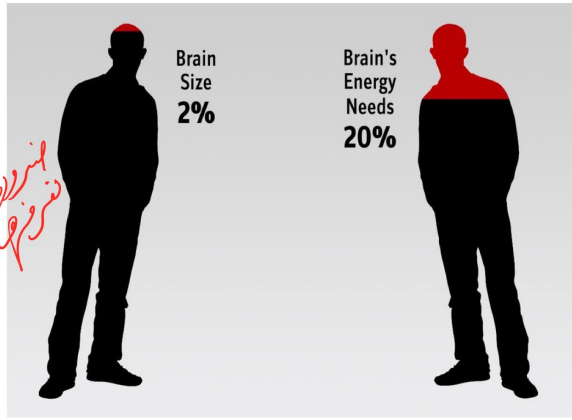
Brain Energy Metabolism I

Dr. Nesrin Mwafi
Biochemistry & Molecular Biology Department
Faculty of Medicine, Mutah University

Brain Energy Needs

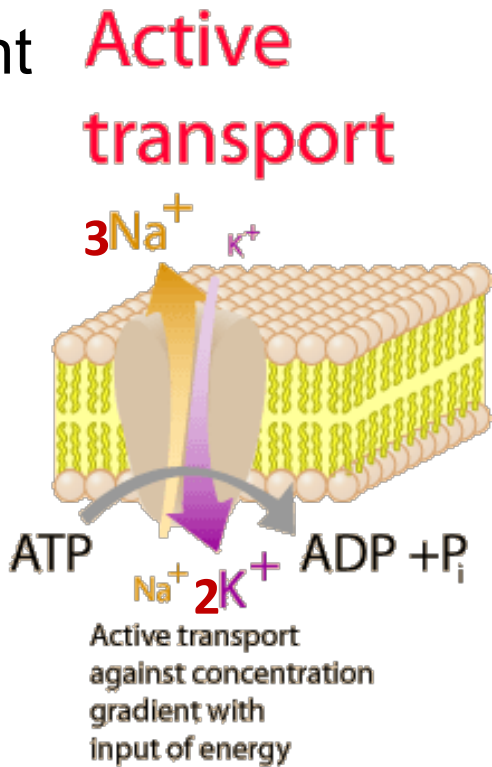
- Although the human brain constitutes only **2 %** of the total body weight, its metabolic demands are extremely high
- The brain receives **15%** of the cardiac output, **20%** of total body oxygen consumption and **25%** of total body glucose utilization



- The brain needs a constant supply of oxygen and glucose to function.
- Cerebral hypoxia can lead to irreversible neuronal damage after about 5 minutes. also, severe hypoglycemia kills the neurons.

Brain Energy Expenditure

- Glucose is the primary energy substrate of the brain, where it is almost entirely oxidized to $6CO_2$ and $6H_2O$ through its sequential processing by glycolysis, tricarboxylic acid (TCA) cycle and the associated oxidative phosphorylation resulting in **30 ATP molecules/ glucose**
- Na^+/K^+– ATPase pump: is an ATP-dependent transporter found in the membrane of neuronal and glial cells responsible for the active transport of 3 Na^+ out and 2 K^+ in
- The main energy-consuming process in brain is the maintenance of ionic gradients across the plasma membrane which is achieved by ionic pumps fueled by ATP, particularly Na^+/K^+– ATPase pump



Oxygen-Glucose Uncoupling

- The respiratory quotient of brain (**RQ**) is very close to 1. This means that the brain metabolism utilizes almost exclusively carbohydrate sources, particularly glucose

