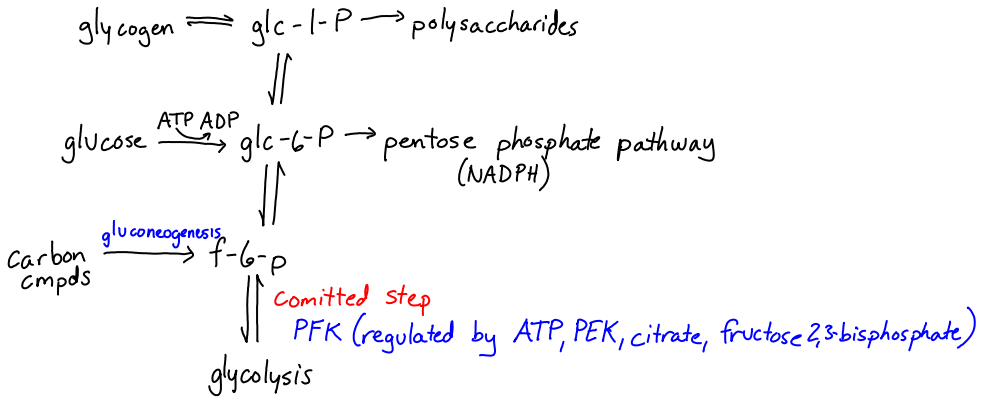
Lecture 08/05

Tuesday, August 05, 2008
10:00 AM

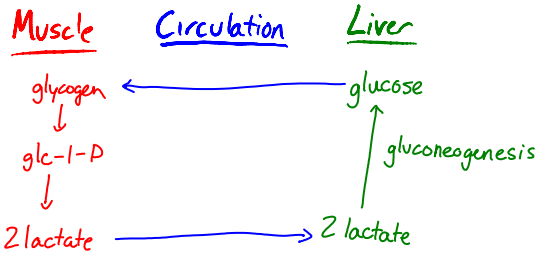
Notes 0805

Audio recording started: 10:02 AM Tuesday, August 05, 2008

- **Interconvertable Pool of Hexoses** - freely reversable pool



- **Glycolysis**
  - Interconvertable pool of trioses (3PG, 2PG, PEP)
  - How many ATPs produced? 2 ATP
- **Gluconeogenesis**
  - Making glucose from non carbohydrate precursor
  - Bacteria: can grow on most carbon media (for example grow on succinate through utilizing gluconeogenesis)
  - Mammals:
    - liver has stored glycogen and adipose tissue that it breaks down for energy. Liver has finite amounts of glycogen and brain needs constant supply of glucose via gluconeogenesis and breakdown of protein (muscle) and fats.
    - **Cori cycle** - recycling of components



  - Why can't reverse of glycolysis work?

$$\text{glucose} + 2ADP + 2P_i \longrightarrow 2 \text{ lactate} + 2ATP + 2H_2O \qquad \Delta G^{\circ\prime} = -32 \text{ kcal/mol}$$

$$2 \text{ lactate} + 2ATP + 2H_2O \longrightarrow \text{glucose} + 2ADP + 2P_i \qquad \Delta G^{\circ\prime} = +32 \text{ kcal/mol}$$

    - Look at $\Delta G^{0\prime}$ (kcal/mol) stepwise of reverse reaction of glycolysis

$\Delta G^{0\prime}$ (kcal/mol)	Step	Reaction	Notes
+15	Step 1	2 pyruvate + 2ATP -> PEP + 2 ADP	
+3.4	Step 2	F-1,6-BisP + ADP -> f-6-P + ADP	
+4	Step 3	G-6-P + ADP -> G + ATP	
+22.4	Total	Overall reaction	

    - Look at $\Delta G^{0\prime}$ (kcal/mol) stepwise of actual gluconeogenesis

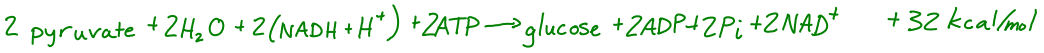
$\Delta G^{0\prime}$ (kcal/mol)	Step	Reaction	Notes
+0.4	Step 1	2 pyruvate + 2ATP + 2GTP -> 2PEP + 2ADP + 2GDP +2Pi	Sum of two enzyme activities (pyruvate carboxylase and PEP carboxykinase)
-4.0	Step 2	F-1,6-BP + H_2O -> F-6-P + Pi	F-1,6bisphosphatase
-3.3	Step 3	G-6-P + H_2O -> glucose + Pi	Glucose-6-phosphatase
-6.9	Total	Overall reaction	

    - Thermodynamic gain

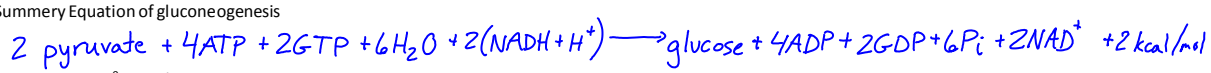
- -6.9 - (22.4) = -29.3 kcal/mol
- Replacing irreversible reactions of glycolysis

- See handout pg 103 for energy difference glycolysis and gluconeogenesis
  - Pyruvate to phosphoenolpyruvate
    - Biotin is CO_2 carrying cofactor

- Summary Equation of hypothetical reversal of glycolysis



- Summery Equation of gluconeogenesis



  - Energy $\Delta G^{0'}$ (kcal/mol) calculation: How many ATP equivalents are used? 6 (4ATP + 2GTP)
    - $\Delta G^{0'}$ (kcal/mol) = +32kcal/mol + 4ATP(-7.5kcal/mol) = +2kcal/mol
    - Compare to previously calculated -29.3 kcal/mol and this -30kcal/mol from 4ATP

  In a liver cell, gluconeogenesis is more favorable than +2kcal/mol

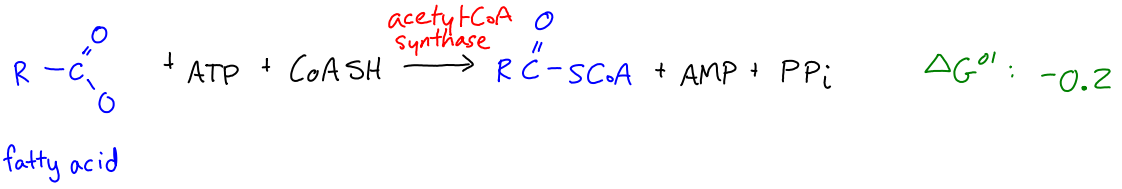
Lecture 08/06

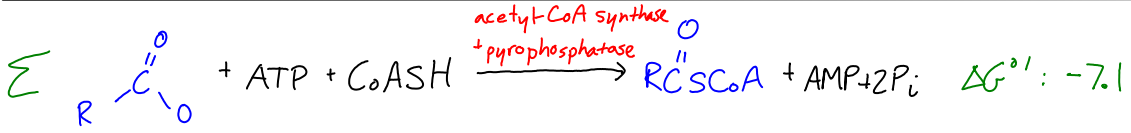
Wednesday, August 06, 2008
10:03 AM

Lecture 0806
Audio recording started: 10:03 AM Wednesday, August 06, 2008

- **Gluconeogenesis**
  - Kidney can also do gluconeogenesis
  - Most of gluconeogenesis occurs in cytosol of liver cells
  - Shuttle system (see handout)
    - Oxaloacetate from mitochondrion shuttled to cytosol
      - Reduced to malate or oxidized to aspartate for shuttle into cytosol
      - Conversion to PEP by PEP carboxykinase to for shuttle into cytosol
    - What dictates if
      - If amino acid is primary source of carbon then goes by aspartate/malate shuttle
      - If have lactate as carbon source then goes by PEP
      - Cytosol doesn't have a lot of NADH, so NADH concentration in cytosol drives the difference of PEP versus aspartate/malate shuttle
        - High NADH in cytosole causes malate aspartate pathway to cytosol to back up
    - $\Delta G'^{0} = 0$ in shuttle system and is driven by concentration
  - What else can serve as carbon source for gluconeogenesis?
    - Citric acid cycle intermediates and amino acids that feed into citric acid cycle because they ultimately form oxaloacetate
    - Exception Acetyl-CoA cannot be used to net synthesize glucose because its carbons are lost via 2x CO_2 in citric acid cycle

- **Fatty Acid Metabolism**
  - Different types of fatty acids (don't memorize all fatty acids on handout)
  - Trans fatty acids don't occur in nature. Enzymes cannot metabolize
    - Esterified to adipose tissue, clip off and go into lipoproteins.
  - Dietary fat is triacylglycerol
  - Body stores fatty acids as triacylglycerol
  - CNS doesn't do beta-oxidation, most other tissue types do
  - Acyl-CoA synthetase
    - ATP + Fatty Acid -> Acyl-adenylase intermediate + pyrophosphate -> fatty-acyl CoA + AMP
    - 3 different versions of acyl-CoA synthetase
      - 1 for long chain fatty acids, 1 for medium, 1 for short

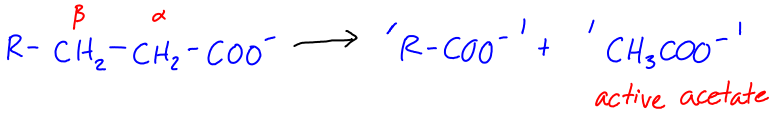




  - Carnitine shuttle system (see handout)
    - Beta-oxidation is in inner mitochondrial membrane
    - Phosphatase is outside the inner matrix. Inner membrane in impermeable of acyl -CoA
    - (don't have to know structure of carnitine)
    - Important things:
      1. No free energy change involved.

2. Carnetine acyltransferase I is very regulated - dictates decision in cell to oxidize a fatty acid or synthesize a fatty acid

- Oxidation of fatty acids (β-oxidation)
  - Oxidation occurs on β-carbon



  - Oxidation clips off 2 carbons at a time as acetyl-CoA (see handout)
  - Notice succinate to oxaloacetate is a very similar pathway (FAD to FADH2 to trans double bond. Hydrate with H_2O, NAD^+ to NADH + H+ to make keto)

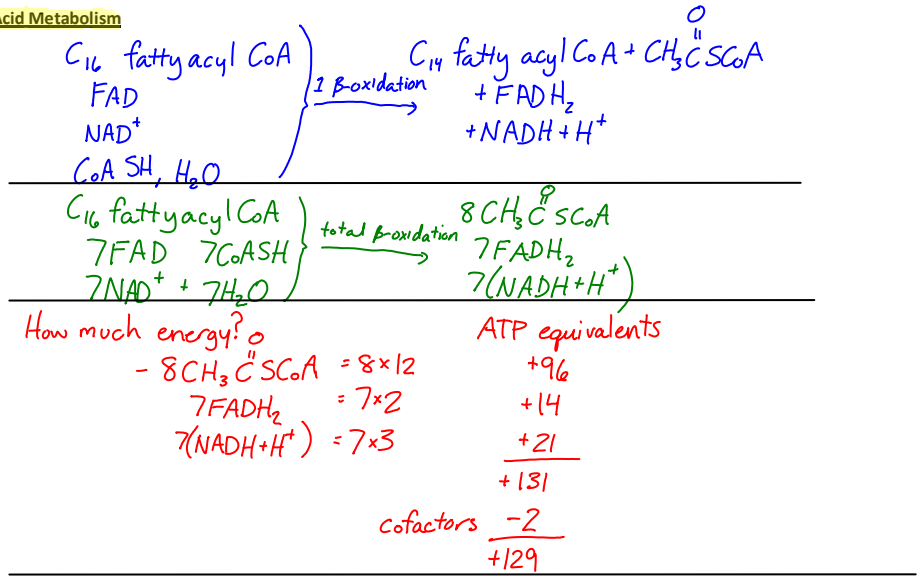
Lecture 08/07

Thursday, August 07, 2008
10:02 AM

Lecture 0807
Audio recording started: 10:02 AM Thursday, August 07, 2008
Audio recording started: 10:22 AM Thursday, August 07, 2008

Lecture 0807

- **Fatty Acid Metabolism**



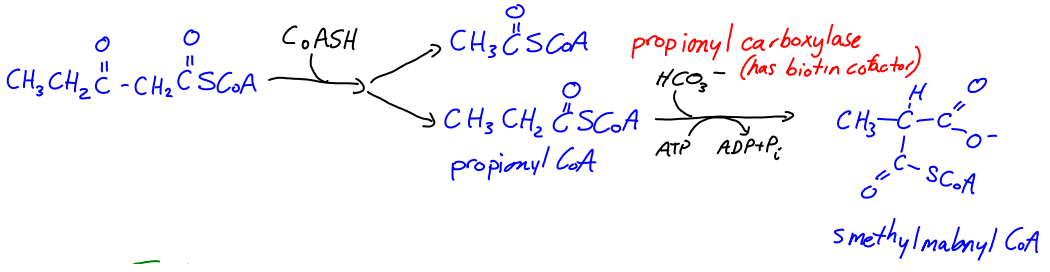
  - **Thermodynamics of palmitic acid**

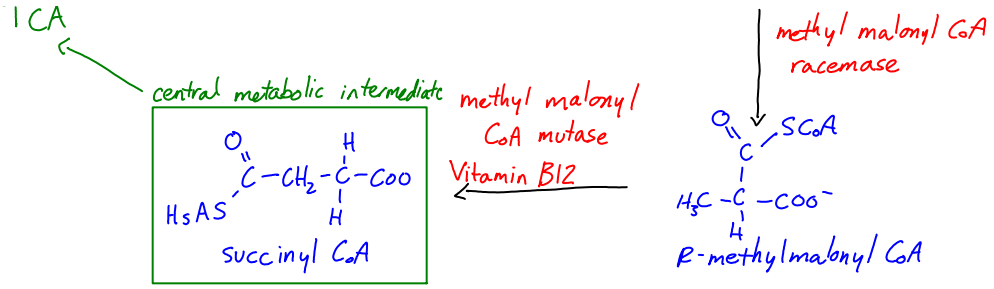
Equation of palmitic acid oxidation	$\Delta G^{0'}$ kcal/mol	Notes
$C_{16}H_{32}O_2 + 23O_2 \rightarrow 16CO_2 + 16H_2O$	-1398	
$131ADP + 131P_i \rightarrow 131\ ATP + 131H_2O$	+983	
$ATP + 2H_2O \rightarrow AMP + 2P_i$	-15	
Total: palmiti cacid + $23O_2$ + $131ADP + 131P_i \rightarrow 16CO_2 +$ $145H_2O$ + 130ATP + AMP + $2P_i$	-430	Why 130 ATP vs 131 ATP? Each are actually 129 ATP equivalents

    - β-oxidation of fats creates lots of water as byproduct. Useful for camels, whales, hibernating animals

  - **Unsaturated fatty acids (double bonds)** see handout figure 17.5 and 17.6 though don't need to memorize
    - Enoyl-CoA isomerase, isomerases from Δ^3 cis to Δ^2 trans (Δ^2 trans is an intermediate of β-oxidation)
    - Δ^4-cis changed to Δ^2-trans to Δ^3-trans to Δ^2 trans
    - Overlap between catabolic and anabolic pathway.
    - When β-oxidation is occurring, when it generates intermediate that has a cis double bond that is too close to the business end where the chemistry is being done, then **auxiliary enzymes** must be present to create a substrate that the β-oxidation enzymes can deal with.

