METABOLISM

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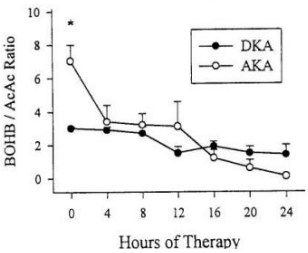
ARKAN ACADEMY

❖ Ketone bodies

- Used as a source of energy in the case of *starvation* in several tissues except RBCs and liver
  - It is produced in the **liver** by the condensation of acetyl CoA molecules
  - In starvation, ketone bodies reform 2 acetyl CoA and enter TCA cycle
  - Ketone bodies include *acetoacetate*, 3-hydroxybutyrate (*β-hydroxybutyrate*) and *acetone* (which is a **volatile** molecule responsible for the fruity odor of fasting or diabetic individuals)
  - Ketone bodies are soluble (don't require a carrier), fast (rapid) and represent a spare glucose
- Ketone bodies are responsible in generating 3-4% of energy at wake-up time and 30-40% of energy at prolonged fasting (The longer the starvation period the greater the dependence on ketone bodies)
- Synthesis of ketone bodies occurs in the **mitochondrial matrix**:
  - *2 acetyl CoA* condense in a reversible reaction catalyzed by ***thiolase*** forming *acetoacetyl CoA*
    - ✓ Thiolase is the same enzyme that catalyzes thiolytic cleavage of ketoacyl CoA in β oxidation
  - 3rd Acetyl CoA is added by 3-hydroxy-3-methylglutaryl ***(HMG) CoA synthase*** forming *HMG CoA*
    - ✓ It is the **rate limiting** step
    - ✓ HMG CoA can get out of the mitochondria to be used in cholesterol synthesis
  - ***HMG CoA lyase*** cleave it into *acetyl CoA* and *Acetoacetate*
  - Acetoacetate can be broken down into **acetone** or can be converted into **β-hydroxybutyrate** by ***3-hydroxybuterate dehydrogenase***, oxidizing NADH into NAD^+ (this reaction is reversible and goes in equilibrium)

> Acetone mostly goes to the lungs
> β-hydroxybutyrate and Acetoacetate go to skeletal and cardiac muscles and other tissues

- In the tissues, ketone bodies are utilized by:
  - *β-hydroxybutyrate* is converted back into acetoacetate by ***3-hydroxybuterate dehydrogenase***
    - ✓ It reduces NAD^+ into NADH
  - *Acetoacetate* is converted into *acetoacetyl CoA* by ***thiophorase***
    - ✓ Liver lack Thiophorase so it can't utilize ketone bodies
  - Acetoacetyl CoA is cleaved into *2 Acetyl CoA* by ***thiolase*** (reversible reaction)
- Normally, the levels of Ketone bodies **<3 mg/dl**, NAD^+ : NADH is 10:1 and 3HB : AcAc is ~ 1:1
  - Under **starvation** and **uncontrolled diabetes**, Levels of ketone bodies: **90 mg/dl** and urinary excretion of ketone bodies may be 5,000 mg/24 hours
  - That causes **acidemia** (ketoacidosis), **dehydration** and **fruity odor** of breath
    - ✓ This type of acidemia is called **Diabetic Ketoacidosis (DKA)**
- **Alcoholic Ketoacidosis (AKA)** is caused by the dinking of ethanol which:
  - Triggers catecholamines (epinephrine), cortisol and glucagon which increases FA mobilization (utilization) by β-oxidation
  - Decrease the ability to intake food and water
  - Pyruvate is converted into lactate and gluconeogenesis is suppressed
    - ✓ That causes ***hypovolemia***, ***heart failure***, and ***sepsis***



- DKA ⇨ NAD^+ : NADH is 10:1 and 3HB : AcAc is ~ 1:1
- AKA ⇨ NAD^+ : NADH is 1:1 and 3HB : AcAc is ~ 3:1

- AKA individuals **do not have a fruity breath** odor because it produces less acetone

❖ Glycerophospholipids

- Glycerophospholipids include:
  - ➢ *Phosphatidic acid* which is the precursor of glycerophospholipids
    - ✓ It consists of Glycerol + 2FAs + Phosphate group
    - ✓ FAs and phosphate are linked to the glycerol backbone by **ester** bonds
  - ➢ *Phosphatidylcholine* (lecithin), *Phosphatidylethanolamine*, *Phosphatidylserine*, *Phosphatidylinositol*
    - ✓ They have a head group on the phosphate, bound by **phosphodiester** bond
  - ➢ *Cardiolipin* has 2 phosphate groups
    - ✓ Cardiolipin the only phospholipid localized exclusively to the **mitochondria** of mammalian cells
  - ➢ *Plasmalogens* has 1 fatty acid (ester bond) + 1 fatty alcohol (**ether** bond) + phosphate

