



# Brain Energy Metabolism II



Dr. Nesrin Mwafi

Biochemistry & Molecular Biology Department

Faculty of Medicine, Mutah University

# Glucose Metabolism Produce Energy



- Glucose metabolism in the brain is similar to that in other tissues. In an aerobic conditions, it includes three principle metabolic pathways:
  1. Glycolysis
  2. Tricarboxylic acid cycle (TCA) or Krebs cycle
  3. Oxidative phosphorylation and the electron transport chain (ETC)

# 1. Glycolysis



- Glycolysis is the metabolic pathway which converts glucose (C6) into pyruvate (C3)
- It occurs in the cell cytosol . Glycolysis is a sequence of ten oxygen-independent and enzyme-catalyzed steps with the intermediates provide entry points to the cycle
- When the glycolysis end products (pyruvate and NADH) are disposed in presence of O<sub>2</sub>, the process is then called aerobic. Alternatively, in an anaerobic conditions, the products are removed via the lactic acid fermentation process

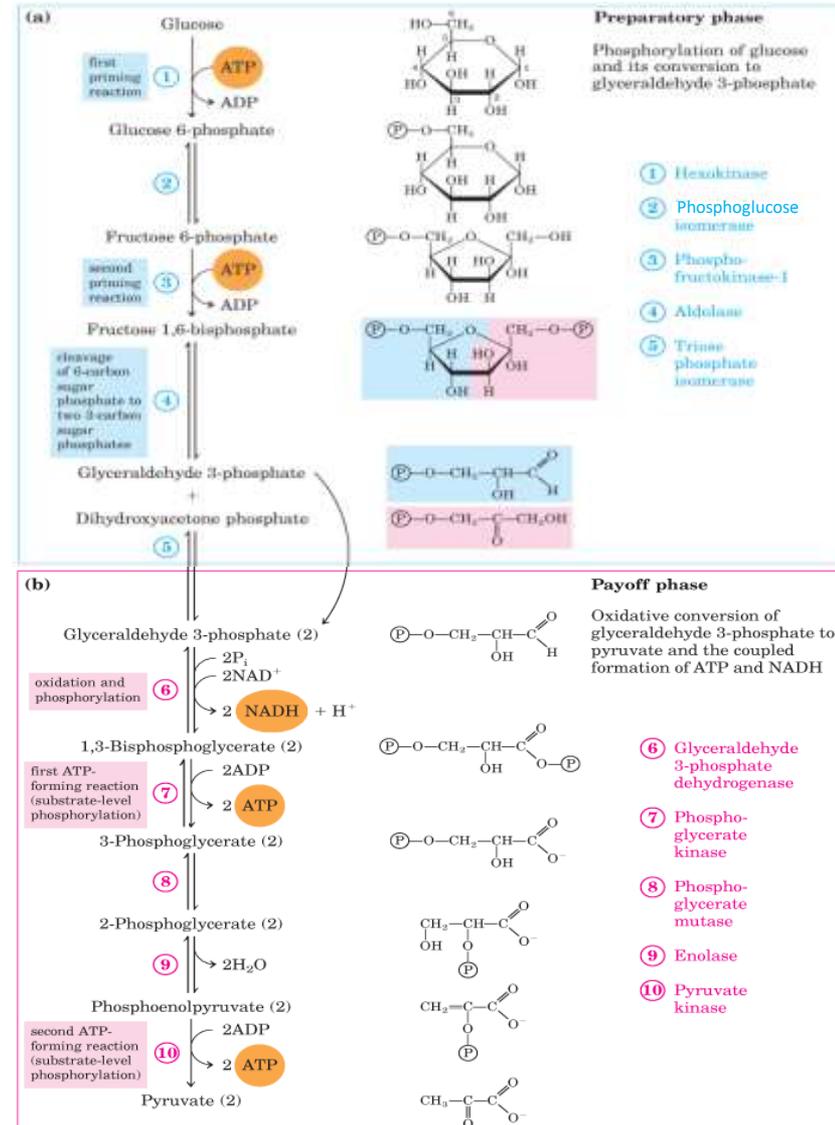
# 1. Glycolysis



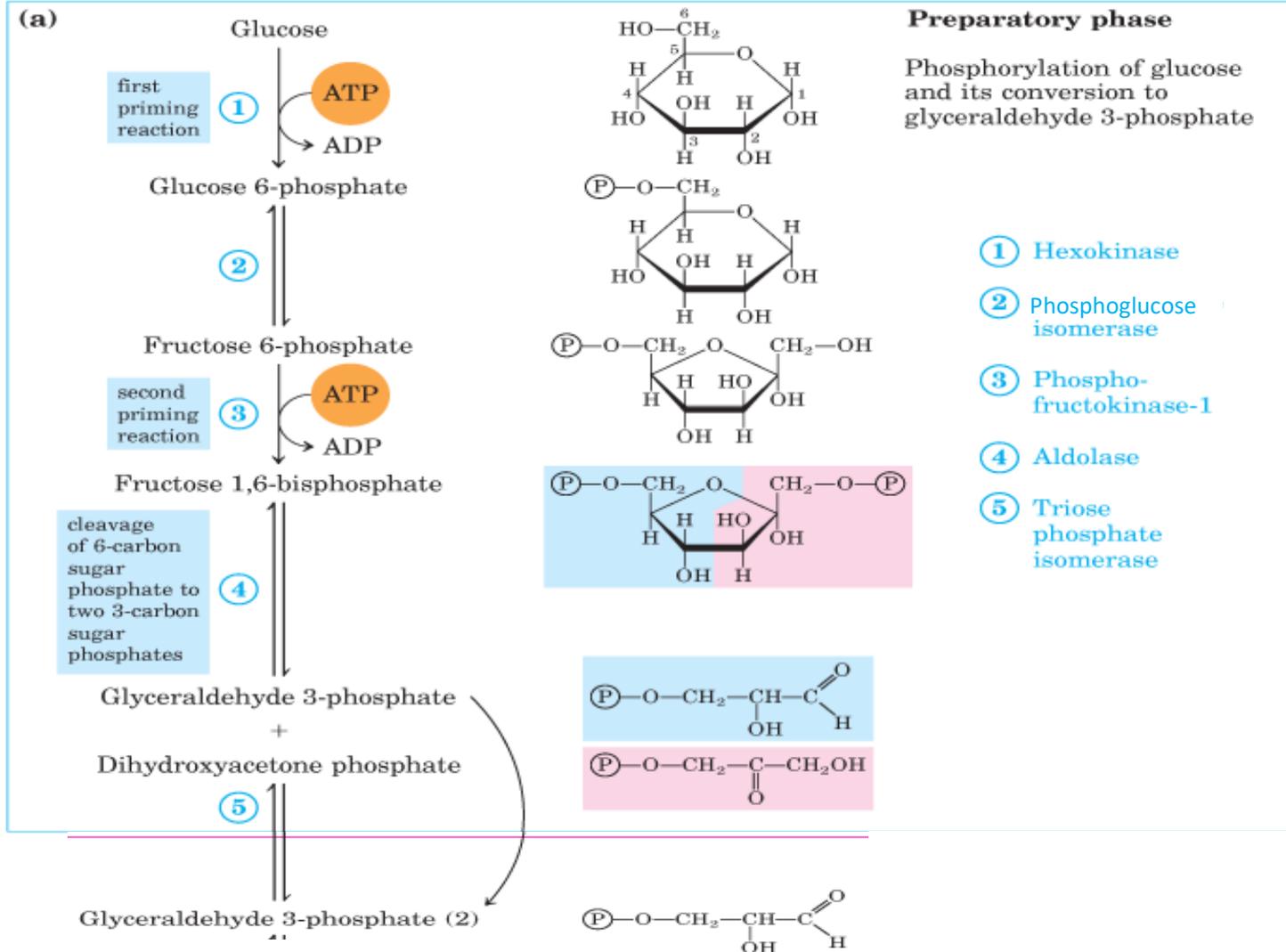
- The entire pathway is divided into two distinct phases:

## a) Energy Investment Phase (Preparatory Phase)

## b) Energy Generation Phase (Pay Off Phase)



# a) Preparatory Phase

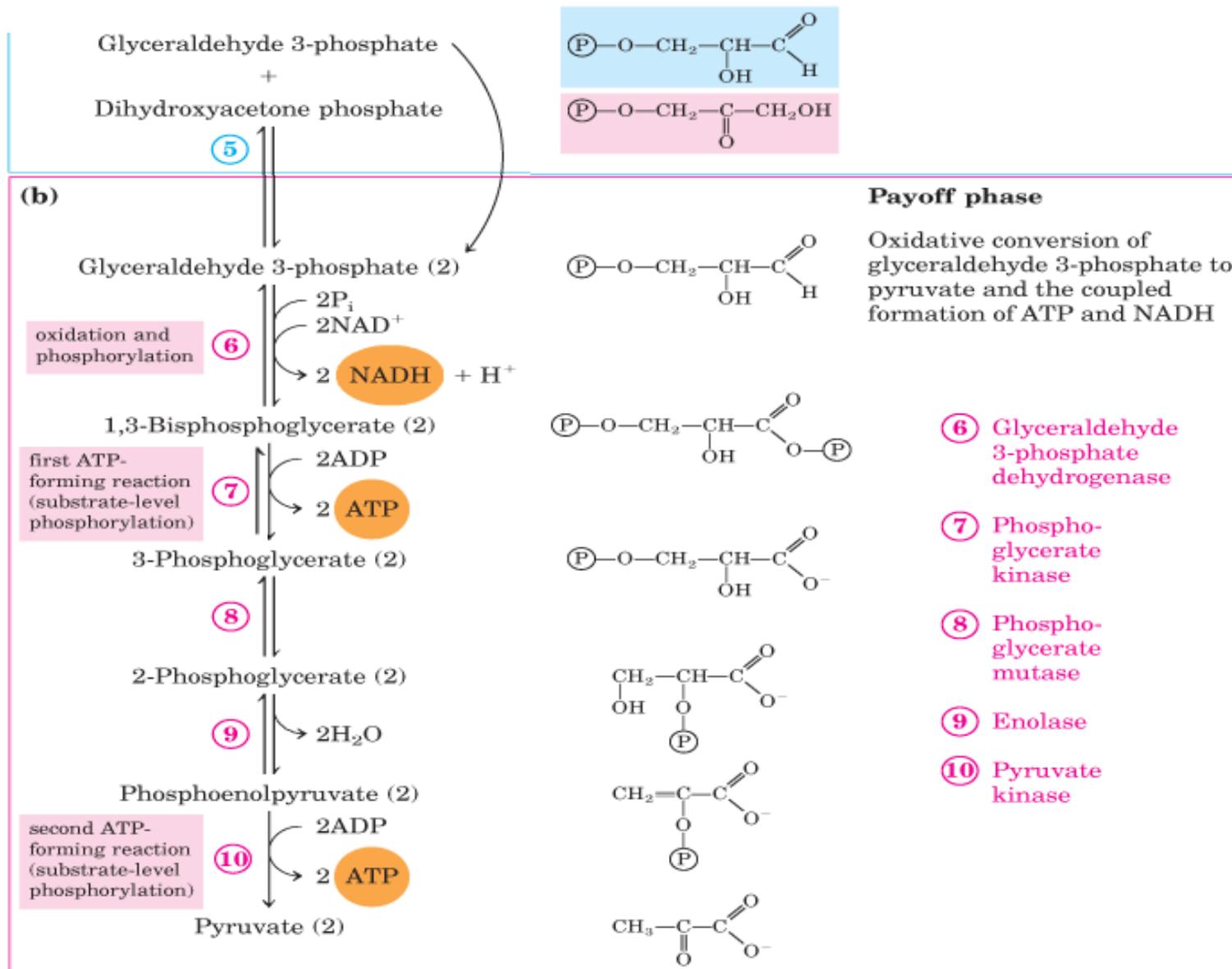


## a) Preparatory Phase



- **Step 1:** This first priming reaction is important to maintain the influx of glucose and at the same time to trap the transported glucose molecules inside the cell
- **Step 2:** Phosphoglucose isomerase (PGI) interconverts G6P and F6P. Indeed, Mannose and Fructose can enter the glycolytic pathway at this point
- **Step 3:** This is a **rate limiting** or key regulatory step because phosphofructokinase-1 (**PFK-1**) is an allosteric enzyme and its activity can be controlled
- **Step 4:** The cleavage to 2 triose phosphates: **DHAP** (dihydroxyacetone phosphate) and **GADP** (glyceraldehyde-3-phosphate)
- **Step 5:** Isomerization of DHAP by triose phosphate isomerase (TPI) to proceed further in glycolysis

