METABOLISM

بسم الله الرحمن الرحيم

FINAL – Lecture 10

Ketogenesis

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

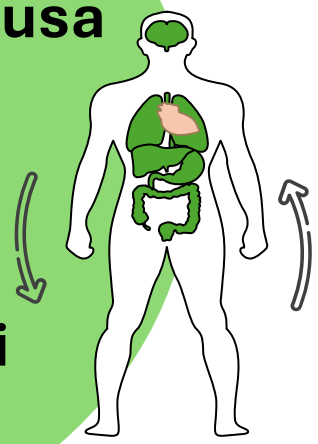
اللهم استعملنا ولا تستبدلنا

Written by:

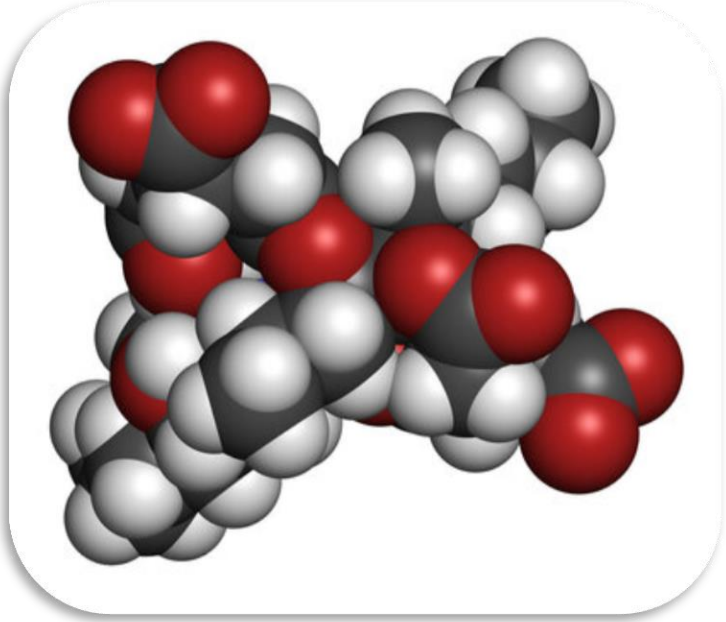
- **Abd AL Rahman Musa**

Reviewed by:

- **Mahmoud Aljunaidi**



Quiz on the previous lecture



Ketogenesis

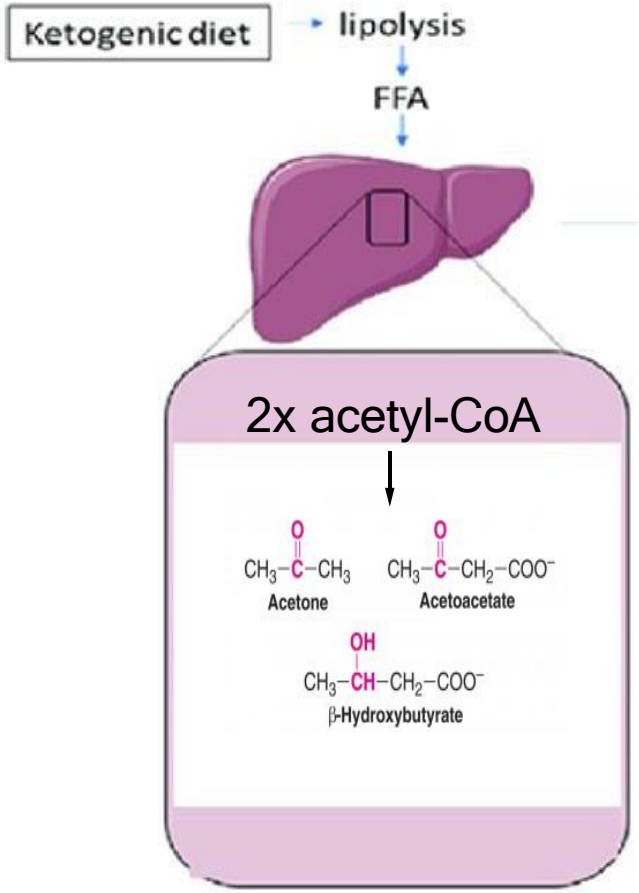
Dr. Diala Abu-Hassan

وَتَوَكَّلْ عَلَى الْحَيِّ الَّذِي لَا يَمُوتُ وَسَبِّحْ بِحَمْدِهِ ۚ وَكَفَىٰ بِهِ بِذُنُوبِ عِبَادِهِ خَبِيرًا

Resources

- This lecture
- Lippincott's Biochemistry, Ch. 16
- Diabetic, alcoholic and starvation ketoacidosis
  - https://derangedphysiology.com/main/cicm-primary-exam/required-reading/acid-base-physiology/acid-base-disturbances/Chapter%20617/diabetic-alcoholic-and-starvation-ketoacidosis
- Deep Dive – Alcoholic Ketoacidosis
  - https://aomcfoamed.com/2020/01/14/deep-dive-alcoholic-ketoacidosis/
- Alcoholic Ketoacidosis: Mind the Gap, Give Patients What They Need
  - https://www.emra.org/emresident/article/alcoholic-ketoacidosis/

What are ketone bodies?

