Fatty acid Catabolism (Oxidation)

- Fatty acids are an important source of energy used mainly by Liver and Muscles but NOT brain or RBCs.
- Fatty acids are stored as Triglyceride in adipocytes where each 3 fatty acids are esterified to one molecule of glycerol.
- During fasting or starvation; body cells increase utilization of fatty acids as source of energy, so triglycerides are hydrolyzed by hormone sensitive lipase/DAG and MAG lipases to release free fatty acids, which then carried in blood by albumin to body tissue.
- Fatty acids (Fat) store more energy than carbohydrate or protein (fat is a long term energy storage).
- Fat is the major storage form of energy (most of your energy is stored as fat).
- Carbohydrate release energy quickly but not a major form of energy storage (maximum 500 mg of glucose is stored as glycogen).

يعني معظم الطاقة اللي انتا مخزنها بجسمك مخزنة على شكل دهون مش كربوهيدرات
الدهون وزنها خفيف وفيها طاقة عالية
افضل الك تحمل بجسمك كيلوغرام دهون من انك تحمل كيلوغرام كربوهيدرات لانو
كيلوغرام الدهون بحتوي على أكثر من ضعف الطاقة الموجودة بكيلوغرام الكربوهيدرات.
Fatty acid Catabolism

• First step in fatty acid catabolism called Activation:

\[
\text{ATP} \rightarrow \text{AMP} + 2\text{Pi} = 2\text{ATP} \rightarrow 2\text{ADP} + 2\text{Pi}
\]

\[
2\text{ATP} \rightarrow 2\text{ADP} + 2\text{Pi}
\]

**Note:** Acyl-CoA is a general name FA-CoA

- Palmitate (16:0) → Palmitoyl-CoA
- Stearate (18:0) → Stearyl-CoA
- Acetate (2:0) → Acetyl-CoA

**The Activation Step**

- Long Chain Fatty acids (LCFA)
  - Location: outer Mitochondrial membrane at Cytosolic Side in the Cytosol
- Short and Medium chain Fatty acids
  - such as Milk Fat
  - Location: Mitochondrial Matrix

• The rest of steps occur in the mitochondrial matrix, So Long chain Acyl-CoA should be transported to mitochondrial matrix

• BUT, the inner mitochondrial membrane is impermeable to long chain Acyl-CoA!! What we do???
What we do?? Carnitine Shuttle

1. LCFA is activated in the cytosol forming Acyl-CoA
2. Long chain Acyl-CoA cross the outer mitochondrial membrane to the intermembrane space
3. \textbf{CAT-I} remove CoA and bind Carnitine forming Acyl-Carnitine
4. Acyl-Carnitine cross the inner membrane by special carrier called \textbf{Carnitine-AcylCarnitine Translocase (Antiporter)}
5. In the matrix \textbf{CAT-II} remove Carnitine and bind CoA forming long chain Acyl-CoA in the matrix

\textbf{CAT-I}: Carnitine-Acyl Transferase I also called Carnitine Palmitoyl Transferase I (CPT I)
\textbf{CAT-II}: Carnitine-Acyl Transferase II also called Carnitine Palmitoyl Transferase II (CPT II)

This process called \textbf{Carnitine Shuttle} required only for catabolism of long chain fatty acids and it’s the rate limiting step of catabolism of long chain fatty acids
Genetic Deficiency of CAT-I and CAT-II

Deficiency of CAT-I:
- Affect mainly Liver
- Low energy production during fasting; inhibiting gluconeogenesis leading to sever hypoglycemia, coma

Deficiency of CAT-II
- affect heart or Skeletal muscle
- Leads to Cardiomegaly and muscle weakness

Treatment:
- Avoidance of fasting
- Diet with high carbohydrate and low fat
- Short and medium chain fatty acids such as Milk fat that does not need CAT transport system

Q: Expect what will happen if someone has carnitine deficiency or Carnitine-Acyl-Carnitine Translocase genetic deficiency?
Q: calculate the net ATP produced from catabolism of Palmitic acid (16:0)?

\[
\text{# of Acetyl-CoA} = \frac{16}{2} = 8 \times 12 = 96
\]

\[
\text{# of turns} = \frac{16}{2} - 1 = 7 \times 5 = 35
\]

Net = 96 + 35 = 131 – (2ATP)?

The process of catabolism of Acyl-CoA in the Mitochondrial Matrix called β-oxidation turns of Cycles

For Acyl-CoA 18C (Stearyl-CoA)

Each Round of β-Oxidation produce One FADH₂, One NADH, One Acetyl-CoA, and a Fatty Acyl-CoA Shortened by Two Carbons

Each Acetyl-CoA Released in Matrix is Oxidized in the Citric Acid Cycle.