$$C_6H_{12}O_6 + 6\ O_2 \rightarrow 6\ CO_2 + 6\ H_2O$$

Respiratory Quotient= vCO_2 / vO_2

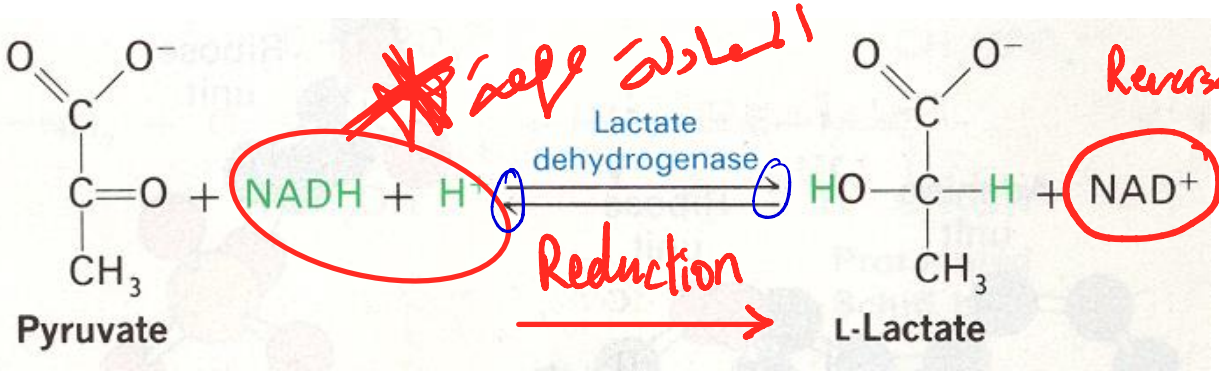
$= 6CO_2 / 6\ O_2$

RQ = 1

Oxygen-Glucose Uncoupling

- O_2 consumption rate of brain is 160 mmol /100 g/min but the measured glucose utilization rate is 31 mmol /100 g/min which is slightly higher than the predicated value of 26.6 mmol /100 g/min
- The fate of the excess **4.4 mmol** of glucose:

1. Stored as **glycogen** in astrocytes
2. Limited amount of glucose is metabolized only by glycolysis where the pyruvate is converted to lactate via **anaerobic fermentation** process (particularly in astrocytes)



- Different active areas in brain tissue are associated with high level of lactate

it's preferential تتصرف على خطوات.

Energy Substrates for Brain

1. Glucose is the exclusive substrate for oxidative metabolism used to produce energy in the form of ATP molecules under aerobic conditions and very limited extent under anaerobic conditions (fermentation)
2. Ketone bodies particularly acetoacetate (AcAc) and D-3-hydroxybutyrate (3-HB) become energy substrates for the brain in particular circumstances:

Alternative

insulin independent بتعتمد على

فلو الانسولين مو موجود ماعني غاية من glucose لحال.

- Ketogenic conditions (Starvation & Diabetes)
- Breastfed neonates

يستفيدوا من الإثنين.

!!