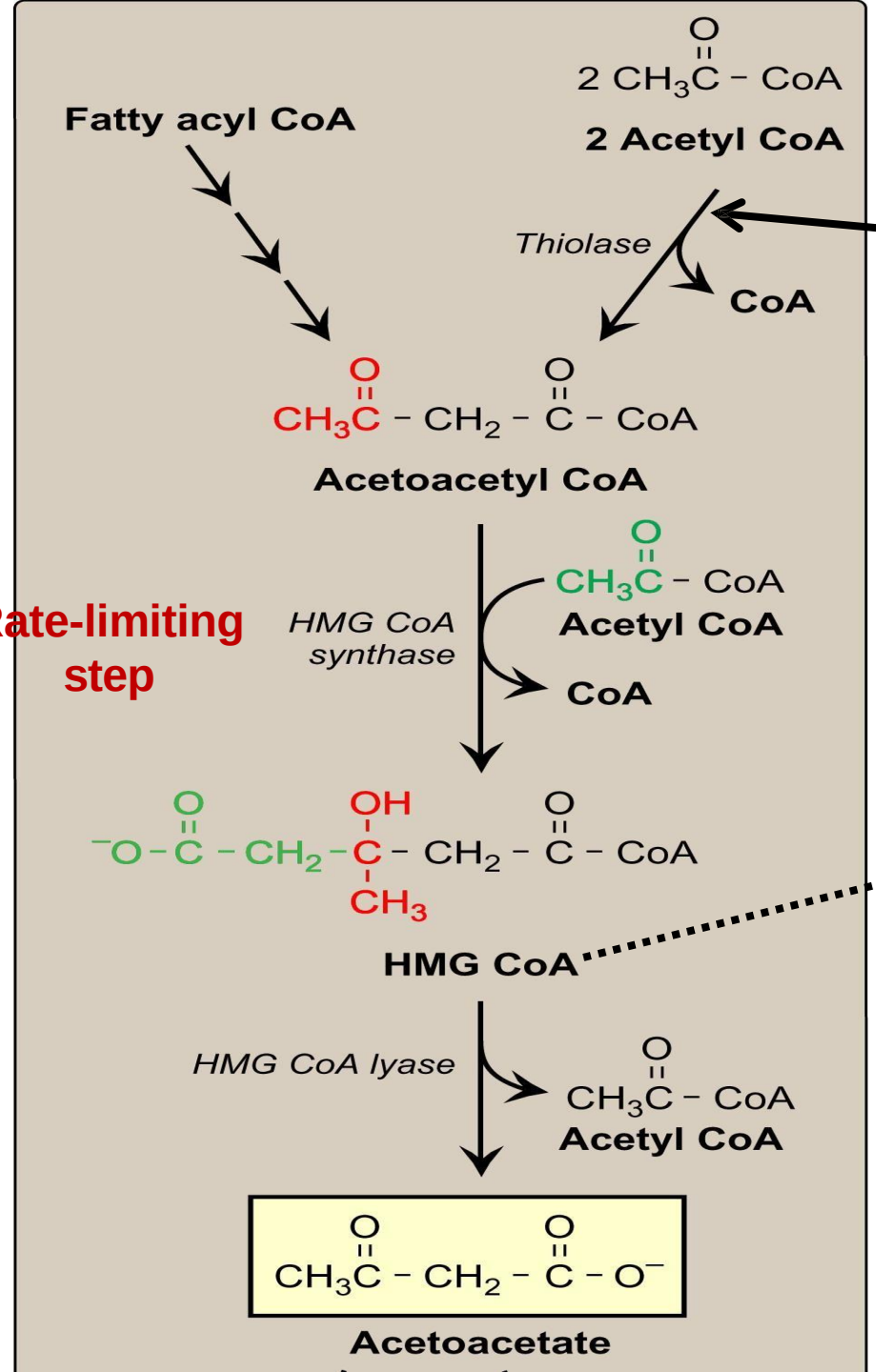


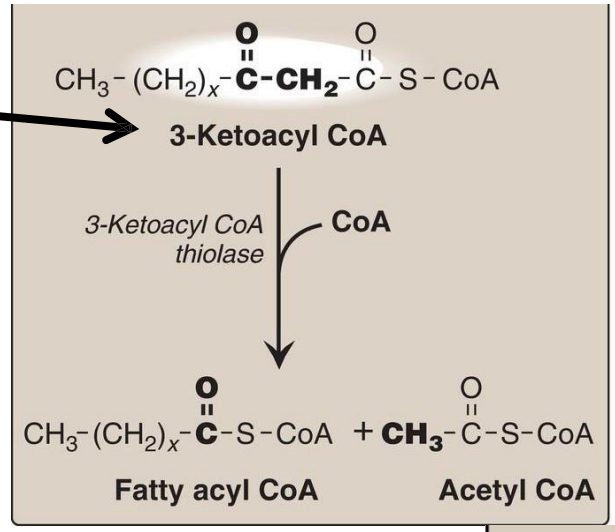
- Ketone bodies are produced from 2 **acetyl-CoA** in the **liver** (hepatocytes) for the use of other tissues (e.g. muscle, heart, brain, …etc., but not RBC and liver) to use as a source of energy in case of starvation by re-forming acetyl CoA.
- **Classification (types) of ketone bodies** :They are acetoacetate (4C), 3-hydroxybutyrate (AKA β- hydroxybutyrate)- (4C), and acetone (volatile)- (3C).
- **When are ketone bodies produced** : At high rate during:
- -Fasting → When glucagon concentration is high, and the metabolism of fatty acid is activated.
- - Uncontrolled Diabetes Mellitus
- **Advantages**:
  - Soluble (no carrier is needed); they're small molecules that are soluble because of polar groups bearing (see figure), enhancing their movement in plasma.