  - **Odd chain fatty acid**
    - Final catalytic step of thiolitic cleavage from fatty acid to create a primary metabolic intermediate





- Concepts in odd chain fatty acid metabolism
  - **Anaplerotic** - replenishment reaction
    - Odd chain fatty acids can replenish TCA intermediates
    - Even chain fatty acids cannot replenish TCA intermediates & glucose due to
  - **Cofactors**
    - Covalently bound to enzymes (ie propionyl carboxylase) - see handout
    - Cofactors have complicated structures and participate in complicated reaction mechanisms. Do not need to know mechanisms
    - First question in exam: 5 pictures of cofactors
      - Identify them (name)
      - Their Function (1C carrier)
      - 1 Enzyme that contains them
      - 1 Reaction that uses them
      - What are the reactive atoms (circle them)
    - **Biotin**
      - Biotin is an activated carbon carrier
    - **Vitamin B12**
      - Tetraporol - structure type (heme, chlorophyl, vitamin B_{12})
      - Co is central atom in tetraporol

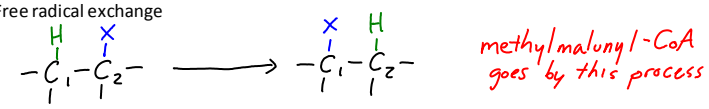
Notes 08/08

Friday, August 08, 2008
9:59 AM

Notes 0808

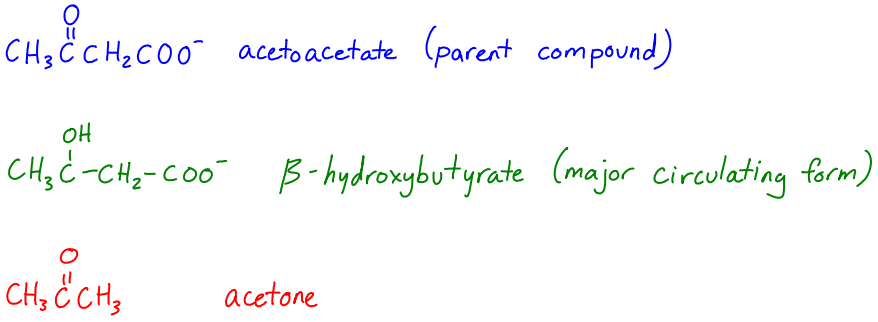
Audio recording started: 10:02 AM Friday, August 08, 2008

- **Vitamin B12 (cont 08/07)**
  - 2 types of reactions
    1. Free radical exchange

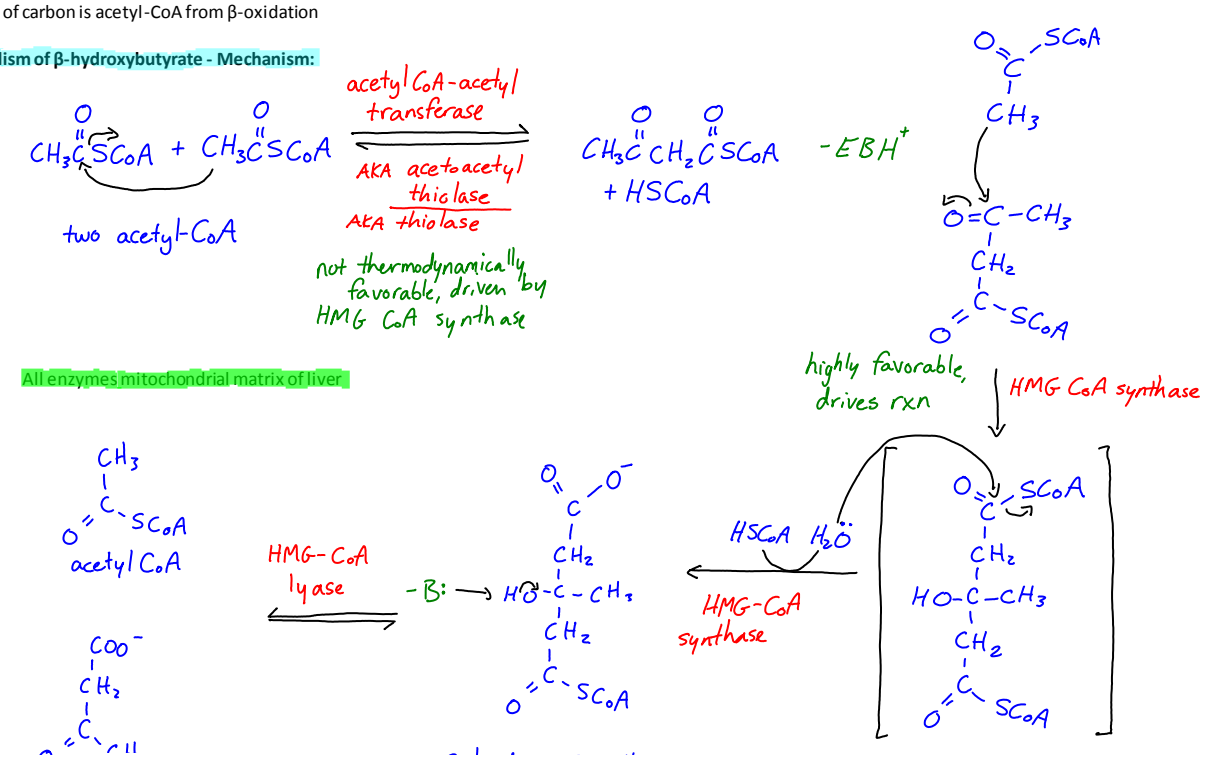


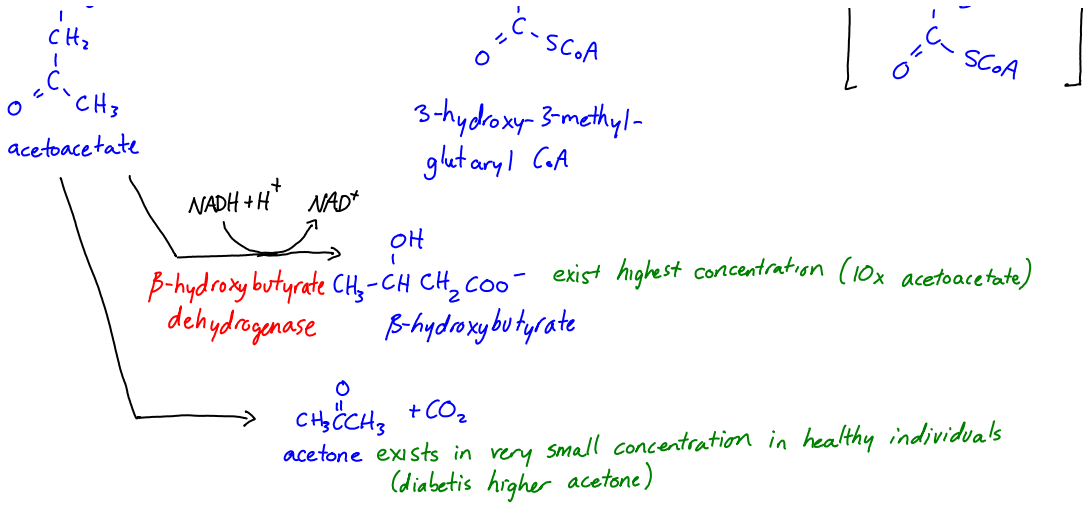
    2. Vitamin B12 transfers methyl groups from 1 group to another

- **Ketone bodies**

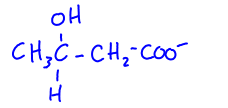
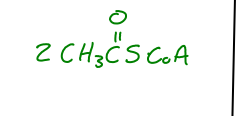
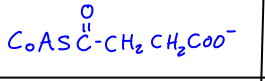
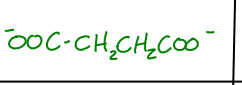


  - Ketone bodies form under fasting conditions or diabetes and synthesized in the liver
  - Source of carbon is acetyl-CoA from β-oxidation
  - **Anabolism of β-hydroxybutyrate - Mechanism:**



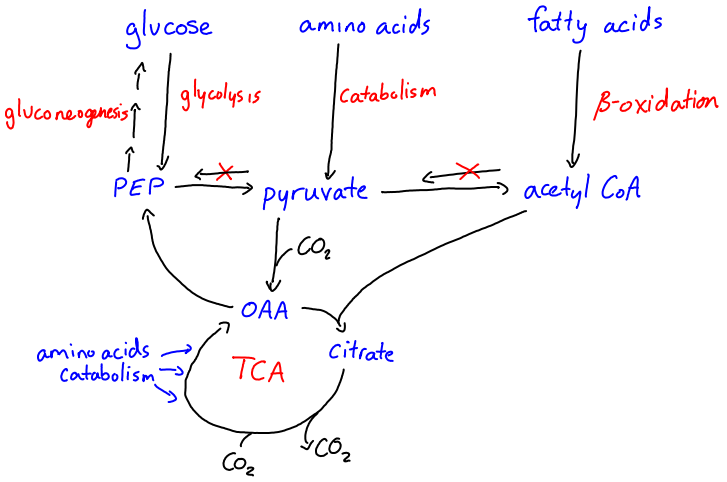


- **Catabolism of β-hydroxybutyrate (see handout 17.11)**
  - How many ATP?

		ATP
		24
		—
NAD^+	$NADH + H^+$	3
CoASH	total 27	

  - Liver does not have β-oxoacid-CoA transferase so it cannot perform catabolism of β-hydroxybutyrate
  - Fatty acids are insoluble and hard to transport so β-hydroxybutyrate (soluble) allows for easy circulation

- **Big Picture Metabolic Pathways**



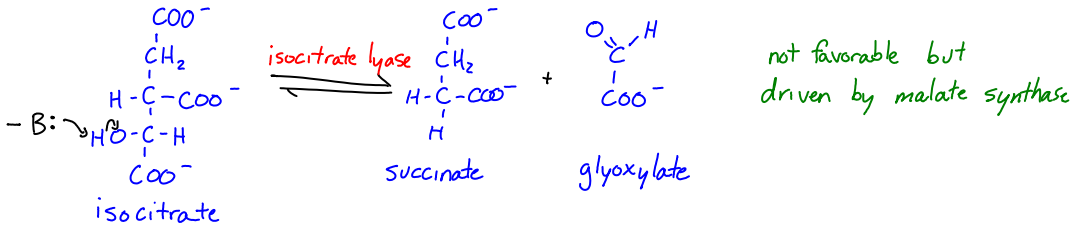
Notes 08/11

Monday, August 11, 2008
10:02 AM

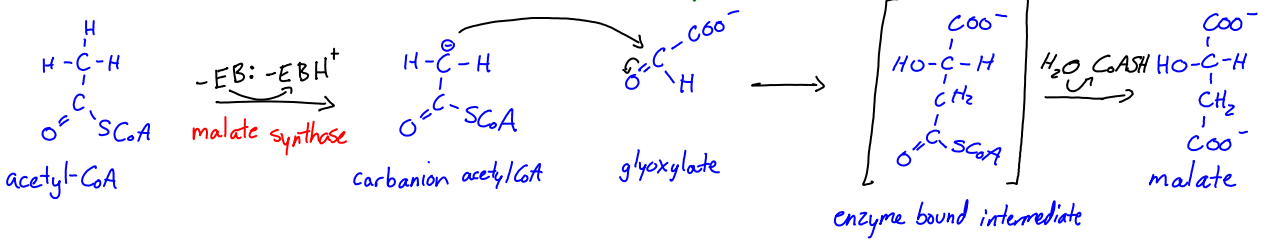
Notes 0811

Audio recording started: 10:03 AM Monday, August 11, 2008

- Glyoxylate Cycle
  1. Isocitrate lyase

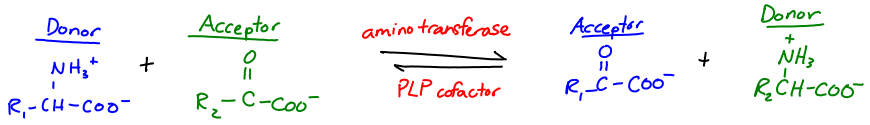


  2. Malate synthase (resembles aldolase mechanism → basic aldol cleavage)



     - Glyoxylate cycle in bacteria (see handout)
       - Bacteria can grow on media (acetate) that produce acetyl-CoA via glyoxylate pathway.
       - Problems:
         - Don't write balanced equation: 2 acetyl-CoA in, 4
       - What dictates which direction?
         - ATP concentration. When high ATP, carbons go through glyoxylate, when low ATP go by citric acid cycle
         - Regulated enzymes
           - malate synthase (high ATP = malate synthase stimulated; low ATP = inhibited)
           - isocitrate dehydrogenase (low ATP=stimulated; high ATP=inhibited
     - Glyoxylate in plants
       - Plants can't grow on acetate.
       - Glyoxylate pathway is associated with fatty acid catabolism
       - Plant seeds have mixtures of carbohydrates and fatty acids for energy storage for germination period
         - Plants that store fatty acids for germination have an organelle: glyoxysome which does β-oxidation of fatty acids
           - To keep cycle driven, need sufficient OAA in glyoxysome to condense with acetyl-CoA. -> A shuttle system to replenish OAA in gloxysome. Without this the whole cycle will stop.
           - Don't focus on stoicheometry

- Amino Acid Catabolism
  - Removing amino group is the 1st step in amino acid catabolism
    - Transamination



      - α-ketoglutarate and glutamate are almost always the donors and acceptors
      - Cofactor: pyridoxal phosphate (PLP)
        - Derived from vitamin B_6
      - Mechanism (equilibrium driven freely reversible)
        1. Transimination
           - Enzyme-PLP is schiff base
           - Deprotenation
        2. Tautomerization
           - Carbanion intermediate (resonance stabilized)
           - Lys from enzyme protenates
        3. Hydrolysis
           - Heterocyclic ring draws electrons down making N-H bond particularly susceptible to hydrolysis

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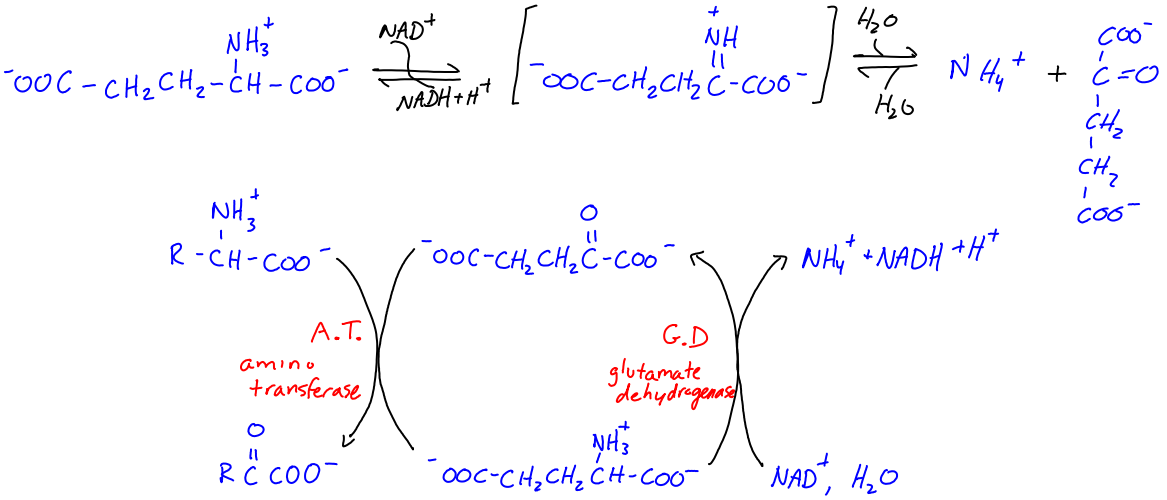
Notes 08/12

Tuesday, August 12, 2008
10:03 AM

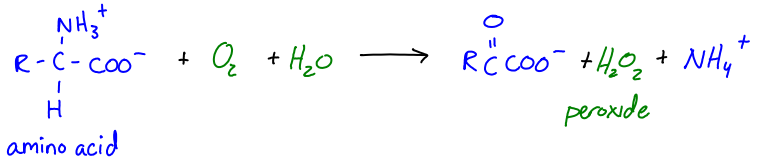
Notes 0812

Audio recording started: 10:03 AM Tuesday, August 12, 2008

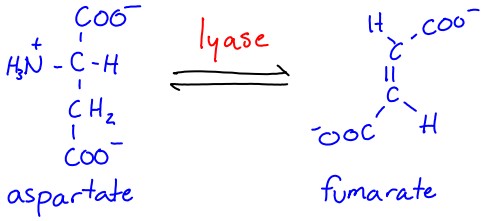
- Amino Removal
    1. Glutamate Dehydrogenase



