L -

Gluconeogenesis

What does your body do if you don't have enough glucose?

Gluconeogenesis:

Needed to produce glucose for the brain when food isn't available.
Glycogen stores are depleted in 12 to 18 hours.
Use other **non-carbohydrate** sources
(glycerol , lactate, some amino acids, & (in plants) acetyl-CoA)
to make glucose for brain fuel.

The liver is the major site of **gluconeogenesis**.

Gluconeogenesis

- A metabolic pathway that results in the generation of glucose from non-carbohydrate carbon substrates.

- It is one of the two main mechanisms the body uses to keep blood glucose levels from dropping too low .

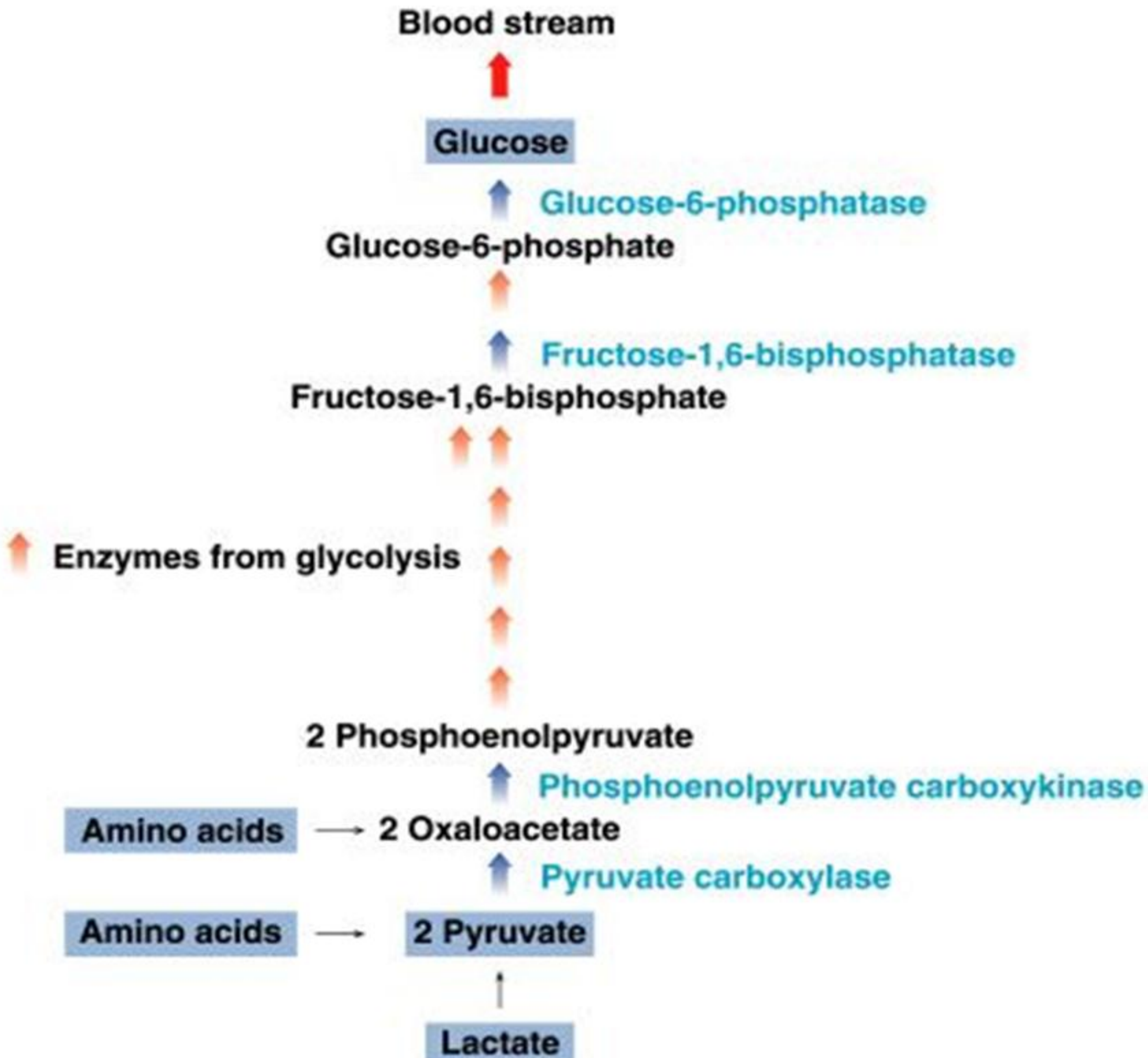
- In animals, gluconeogenesis takes place mainly in the liver.

- This process occurs during periods of fasting, starvation, or intense exercise.