- Synthesis of glycerophospholipids occurs in **SER** except plasmalogens
  - ➢ Before the addition of the head group, glycerol must be activated forming glycerol 3-phosphate
  - ➢ It is done by **CDP** either by CDP-DAG (inositol, serine) or CDP-alcohol (choline, Ethanolamine)
- Ethanolamine and choline are activated by CDP-alcohol
- Synthesis of PE and PC
  - ➢ Choline or ethanolamine are phosphorylated by ***kinase*** forming phosphoethanolamine or phosphocholine
  - ➢ They are activated by ***transferase*** forming CDP-choline or CDP-ethanolamine
  - ➢ P-choline or P-ethanolamine transferred into DAG by another ***transferase*** releasing CMP

> Choline and ethanolamine are obtained from diet (main), synthesized, or recycled from the turnover of pre-existing phospholipids

- ***PEMT*** (Phosphatidylethanolamine N-methyltransferase) transfer methyl from a methyl donor called ***S-adenosylmethionine*** into PE forming PC (**PE → PC**)
- **PS → PE** by PS decarboxylase (***PSD***) or PS synthase (***PSS***)
- **PS → PC** by PS synthase (***PSS***)
- **PE or PC → PS** by PS synthase (***PSS***)

- Phosphatidylinositol synthesis involves inositol combination with CDP-DAG by ***PI synthase*** to produce
  - ➢ It is a reservoir of arachidonate
  - ➢ It also produces ***signaling*** molecules (PIP_2, IP_3, DAG) when cleaved by phospholipase C (PLC)
    - ✓ When a hormone binds its receptor, *Gq* protein attaches to the receptor and binds GTP activating it causing *α-subunit* to dissociate to activate PLC which cleaves PIP_2 into IP_3 and DAG
    - ✓ IP_3 activates the *Ca^{+2}-channels* in the SER which activates protein kinase C (***PKC***)
    - ✓ DAG activates ***PKC*** directly
  - ➢ ***Glycosyl phosphatidylinositol (GPI)*** attaches proteins to the plasma membrane
    - ✓ GPI aids in the lateral movement of membrane proteins such as lipoprotein lipase (LPL)

- **Phosphatidylglycerol:** It is a molecule consists of 2 glycerol + 2 FA + 1 Phosphate
- **Cardiolipin:** It is a molecule consists of 3 glycerol + 4 FA + 2 Phosphate
- They are synthesized by:
  - ➢ Phosphatidic acid interacts with CTP forming CDP-DAG
  - ➢ *CDP-DAG* interacts with *glycerol 3-phosphate* forming Phosphatidylglycerol 3-phosphate
  - ➢ Dephosphorylation forming *Phosphatidylglycerol*
  - ➢ *Phosphatidylglycerol 3-phosphate* interacts with *CDP-glycerol* by cardiolipin synthase forming **cardiolipin** and CMP