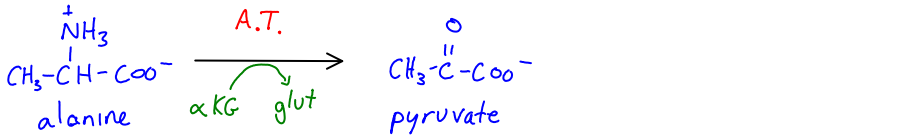
    2. Amino Acid Oxidases

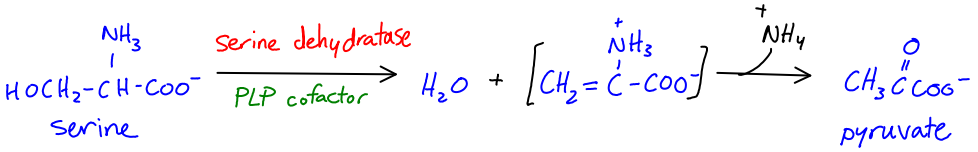


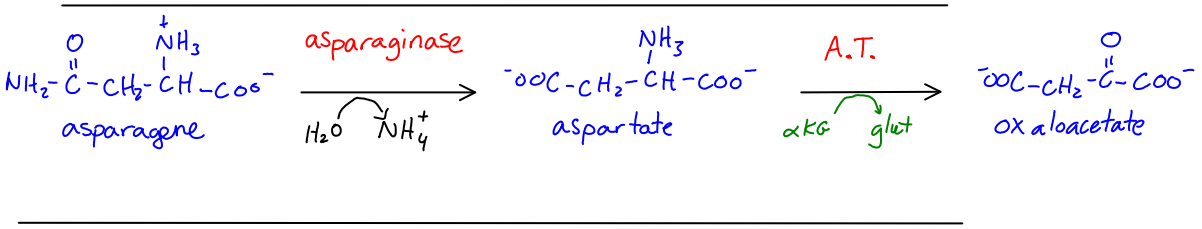
    3. Lyase



- Pathways using Amino Removal







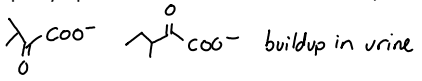
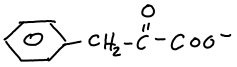
- Handout Figure 24-13
  - Histidine catabolic pathway - don not need to know
  - Some organisms use NAD or NAD(P)$^+$ - can use whatever on tests
  - Know argnine, proline, and glutamine pathways

- Branched chain amino acids (see handout figure 24-15)
  - Got a lot of ATP from branched chain amino acids
  - TPP coenzyme

- Which amino acids are glucogenic or ketogenic or both? (see figure 24-8)
  - Glucogenic - protien turned into glucose
  - Ketogenic only - protein only turned acetyl-CoA and then to keto bodies
  - Give starved diabetic mouse an amino acid and examine product of glucose or keto bodies in its urine

- MSG - glutamate can be neurotoxic and causes headaches when consumed by some

- Genetic Amino Acid Catabolism Diseases

Amino Acid	Deficient Enzyme	Symptoms	Treatment
Valine Isoleucine	Alpha-ketoacid dehydrogenase	Maple syrup urine disease - mental retardation, fatal  buildup in urine	Reduce branched chain fatty acid in diet
Phenylalanine	Phenylalaninehydroxylase Phe → tyr	Causes mental retardation 	Reduce diet with phenylalanine Diet drinks - aspartame converts to phenylalaine

Notes 08/13

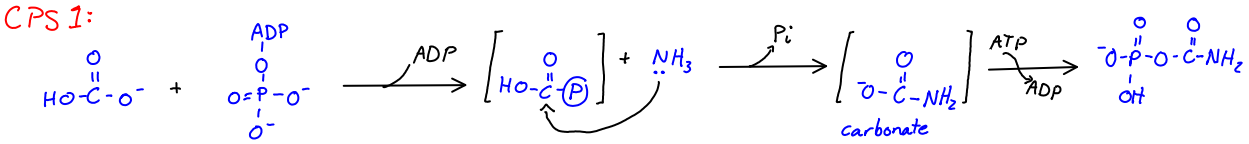
Wednesday, August 13, 2008
10:06 AM

Notes 0813

Audio recording started: 10:06 AM Wednesday, August 13, 2008

Excreted forms	Species
NH_4^+	Aquatic
Urea 	Terrestrial animals (moderate H_2O intake
Uric acid	Low H_2O intake

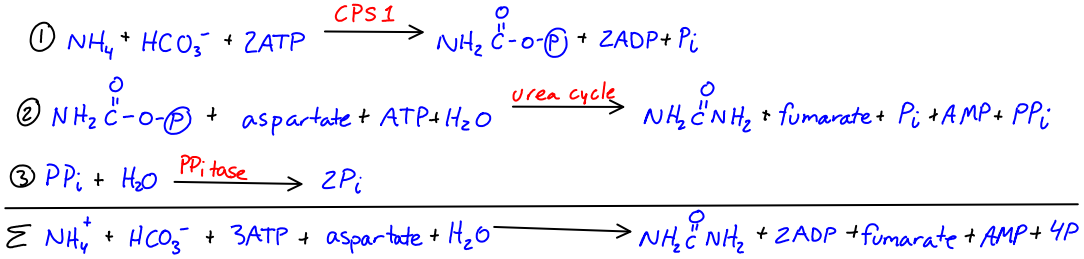
- Ammonia + aspartate
- Carbomoyl Posphate
- Carbamoyl Phosphate synthestase I (CPS I)



- Urea cycle - discovered by Kreb (see handout figure 24-4)
  - Some of cycle in mitochondria and some in cytosol.
    - Cytosol enzymes are associated together for channeling (same for mitochondria enzymes)
  - Enzymes:

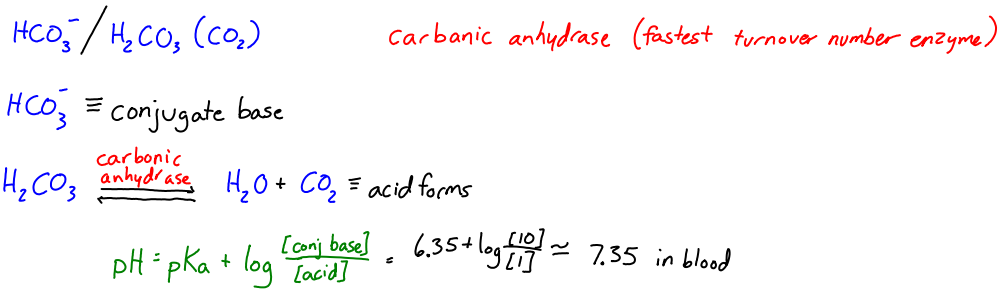
Step	Enzyme	Location	Reaction
Step 2	Ornithine transcarbamoylase	Mitochondria in association with CPS I	Ornithine + carbamoyl phosphate -> citriline + P_i
Step 3	Arginosuccinate synthetase	Cytoplasm In association with cytoplasm urea cycle enzymes	Citrulline + aspartate + ATP -> arginosuccinate + AMP + $2P_i$
Step 4	Arginosuccinase	Cytoplasm In association with cytoplasm urea cycle enzymes	Arginosuccinate -> Arginine + fumarate
Step 5	Arginase	Cytosol In association with cytoplasm urea cycle enzymes	Arginine + H_2O -> urea + ornithine

  - Summary reaction:



    - Conclusions:
      - Energy is required for urea synthesis
      - 4 ATP for one urea

  - Urea cycle affects bicarbonate concentration which is the buffer in blood



Notes 08/14

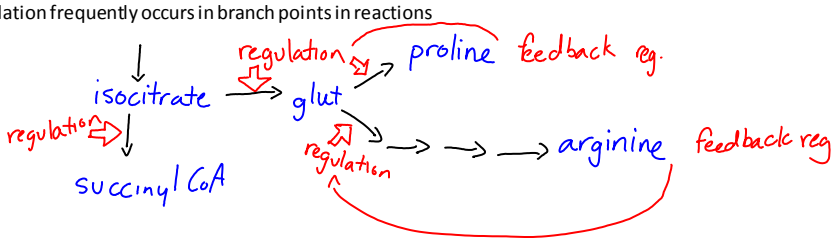
Thursday, August 14, 2008
9:59 AM

Notes 0814

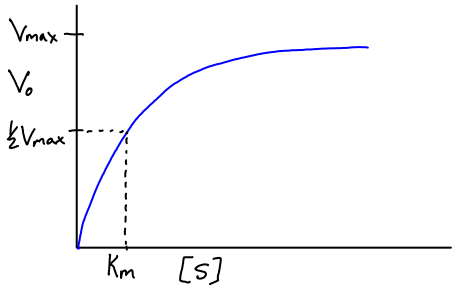
Audio recording started: 10:01 AM Thursday, August 14, 2008

- Urea cycle (continued)
  - See handout 24-7 (relationship urea cycle and TCA)
  - Amonia in urea comes from:
    1. Amino acid -> glutamate -> NH_3 -> carbamoyl phosphate -> urea cycle
    2. Amino acid -> glutamate -> aspartate -> urea cycle

- Regulation (Enzymes and hormones)
  - Why regulate? - conserve resources and prevent a futile cycle
  - Kinetic Regulation of Enzymes
  - Regulation frequently occurs in branch points in reactions



  - Enzyme Kinetics:

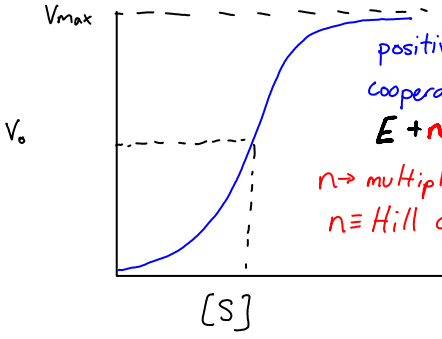


$$E + S \rightleftharpoons ES \rightarrow E + P$$

Assumptions

① steady state ([ES] constant)
② [S] >>> [E]
③ ES complex formation occurs
④ V ≡ initial velocity

$$V = \frac{V_{max}[S]}{K_m + [S]}$$



positive cooperativity

$$E + nS \rightleftharpoons ESn \rightarrow E + nP$$

n → multiple subunits
n ≡ Hill coefficient

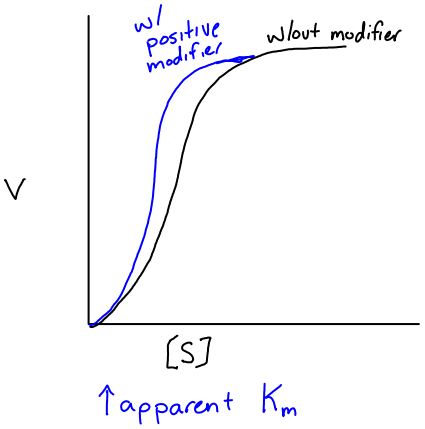
$$V = \frac{V_{max}[S]^n}{[S_{0.5}]^n + [S]^n}$$

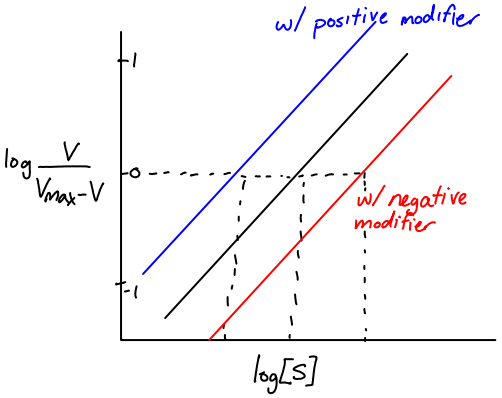
- Cannot do lineweaver burk for sigmoidal (will not be linear) - do a Hill Plot

$$\frac{V}{V_{max} - V} = \frac{[S]^n}{[S_{0.5}]^n}$$

$$\log\left(\frac{V}{V_{max}-V}\right) = n\log[S] - n\log[S_{0.5}]$$

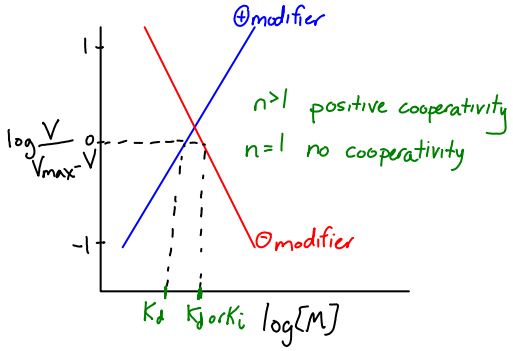
- Isocitrate dehydrogenase regulated by ATP and AMP levels (regulated by intracellular modifiers) and not the substrate itself





- ATP is negative modifier of isocitrate dehydrogenase
- AMP is positive modifier of isocitrate dehydrogenase
- Feedback inhibition for isocitrate dehydrogenase - ATP

Hill Plot (rate vs. modifier concentration)



Hill plot of modifier and shows
1. N for modifier
2. Kd disassocation constant for positive/Kd or Ki for negative

K_{cat}

$$E + S \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} ES \xrightarrow{k_2} E + P$$

$V_{max} = K_2[E_t]$ $\quad k_2 \equiv k_{cat} \equiv$ turnover number

k_{cat} changed by:
① covalent modification
② protein-protein interaction

E_t - can also modify rate

Notes 08/15

Friday, August 15, 2008
9:58 AM

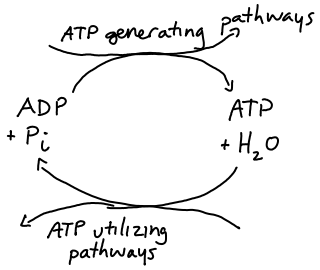
Notes 0815

Audio recording started: 10:03 AM Friday, August 15, 2008

- Enzyme Regulation
  - Isocitrate dehydrogenase:

Isocitrate dehydrogenase modified by:

AMP (or ADP)	+ modifiers
ATP	- modifier



  - Adenylate Energy Charge (E.C.) - represents ratio of charged to uncharged adenylates

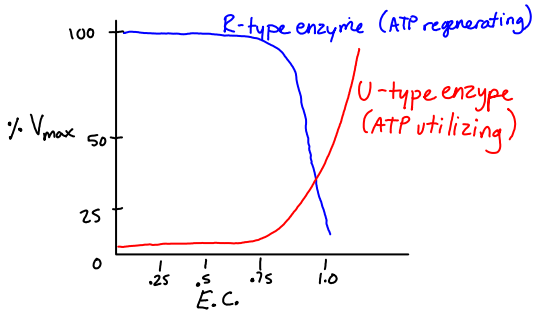
$$E.C. = \frac{[ATP] + \frac{1}{2}[ADP]}{[AMP] + [ADP] + [AMP]}$$

why ½[ADP]? ↳ 2 ADP $\xrightarrow{\text{adenylate kinase}}$ ATP + AMP

Living Cell:
[ATP] = 5mM
[ADP] = 1mM
[AMP] = 0.2mM

$E.C. = \frac{5 + 0.5}{5 + 1 + 0.2} = 0.89$

E.C. in living cells ~ 0.85 - 0.95

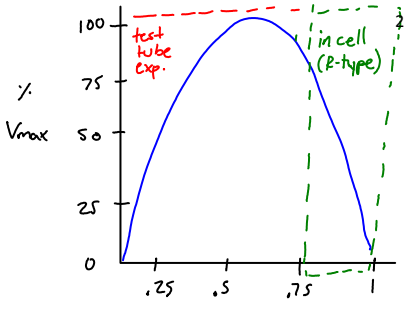


R-type
Enzyme has regulatory adenylate binding site (distinct from substrate active site) for ATP, ADP, AMP that affects enzyme activity. AMP binding affinity for site is much higher since AMP is in low concentration compared to ATP

