# Brain Energy Metabolism II

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# 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

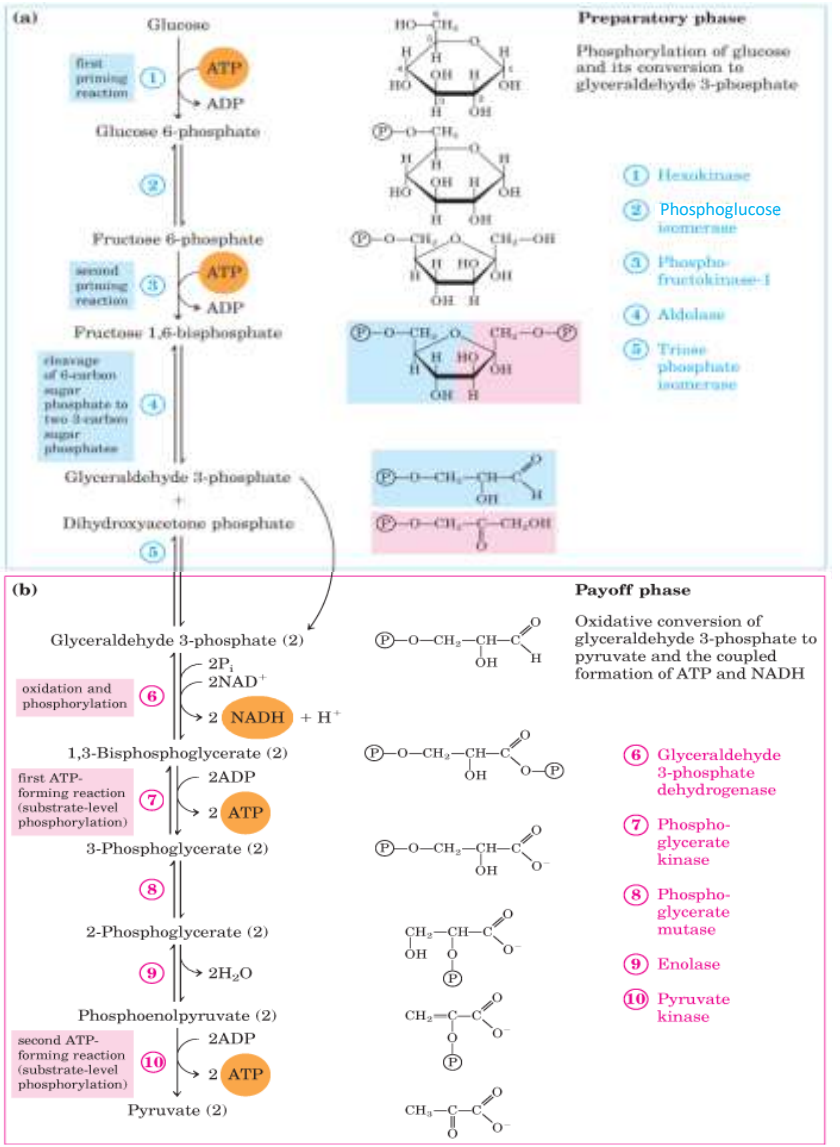
- Glycolysis is the metabolic pathway which converts glucose (C6) into pyruvate (C3)
- It occurs in the cell cytosol . Glycolysis is a sequence of ten oxygen-independent and enzyme-catalyzed steps with the intermediates provide entry points to the cycle
- When the glycolysis end products (pyruvate and NADH) are disposed in presence of O2, the process is then called aerobic. Alternatively, in an anaerobic conditions, the products are removed via the lactic acid fermentation process

# 1. Glycolysis

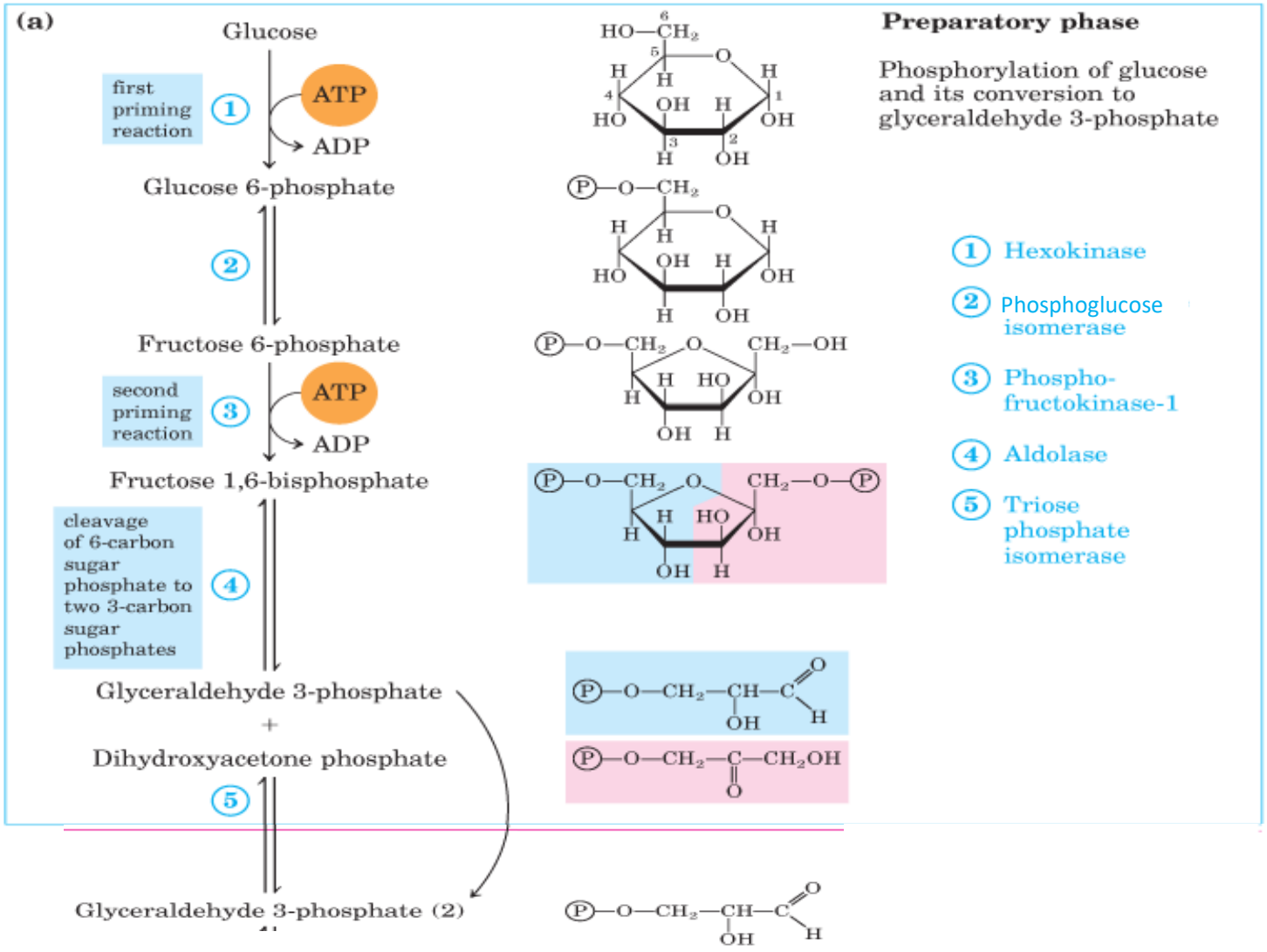
- The entire pathway is divided into two distinct phases:

a) **Energy Investment Phase (Preparatory Phase)**

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



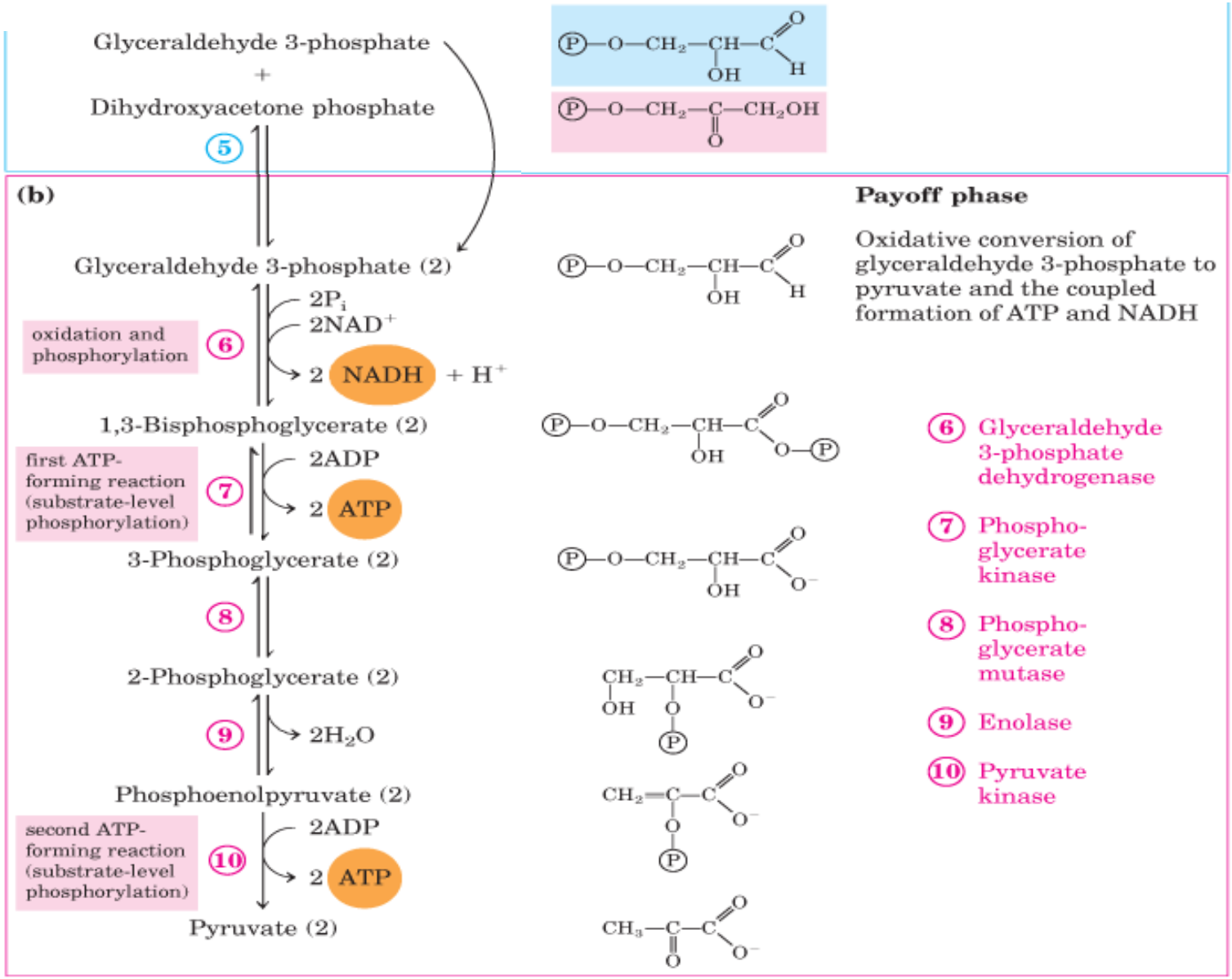
# a) Preparatory Phase



# 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

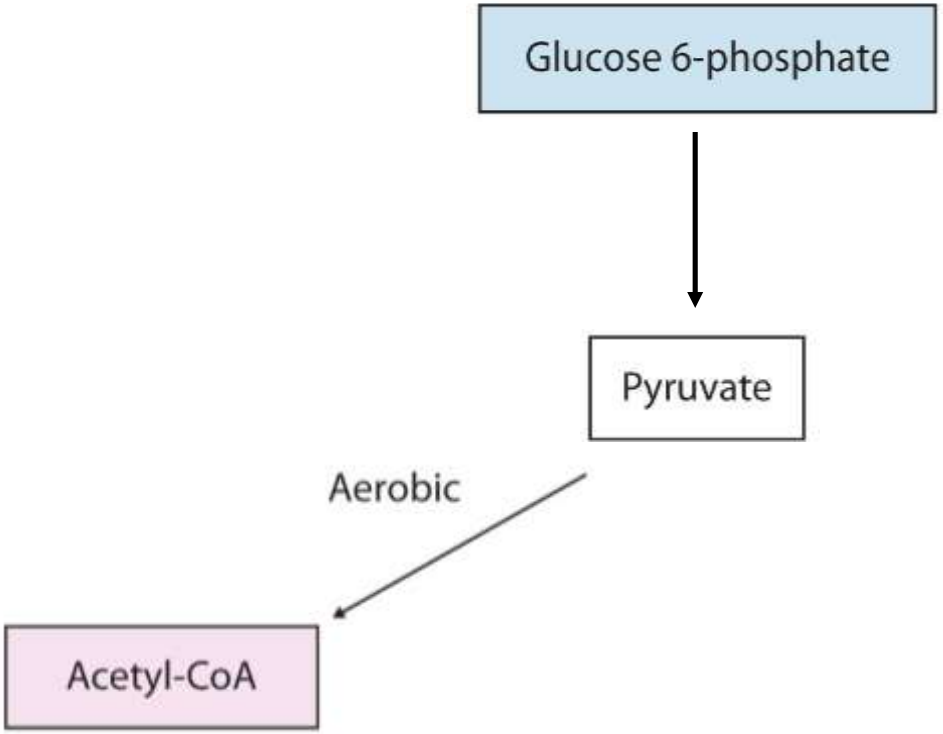
# b) Pay Off Phase



# 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 $NAD^+$(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



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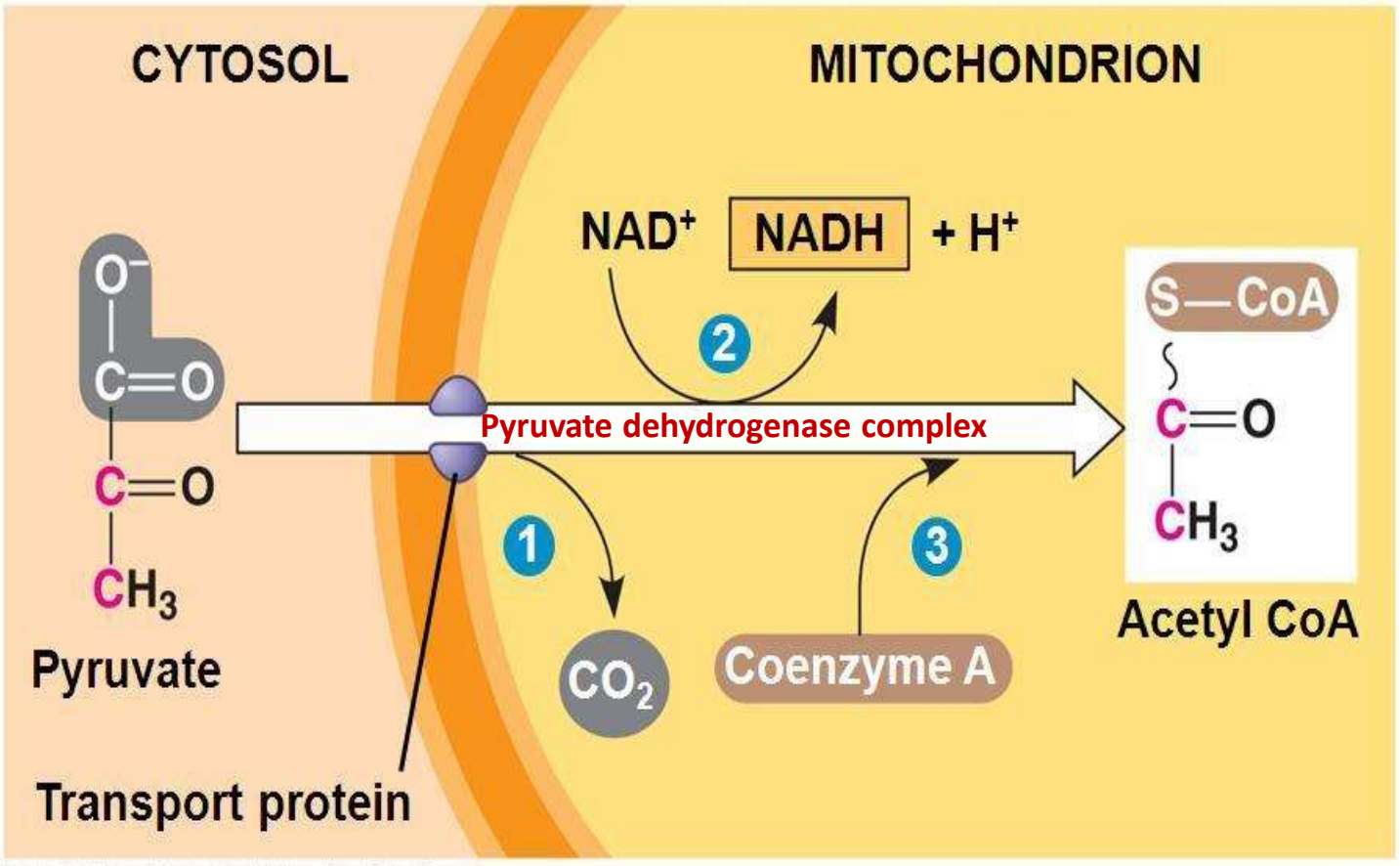

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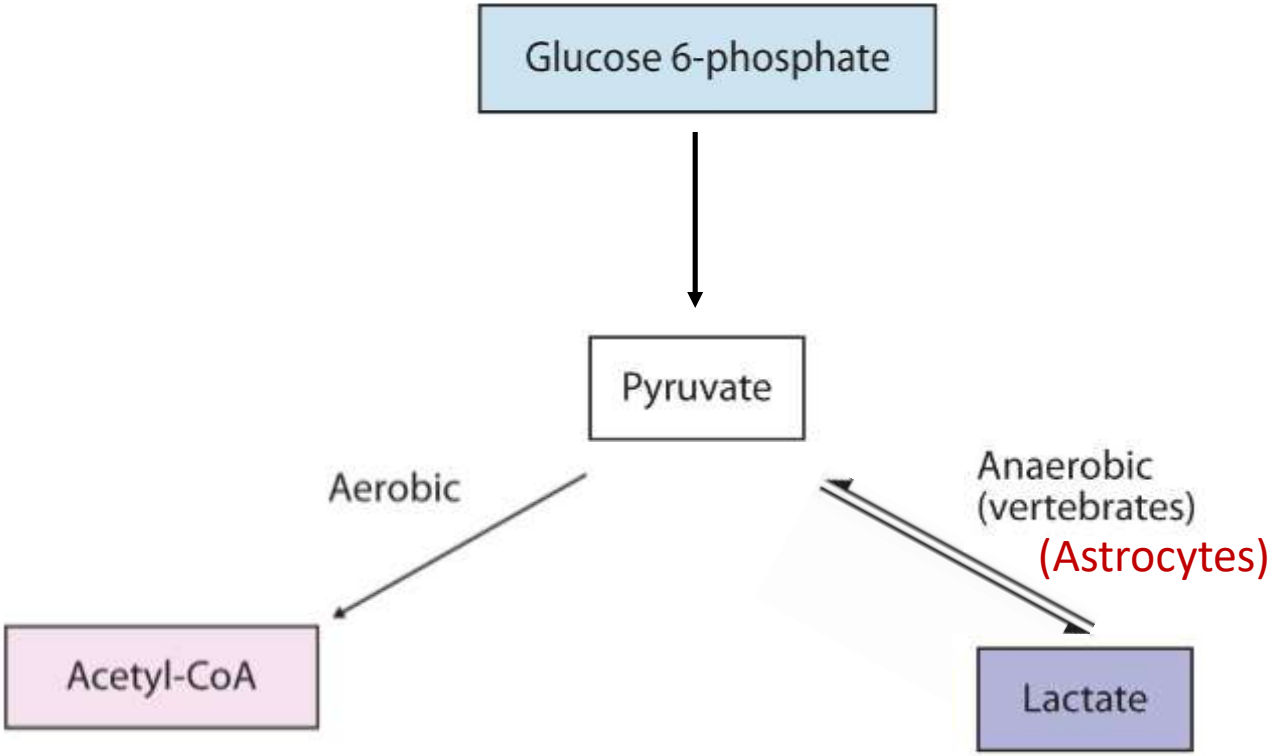

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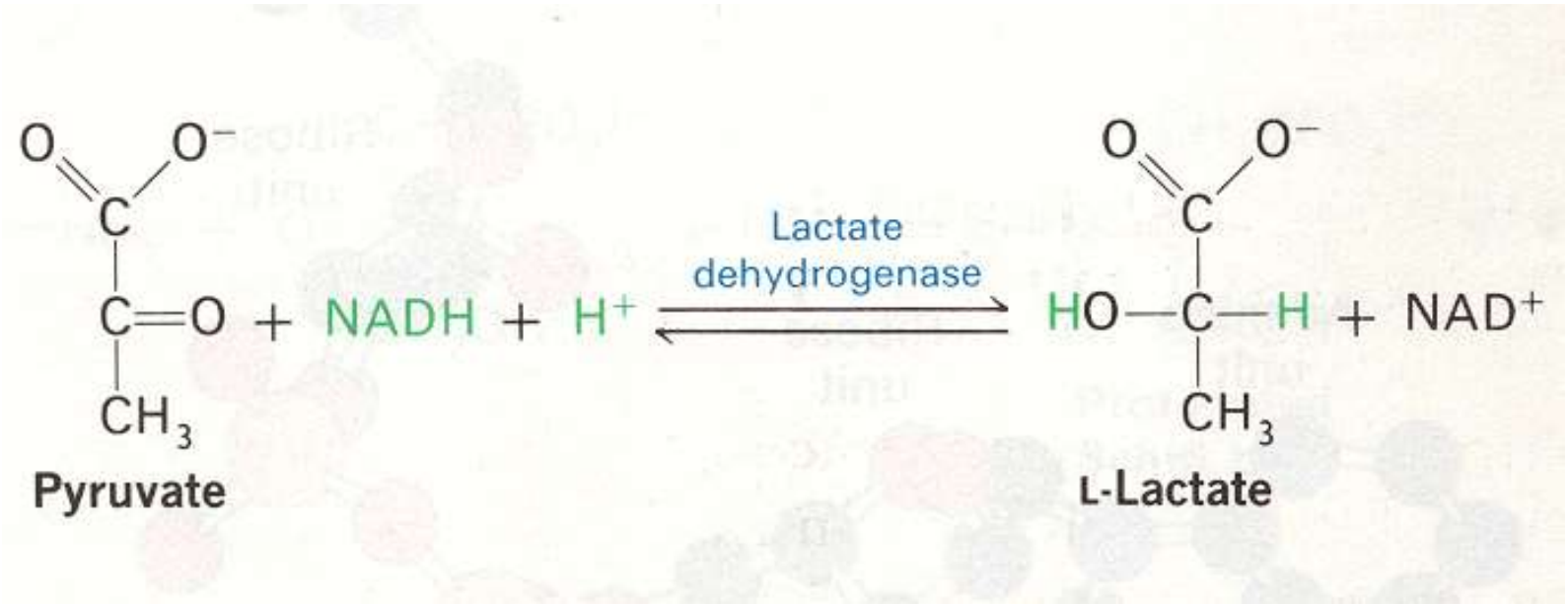

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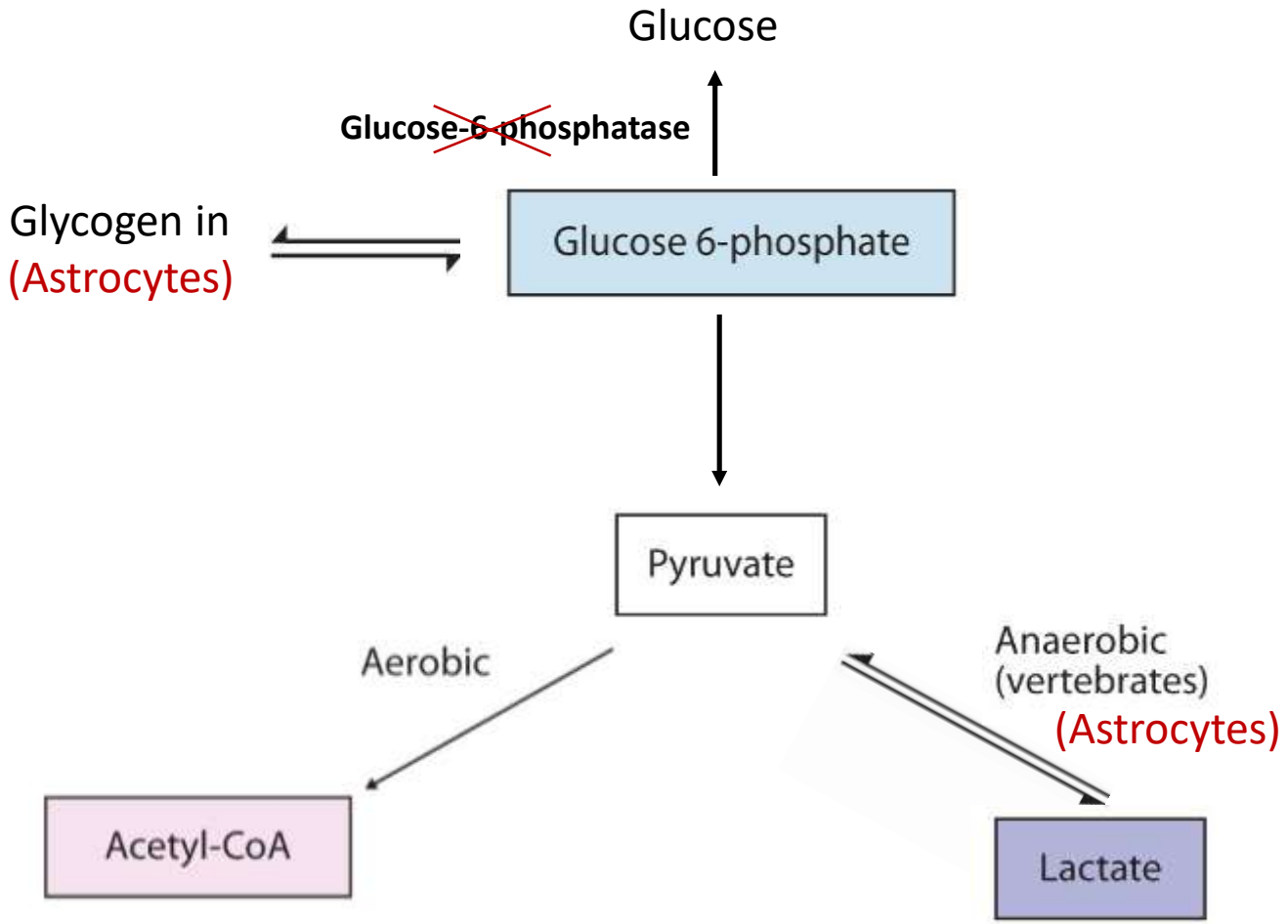
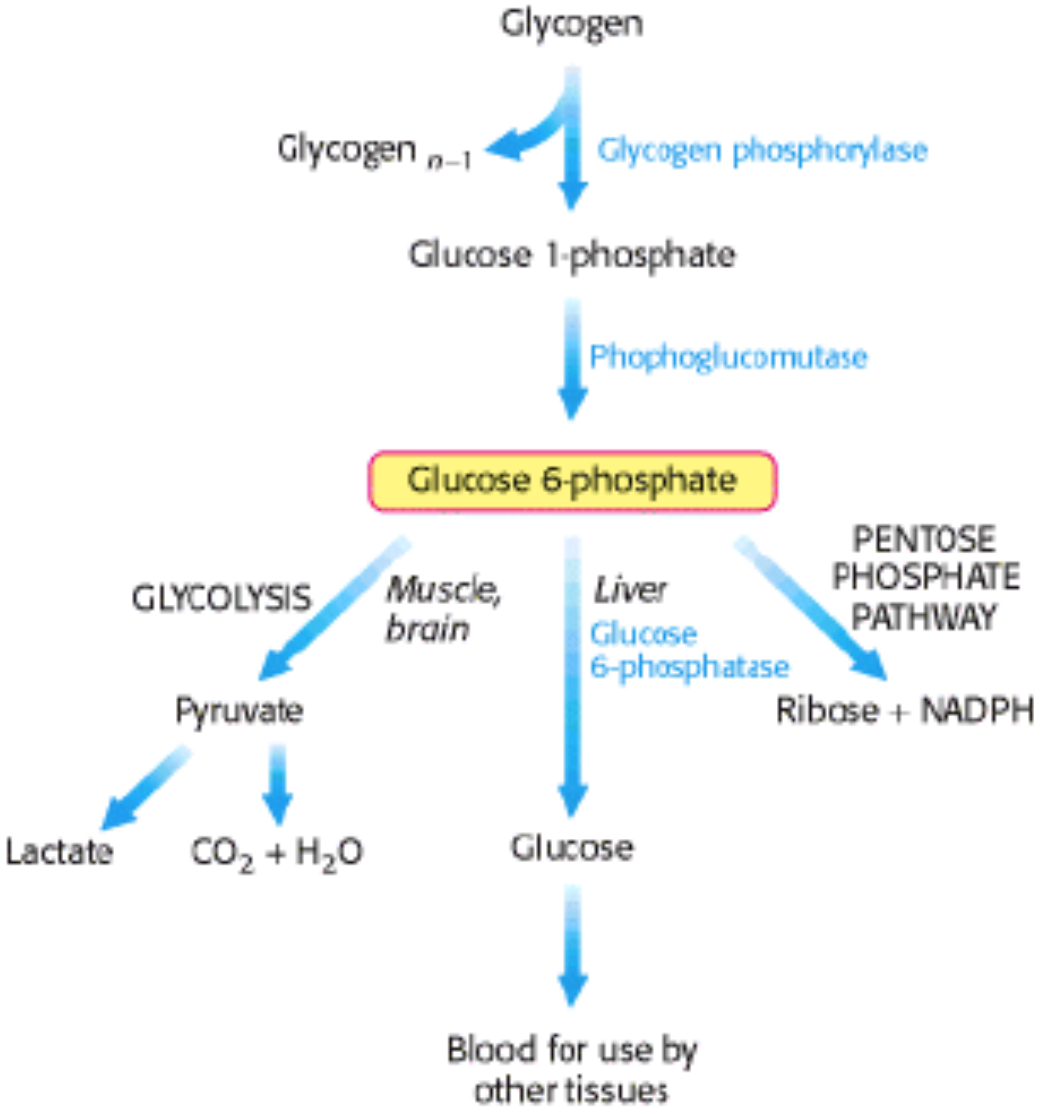


# Glycogen in Brain

- Very limited amount of glycogen (3-12 μmol /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-phospatase 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 β-oxidation, reversible) and CHO metabolism (pyruvate, irreversible)

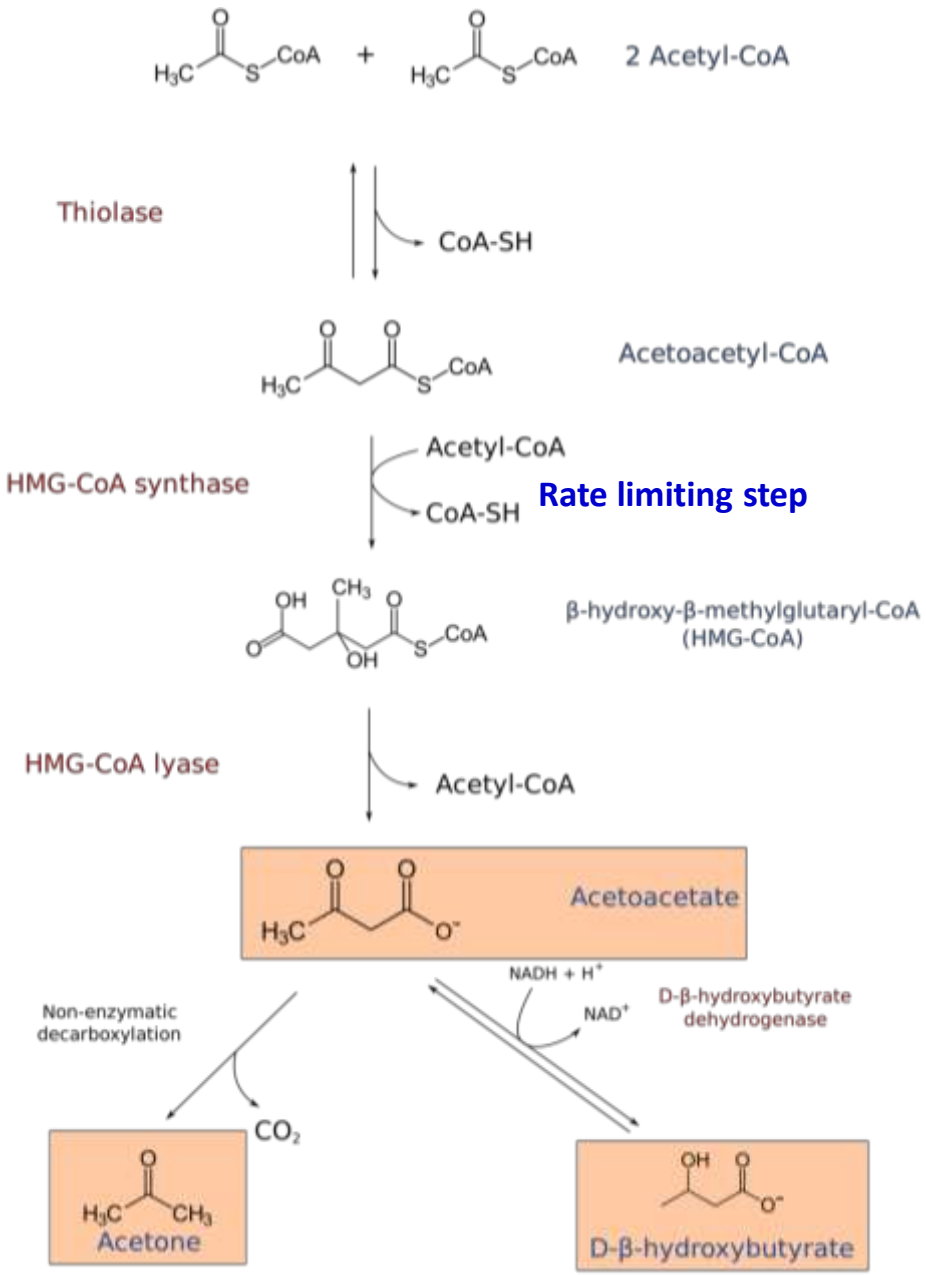
- Fates of Acetyl CoA:

  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 β-hydroxy-β-methylglutaryl-CoA (HMG-CoA)
- HMG-CoA is converted to acetoacetate which undergoes either NADH-dependent reduction to β-hydroxybutyrate (reversible reaction) or spontaneous decarboxylation to acetone (in very small amounts)

# Ketogenesis



# Ketogenesis

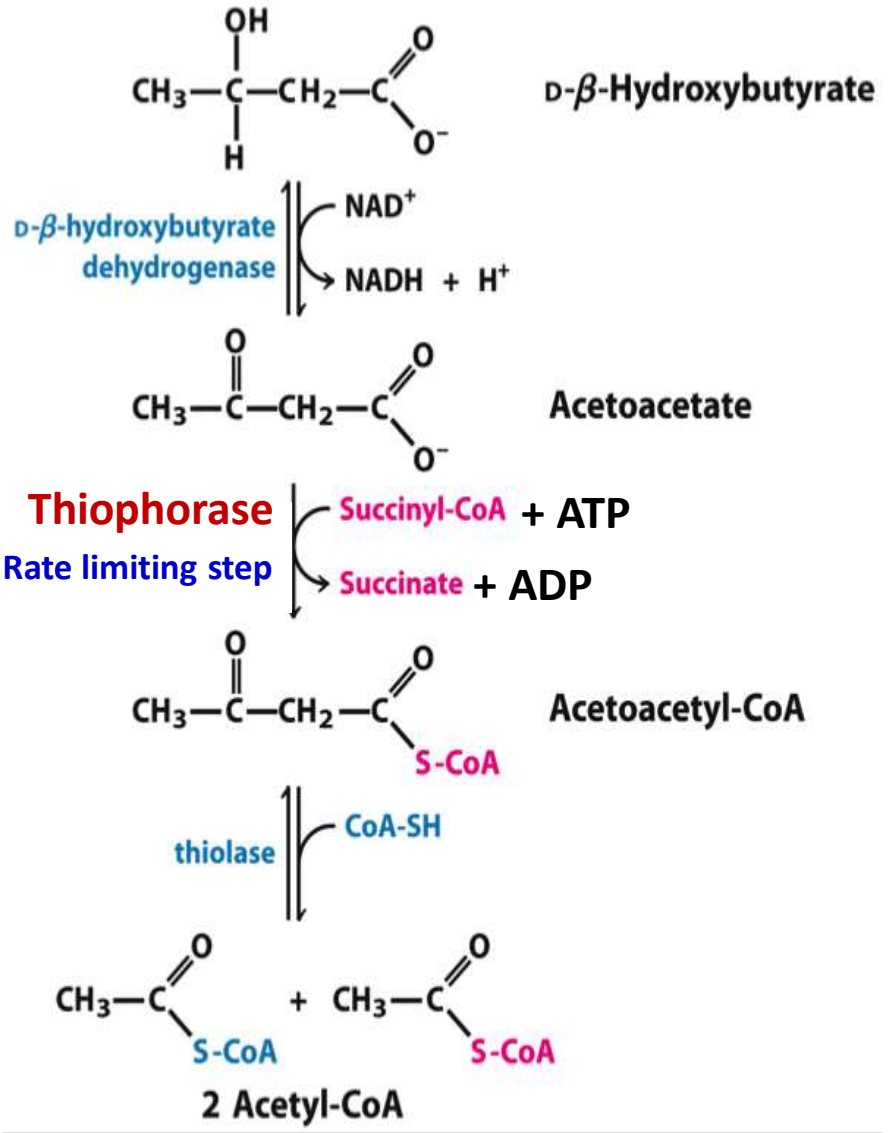
- HMG-CoA synthase is primarily expressed in hepatocytes and catalyzes the rate-limiting step in ketogenesis
- Ketone bodies are produced in the liver from accumulated Acetyl CoA during ketogenic conditions (uncontrolled diabetes and starvation) due to enhanced fat catabolism (β-oxidation of fatty acids)

# Ketone Bodies

- Ketone bodies (KB) are three water soluble molecules: acetoacetate, β-hydroxybutyrate (β-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 β-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 β-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)

- **Thiophorase** 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

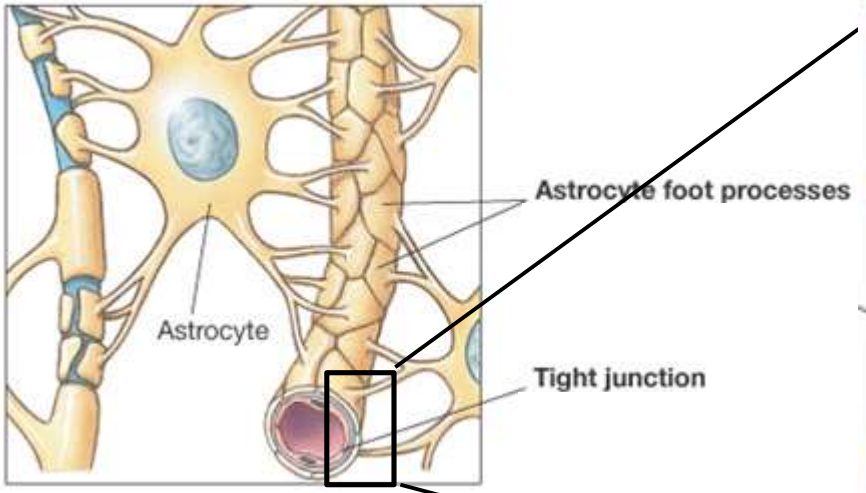


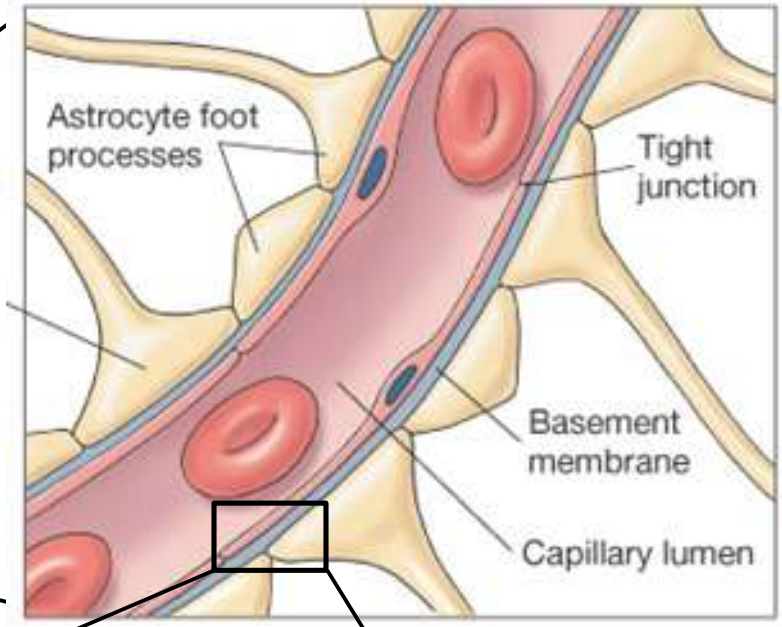
# Blood-Brain Barrier (BBB)

- 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



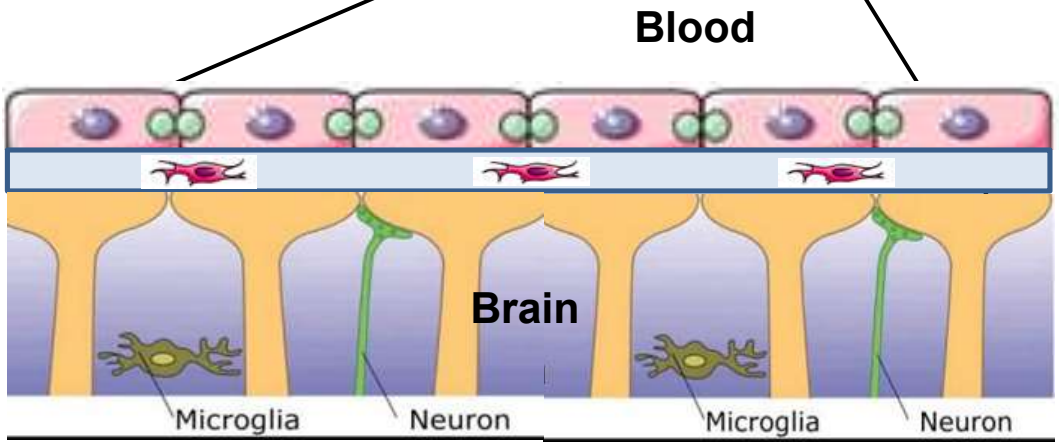




Endothelial Cell

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:

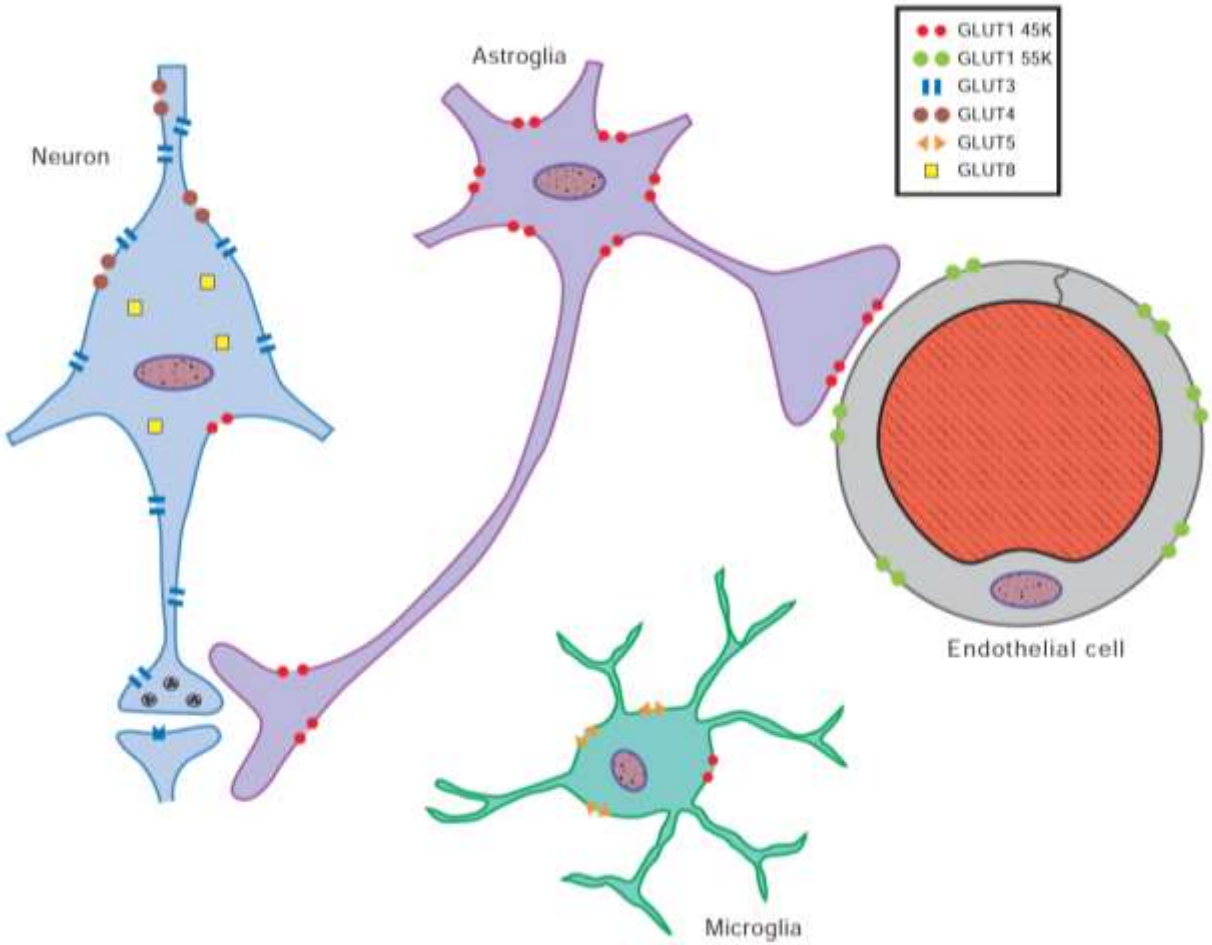
❖ 55-KDa isoform of GLUT1 essentially localized on endothelial cells of BBB

❖ 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.