Fatty Acid Metabolism

1. Fatty acid synthesis
Insulin Effects

figure 1

- **Liver**
  - increased fatty acid synthesis
    - glycolysis, PDH, FA synthesis
  - increased TG synthesis and transport as VLDL

- **Adipose**
  - increased VLDL metabolism
    - lipoprotein lipase
  - increased storage of lipid
    - glycolysis
Overview of Fatty Acid Metabolism: Glucagon/Epinephrine Effects

- Adipose
  - increased TG mobilization
    - hormone-sensitive lipase
- Increased FA oxidation
  - all tissues except CNS and RBC
Fatty Acid Synthesis

**figure 3**

- **Glycolysis**
  - cytoplasmic

- **PDH**
  - mitochondria

- **FA synthesis**
  - cytoplasmic
    - **Citrate Shuttle**
      - moves AcCo cytoplasm
      - produces 50% NADPH via malic enzyme
      - Pyruvate malate cycle
Fatty Acid Synthesis Pathway

Acetyl CoA Carboxylase

- ‘first reaction’ of fatty acid synthesis
- \( \text{AcCoA} + \text{ATP} + \text{CO}_2 \rightarrow \text{malonyl-CoA} + \text{ADP} + \text{Pi} \)
- malonyl-CoA serves as activated donor of acetyl groups in FA synthesis
Fatty Acid Synthesis Pathway

FA Synthase Complex

- Priming reactions
  - transacetylases
- (1) condensation
- (2) reduction
- (3) dehydration
- (4) reduction
Regulation of FA synthesis:
Acetyl CoA Carboxylase

- **Allosteric regulation**
  - stimulated by citrate
    - feed forward activation
  - inhibited by palmitoyl CoA
    - hi B-oxidation (fasted state)
    - or esterification to TG limiting

- **Inducible enzyme**
  - Induced by insulin
  - Repressed by glucagon
Regulation of FA synthesis:

**Acetyl CoA Carboxylase**

**figure 5**

- **Covalent Regulation**
  - **Activation (fed state)**
    - insulin induces protein phosphatase
    - activates ACC
  - **Inactivation (starved state)**
    - glucagon increases cAMP
    - activates protein kinase A
    - inactivates ACC
Lipid Metabolism in Fat Cells: Fed State

- **Insulin**
  - stimulates LPL
    - increased uptake of F from chylomicrons and VLDL
  - stimulates glycolysis
    - increased glycerol phosphate synthesis
    - increases esterification
  - induces HSL-phosphatase
    - inactivates HSL
- net effect: TG storage
Lipid Metabolism in Fat Cells: Starved or Exercising State

- Glucagon, epinephrine
- activates adenylate cyclase
  - increases cAMP
  - activates protein kinase A
  - activates HSL
- net effect: TG mobilization and increased FFA
Oxidation of Fatty Acids

The Carnitine Shuttle

- B-oxidation in mitochondria
- IMM impermeable to FA-CoA
- transport of FA across IMM requires the carnitine shuttle
B-Oxidation

figure 9

- FAD-dependent dehydrogenation
- hydration
- NAD-dependent dehydrogenation
- cleavage
Coordinate Regulation of Fatty Acid Oxidation and Fatty Acid Synthesis by Allosteric Effectors

**Feeding**
- CAT-1 allosterically inhibited by malonyl-CoA
- ACC allosterically activated by citrate
- net effect: FA synthesis

**Starvation**
- ACC inhibited by FA-CoA
- no malonyl-CoA to inhibit CAT-1
- net effect: FA oxidation
Hepatic Ketone Body Synthesis

- Occurs during starvation or prolonged exercise
  - result of elevated FFA
    - high HSL activity
  - High FFA exceeds liver energy needs
  - KB are partially oxidized FA
    - 7 kcal/g
Utilization of Ketone Bodies by Extrahepatic Tissues

- When [KB] = 1-3mM, then KB oxidation takes place
  - 3 days starvation [KB]=3mM
  - 3 weeks starvation [KB]=7mM
  - brain succ-CoA-AcAc-CoA transferase induced when [KB]=2-3mM
    - Allows the brain to utilize KB as energy source
    - Markedly reduces
      - glucose needs
      - protein catabolism for gluconeogenesis
Clinical significances of impairment of β-oxidation:
1. acquired and genetic deficiency of carnitine substance.
2. genetic deficiency of one or more of enzymes of pathway. Hypoglycemia, muscle weakness, cardiomyopathy, coma and death
Ketosis: Increased production of ketone bodies (K.Bs) with ketonemia and ketonuria. This may occur in physiologic conditions; prolonged fasting and starvation, and in pathological condition; uncontrolled D M.