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Ketogenesis
Objectives

- Definition
- Site
- Function
- Steps
Ketogenesis

Def.: Formation of ketone bodies (acetoacetic acid, β- hydroxyl butyric acid and acetone) from acetyl-CoA.

The source of acetyl coA resulting is B oxidation of FA in excess of optimal function of Kreb’s cycle.

Site: Mitochondria of liver
Steps of Ketogenesis:

Thiolase:

2 CH₃ – C ~ SCoA \rightarrow CH₃ – C – CH₂ – C ~ SCoA

Deacylase:

CH₃ – C – CH₂ – COOH

2 Acetyl CoA

AAA

CoA~SH

Aceto Acetyl CoA

CoA~SH
\[
\text{HMG CoA synthetase} \rightarrow \text{Aceto Acetyl CoA} + \text{Acetyl CoA} \rightarrow \text{HMG CoA}
\]
HMG CoA

HMG CoA lyase

CH3 – C – CH2 – C OH + CH3 – C ~ SCoA

AAA Acetyl CoA
\[ \text{B hydroxy butyrate} \xrightarrow{\text{Dehydrogenase}} \text{CO}_2 \]

\[ \text{B hydroxy butyrate} \xrightarrow{\text{Spontaneously}} \text{Acetone} \]
Function:

- Ketone bodies go via blood to extrahepatic tissues where they become oxidized to CO2 and water (ketolysis).

- Although most tissues can oxidize FA they can be more easily oxidize ketone bodies.

- Ketogenesis may be considered as a preparatory step performed in the liver to facilitate the oxidation of FA by extrahepatic tissues.

- Ketogenesis becomes of great significant during starvation when carbohydrate stores are depleted and oxidation of fats becomes a major source of energy to the body.

- The brain normally uses glucose as the only fuel. It takes about 5-6 weeks to be adapted for ketone bodies utilization, but can not utilize FA.

- The total ketone bodies concentration in the blood does not exceed 0.2 mmol/L.
Control of ketogenesis:

- Fatty acids are the precursors of ketone bodies in the liver. In fed and fasting state the liver has the ability to extract about 30% or more of FA passing through it.
- Therefore the factors regulating mobilization of FFA from adipose tissue are important in controlling ketogenesis.
Control of ketogenesis:

- Ketogenesis is increased in starvation due to increase lipolysis and also increased by high fat diet.
- FFA after being activated in the liver to acyl-CoA will undergo one of 2 pathways.
  - Esterification to form acyl glycerol or phospholipids.
  - Oxidation to give acetyl-CoA.
Control of ketogenesis:

Acetyl-CoA is oxidized in citric acid cycle or it enters the pathway of ketogenesis, this depends upon the amount of energy present in the cell:

- If there is excess ATP molecules acetyl-CoA from ketone bodies (one molecule of palmitic gives 33 mole of ATP on conversion to acetoacetate and 21 ATP on conversion to β-hydroxybutyrate).
- If there is decreased ATP mole in the cell acetyl-CoA undergoes further oxidation via Kreb’s cycle (one mole of palmitic give 129 ATP).

• Thus, ketogenesis may be regarded as a mechanism that allows the liver to oxidize an increasing quantity of FFA without ↑ its total energy expenditure.
Control of ketogenesis:

- Triacylglycerol (ADIPOSE TISSUE) → Lipolysis → FFA → FFA
- BLOOD

LIVER

- CPT-1 gateway → Acyl-CoA → Esterification → Acylglycerols
- β-Oxidation → Acetyl-CoA → Ketogenesis
- Citric acid cycle → Ketone bodies → CO₂ + H₂O
Partition of Acetyl CoA between oxidation and KB production

- Complete oxidation of palmitate: 129 ATP

- If acetoacetate is the end product:
  - 7 cycles of beta oxidation of palmitate forms 8 acetyl CoA, which join to form 4 acetoacetate.
  - 5 ATP for each cycle of beta oxidation. Total ATP formed 35.
  - 2 are used for initial activation.
  - Thus 33 ATP are formed if acetoacetate is the end product.

- If β-OH butyrate is the end product:
  - 4 acetoacetate form 4 β-OH butyrate using 4 NADH (i.e., 12 ATP)
  - Thus 33 - 12 = 21 ATP
Partition of Acetyl CoA between the pathway of ketogenesis and oxidation to CO$_2$

- This partition is so regulated that the total free energy captured in ATP which results from the oxidation of FFAs remains constant.

- Ketogenesis allows liver to oxidize increasing quantities of FAs within a tightly coupled system of oxidative phosphorylation, without increasing its total energy expenditure.
Thank You