  - Fast (their degradation of acetyl CoA is fast)
  - Spare for glucose (to be explained)

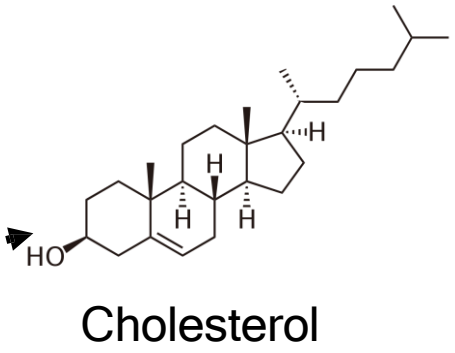
- **At wake-up time: 3-4% of energy**
- **Prolonged fasting: 30-40%**

Recall: Ketogenesis is activated at high concentration of Acetyl-CoA (after lipolysis of TAG)

Ketogenesis reactions

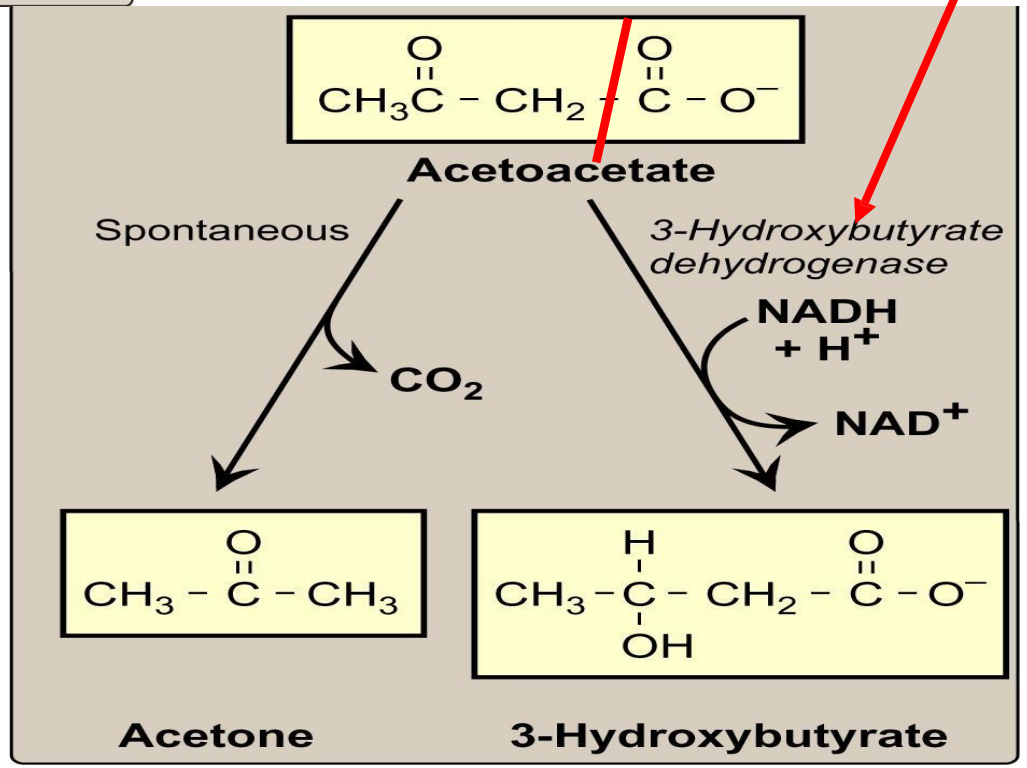






Cholesterol

NAD+/NADH



Explanation of the previous slide- ketogenesis

1. We obtain **2 Acetyl coA** from the degradation of fatty acids, we need thiolsase enzyme to and this step **produces Acetoacetyl-CoA**

Remove one CoA

Connect the 2 molecules together

- There are 2 types of thiolase enzyme:
  1) One that breaks down bonds to produce fatty acyl-CoA, 3-ketoacyl CoA thiolase for example.
  2) Another that joins 2 acetyl-CoA and exclude one CoA, as the one the one used in the previous step.

