Fatty Acid Oxidation Disorders 101

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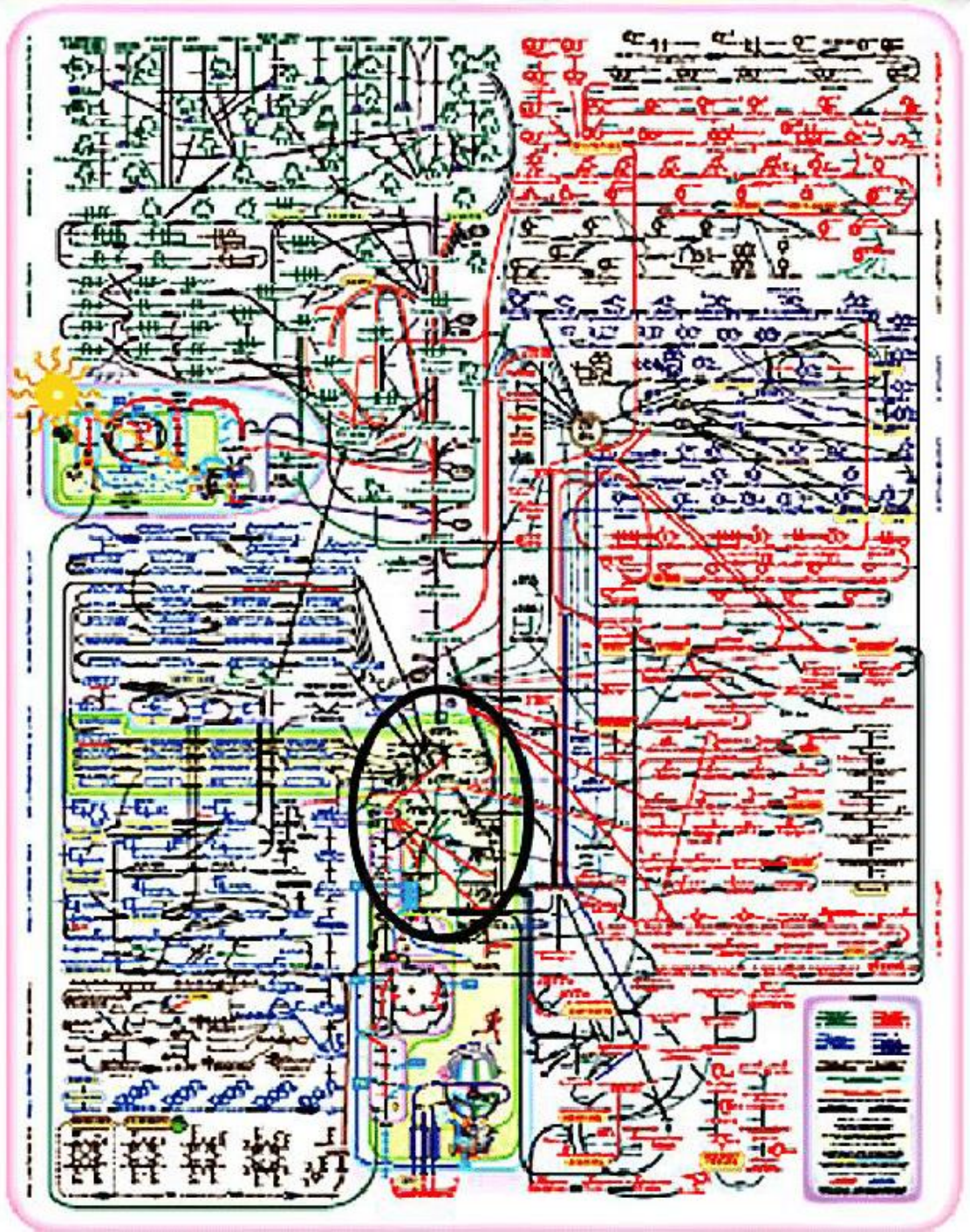
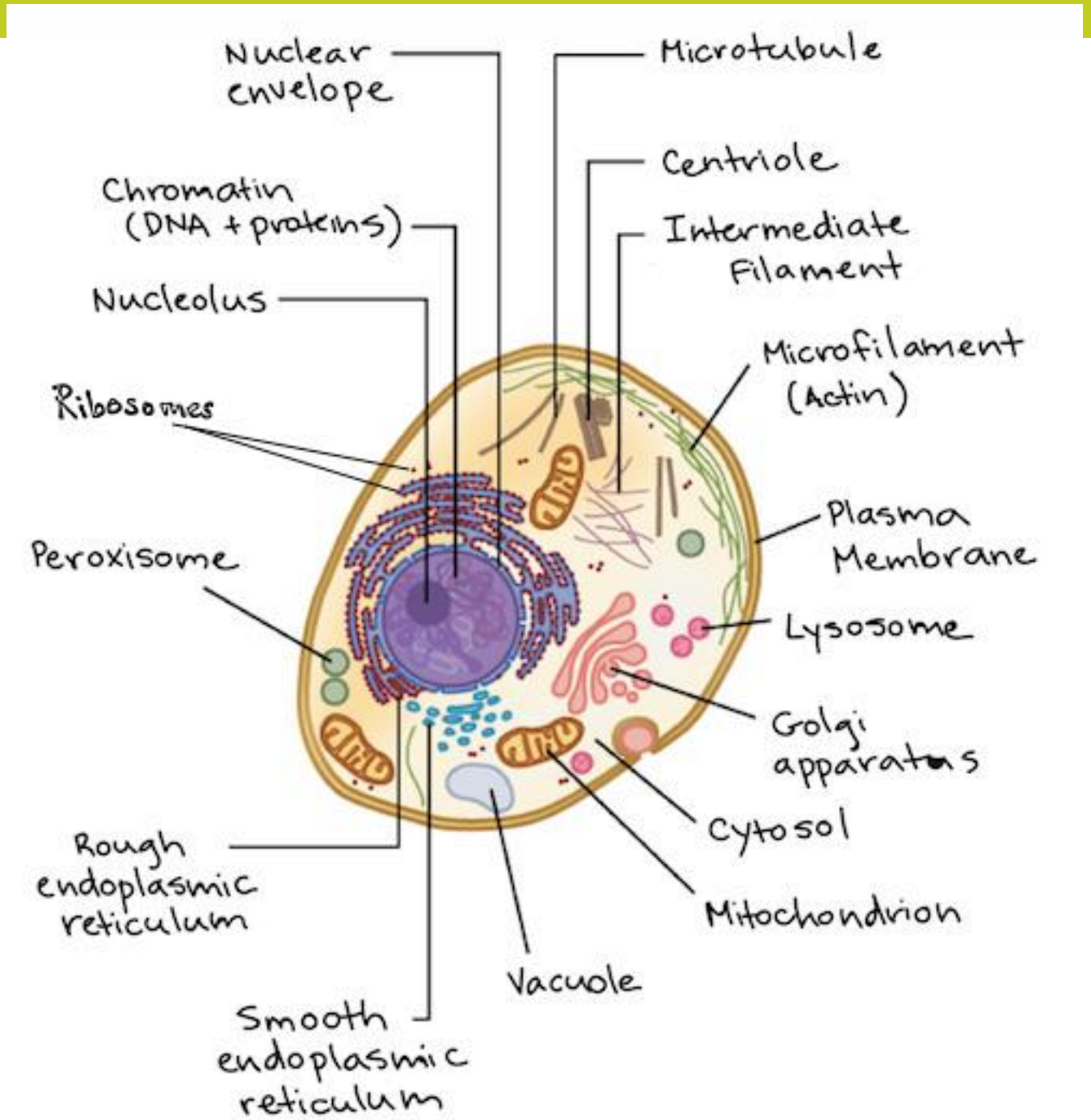



