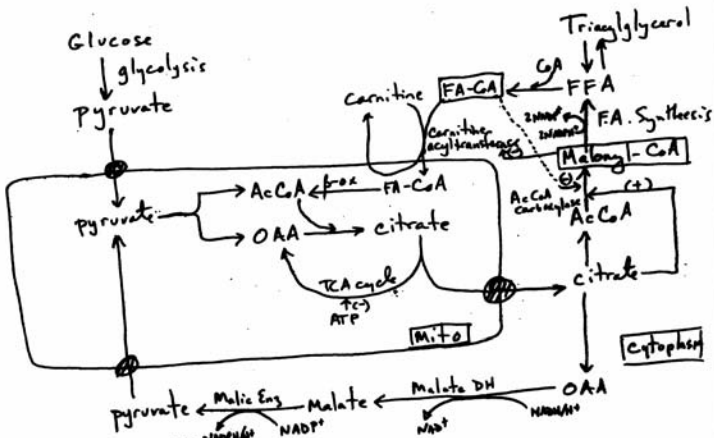
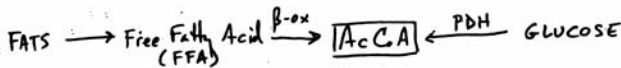


Regulation of Fatty Acid Metabolism



Regulation of FA Metabolism occurs via regulation of acetyl-CoA carboxylase.

CITRATE - activates AcCoA carboxylase by promoting its polymerization into the active form. (liver, adipose tissue, lactating mammary gland)

MALONYL-CoA - inhibits carnitine acyl-transferase I and therefore prevents FA-CoA from being oxidized by β -oxidation.

FA-CoA - when present in high concentration in the cytosol, will inhibit AcCoA carboxylase by competing with citrate. The enzyme de-polymerizes + is less active (long-chain FA's have most potent effect.) As a result, [Malonyl-CoA] \downarrow and FA-CoA can enter the mito via carnitine-acyl transferase.

Regulation of Fatty Acid Synthesis is by Regulation of AcCoA carboxylase.



- contains biotin

- requires 1 ATP

- Citrate is allosteric activator (liver, fat, mammary glands)

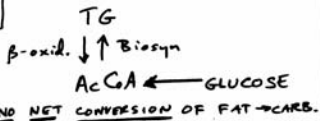
[citrate]↑ causes polymerization of 30-40 inactive monomers into a fully active polymer

[citrate]↓ then [AcCoA]↓ and AcCoA Carboxylase activity ↓

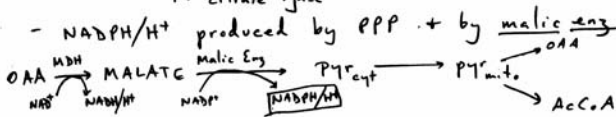
- long fatty acyl-CoA (product of pathway) provides negative feedback inhibition; competes with citrate for allosteric site
affinity of fatty acyl-CoA ↑ w/ increasing chain length
Binding of fatty acyl-CoA results in dissociation + inactivation of AcCoA carboxylase polymer

- When AcCoA Carboxylase is inhibited, [Malonyl-CoA] ↓
acyltransferase I is no longer inhibited
Fatty acyl-CoA molecules are transported into mito
β-oxidation resumes