2. **Acetoacetyl-CoA** joins with another acetyl CoA in a condensation reaction to **produce HMG CoA** catalyzed by the enzyme **HMG CoA synthase.**
   - Formation of HMG CoA is the **rate limiting step;** as it is the slowest step.
   - Note: HMG coA is an important intermediate; because it's related with cholesterol synthesis

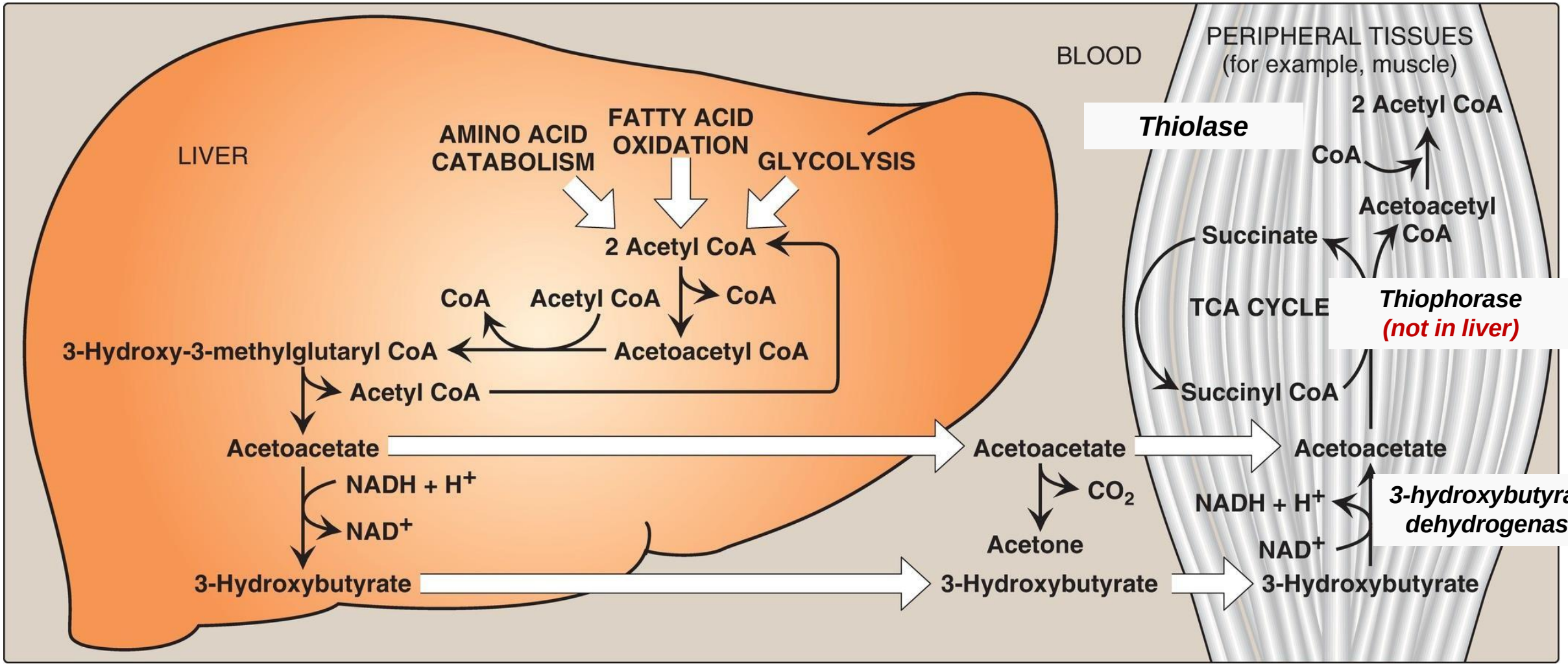
3. **HMG CoA** then is **degraded to Acetoactate** by the removal of 1 Acetyl-CoA through **HMG CoA lyase.**

4. **Acetoacetate** can be spontaneously decarboxylated into **acetone,** but it's a final product which can't be used, so it will be excreted out.

Or

4. The carbonyl group in **Acetoacetate** can be reduced to OH through 3-hydoxybutyrate dehydrogenase enzyme to **produce 3-hydoxybutyrate,** accompanied with the oxidation of NADH to NAD^+.
   - Note: this reaction corrects the ratio of NAD+/NADH; which is important to many reactions of the cells.

