Lactic Acidosis

- Direct inhibition of oxidative phosphorylation
- Hypoxia in any tissue
- Alcohol intoxication (high NADH/NAD+)
- ↓ Gluconeogenesis
- ↓ Pyruvate Dehydrogenase
- ↓ TCA cycle activity
- ↓ Pyruvate carboxylase
Inorganic Inhibitors of Glycolysis

Fluoride

- Fluoride inhibits Enolase

Fluoridated water $\rightarrow$ bacterial enolase $\rightarrow$
Prevention of Dental Carries

Inorganic Inhibitors of Glycolysis

Arsenic Poisoning

- Pentavalent Arsenic (Arsenate)
  competes with phosphate as
  as a substrate for GA3PDH
  $\downarrow$ ATP synthesis
- Trivalent Arsenic (Arsenite)
  Forms stable complex with -SH
  of lipoic acid
  $\downarrow$ Pyruvate Dehydrogenase
  $\downarrow$ α ketoglutarate Dehydrogenase
  $\rightarrow$ Neurological dissturbances........DEATH
Pyruvate Kinase Deficiency

- The most common among glycolytic enzymes deficiencies
- RBC’s are affected
- Mild to severe chronic hemolytic anemia
- ATP is needed for Na⁺/K⁺ pump to maintain the flexible shape of the cell
- Low ATP → premature death of RBC
- Abnormal enzyme; mostly altered kinetic properties

Alterations observed with various mutant forms of pyruvate kinase
Regulation by ATP and AMP; why AMP

ADP + ADP $\rightleftharpoons$ ATP + AMP

Regulation of PFK by Fructose 2,6-bisphosphate

Fruc. 6-phosphate + ATP $\rightarrow$ Fruc. 2,6-bisphosphate + ADP
Glucose $\xrightarrow{\text{Glucokinase}}$ Glucose 6-P

Fructose 6-P $\xrightarrow{\text{PFK}}$ Fructose 1,6-bis-P

Phosphoenolpyruvate $\xrightarrow{\text{PK}}$ Pyruvate

Glucagon and Insulin regulate the process.
Gluconeogenesis

Suggested Reading:
Lippincot’s Illustrated reviews: Biochemistry
Glucose Synthesis is Required for Survival

- Brain is dependent on glucose 120g/day
- Body glucose reserve is limited
  ≈ 20 g (extra cellular fluid)
  ≈ 75 g (liver glycogen); enough for 16 hours
  ≈ 400 g (muscle glycogen); for muscle use only
  Main source of energy for resting muscle in postabsorptive state
- 70 Kg man has ≈ 15 Kg fat
  - Fatty acids can not be converted to glucose
  - Utilization of FA is increased 4-5 X in prolonged fasting
  - In prolonged fasting; FA → ketone bodies at high rate

Gluconeogenesis occurs mainly in the liver

Tissues that do not oxidize glc. completely
  e.g RBCs
  Exercising muscle

Muscle A.Acids

Adipose tissue

Lactate

alanine

glycerol

Glucose

Peripheral tissues
Entrance of substrates into gluconeogenesis

Lactate → Pyruvate ← Amino acids
Amino acids → oxaloacetate ← propionate
Glycerol → Triosephosphates ← Fructose
Galactose → Glucose

Glucose
Glucose 6-phosphate
Fructose 6-phosphate
Fructose 1,6-bisphosphate
2 Phosphoenolpyruvate
Oxaloacetate
Pyruvate
Formation and Hydrolysis of Glucose 6-phosphate

\[
\begin{align*}
\text{Glc.} + \text{Pi} & \rightarrow \text{Glc. 6-phosphate} + \text{H}_2\text{O} \quad \Delta G = +\text{ve} \\
\text{ATP} + \text{H}_2\text{O} & \rightarrow \text{ADP} + \text{P}_i \quad \Delta G = -\text{ve}
\end{align*}
\]

\[
\begin{align*}
\text{Glc.} + \text{ATP} & \rightarrow \text{Glc. 6-phosphate} + \text{ADP} \quad \Delta G = -\text{ve} \\
\text{Glc. 6-phosphate} + \text{H}_2\text{O} & \rightarrow \text{Glc.} + \text{P}_i \quad \Delta G = -\text{ve}
\end{align*}
\]