# b) Pay Off Phase

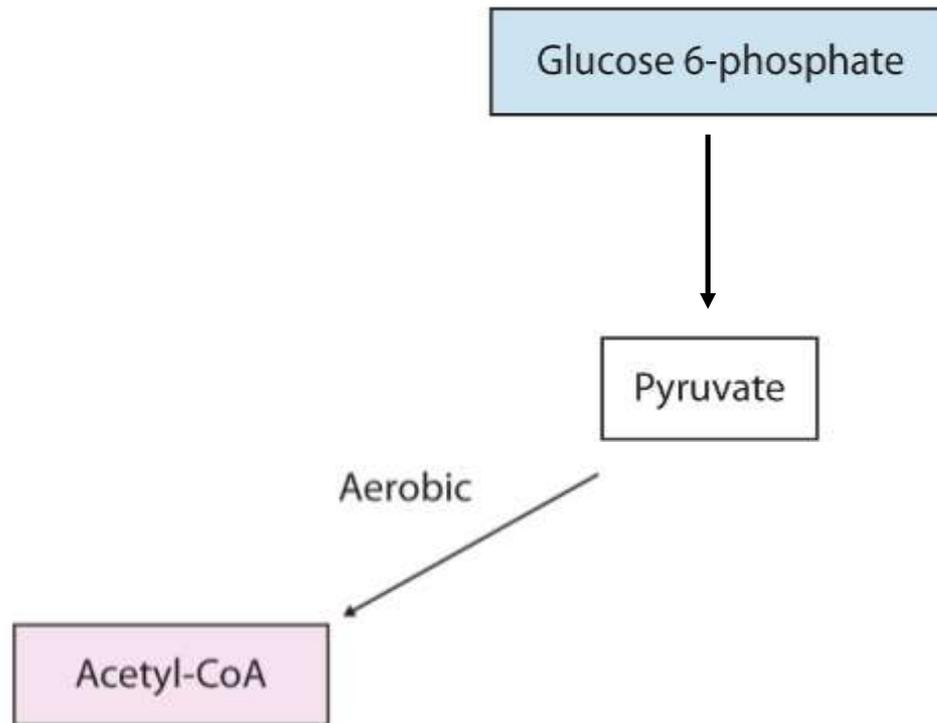


## b) Pay Off Phase

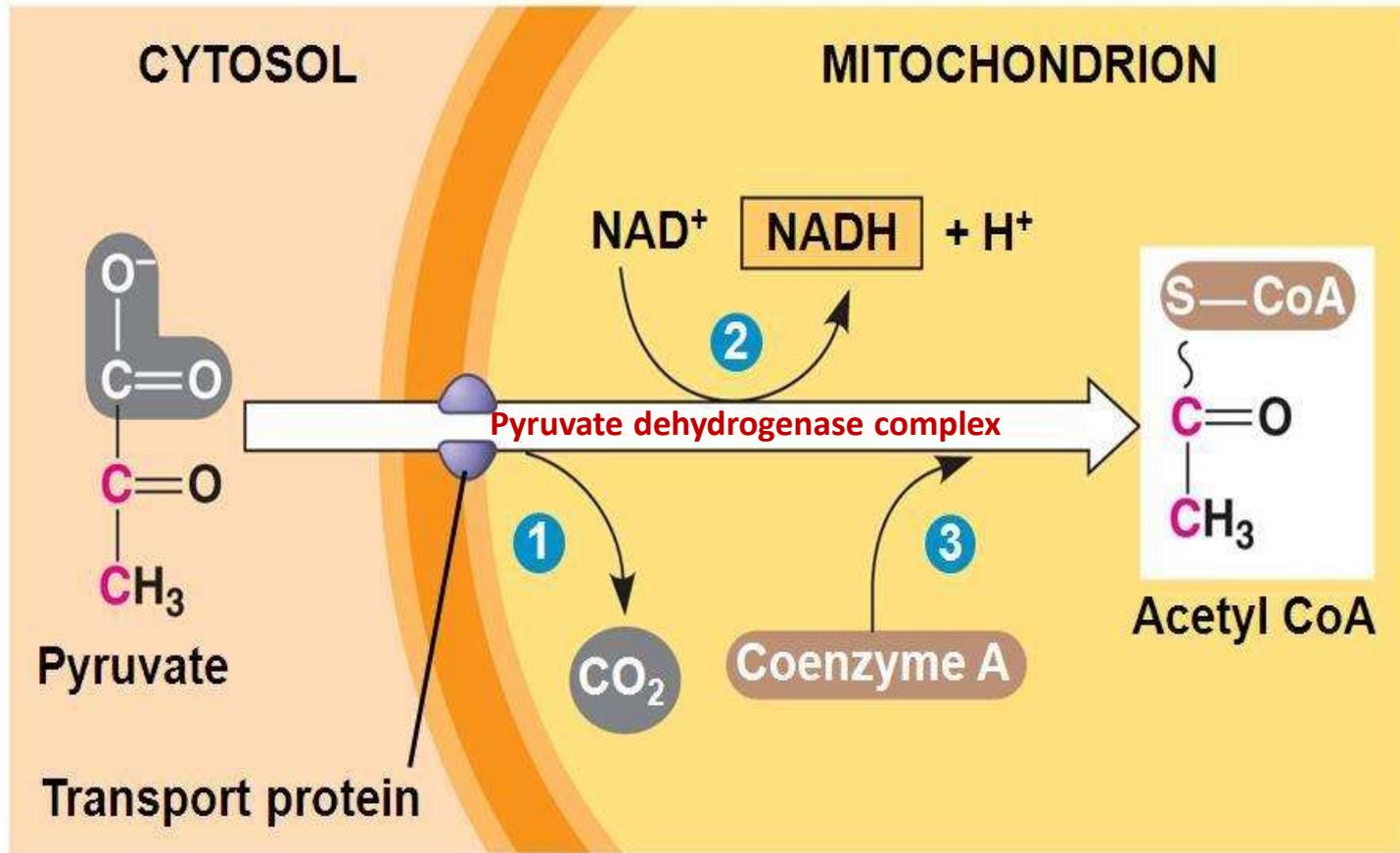


- **Step 6:** Dehydrogenase enzyme catalyzes the oxidative phosphorylation of GADP (electron donor) into super-high-energy compound (**1,3-BPG**) and the transfer of electrons into the coenzyme  $\text{NAD}^+$  (electron acceptor) forming **NADH**
- **Step 7:** The **first ATP** molecule is generated by the substrate-level phosphorylation process catalyzed by phosphoglycerate kinase (PGK)
- **Step 8:** Phosphoglycerate mutase (PGM) catalyzes the internal shifting of P group from C3 to C2
- **Step 9:** The synthesis of the second super-high-energy compound **phosphoenolpyruvate (PEP)** in a simple dehydration reaction catalyzed via enolase enzyme
- **Step 10:** The **second ATP** molecule is generated by the substrate-level phosphorylation process catalyzed by pyruvate kinase (PK). Pyruvate is the final product of glycolysis

