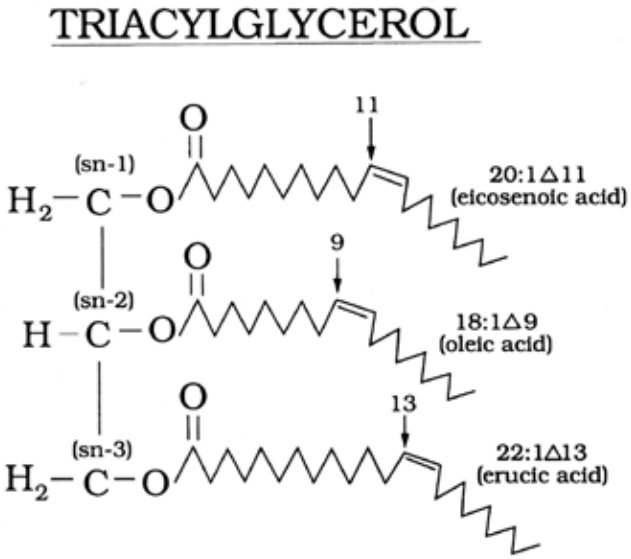
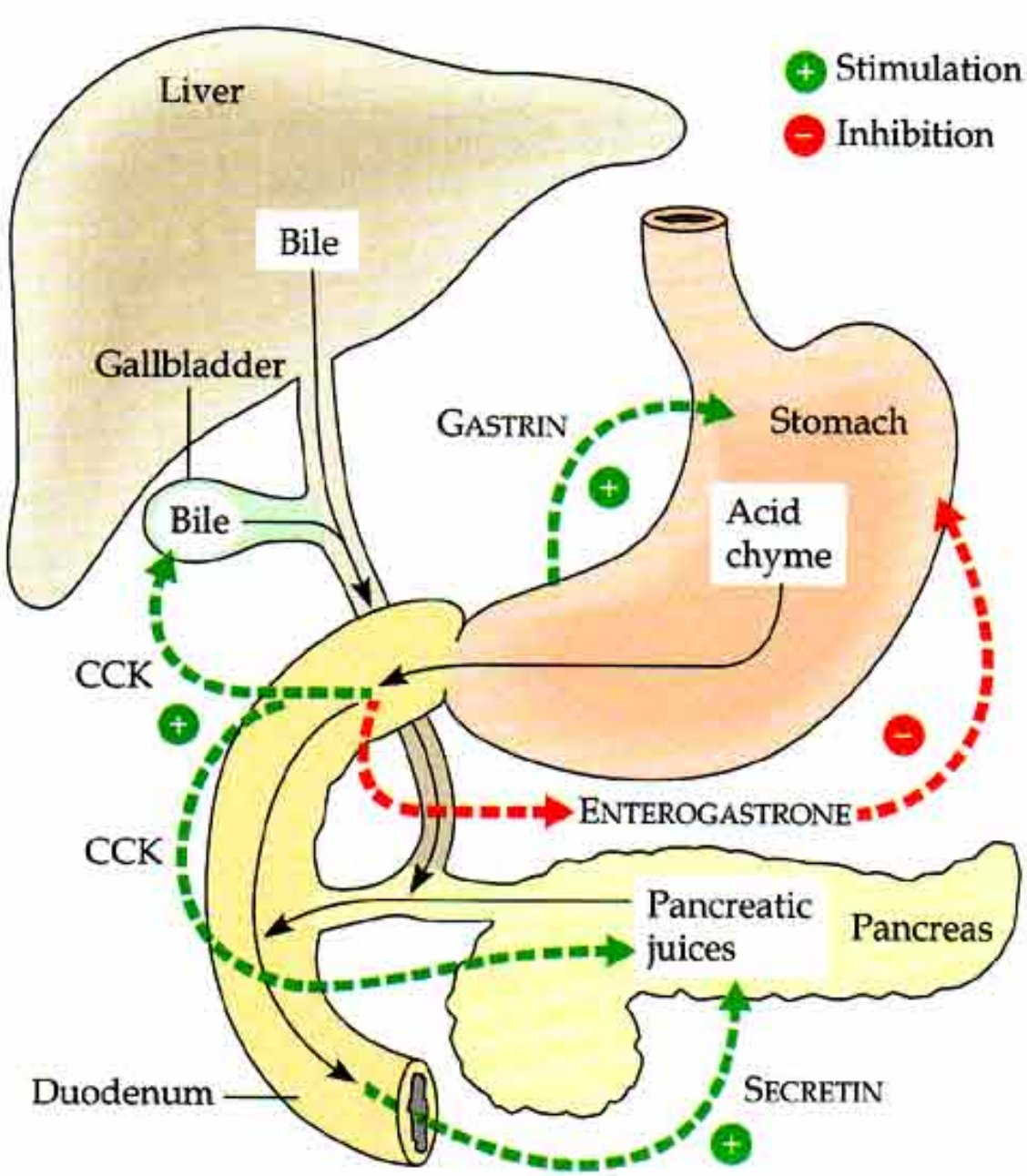
Digestion and Absorption of Lipids



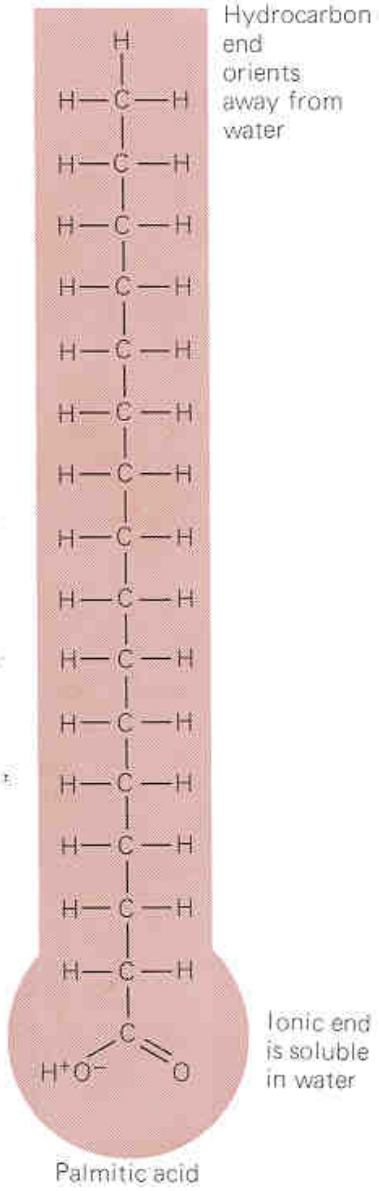
- 98% of ingested lipids are triacylglycerols (TAGs)
- Digestion in the Mouth: enzymes are **aqueous**
  -little effect on lipids
- Digestion in the Stomach: causes a large ***physical*** change:
  -Churned into droplets: **"Chyme"**

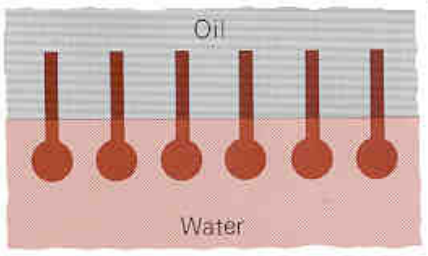


Gastric Lipase: Begins actual lipid digestion. ~10% of TAGs are hydrolyzed in the **stomach**.

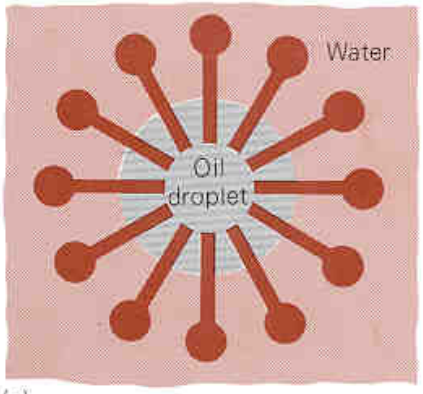
Chyme stimulates **cholecystokinin** (CCK) to release **bile** from gallbladder.