Use of ketone bodies



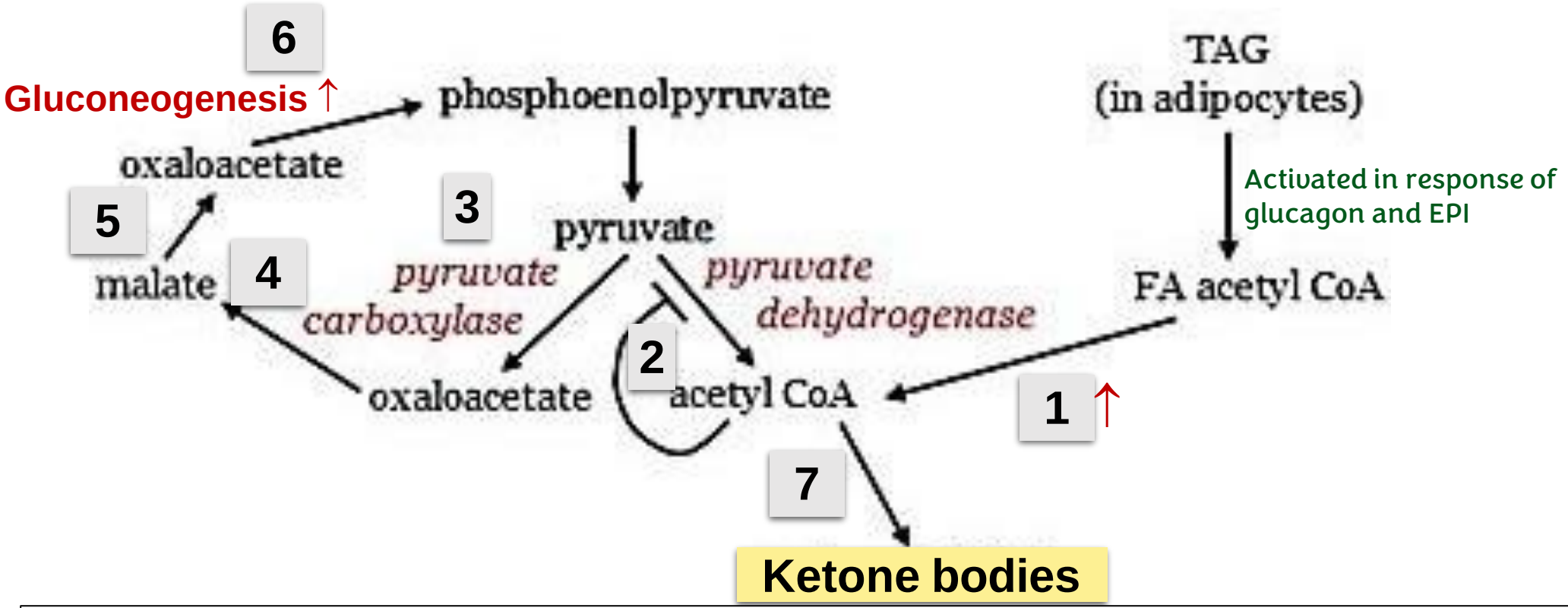
Use of Ketone Bodies by peripheral tissues:
Skeletal muscle, cardiac muscle and
in brain during prolonged fasting (starvation)

Elaboration of the illustration

1. Starting with **Acetyl-CoA** that comes from various pathways (mainly fatty acid oxidation, and from ketogenic A.A catabolism, glycolysis, etc.).
2. Going through the ketogenesis pathway, and eventually producing AcAc and 3HB.
3. ACAC or 3HB exit the liver to the **bloodstream**.
    - In blood stream, ACAC can get degraded into acetone.
4. Then they are reuptaken by the muscle cells/neurons.
5. The 3HB will be <u>oxidized</u> back to ACAC by **<u>3-hydroxybutyrate DH</u>** enzyme, accompanied with the reduction of NAD^+ to NADH.
6. ACAC **molecules** get converted by **thiophorase** to **acetoacytel CoA.**
7. Then, acetoacetyl-CoA will be cleaved to 2 Acetyl-CoA by **thiolase.**
8. Finally, the produced **Acetyl-CoA** can be used in the **muscle** as a source of **energy**.

3HB = 3-hydroxybutyrate
ACAC = Acetoacete

Under glucose-poor condition (fasting)



When cellular glucose is low, oxaloacetate is diverted into gluconeogenesis.

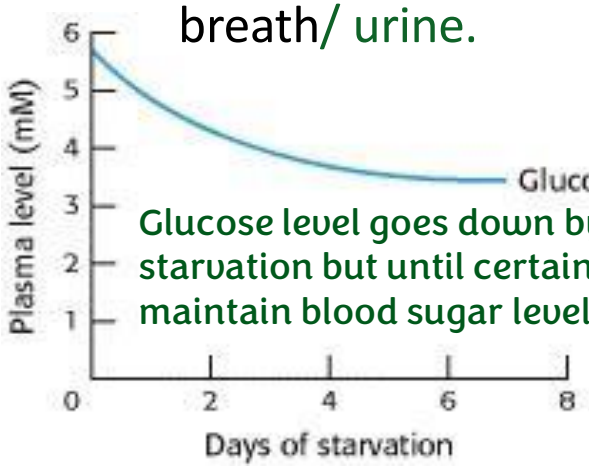
1. **Excess FA breakdown produces large amounts of acetyl CoA By beta oxidation mainly**
2. **Acetyl CoA inhibits pyruvate dehydrogenase.**
3. **Pyruvate is diverted toward oxaloacetate by pyruvate carboxylase,** toward gluconeogenesis.
4. **Oxaloacetate is converted to malate to exit the mitochondria ,**
5. **and then back to oxaloacetate in the cytosol**
6. **Gluconeogenesis is activated and oxaloacetate is depleted.**
7. **Acetyl CoA is diverted into ketogenesis**

