# Gluconeogenesis

Liver

Kidney

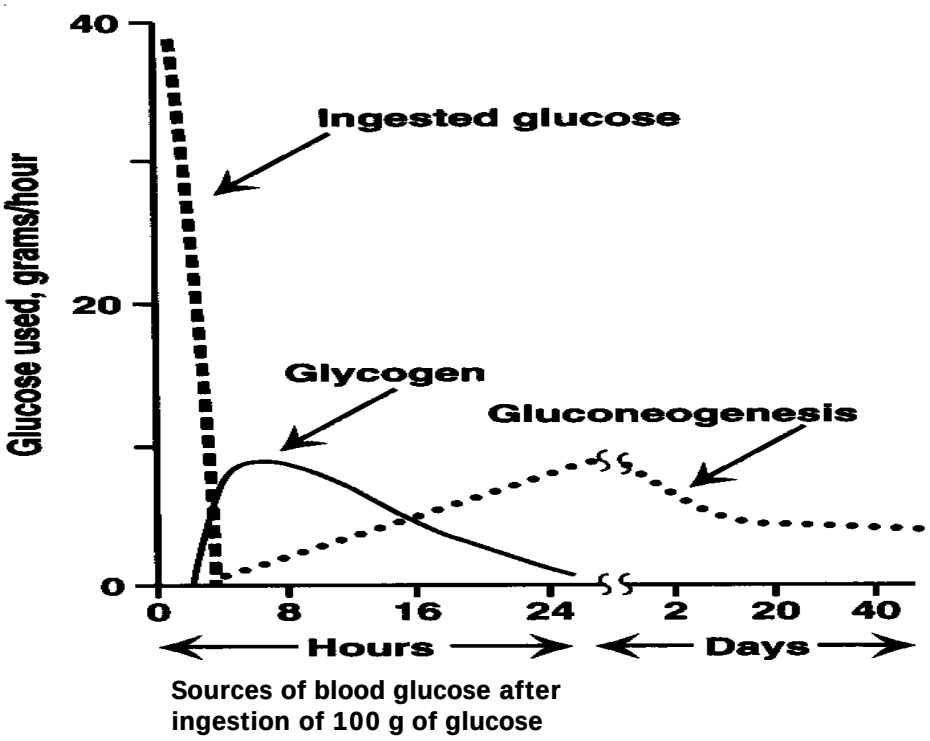
Small intestine

# Objectives

- Give the definition for gluconeogenesis
- Know the three irreversible steps in glycolysis that require special enzyme steps to go in the reverse direction
- Know the energy requiring steps and how phosphoglycerate kinase works in reverse direction
- Understand the role of Fructose-2,6-bisphosphate in gluconeogenesis
- Understand the role of acetyl CoA in gluconeogenesis
- Know the gluconeogenic steps that require NADH, and the relevance of the NADH shuttles from cytoplasm to mitochondria
- Essential role of the vitamins niacin and biotin in gluconeogenesis
- Alcohol, Atkins diet and Metformin

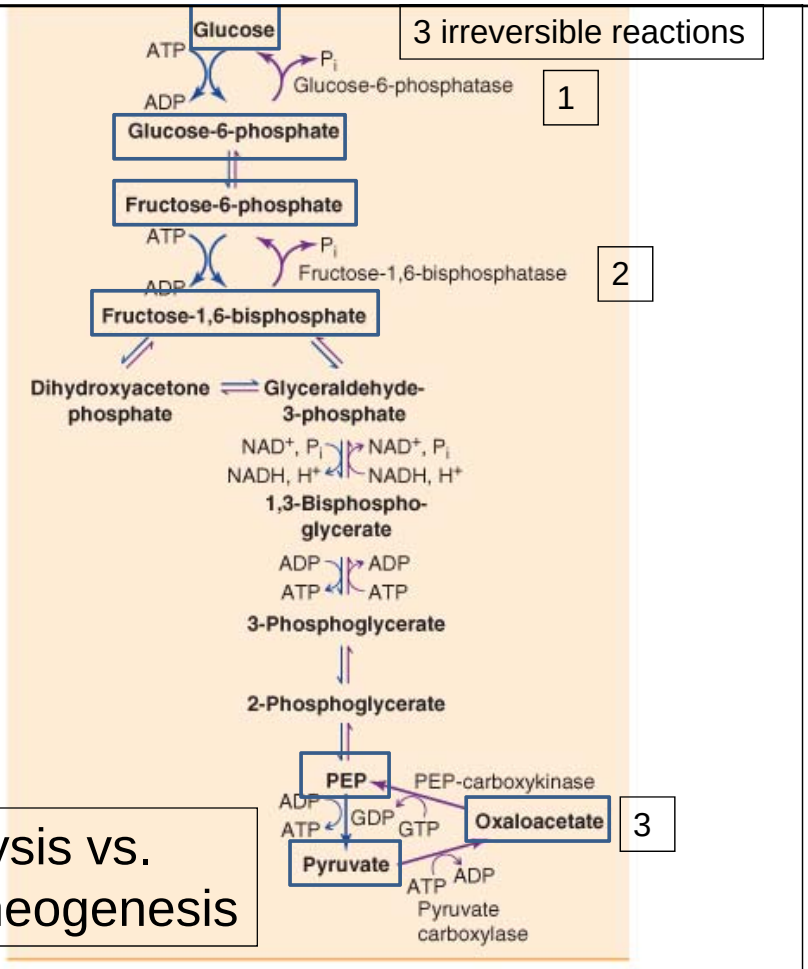
- Liver is the primary site of gluconeogenesis (90%); kidney is a minor contributor to gluconeogenesis (10%)
- Definition: Synthesis of glucose from amino acids, lactate, glycerol, and propionate
- Acetyl-CoA is not a precursor for gluconeogenesis
  - it is an energy supply and also an activator of pyruvate carboxylase & inhibitor of pyruvate dehydrogenase in mitochondria
- Reciprocal regulation of glycolysis and gluconeogenesis maintains blood glucose level
- Glycolysis and gluconeogenesis are regulated by
  - hormone-induced enzyme phosphorylations
  - allosteric effectors