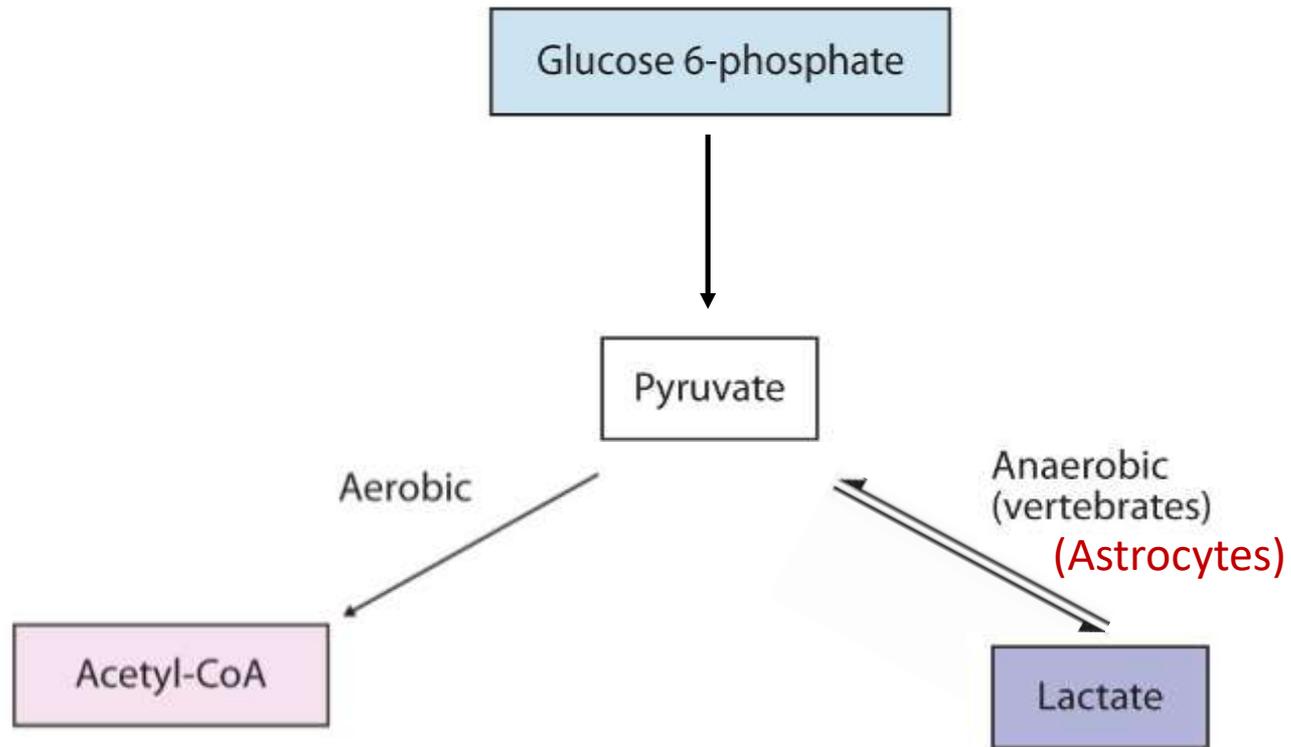
# Metabolic Fates of Pyruvate in Brain



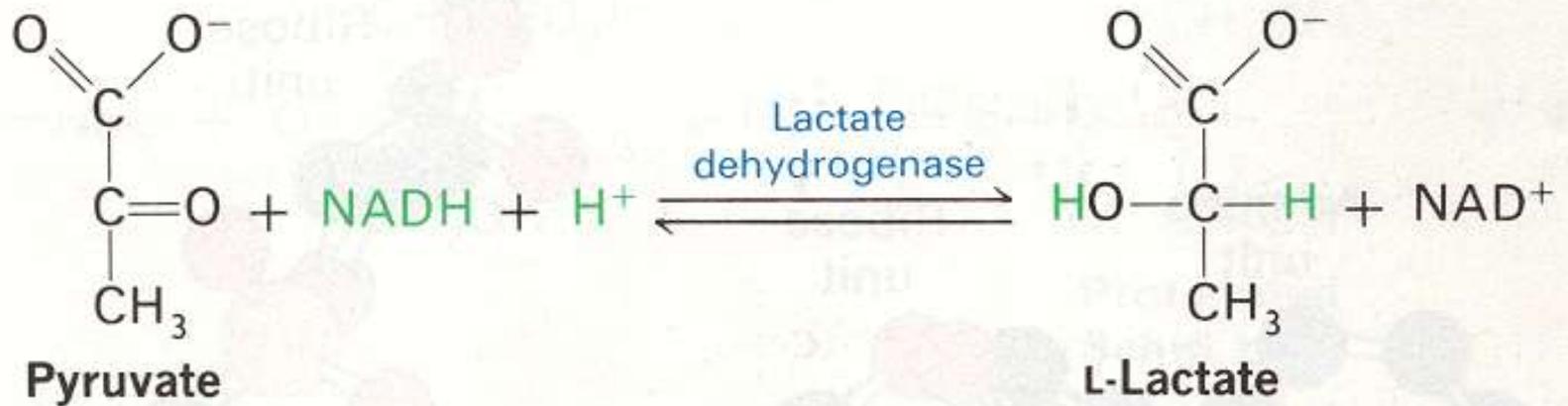
# Metabolic Fates of Pyruvate in Brain



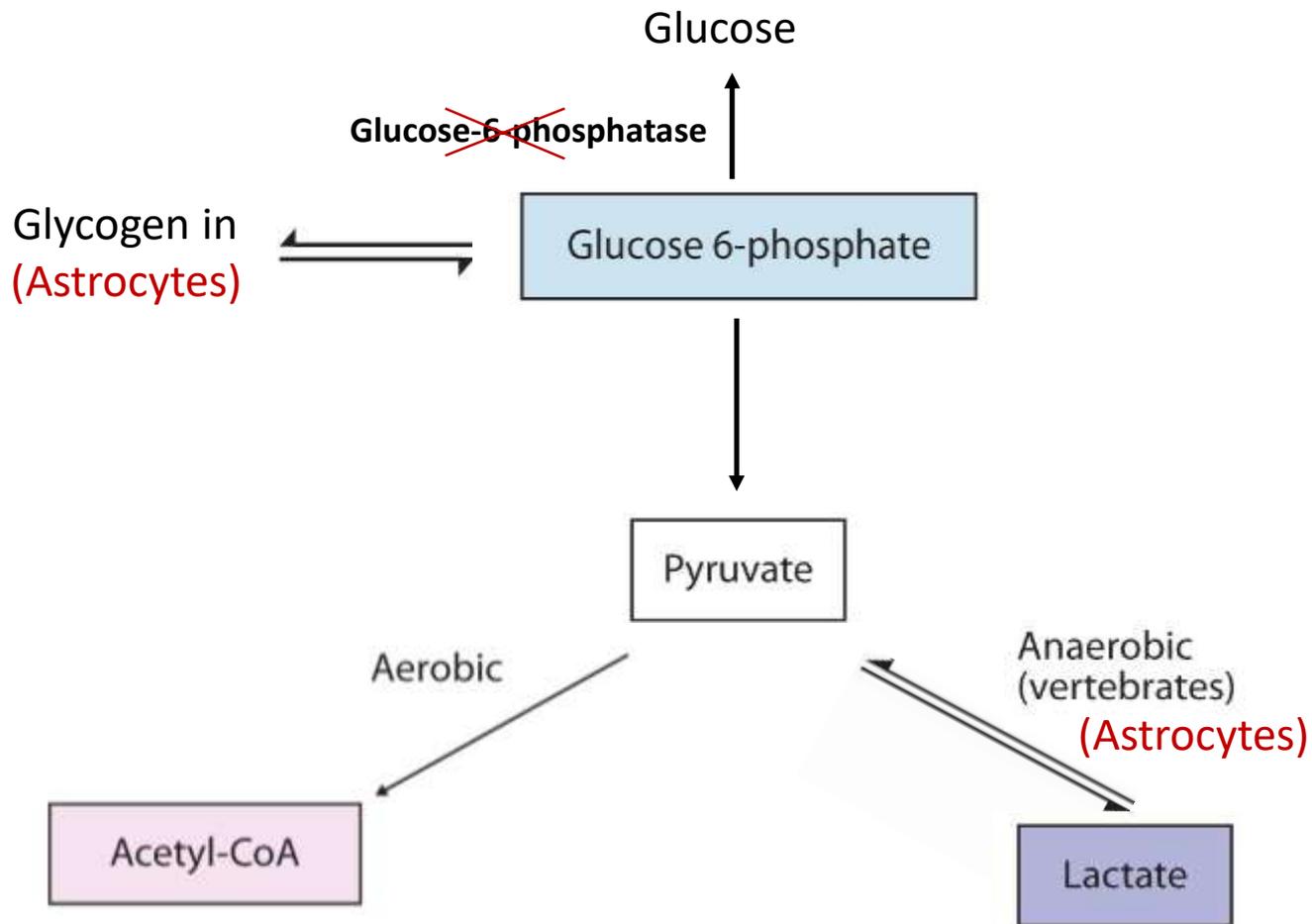
# Metabolic Fates of Pyruvate in Brain



# Metabolic Fates of Pyruvate in Brain



# Metabolic Fates of Pyruvate in Brain

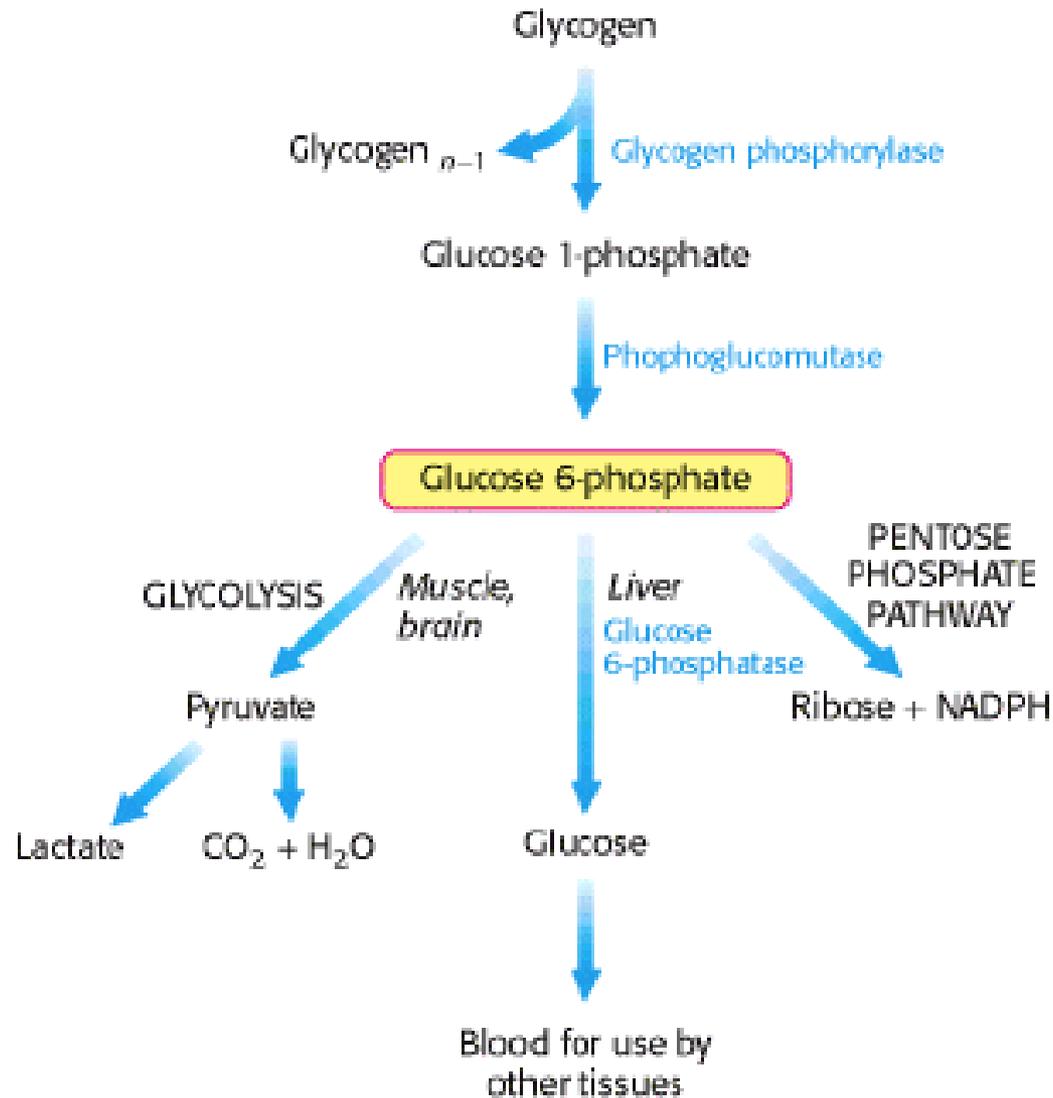


# Glycogen in Brain



- Very limited amount of glycogen (3-12  $\mu\text{mol}$  /g tissue) is stored in brain predominantly in astrocytes
- Actually its role as energy source during hypoglycemia is restricted to few minutes
- Glycogenolysis or glycogen mobilization is the process of glycogen breakdown to glucose units. It occurs in the cytosol of glycogen-containing cells such as brain
- Glycogenolysis produces monomers of glucose 1-phosphate which is then converted to G6p by phosphoglucomutase enzyme

# Glycogenolysis



# Fates of Glucose 6-phosphate



- The produced G6p has many possible routes. In brain, G6p molecules join the glycolysis and used as **fuel**.
- Indeed, due to the lack of glucose 6-phosphatase enzyme in brain and muscle tissues, G6p can't be converted back to glucose to be released in the blood as the case in liver cells