Bile is an emulsifier



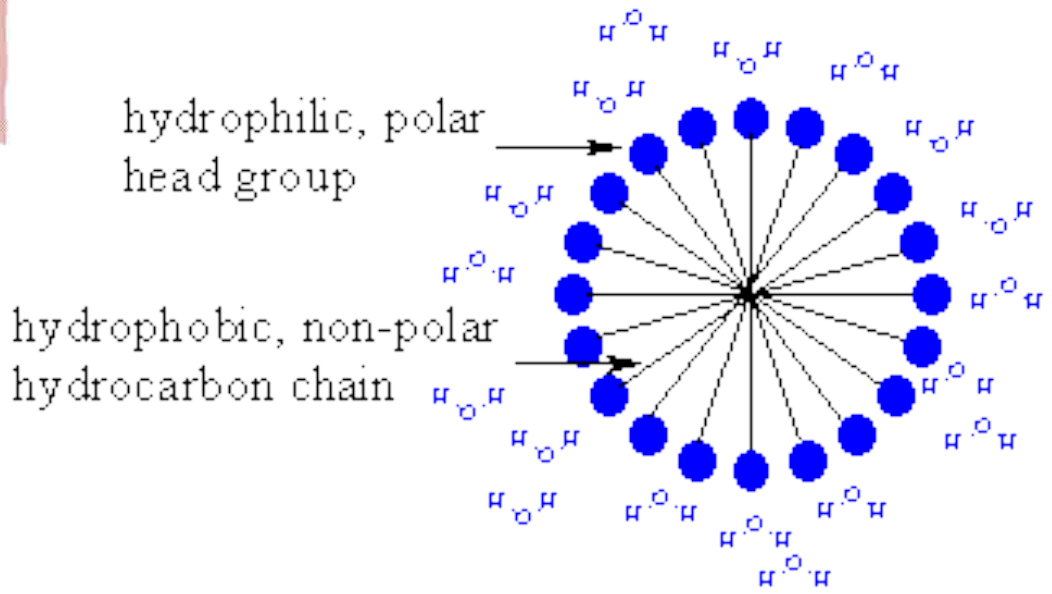


(b)

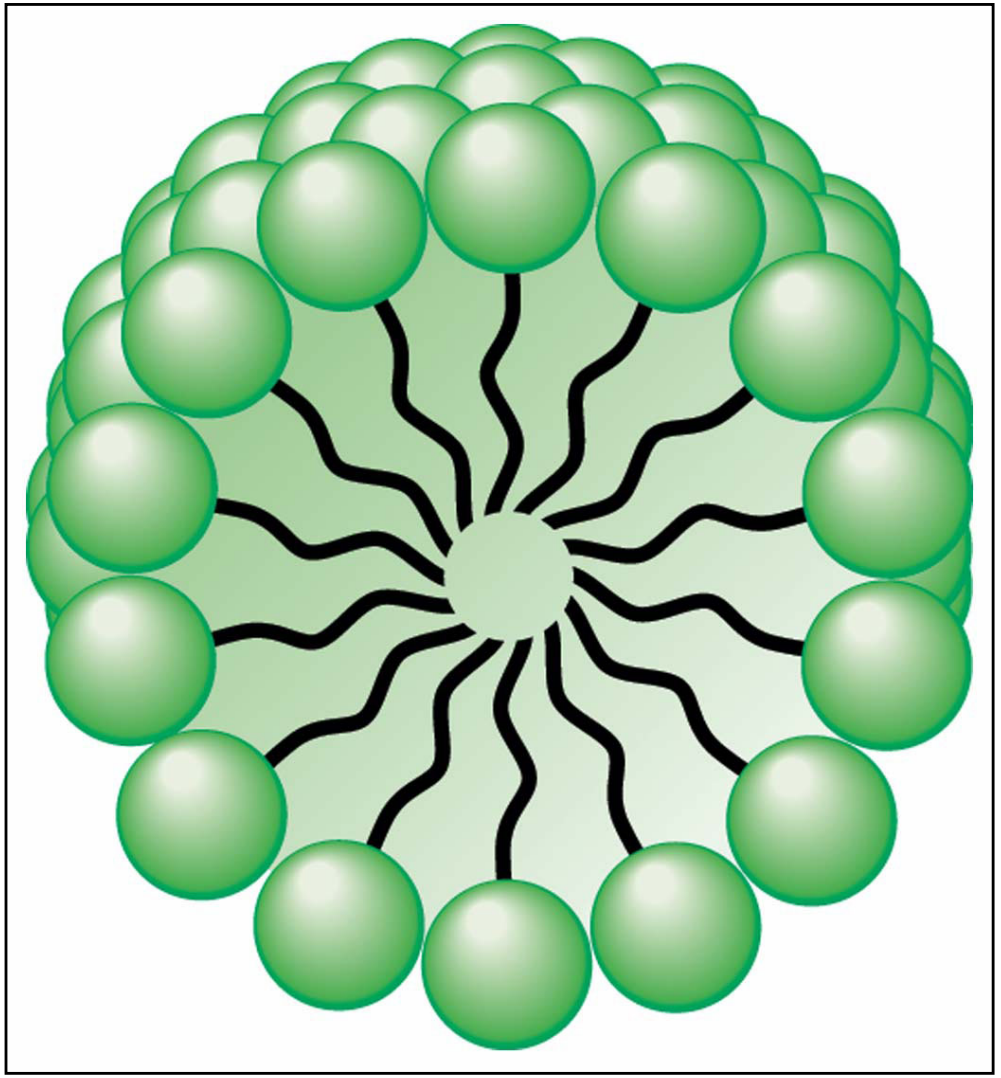


(c)

Oil droplets will form spherical **micelle** shapes. Bile salts aid this process clumping fatty acids and monacylglycerols.



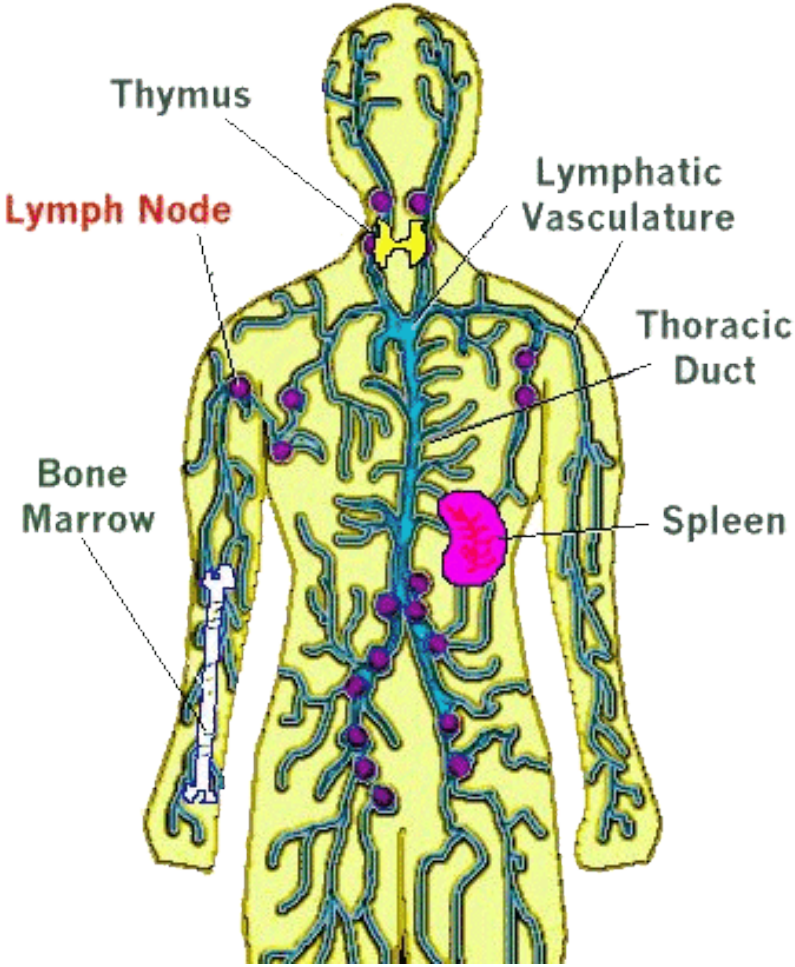
Fatty acid micelle:
hydrophobic fatty acids &
monoacylglycerols
are in the interior.
Bile salts on exterior.

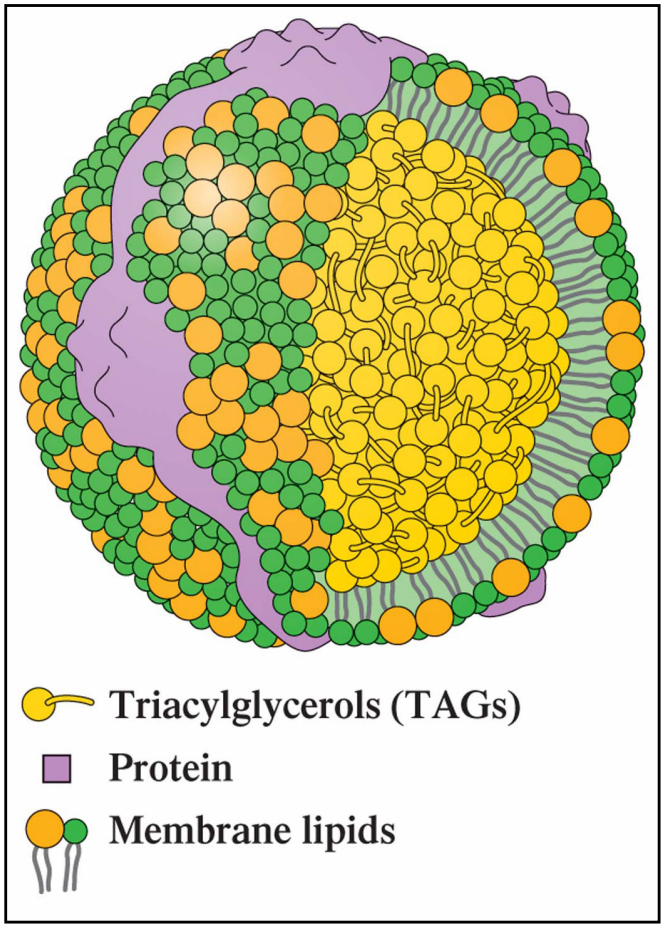


Micelles are small
enough to penetrate
membrane of
intestinal cells.

Free fatty acids & monoacylglycerols are reformed into **triacylglycerols**.

TAGs are combined with membrane & water soluble proteins to form a **chylomicron**, a lipoprotein.