Diabetic ketoacidosis

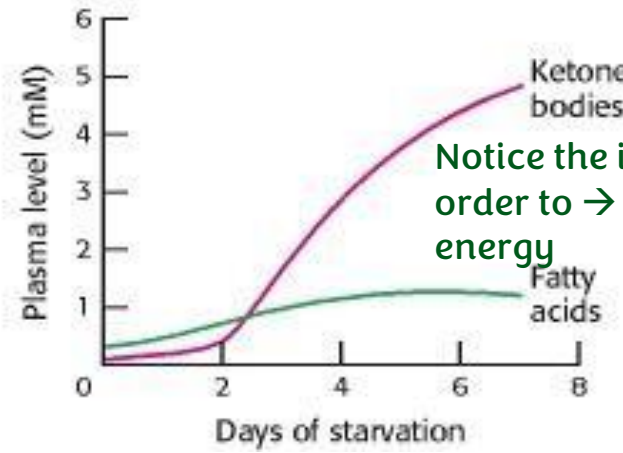
- Normally,
  - Levels of ketone bodies: <3 mg/dl
  - 3HB:AcAc is ~1:1 **3-hydoxybutyrate: acetoacetate**
- Under uncontrolled diabetes,
  - Levels of ketone bodies: 90 mg/dl and urinary excretion of ketone bodies may be 5,000 mg/24 hours. **This high level of ketone bodies in the urine is responsible for its bad smell.**

The level of ketone bodies may increase more than this due to:
1. undiagnosed cases.
2. Cases are not committed to treatment.

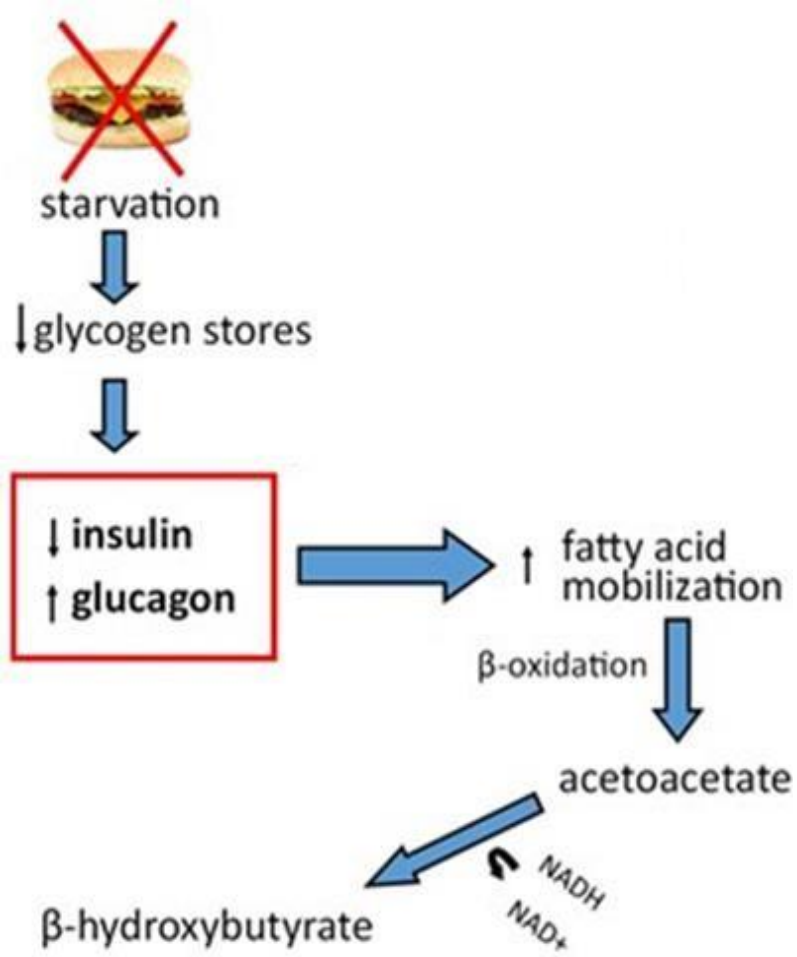
- The end-results:
  - Acidemia (ketoacidosis), dehydration**(because of the dragging of H2O molecules due to the high amount of sugar in the blood)** and fruity odor of breath/ urine.