# Acetyl CoA Fate



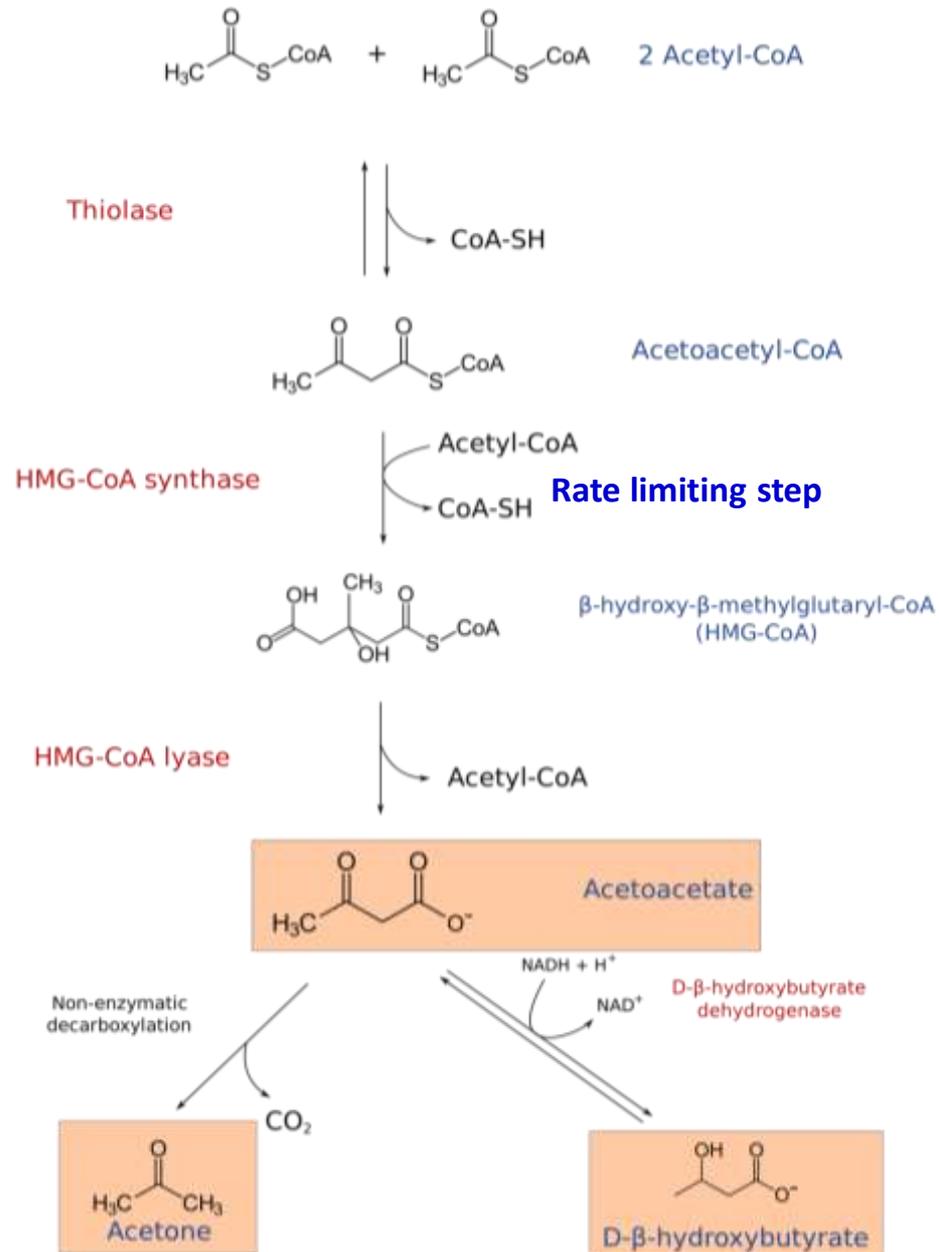
- Sources of Acetyl CoA: fat metabolism (fatty acids  $\beta$ -oxidation, reversible) and CHO metabolism (pyruvate, irreversible)
- Fates of Acetyl CoA:
  1. It can enter the Krebs cycle for energy production
  2. Used for biosynthesis of fatty acids **but not CHO**
  3. Formation of ketone bodies (**Ketogenesis**)

# Ketogenesis



- Ketogenesis is the process of ketone bodies production from acetyl CoA mainly in **the mitochondrial matrix of hepatocytes**
- Ketogenesis occurs when acetyl CoA accumulates beyond its capacity to be oxidized (via Krebs cycle) or used for fatty acids synthesis (lipogenesis)
- When acetyl CoA level is high, 2 molecules of acetyl CoA undergo a reversal of thiolase reaction to acetoacetyl CoA which reacts with a third molecule of acetyl CoA to produce  $\beta$ -hydroxy- $\beta$ -methylglutaryl-CoA (HMG-CoA)
- HMG-CoA is converted to acetoacetate which undergoes either NADH-dependent reduction to  $\beta$ -hydroxybutyrate (reversible reaction) or spontaneous decarboxylation to acetone (in very small amounts)

# Ketogenesis



# Ketogenesis



- HMG-CoA synthase is primarily expressed in hepatocytes and catalyzes the rate-limiting step in ketogenesis
- Ketone bodies are produced in the liver from **accumulated Acetyl CoA** during ketogenic conditions (uncontrolled diabetes and starvation) due to **enhanced fat catabolism** ( $\beta$ -oxidation of fatty acids)