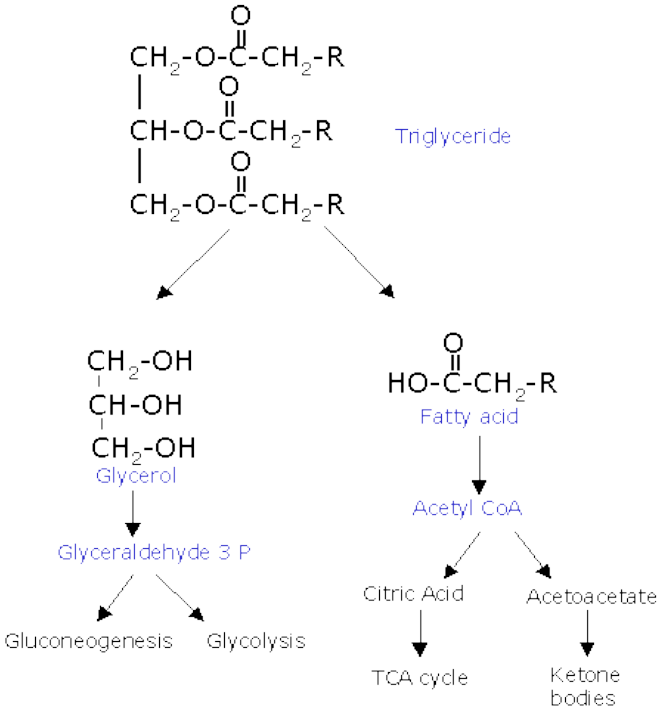


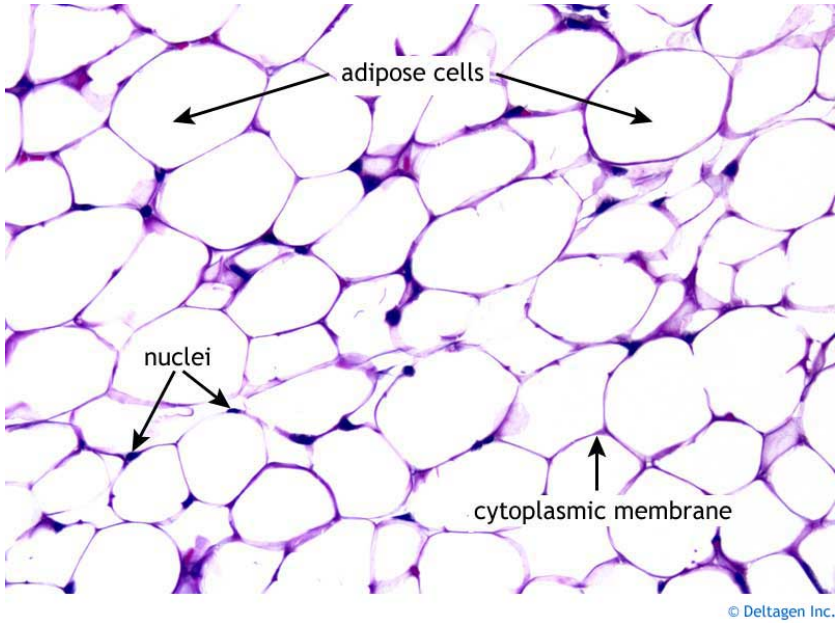


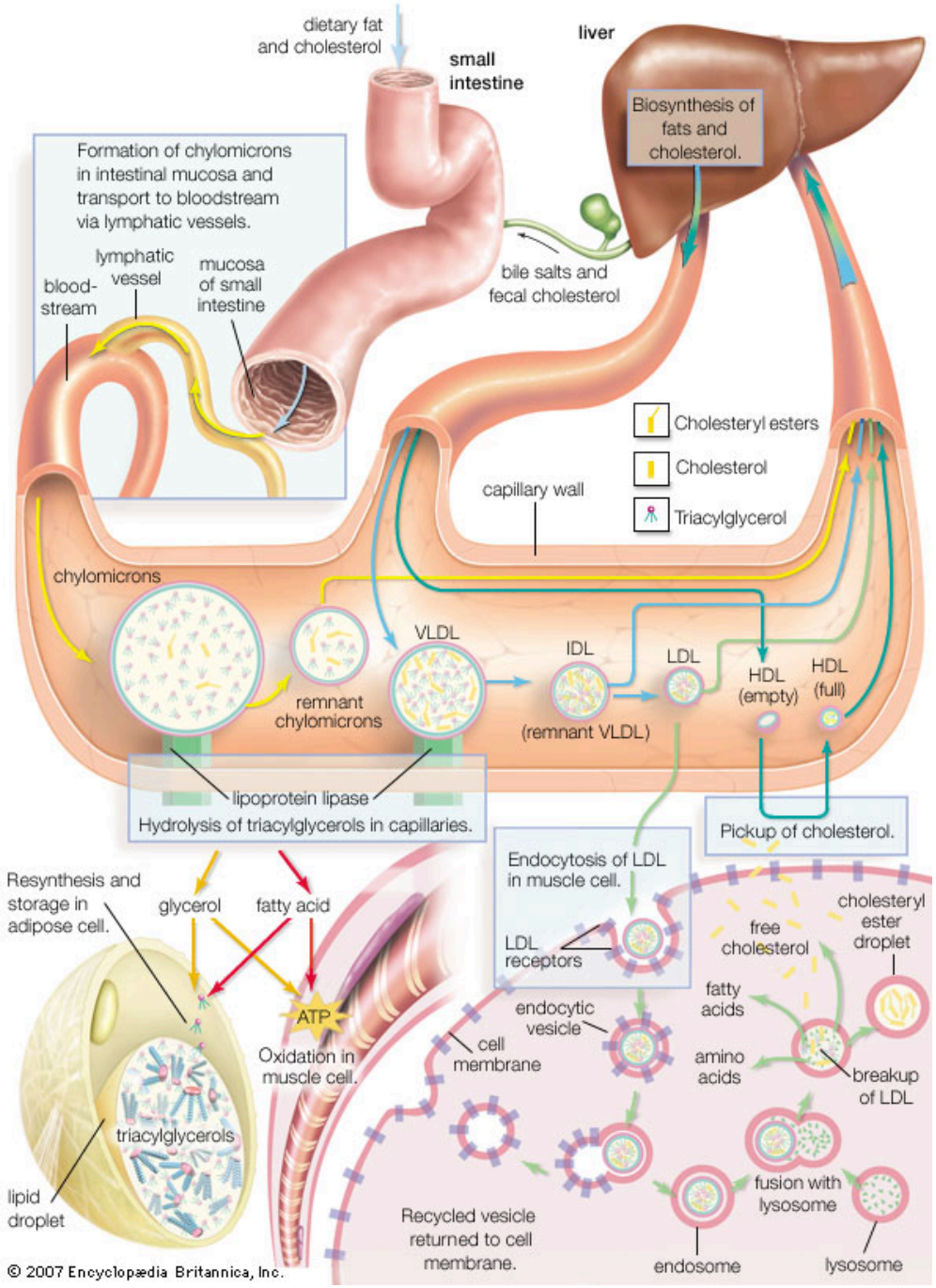
Chylomicrons carry TAGs from intestinal cells into bloodstream via the **lymph system**.

Triacylglycerols reach bloodstream
& are hydrolyzed down to **glycerol** and **fatty acids**.

These are absorbed by cells and
processed further for energy by forming **acetyl CoA**.
or
Stored as lipids in fat cells (adipose tissue)