LOST
CONFUSED
UNSURE
UNCLEAR
PERPLEXED
DISORIENTED
BEWILDERED


Don't Look Back
... You're Not
Going That Way


Nuclear envelope
Microtubule
Centriole
Chromatin (DNA + proteins)
Intermediate Filament
Nucleolus
Microfilament (Actin)
Ribosomes
Plasma Membrane
Peroxisome
Lysosome
Golgi apparatus
Cytosol
Rough endoplasmic reticulum
Mitochondrion
Vacuole
Smooth endoplasmic reticulum

What is Fat?

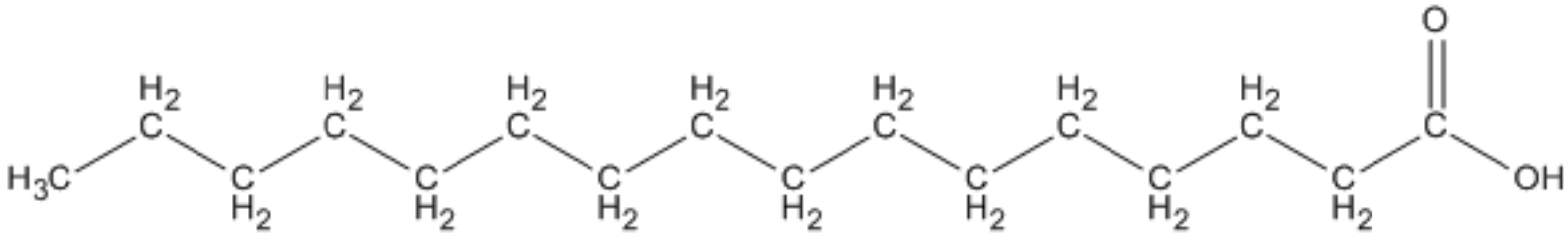
- Fat is the most efficient energy source in the body
- Fat is made up of chains of carbons and hydrogens
  - Hydrocarbon
- Short chain fats have 4-6 carbons (mostly made from oxidation of longer chain FA or gut fermentation)
- Medium chain fats have 6-10 carbons (made from oxidation of longer chain FA, also coconut oil, palm oil, MCT)
- Long chain fats have 12-18 carbons (oils, fatty meat, nuts, etc)

What is Fat?

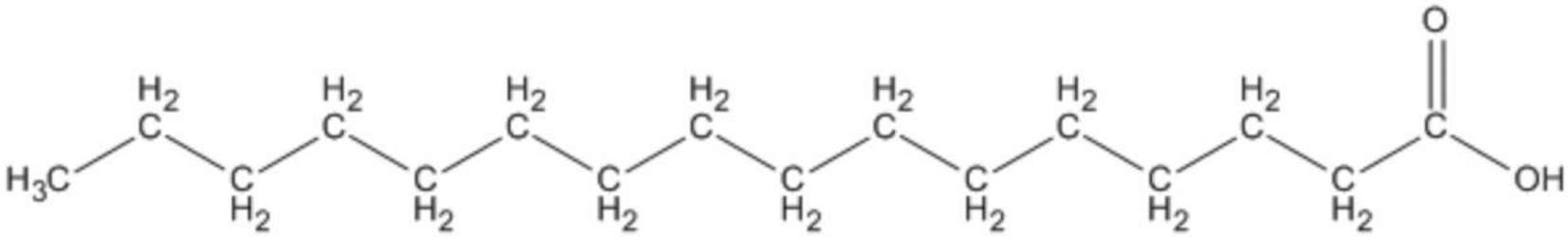
- Fat is oxidized (burned to make energy) in the liver
- Each cycle of fat oxidation takes off 2 carbons that are burned for energy or turned into a ketone and exported out to be burned for energy in another organ
- The energy from fat metabolism is used to make glucose

- So, fatty acid oxidation disorders tend to present during fasting, with inadequate ketone formation (hypoketosis) and hypoglycemia
- Ketones are the preferred fuel for the heart

A Picture is Worth a Thousand Words

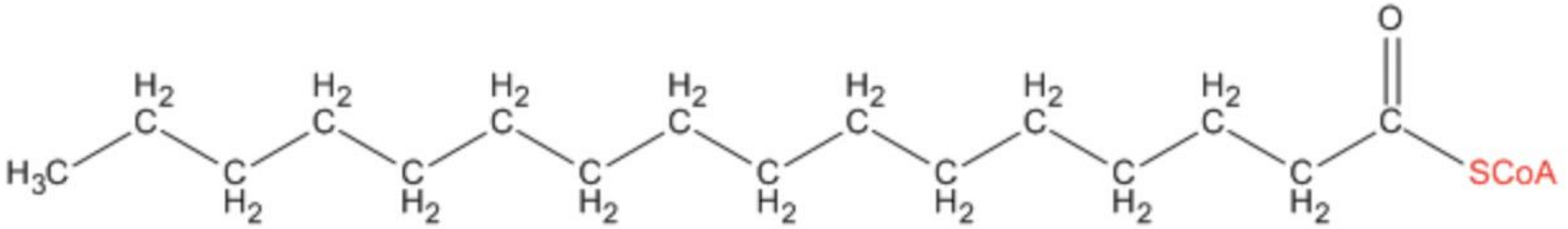


First, the fat has to be activated (by the addition of CoA (Coenzyme A)



A fatty acid is chemically not very reactive.

The enzym fatty acyl-CoA synthetase associates a Coenzyme A to the fatty acid.



