Assist. Prof. Dr. Shakir .F. Tuleab
Ph. D. Biochemistry
University of Anbar
College Of Education For Pure Sciences
Chemistry department

KETONE BODIES METABOLISM

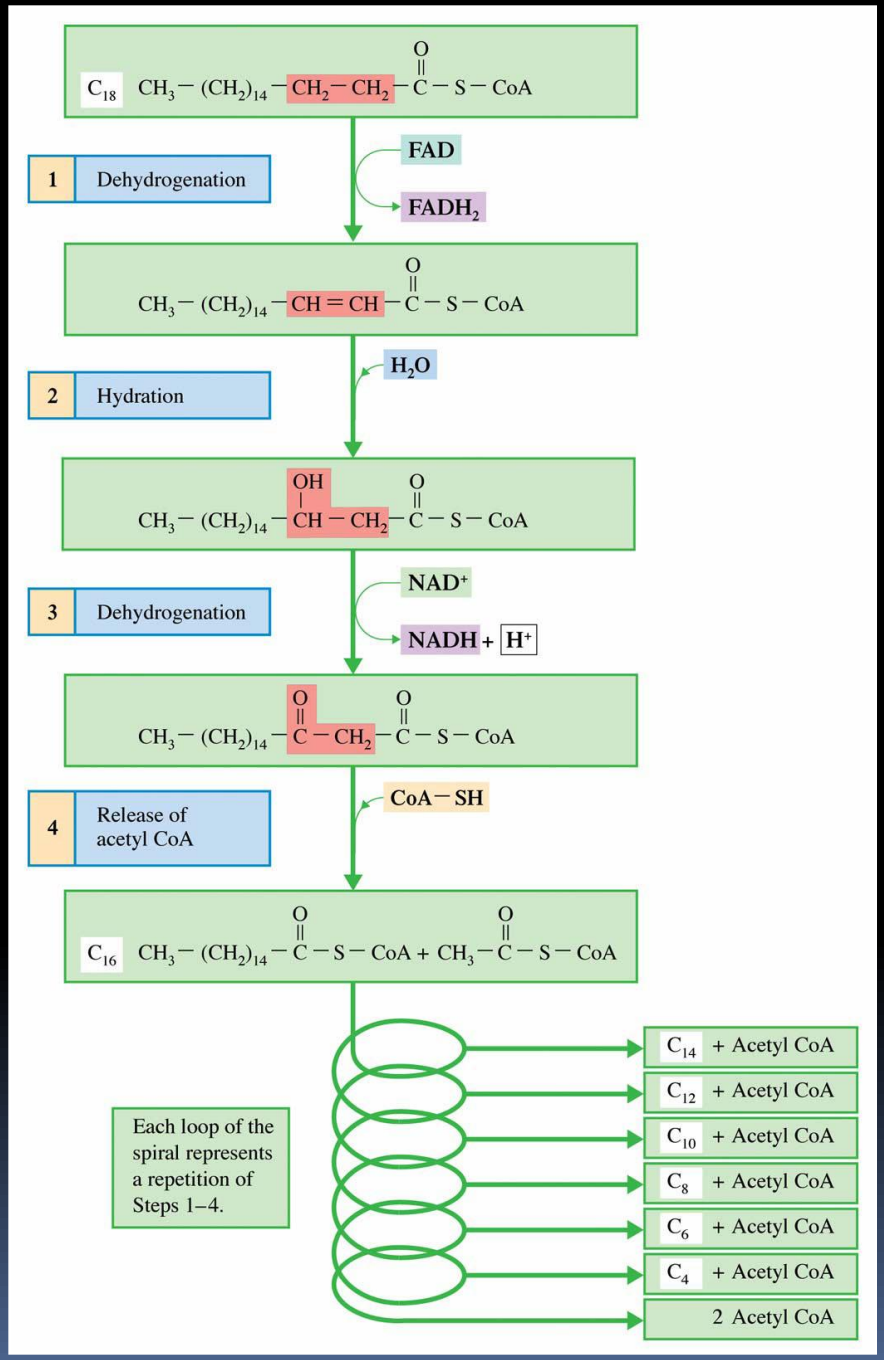
Fatty acid oxidation

3 steps to break down fatty acids to make energy

1. Fatty acid must be **activated**: bond to coenzyme A
2. Fatty acid must be **transported** into mitochondrial matrix: uses a shuttle mechanism
3. Fatty acid repeatedly **oxidized**, cycling thru 4 reactions: produces Acetyl CoA, $FADH_2$, & NADH

Reactions of the fatty acid spiral for an 18:0 fatty acid (stearic acid).

Repeats as a **spiral** because each section becomes shorter by 2 carbons



Fatty acid activation

[redacted]

Summary of fatty acid activation:

fatty acid + ATP → acyl-adenylate + PP_i

PP_i → 2 P_i

acyladenylate + HS-CoA → **acyl-CoA** + AMP

Thiokinase

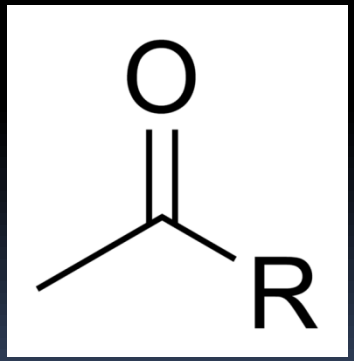
Overall:

fatty acid + ATP + **HS-CoA** → **acyl-CoA** + AMP + 2 P_i

The longer chain F.A.s cannot diffuse across mitochondrial membrane - must be transported.
Uses a carrier protein:
carnitine (derivative of amino acid lysine)