dietary fat and cholesterol
small intestine
liver
Biosynthesis of fats and cholesterol.
Formation of chylomicrons in intestinal mucosa and transport to bloodstream via lymphatic vessels.
lymphatic vessel
blood-stream
mucosa of small intestine
bile salts and fecal cholesterol
Cholesteryl esters
Cholesterol
Triacylglycerol
capillary wall
chylomicrons
VLDL
IDL
LDL
HDL (empty)
HDL (full)
remnant chylomicrons
(remnant VLDL)
lipoprotein lipase
Hydrolysis of triacylglycerols in capillaries.
Pickup of cholesterol.
Endocytosis of LDL in muscle cell.
LDL receptors
Resynthesis and storage in adipose cell.
glycerol
fatty acid
ATP
Oxidation in muscle cell.
triacylglycerols
lipid droplet
endocytic vesicle
cell membrane
free cholesterol
cholesteryl ester droplet
fatty acids
amino acids
breakup of LDL
fusion with lysosome
Recycled vesicle returned to cell membrane.
endosome
lysosome
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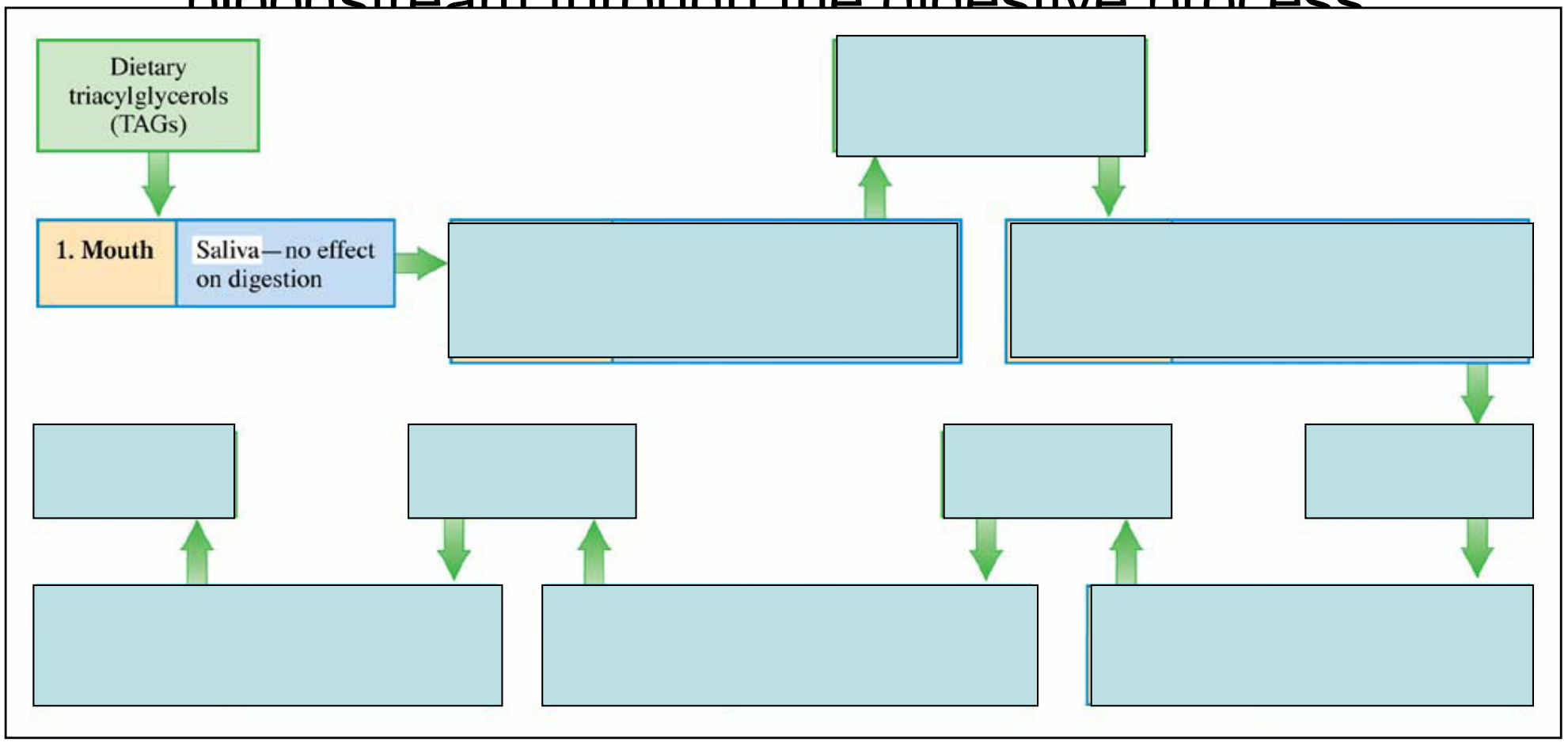
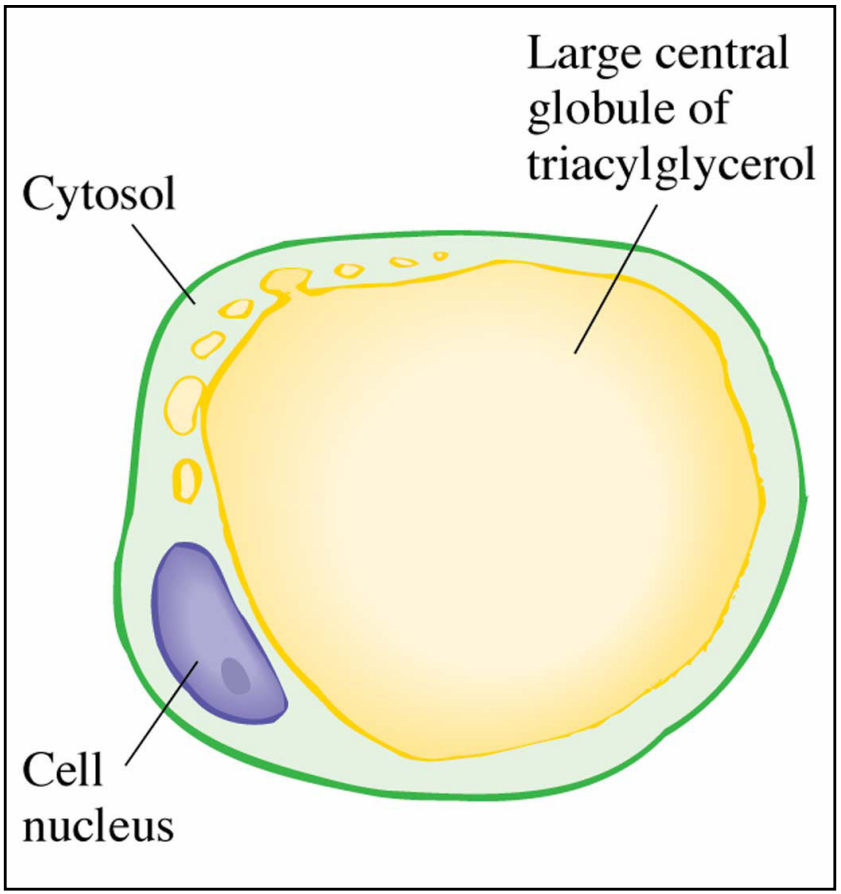
Summary of events that must occur before triacyglycerols (TAGs) can reach the bloodstream through the digestive process



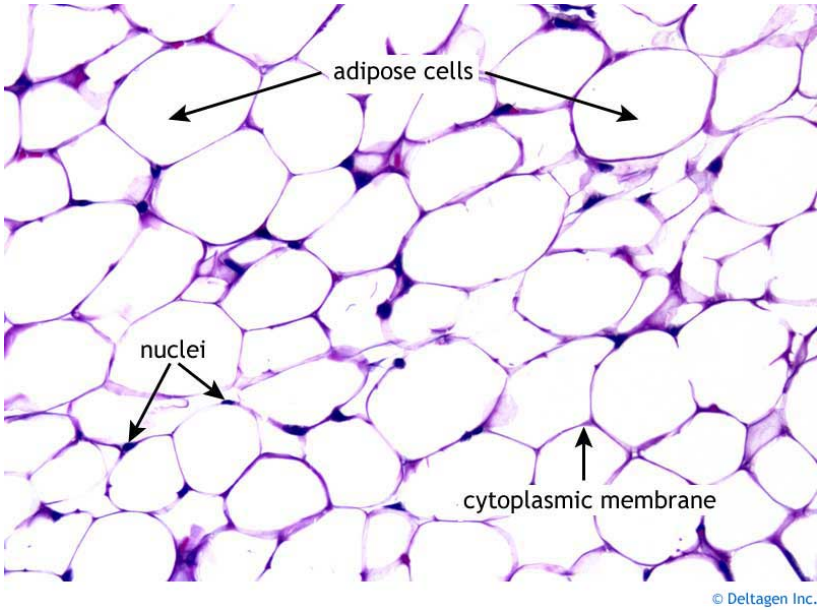
Triglyceride Storage & Mobilization

Storage of triacylglycerol is in **adipocytes**

Fatty acids stored primarily as triacylglycerol.



Triacylglycerol is **hydrolyzed** to release **fatty acids** when needed.



Adipocytes are found mostly in the abdominal cavity and subcutaneous tissue.
Store **energy**, **insulation** against heat loss,
shock absorber for organs.

Adipocytes are metabolically very active:
triacylglycerol constantly hydrolyzed & re-synthesized.

Hormonal control of lipolysis

The breakdown of triglycerides by lipases is under hormonal control.

Hormones involved are:

Epinephrine, glucagon, and insulin.