Glucose level goes down by starvation but until certain limit maintain blood sugar levels

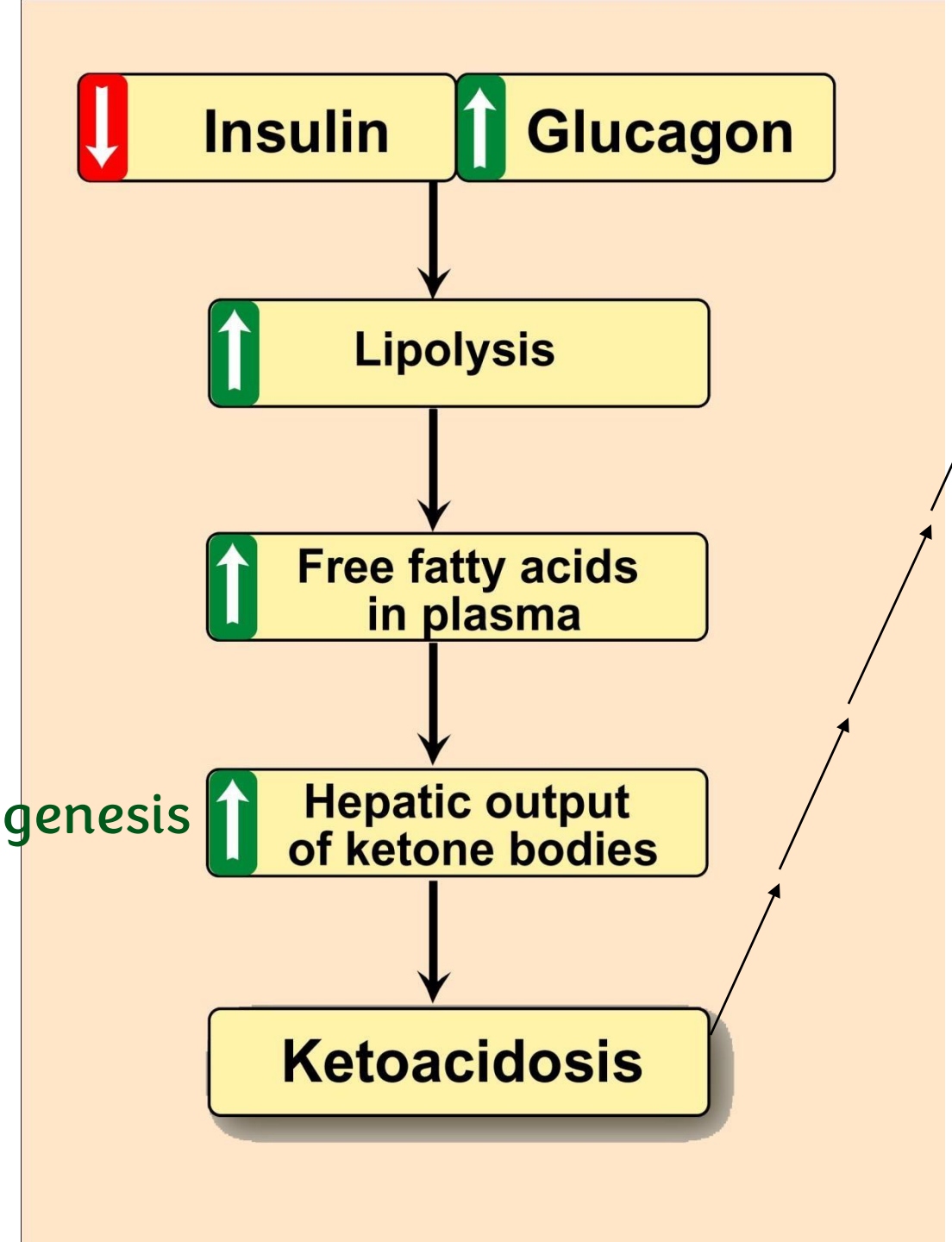


Notice the increase in order to → to produce energy



In uncontrolled diabetic patients, the glucose won't reach cells efficiently, so the cells will starve and activate the degradation of fatty acids by increasing glucagon and decreasing insulin which will produce more formation of ketone bodies resulting in diabetic ketoacidosis.