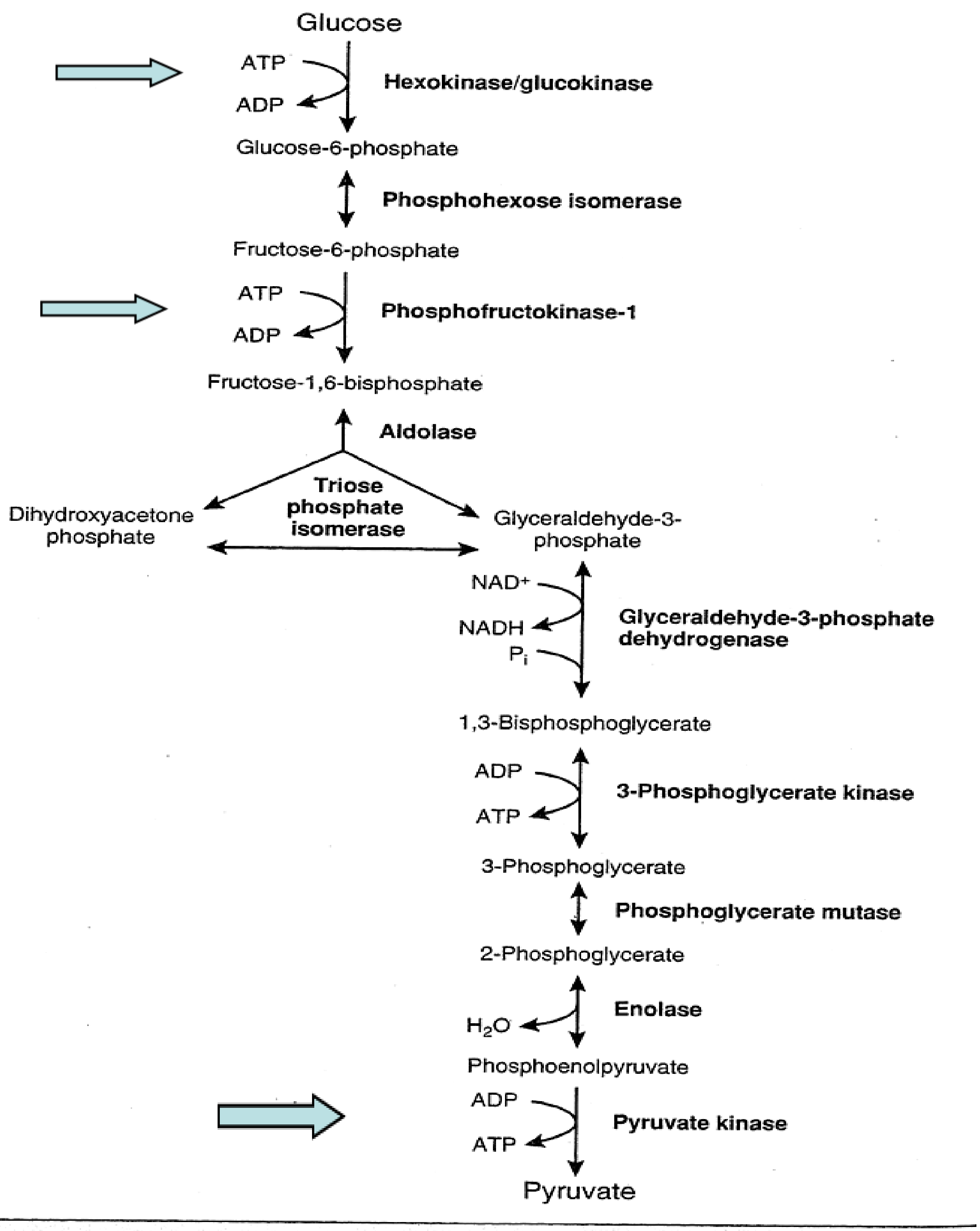
Gluconeogenesis Reactions

The reaction sequence in gluconeogenesis is largely the reverse of glycolysis. Recall, however, that three glycolytic reactions (the reactions catalyzed by hexokinase, PFK-1, and pyruvate kinase) are irreversible.

In gluconeogenesis, alternate reactions catalyzed by different enzymes are used to bypass these obstacles. The reactions unique to gluconeogenesis are listed next.



Gluconeogenesis



Basically, gluconeogenesis pathway is a reverse of glycolysis but has three bypass.

Irreversible glycolytic steps bypassed

Glycolysis	Gluconeogenesis
1.Hexokinase	by Glucose-6-phosphatase
2.Phosphofructokinase-1	by Fructose 1,6-bisphosphatase
3.Pyruvate kinase (PyrK**)**	by Pyruvate Carboxylase and Phosphoenolpyruvate carboxykinase

1- ***Glucose-6-Phosphatase*** catalyzes:

glucose-6-phosphate + H_2O → glucose + P_i

- This is primarily a function of the liver to buffer blood glucose levels
- ***Glucose-6-Phosphatase*** is NOT present in brain and muscle!

2- ***Fructose-1,6-bisphosphatase*** catalyzes:

fructose-1,6-bisP + H2O → fructose-6-P + Pi

3-Pyruvate carboxylase and PEP carboxykinase catalyze:

Pyruvate + ATP+ GTP → PEP + ADP + GDP + Pi + CO2

Substrates for gluconeogenesis

Gluconeogenic precursors are molecules that can be used to produce a net synthesis of glucose. They include intermediates of glycolysis and the tricarboxylic acid (TCA) cycle. Glycerol, lactate, and the α-keto acids obtained from the transamination of glucogenic amino acids are the most important gluconeogenic precursors.

A. Glycerol

Glycerol is released during the hydrolysis of triacylglycerols in adipose tissue , and is delivered by the blood to the liver.

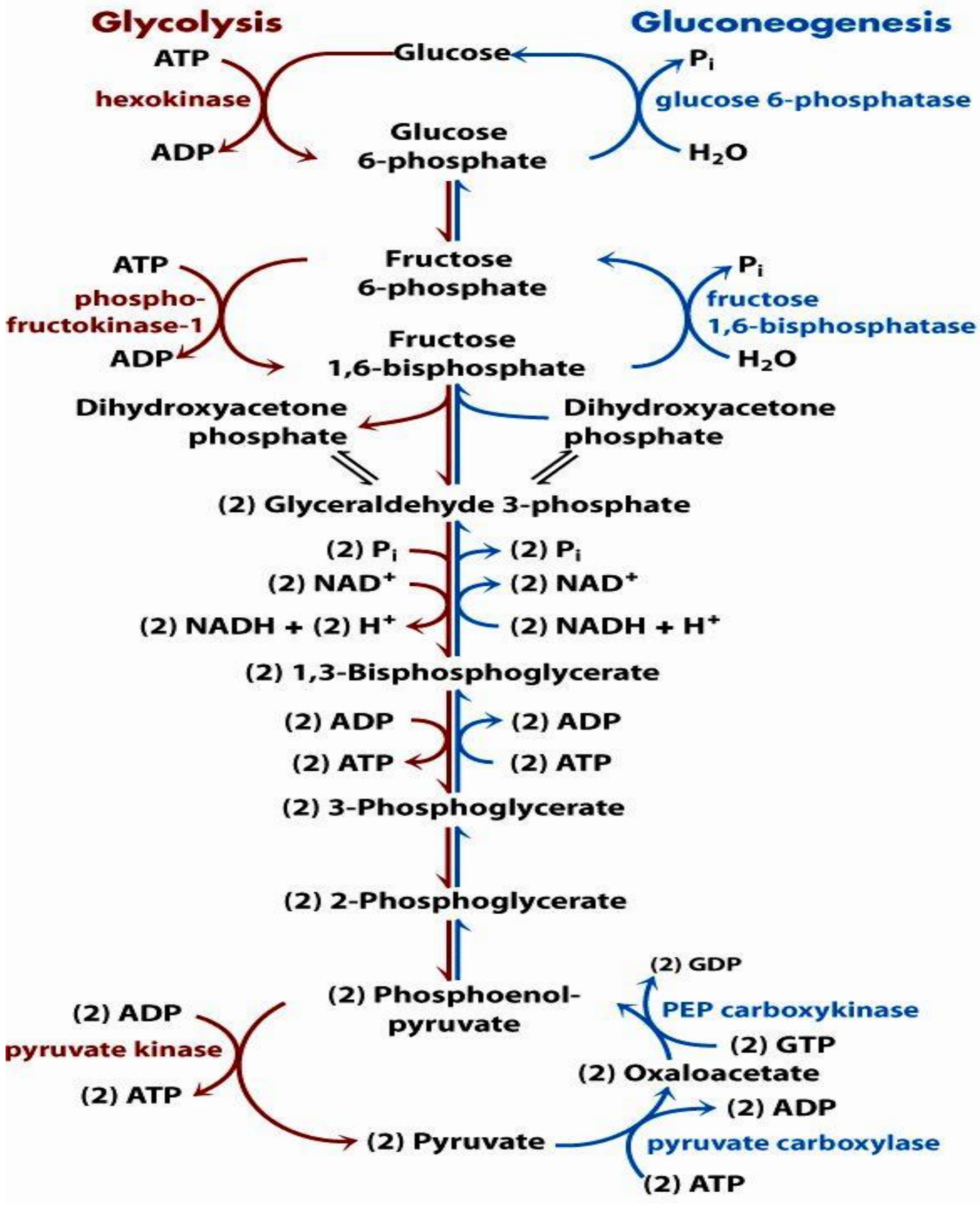
Glycerol is phosphorylated by ***glycerol kinase*** to glycerol phosphate, which is oxidized by **glycerolphosphate dehydrogenase** to **dihydroxy acetone phosphate** DHAP—an intermediate of glycolysis. [Note: Adipocytes cannot phosphorylate glycerol because they essentially lack ***glycerol kinase***.]

B. Lactate

Lactate is released into the blood by exercising skeletal muscle, and by cells that lack mitochondria, such as red blood cells. In the Cori cycle, blood borne glucose is converted by exercising muscle to lactate, which diffuses into the blood. This lactate is taken up by the liver and reconverted to glucose, which is released back into the circulation

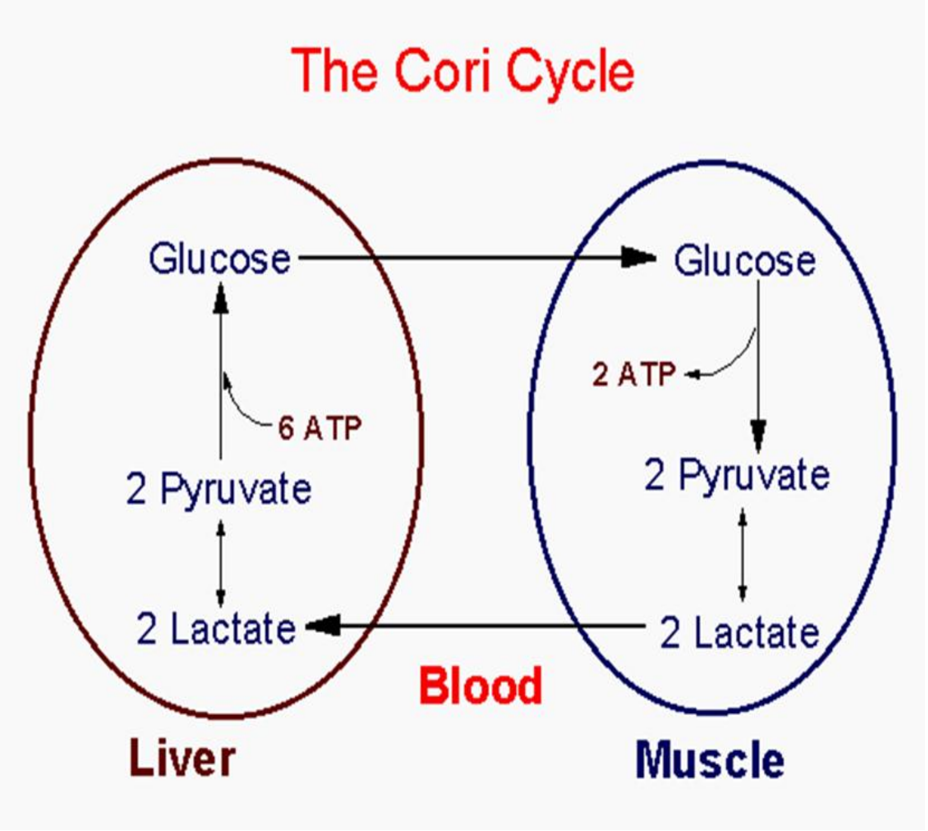
C. Amino acids

Amino acids derived from hydrolysis of tissue proteins are the major sources of glucose during a fast. α-Ketoacids, such as α-keto - glutarate, are derived from the metabolism of glucogenic amino acids . These α-ketoacids can enter the TCA cycle and form oxaloacetate (OAA)—a direct precursor of phosphoenol - pyruvate (PEP).


Glycolysis
Gluconeogenesis
Glucose
ATP
hexokinase
ADP
Glucose 6-phosphate
P_i
glucose 6-phosphatase
H_2O
Fructose 6-phosphate
ATP
phospho-fructokinase-1
ADP
Fructose 1,6-bisphosphate
P_i
fructose 1,6-bisphosphatase
H_2O
Dihydroxyacetone phosphate
Dihydroxyacetone phosphate
(2) Glyceraldehyde 3-phosphate
(2) P_i
(2) NAD^+
(2) NADH + (2) H^+
(2) P_i
(2) NAD^+
(2) NADH + H^+
(2) 1,3-Bisphosphoglycerate
(2) ADP
(2) ATP
(2) ADP
(2) ATP
(2) 3-Phosphoglycerate
(2) 2-Phosphoglycerate
(2) Phosphoenol-pyruvate
(2) GDP
PEP carboxykinase
(2) GTP
(2) Oxaloacetate
(2) ADP
pyruvate kinase
(2) ATP
(2) Pyruvate
(2) ADP
pyruvate carboxylase
(2) ATP

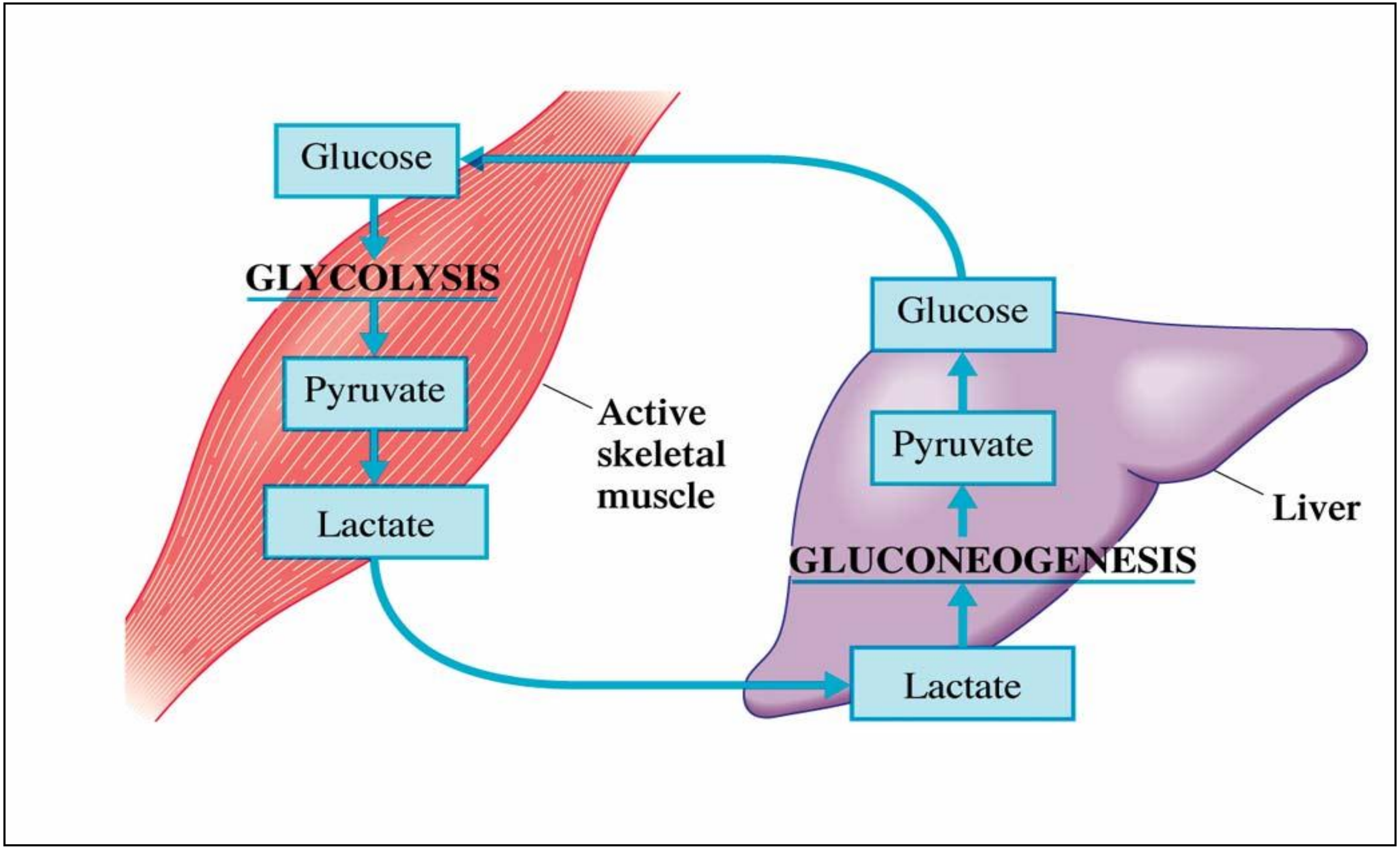
- **Lactate and glucose shuttle between active muscle/RBC and liver**
- **When anaerobic conditions occur in active muscle, glycolysis produces lactate**
- **The lactate moves through the blood stream to the liver, where it is oxidized back to pyruvate.**
- **Gluconeogenesis converts pyruvate to glucose, which is carried back to the muscles**
- **The Cori cycle is the flow of lactate and glucose between the muscles and the liver**
- **Liver gluconeogenesis supplies the blood glucose for use by muscle, RBC's and brain (120 g/day)**

- **Note: the brain fully oxidizes glucose, so it does not funnel back lactate**



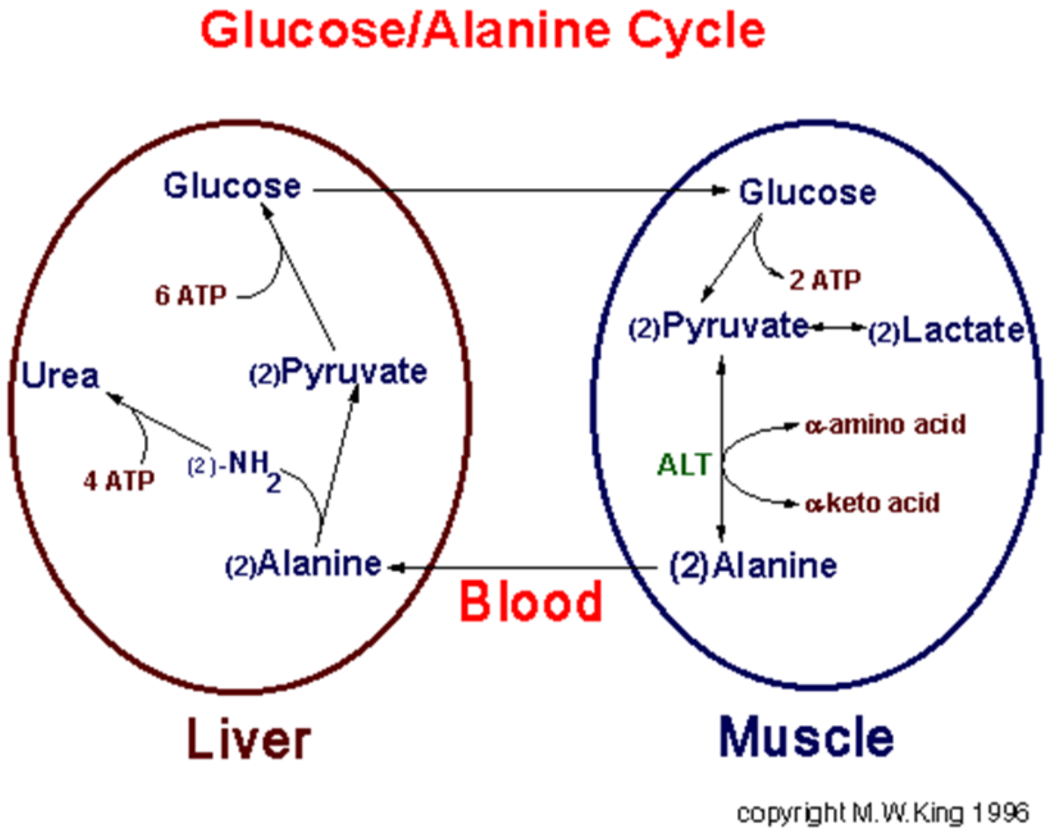
Gerti and Carl Cori won 1947 Nobel Prize in physiology / medicine for discovery of the enzyme that starts the conversion of glycogen to glucose

The Cori cycle: processing lactate made during anaerobic exercise



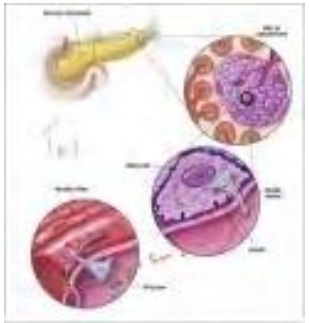
•**The liver can also use the amino acid Alanine similarly to Lactate**

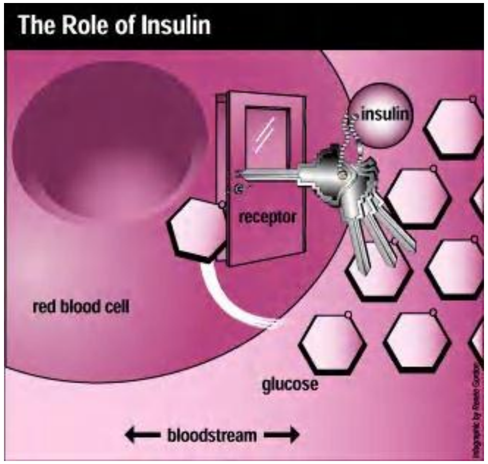
• **Following transamination to pyruvate, gluconeogenesis allows the liver to convert it to glucose for secretion into the blood**



Hormonal Control of Carbohydrate Metabolism

- Enzymes control the metabolism of carbohydrates, but...
- Several hormones also affect carbohydrates metabolism
  - Insulin
  - Glucagon
  - Epinephrine





Low blood [glucose]

↓

Increased glucagon secretion

↓

Increased [cAMP]

↓

Increased enzyme phosphorylation

↓

Activation of FBPase-2 and inactivation of PFK-2

↓

Decreased [F2,6P]

↓

Inhibition of PFK and activation of FBPase

↓

Increased gluconeogenesis

1-Insulin: insulin is produced by B-cells of the islets of Langerhans in response to hyperglycemia (elevated blood glucose level). Some amino acids, free fatty acids, ketone bodies, drugs such as tolbutamide also cause the secretion of insulin. Insulin is basically a hypoglycemic hormone that lowers in blood glucose level through various means. lt is an anti-diabetogenic hormone.

2. Glucagon: Glucagon is synthesized by alpha-cells of the islets of Langerhans of the pancreas. Hypoglycemia (low blood glucose level) stimulates its production. Glucagon is basically involved in elevating blood glucose concentration. it enhances gluconeogenesis and glycogenolysis.