# Relevance of gluconeogenesis to blood glucose after a normal meal




Sources of blood glucose after ingestion of 100 g of glucose

# Glycolysis vs. Gluconeogenesis



# Fructose-2,6-bisphosphate and Gluconeogenesis

- F2,6-BP inhibits gluconeogenesis via inhibition of Fructose-2,6-bisphosphatase
- Glucagon decreases F2,6-BP levels in liver
- cAMP is inversely proportional to [F2,6-BP]
- cAMP inhibits PFK2 and activates F2,6-Bpase
- Glucagon accelerates gluconeogenesis whereas insulin inhibits gluconeogenesis

- Glucogenic amino acids:

Pyruvate or one of the TCA cycle intermediates: α-KG, succinyl CoA, oxaloacetate

All of them converge to oxaloacetate

- Lactate: it gets converted into pyruvate

Cori cycle: Glucose > pyruvate > lactate in muscle

Lactate > pyruvate > glucose in liver

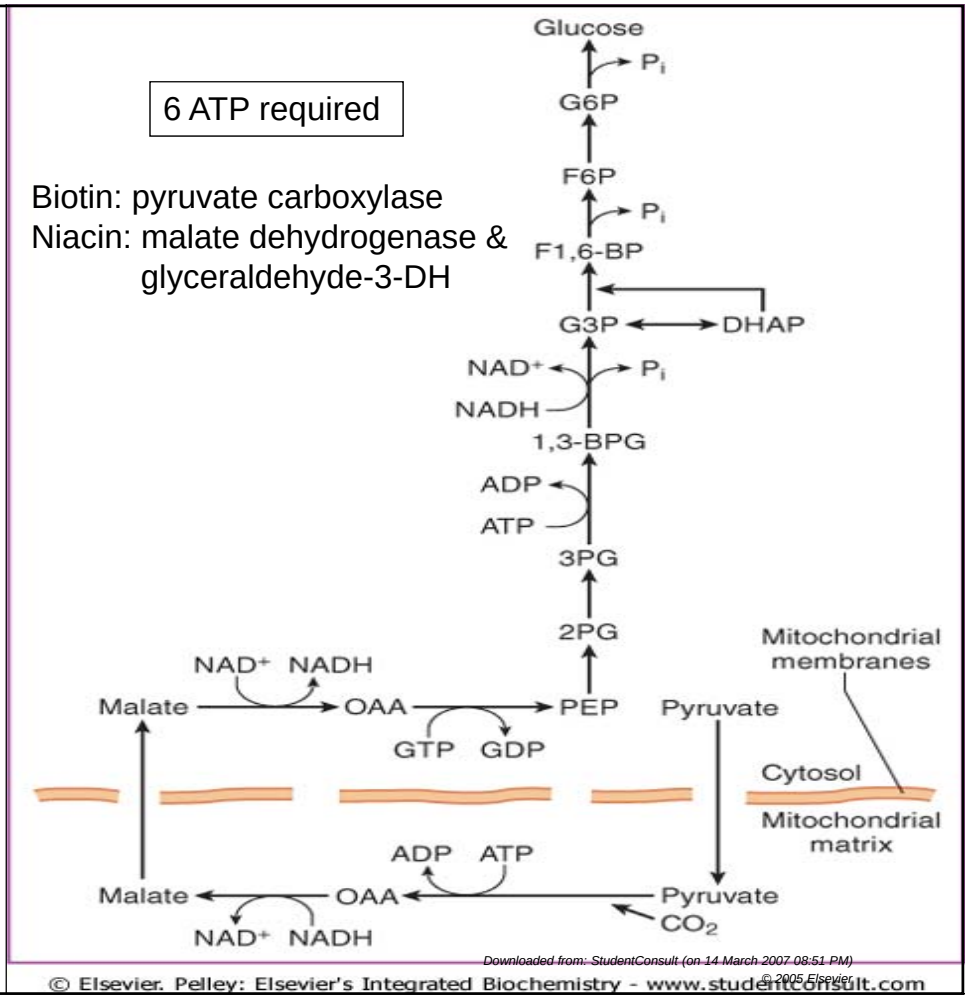
Glucose-alanine cycle: Glucose > pyruvate > alanine in muscle;
Alanine > pyruvate > glucose in liver