(“activated fatty acid)

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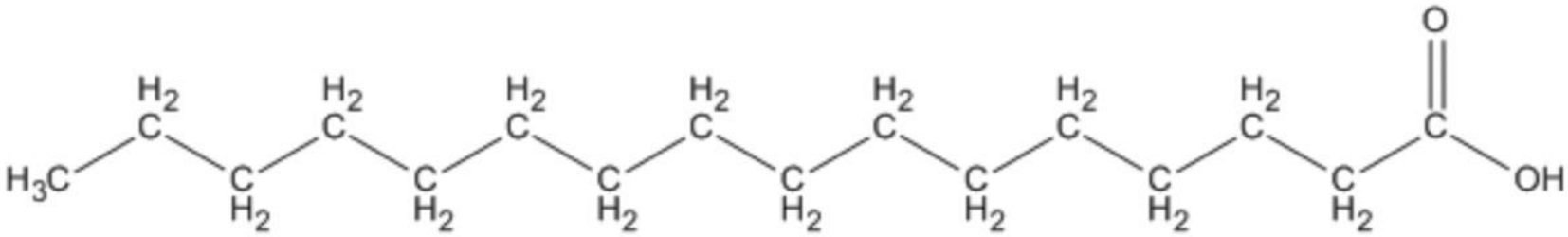

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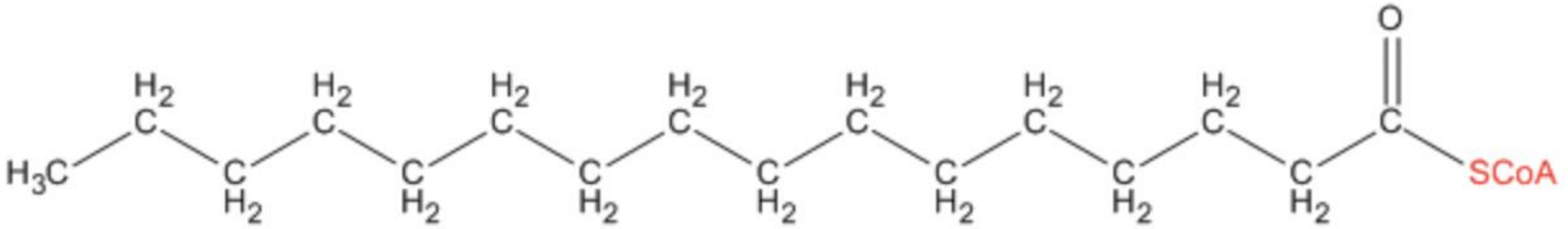

Acyl CoA

("activated fatty acid)

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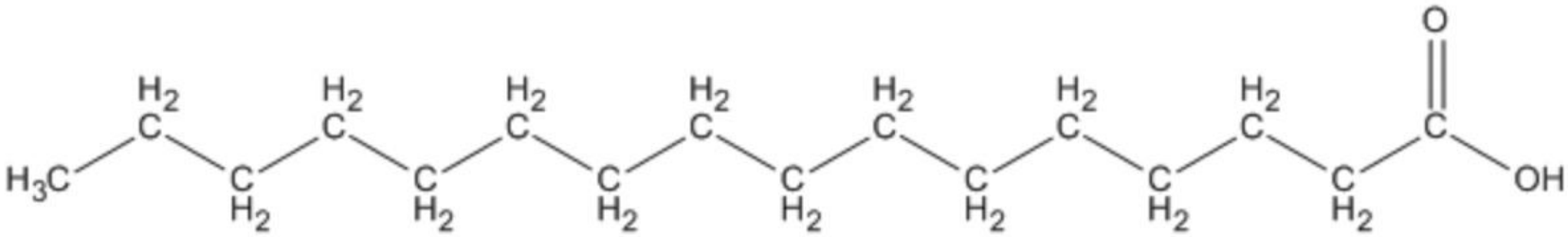

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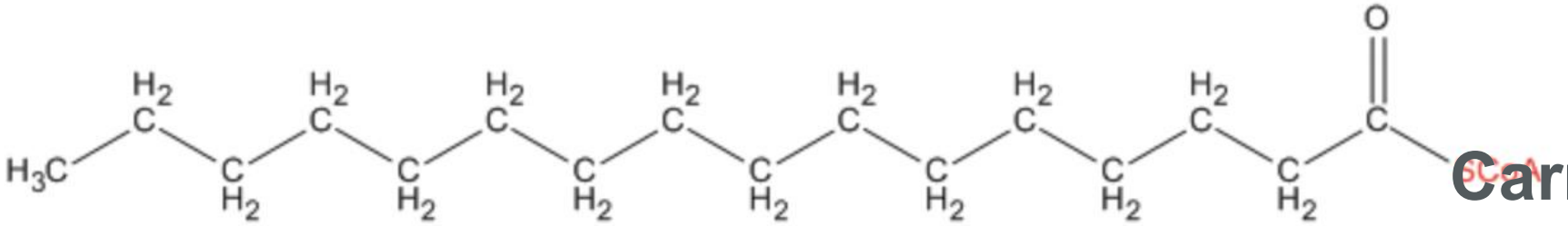
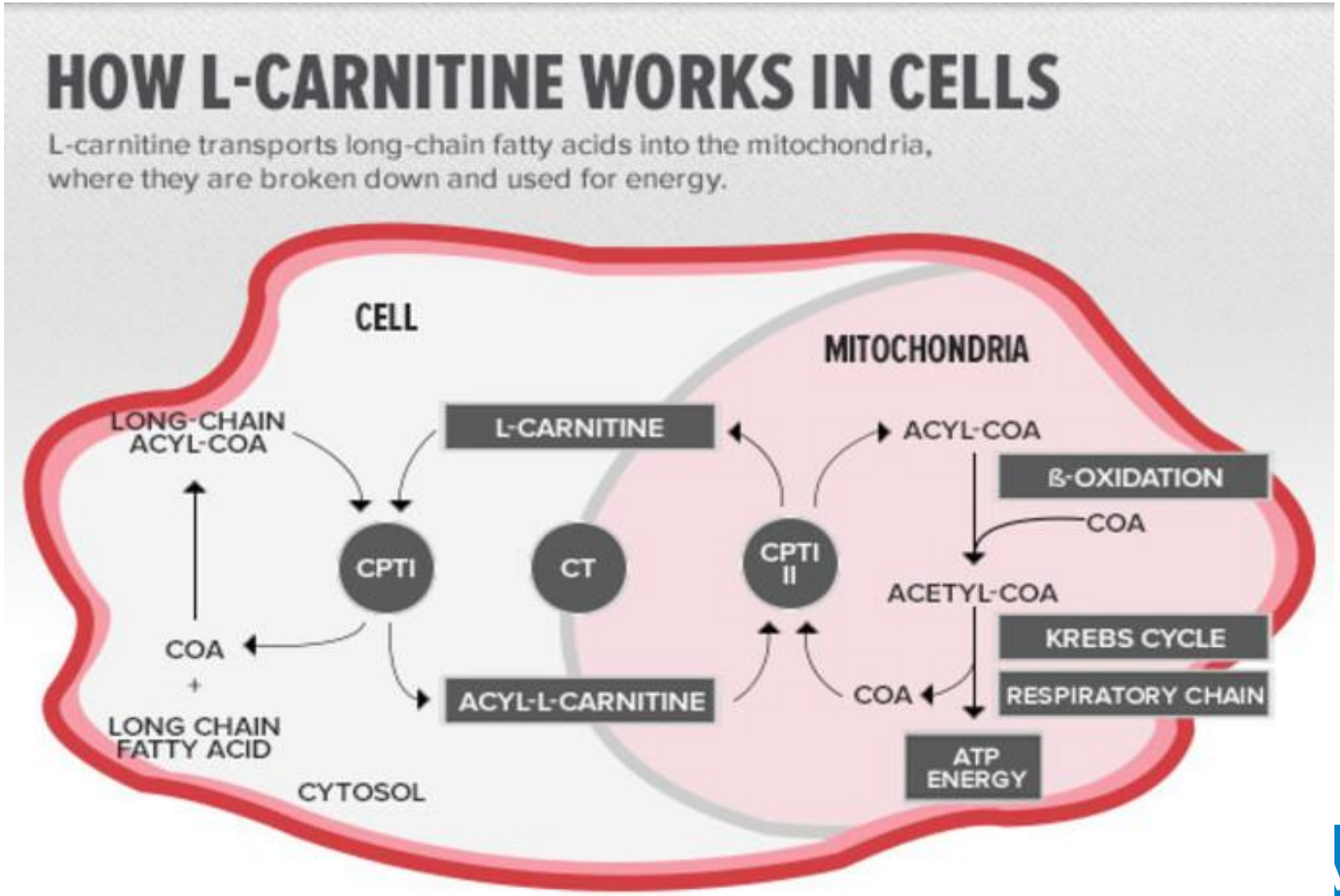