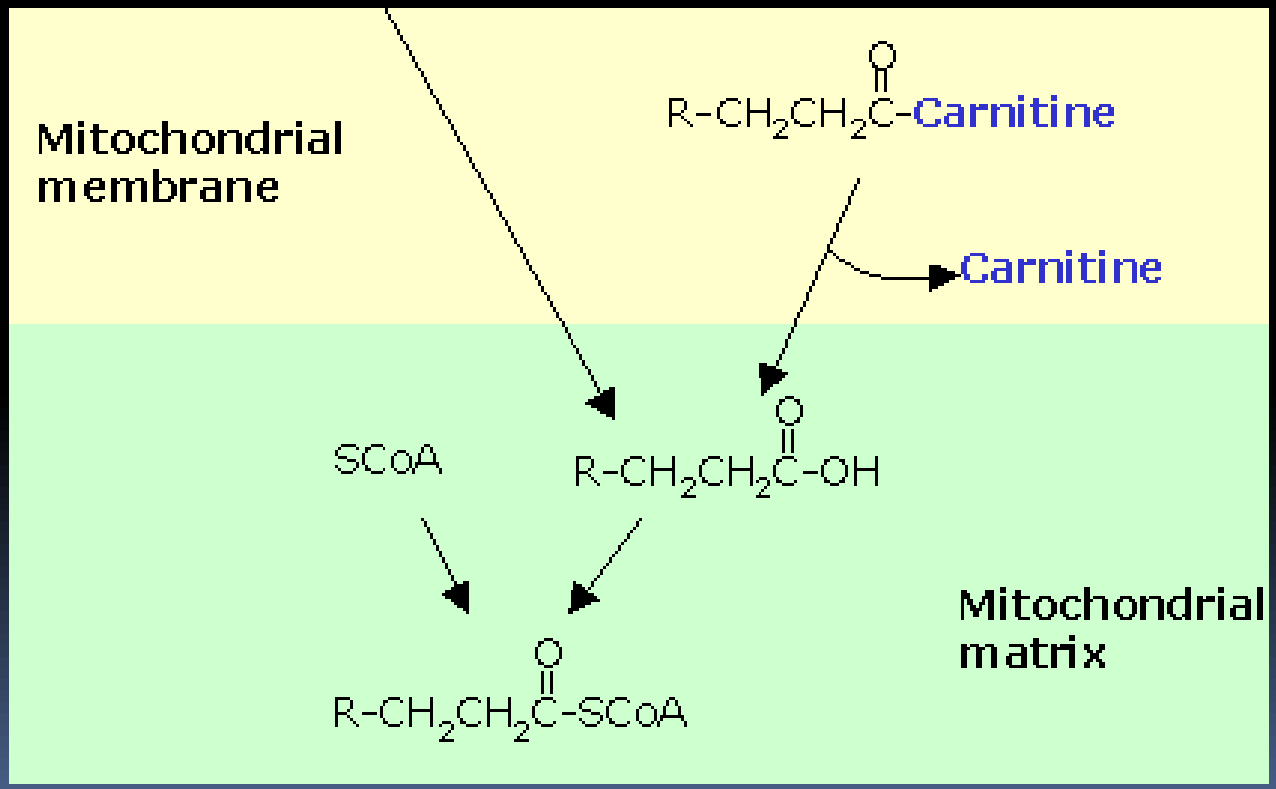
Found in red meats & dairy products,
can also be synthesized by the body.

Reminder: an **acyl group** is derived from a carboxylic acid (like a fatty acid) with its –OH group removed