- Glycerol: Lipolysis in adipose tissue (TG > free fatty acids and glycerol)

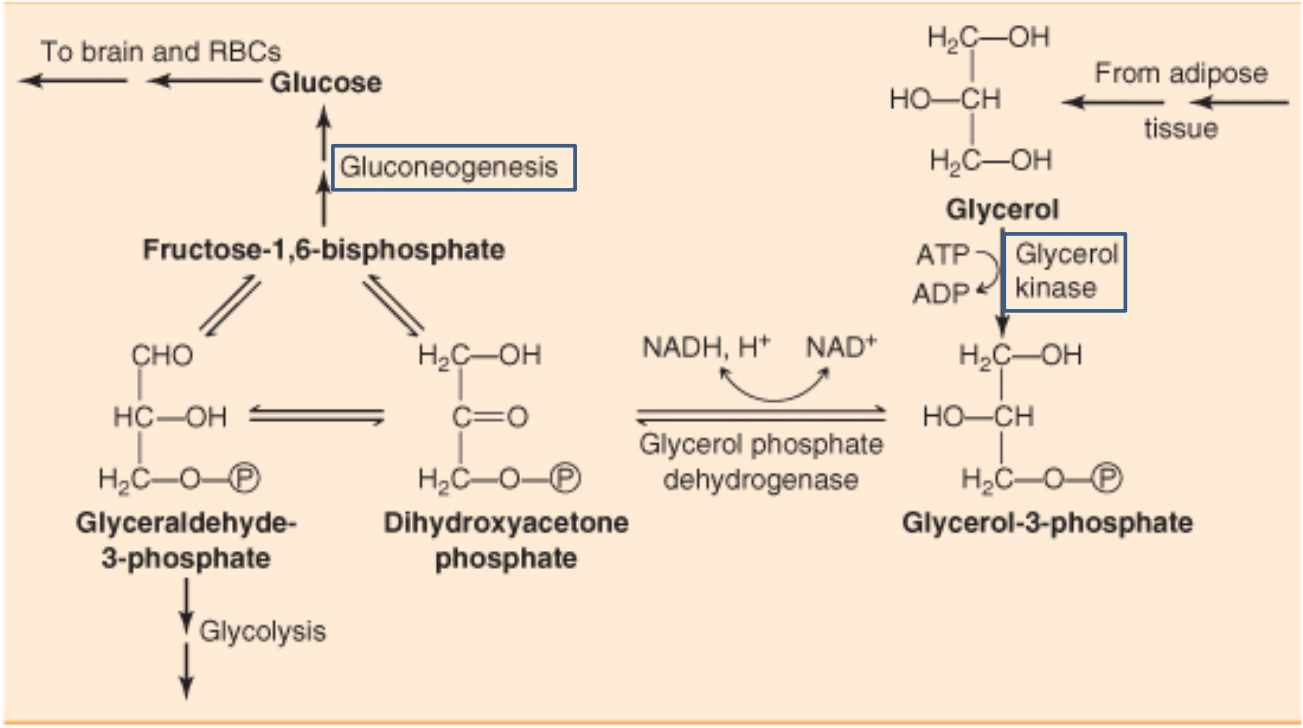
Glycerol > α-glycerophosphate > DHAP

- Propionate: Propionyl CoA can arise from isoleucine and also from beta-oxidation of odd-chain fatty acids; propionyl CoA is converted into succinyl CoA; this requires biotin & vitamin $B_{12}$