Carnitine

Acyl Carnitine

("activated fatty acid)

Long Chain Fat can't get into the mitochondria by itself – it has to first be attached to Carnitine



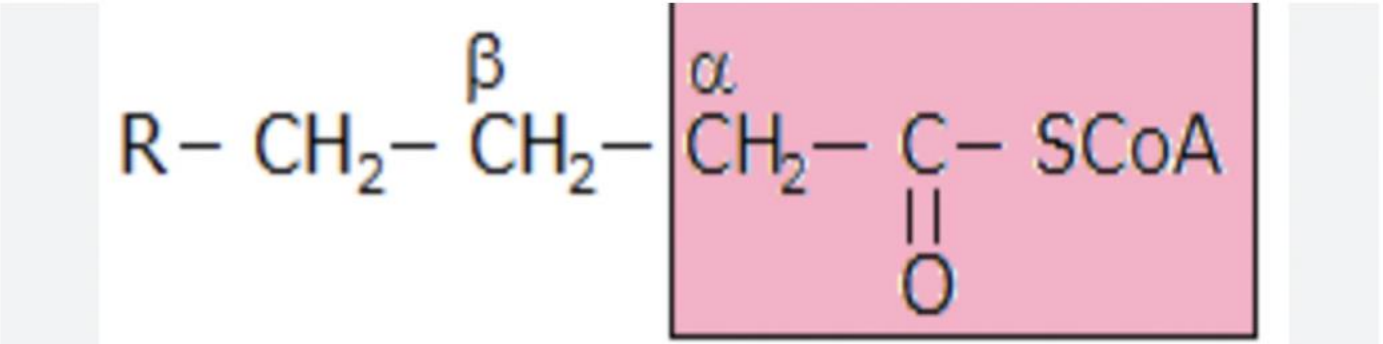
Carnitine Cycle FAOD

- **CPT1 deficiency (can't attach carnitine to the fat)**
- **CACT (translocase) deficiency – (can't pass the fat/carnitine compound (acylcarnitine) into the mitochondria)**
- **CPT II deficiency – (can't release the carnitine from the fat)**

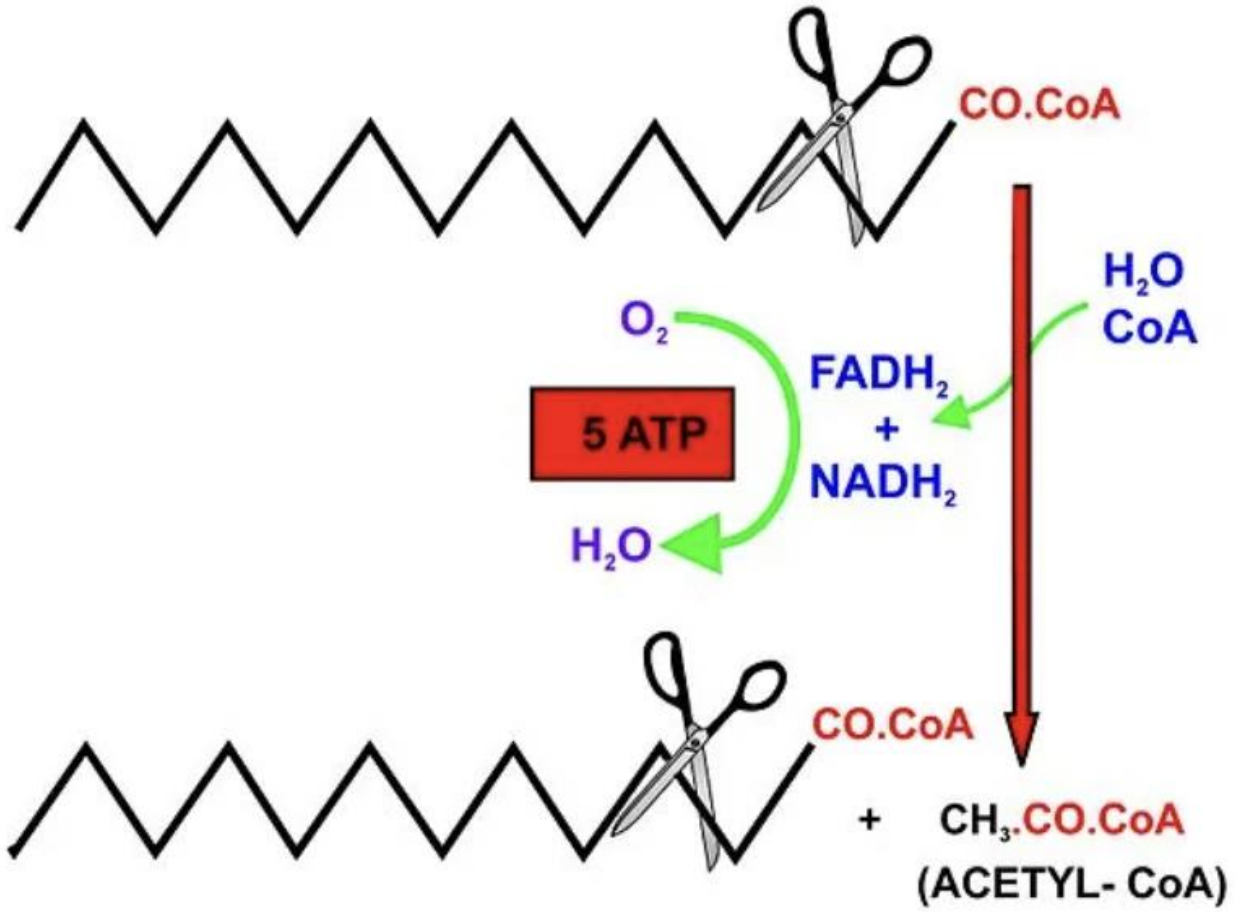
Carnitine Cycle Defects

- Share features with long chain FAOD
- Mild to Severe
- Fasting intolerance, Exercise intolerance, hypoketotic hypoglycemia
- Failure of high energy requiring organs, heart, liver, kidney