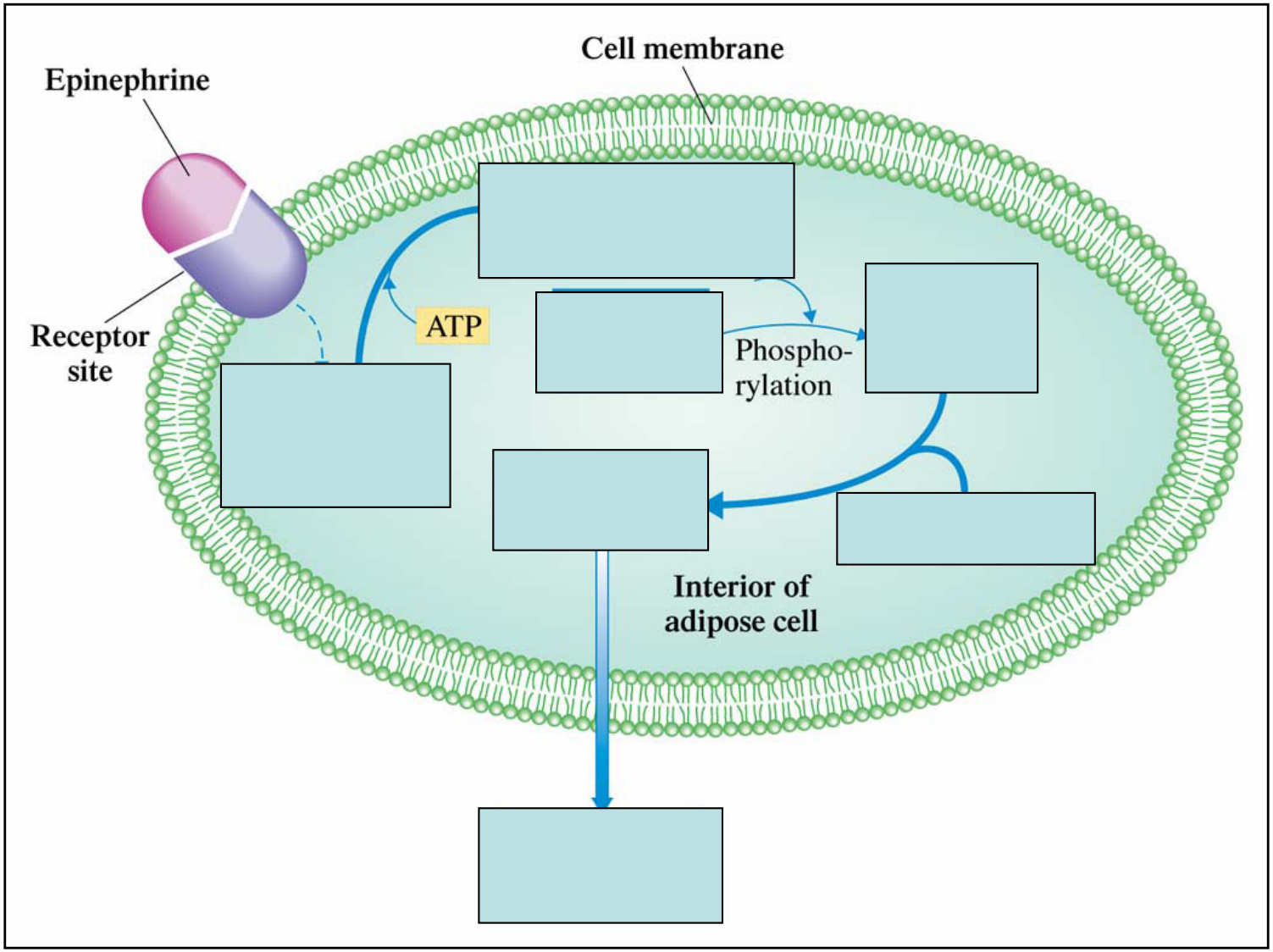
Epinephrine & glucagon:

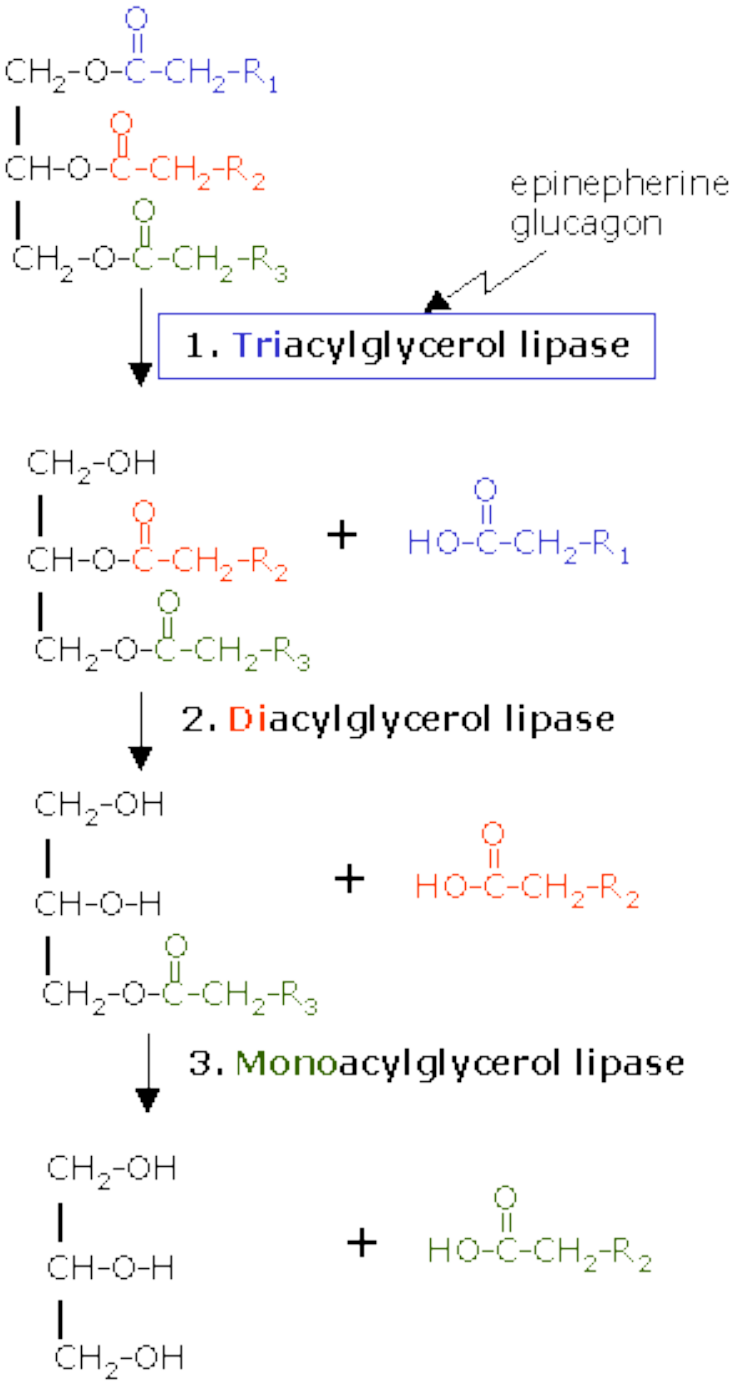
promote breakdown of fat (lipolysis)

Insulin:

inhibits lipolysis.

Hydrolysis of stored triacylglycerols in adipose tissue is triggered by hormones that stimulate cAMP production within adipose cells.



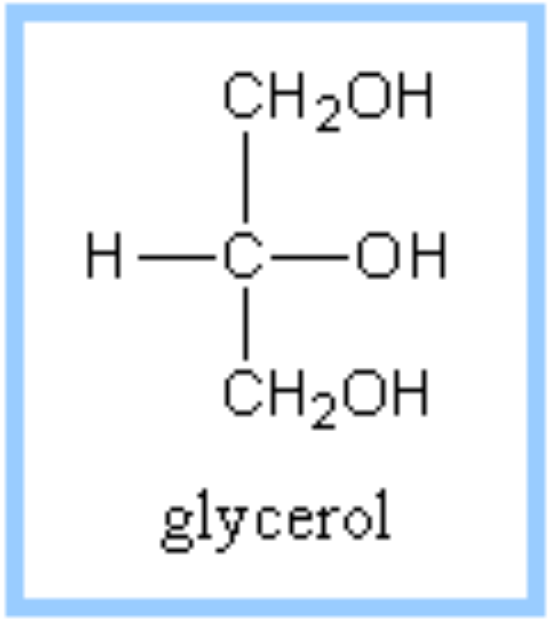


Third time is a charm!

TAGs hydrolyzed
a 3rd time
to form fatty acids.

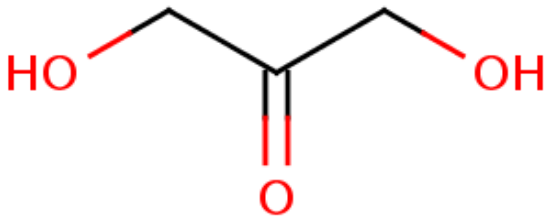
Triacylglycerol lipase
Diacyclglycerol lipase
Monoacylglycerol lipase
Only triacylglycerol lipase is activated by epinephrine.

Glycerol Metabolism



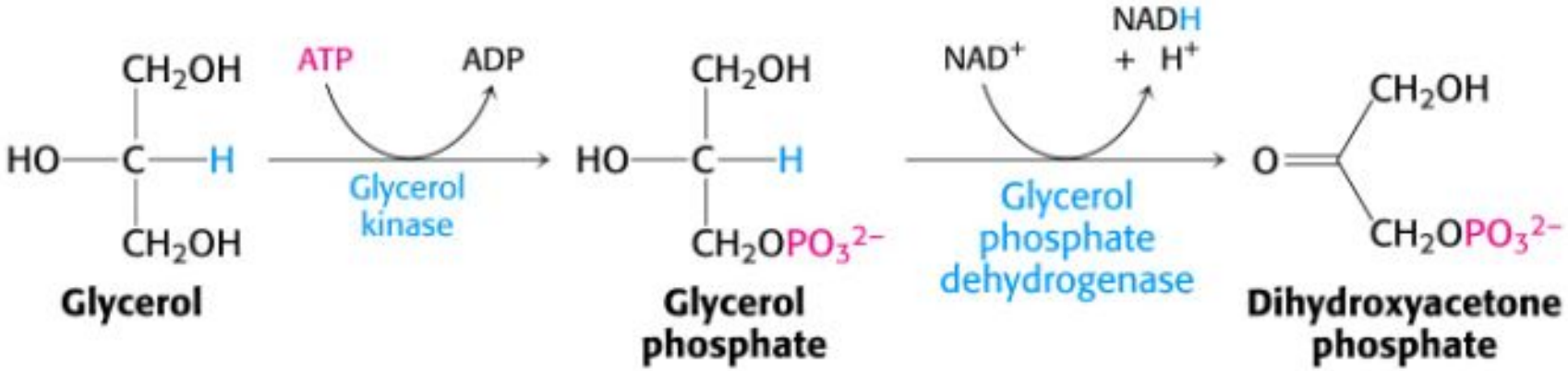
One glycerol formed for each TAG hydrolyzed.
Enter bloodstream & go to liver or kidneys for processing.