U-Type

doesn't have adenylate reg. binding site
ATP & ADP compete active site, ATP is substrate & in active site.
competitive inhibition

  - PFK - phosphofructokinase



2 binding sites for ATP on pfk:
1. Active site for ATP as substrate (higher affinity for ATP in PFK)
2. Regulatory ATP site (lower affinity for ATP in PFK but binds when active site is saturated)

  - Regulatory enzymes occur at irreversible steps

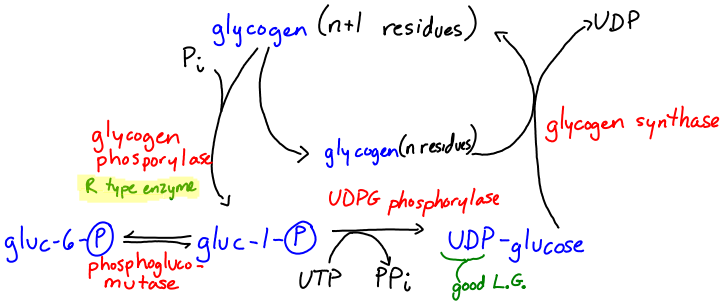
Notes 08/18

Monday, August 18, 2008
9:52 AM

Notes 0818

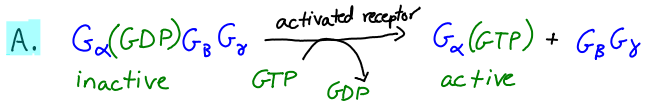
Audio recording started: 10:02 AM Monday, August 18, 2008

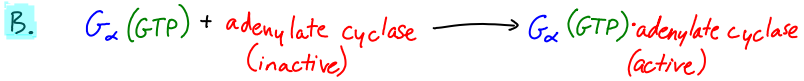
- Hormones can over-ride regulation by intracellular modifiers
- Regulation of glycogen breakdown and synthesis in liver:



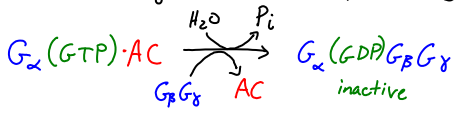
- Talk about 3 hormones in class:
  1. Insulin
     - Produced in response to high blood glucose, beta cells from panaceas,
     - Mission: Promote uptake and storage of glucose
  2. Glucagon
     - Produced in response to low levels of blood glucose, produced alpha cells in Islets of Langerans pancreas
     - Mission: program liver to increase blood glucose
     - Works also on adipose tissue to stimulate mobilization of fatty acids (clip off triacylglycerol of adipose tissue and transported to sites of oxidation)
  3. Epinephrine
     - Stimulates glycogen breakdwon in muscle, liver, fatty acid mobilization, etc... will talk more about later

2. Glucagon:
   - Increase blood glucose, so stimulates glycogen breakdown.
   - Stimulates gluconeogenesis
   - G protein - bind GTP and GDP. Large family of signal transduction proteins.
     - Glucagon stimulates a heterotrimeric G protein
     - G protein alpha subunit occupied by GDP, inactive
     - Glucagon binds to liver transmembrane receptor protein, conformational change, interacts with G protein, GTP binds instead of GDP, activates AC, activtes cAMP (second messenger)

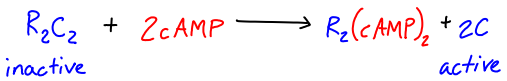




C_1 inactivation (not regulated. Constantly occuring and being degraded. Need constant hormone bound for activity.



   - cAMP stimulates cAMP dependent protien kinase
     - cAMP protein kinase has 4 subunits (2 regulatory)



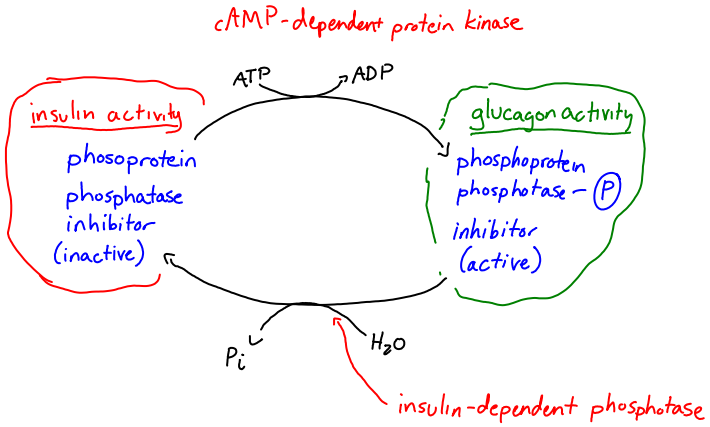
- Amount of active cAMP dependent protein kinase is directly proportional to cAMP levels in the cell.

- cAMP dependent protien kinase
  - When active (see diagram) phosphorylates 2 proteins
    1. Phosphylase kinase b (inactive) -> phosphorylase kinase a (active)
       - Also known as PKA
       - Phosphorylase kinase a then activates phosphorylase a (active) by phosphorylation to break down glycogen to G-1-P

    2. Both cAMP dependent protein kinase and PKA activate **glycogen synthase** (less active) to prevent futile cycle

- glucagon favors phosphorylation to stimulate glycogen breakdown in the liver

- Glucagon re-enforces the phosphorylated state by causing the activation of a phosphatase inhibitor



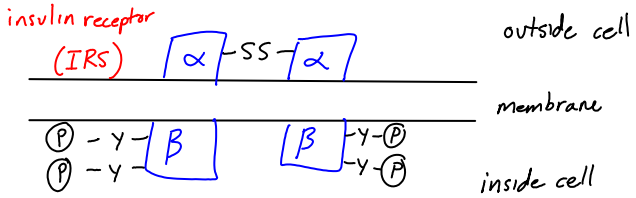
Notes 08/19

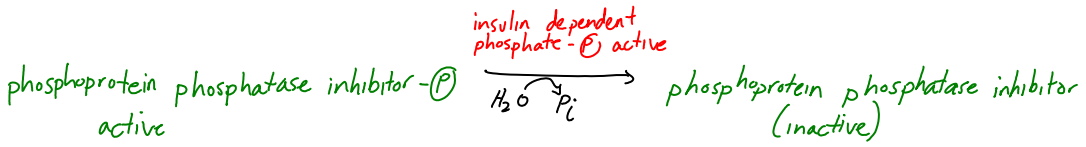
Tuesday, August 19, 2008
10:02 AM

Notes 0819

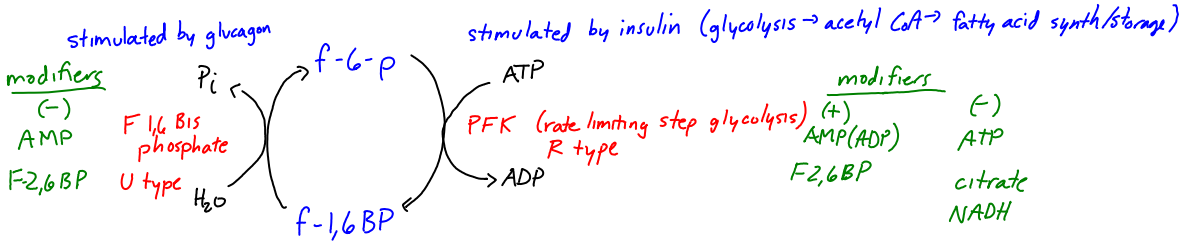
Audio recording started: 10:03 AM Tuesday, August 19, 2008

- cAMP dependent protien kinase acts on
  - Phosphtase inhibitor
  - Phosphorylase kinase a
  - Glycogen synthase
- Insulin - dephosphorylated state of hormonal cascade for glycogen metabolism. Promotes synthesis of glycogen.

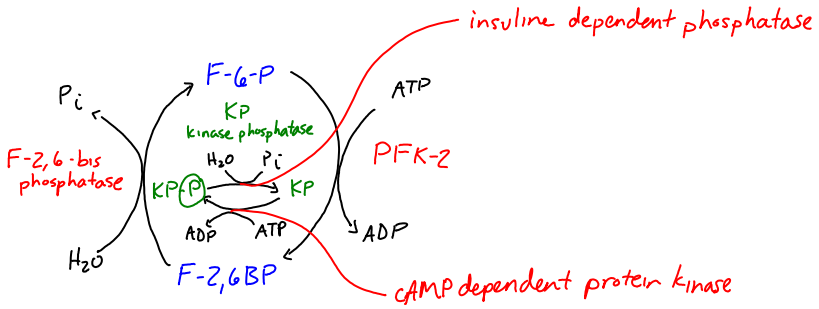




- Insulin and glucagon affect glycolysis in the liver by conversion of F6P to F1,6BP



  - Insulin and glucagon affect level of F-2,6BP
    - F2,6BP stimulates PFK by:
      1. lowering the Km for f-6-p
      2. Increases Ki for ATP and citrate (inhibitor disassociates easier stimulating PFK activity)
    - Inhibits f-1,6bisphosphatase
      1. Decreasing Ki for AMP (enzyme more sensitive toward inhibition by AMP)



f-2,6-bisphosphatase is like a second messenger (not a metabolite)

Notes 08/20

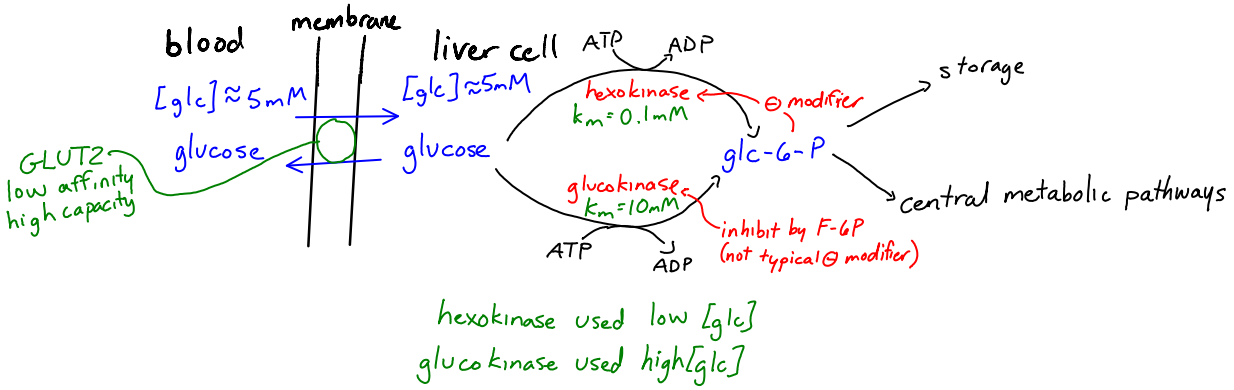
Wednesday, August 20, 2008
9:59 AM

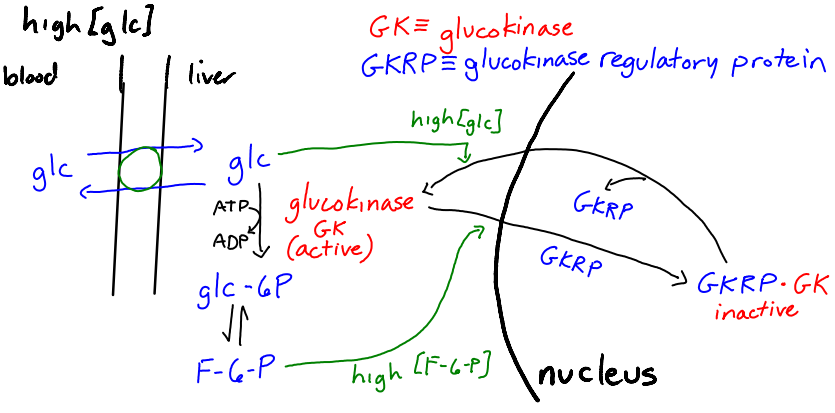
Notes 0820

Audio recording started: 10:02 AM Wednesday, August 20, 2008

Liver	Form present	Pfk-2	f-2,6bisphosphatase	[f-2,6BP]	Effect	Notes
Insulin	K/P (kinase phosphatase)	+	-	High	Favor glycolysis	
Glucagon	K/P-P	-	+	Low	Favor gluconeogenesis	
Muscle	**Form present**	**Pfk-2**	**f-2,6bisphosphatase**	**[f-2,6BP]**	**Effect**	**Notes**
Insulin	K/P (different isoenzyme)	-	+	Low	slow glycolysis	Muscle cells don't do gluconeogenesis, dumps glucose into glycogen stores
Epinephrine	K/P-P	+	-	high	Stimulates glycolysis	Increasing Ca^{2+} will increase K/P-P to stimulate glycolysis

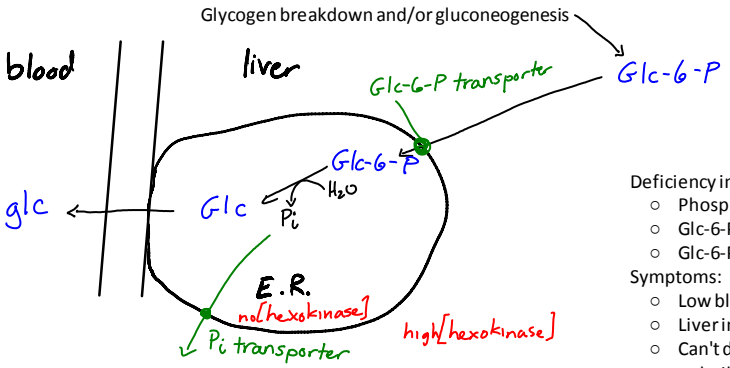
- Midterm material stops here. Following info will not be for midterm.
- Glucose trafficking
  - Tissue specific transporters
  - Glucose uptake in liver cells:





Pancreas also has GLUT2 transporter and equilibrate similar to liver as to gave blood glucose levels.
Insulin secretion in beta cells is based on EC (energy charge).
Can't have enzyme like hexakinase because it is inhibited by G-6-P, have glucokinase instead which allows for high EC

  - Glucose release in liver cells:



Deficiency in (glycogen storage diseases):
- Phosphate transporter
- Glc-6-P transporter
- Glc-6-P phosphatase

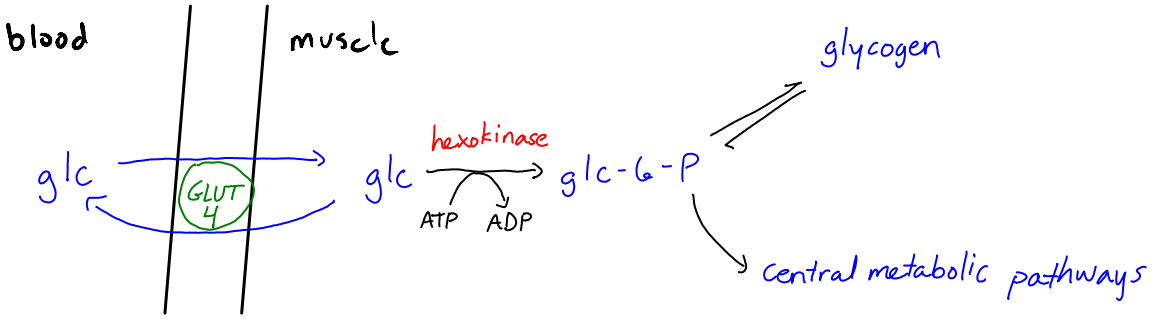
Symptoms:
- Low blood sugar when fasting
- Liver infiltrated with glycogen
- Can't do Cori cycle without gluconeogenesis so buildup of lactic acid (lactic acidemia)