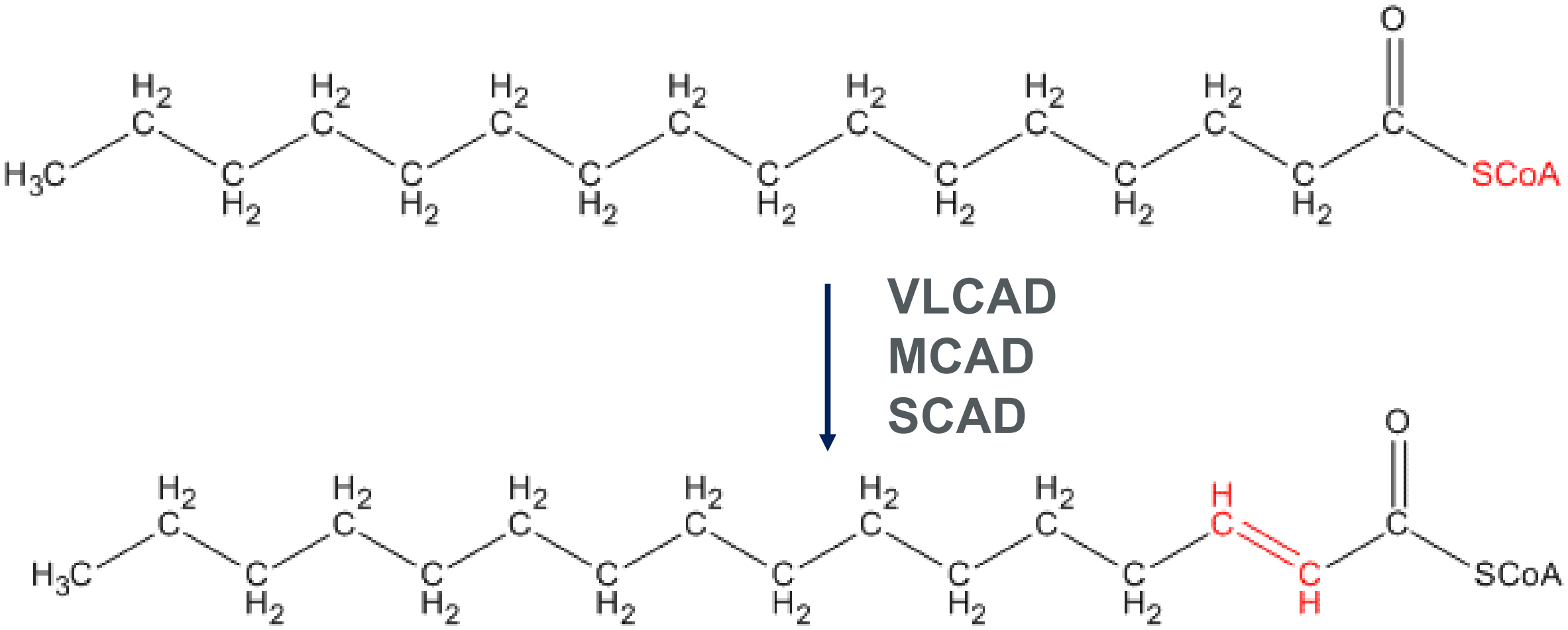
What is beta-oxidation?