Converted in 2 steps to
Dihydroxyacetone phosphate



Where will the phosphate be attached?

Uses up one ATP
Reduces one NAD^+ to NADH

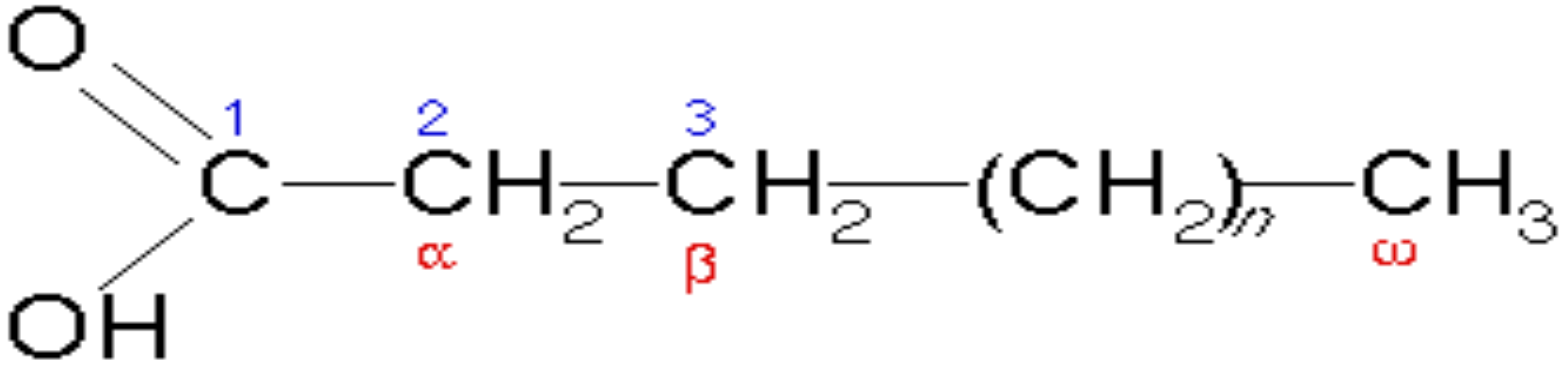


Primary hydroxyl group is phosphorylated

Oxidized to form a Ketone

Fatty acids can also be
broken down for energy.
What kind of reaction is needed?
Oxidation!

Quick review first on fatty acid
numbers & letters:

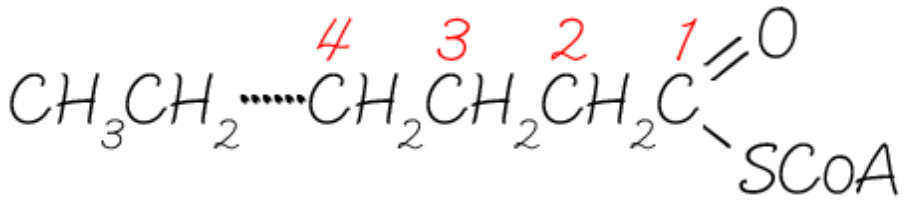


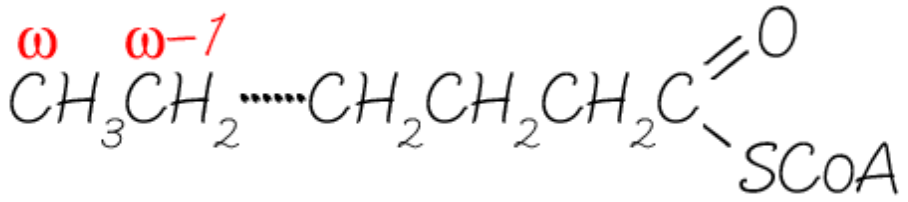
Fatty acid numbering system

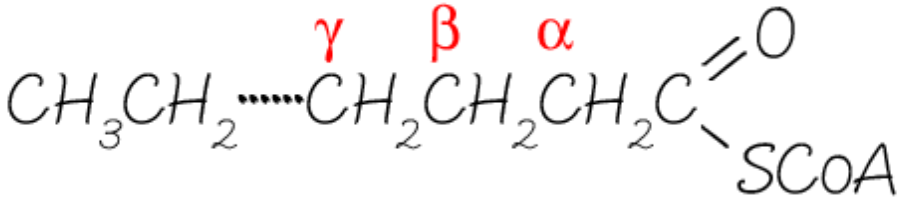
Fatty acid oxidation

- Also called beta-oxidation
- Because most action occurs on the beta-carbon atom
  - Old fashioned nomenclature ☺
- Requires tissues to have mitocondria
- Reciprocally regulated with glucose oxidation
  - Fatty acid oxidation inhibits glucose oxidation
  - Insulin inhibits fatty acid oxidaiton
- Consumes a lot of FAD, NAD, CoA
  - Availability of cofactors is important