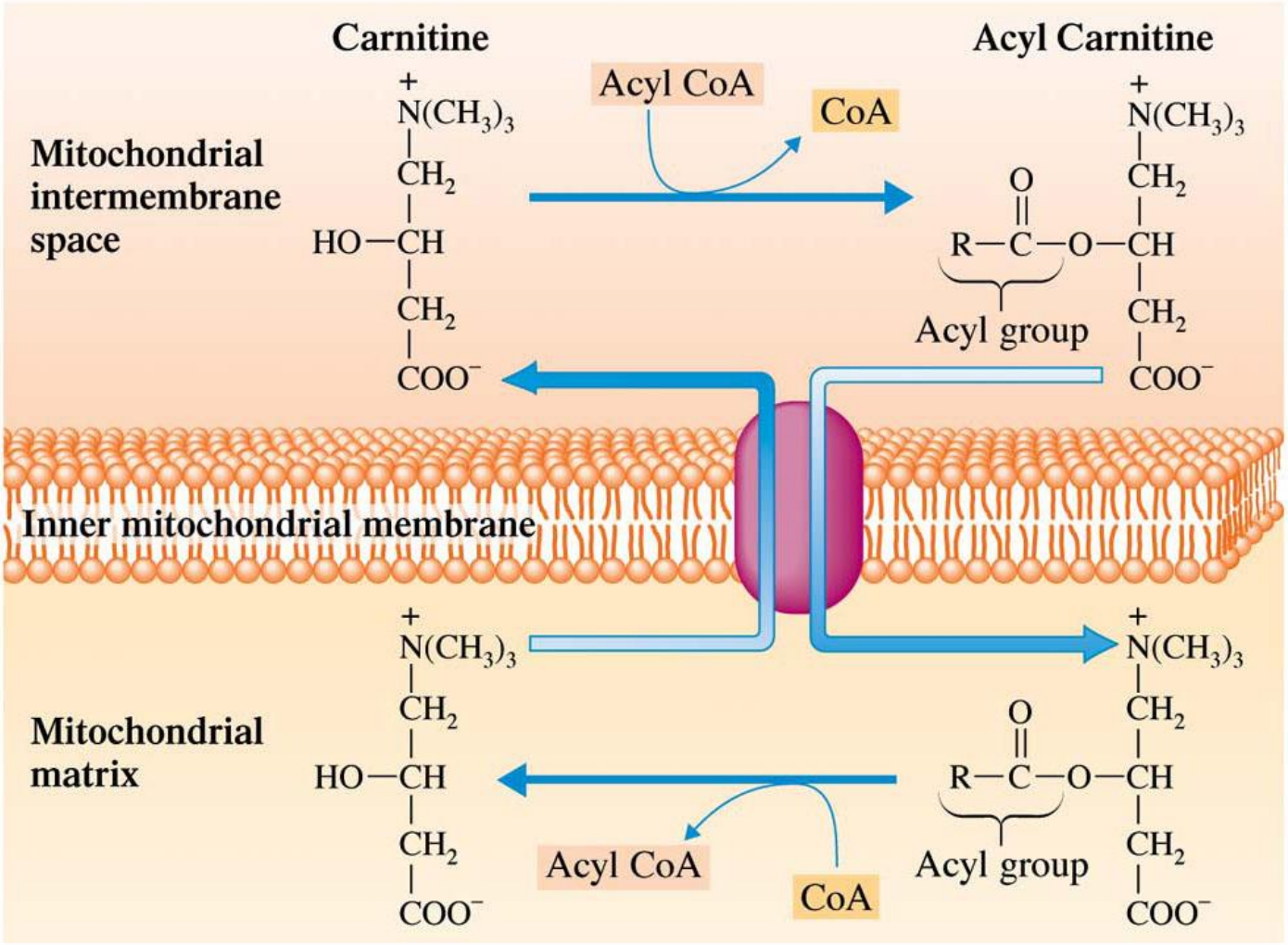


Long chain fatty acids

Short chain fatty acids



Long chain fatty acids are transported across the inner mitochondrial membrane in the form of **acyl carnitine**.



People with low **carnitine** levels often have lipid deposition in the muscles, become irritable & weak. Severe disorders can be fatal!

Companies selling nutritional products promote **carnitine** as an important dietary supplement.

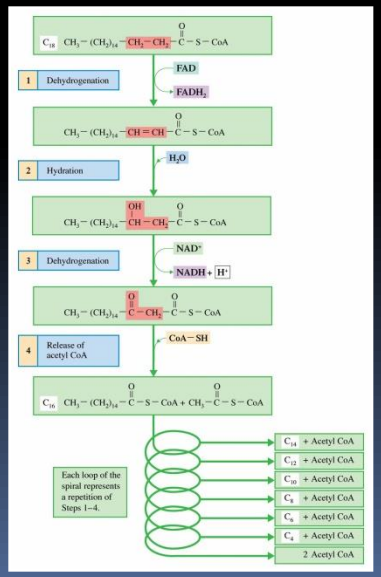
ATP production from Fatty Acid Oxidation

How does energy output compare to glucose oxidation?

All turns (except last) of the F.A. spiral make:
one NADH & one $FADH_2$

One Acetyl CoA forms at each turn,
& two Acetyl CoA form at last step.

These are processed in Krebs cycle, E.T.C. and oxidative phosphorylation.



ATP production from Fatty Acid Oxidation

An 18C **stearic** fatty acid will create:

9 acetyl CoA, which form **90 ATP**

8 FADH2 which form **12 ATP**

& 8 NADH which form **20 ATP**

Total = 122 ATP (-2 ATP for F.A. activation)

=**120 ATP!**

An 18C **stearic** fatty acid will create = **120 ATP**

1 Glucose will = 32 ATP
1 Stearic acid will = 120 ATP

3x 6C Glucose = 18 Carbons
32 ATP x 3 =**96 ATP**
Lipids are **25% more efficient** at energy storage!

In terms of energy from food:

Fatty acids yield > 2x the energy per gram.

1 gram of carbohydrates = **4 kcal** (food calories)

1 gram of fat = **9 kcal** of energy

Which fuel is the most commonly used?

Skeletal muscles ***at rest*** use **fatty acids**;

Active skeletal muscles use **glucose**

Cardiac muscles: 1st fatty acids,
then Ketone bodies, glucose, & lactate.

Liver prefers to use fatty acids

Brain only uses glucose & ketone bodies

Ketone Bodies

Usually lipid and carb metabolism are balanced.
Acetyl CoA from FA spiral processed in Krebs cycle.
Hooks to **oxaloacetate** to make citrate.

Oxaloacetate forms from **pyruvate**
The product of **glycolysis**.

Conversion to oxaloacetate uses
pyruvate carboxylase enzyme.