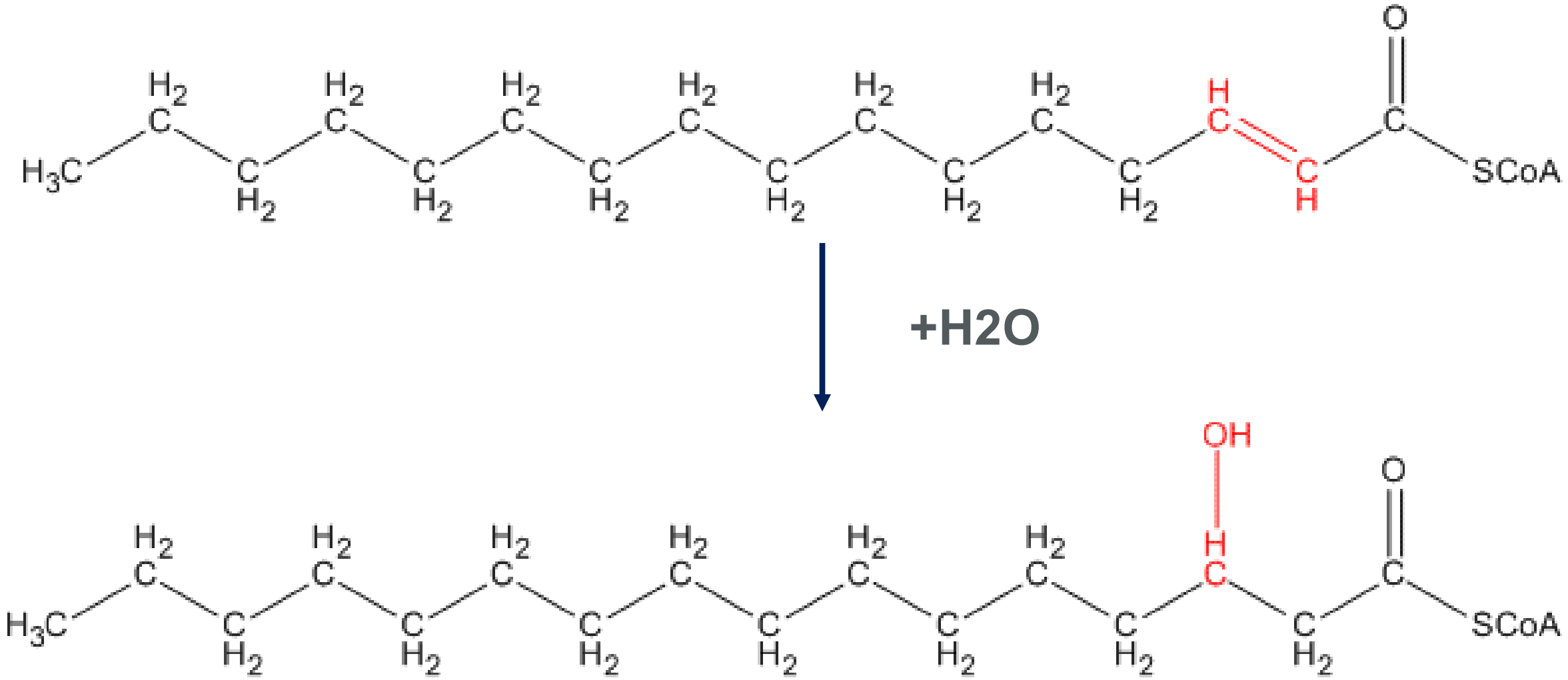
Beta-oxidation



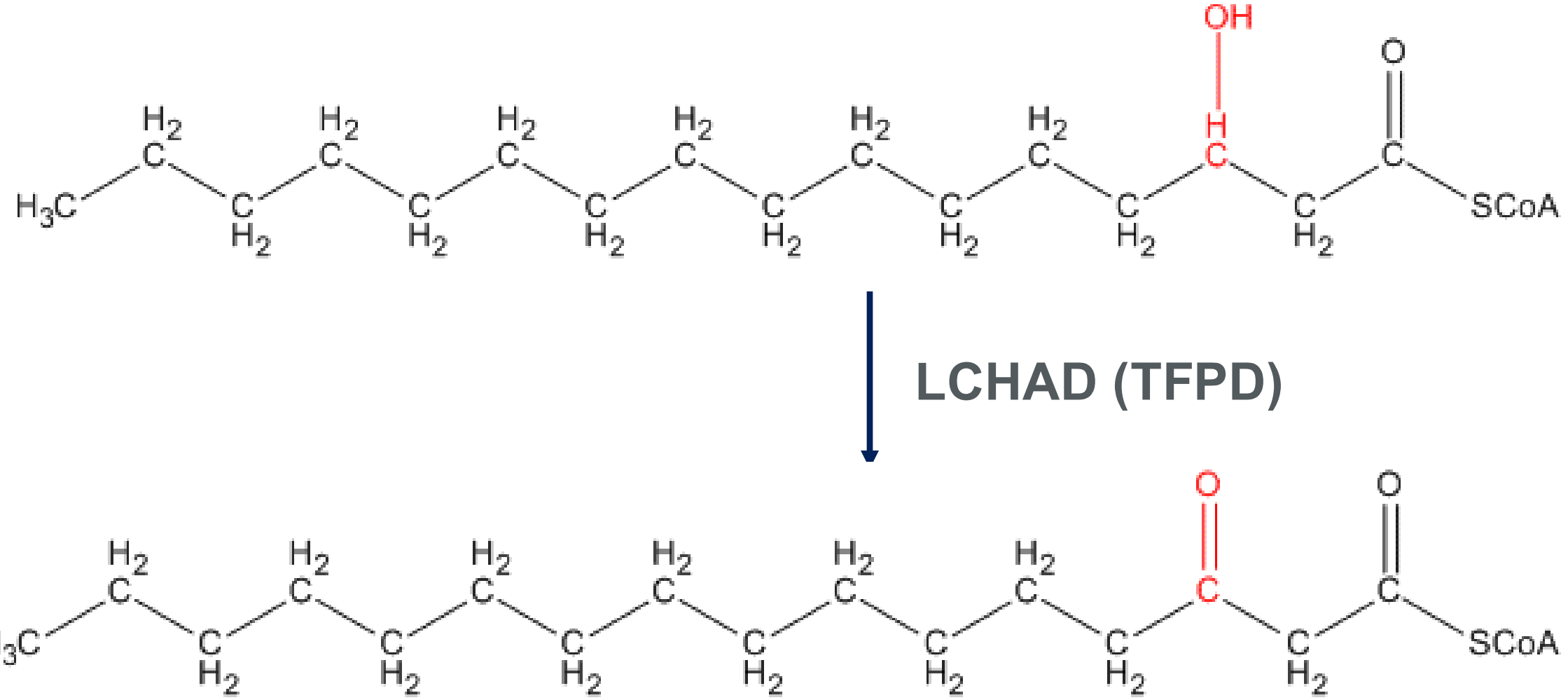
Beta-oxidation Step 1 – AcylCoA Dehydrogenase