Notes 08/21

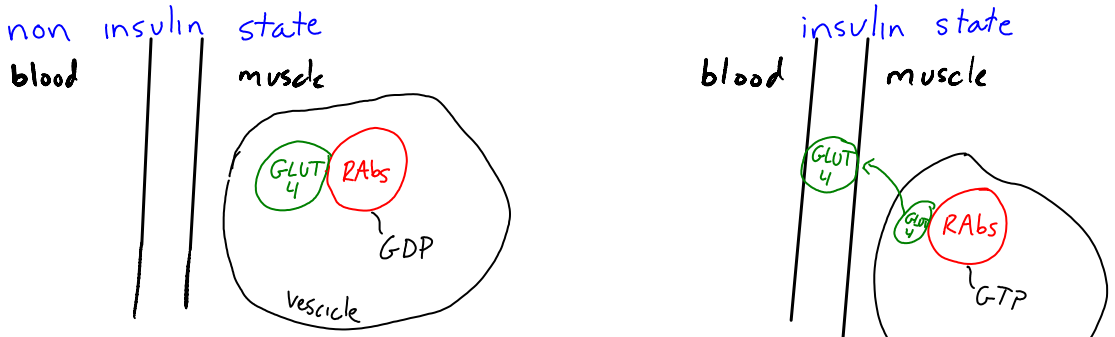
Thursday, August 21, 2008
10:03 AM

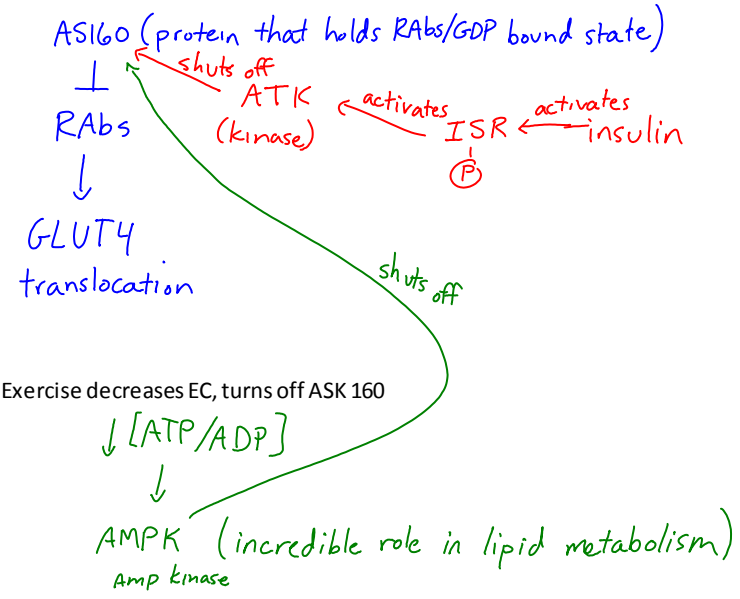
Notes 0821

Audio recording started: 10:03 AM Thursday, August 21, 2008



- Insulin increases GLUT 4 receptors on cell membrane





- Exercise decreases EC, turns off ASK 160

AMPK (incredible role in lipid metabolism)
AMP kinase

- Photosynthesis
  - 2 types of photosynthesizing organisms
    - Eukaryotes
      - Green plants (O_2 evolving photosynthesis)
      - Algae (O_2 evolving photosynthesis)
    - Bacteria
      - Cyanobacteria (O_2 evolving photosynthesis)
      - Other bacteria (anaerobic photosynthesis)

  - Van Neil equation

$$H_2O + A \longrightarrow O + AH_2$$

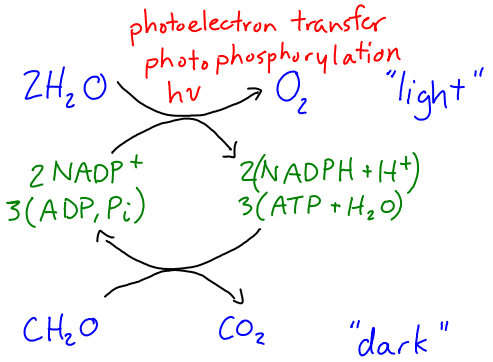
	H_2O: e^- donor	A: e^- acceptor	O: oxidized donor	AH_2: reduced acceptor
O_2 evolving	H_2O	CO_2	O_2	CH_2O
anaerobic	H_2S	NO_3^-	S°	NH_3
anaerobic	organic substrate	H^+, N_2	oxidized substrates	H_2, $2NH_3$

$$H_2O + CO_2 \xrightarrow{h\nu} CH_2O + O_2$$

$$6H_2O + 6CO_2 \xrightarrow{h\nu} \underbrace{C_6H_{12}O_6}_{\text{carbohydrate}} + 6O_2$$

- 2 sides of thylakoid membrane:
  - Outside: Lumen
  - Inside: Stroma - fixing CO_2 into carbohydrate

- 2 types of reactions
  - Light and dark reactions - occur only in the light



Review for Midterm

Friday, August 22, 2008
10:07 AM

Review

Audio recording started: 10:07 AM Friday, August 22, 2008

- Glycolysis - interconvertable pool

- Malate/aspartate shuttle
  - When PEP vs. malate/aspartate

- Fatty acid catabolism
  - Lots of structures on 1st page… won't ask
  - Know how to draw palmatate
  - Fatty acid must be activated by enzyme fatty acyl coa synthetase (on outer membrane of matrix) (won't worry about structures or mechanism)
    - Carnatine shuttle - know how it operates
      - Carnatine acyl transferase I is important regulatory enzyme
  - Acyl coa is in matrix and now beta oxidation - know how much ATP (NADH 3 atp, acetyl Coa is 12 ATP, FADH 2ATP) . Know structures and steps etc
    - Unsaturated beta oxidation - don't worry about
    - Odd chain fatty acid - propinyl coa to succinyl coa - know structures, enzymes, etc
  - Even chain can't be used to replenish citric acid cycle but odd chain (propinyl to succinyl coa. Can be used for net synthesis of glucose)

- Ketone bodies
  - Acetyl coa from fatty acid metabolism has 2 fates
    - Carbon completely oxidized by TCA and get ATP
    - Used in synthesis of ketone bodies (synthesized liver mitochondrial matrix)
  - Know pathway, enzymes, and structures, mechanisms
  - Know why liver cannot catabolize ketone bodies (lack enzyme)

- Know mechanisms that are similar

- Glyoxylate - certain microorganisms can grow on substrates that solely produce acetyl-CoA, need way to replenish TCA… glyoxylate
  - Acetate, even chain fatty acids as only growth medium
  - Isocitrate lyase and malate synthase
  - Know the glyoxylate pathway. Know structures, enzymes, mechanism
  - Seeds of some oil producing plants can use those fatty acids as energy source during germination before photosynthesis… developmentally regulated. Glyoxisome organelle contains beta oxidation enzymes and glyoxylate pathways.
  - In order to do glyoxylate in glyoxisome there must be a pool for oxaloacetate

- Aminio acid catabolism
  - Responsible of enzymes and pathways
  - Alanine - AT to get pyruvate
  - Serine
  - Asparagine
  - Aspartate
  - Arganine!
  - Proline!
  - Glutamine!
  - Glutamate !
  - Isoleucine - complicated pathway.

  - Strategy
    1. Remove amino group (amino transferase reaction (PLP but won't deal with)). Alpha keto glutarate - glutamate . Keto acid skeleton

       - Some amino acids ketogenic, glucogenic (don't need to know)

- Urea cycle - know it.
  - ATPs
  - Mechanism
  - Contributes to pH balance -> aids in excretion of bicarbonate -> lower pH of blood (acidify)

- Hormones
  - Insulin, glucagon

    - Nothing about glucose trafficking
    - Glycogen breakdown and synthesis
    - Glycolysis and gluconeogenesis
    - True false questions (resonable unreasonable)

- Comparison with skeletal muscle - know the table in notes

- Don't memorize glycolysis and gluconeogenesis

Notes 08/22

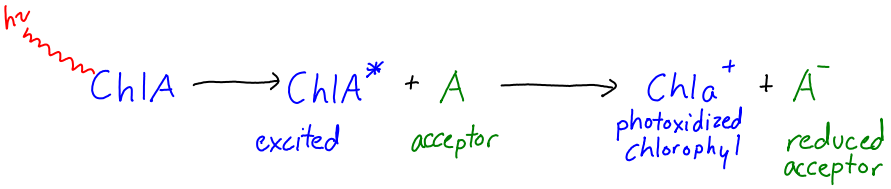
Tuesday, August 26, 2008
10:03 AM

Notes 0822

Audio recording started: 10:03 AM Tuesday, August 26, 2008

Photosynthesis

- Handout pg 2.
  - Don't need to memorize table
  - Chlorophyll a, chlorophyll b, and cartenoids absorb energy (photons) and transfer to reaction center
- Handout pg 3.
  - Reaction centers P-700 and P-680



  - Unfavorable electron transport driven by absorption of light to create NADPH and ATP

- Z-cheme of photosynthesis
  - Water is used to replenish electrons from photoxidized P680. Light drives reaction, not water donating electrons
  - +0.8 to -0.32 redox potential is not favorable (mammal respiration is -0.32 to +0.8 which is favorable).
  - Cytochrome b_6F complex are purely electron carriers -> protons pumped from stroma to luma.
  - Plastocyanine - donates to photoxidized P700
  - Fd-$NADP^+$ reductase

  - How many photons have to absorb to make NADPH?

quantum requirements

$$H_2O + NADP^+ \xrightarrow{h\nu} \tfrac{1}{2} O_2 + NADPH + H^+ \quad \text{4 } h\nu$$

$$2H_2O + 2NADP^+ \xrightarrow{h\nu} O_2 + 2NADPH + 2H^+ \quad \text{8 } h\nu$$

  - Cyclic pathway allows for proton pump from stroma to lumen for ATP synthesis
  - NADPH production is from noncyclic pathway.
  - Balance of ATP to NADPH is maintained from high [NADPH] feedback on noncyclic and favoring cyclic pathway for ATP synthesis

  - Stoicheiometry
    - 3 protons for 1 ATP

$$2e^-: \; H_2O + NADP^+ + 1.5\,ADP + 1.5\,P_i \xrightarrow{4h\nu} \tfrac{1}{2} O_2 + NADPH + H^+ + 1.5\,ATP$$

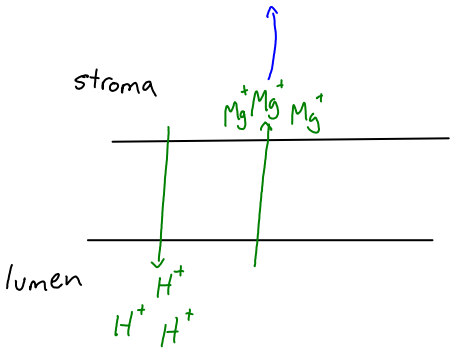
$$4e^-: \; 2H_2O + 2NADP^+ + 3ADP + 3P_i \xrightarrow{8h\nu} O_2 + 2NADPH + 2H^+ + 3ATP$$

electochemical gradient

$$\Delta\mu_{H^+} = 2f\Delta\psi + 2.3RT\,\Delta pH$$

membrane potential — electrical

pH gradient — chemical



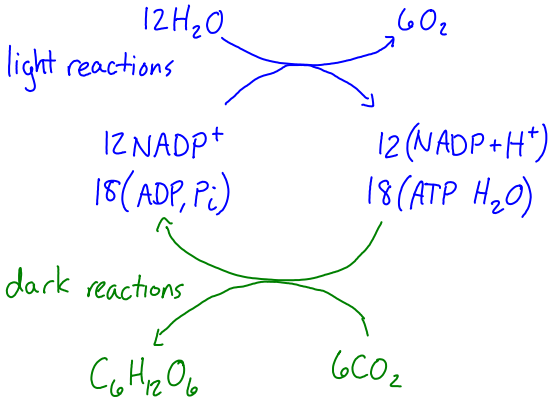
- Buffering in mitochondria is mostly membrane potential.

Notes 08/27

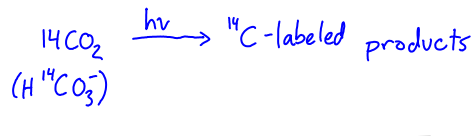
Wednesday, August 27, 2008
10:00 AM

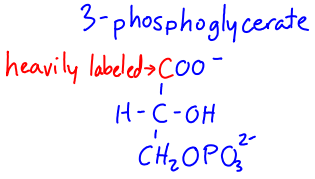
Notes 0827

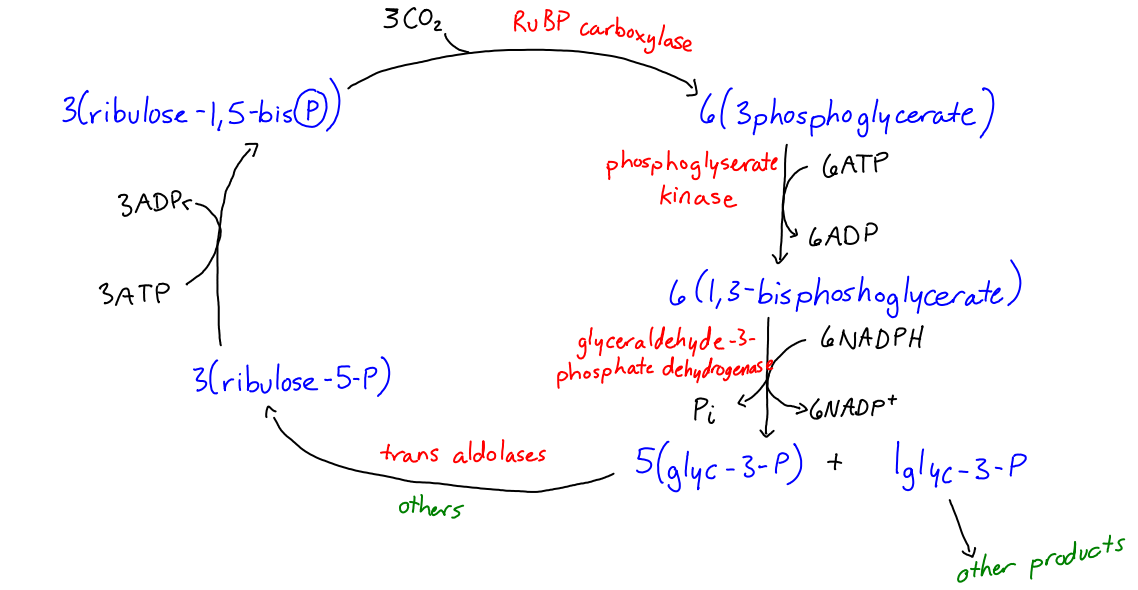
Audio recording started: 10:02 AM Wednesday, August 27, 2008



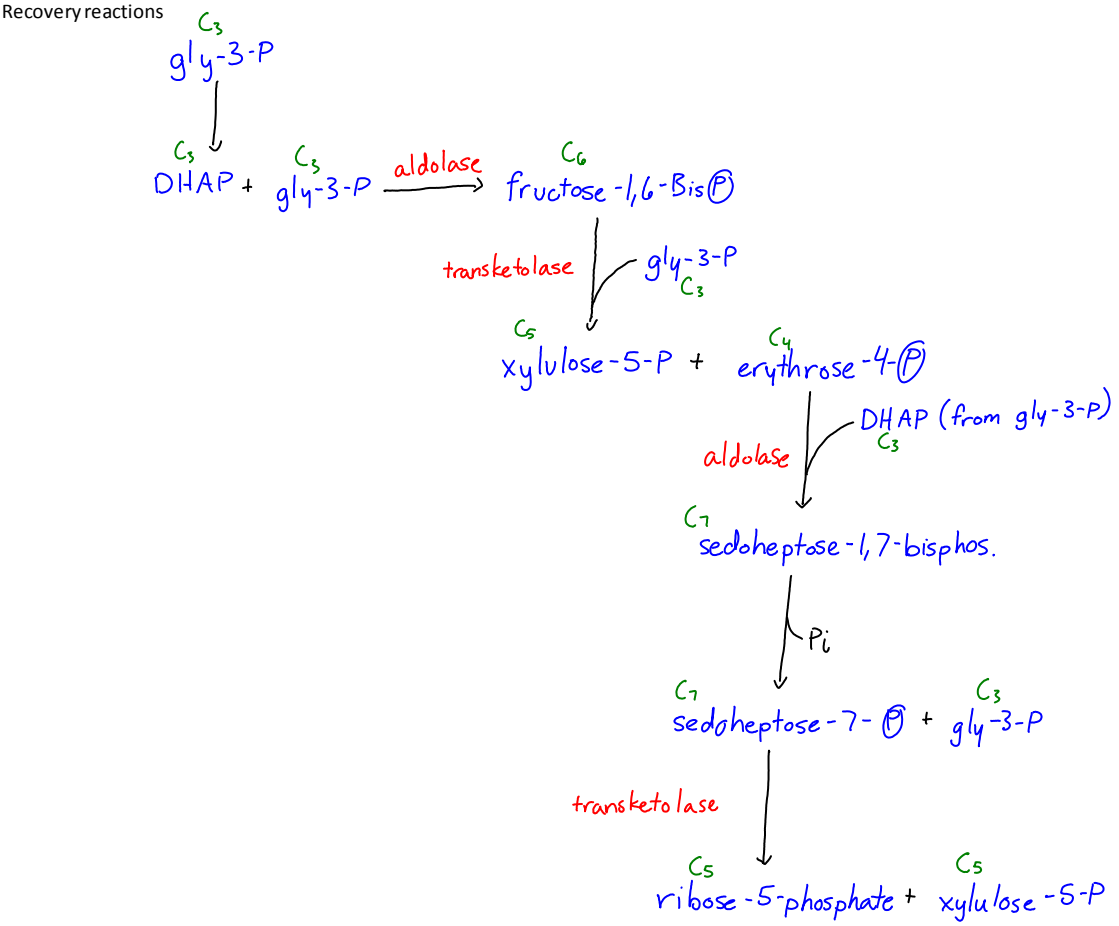
- Calvin cycle
  - Scenedesmas (green algae) radioisotope carbon and interrupted (killed) at different time periods to discover order

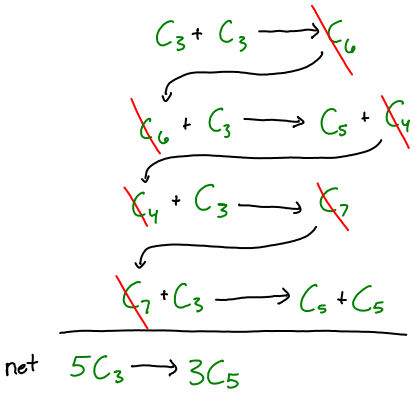






Recovery reactions





- Transketolase has cofactor - TPP (B1 vitamin) - carries activated 2 carbon units

- Energetics

Hypthetical process	$6CO_2 + 6H_2O \rightarrow C_6H_{12}O_6 + 6O_2$	$\Delta G^{0'}$ = +686kcal/mol	Notes: no light energy
Real process	$6CO_2 + 6H_2O$ 12(NADPH + H^+) + 18ATP-> $C_6H_{12}O_6 + 6O_2$ 18(ADP, P_i) + 12$NADP^+$	$\Delta G^{0'}$ = -120kcal/mol	Favorable by light energy

  - How many quanta required?

# CO_2 fixed	# NADPH required	# of electrons required	# of ATP required	# ATP produced	# of hv required
1	2	$4e^-$	3	3	8
6	12	$24e^-$	18	18	48

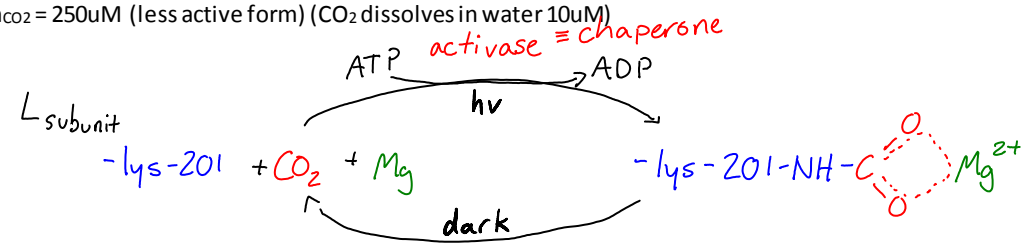
Notes 08/28

Thursday, August 28, 2008
10:06 AM

Notes

Audio recording started: 10:06 AM Thursday, August 28, 2008

- Ribulose -1,5 bisphosphate carboxylase. Canalized by light
  - 16 subunit enzyme: L_8S_8 (8 large, 8 small)
  - Km_{CO2} = 250uM (less active form) (CO_2 dissolves in water 10uM)

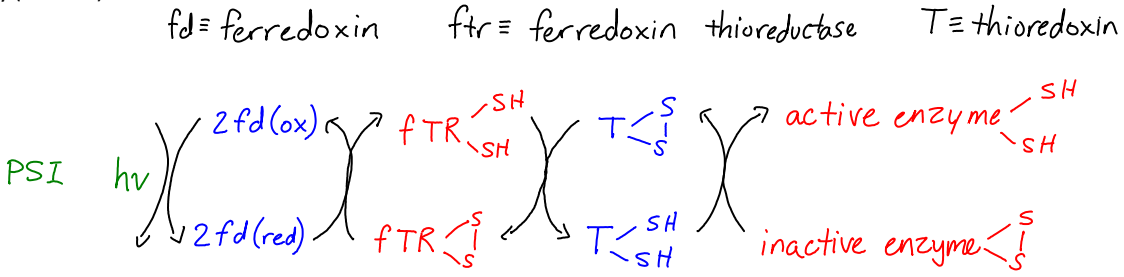


    - 2-carboxyl arabinitol (pentose alcohol) binds and blocks binding of CO_2

  - How light regulates process?
  - Factors for light activation:
    1. [Mg^{++}] increases in stroma in light
    2. Higher pH in stroma in light (lys side chain unprotinated -NH_2)
    3. Higher ATP in stroma in light

- 4 other enzymes in calvin cycle regulated by light
  1. 5-phosphoribulokinase
  2. Glyceraldehyde-3-phosphate dehydrogenase ($NADP^+$)
  3. F-1,6bisphosphatase
  4. Sedoheptulose-1,7bisphosphate

  - Pathway (for all 4):



System	CO_2	O_2
Photosynthesis	Uptake	Release
Photorespiration	Release	uptake

  - Photorespiration - light dependent

[CO_2]	[O_2]	Relative efficiency of phtosynthesis (efficiency = amount of quanta needed to fix a CO_2)
[atm] 10mM	21%	100%
[atm]	2%	145%

- Oxygen can compete for active site of RuBP carboxylase-oxygenase to give 3PG and 2-phosphoglycolate (phosphoglycolate has to recycle carbons which takes energy)

- Metabolism of phosphoglycolate:
  - RuBP + O_2 -> 2-phosphoglycolate + 3PG
  - 2-phosphoglycolate -> P_i + glycolate
  - ->glyoxylate
  - ->glycine
  - ->serine + CO_2 (glycine cleavage pathway. Requires 2 glycines)
  - Lose 2 ATP which makes photosynthesis inefficient

- Raise temp and/or light intensity, electron transport is faster and less efficient
- C_4 plants fix CO_2 into 4 carbon compound and are well designed to combat photorespiration problem and grow in warm temperatures

Notes 08/29

Friday, August 29, 2008
10:03 AM

Notes 0829

Audio recording started: 10:03 AM Friday, August 29, 2008

- C_4 plants are adapted to deal with photorespiration
  - C_4 plants have different anatomy
    - Mesophyll cells surround bundle sheath cells
  - There are many types of C_4 but just need to know malate dehydrogenase, decarboxylating type shown in notes
    - PEP carboxylase has high affinity for CO_2
    - Malate transported and regenerated and goes onto rubisco.
    - CO_2 is not very soluble in water so this converts it to malate which is very soluble in water.
    - When decarboxylate malate, coupled to NADPH production. If have high NADPH then goes by cyclic electron transport to level out NADPH/ATP levels. Cyclic does not produce oxygen.
    - Photosynthesis by C_4 plants costs an extra 2 ATP for each CO_2 fixed due to pyruvate to PEP conversion to replenish
    - CO_2 fixation is spatially fixated
  - Crassulacean acid metabolism plants (CAM) - cactus, aloe, etc
    - CO_2 fixation separated in time rather than spatially fixated like C_4
    - CAM plants accumulate dicarboxylic acids (malate, OAA) at night as stomata open up and PEP carboxylase acts to make dicarboxylic acids for storage
    - When lights come on stomata close and calvin cycle enzymes turn on.

- NADPH
  - Compare reduction potential of NADP and NADPH
    - E_0' for $NAD^+/NADH + H^+ = -0.32V$
    - E_0' for $NADP^+/NADPH + H^+ = -0.32V$
  - Functions:
    1. NAD serves as electron acceptor (oxidant) for substrate oxidations
    2. NADPH serves as an electron donor (reductant) for biosynthetic substrate reductions

In liver

$$\frac{[NADH]}{[NAD^+]} \simeq \frac{1}{100}$$

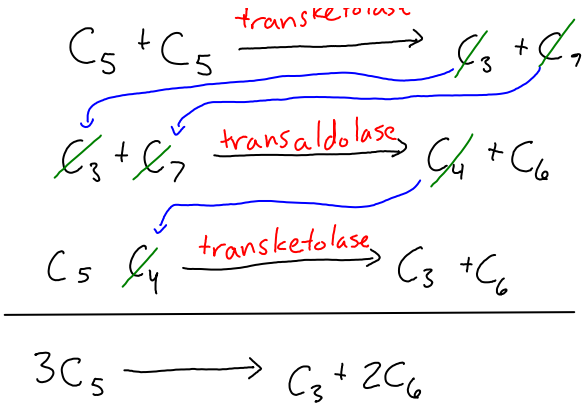
$$E' = E_0' - 2.3\frac{RT}{nF}\log\frac{[reduced]}{[oxidized]}$$

$$\frac{[NADPH+H^+]}{[NADP^+]} \simeq \frac{100}{1}$$

for $[NADH]/[NAD^+] = 10^{-2}$ $\quad E' = -0.32V + 0.06V = -0.26V$ accept e^-

for $[NADPH+H^+/NADP^+] = 10^2$ $\quad E' = -0.32V - 0.06V = -0.38V$ donate e^-

  - NADPH utilization pathways and regenerating pathways maintain 100/1 ratio
    - Regenerating - photosynthesis



- NADPH is used to reduce Spectrin - keeps red blood cells in good shape

- Transketolase uses coenzyme TPP
  - TPP - resonnance stablized 2 carbon carrier

Notes 09/02

Tuesday, September 02, 2008
10:01 AM

Notes 0902

Audio recording started: 10:02 AM Tuesday, September 02, 2008

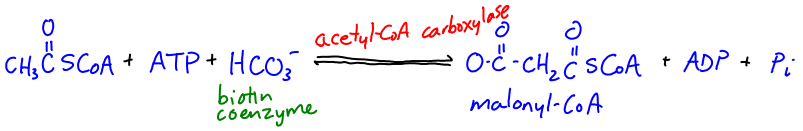
- Ways to regenerate NADPH
  1. Glucose-6-P dehydrogenase
  2. 6-P-gluconate dehydrogenase
  3. $NADP^+$ malic dehydrogenase, decarboxylating ("malic enzyme")
     - In cytosol
  4. $NADP^+$ isocitrate dehydrogenase
     - In cytosol, different than TCA enzyme because uses NADPH and not NADH
  5. Non-cyclic photoelectron transport in photosynthetic plants
  6. Mitochondrial energy-dependent transhydrogenasion
     - Proton motive force

- Pentose phosphate pathway (regulation)
  - What dictates glucose goes through glycolysis or pentose phosphate? = EC (interconvertable pool of hexoses)
  - NADPH is competitive inhibitor of NADH for PFK
    - When NADPH is high then PFK activity is slow

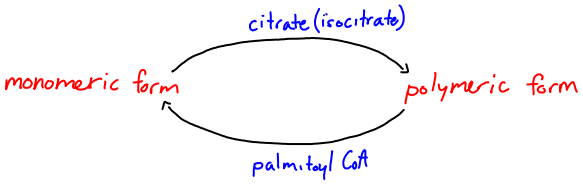
- Fatty acid biosynthesis (not reversal of beta oxidation)

	Fatty acid synthesis	Reverse beta oxidation
location	Cytosol	Mitochondria
Substrates	Acetyl-CoA	Acetyl-Coa
Reductants	NADPH, ATP, HCO^-	$FADH_2$, NADH + H^+

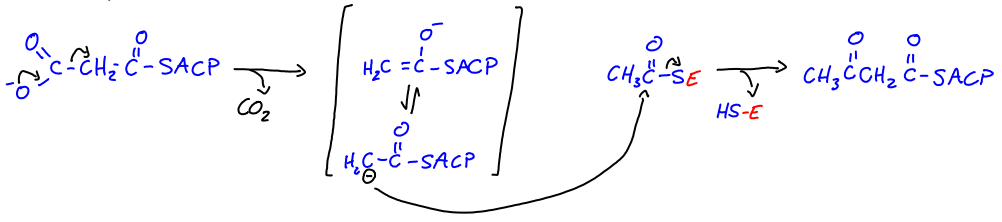
  - Acetyl-CoA carboxylase rate limiting step and highly regulated



    - Exists in filaments of polymeric and monomeric form



  - Fatty acid synthase
    - 6 catalytic activities
    - Associated protein (acyl-carrier protein or ACP)
    - Malonyl-CoA is source of carbons (built 2C at a time) with acetyl-CoA rate limiting step producing malonly-CoA
    - Mechanism of step 3:



    - Termination enzymes stop chains from continually growing.
      - Temperature can determine in e.coli if fatty acids are terminated at shorter or longer lengths

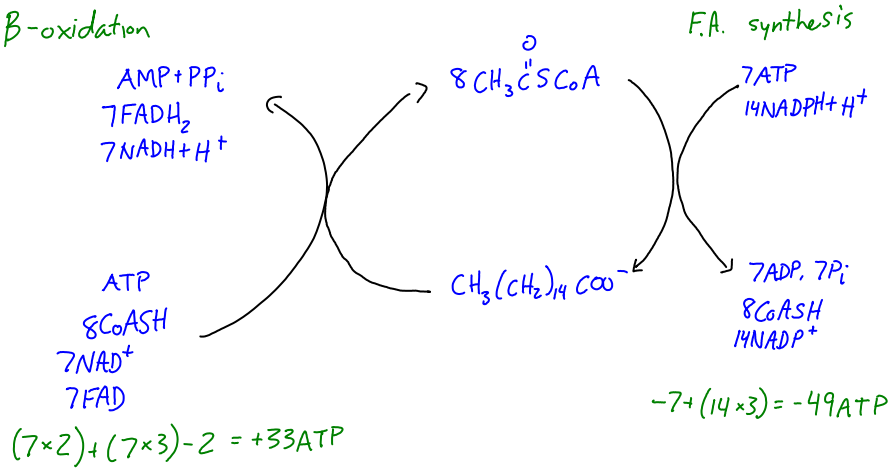
- How many ATP?