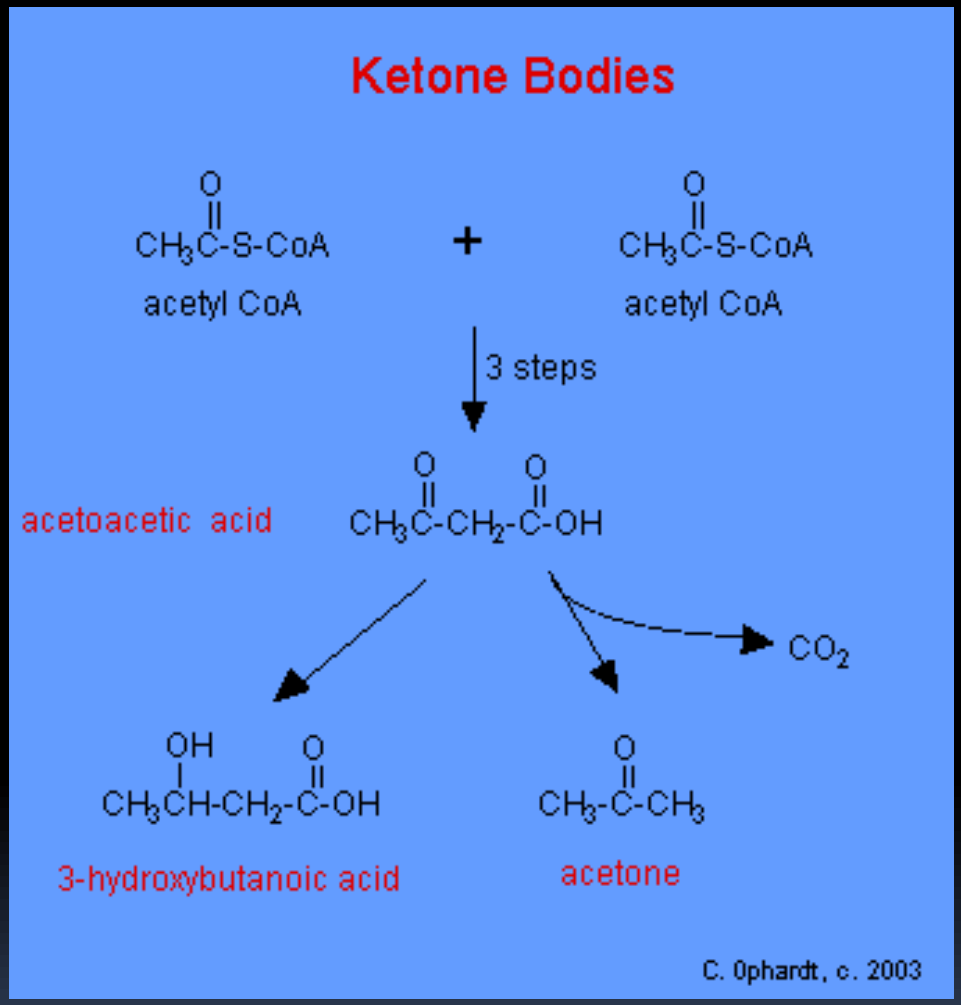
What upsets the lipid / carbohydrate balance?

What upsets the lipid / carbohydrate balance?

1. Diet: High fat / Low carbohydrates
2. Diabetes: body cannot process glucose properly
3. Long-term fasting: starvation, crash diets, etc.

- Inadequate amount of **oxaloacetate** forms.
- **Oxaloacetate** already present is used in **gluconeogenesis** to make **glucose**.
- **Acetyl CoA** cannot be processed in Krebs cycle!
- Excess **Acetyl CoA** makes **ketone bodies**.