# From Pyruvate To Glucose



# Glycerol Kinase Is Only In The Liver



# Interrelationship between fatty acid oxidation and gluconeogenesis

- When fatty acid oxidation is favored in liver, gluconeogenesis is accelerated
- This occurs when blood glucose is low
- Fatty acid oxidation produces acetyl CoA
- Acetyl CoA activates pyruvate carboxylase and inhibits PDH
- Thus, conversion of pyruvate into acetyl CoA is prevented whereas conversion of pyruvate into oxaloacetate is favored
- Oxaloacetate promotes oxidation of fatty acid-derived acetyl CoA in TCA cycle as a catalyst and also serves as the carbon source for gluconeogenesis

## Alcohol and gluconeogenesis

- Alcohol is metabolized mostly in liver
- It increases NADH/$NAD^+$ ratio by alcohol dehydrogenase and aldehyde dehydrogenase
- Increased NADH/$NAD^+$ ratio prevents the use of gluconeogenic substrates for glucose production
- Pyruvate > Lactate
- Oxaloacetate > Malate
- Dihydroxyacetone-P > α-Glycerophosphate

Alcohol inhibits gluconeogenesis; it can cause hypoglycemia after fasting when gluconeogenesis is needed to maintain blood glucose levels

# Atkins diet and gluconeogenesis

- Atkins diet is used for weight loss
- High-protein, high-fat, and low-carbohydrate diet
- As there is very little dietary glucose, gluconeogenesis is active in liver most of the time
- Lipolysis is induced in adipocytes that releases free fatty acids and glycerol into circulation; this reduces weight
- Free fatty acids can serve as energy source for liver, muscle and heart, but cannot support gluconeogenesis (even-number fatty acids > acetyl CoA); glycerol can support gluconeogenesis, but the contribution is not that significant
- Dietary protein provides amino acids; glucogenic amino acids are converted into various TCA cycle intermediates, which converge to oxaloacetate, the glucogenic substrate
- Pyruvate, $\alpha$-ketoglutarate, succinyl CoA, and oxaloacetate support gluconeogenesis with people on Atkins diet

# Metformin, an anti-diabetic drug

- Metformin acts on liver
- It reduces the glucose output from liver, thus decreasing blood glucose levels
- It is an inhibitor of gluconeogenesis
- It is an activator of AMPK (AMP-activated kinase)
- AMPK is a marker for energy depletion in liver, thus activating catabolic pathways (glycolysis) and inhibiting anabolic pathways (gluconeogenesis)
- It is also an inhibitor of α-glycerophosphate shuttle, thus increasing NADH/$NAD^+$ ratio in cytoplasm and hence preventing the use of lactate, oxaloacetate and α-glycerophosphate in gluconeogenesis

# NADH Shuttles

- The purpose of these shuttles is to carry electrons present in NADH in cytoplasm into mitochondria for ETC
- There are two shuttles

α-Glycerophosphate shuttle and Malate-aspartate shuttle

- α-GPS converts cytoplasmic NADH into mitochondrial $FADH_2$
- MAS converts cytoplasmic NDAH into mitochondrial NADH

Inhibition of both shuttles will increase $NADH/NAD^+$ ratio and thus interfere with the use of lactate, oxaloacetate and α-glycerophosphate for gluconeogenesis

# Von Gierke disease

- Autosomal recessive
- Defective glucose generation from glucose-6-phosphate
- Mutations in glucose-6-phosphatase in ER (Type 1a)
- Mutations in glucose-6-phosphate transporter in ER (Type 1b)
- Glucose-6-phosphate is central to glycogenolysis, glycolysis, and hexose monophosphate shunt
- In von Gierke disease, G6P accumulates, leading to hypoglycemia, glycogen storage, elevated pyruvate from enhanced glycolysis leading to lactic acidosis, hyperalaninemia and hyperlipidemia, elevated ribose-5-phosphate from enhanced HMP shunt leading to increased purine synthesis and hence in hyperuricemia (gout)
- Hepatomegaly, kidney dysfunction, hypoglycemic seizures, delayed puberty in girls (polycystic ovaries but not PCOS)
- Treatment: Maintain blood glucose levels (IV glucose or TPN)

Hormones that increase blood glucose levels

Glucagon

Epinephrine

Norepinephrine

Glucocorticoids (cortisol)

Growth hormone

Adrenocorticotropic hormone

Hormones that decrease blood glucose levels

Insulin

A 25-year-old man is found in a semicomatose state and is taken to the emergency department by friends, who say that the man has not eaten for the past 4 days. Which of the following substances has most likely been this patient's primary source of glucose?

- A. Amino acids from muscle proteins
- B. Amino acids from liver proteins
- C. Fatty acids from adipose tissue
- D. Glycogen from muscle tissue

# Insulin, Glucagon, Epinephrine

| **Tissue** | **Responds to Insulin** | **Counter-regulatory hormone** |
|---|---|---|
| Liver | Yes | Glucagon |
| Adipose | Yes | Epinephrine |
| Muscle | Yes | Epinephrine |