Total = 108 + 40 = 148 ATP
**β-Oxidation Reactions**

1. **Dehydrogenation “Oxidation”:** Removal of 2H from C2 and C3 forming 
   *Trans*-enoyl-CoA (FAD is reduced to FADH$_2$), this step catalyzed by
   **Acyl-CoA Dehydrogenase**

2. **Hydration:** Addition of H$_2$O breaking the double bond (OH added to C3 and
   H to C2) forming **L-3-Hydroxy Acyl-CoA**, this step is catalyzed by **Hydratase**

3. **Dehydrogenation “Oxidation”:** Removal of 2H from C3 forming **3-Ketoacyl-CoA**
   (NAD$^+$ is reduced to NADH), this step catalyzed by **3-Hydroxyacyl-CoA Dehydrogenase**

4. **Thiolytic Cleavage:** Release of 2C as Acetyl-CoA and the remaining Acyl is bonded to CoA; this step is catalyzed by
   **Thiolase**
Each step in the $\beta$-oxidation cycle is catalyzed by enzymes specific to particular chain length; for example we have 4 Acyl-CoA dehydrogenases for the first step:
- Very long chain Acyl-CoA dehydrogenase
- Long chain Acyl-CoA dehydrogenase
- **Medium chain Acyl-CoA dehydrogenase (MCAD)**
- Short chain acyl-CoA dehydrogenase

**MCAD deficiency** is the most common inborn errors of $\beta$-Oxidation 1:14000 birth; result in decreased ability to oxidize medium chain fatty acids which accumulate and appears in the urine.

**Symptoms:** Severe hypoglycemia, sudden infant death syndrome (SIDS) because milk contains mainly MCFA.

**Treatment:** avoid fasting, high Carbohydrate diet

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**VLCFA:** very long chain fatty acids

**LCFA:** long chain fatty acids

**MCFA:** medium chain fatty acids

**SCFA:** short chain fatty acids
Q: for Catabolism of stearic acid (18:0):

a. How many acetyl-CoA produced? 9 Acetyl-CoA

b. How many beta-oxidation cycles required? 8 β-oxidation cycles

c. The Net ATP produced when completely oxidized to CO₂ and H₂O?
   (9 acetyl-CoA x 12ATP) + (8 cycles x 5ATP) – (2ATP for activation) = 146 ATP

a. Total CoASH required? 9 CoASH required (1 for activation and 8 for 8 β-oxidation cycles)

b. How many water molecules required? 8 H₂O molecules

c. How many NADH produced in β-Oxidation? 8 NADH

d. How many FADH₂ produced in β-Oxidation? 8 FADH₂

Q: Calculate ATP results from complete oxidation of Palmitic acid?
Q: Calculate ATP result from complete oxidation of Palmitoyl-CoA?
Reactions 1, 2, and 3 in β-oxidation resembles steps 6, 7, and 8 in TCA cycle

Trans Fat: unsaturated fatty acid with Trans double bond

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Q: which give me more energy; Saturated or Unsaturated fatty acids??

Saturated; more oxidation steps $\rightarrow$ more FADH$_2$ $\rightarrow$more ATP
Linoleic Acid 18:2(9,12)

NADPH-dependant 2,4-dienoyl-CoA Reductase: break double bond  C2=C3 & C4=C5 form new = C3=C4

Consume NADPH

= at odd C → Isomerase
= at even C → Reductase + Isomerase
Fatty acids with Odd number of Carbons (rare 10% of Dietary fatty acids)

15:0

Last Cycle will yield:
- Acetyl-CoA (2C)
- Propionyl-CoA (3C)

Q: Vitamin B12 deficiency will accumulate ..................

Note:
Heritable Methylmalonic academia and aciduria can result from:
- Mutase deficiency
- Deficiency of the enzyme that convert vitamin B12 to its active form
- Vitamin B12 deficiency result in accumulation of Methylmalonic acid in the blood and urine → **Methylmalonic academia and aciduria** also there will be accumulation of odd carbon fatty acids in the cell membrane of neurons leading to neurological manifestation

  High methyl-Malonyl-CoA can be used to detect Vitamin B12 deficiency

  Note:
  Heritable Methylmalonic academia and aciduria can result from:
  - **Mutase deficiency** either absent, deficient or has reduced affinity for its coenzyme
  - Deficiency of the enzyme that convert vit B12 to the it’s active form