3 Ketone Bodies:



Two 4 carbon chain acids & a 3 carbon ketone

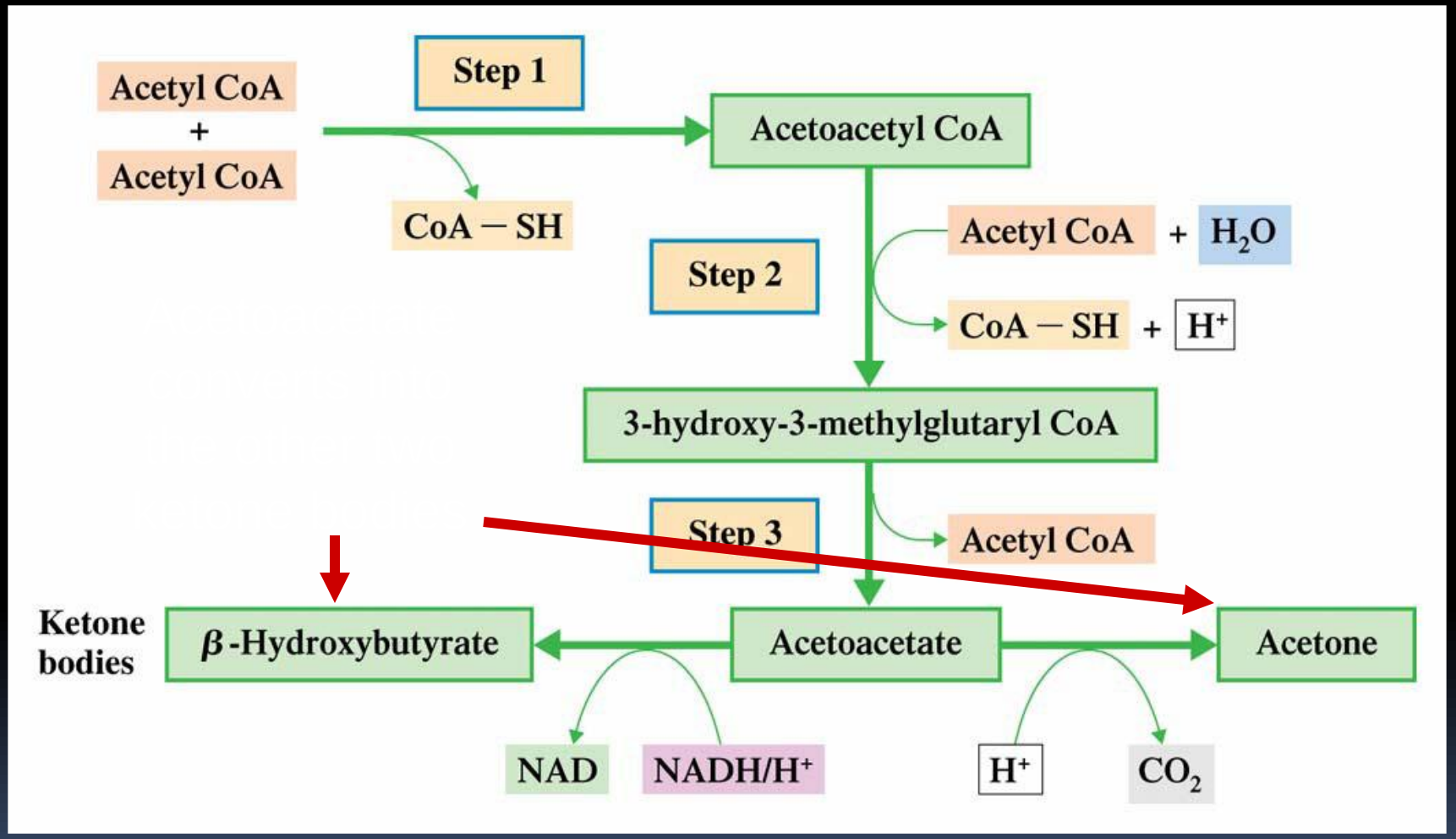
Inadequate amount of **oxaloacetate** in turn increases release of ketone bodies from liver for use as fuel by other tissues. Early stages of starvation, when last remnants of fat are oxidized, heart & skeletal muscles will consume **ketone bodies** preserving glucose for the **brain**.

β-Ketothiolase.
condensing 2 acetyl-CoA
→ acetoacetyl-CoA

HMG-CoA Synthase
Condensation forms
hydroxymethylglutaryl-CoA

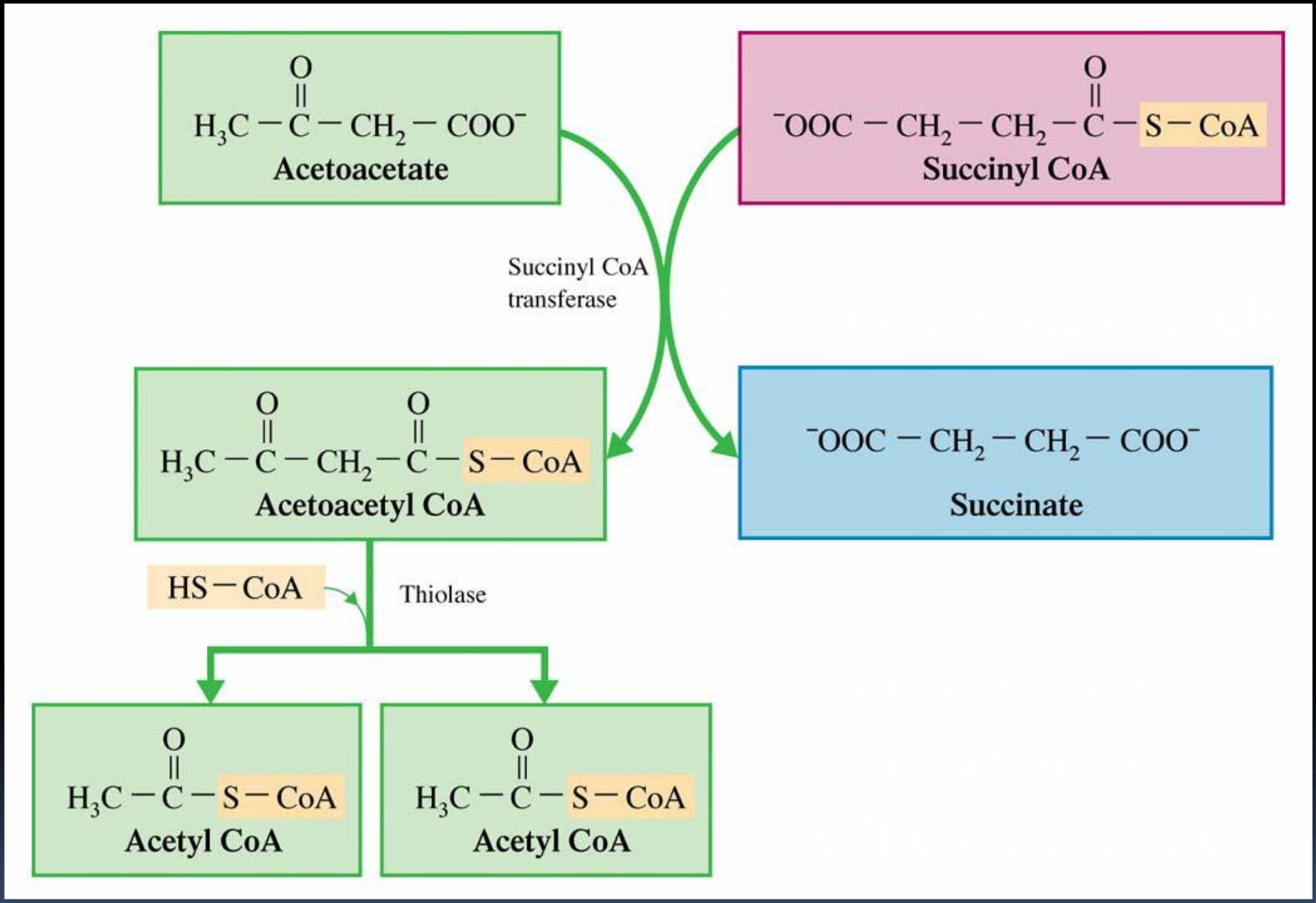
HMG-CoA Lyase
splits HMG-CoA →
acetoacetate +
acetyl-CoA.