Biosynthesis vs. β -OXIDATION

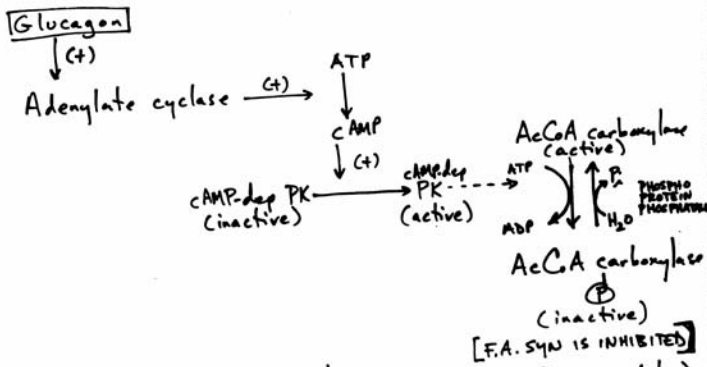


- Simple reversal of β -oxidation does not occur; thiolase rxn lies far in direction of products.
- Biosynthetic pathway has intermediates bound to -SH of phosphopantetheine (instead of ~~CoA~~ CoA); contains energy-rich Thioester bond. Phosphopantetheine is covalently bound to a multi-enzyme complex called FATTY ACID SYNTHASE
- Biosynthesis uses NADPH/H⁺ & oxidizes it \rightarrow NADP⁺ (β -ox produces NADH⁺/H⁺ + FADH₂)
- Biosynthesis occurs in cytosol (requires AcCoA, NADPH/H⁺ (From PPP)) (β -ox occurs in mitochondria)
 - Transport of AcCoA from mito \rightarrow cyto occurs by condensing AcCoA w/ OAA \rightarrow citrate; citrate transported out via tricarbox. carrier
 citrate (cyt) $\xrightarrow[\text{citrate lyase}]{\text{ATP-dep.}}$ AcCoA + OAA
 - NADPH/H⁺ produced by PPP + by malic enz

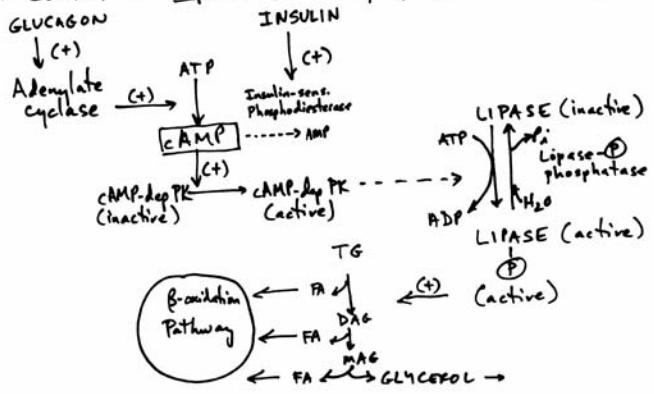


FATTY ACID METABOLISM IS REGULATED HORMONALLY
 VIA cAMP-dep PK
 GLUCAGON CONTROLS ACTIVITY OF AcCoA CARBOXYLASE
 " " " " LIPASE

I. Control of AcCoA Carboxylase (F.A. Syn Inhibited)

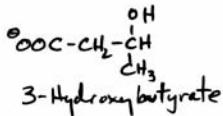
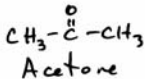
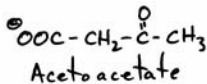


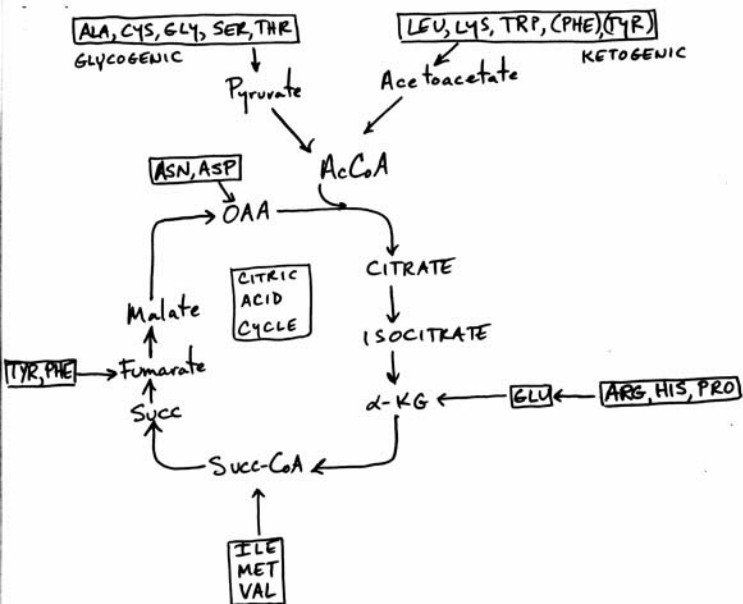
II. Control of Lipase Activity (Supplies F.A. for β-oxidation)



