# Metabolisme Karbohidrat

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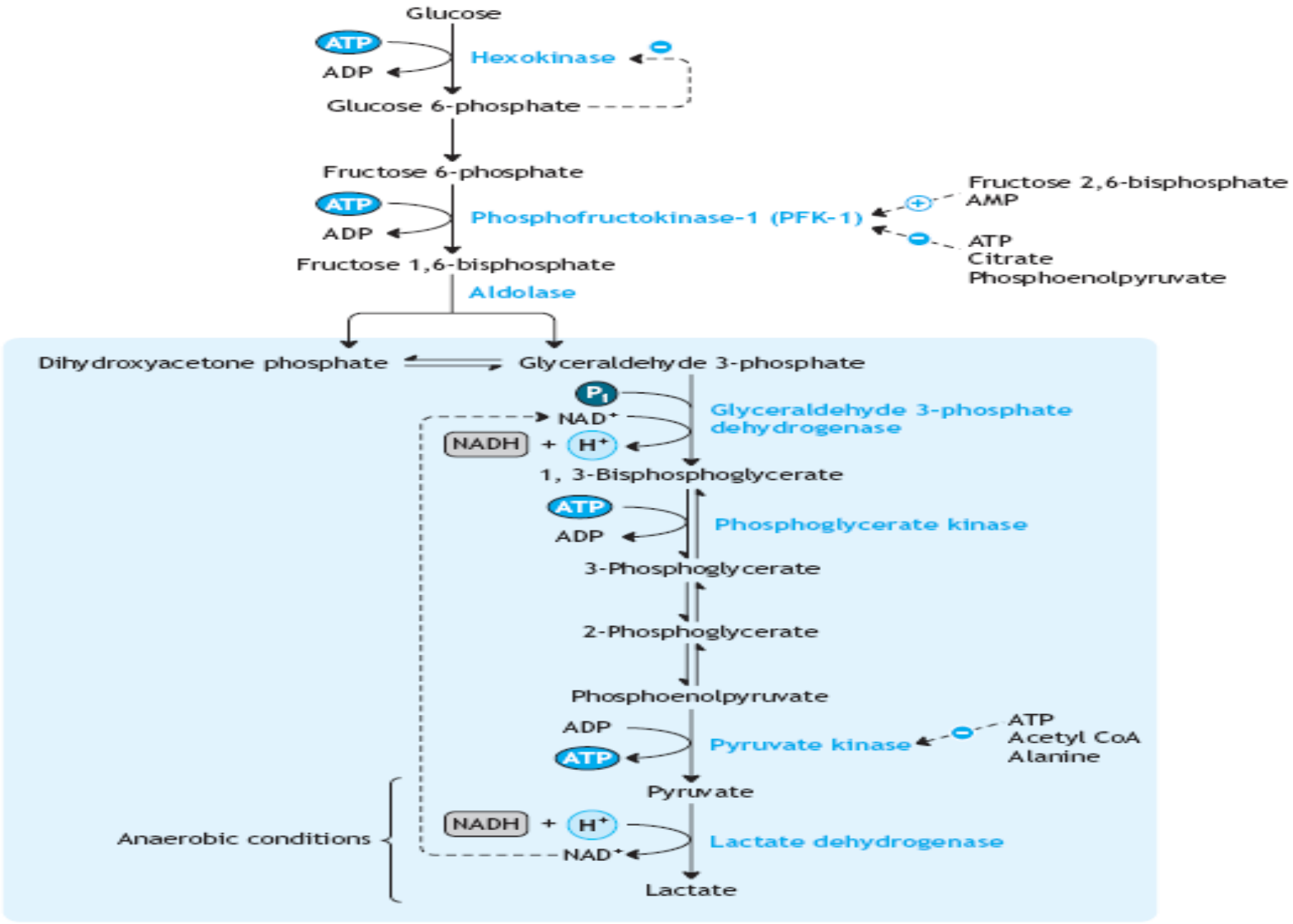
# Glycolisis


Glucose
ATP
ADP
Hexokinase
Glucose 6-phosphate
Fructose 6-phosphate
ATP
ADP
Phosphofructokinase-1 (PFK-1)
Fructose 2,6-bisphosphate
AMP
ATP
Citrate
Phosphoenolpyruvate
Fructose 1,6-bisphosphate
Aldolase
Dihydroxyacetone phosphate
Glyceraldehyde 3-phosphate
Pi
NAD+
NADH + H+
Glyceraldehyde 3-phosphate dehydrogenase
1, 3-Bisphosphoglycerate
ATP
ADP
Phosphoglycerate kinase
3-Phosphoglycerate
2-Phosphoglycerate
Phosphoenolpyruvate
ADP
ATP
Pyruvate kinase
ATP
Acetyl CoA
Alanine
Pyruvate
Anaerobic conditions
NADH + H+
NAD+
Lactate dehydrogenase
Lactate

# Glycolisis

- **Glycolysis is the process by which glucose is broken down to pyruvate in order** to begin obtaining some of the **energy stored in the glucose molecule for use by** the body.
- Two key enzymes, ***hexokinase*** **and** ***glucokinase*****,** catalyze the reaction of glucose with ATP to form **glucose 6-phosphate, which becomes trapped in the cell and** subject to metabolism.

# Glycolisis

- The steps of glycolysis. Feedback inhibition of glucose phosphorylation by hexokinase, inhibition of pyruvate kinase, and the main regulatory, rate-limiting step catalyzed by phosphofructokinase (PFK-1) are indicated.
- Pyruvate formation and substrate-level phosphorylation are the main outcomes of these reactions.
- Regeneration of NAD+ occurs by reduction of pyruvate to lactate during anaerobic glycolysis.

- **1. The principal enzyme catalyzing this reaction, hexokinase, is found in all** cells and has a **high affinity (low *Km) for glucose.***
  - **a. The high affinity of hexokinase for glucose means that even when glucose** levels in the body are low, cells can efficiently take up glucose and obtain energy from it.
  - **b. Glucose 6-phosphate inhibits hexokinase, preventing cells from metabolizing** excess glucose and harming other cells by reducing glucose available in the blood for metabolism.
- **2. Glucokinase is found in the liver and is responsible for dealing with the high** levels of glucose available after a meal.
  - **a. Glucokinase has a low affinity (high *Km) for glucose but has a high Vmax.***
  - **b. Elevation of blood glucose levels after a meal stimulates the pancreas to secrete insulin, which among its many actions induces synthesis of glucokinase** by the liver.
- **3. The negative charge of glucose 6-phosphate prevents it from diffusing** across the plasma membrane and effectively **traps glucose inside the cell for** future metabolism.