Ketogenesis involves the production of ketone bodies from acetyl CoA.



2 acetyl CoA + H_2O → acetoacetate + 2 CoA + H^+

The pathway using acetoacetate as a fuel.



Acetoacetate: Water soluble transportable acetyl CoA

The significance of Ketone Body formation:

Overall accumulation in urine and blood = ***ketosis***

Elevated ketone body formation:
50 – 100x higher
>20 mg/100mL = **ketonemia**
>70 mg/100 mL flushes out of kidneys
and excreted into the urine = ***ketonuria***

The sweet smell of acetone is on the breath

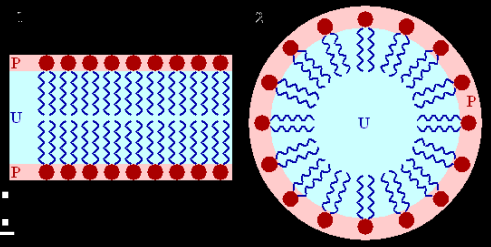
Two ketone bodies are **acids**.
Blood can become acidified = ***keto* acidosis**

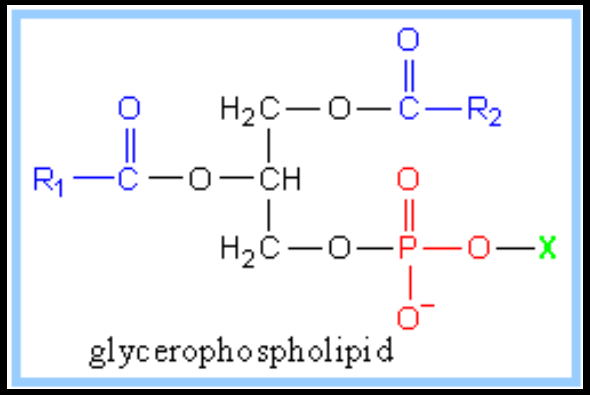
Lipogenesis

Metabolic pathway for the
synthesis of fatty acids
from acetyl-CoA

Occurs any time that dietary nutrients
exceed what the body needs
for **energy** requirements

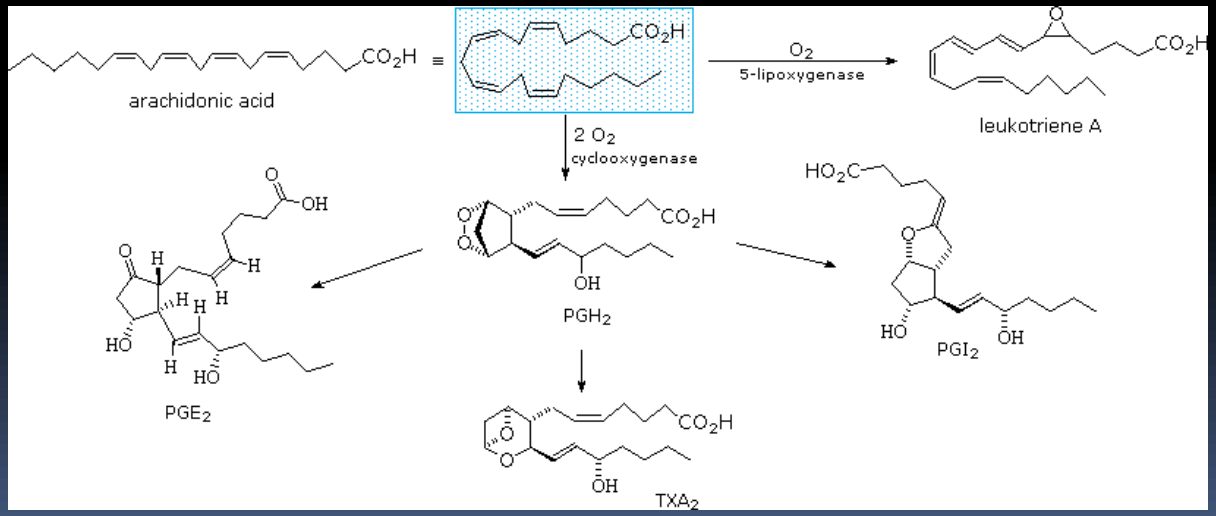
Fatty acids are ***intermediates*** in the synthesis of other important compounds.