fatty acid synth

$$7\,CH_3\overset{O}{\overset{\|}{C}}SCoA + 7HCO_3^- + 7ATP \longrightarrow 7\,^-OOC\text{-}CH_2\overset{O}{\overset{\|}{C}}SCoA + 7ADP + 7P_i$$

$$7\,^-OOC\text{-}CH_2\overset{O}{\overset{\|}{C}}SCoA + CH_3\overset{O}{\overset{\|}{C}}SCoA + 14(NADPH + H^+) \longrightarrow CH_3(CH_2)_{14}COO^- + 8CoASH + 14NADP^+ + 7HCO_3^-$$

$$\Sigma\ 8\,CH_3\overset{O}{\overset{\|}{C}}SCoA + 7ATP + 14(NADPH + H^+) \longrightarrow CH_3(CH_2)_{14}COO^- + 8CoA$$



Notes 09/03

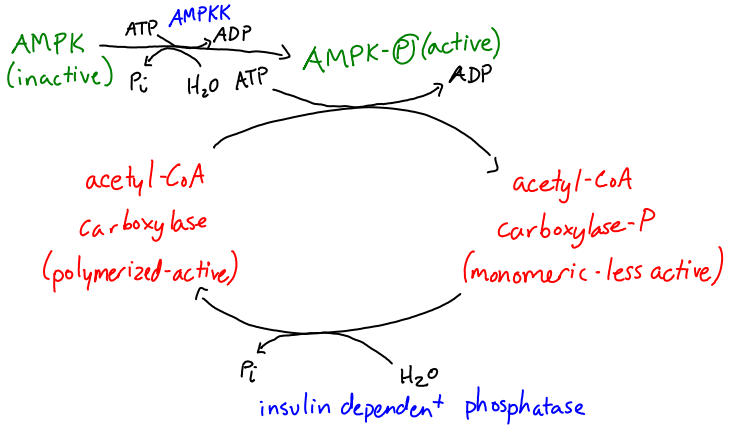
Wednesday, September 03, 2008
10:03 AM

Notes 0903

Audio recording started: 10:03 AM Wednesday, September 03, 2008

- Fatty Acid Synthesis
  - Tricarboxylic transport system
    - Transport driven by ATP, not ΔG=0 like shuttle systems
    - Can transport citrate and isocitrate
    - ATP citrate lyase creates oxaloacetate and acetyl coa from citrate.
    - Oxaloacetate to pyruvate converts NADH to NADPH (2 step)
    - Citrate regulates PFK

- Regulation of fatty acid biosynthesis and oxidation in liver (see handout)
  1. Carnitine acyl transferase I
     - Transports fatty acyl coa into mitochondria for beta oxidation
     - Neg modifier: malonyl coa
       - High malonyl coa in cytosol, carnitine acyl transferase is inhibited
  2. Isocitrate dehydrogenase
     - Isocitrate to alpha-ketoglutarate
     - R type enzyme: Regulated by adenylates.
       - High ATP slows activity of isocitrate dehydrogenase
       - High ATP favors movement of citrate to cytosol
  3. Citrate lyase
     - Regulated by energy charge (U type enzyme)
  4. ....
     - Positively regulated by high levels of NADPH
       - G6PDH creates NADPH is cytosol. Increase activity by increasing glucose amount or inhibit PFK activity (interconvertable pool). PFK is regulated by energy charge and citrate.
  5. Acetyl-coa transferase
     - Polymerized active form and monomeric less active form
     - Polymerized form is favored by high levels of citrate



AMPKK - AMP kinase kinase

AMPK - AMP kinase

When AMPK is bound by AMP, it can be phosphorylated by AMPKK

AMPK cannot be phosphorylated (active) unless AMP levels are high (EC is low) via conformational change by bound AMP

- Liver in glucagon state
  - Making glucose by gluconeogenesis and making ketone bodies
  - Do not want to be doing fatty acid biosynthesis under glucagon state
  - Glucagon favors phosphorylated state - creates phosphatase inhibitor which favors phosphorylated state

- Why does fatty acid synthesis not use cAMP dependent kinase
  - Not all tissues respond to glucagon and cAMP dependent kinase
  - Universal regulation system sensitive to local energy charge of AMPK and AMPKK better suits all tissue types
  - In liver cells activity can have high activity in high energy situations by cAMP and hormonal regulation

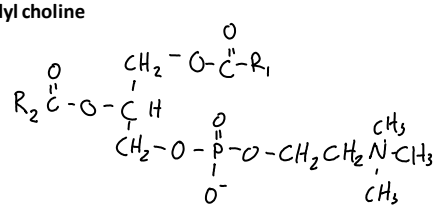
- In an AMPK state, stimulates mitochondrial oxidation in muscle cells. In AMPK activated state muscle cells produce more mitochondria.
- Exercise for mild type II diabetes - oxidation state is stimulated and can overcome some mild diabetes

- Isoform of acetyl-Coa Carboxylase

- ACC2-muscle
  - Heart and muscle do not need to synthesize fatty acids but why have this isozyme?
    - To synthesize malonyl-CoA
    - Malonyl-CoA inhibits carnitine acyl-transferase I
      - Acetyl-coa carboxylase II (muscle) is there purely for regulating beta-oxidation
      - EC low then beta-oxidation is activated

- Hormone state of triacyl-glycerol
  - Glucagon mobilizes fatty acids
  - **Hormone sensitive lipase** in adipose tissue - breaks down triacylglycerol to fatty acids.
    - Activated by glucagon and epinephrine
    - 2 states, phosphorylated and non-phosphorylated state

- **Phosphatidyl choline**



Fatty acids
Glycerol
Phosphate
Ethanolamine
methyl

Notes 09/04

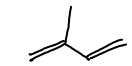
Thursday, September 04, 2008
10:02 AM

Notes 0904

Audio recording started: 10:03 AM Thursday, September 04, 2008

- Biosynthesis of triacylglcerols
  1. Diacylglycerol
     - Fatty acyl-CoA synthetase same as in beta-oxidation
     - Costs 4 ATP equivalents
  2. Phosphoethanolamine
     - Serine -> ethanolymaine
     - Activate ethanolymine with kinase and CDP and transferred to diacylglycerol
     - Costs 3 ATP equivalents
  3. Phosphatidyl choline
     - Methionine + ATP -> S-adenosylmethionine (SAM)
       - SAM has active methyl for transfer (like cofactor)
     - Phosphoethanolamine + SAM --methyl transferase 3x --> S-adenosylhomocysteine (SAH) + phosphatidyl choline
     - Costs 9 ATP equivalents (3x3)
  - Total costs energy 16 ATP
  - Possible in class exercise, calculate ATP required to assemble a glycolipid or something, don't focus on memorizing this specific pathway but logic and energy behind it.

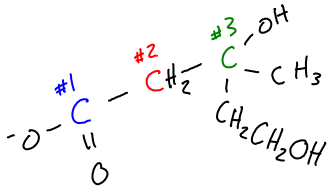
- Isoprene



isoprene

C_{10} = monoterpene
C_{15} = sesquiterpene
C_{20} = diterpene
C_{30} = triterpene ≡ sterol
C_{40} = tetraterpenes ≡ cartenoids

- Cholesterol
  - 32 step biosynthetic pathway
  - Acetate is source of all 27 carbons of cholesterol
  - Pathway elucidated by radio labeling
    - 3-R-mevalonic acid (early isotope labeled intermediate)

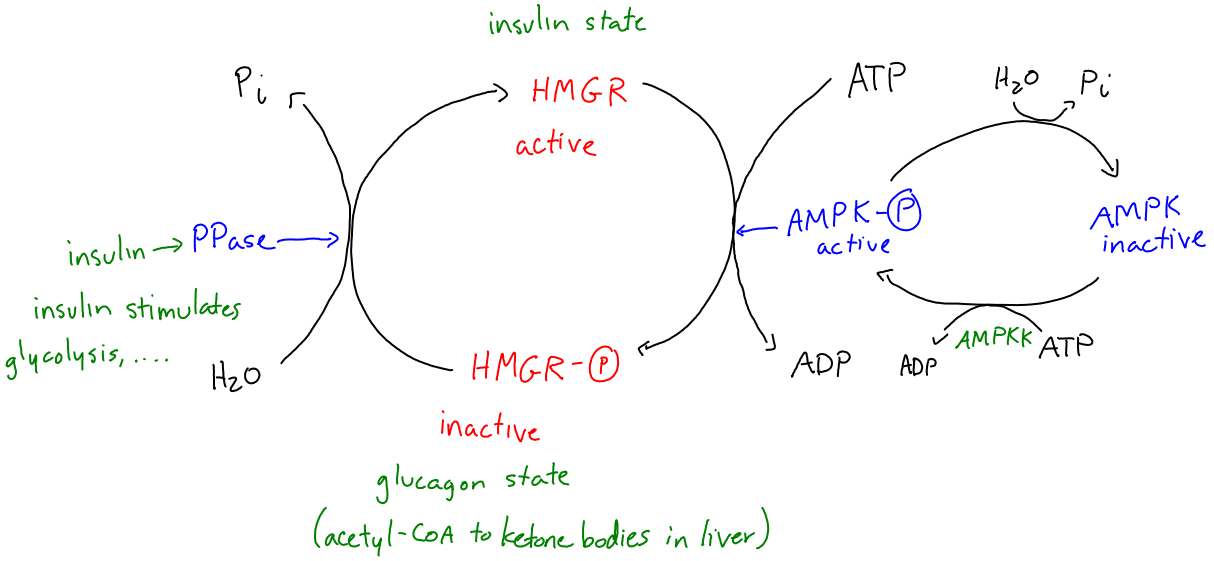


#2 radiolabeled carbon incorperated
#1 not, must be cleaved in pathway

  - Cholesterol metabolism happens in cytosol, uses some of same enzymes in ketone body pathways but have cytosol forms instead of mitochondrial forms.
  - HMG-Coa reductase is rate limiting step and regulated by cholesterol, hormones
  - Phosphotransferase, kinase, and decarboxylase to isopentenyl pyrophosphate
  - Head to tail condensation by prenyl transferase 2x

- Head to head condensation by squalene synthase with NADPh -> NADP
- Squaline to lanosterol by squalene epoxidase
- Lanosterol to cholesterol
  - Some carbon loss through 2 decarboxylations and formic acid released to go from C30 to C27. Lots of loss of double bonds and oxidation. Lots of NADPH used

- Regulation of cholesterol synthesis
  - HMG-Coa reductase is highly regulated
    - Transcriptionally regulated
    - Feedback inhibition by cholesterol levels
    - Regulated by phosphorylation



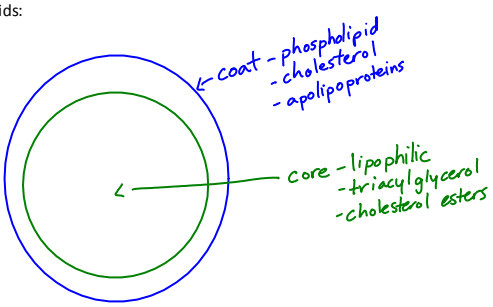
Notes 09/05

Friday, September 05, 2008
10:02 AM

Notes 0905

Audio recording started: 10:03 AM Friday, September 05, 2008

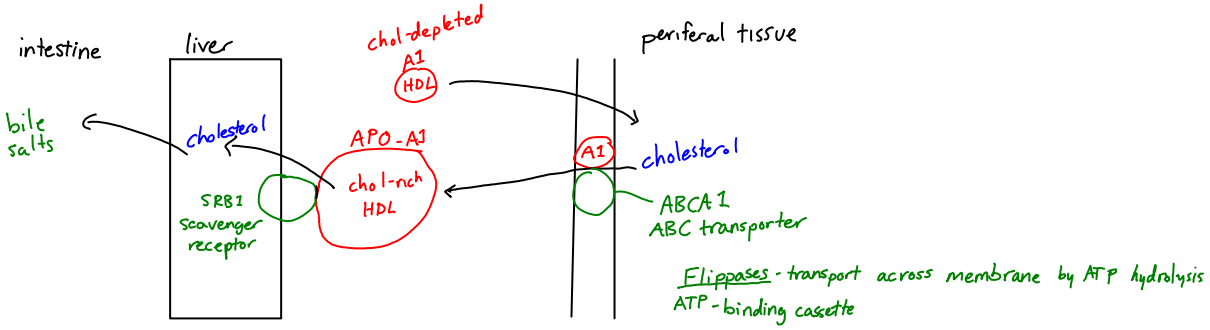
- Lipoproteins transport lipids:



- Apolipoprtoines
  - Chylomicrons
    - Types (ordered decreasing size and increasing density)
      1) VLDL (TG rich, low density, large size)
      2) IDL
      3) LDL
      4) HDL (cholesterol rich, high density, small size)
    - High TG/Cholesterol = lower density

- Handout figure 11-53
  - Dietary fat (TG) broken by lipases and repackaged into chylomicrons.
  - CII = activates lipoprotein lipase (come from HDL)
  - ApoE = activates lipoprotein lipase (come from HDL)
  - ApoB-48 = binds remants receptor
    - Remants receptor on liver cells
  - When VLDL is released from liver cells, doesn't have ApoE and C-II (those come from HDL)
  - IDL thought to be a transition from VLDL to LDL, but have no real discovered function different from LDL.
  - LDL function is to deliver cholesterol to peripheral tissues
    - Has ApoB100 protein= binds to LDL receptors on liver

- Delivery of LDL to extra hepatic tissues
  - ApoB100 binds LDL receptor and taken up by andocytosis (receptor mediated endocytosis)
    - Increase in ACAT synthesis (acyl-coa cholesterol acyltransferase) which breaks down cholesterol to cholesterol ester droplet
    - Decrease HMG-Coa reductase synthesis (neg feedback for in cell cholesterol synthesis)
    - Decrease LDL receptor synthesis
      - High cholesterol diet isn't uptaken by cells over time and circulates around causing atherosclerosis and other health issues
      - HDL has role in eliminating LDL
  - No catabolic pathway for cholesterol in humans, can only excrete as bile salts
    - Liver puts cholesterol into gall bladder and excreted into intestine as bile salts.
    - Can consume cholesterol by steriod hormone synthesis but not significant sink to rid of cholesterol
  - HDL participates in extra cholesterol transport from extra hepatic tissue to liver



  - Ratio of high HDL and low LDL is a sign of good health

- Tangier's Disease - HDL deficiency
  - Island off Virginia with entire population descendents of 5 settlers. Very rare
  - Homozygous die of heart attack
  - Heterozygous get heart attacks in 30's

- Deficiency in ABCA1 transporter

- Familial Hypocholesterolemia - LDL receptor deficiency
  - Very common
    - Heterozygous 1 in 500 to 1 in 1000 depending on population, heart attacks in 40s untreated
    - Homozygous and not treated heart attacks early 20s
  - Treatment
    - Inhibitors of HMG-Coa reductase (statins)
    - Cholestyramine - more dramatic treatment
      - plastic beads that absorb bile salts
      - Pulls out cholesterol form liver

- How to increase HDL
  - Increase aerobic exercise
  - Lose weight
  - Quit smoking
  - Increase intake of omega-3-fatty acids
  - Decrease trans fat
  - Increase ratio mono and polyunsaturated fats
  - 1-2 drinks of alcohol per day
  - Increase soluble fiber
  - Low fat diet (30% total calories)
  - large quantities of nyacin - will obscure drug urine tests but not good for you

- Soluble fiber gives gas
  - Can't digest but anaerobic bacteria in lower intestine can.
  - Some bacteria ferments to butyric acid

- Ruminents (cows, sheep, deer)
  - Can't digest cellulose but bacteria in their gut ferments them and use butyric acid + other acids as energy source.

