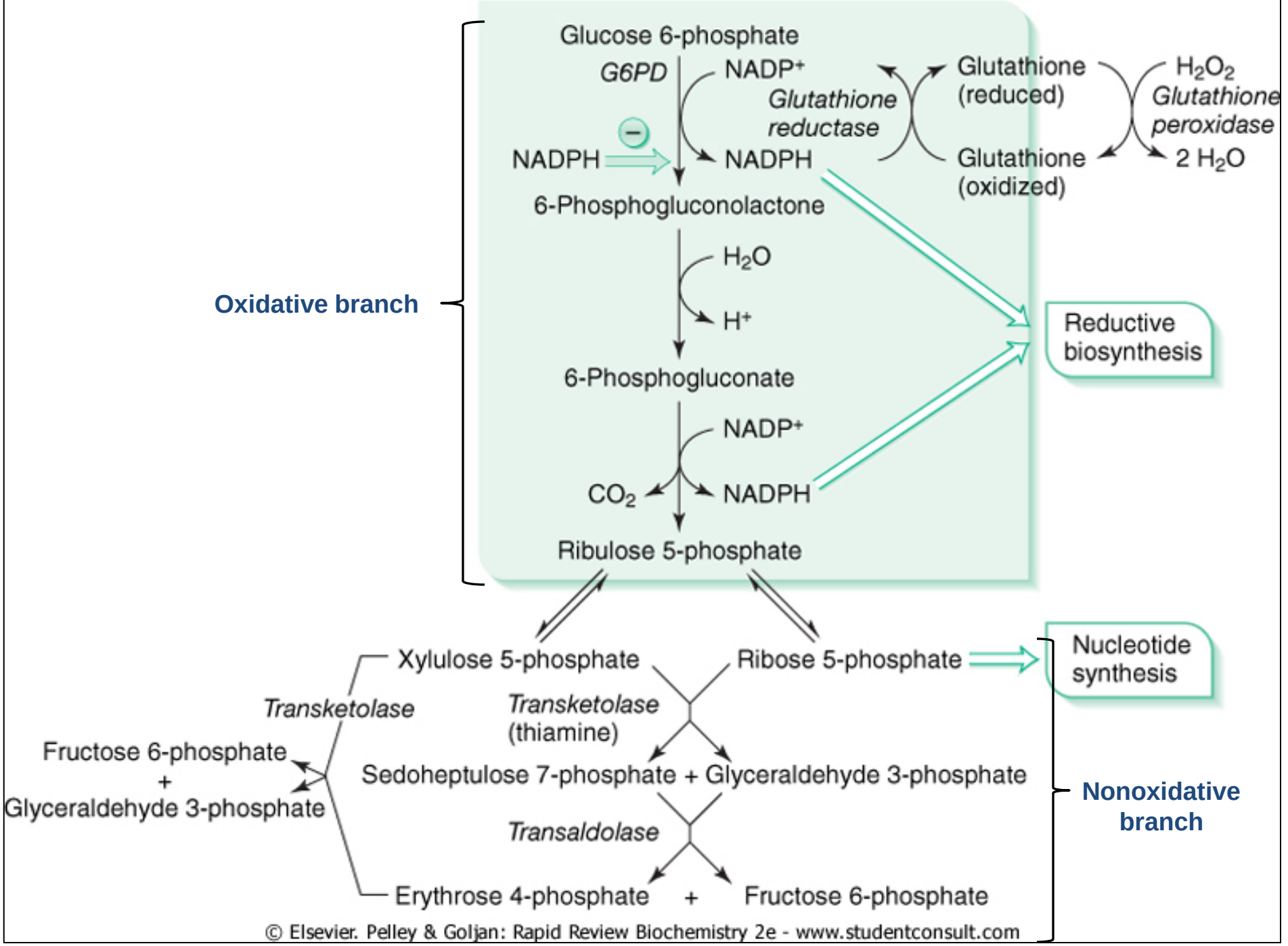
- Elevated blood galactose
- Clinical presentation limited to cataracts
- Cataract occurs only in adults

Pentose Phosphate Pathway

- Metabolic role: Supplies NADPH and ribose 5-phosphate; present in all cells
- Important in tissues that use NADPH
- NADPH is needed for synthesis of cholesterol, fatty acids, steroid hormones, antioxidant machinery, and also for generation of reactive oxygen species
- Liver, adipose tissue, ovary, testes, adrenal cortex, erythrocytes, phagocytes

Pentose Phosphate Pathway Flexible Output

Branch Utilized	Output
1. Oxidative branch only	1. Ribose-5-P plus NADPH
2. Oxidative branch plus nonoxidative branch	2. NADPH only (Ribose-5-P goes through glycolysis)
3. Nonoxidative branch only	3. Ribose-5-P only


Glucose 6-phosphate
G6PD
NADP+
NADPH
NADPH
Glutathione reductase
Glutathione (reduced)
Glutathione (oxidized)
H2O2
Glutathione peroxidase
2 H2O
6-Phosphogluconolactone
H2O
H+
6-Phosphogluconate
NADP+
CO2
NADPH
Ribulose 5-phosphate
Oxidative branch
Reductive biosynthesis
Xylulose 5-phosphate
Ribose 5-phosphate
Nucleotide synthesis
Transketolase
Transketolase (thiamine)
Fructose 6-phosphate
+
Glyceraldehyde 3-phosphate
Sedoheptulose 7-phosphate + Glyceraldehyde 3-phosphate
Transaldolase
Erythrose 4-phosphate + Fructose 6-phosphate
Nonoxidative branch
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Thiamine and Pentose Phosphate Pathway

- The non-oxidative arm of the pathway contains several enzymes (Phosphopentose isomerase, Phosphopentose epimerase, Transketolase, Transaldolase)
- Transketolase is a thiamine-dependent enzyme
- Only thiamine-dependent enzyme that is present in cytosol
- There are three enzymes that are thiamine-dependent, but all three of them are located in mitochondria
- Among the four thiamine-dependent enzymes in mammalian cells, mature erythrocytes contain only one: Transketolase
- Assay of transketolase in peripheral blood erythrocytes can be used to diagnose thiamine status

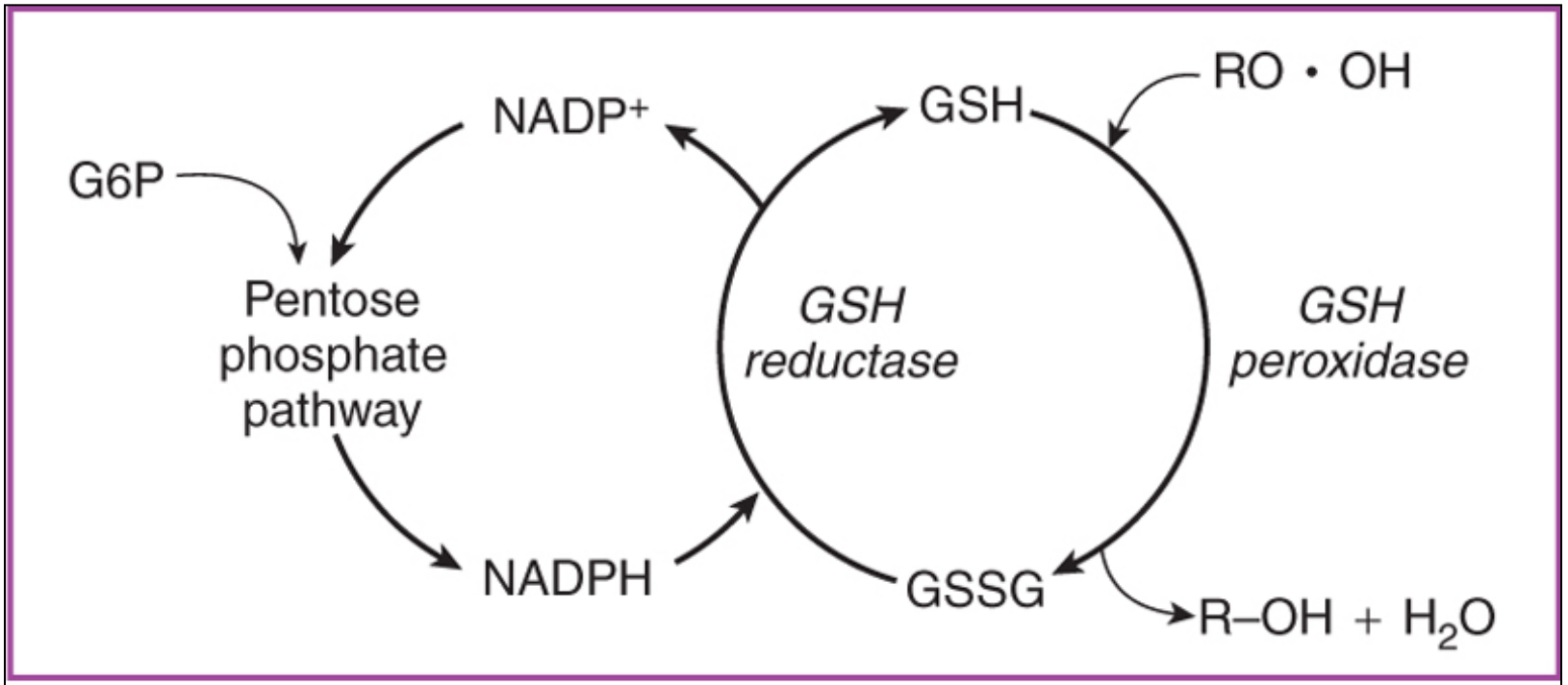
Wernicke-Kosakoff syndrome and Beriberi

- Thiamine deficiency causes Wernicke-Korsakoff syndrome and beriberi
- WK syndrome occurs in chronic alcoholics
- Ataxia, ophthalmoplegia, amnesia, confusion, confabulation

- Beriberi is a nutritional deficiency of thiamine
- Wet beriberi and dry beriberi depending on whether the cardiovascular system is affected (wet) or neurological system is affected (dry)

Glutathione As An Antioxidant

- Reduced form of glutathione serves as an antioxidant; neutralizes free radicals (from electron transport)
- Glutathione peroxidase uses free radical to oxidize glutathione
- Glutathione reductase regenerates reduced glutathione



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Glucose-6-P dehydrogenase (G6PD) deficiency

- G6PD is located on X chromosome
- Genetic mutations affect primarily males
- Quite common in African Americans, Chinese, and peoples of Middle Eastern countries
- Complete loss of enzyme activity is lethal
- Partial defects in enzyme activity cause hemolytic anemia, mostly when subjected to oxidative stress (drugs, diet, disease)

G6PD deficiency

- Methemoglobin (Fe^{3+}) levels go up in RBC
- Glutathione levels go down; GS-SG goes up
- Hemoglobin gets cross-linked, aggregates, and gets attached to RBC plasma membrane
- Heinz bodies, Bite cells
- Intravascular hemolysis
- Hemolytic anemia, jaundice, gallstones
- Presence of hemoglobin in urine (coca cola-colored urine)

G6PD deficiency

- Primaquine sensitivity in glucose 6-phosphate dehydrogenase deficiency
  - Quinones can generate peroxides
  - Don’t prescribe antimalarial drugs to AA males without testing for G6PD deficiency
- Favism
  - Fava beans contain oxidant compounds
  - Only G6PD patients are affected