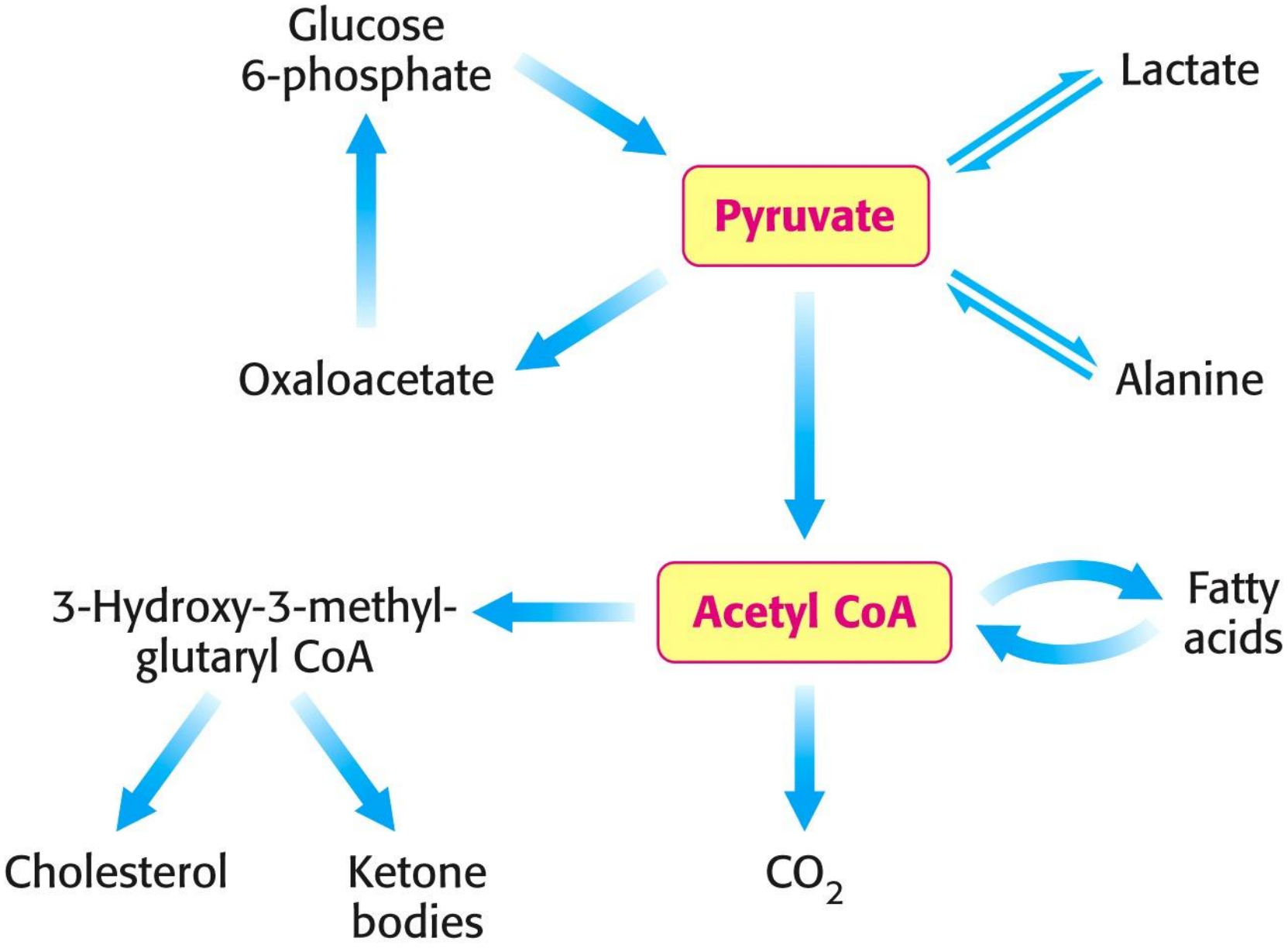




Examples include:

- Phospholipids (in membranes)
- Eicosanoids, including prostaglandins & leucotrienes