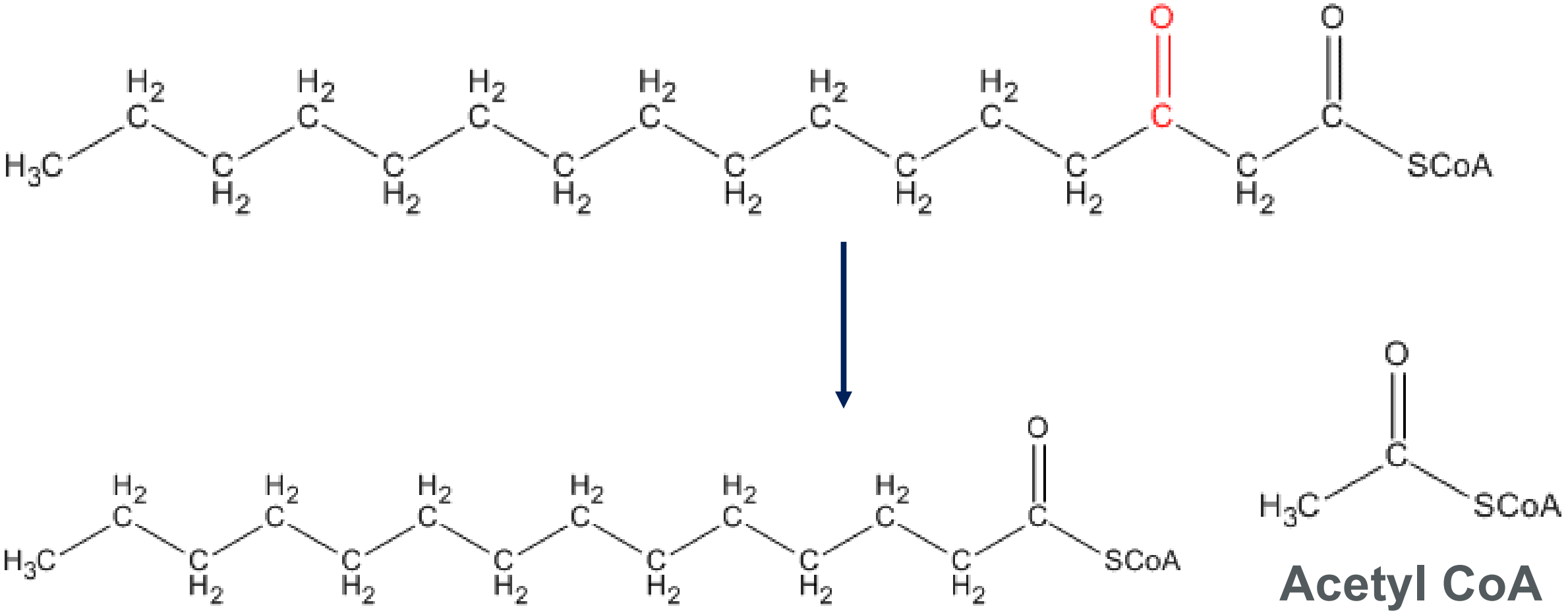
Beta-oxidation Step 2 – Hydratase



Beta-oxidation Step 3 – Hydroxy AcylCoA Dehydrogenase



Beta-oxidation Step 4 – Thiolase

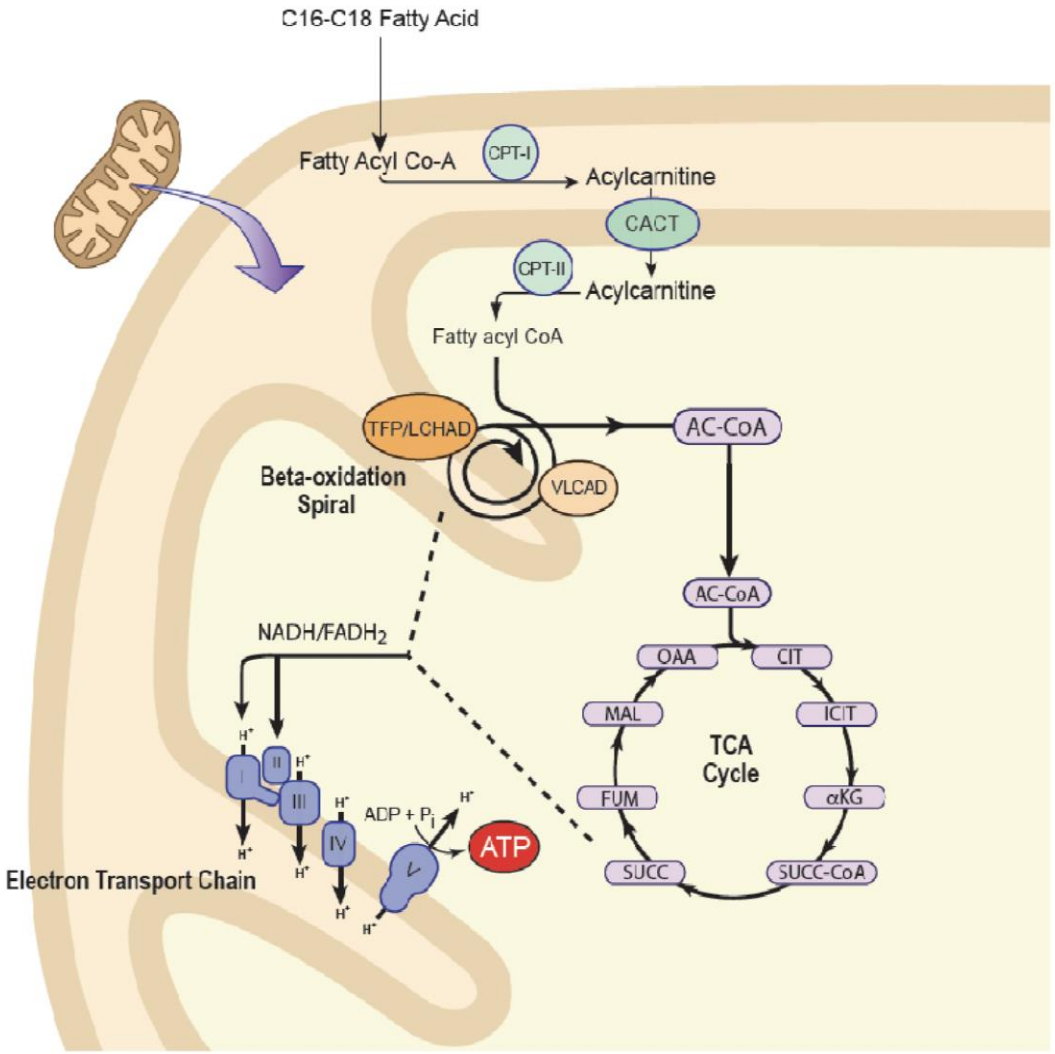


Acetyl CoA Ketone

Beta Oxidation Disorders

- VLCAD Deficiency
  - Mild to Severe, Hypoglycemia, Rhabdomyolysis, Cardiomyopathy
- MCAD Deficiency
  - Hypoketotic hypoglycemia when fasting
- SCAD Deficiency
  - Significance is controversial
- LCHAD/TFP Deficiency
  - Variable severity, Hypoglycemia, Rhabdomyolysis, Retinopathy

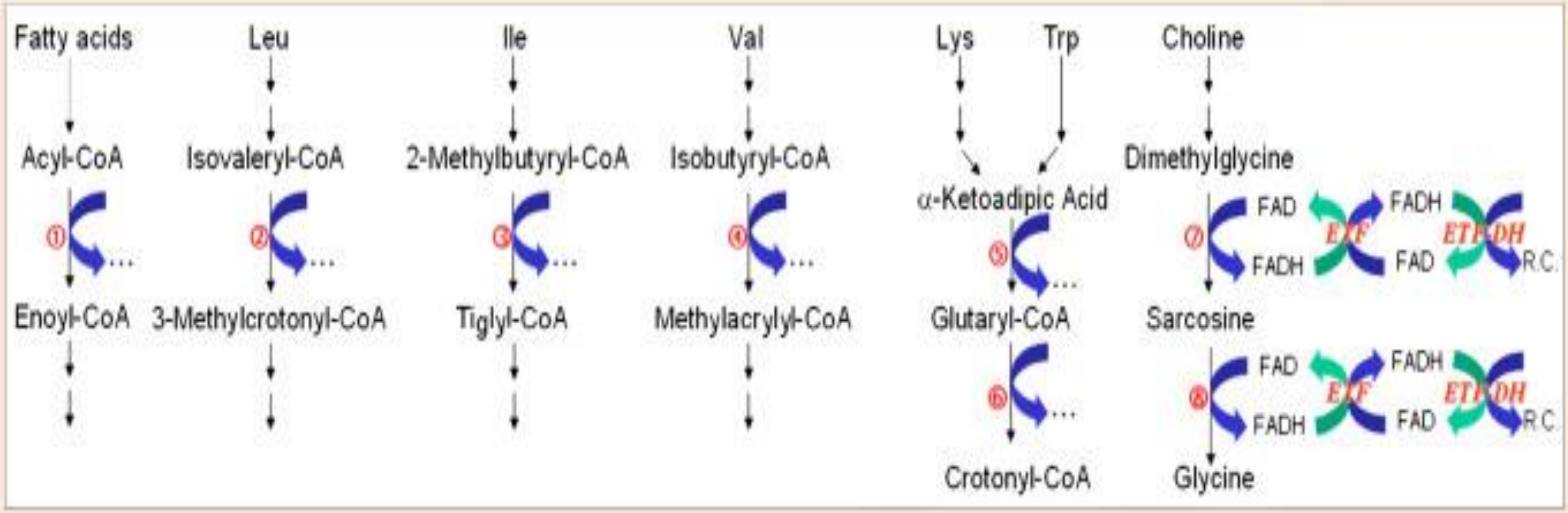
Energy metabolism interactions



- Multiple pathways
- Functionally and physically interact
- Overlap in clinical symptoms
- Secondary symptoms may dominate clinical picture