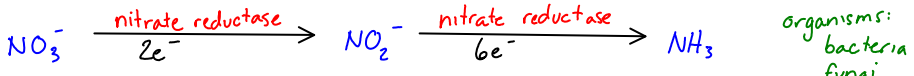
Notes 09/08

Monday, September 08, 2008
10:00 AM

Notes 0908

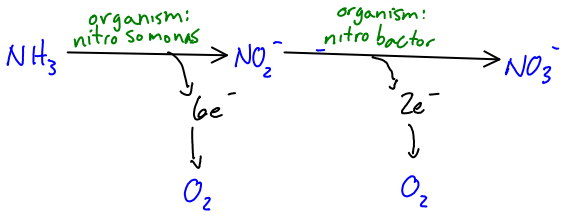
Audio recording started: 10:04 AM Monday, September 08, 2008

- Inorganic nitrogen metabolism
  - NO_3^- nitrate is most abundant form
  - Assimilatory $NO_3^- + NO_2^-$ reduction

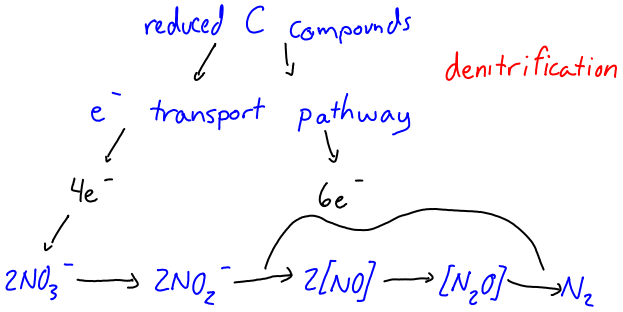


organisms:
bacteria
fungi
plant

  - Nitrification (aerobic resparatory process)



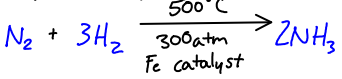
  - Electron acceptor



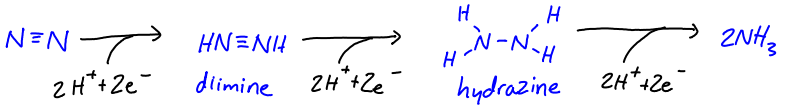
  - Nitrogen fixation

Type	Product	% production	Notes
Biologic N_2 fixation	NH_3	79%	Reductive process
Lightning	NO_3^-	9%	Oxidative process
Industrial process	12%	12%	Reductive process

    - Industrial process
      - Invented by Fritz Haber (1910)



    - Biological
      - $N_2 + 16ATP + 8fd_{(red)} + 6H^+ + 2H^+ + 16H_2O \rightarrow 2NH_3 + 16ADP + 16Pi + 8fd_{(ox)} + H_2$
        - $6e^-$: $N_2 + 6e^- \rightarrow 2NH_3$ (12ATP)
        - $2e^-$: $2H^+ + 2e^- \rightarrow H_2$ (4ATP)
        - 2ATP per e^- transfer
      - Nitrogenase structure
        - Cell metabolism reduces Fd
        - Reduce Fe protein
          - Exchange of ADP to ATP to reduce Fe protein
          - Conformation change of protein that favors electron transfer (similar to G protein)
        - Transfer electrons to MoFe protein
        - MoFe protein transfersprotons and makes NH_3



$HN{\equiv}NH + H_2 \longrightarrow N_2 + 2H_2$ reverse rxn occurs, futal process → why such expensive process

20-30 ATP in cells

- Iron proteins are very sensitive to oxygen degradation
- Bacteria
  - Anaerobic (soils, sediments, guts of termites, association of photosynthetic systems)
- Rhizobia - legumes
  - Many have bacteria on symbiotic relationship
  - Rhizobia live inside leg cells of legumes.

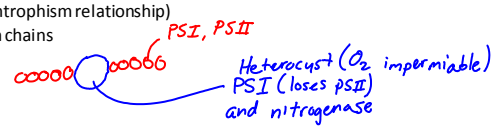
Notes 09/09

Tuesday, September 09, 2008
10:02 AM

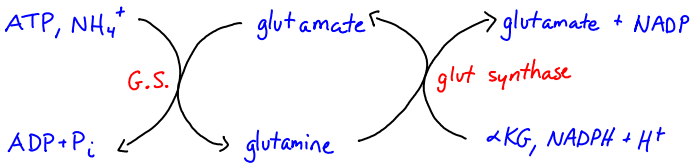
Notes 0909

Audio recording started: 10:03 AM Tuesday, September 09, 2008

- Nitrogen fixation
  - Efficient nitrogen fixation is done in aerobic conditions in association with photosynthetic activity.
    - Risobial association with plants
      - All plants secrete a flavin from roots, and if the right risobian encounters the signal, it induces the synthesis of a glycolipid which causes cell divisions and differentiation.
      - Bacteria invades through root hairs and enter plant cell and continue to divide into a root nodule.
      - Fix nitrogen inside by symbiotic association
        - Bacteria receive carbon for ATP or reductant for nitrogenase
        - Plant gets the ammonia from bacteria
        - Beats oxygen problem
          - Leghemoglobin protein absorbs oxygen to provide anaerobic conditions
          - Specialized respiratory chain sucks oxygen off leghemoglobin
          - Nitrogenase is able to function without oxygen damage
    - Cyanobacteria
      - Many cyanobacteria do nitrogen fixation
      - Cyanobacteria do photosynthesis
        - Anabaena (syntrophism relationship)
          - Grows in chains

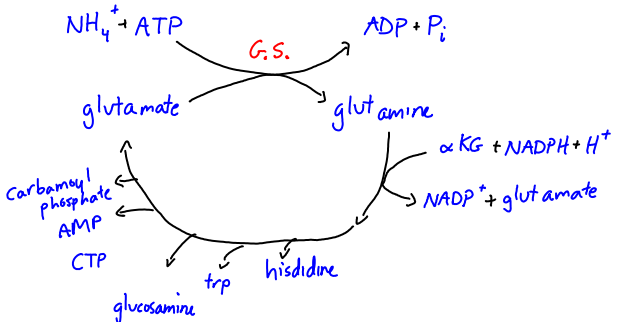


- Incorporation of N fixation (mammals don't do much of this etc)
  1. Glutamine synthetase
     - High affinity for ammonia, can scavenge ammonia form environment (low Km).
     - Highly regulated enzyme
  2. Glutamate dehydrogenase
     - Have seen reverse reaction, freely reversible reaction
     - Has low affinity for ammonia (high Km), used when ammonia is abundant
  3. Glutamate synthase
     - Used under low ammonia conditions and often coupled to glutamine synthetase



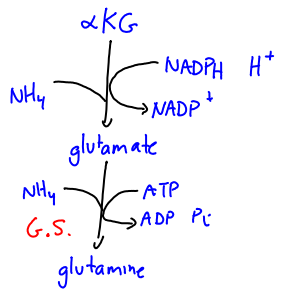
Summary: $\alpha KG + ATP + NH_4^+ + NADPH + H^+ \longrightarrow$ glutamate + $ADP + P_i + NADP^+$
↳ then donates to amino acid synthesis

low $[NH_4^+]$ GS is 20-30x more active than in high conditions

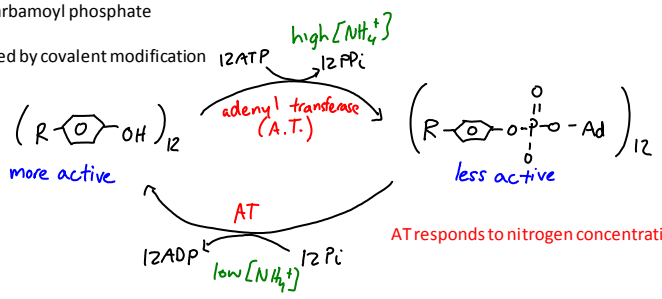


glucosamine trp

high $[NH_4^+]$



- Glutamine synthetase
  - Does not have any allosterism for modifiers
  - 12 subunits (2 stacked hexamers stacked)
  - 12 substrate binding sites
  - Regulated by feedback inhibition as well as ammonia
  - Negative modifiers for glutamine synthesis (feedback inhibition)
    - Serine
    - Glycine
    - Alanine
    - Histidine
    - Trp
    - AMP
    - CTP
    - Glucosamine-6-P
    - Carbamoyl phosphate
  - Regulated by covalent modification



AT responds to nitrogen concentration cell

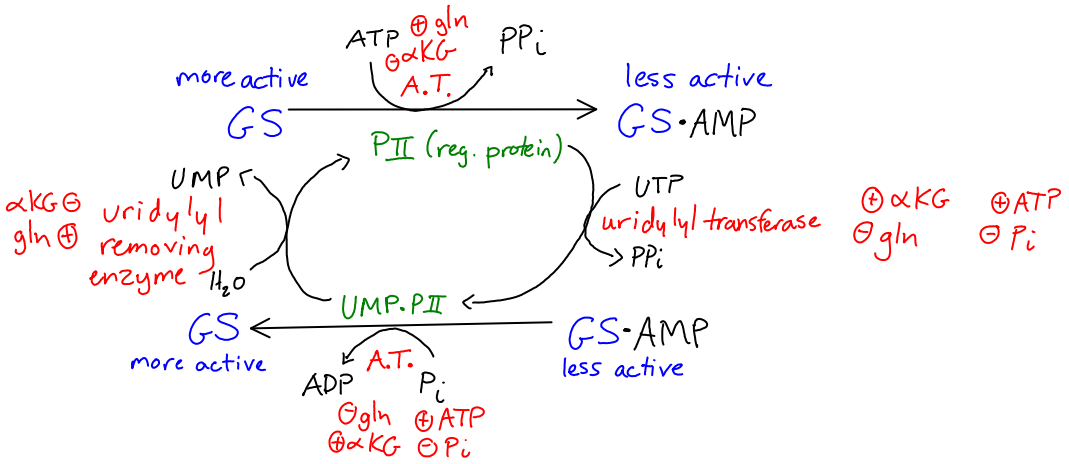
Notes 09/10

Wednesday, September 10, 2008
10:01 AM

Notes 0910

Audio recording started: 10:08 AM Wednesday, September 10, 2008

- Glutamine synthetase - major enzyme for scavenging ammonia from environment



  - 18 control parameters for glutamine synthetase, don't figure out all 18 but know how system is regulated by covalent modification and how these components interrelate

- Biosynthetic pathways to amino acids
  - Amino acids come from central metabolic pathway intermediates
  - Pathways grouped into families
  - Serine (don't need to know enzyme names)
  - Cysteine (PLP, for o-acetylserine to cysteine. PLP Catalyzes transfer of sulfide)
  - Glycine
    - PLP and THF cofactors
  - THF is a cofactor
    - Has any number of glutamates on end
    - Parent benzoic acid
    - 2-amin-4-oxo-6-methylpterin
    - Comes from folic acid
      - Folate -> DHF -> THF (2 reductions)
    - Reactive bits, N5 or N10 of THF
    - Can carry methyl, methlene, methenyl, formyl, formimino groups
  - Glutamine related (see handout)
    - Arginine
      1. n-acetyl glutamate synthase
      2. n-acetyl glutamate kinase
         - n-acetyl glutamate semialdehyde
      4. AT
      - Ornathine -> citrulline -> arginosuccinate
    - Proline
      9. Glutamyl kinase
    - Biochemical concepts
      1. acetyl group in arginine is like a protecting group so that it doesn't cyclize spontaneously like in proline.
      2. N-acetyl glutamate - required positive modifier of CPSI (carbamyl phosphate

synthetase I)
        - Don't want to make carbamoyl phosphate unless have something to accept it
        - Pool of glutamate measures amount of nitrogen present. *** (used for all AT reactions, so cells use glutamate concentration to measure ammonia amount)
- Q#1 on final
    - 5 cofactors
        - Circle reactive bits

Review Final

Thursday, September 11, 2008
10:36 AM

Review Final

Audio recording started: 10:37 AM Thursday, September 11, 2008

- Cofactors
  - FAD
  - CoA
  - Sam
  - NAD^+
  - pyridoxalP
  - Biotin
  - Vit B12
  - Thiamine pyrophosphate
  - Tetrahydrofolate

- Photosynthesis
  - Z scheme - quanta for NAD -> NADPH (4hv, 1.5ATP)
  - Calvin cycle -> what for
    - Structures
    - Where NADPH and ATP is used -> quantum requirements
    - Names of enzymes
  - Regulation rubisco -> light regulation/activase + carbamate (lowers Km for co2)
    - Reg of calvin cycle by e transport
    - Regulation of calvin cycle by e transport
      - Phosphorubisco kinase
      - GAP dehydragonse
      - Glucose 6 phosophate
      - Sedoheptulose
      - 1-6 bisphosphate
        - These enzymes are on when the lights are on

      Phosphorespiration pathway
      Structures and enzymes

  - C_4 and CAM
    - Dicarboxylic acids
    - Pathway of co
    - Atp difference between the other c02 fixation--> 2atp
    - Biochem factors
      - High affinity enzyme PEP carboxylase
      - Bundle sheet does photosynthesis

- NADPH - what's up with that
  - Know production phase of pentose phosphate pathway (2 dehydrogenases)
  - Transketolase mechanism (don't worry), but will need to mention in TPP cofactor problem

- Reactions used to use NADPH

- Fatty acid biosynthesis
  - Know pathway inside and out
  - Regulation - major sites and
    - cellular factors that contribute beta oxidation or fatty acid synthesis
      - EC
      - Carnetine dehydrgotenase
      - Citrate lyase
      - Etc etc
      - NADPH and NAD
      - Hormones - regulate acetylcarboxylase activity.
        - Acetylcarboxylase must be covalently modified by AMPK
        - Insulin favors dephosphorylated
      - Citrate

- Assemble phospholipid
  - No question on pospholipid assembly

- Cholesterol biosynthesis
  - Know entire pathway in detail from acetylcoa to ispentylpyrophosphate (can write structures)
  - What happens to ispentyl pyrophosphate to squalene but don't have to draw out exactly
  - Squalene becomes lenosterol, need to know idea of how happens… what is reduced
  - HMG-Coa Reductase - strategy phosphorylated by AMPK, regulated by EC and AMPK like fatty acid synthesis but plus feedback inhibition by cholesterol

- Lipoprotein
  - Know major function of lipoproteins
    - Chylomicron - transport fatty acids to periferal tissues (dietery fatty acid)
    - VLDL - andogeniously derrived fatty acid to deliver to periferial tissue
    - LDL - transport cholesterol to all tissues
    - HDL - reverse cholesterol transport
  - Know how LDL is taken up
    - Decreases HMG-CoA reducatase and LDL acceptor amount
    - HDL takes out of liver
    - Liver can make bile salts to extreme to cholesterol into intestine.
    - No catabolic pathway for cholesterol in mammals.

- Inorganic nitrogen metabolism
  - Similtory/dissimilatory nitrogen reduction
  - Denitrogenification
  - Nitrogen fixation (energy cost, nitrogenase)
  - Biochemical dilemma of nitrogenase (O_2 sensitive)
    - Photosynthetic partnering up
      - Risobial legume association
        - heme protein
      - Anobena, cyanobacteria
  - Uptake of ammonia
    - Glutamine synthetase and others
      - Glutamine synthetase regulation (covalent modification)

- Amino acid biosynthetic pathways
  - know

Final Exam Questions

Thursday, September 11, 2008
1:37 PM

1. Cofactors (15-30pts)
2. 30pts
    a. Photosynthesis 4 parts
    b. 1/2 involves structures -> calvin cycle
3. 18pts (2pnts + 2pt)
    a. Inorganic nitrogen metabolism (no structures)
4. Nitrogen metabolism (20pt)
5. No structures -> 25pts
    a. Genetic diseases
    b. 5 parts -> may illustrate reaction
    c. (maple syrup disease)

6. 26pts
    a. Fatty acid biosyntehsis
    b. Possible structures
    c. 1/2 of problem -> data from paper to interprate
    d. Regulation emphasis

7. 26pts
    a. Fatty acid/lipid biosynth
    b. Structures
    c. Regulation emphasis

8. 25pt
    a. Regulation
    b. Data enterpretatoin