KETONE BODIES PROVIDE ENERGY FOR MUSCLE TISSUE

- Represent condensation products of AcCoA
Acetoacetate, 3-Hydroxybutyrate, acetone
- Provide energy to muscle (skeletal and heart)
- Synthesized in liver from AcCoA (produced by β -oxidation of fatty acids)
- levels vary inversely with blood glucose
levels are high during starvation, diabetes
- In extended starvation, brain tissue will utilize ketone bodies
(blood levels are very high \equiv ketosis) Acetone_{breath}
- When [ketone bodies] in blood exceeds the requirements of peripheral tissues get \downarrow blood pH (acidosis) \rightarrow coma, death.

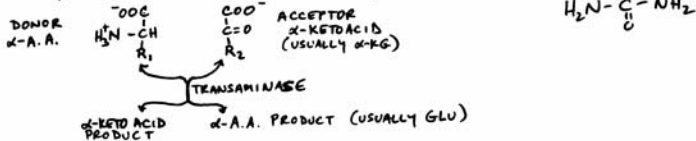




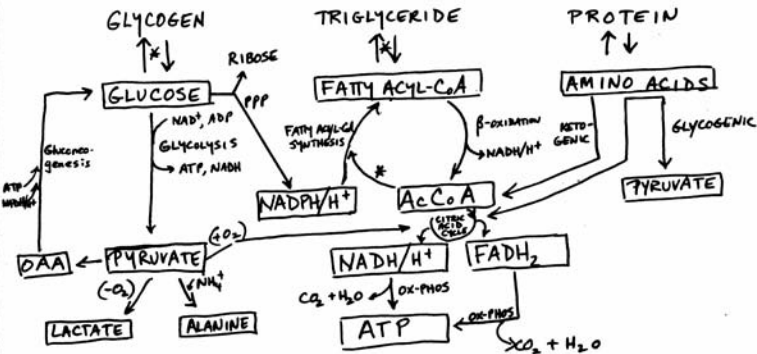
GLYCOGENIC AMINO ACIDS : AMINO ACIDS WHOSE CARBON SKELETONS CAN BE CONVERTED TO GLUCOSE

KETOGENIC AMINO ACIDS : AMINO ACIDS WHOSE CARBON SKELETONS CAN BE CONVERTED TO KETONE BODIES / FATS

IN ALL CASES, THE AMINO GROUP IS REMOVED VIA TRANSAMINASES AN EXCRETED EITHER DIRECTLY AS NH_4^+ OR AS UREA



METABOLIC INTER-RELATIONSHIPS



* UNDER HORMONAL CONTROL

Levels of Regulation

Hormonal control: [cAMP] levels increase and pathways under control by cAMP-dependent protein kinase are turned on/off via phospho-dephospho control.

Compartmentation: Pathways are segregated into separate cellular compartments or organelles, e.g. fat biosynthesis occurs in the cytosol and fat catabolism (β -oxidation) occurs in the mitochondria.

Covalent modification: Phospho-dephospho regulation of key enzymes, e.g. PDH, AcCoA carboxylase, glycogen phosphorylase, glycogen synthase.

Allosteric control: Regulation of enzyme activities by ratios of effector molecules: $\frac{[ATP]}{[ADP]}$, $\frac{[NADH/H^+]}{[NAD^+]}$, $\frac{[AcCoA]}{[CoASH]}$, $\frac{[NADPH/H^+]}{[NADP^+]}$

Also: Ca^{2+} , and product feedback inhibition