Defects in Energy Production (MADD/GA2)

- Beta-oxidation sends electrons directly to the electron transport chain where the energy is actually made
  - AKA oxidative phosphorylation
  - Defect is in ETFCH,ETFA or ETFB
- Other acyl-CoA dehydrogenase enzymes share the same pathway
  - Glutaryl CoA dehydrogenase
  - Amino acids valine, leucine, isoleucine
  - Others
- Variable severity from neonatal lethal to adult onset muscle



① VLCAD, MCAD, SCAD

② IVD

③ SBCAD

④ ACAD8

⑤ α-ketoadipic DH

⑥ glutaryl-CoA DH

⑦ dimethylglycine DH

⑧ sarcosine DH

Treatment

Carnitine is a fickle lover and esterifies any FAO intermediate

Block in fat metabolism pathway

↓

Buildup of acylcarnitines → **Evidence for cardiotoxicity (in mice)**

↓

Excretion of acylcarnitines

↓

Carnitine deficiency → **Decreased residual FAO**

Treatment – Carnitine Cycle Disorders

- Prevent Fasting
- Supplement MCT
- Others as needed

Treatment- Long Chain FAOD

- Fasting Prevention
- Supplement MCT
- +/- Dietary Long Chain Fat Restriction
- Others as indicated

- Use of carnitine is controversial

Treatment- Medium Chain FAOD

- Fasting Prevention
- “Heart Healthy” Diet

- Occasional carnitine deficiency

Treatment MADD/GA2

- Dietary fat restriction
- Dietary protein restriction
- One or more of:
  - Riboflavin (vitamin cofactor for the ETF enzyme)
  - Coenzyme Q10
  - +/- Carnitine
- Fasting prevention

Riboflavin Tip

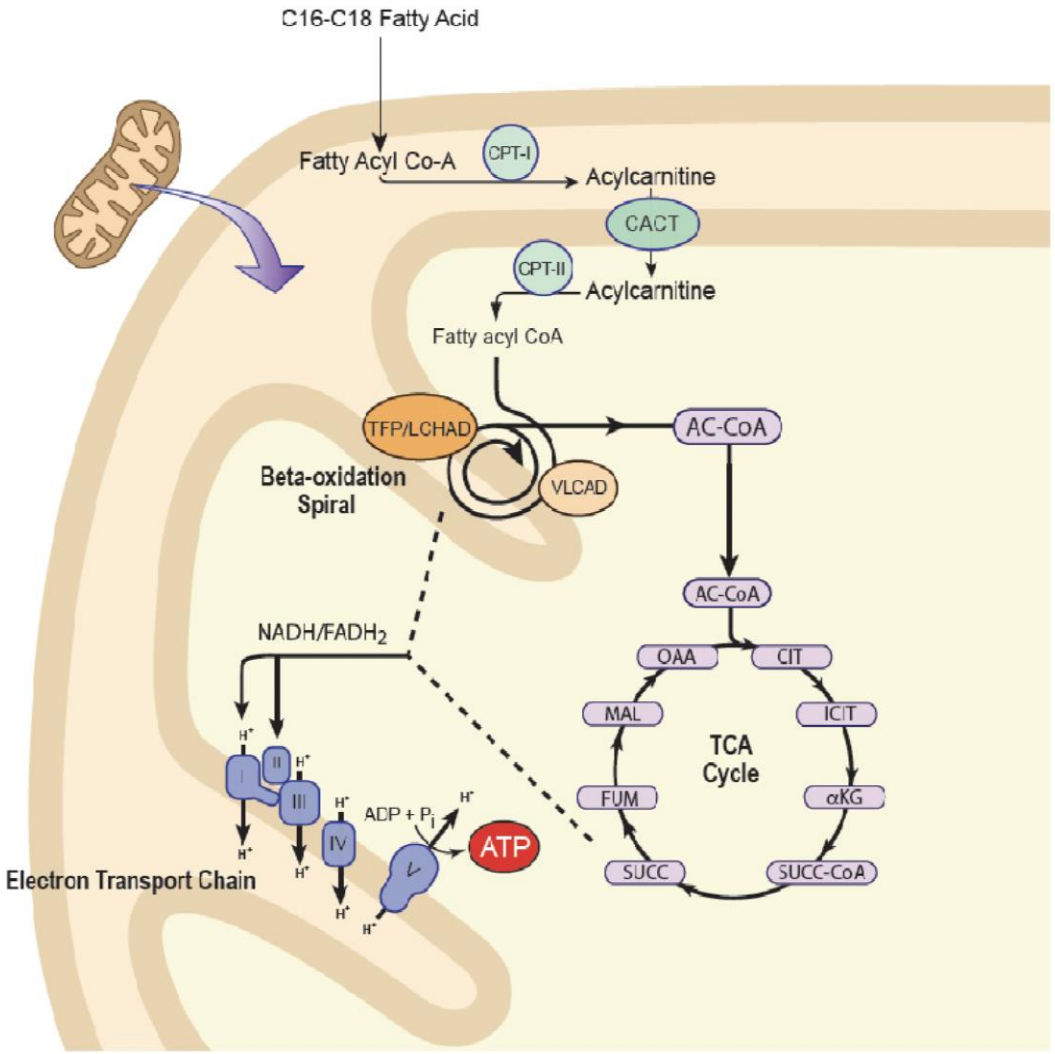
- Microencapsulated riboflavin is available
- Manufactured by Solace

Even better MCT supplement for LCFAOD

- Triheptanoin (Doljovi)
- 7 carbon fat

- FAOD breaks the fat down down (7 carbons, 5 carbons, 3 carbons) until a 3 carbon piece is left
- This 3 carbon piece feeds metabolism by replenishing the Kreb's cycle
- Provides energy from fat metabolism plus replenishes other depleted intermediates
- Might make it easier for the body to make glucose

Energy metabolism interactions



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Thank you Questions?