glucose و Ketone bodies

Adaptive

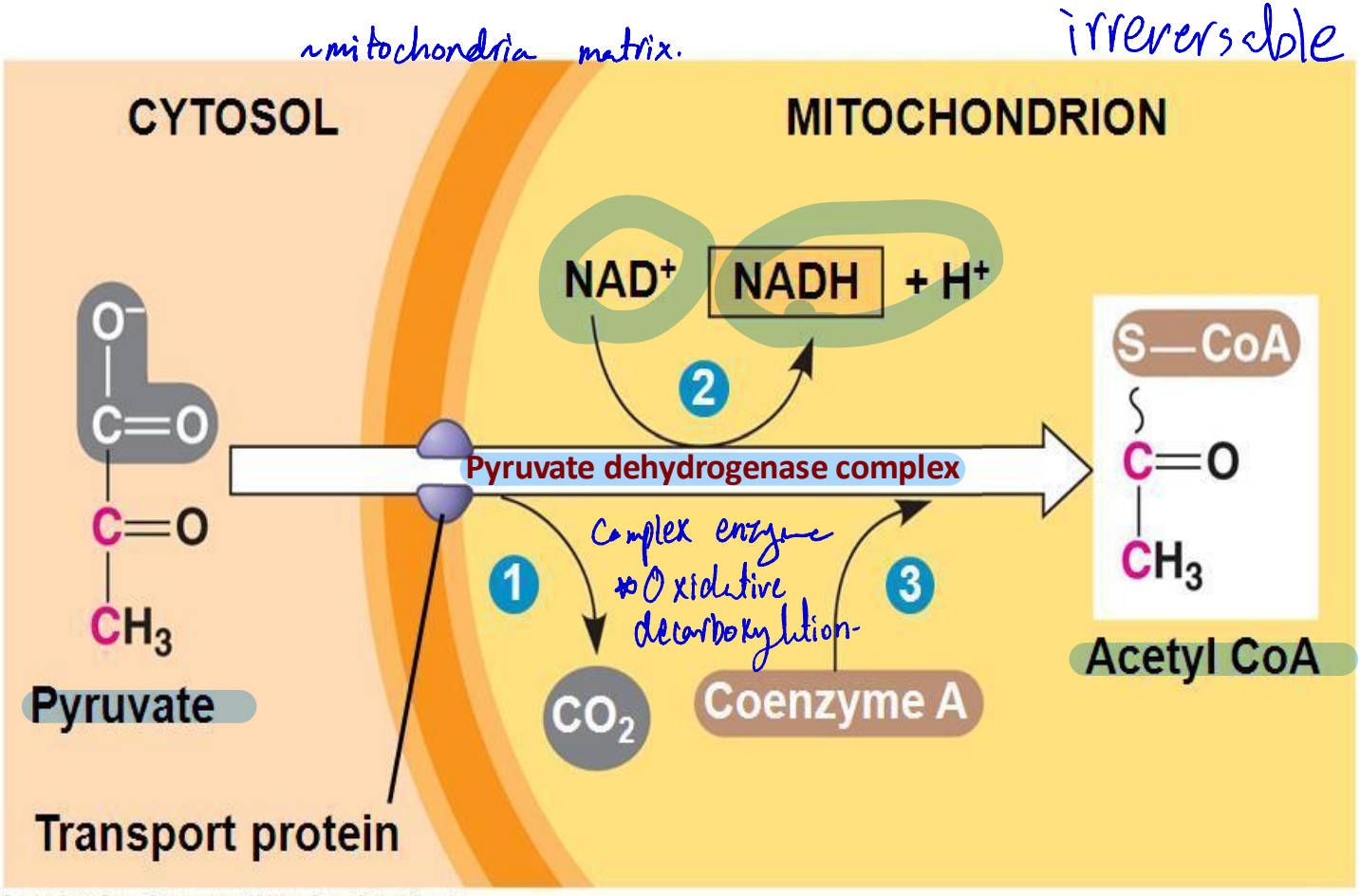
Brain Energy Metabolism II

Dr. Nesrin Mwafi

Biochemistry & Molecular Biology Department

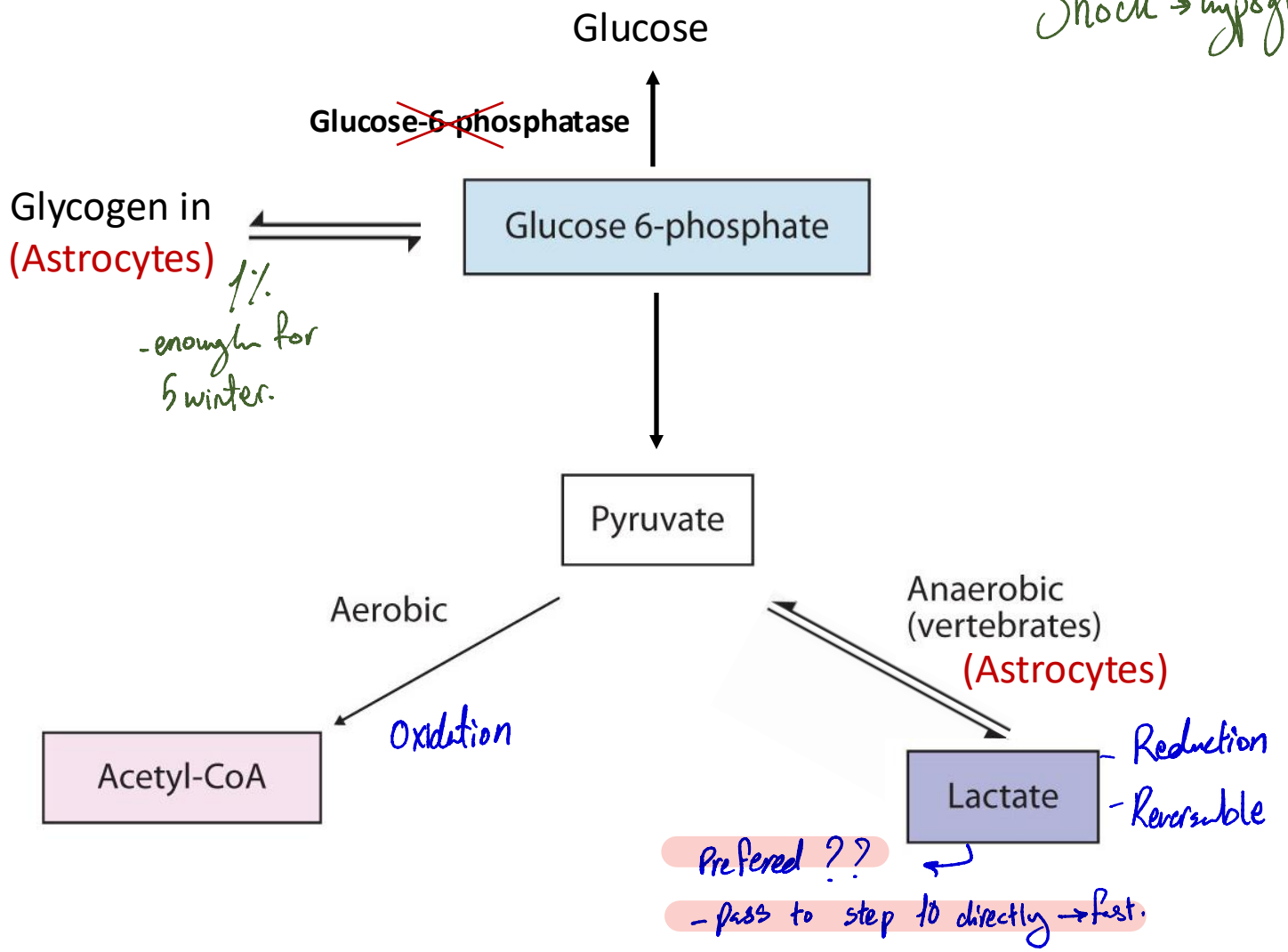
Faculty of Medicine, Mutah University

Metabolic Fates of Pyruvate in Brain