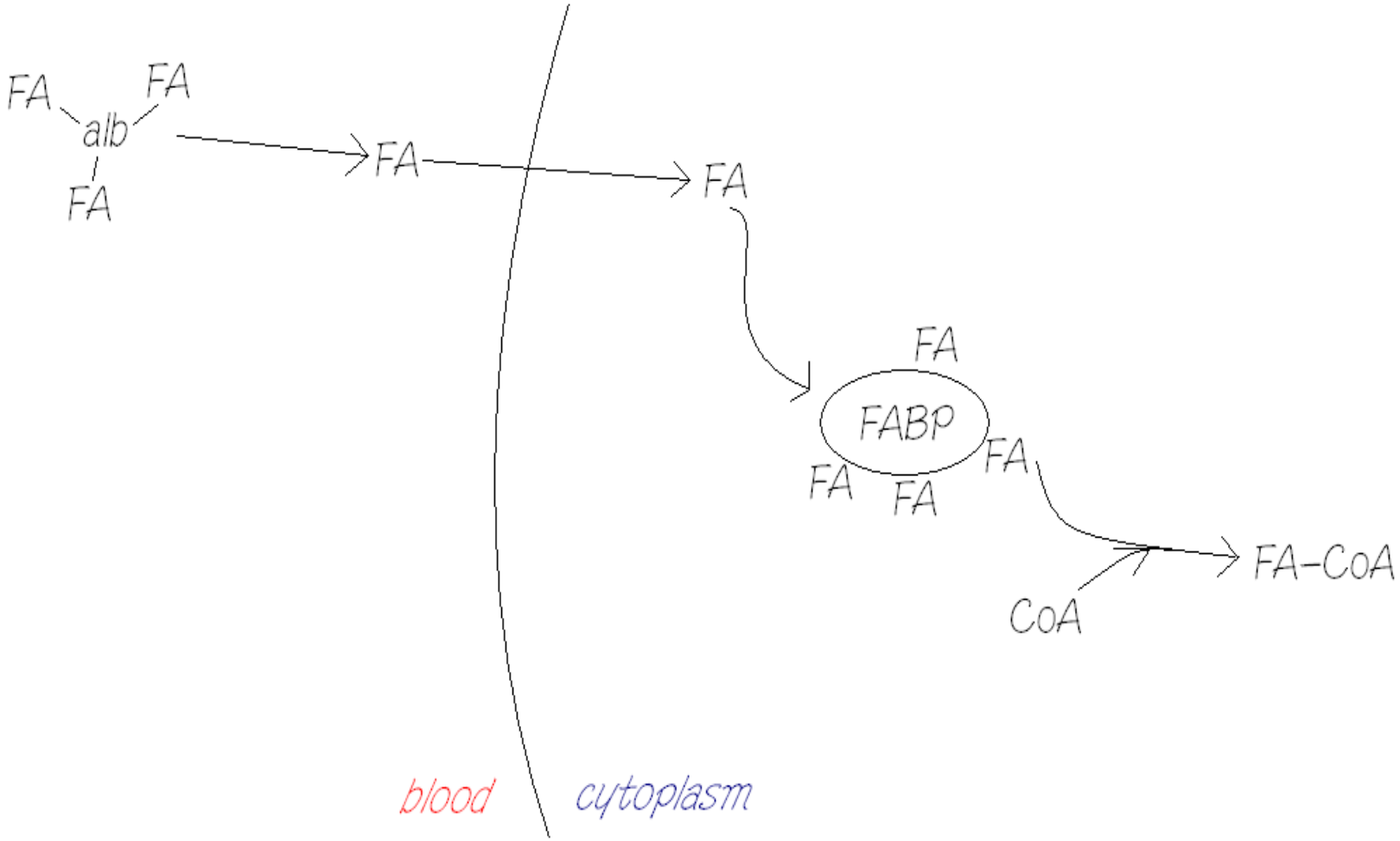
Different Naming Systems







Transport of FA

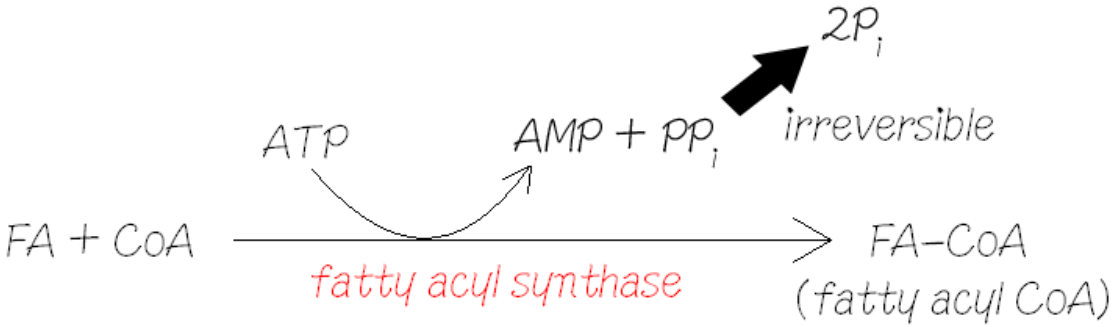


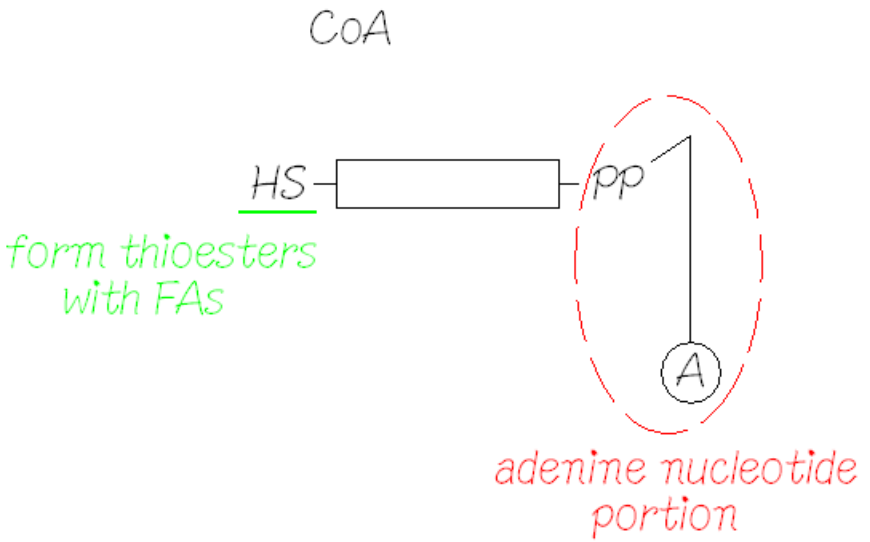
Transport of FA

- FA needs to be transported from blood into tissues
- FA is carried in blood on albumin, which has several binding sites for FA
- There are specific transporters for FA: CD36/FATP
  - CD36 moves to the cell surface whenever there is a need to take up FA at a rapid rate
- FA is carried on FABP (fatty acid binding protein) in cytoplasm

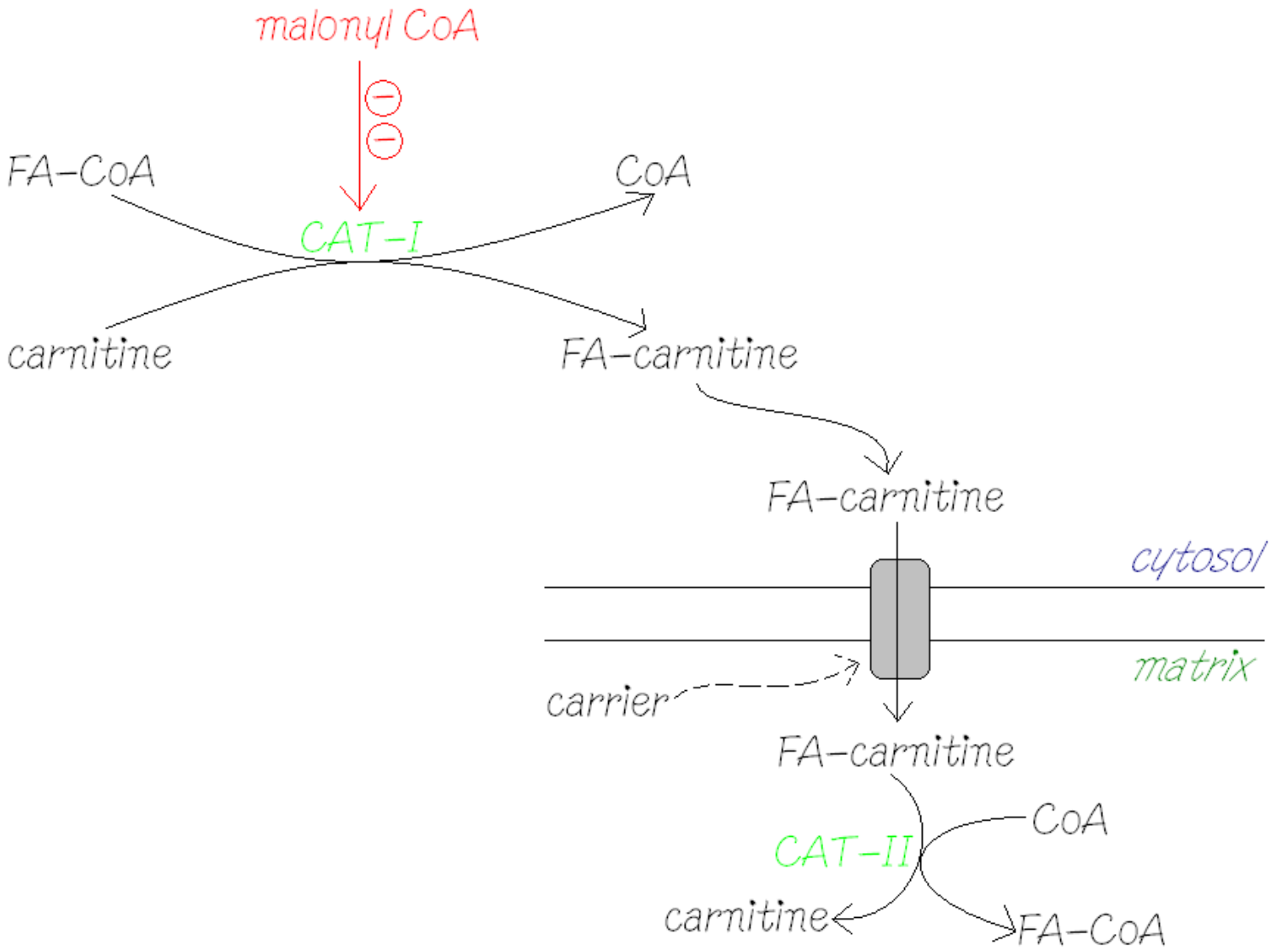
Trapping of FA

- FA is trapped by CoA
- CoA - not only traps FA, but also "activates" it (primes it)
- Requires quite a lot of energy, ∴ ATP is not converted into ADP, but AMP





Transport of FA: Mitochondria



Transport of FA: Mitochondria

- FA-CoA cannot cross the inner-mitochondrial membrane
  - FA needs to be transferred to carnitine in order to get into the mitochondria (carnitine forms ester with FA)
- CAT = carnitine acyl transferase
  - Converts FA into a form that can be taken into the mitochondria (by specific carrier)
  - Regenerates CoA –
    - CoA is needed for trapping more FA
- CoA: pool in cytoplasm and pool in mitochondria never mix → compartmentalization, ∴ CoA can be at different concentration in the cytoplasm & in the mitochondria

Transport of FA: Mitochondria

- Malonyl CoA is a very strong inhibitor of CAT-I
- CAT-I is the key regulator of fat oxidation - once FA gets into the mitochondria, it will be oxidized (i.e. the only fate of mitochondrial FA-CoA is oxidation)
- Alternative fate of FA-CoA in the cytoplasm is esterification with glycerol-3-phosphate to form lipid
- Insulin inhibits CAT-I via ↑ malonyl CoA
  - Which is produced by acetyl CoA carboxylase
  - Normally associated with lipogenesis but occurs in muscle tissue too in a regulatory role