# Key regulatory enzyme

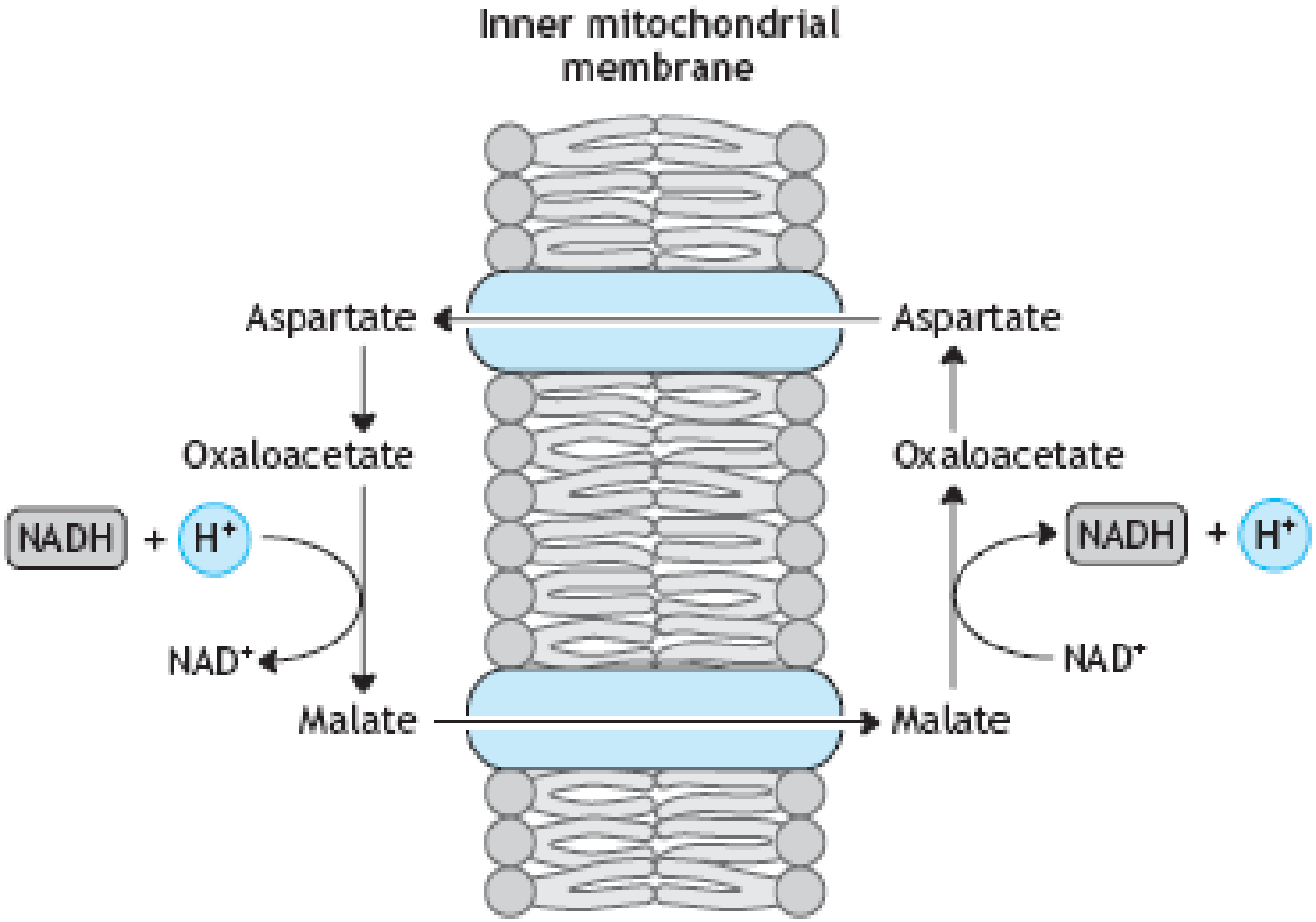
- The key regulatory enzyme **phosphofructokinase-1 (PFK-1) catalyzes the synthesis** of **fructose 1,6-bisphosphate.**
- **ATP : phosphate donor for this reaction; two high-energy phosphates** must be invested at the start of glycolysis.
- **PFK-1 catalyzes this irreversible and rate-limiting step in glycolysis and is highly regulated.**
- **PFK-1: subject to allosteric inhibition by ATP, citrate, and phosphoenolpyruvate,** all of which are elevated when the cell has a high level of energy reserves.
  - **AMP is a very sensitive indicator of the cell's energy needs because of** rapid interconversion of adenine nucleotides and is an important **activator of PFK-1.**
  - **PFK-1 is also activated by fructose 2,6-bisphosphate, which is made by** the action of a second phosphofructokinase, PFK-2, using fructose 6-phosphate and ATP as substrates.

- Another key enzyme, **pyruvate kinase, catalyzes the conversion of phosphoenolpyruvate** to **pyruvate and the formation of a second ATP in glycolysis.**
  - **Pyruvate kinase is inhibited by compounds that are elevated when the cell has** high energy reserves or molecules with potential for energy generation.
  - **High ATP levels inhibit pyruvate kinase.**
  - **High amounts of acetyl CoA that can be converted to ATP through the tricarboxylic** acid cycle inhibit pyruvate kinase.
  - **High alanine levels inhibit pyuvate kinase; alanine can be converted to pyruvate**

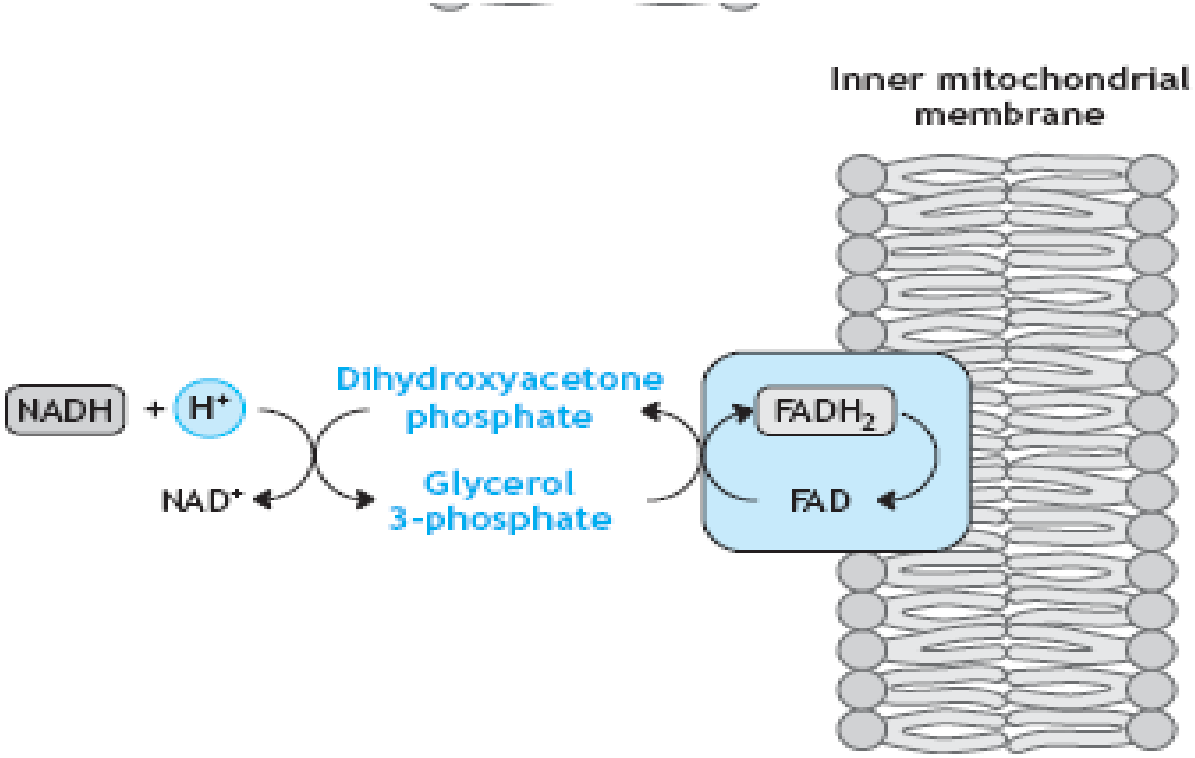
# PYRUVATE KINASE DEFICIENCY

- *Inherited deficiency of pyruvate kinase* ***impairs glycolysis in all cells but has the most acute effect on*** *RBCs.*
- *Anaerobic glycolysis is the only energy source available for maintenance of RBC viability, so the increased rate of erythrocyte death leads to* ***hemolytic anemia.***
- *Pyruvate kinase deficiency affects 1 in 10,000 people and is the most common inherited disorder of glycolysis.*
- *Most cases are due to decreased expression of pyruvate kinase activity, usually to* ***5–25% of normal levels; complete loss of pyruvate kinase activity can cause embryonic death***

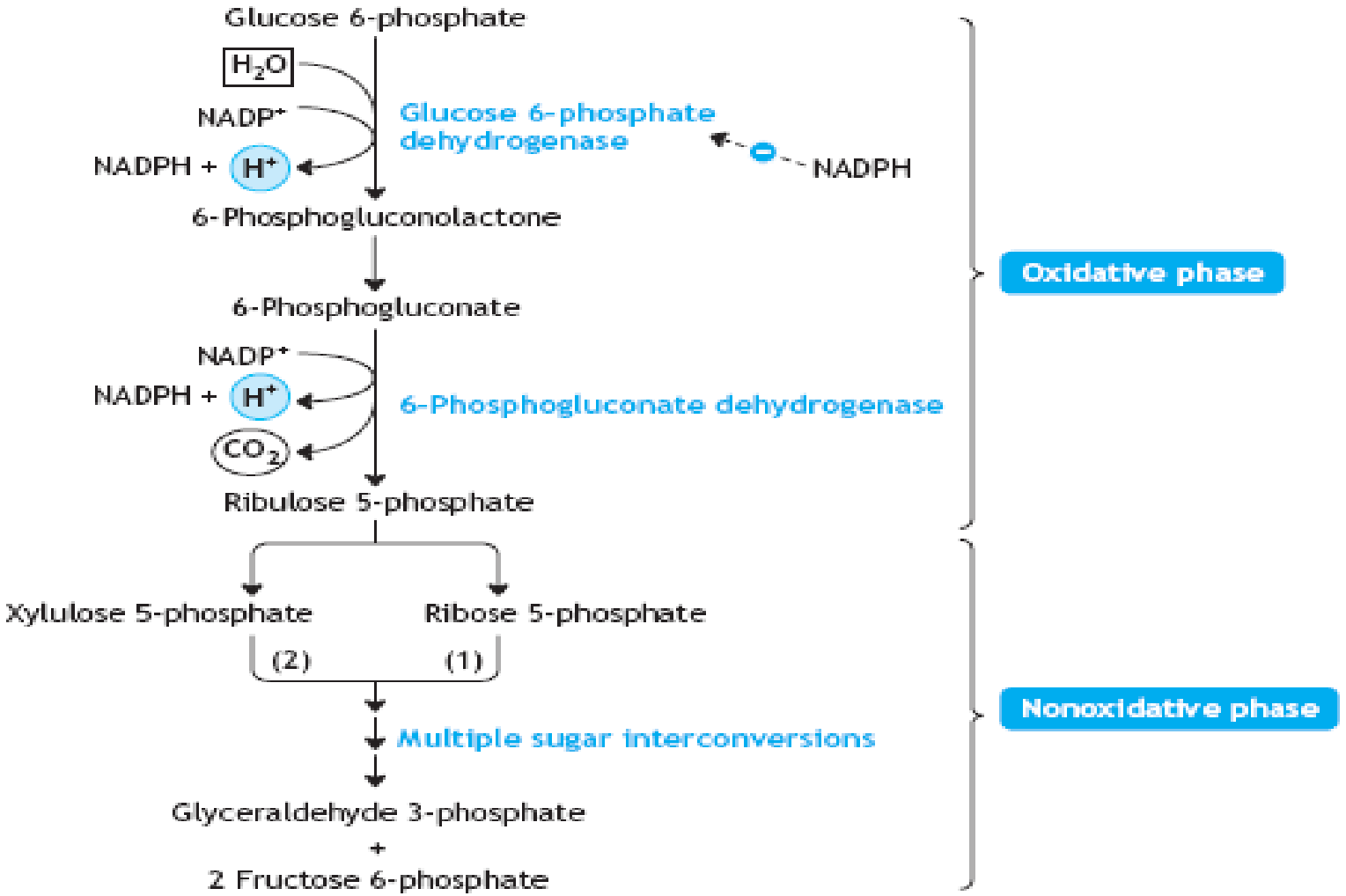
# The malate-aspartate shuttle.



# The glycerol 3-phosphate shuttle.



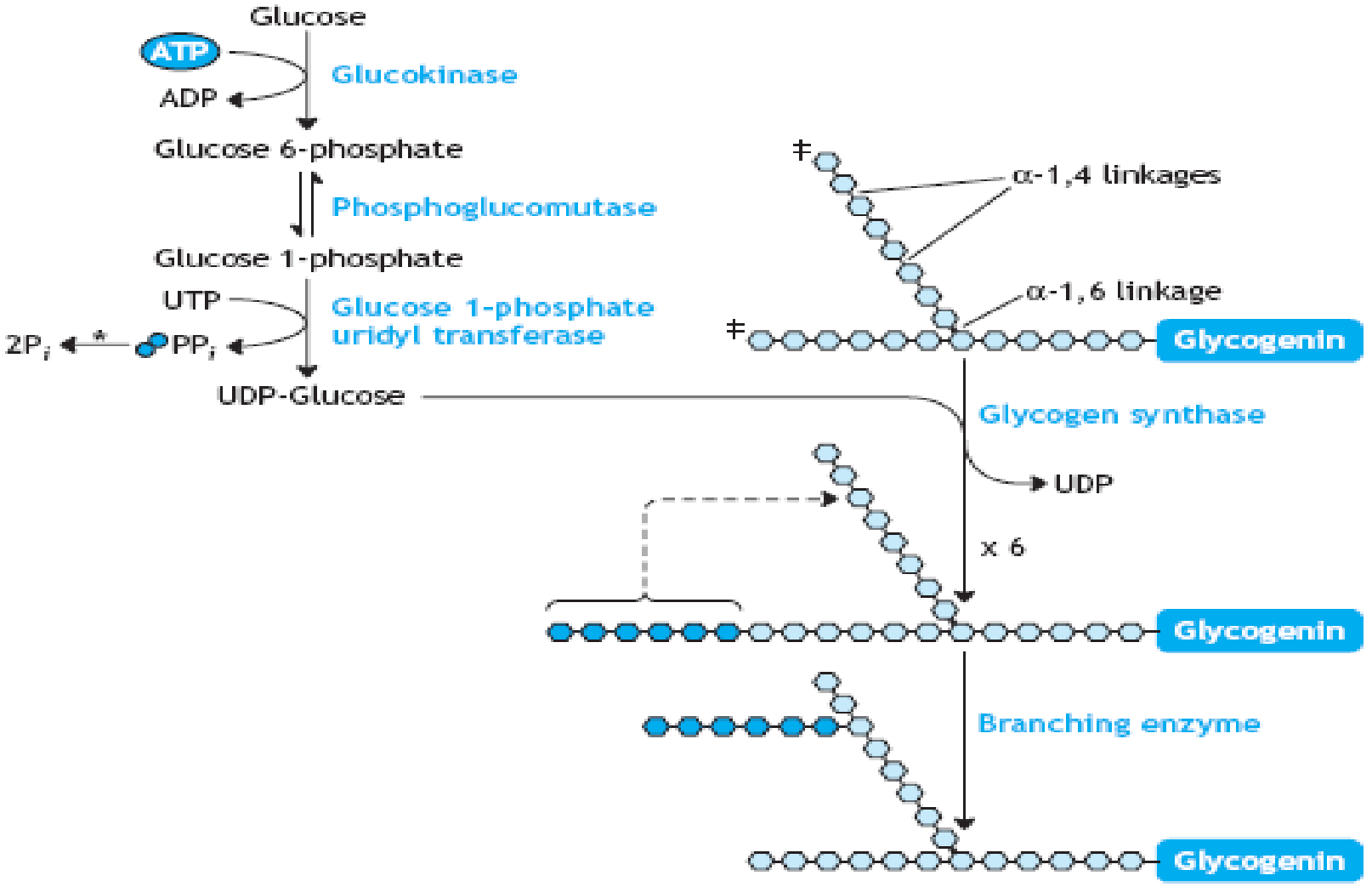
# pentose phosphate pathway



# G6PD DEFICIENCY CAUSES SENSITIVITY TO OXIDANTS

- *G6PD deficiency is the most common genetic disease in the world, affecting over 400 million people, most of whom are men, because the gene is located on the X chromosome.*
- *Persons with G6PD deficiency are normally asymptomatic, but their RBCs are susceptible to* ***oxidative damage because they have impaired production of NADPH.***

# Glycogenesis



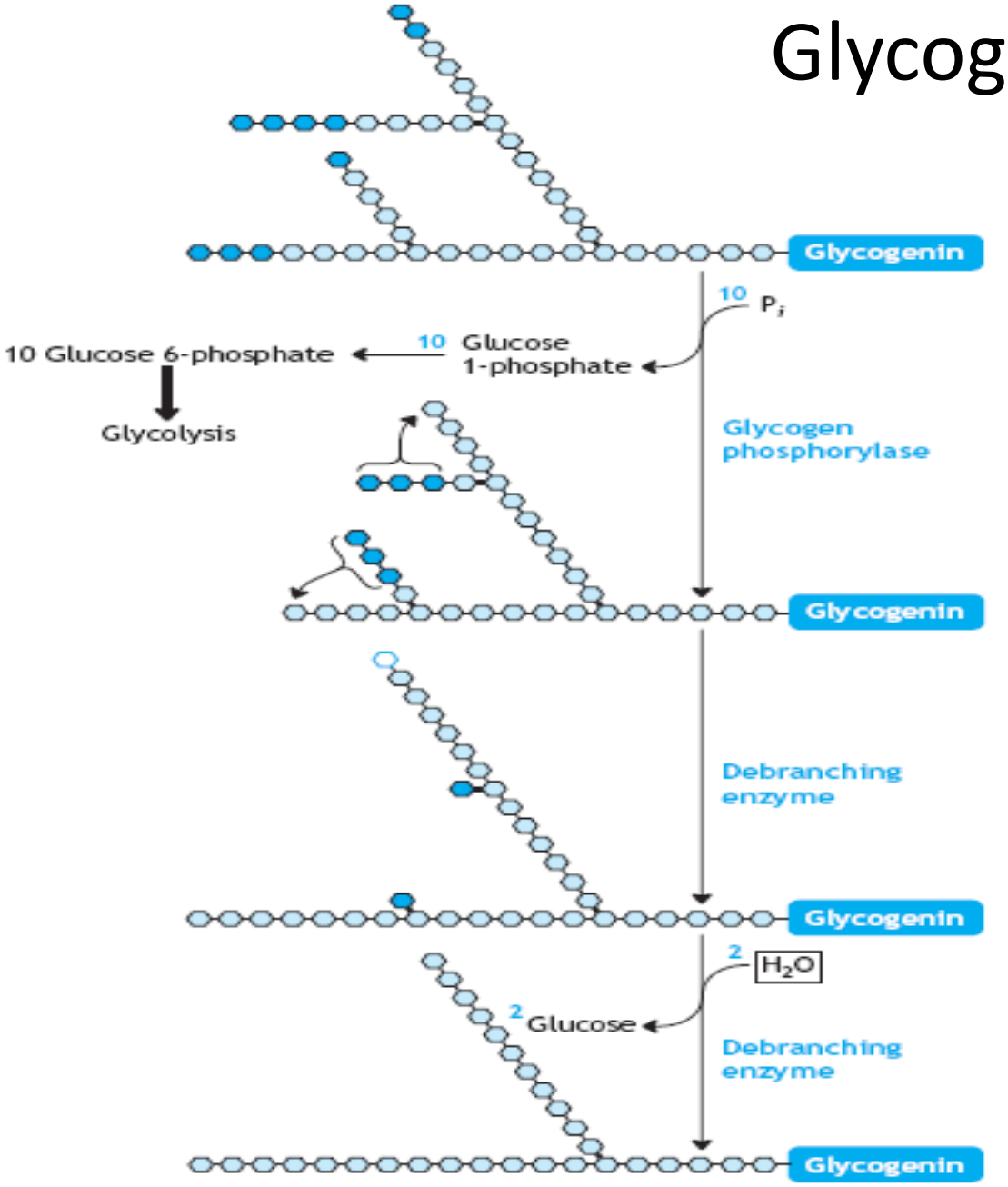
# Glycogenesis

- Uridine diphosphate (UDP)-glucose is synthesized and serves to donate glucose to an α-1,4 linkage at the non-reducing ends of a preexisting glycogen chain, which is covalently attached to the protein glycogenin.
- The asterisk indicates coupling of this reaction to hydrolysis of PP*i to Pi in* order to drive formation of UDP-glucose.
- Branching enzyme removes terminal residues and reattaches them to form an α-1,6 branch that can then be further extended by glycogen synthase.

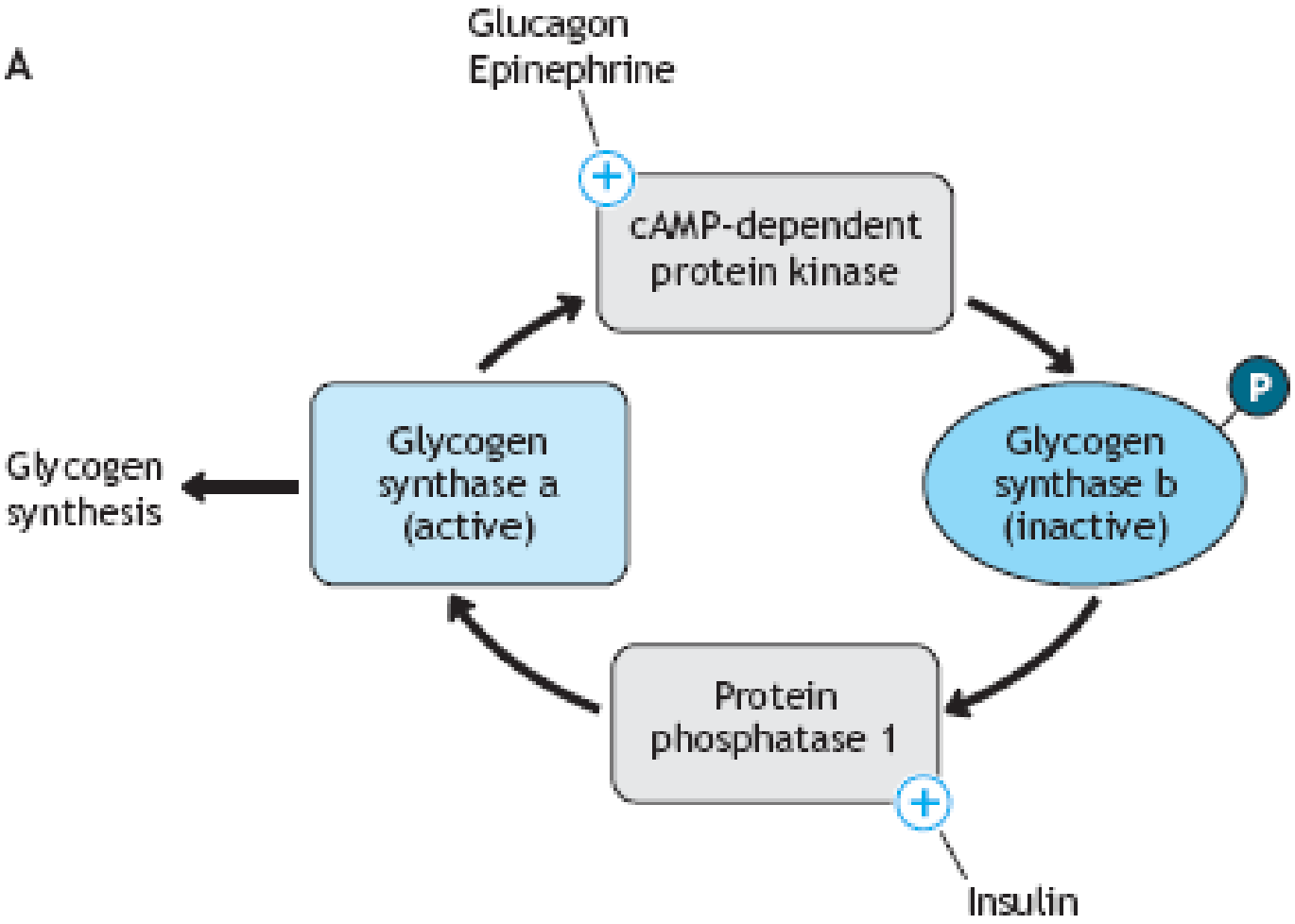
# GLYCOGEN STORAGE DISEASES

- *Deficiency of the enzymes of glycogen metabolism affects the ability of cells to store or use glycogen; as a result, regulation of blood glucose levels can be severely impaired during short-term fasting.*
- *Glycogen storage diseases produce **severe hypoglycemia, even on an overnight fast, and are frequently** diagnosed when the patient goes into **hypoglycemic shock while sleeping.***
- *Untreated, glycogen storage diseases can lead to **mental retardation or even death due to the energy** loss in the brain consequent to low blood glucose levels.*
- *The most common glycogen storage disease, Type I or **von Gierke disease, is a deficiency in glucose** 6-phosphatase in which glycogen structures are normal; however, the liver is unable to dephosphorylate glucose 6-phosphate, and it remains trapped in the cell.*
- *Blood glucose levels in patients with von Gierke disease fall precipitously upon fasting, such as occurs overnight during sleep, so treatment is to eat meals often to prevent hypoglycemic coma.*

# Glycogenolysis

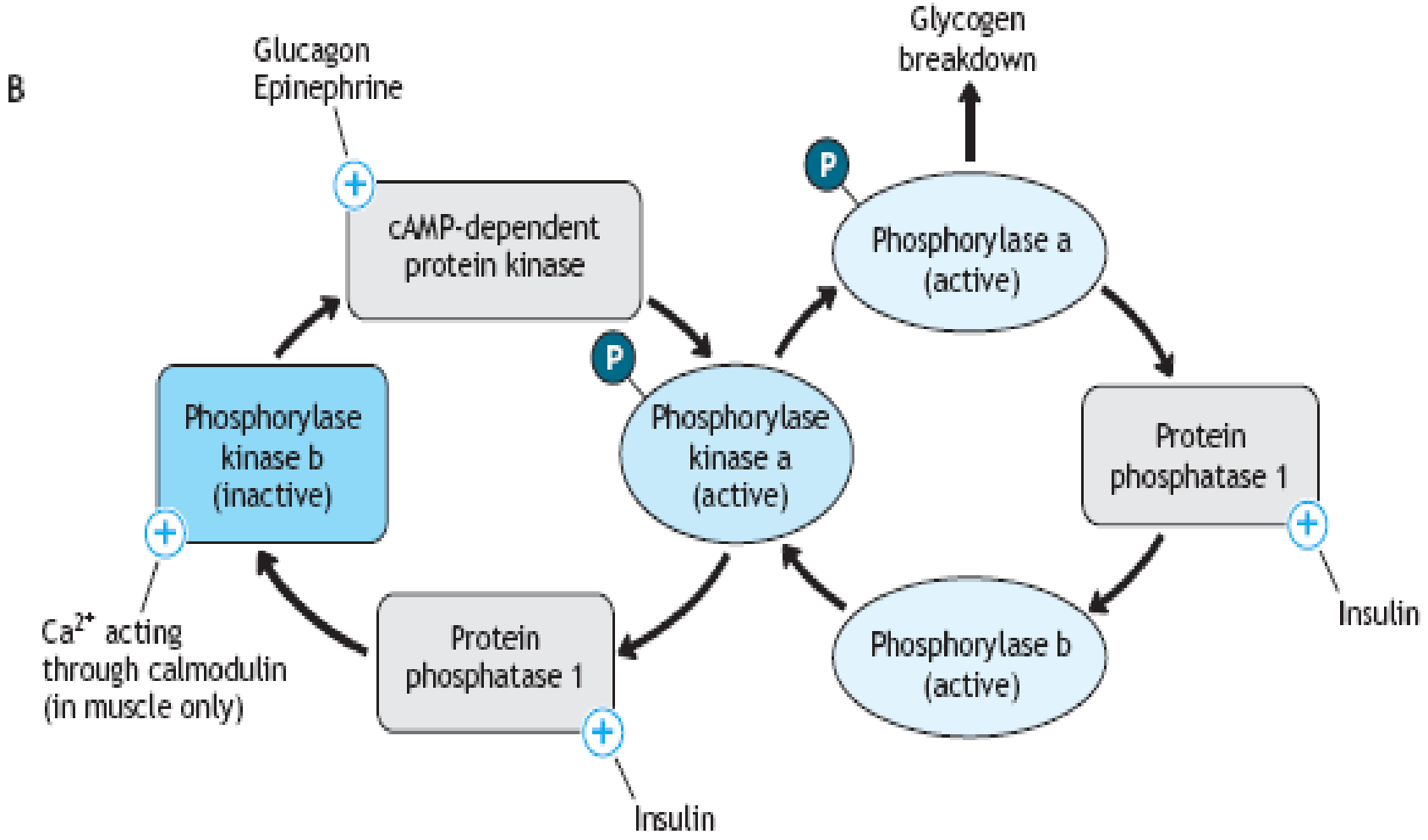


# Glycogenesis



- Activation of cyclic AMP (cAMP)–dependent protein kinase by the action of glucagon or epinephrine binding to their cell-surface receptors leads to phosphorylation and inactivation of glycogen synthase.
- Reactivation is catalyzed by protein phosphatase I, which is activated as a result of insulin binding to its cell-surface receptor.

# Hormonal regulation of glycogen metabolism



- The activity of glycogen phosphorylase is controlled by reversible phosphorylation, in a manner opposite to that of glycogen synthase.
- The effects of glucagon and epinephrine are still mediated by cAMP-dependent protein kinase, but through phosphorylase kinase, which itself is regulated by a phosphorylation-dephosphorylation cycle.
- Insulin action promotes dephosphorylation both of phosphorylase kinase and of phosphorylase itself, which inhibits glycogen breakdown

Conversion of mitochondrial

pyruvate to cytosolic phosphoenolpyruvate

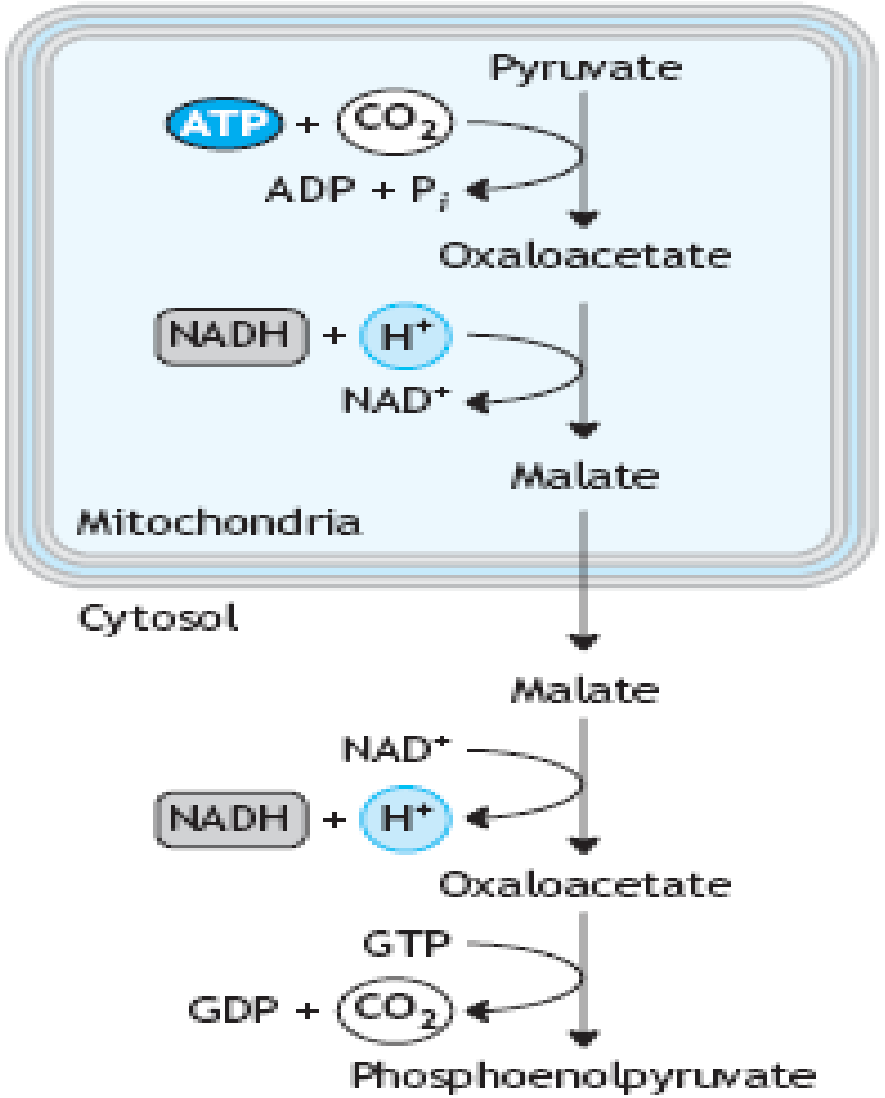
to initiate gluconeogenesis.

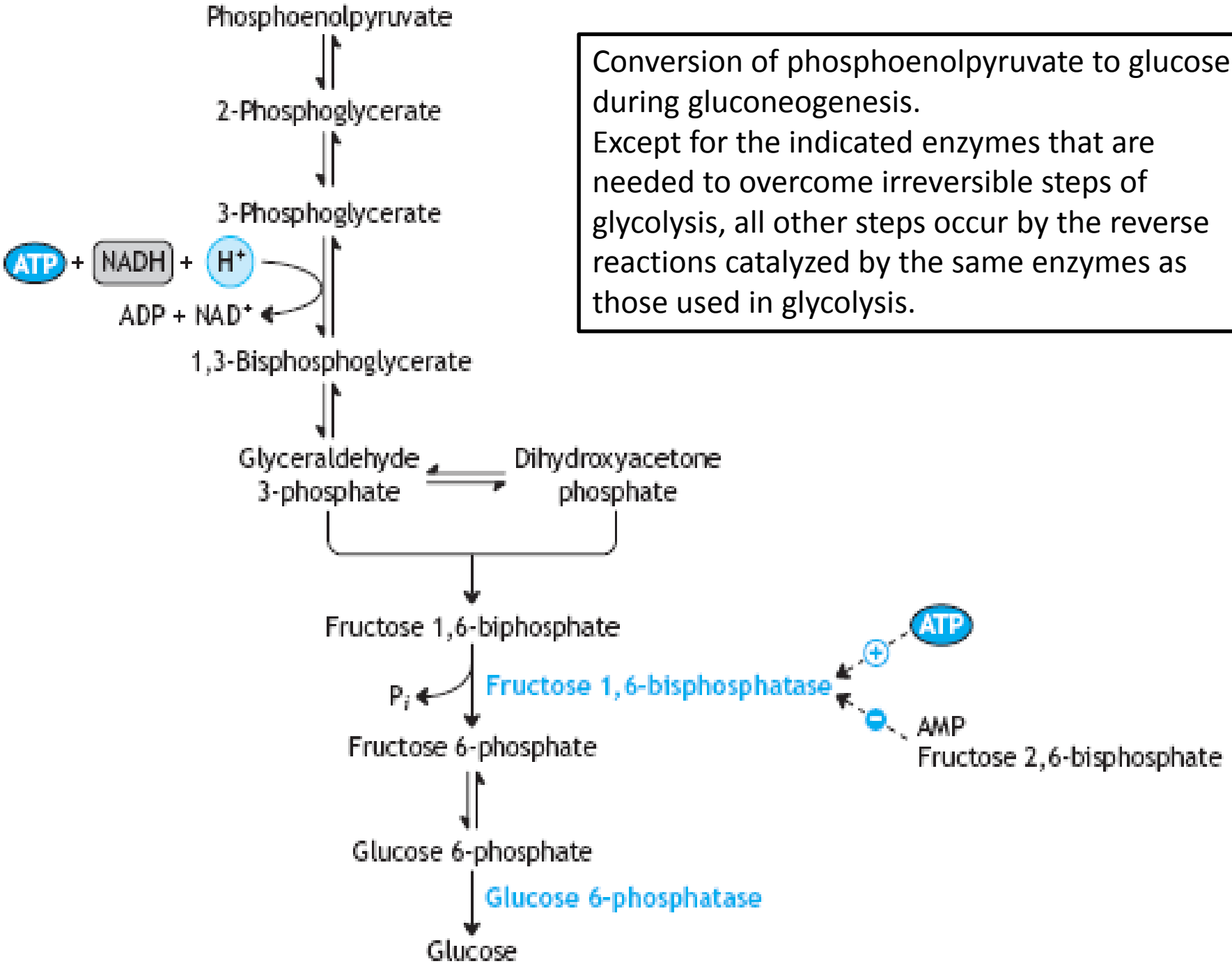
Oxaloacetate

cannot pass across the inner mitochondrial

membrane, so it is reduced to malate,

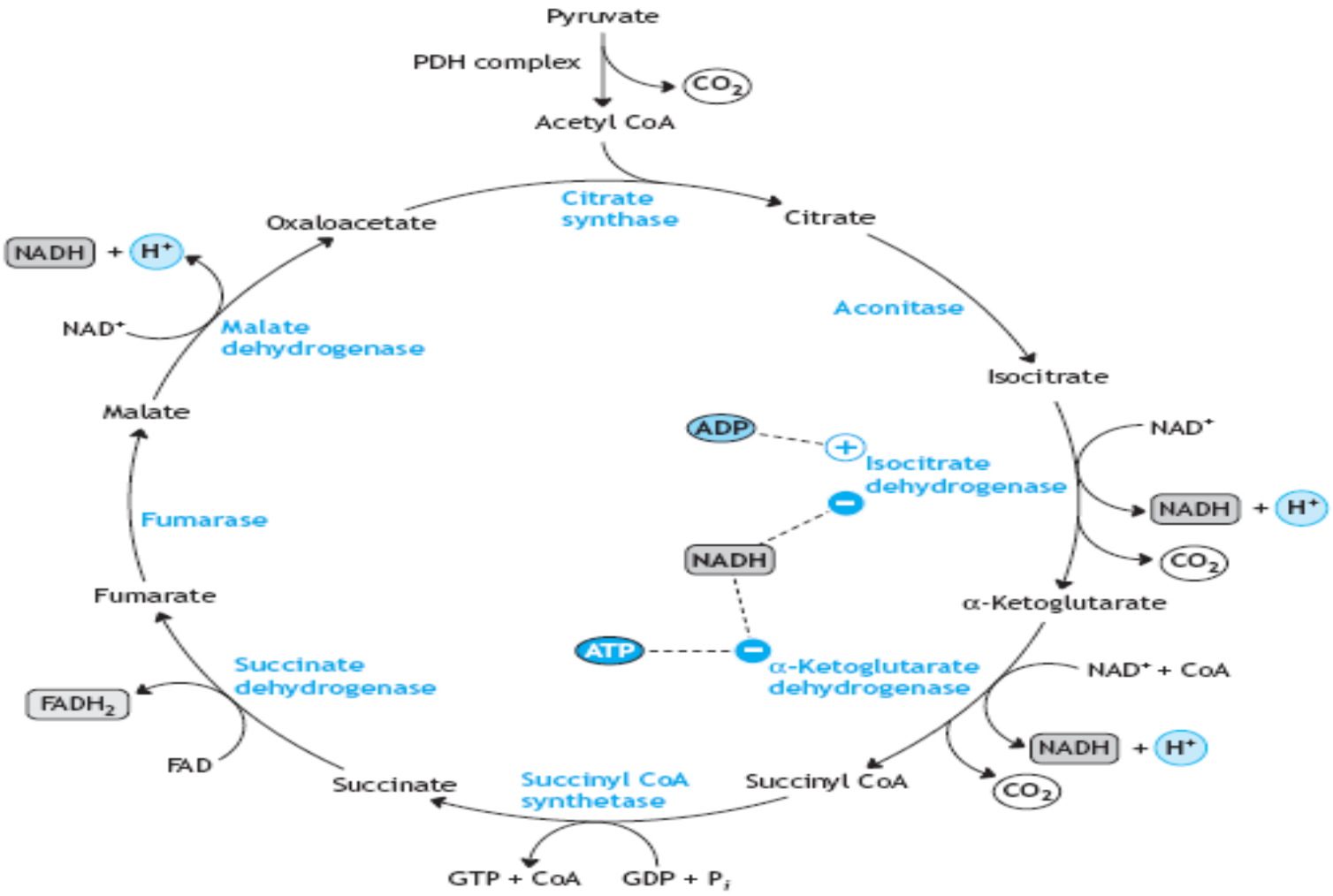
which can do so.

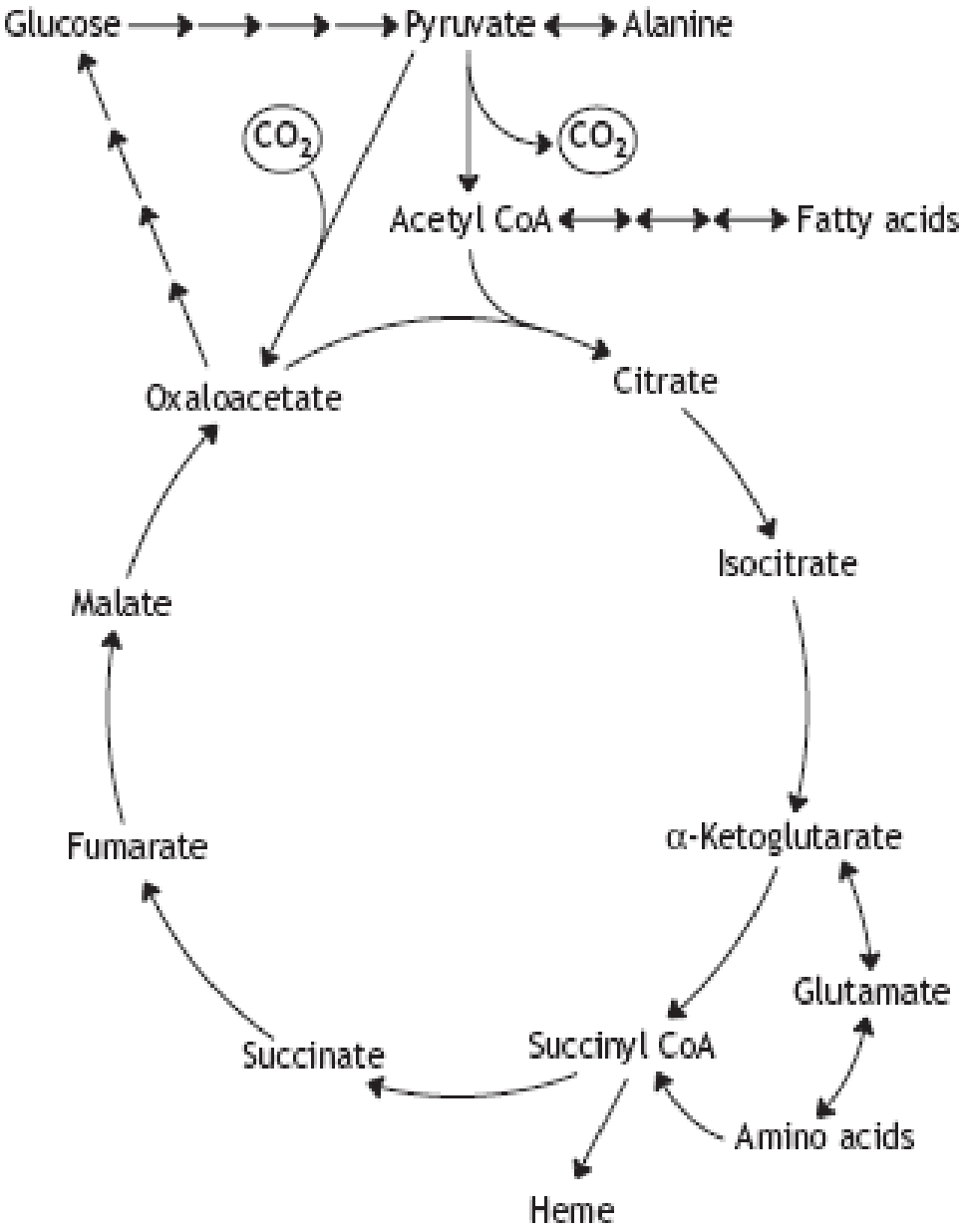





Conversion of phosphoenolpyruvate to glucose during gluconeogenesis.
Except for the indicated enzymes that are needed to overcome irreversible steps of glycolysis, all other steps occur by the reverse reactions catalyzed by the same enzymes as those used in glycolysis.

Reactions of the tricarboxylic acid cycle. Acetyl CoA is converted to CO2 (ovals) and electrons are released to NADH and FADH2 (boxes). Key regulatory points are indicated. PDH, pyruvate dehydrogenase.






Interactions between metabolic pathways and the tricarboxylic acid cycle (TCA).

**Catabolic pathways feed carbon skeletons into the TCA cycle at various points to complete their metabolism.**

Acetyl CoA and several TCA cycle intermediates serve as precursors for synthesis of complex compounds.

# THIAMINE DEFICIENCY

- *Thiamine pyrophosphate is an essential coenzyme for several critical metabolic enzymes—PDH, α-ketoglutarate dehydrogenase, and transketolase of the pentose phosphate pathway.*
- *Dietary deficiency of thiamine (**vitamin B1) results in an inability to synthesize thiamine pyrophosphate,** and the pathophysiology arises from impaired glucose utilization, especially manifested in the nervous system.*
- *Thiamine deficiency is often seen as a nutritional disease in populations whose sole food source is polished rice, resulting in **beriberi.***
  - *In adults, symptoms include constipation, loss of appetite, nausea, peripheral neuropathy, weakness, muscle atrophy, and fatigue.*
  - *In nursing infants, the disease produces more profound symptoms, including tachycardia, convulsions and, potentially, death.*

# THIAMINE DEFICIENCY

- *Thiamine deficiencies are determined in the clinical laboratory by measuring the activity of **transketolase** in the RBC.*
- *Thiamine deficiency may also develop in alcoholics due to poor nutrition and poor absorption of thiamine in the gastrointestinal tract.*
- *In chronic alcoholics, thiamine deficiency may manifest as **Wernicke-Korsakoff syndrome,** characterized by a unusual neurologic disturbances, including amnesia, apathy, and nystagmus.*

# ARSENIC TOXICITY

- *Arsenic can react irreversibly with the critical sulfhydryl groups of the coenzyme lipoic acid, which inactivates the coenzyme and thus inhibits the PDH complex and the α-ketoglutarate dehydrogenase complex.*
- *Symptoms of poisoning by arsenite (trivalent arsenic) include dermatitis and a variety of neurologic manifestations, including painful* ***paresthesias (tingling and numbness in the extremities).***
- *Acute occupational exposures or direct ingestion cause* ***severe gastrointestinal distress with diarrhea*** *and vomiting, which may lead to dehydration, hypovolemic shock, and death.*