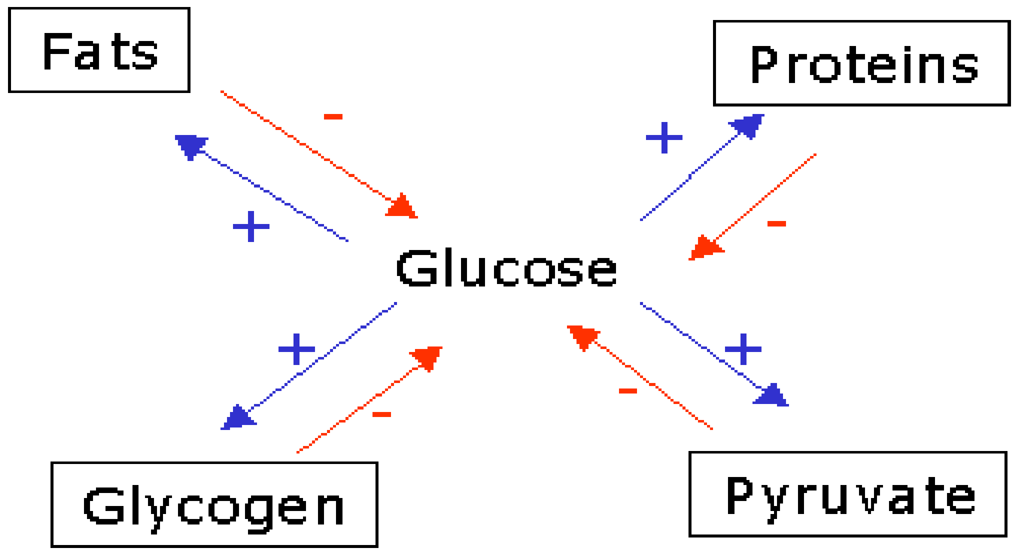
3-Epinephrine: This hormone is secreted by adrenal medulla. lt acts both on muscle and liver to bring about glycogenolysis by increasing phosphorylase activity. The end product is glucose in liver and lactate in muscle. The net outcome is that epinephrine increases blood glucose level.

4. Thyroxine: lt is a hormone of thyroid gland. It elevates blood glucose level by stimulating hepatic glycogenolysis and gluconeogenesis

5. Glucocorticoids: These hormones are produced by adrenal cortex. Clucocorticoids stimulate protein metabolism and increase gluconeogenesis (increase the activities of enzymes-glucose 6-phosphatase and fructose 1,6-bisphosphatase). The glucose utilization by extrahepatic tissues is inhibited by glucocorticoids. The overall effect of glucocorticoids is to elevate blood glucose concentration.

6. Growth hormone and adrenocorticotropic hormone (ACTH): The anterior pituitary gland secretes growth hormone and ACTH. The uptake of glucose by certain tissues (muscle, adipose tissue etc.) is decreased by growth hormone. ACTH decreases glucose utilization. The net effect of both these hormones is hyperglycemic.

Effect of insulin on metabolism

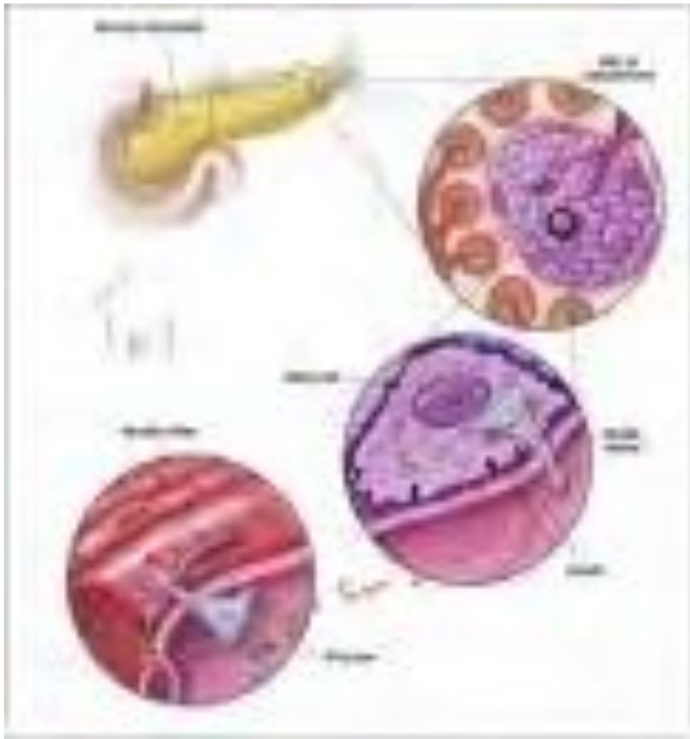


Insulin reduces **glucose** in the blood and **stimulates** conversion of glucose to fats, proteins, ribulose 5-phosphate and glycogen;

inhibits the conversion of fats, proteins, glycogen and ribulose 5-phosphate to glucose