β-oxidation

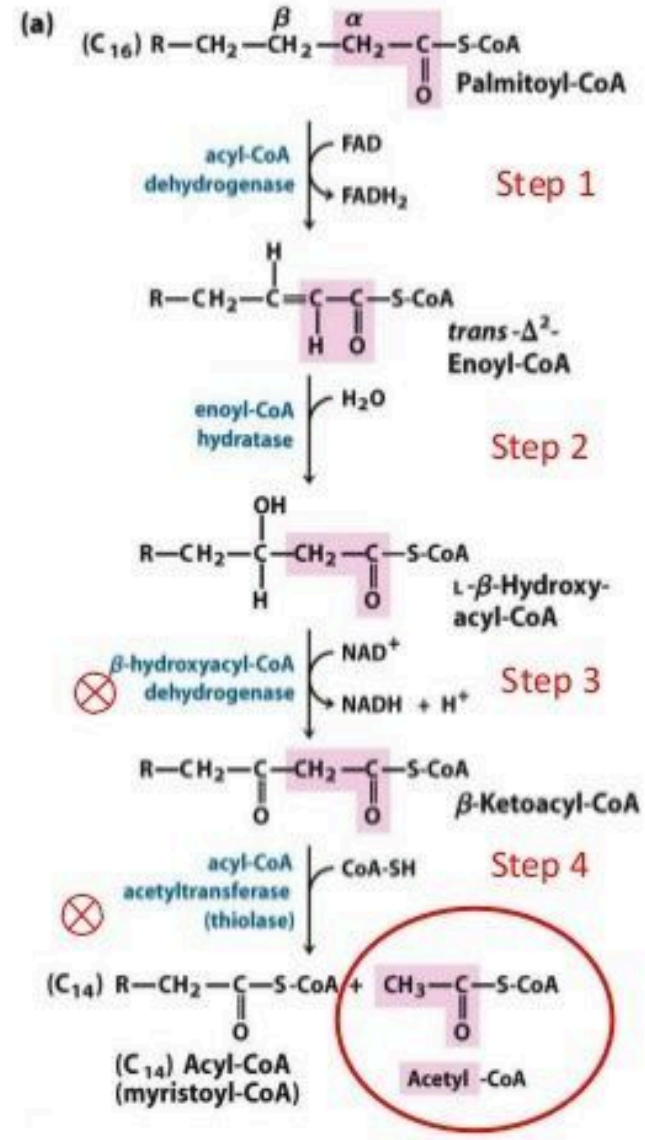
4 Steps of β-oxidation

1. Dehydrogenation of the fatty acyl-CoA to make a trans double bond between α and β carbon.
   - Short, medium, and long chain acyl-CoAdehydrogenases
   - e^- removed transferred to FAD
2. Hydration of the double bond

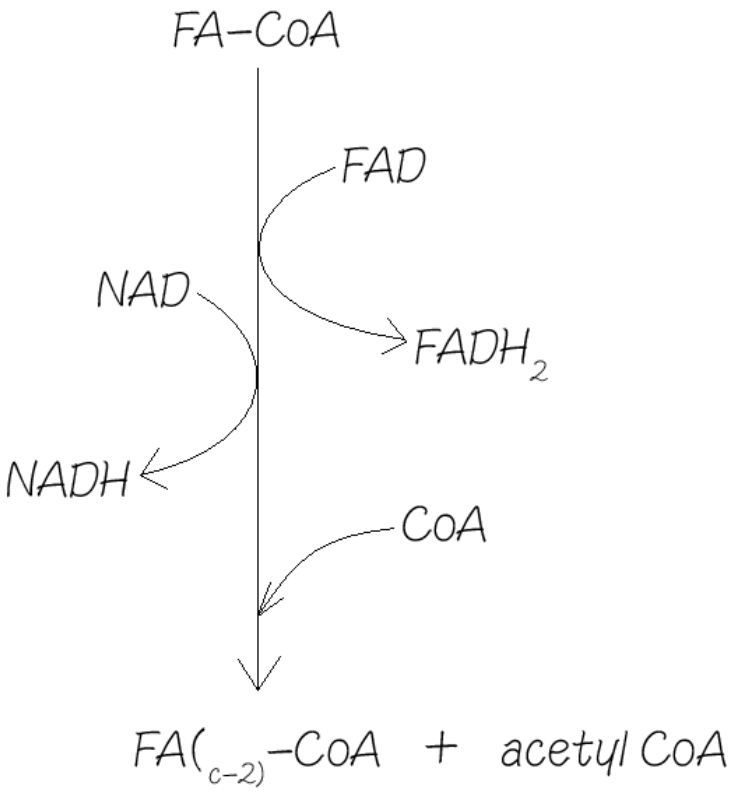
1. Dehydrogenation of the β-hydroxyl group to a ketone

   - e^- removed transferred to NAD^+

1. Acylation – addition of CoA and production of acetyl-CoA



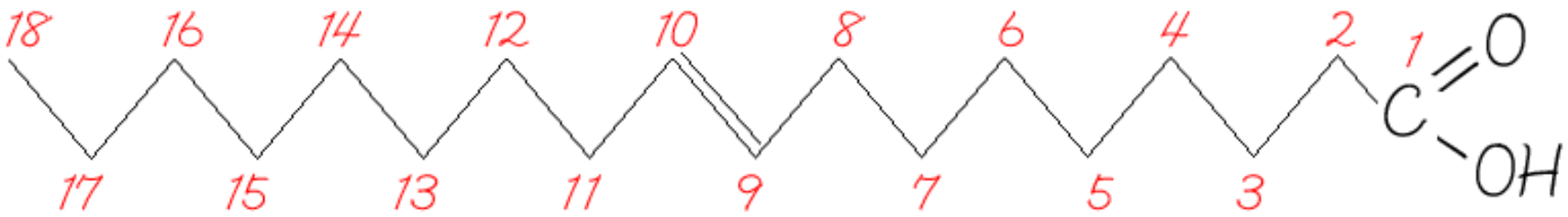
Summary of β-oxidation



- Example: 16C FA-CoA
  - 7 NADH & 7$FADH_2$ are produced, 7 CoA are required
  - 16C FA-CoA → 8 acetyl CoA

Unsaturated FAs

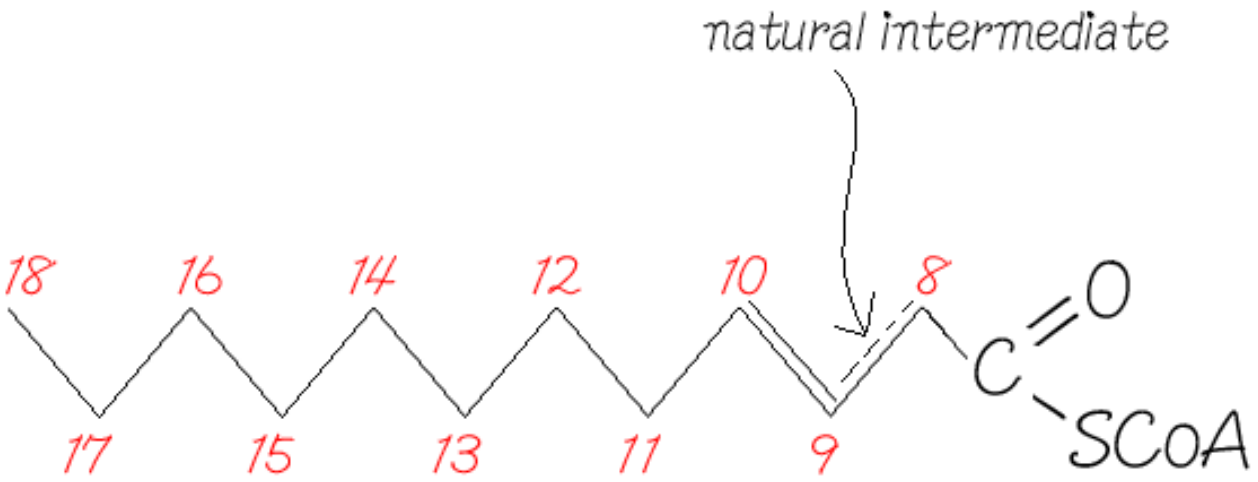
- Examples:
  - C18:1 (9) - oleic
    - 18 carbons, 1 double bond at the 9th position



  - C18:2 (9, 12) - linoleic

Oxidation of Unsaturated FAs

- After 3 rounds of β-oxidation, intermediates would normally have double bonds between α and β carbon, but in unsaturated FAs, the double bonds will be between β and γ carbon → need to move the double bond

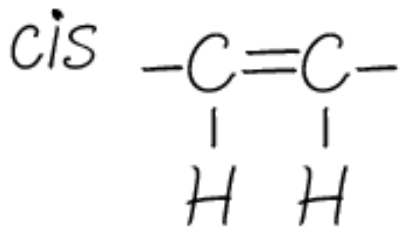


Oxidation of Unsaturated FAs

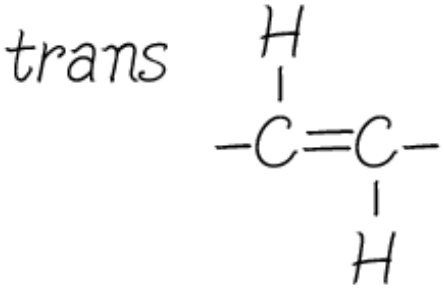
- The process of β-oxidation will halt if the double bonds cannot be moved to the appropriate position
- Our body has enzymes that can shift the double bond position → but only if the double bonds are in cis configuration

Oxidation of Unsaturated FAs

- The double bonds in natural occurring unsaturated FAs are in cis



- The double bonds in unsaturated FAs result from hydrogenation are in both cis and trans



- Polyunsaturated FAs are liquid. To make them more solid – so as to be spreadable like butter, Hs are added to the FAs
- Hydrogenation is a chemical process – using strange temperatures, pressures and catalysts

Ketogenesis

- Only occurs in the liver
- Need lots of NAD, FAD & CoA to keep beta-oxidation going,
  - so need to regenerate co-factors
- NAD & FAD are regenerated in the electron transport chain which is dependent on ATP production/demand
- CoA is regenerated by sending acetyl CoA into Krebs cycle
  - there is limit to how much acetyl CoA can enters the Krebs cycle
  - only when energy is needed
- So normally CoA regeneration is dependent on ATP demand
- Ketogenesis represents an extra way of regenerating CoA
  - Thus allowing beta-oxidation to happen very fast in the liver