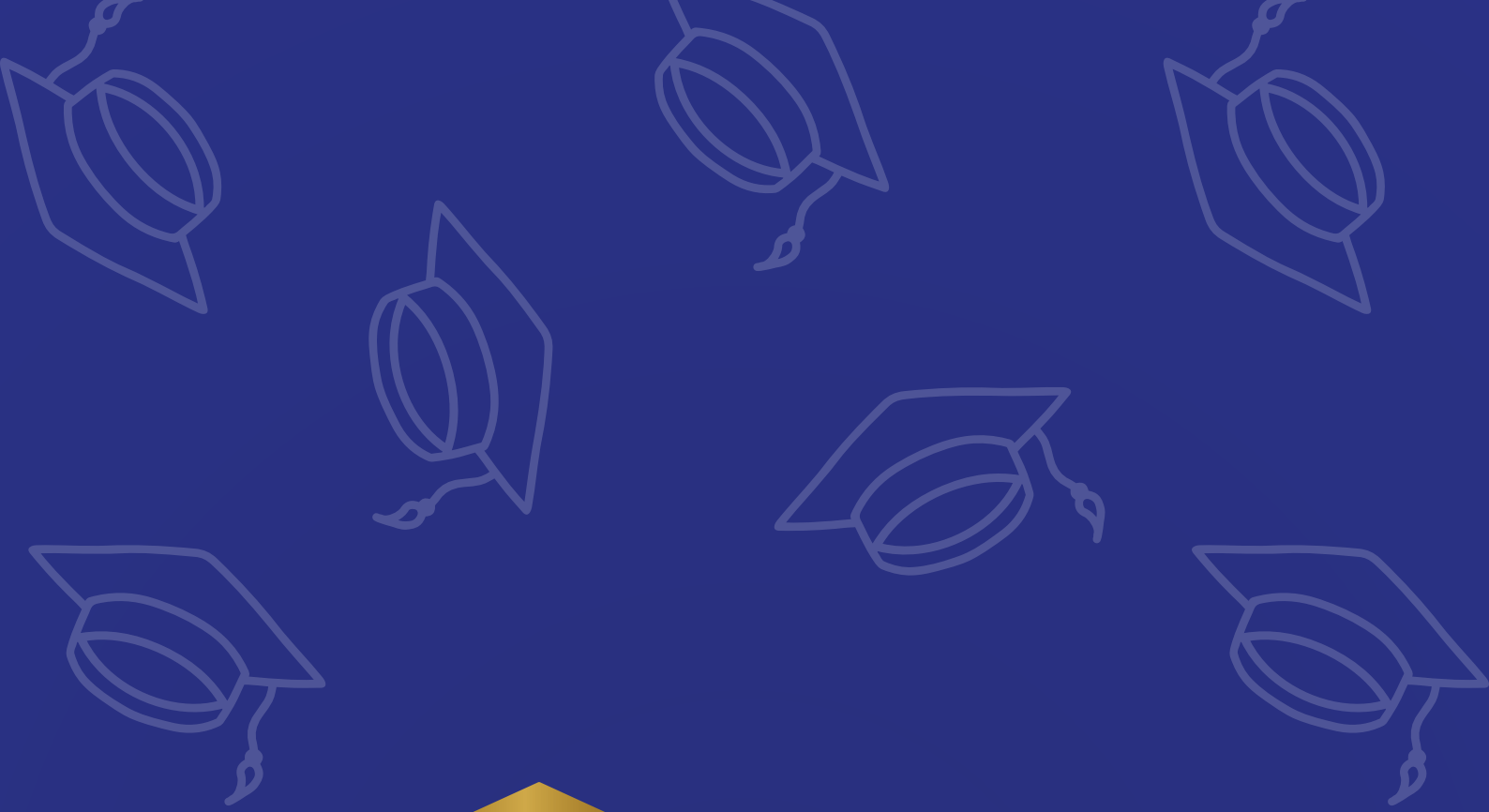
- **Plasmalogens:** FA at carbon 1 is replaced by an unsaturated alkyl group attached by an ether linkage

- **Phosphatidalethanolamine** is abundant in nerve tissue, and structurally similar to PE
- **Phosphatidalcholine** is abundant in heart muscle
- **Platelet-activating factor** has a saturated Alkyl on carbon 1 and an acetyl residue at carbon 2
  - It represents a prothrombotic and inflammatory factor

- **Surfactants:** are complex mixture of lipids (90%) and proteins (10%) that make the extracellular fluid layer *lining the alveoli* and are secreted by *type II pneumocytes* in the lungs
  - Dipalmitoylphosphatidylcholine (**DPPC**) is the major lipid in surfactants
  - Surfactants serve **to decrease the surface tension** of the fluid layer allowing reinflation of alveoli and preventing alveolar collapse (atelectasis)

- ***Respiratory distress syndrome (RDS)*** in preterm infants is associated with insufficient surfactant production and/or secretion
  - Prenatal administration of **glucocorticoids** shortly before delivery to induce expression of specific genes

- Degradation of Phospholipids is done by phospholipases which include:
  - ***Phospholipase A1:*** Releases the FA on *C1*
  - ***Phospholipase A2:*** Releases the FA on *C2*, which is mostly arachidonic acid in *PI*
    - ✓ It presents in many mammalian tissues, pancreatic juice, snake and bee venoms
    - ✓ It is synthesized as a proenzyme (pro-PLA2), which is activated by trypsin and bile salts
    - ✓ Inhibited by glucocorticoids such as cortisol
  - ***Phospholipase C:*** Cleaves the bond *between glycerol and phosphate*
    - ✓ It presents in the liver lysosomes and α-toxin of clostridia and bacilli
  - ***Phospholipase D:*** *cleaves the head group* forming phosphatidic acid
    - ✓ It is followed by **phosphohydrolase** to generate DAG



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