# Ketone Bodies

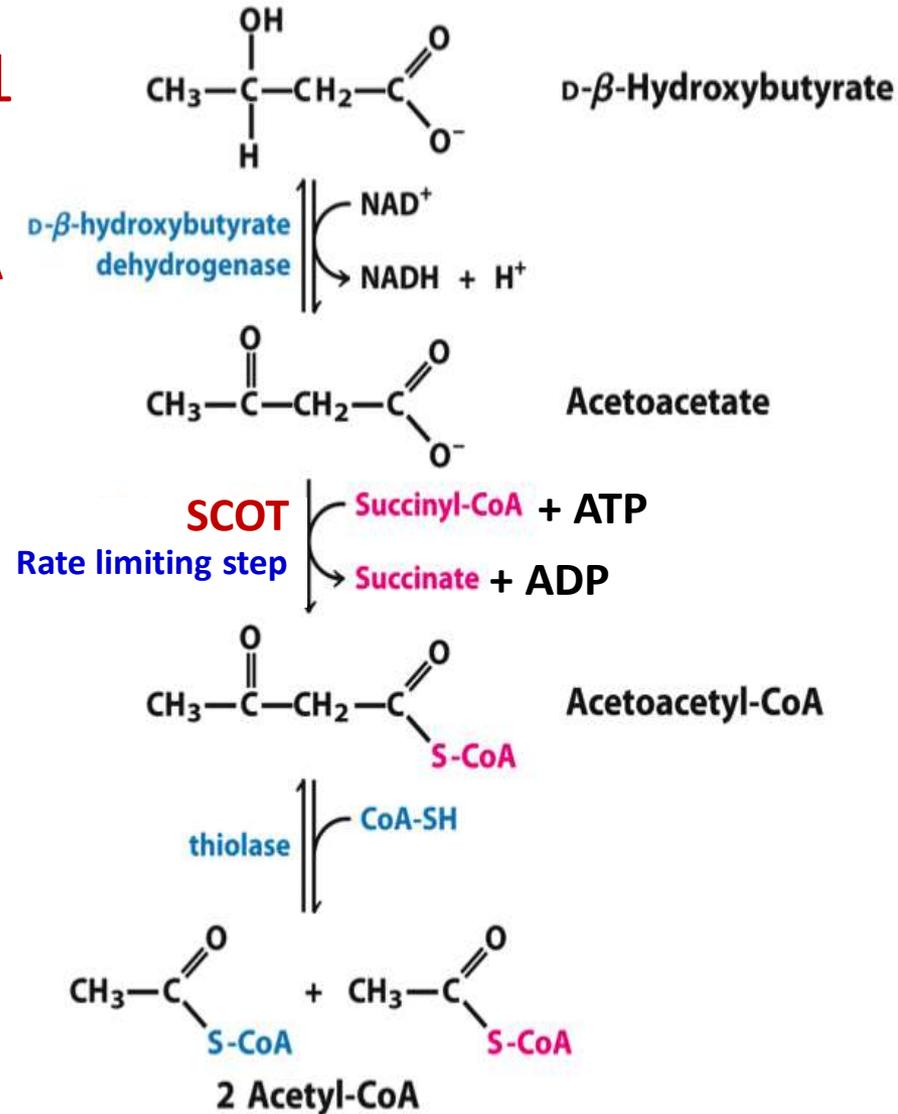


- Ketone bodies (KB) are three water soluble molecules: acetoacetate,  $\beta$ -hydroxybutyrate ( $\beta$ -HB) and acetone
- Ketone bodies are important metabolic fuels for many peripheral tissues under normal conditions, particularly skeletal muscles, and during starvation they become the brain's major fuel source
- Ketone bodies transported from liver to other tissues where both acetoacetate and  $\beta$ -hydroxybutyrate can be reconverted to acetyl CoA for energy production, a process called **ketolysis** which occurs in mitochondria of extrahepatic tissues
- The reconversion first involves the transfer of all  $\beta$ -HB into acetoacetate followed by the enzymatic transfer of CoA moiety from succinyl-CoA to acetoacetate yielding acetoacetyl CoA and succinate (**rate limiting step**). Finally, thiolase converts acetoacetyl CoA to two molecules of acetyl CoA which enters Krebs cycle for energy production

# Oxidation of Ketone Bodies (Ketolysis)



- 3-oxoacid CoA-transferase 1 (OXCT1) also known as succinyl-CoA-3-oxoacid CoA transferase (SCOT) is present sufficiently in extra-hepatic tissues including brain. In contrast, the liver does not contain this enzyme therefore can't oxidize ketone bodies or use them as a fuel

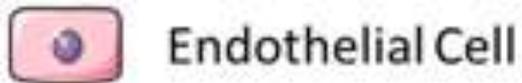
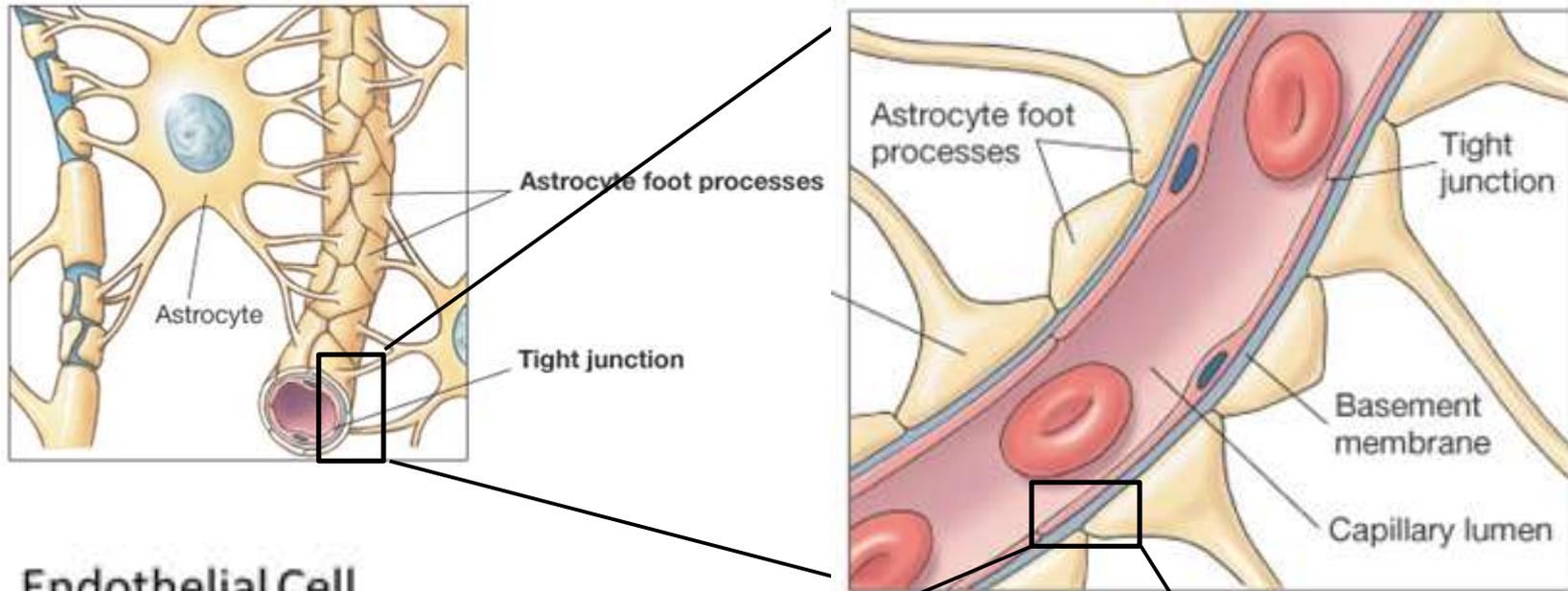