  Symptoms: Metabolic acidosis & Growth retardation

  Note:
  - You know that we cannot synthesize Glucose from Acetyl-CoA, so fatty acids with even number of carbon cannot be precursor for glucose because they are catabolized totally to acetyl-CoA
  - Fatty acids with odd number of carbon, the last 3C atoms only can be used to synthesize Glucose because they are released as propionyl-CoA then converted to succinyl-CoA (TCA cycle intermediate)
Ketone Bodies (Ketoacids)

They are molecules synthesized in the Liver Mitochondria, from Acetyl-CoA (Precursor)

- Normally Ketone Bodies synthesized at Low Rate (less than 20 mmolar)

بالوضع الطبيعي تصنع بكميات قليلة يزداد صناعتها بشكل كبير في حالات:

1. Starvation

2. Uncontrolled Diabetes (Low Insulin), mainly Type I Diabetes

In this cases:
liver cells catabolize fatty acids to Acetyl-CoA, but this Acetyl-CoA cannot go through TCA cycle because of low Oxaloacetate level
Acetyl-CoA will accumulate trapping CoA with it (Remember first step in TCA cycle free CoA from acetyl)
Now if CoA is trapped then we cannot catabolize fatty acids

وسلامتك شو الحل؟؟

Solution: Synthesize Ketone Bodies (Ketogenesis)

So, Acetyl-CoA accumulate in the liver and Can NOT go through TCA Cycle

ketone bodies هو هدف الكبد الوحيد من تصنيع CoA
1. 2 Acetyl-CoA are condensed by thiolase forming Acetoacetyl-CoA
2. 3rd Acetyl-CoA is added forming 6C Hydroxy-Methyl-Glutaryl-CoA (HMG-CoA) by HMG-CoA synthase (this is the rate-limiting step)
3. Then removal of Acetyl-CoA from HMG-CoA by HMG-CoA Lyase yield Acetoacetate (1st Ketone body)
4. Acetoacetate can be:
   - Reduced to β-Hydroxybutyrate (2nd Ketone body)
   - Decarboxylated spontaneously in the blood to Acetone (3rd ketone body) which is eliminated by breath giving fruity odor of the breath

Acetoacetate and β-Hydroxybutyrate can be used by body tissues (NOT Liver or RBCs) as source of energy

Acetone is non-metabolized side product eliminated by breath
Peripheral tissues such as muscles and brain can use Ketone body as source of energy, they are water soluble and can be transported in blood without the need of carrier protein

Actually heart/skeletal muscles prefer ketone bodies as a source of energy, that’s why we synthesize them at low rate under normal physiological conditions.

3-Ketoacyl-CoA transferase is a Mitochondrial enzyme not found in the liver so, Liver and cell that lack mitochondria (RBCs) cannot use Ketone body as source of energy

Brain Prefer Glucose as energy source, but in case of starvation, Brain use Ketone bodies as sources of energy why?

In body tissues:
3-Hydroxybutyrate is oxidized to Acetoacetate, then acetoacetate converted in the Mitochondria to Acetoacetyl-CoA by enzyme called 3-Ketoacyl-CoA transferase (Thiophorase) (Succinyl-CoA is the source of CoA) Then Acetoacetyl-CoA is cleaved by thiolase to 2Acetyl-CoA to be used in Krebs cycle; this process called Ketolysis.
In Starvation or Diabetus Mellitus low insulin/Glucagon ratio and increased Epinephrine increase the rate of Lipolysis (Hydrolysis of TAG) consequently the synthesis of Ketone bodies increase in the liver. Ketone bodies are water soluble molecules they will increase in the blood and Urine (Ketonemia/Ketonuria) Since ketone bodies are acids and increased in the plasma they will ↓pH of the blood (Ketoacidosis).
In kidney cells, if starved or uncontrollable diabetes.

\[ \text{Fatty Acids} \xrightarrow{\beta-	ext{Oxidation}} \text{Acetyl-CoA} \xrightarrow{TCA} \text{CO}_2 \]

\[ \text{Fatty Acids} \xrightarrow{\beta-	ext{Oxidation}} \text{Acetyl-CoA} \xrightarrow{} \text{Ketone Bodies} \]

in the normal state in cases of starvation or uncontrolled diabetes.

In exams, if asked about ATP derived from F.A. breakdown in the liver, we only consider the ATP from the \( \beta \)-oxidation of Palmitic acid:

\[ \text{Palmitic acid} \xrightarrow{} 7 \text{ Cycles} \times 5 = 35 - 2 \]