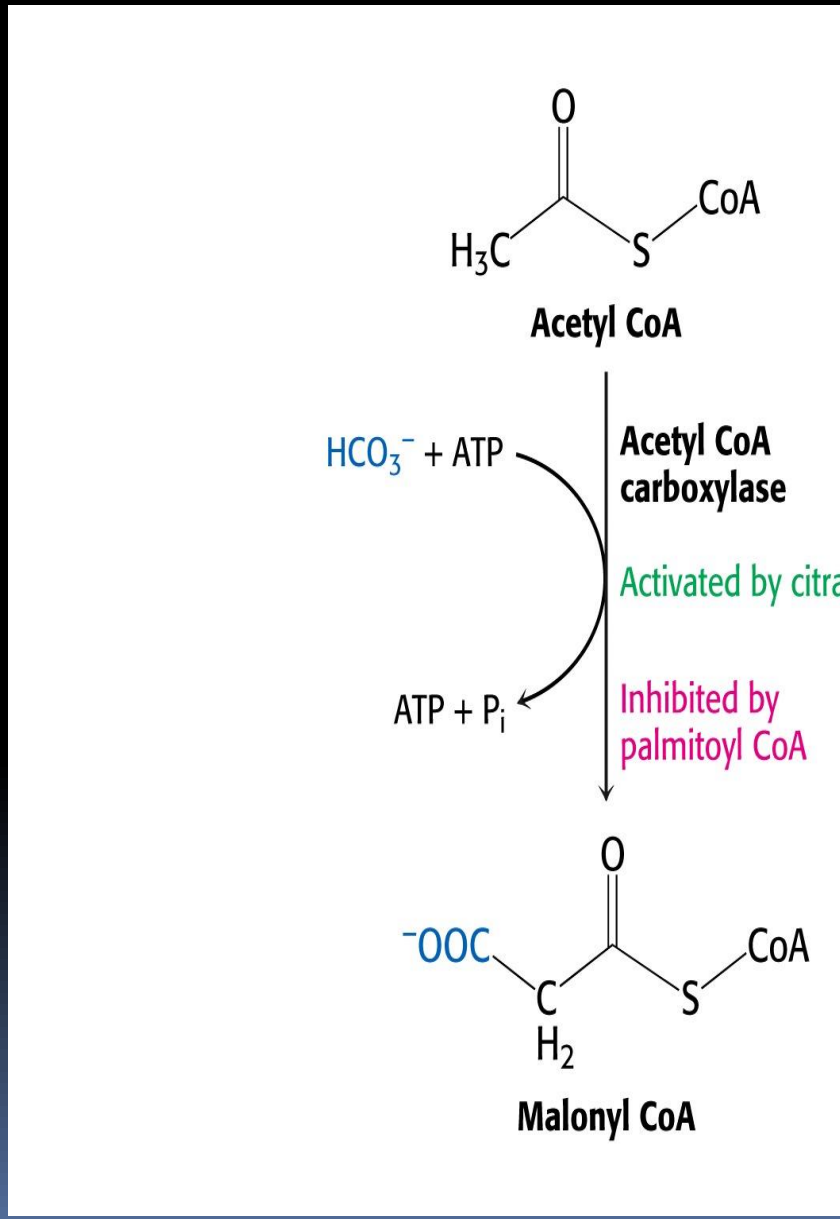

Glucose
6-phosphate
Lactate
Pyruvate
Oxaloacetate
Alanine
Acetyl CoA
3-Hydroxy-3-methyl-
glutaryl CoA
Fatty
acids
Cholesterol
Ketone
bodies
CO_2

Fatty acid Synthesis

Occurs in cytosol.

Acetyl CoA carboxylase catalyzes the 1st committed step.

This step is stimulated by citrate which increases when ATP and acetyl CoA are abundant

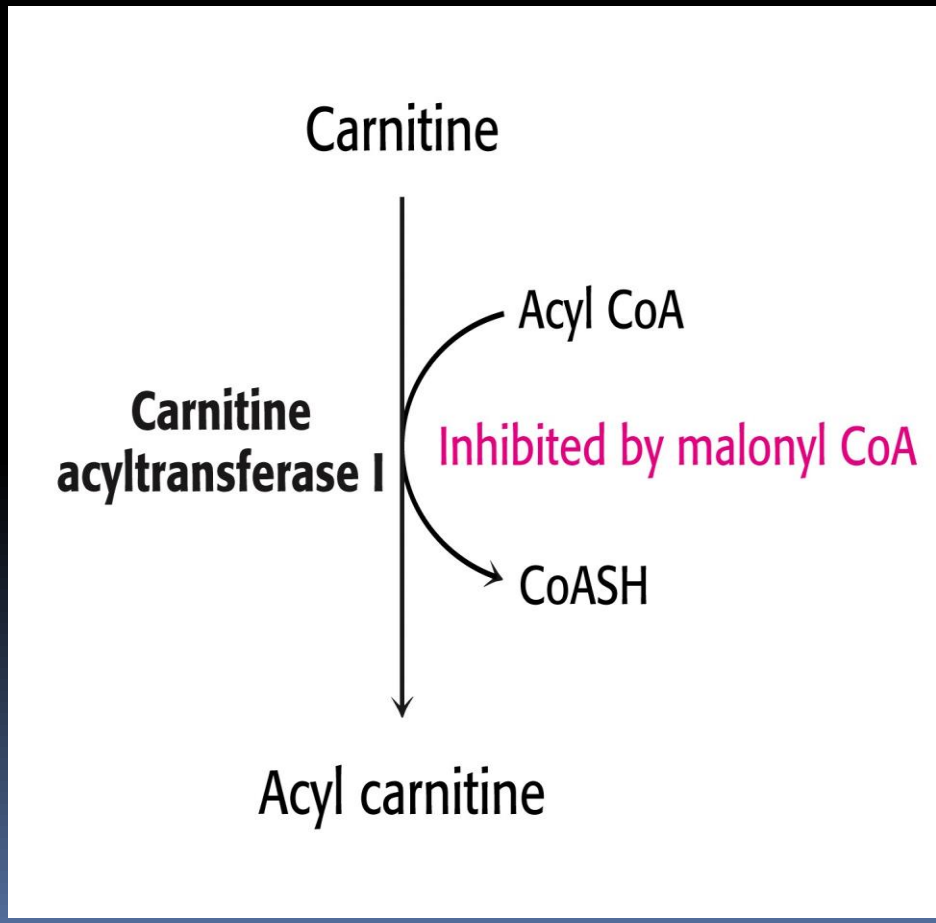


Fatty acid Degradation

Occurs in the mitochondria where fatty acids are degraded to acetyl CoA which then enter the citric acid cycle if the supply of oxaloacetate is adequate. Ketone bodies form if oxaloacetate levels are low.

Carnitine transports the fatty acids into the mitochondria.

Like the citric acid cycle, β-oxidation can continue only if NAD^+ and FAD are regenerated. So, the rate of fatty acid degradation is also coupled to the need for ATP

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attention