Metabolic Fates of Pyruvate in Brain

Shock → hypoglycemia.



Acetyl CoA Fate

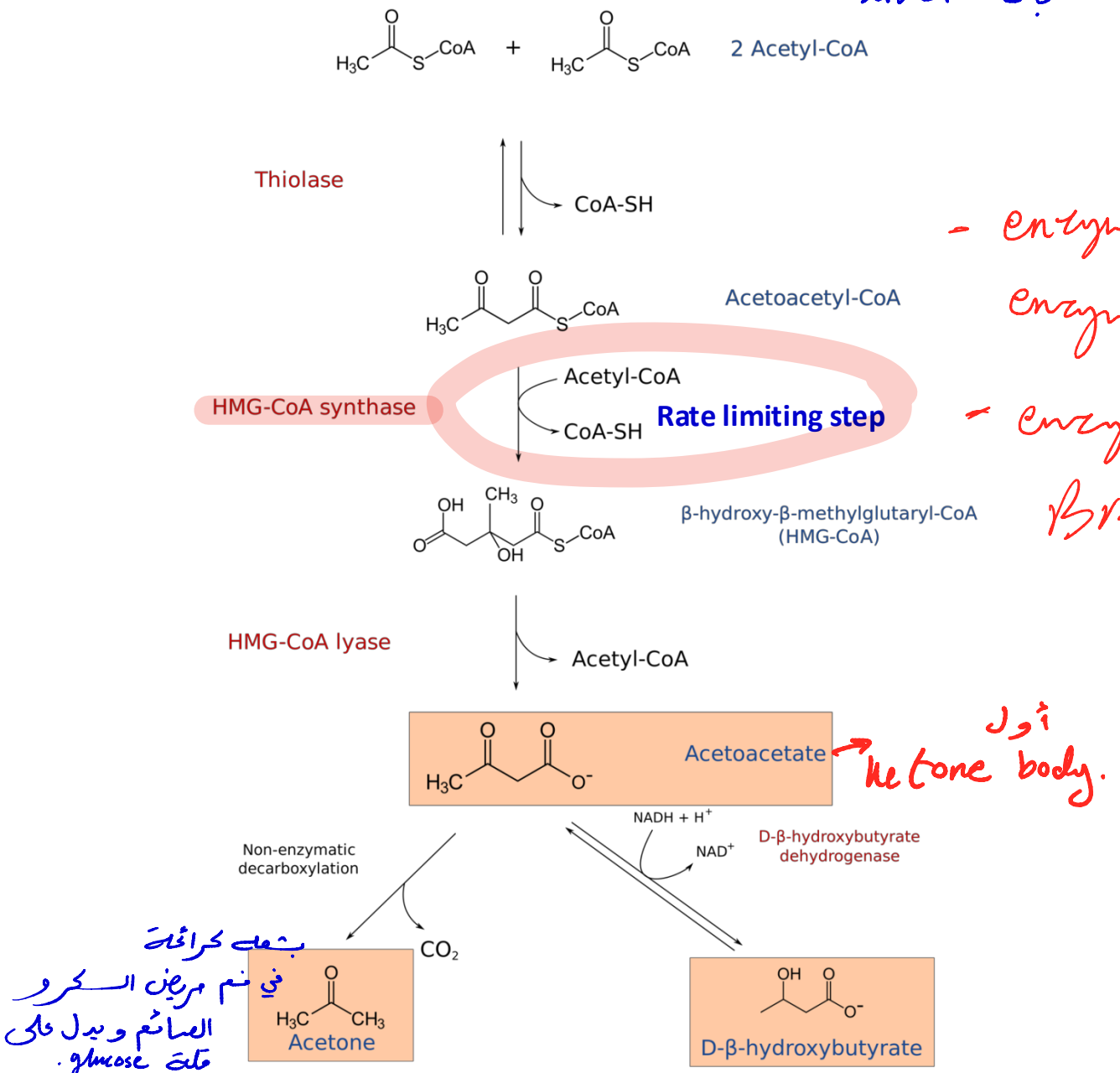
- Sources of Acetyl CoA: fat metabolism (fatty acids β-oxidation, reversible) and CHO metabolism (pyruvate, irreversible)
- Fates of Acetyl CoA: Back bone intermediate

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

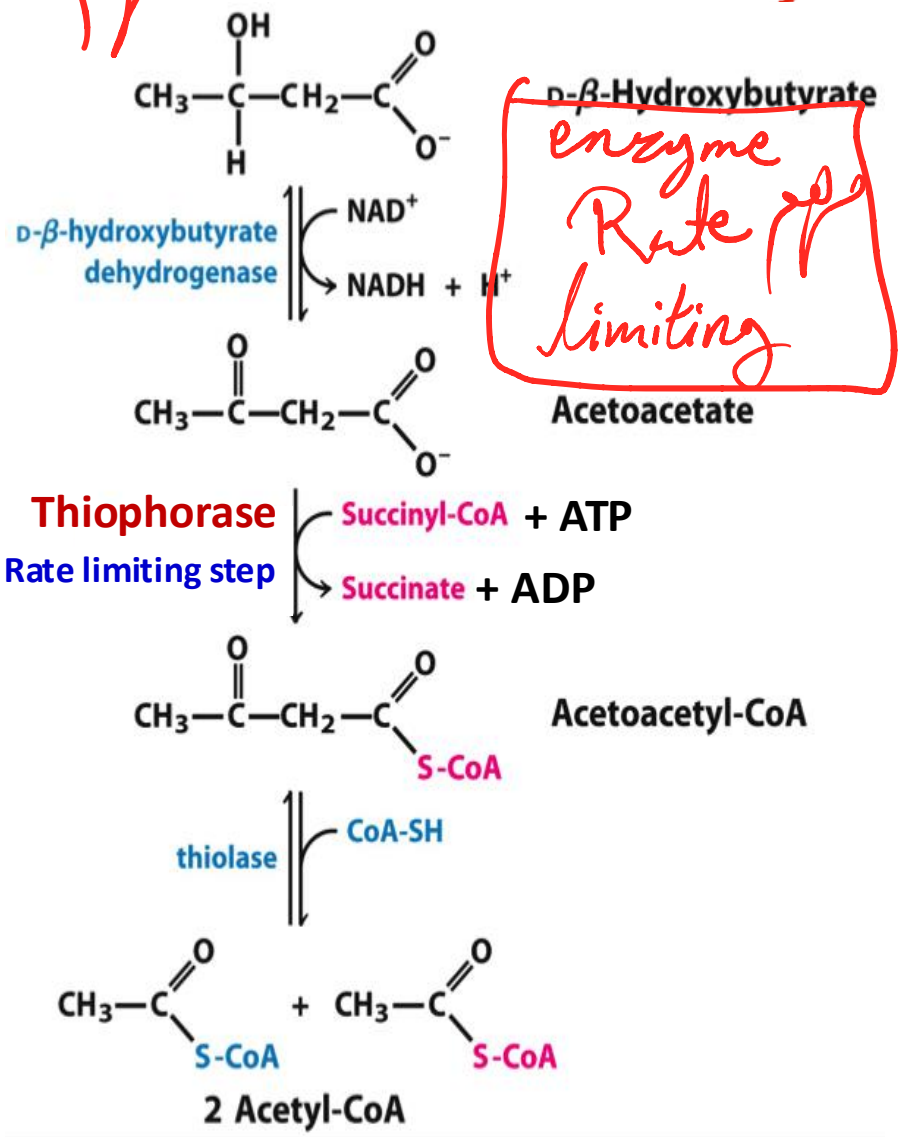
- HMG-CoA synthase is primarily expressed in hepatocytes and catalyzes the rate-limiting step in ketogenesis
- Ketone bodies are produced in the liver from accumulated Acetyl CoA during ketogenic conditions (uncontrolled diabetes and starvation) due to enhanced fat catabolism (β-oxidation of fatty acids)

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)

Glucose Transporters

اعرفوا كل وحدة و مكانها.

- 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)