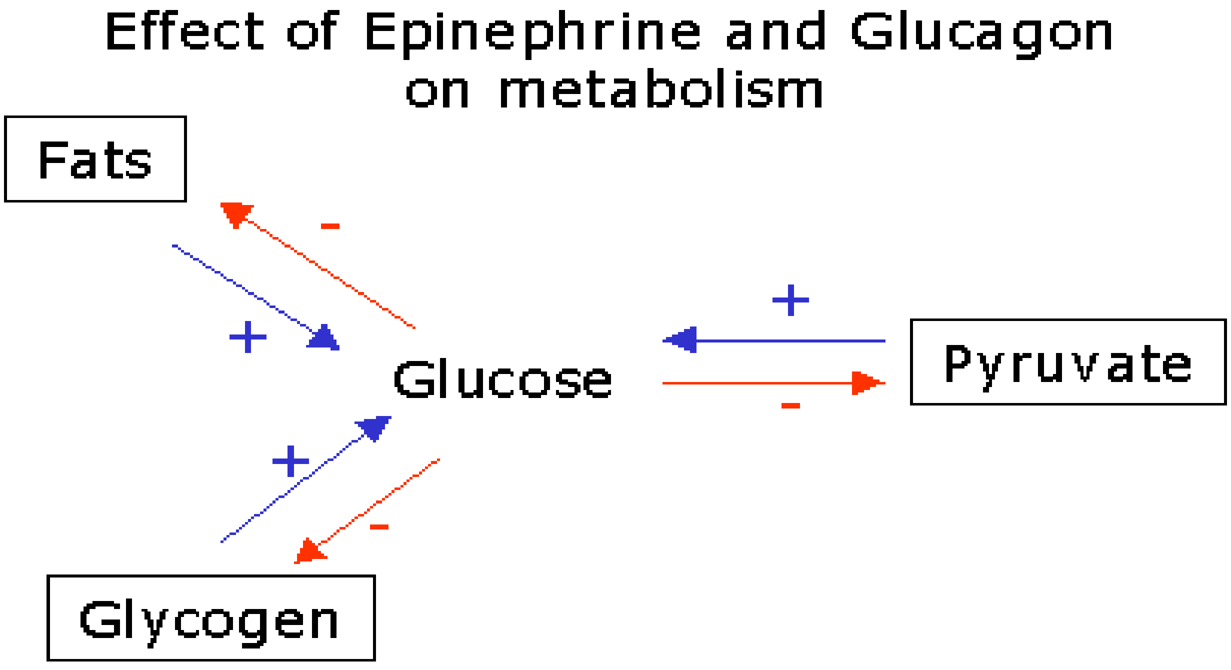
Note: Insulin acts to **reduce glucose** concentrations in the blood and therefore stimulates the conversion of glucose to fats, proteins, ribulose 5 phosphate and glycogen.

inhibits the conversion of fats, proteins, ribulose 5 phosphate and glycogen to glucose



Glucagon is a 29 amino acid peptide hormone formed and released from the **alpha cells** of the **islets of Langerhans**, in the **pancreas.**

Glucagon is a ***hormone*** that opposes the action of insulin - mainly in the liver.



Epinephrine & glucagon have opposite effects to insulin.
Act to **increase glucose** in the blood.
Stimulate conversion of fats, glycogen and pyruvate to **glucose**
Inhibit conversion of glucose to fats, glycogen and pyruvate

Types of diabetes mellitus

Type 1: autoimmune disorder against the Islet cells of pancreas: deficiency in insulin. Usually diagnosed between 5-20. Insulin shots necessary. Hypoglycemia (too little glucose) may result.

Type 2: 80-90 % of all diabetics in US: usually diagnosed over age 40. relative insulin deficiency: either decreased production of insulin, or cells become insulin resistant.

Strong genetic component: very high in Native Americans; high in Blacks & Hispanics. Obesity major risk factor (often controlled with weight loss).

Regulation of blood sugar and Clinical Significance of Blood glucose

□ **Conditions in which hyperglycemia may occur:**

1. Diabetes mellitus. This may arise due to:
a. Pituitary neoplasms.
b. Adrenal hyperplasia.
c. Pregnancy toxaemia.
d. Acute pancreatic necrosis.

2. Convulsions as in:
a. Eclampsia **is the new onset of seizures or coma in a pregnant woman. These seizures are not related to an existing brain condition.**

b. Intracranial trauma (is an injury to the brain caused by an external force also known as a traumatic brain injury (TBI) .
c. Epilepsy.
d. Tetany.

3. Transient conditions:
a. Exposure to cold.
b. Following general anaesthesia.
c. Injection of epinephrine.
d. Intravenous glucose injection.
e. Feeding large quantities of carbohydrates.
f. Excitement

4. Hyperthyroidism: There is increased glucose production by the liver in excess of utilization.

5. Chronic nephritis.

- **Conditions in which hypoglycemia may occur:**

1. Starvation.

2. Hypopituitarism.

3. Hypothyroidism.

4. Hyper insulinism - a) Tumour of pancreas, b) Excess of insulin in therapy.

5. Adrenal cortical insufficiency. is a disorder that occurs when the adrenal glands don't make enough of certain hormones

6. Severe excretion- Glucose utilization is increased and liver glycogen is depleted.

7. Hypoglycemia (manifested by convulsions, weakness, coma and death). Blood glucose level is 40 mg%.