# Blood-Brain Barrier (BBB)



- BBB is a highly selective membrane which allows only very specific molecules to access the CNS so protecting the brain from circulating toxic substances and invading foreign bodies (e.g. bacterial infection)
- Therefore, BBB has a critical role in cerebral homeostasis
- The cellular and structural components of BBB:
  1. Non-fenestrated endothelial cells (ECs) which are connected via tight junctions thus prevent paracellular diffusion. Endothelial cells are supported by a continuous basement membrane (BM)
  2. Astrocytes send processes called end-feet which surround capillary walls to additionally support the ECs and maintain the BBB integrity (play role in BBB development)
  3. Pericytes are embedded in the BM. They have a role in BBB development (e.g. formation of tight junction)

# Blood-Brain Barrier BBB



Endothelial Cell



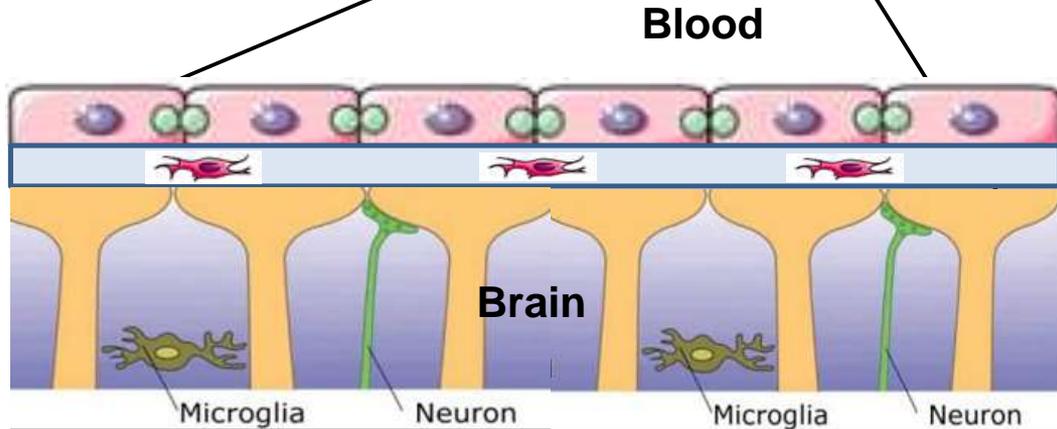
Tight Junction



Pericyte



Astrocyte end-foot

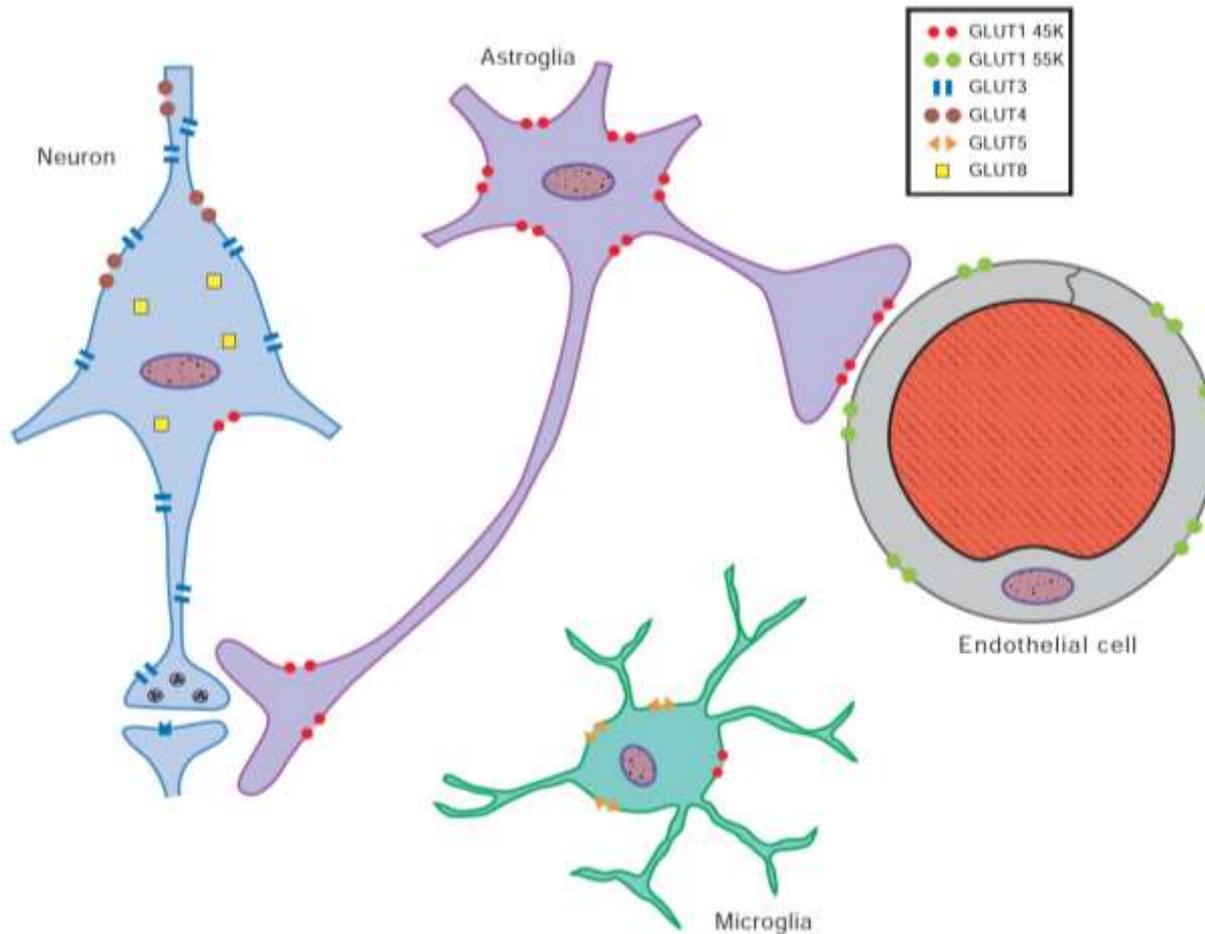


# Glucose Transporters



- Energy substrates cross BBB and reach brain cells via specific transport mechanisms. For example, glucose is hydrophilic molecule which enters the cells through glucose transporters (GLUT), a family of glycosylated transmembrane proteins
- In brain, seven transporters are expressed in a cell-specific manner:
  - ❖ 55-KDa isoform of GLUT1 essentially localized on endothelial cells of BBB
  - ❖ 45-KDa isoform of GLUT1 is localized predominantly in astrocytes (star-shaped non-neuronal cells)
  - ❖ GLUT3 is specific for neurons with GLUT8 and 4 predominate on cell body and proximal dendrites respectively
  - ❖ GLUT5 is localized in microglial cells (resident macrophages of the brain)

# Glucose Transporters



Cellular distribution of the principle glucose transporters in the nervous system.