Diabetic ketoacidosis



Ketogenesis

Increase Excretion in Urine as

Sodium Salt

↓

Loss of water

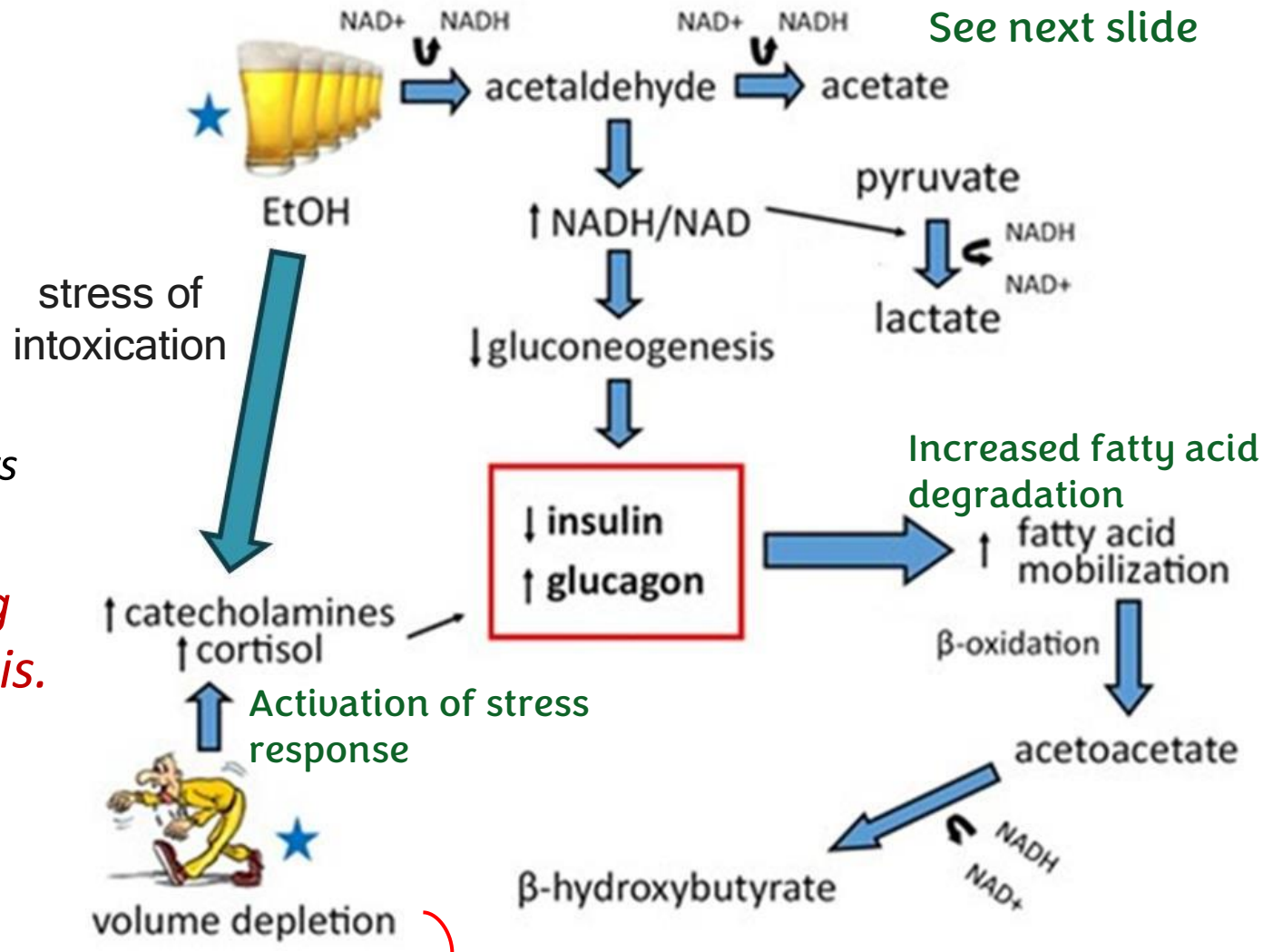
↓

Dehydration

and more frequent urination = polyuria

Alcoholic ketoacidosis caused by alcohol consumption

- Alcohol also causes,
  - Acidemia (ketoacidosis)
- But,
  - 3HB:Ac is ~3:1
    - *The ratio gets back to 1:1 after a few hours*
  - *Gluconeogenesis is suppressed.*
  - *Pyruvate is converted to lactate leading to hypovolemia, heart failure, and sepsis.*



Due to the dragging (loss) of H2O to the urine
this causes hypovolemia which may leads to heart failure and sepsis in these patients.

Explanation of the figure

- Alcoholic beverages will be metabolized in the hepatocytes, then oxidized to **acetaldehyde** by alcohol dehydrogenase and followed by another oxidation to form **acetate**.
- Acetaldehyde and acetate production, both enzymes that produce them **increase** the ratio between **NADH and NAD+** which leads to the **inhibition** of **gluconeogenesis** and other pathways that need more NAD+ than NADH; such as Krebs cycle so lactate will be produced rather than Acetyl-CoA production, as there's insufficient NAD^+ for the cycle to proceed.
- These changes (high NADH/NAD+, reduction of Gluconeogenesis level) would increase glucagon secretion, decrease insulin secretion and other stress hormones, thus **activating stress response** because of acetaldehyde toxicity.
- Activation of stress response, increases the production of both catecholamines and cortisol.
- Eventually, there would be an increase in FAs degradation, thus production of ketone bodies that may get secreted in urine.

For any feedback, scan the code or click on

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1	2 9 9	No quiz In blood stream, ACAC can get degraded into acetate. accompanied with the reduction of NADH to NAD^+ .	Added quiz In blood stream, ACAC can get degraded into acetone. accompanied with the reduction of NAD^+ to NADH.
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي: