CHEM 143 Review

Membranes

Solute transport

$\Delta G = \Delta G^{\circ\prime} + RT \ln \frac{[S_{final}]}{[S_{initial}]} + zF\Delta V$

$S_{initial} \rightleftarrows S_{final}$

transport → Simple diffusion (No protein)

transport → Facilitated Transport (transmembrane protein)

Facilitated Transport → Facilitated Diffusion (channel) $\Delta G < 0$

Facilitated Transport → Active Transport (cotransporters + pumps) $\Delta G > 0$

Simple diffusion – "weasling" moves through membrane affected by concentration and size

$J_{passive} = P\Delta C$

$T_{passive} = A \cdot P\Delta C$

$T_{active} = A \cdot p \cdot v$ (A → area → transporter density/area)

P = permeability constant – larger = more permeable

ΔC = ~~constant~~ concentration gradient

Need to multiply $J_{passive}$ by area!

Total passive transport = $(J_{passive})(\text{Total Area})$

Facilitated Diffusion

$S_{init} + T \rightleftarrows S_{init} \cdot T \rightleftarrows S_{final} + T$

$v = \frac{V_{max}[S]_{init}}{[S]_{init} + K_T}$

$v = J_{facilitated} \cdot Area$

Follows saturation kinetics

GLUT channels regulate blood glucose levels – control intake via GLUT expressed → control speed (k_{cat}) (which ↓) and how much [T] (expression)

$v_{max} = k_{cat}[T]$

GLUT 1 / GLUT3 = basal transporters

- $K_T \approx 1$–2 mM
- operate near V_{max} as blood Glc is 4–7 mM

GLUT4 – muscle cells (glycogen storage)

- K_T > K_T for GLUT1/3 = only work after GLUT1/GLUT3 saturated

GLUT 2 – Pancreas Beta cells

- K_T = 15mM → signal insulin spike

K^+ channels

selectively choose K^+ over Na^+

via K^+ hydration – smaller tighter H_2O bonds = more entropic currency

Cotransporters

Need to pay ΔG price

Move another ion w/ gradient = energetic coupling

$S_{init1} + S_{init2} + T \rightleftarrows S_1 \cdot S_2 \cdot T \rightleftarrows S_{1final} + S_{2final} + T$

$S_1 \cdot S_2 \cdot T \rightleftarrows S_1 \cdot S_2 \cdot T^*$

2 same direction = symporter

2 opposite direction = antiporter

Pumps / $F_o F_1$ ATP synthase

c subunits – proton channel

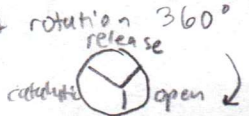
a subunit – interacts w/ c subunits → make one c unit tighter binding and 1 lower binding

proton attached to tight spot, rotates until weak spot, and releases on other side

$ADP + P_i \overset{\alpha_3\beta_3}{\rightleftarrows} ATP$ γ interacts w $\alpha_3\beta_3$

γ-$\alpha\beta$ = open ADP + Pi bind

1 rotation 360° of $\alpha_3\beta_3$ = 3 ATP



In rxn, P_i is Nu^- ADP is E^+

Transmembrane Signal Induction

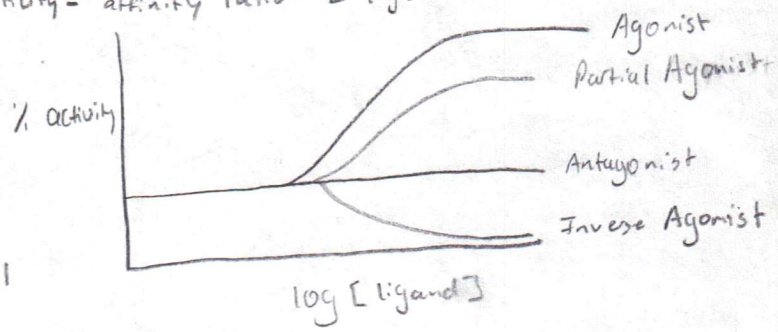
3 types
1) 7TM -
2) RTk -
3) Gated Ion Channel

All allow allostery
Transducers and amplifiers

Transducer - Conformational change indicates signal
Amplifier - Transduction stays "on"

Receptor selectivity vs specificity

1 → 2 - Selectivity = affinity ratio of ligand 2 receptors
2 → 1 - Specificity - affinity ratio - 2 ligands 1 receptor

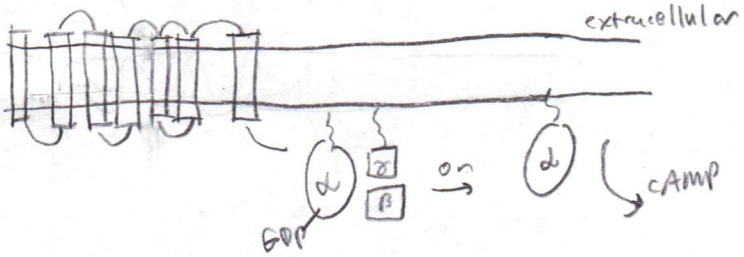


7TMs

Transduction - signal molecule binds to α helices, conformationally changing G protein from GDP → GTP bound state

GTP bound state dissociates from rest of protein, catalyzing other enzymes

Eventually hydrolyzes GTP to reassociate

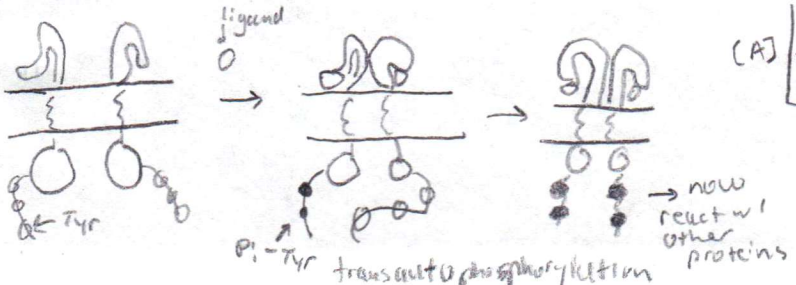


4 types of ligands

1) Agonist - ↑ activity
2) Partial Agonist - ↑ activity but won't reach saturation
3) inverse Agonist - reduce activity below basal levels
4) Antagonist - block function of agonists but doesn't affect intrinsic activity

RTKs

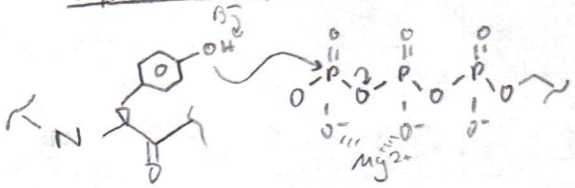
Signal binding dimerizes two proteins to activate kinase

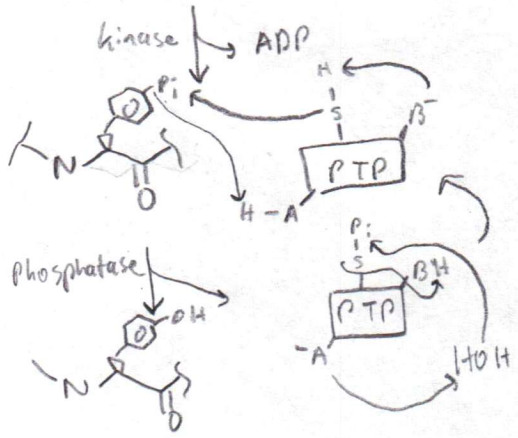


PTMs

allosteric control via covalent modification often reversible via another enzymes

Tyr kinases



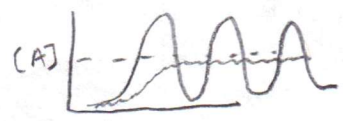


All PTP's have conserved cysteine residue

PTM Reasons

1) Simpler - only need one binding site
- Hexokinase needs N_H^- site, E^+ site, G6P site
IDH just install Pi near active site - diagram repels isocitrate (3 CO_2^- groups)

2) Noise Cancelation



PTM intermediary provides noise dampening affect due to longer adjustment time

PTMs cont.

8 aspects to consider

1) ID of target residue
2) Nature of modification
3) What is cosubstrate
4) Type of enzyme to install PTM
5) Enzyme Mechanism / specificity — chemical / Biological
6) Reversible?
7) Biological Function of target protein
8) PTM control mechanism

(1) Target Residues

Nu⁻ side chains – Amides bad E+

(2) Nature of Modification

Strength of bond dictates PTM duration
ester – hold longer than phosphoanhydride bond

(3) CO substrates

Methyl PTMs via  or FA

S-Adenosyl-Met (SAM)

Nuhwe's Me-I – good E+

R-S-OH sulfenic acid (good E+)

H_2O_2 converts Nu⁻ R-SH → E+ R-S-OH

↳ oxidant — Use of metabolites as cofactor = metabolic sensor status

(4) Type of Enzyme

PTM's power in specificity, not chemistry

(5) Reversibility

PTPs hydrolyze thioesters / amides

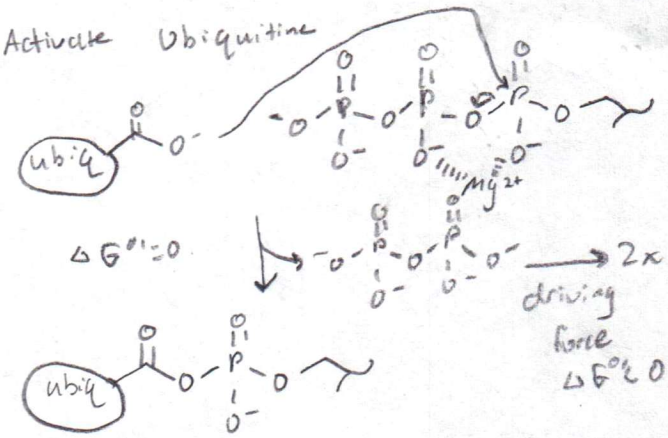
thioethers / Farnesyl-Cys+ hard to remove

Ubiquitin / Ubiquitin Ligase

(3)

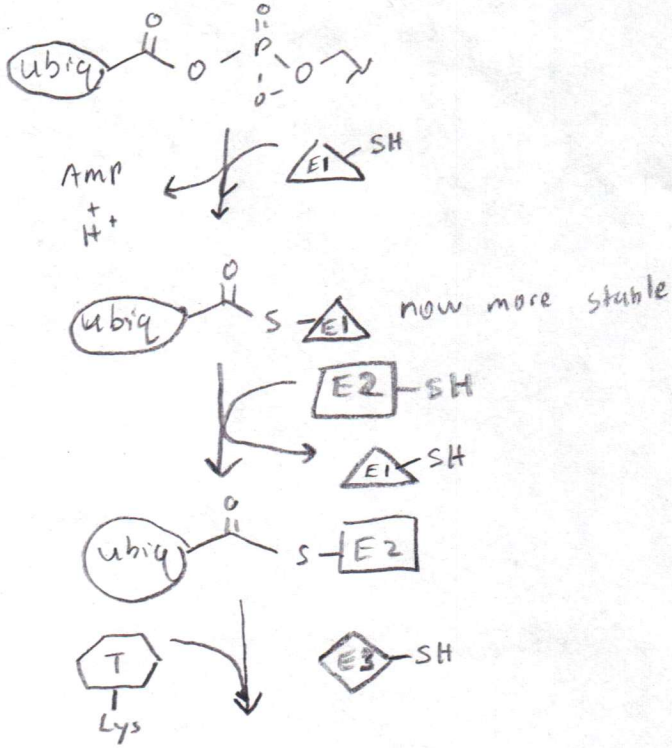
Use ATP mechanism to install ubiquitin on Lys residue of protein

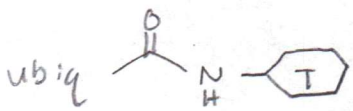
(1) Activate Ubiquitine



(2) Ubiquitinylation of Ligase

Use 3 step process to control where (ubiq) ends up



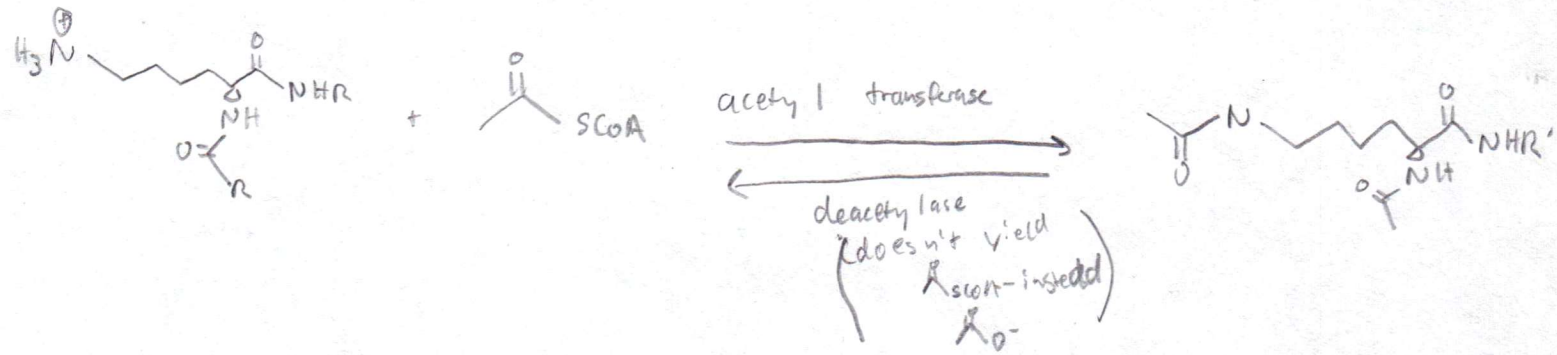


E1 – target agnostic
E2 – recog E1
E3 – recog T
] allows for finer control

Polyubiquitinylation signals ~~cell~~ protein death by proteozome

Proteozome hydrolyzes ubiquitns while degrading protein = PTM reversible

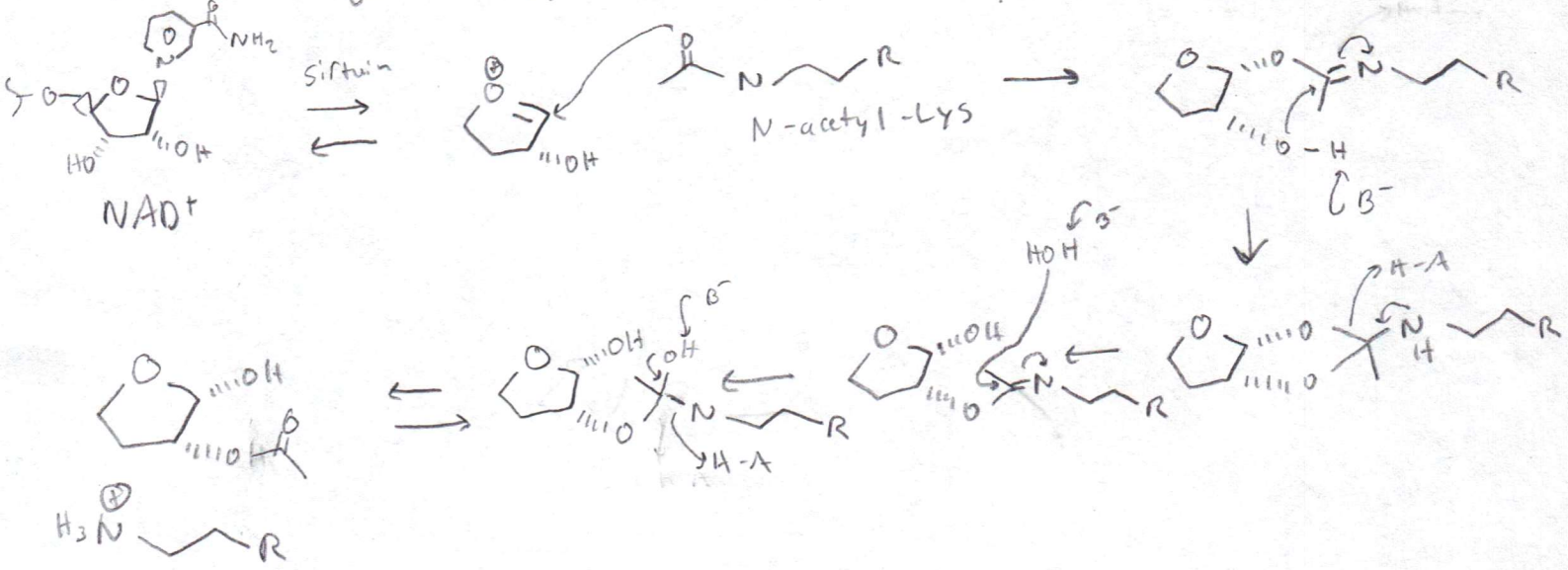
Even more PTMs



Palmitoylation can alter subcellular location

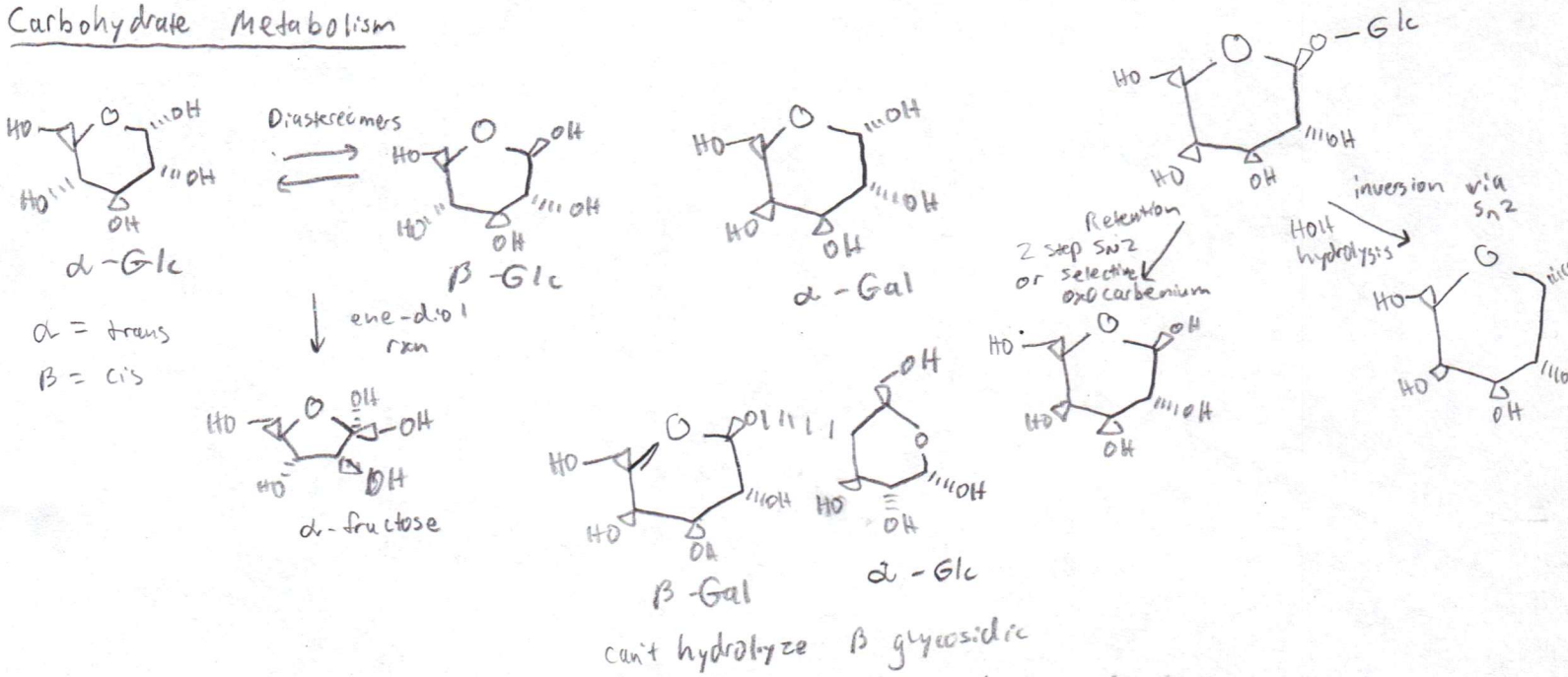
Act as carrier subunits like lipoamide

Deacetylase can require energy:



NAD+ = sensor of oxidoreductant stress

Carbohydrate Metabolism



α = trans

β = cis

can't hydrolyze β glycosidic linkage - humans don't have the enzymes

Carbohydrates cont.

Phosphorylases

Pi is Nu^-

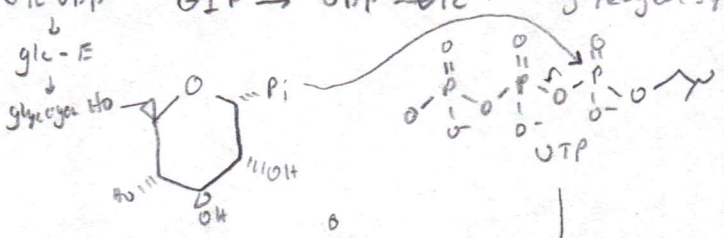
Glycogens branching allows multiple enzymes to break down at once

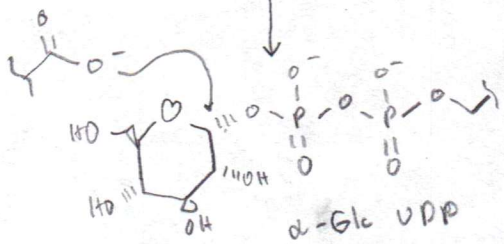
Glycogen phosphorylase
- oxo carbenium then Pi attack

Glycogen Biosynthesis

G1P-Glc UDP → glc-E → glycogen HO

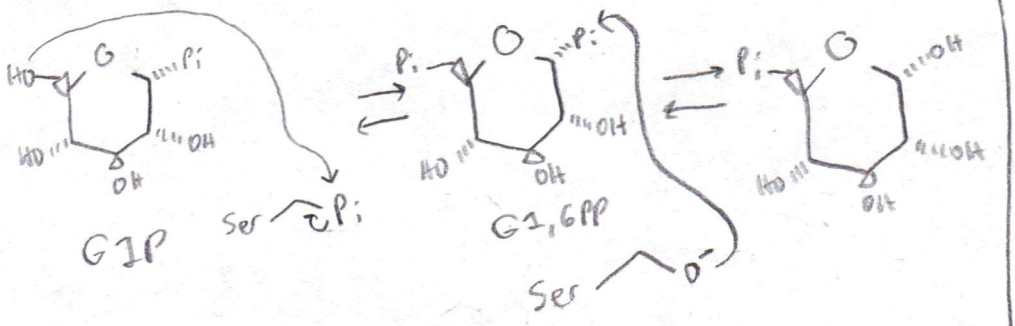
G1P → UDP-Glc → glycogen synthase - glc → glycogen





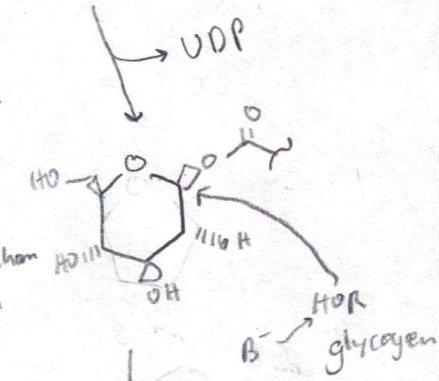
Phospho glucomutase step 4 LeLoir

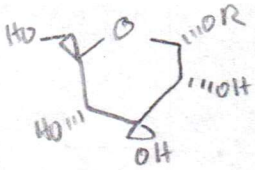
Convert G1P → G6P



glycogen Synthase

use 2 step SN2 for stereochem retention



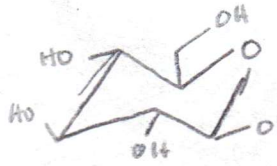


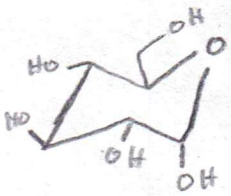
Lactose breakdown via 2 step SN2 = glucose (α) + galactose (β)

LeLoir Pathway

Galactose → G6P for glycolysis

1) Galactose mutarotase = β-gal → α-gal
2) Galactokinase - Add Pi to C1
3) Galactose 1 Phosphate Uridyltransferase
   - Exchange galactose for a glucose
   1 phosphate w/ UDP-Glc via this mechanism

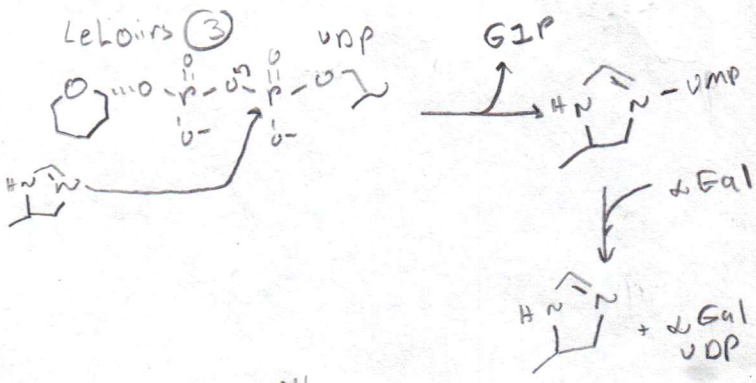




4) Phosphoglucomutase - Transfer Pi C1 → C6
   ↳ Ser-Pi donates to C6 then cleaves C1
5) UDP-Gal 4 Epimerase - Regenerate UDP-Glc
   ↳ Use NAD+ then selective reduction NADH
   ↳ sequential ox → reduc

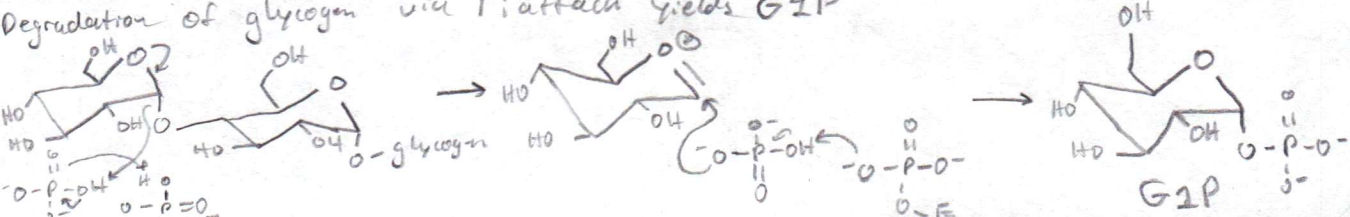
UDP - increases binding

UDP-Gal creation drives rxn forward



Glyconolysis Glycogen phosphorylase

Degradation of glycogen via Pi attack yields G1P



Gluconeogenesis

creation of glucose w/o glycogen

reverse lactate formation

lactate → pyruvate → oxoalacetate → PEP → reverse glycolysis

lose CO_2 = need ATP

glycolysis - gain 2 ATP

gluconeogenesis - lose 4 ATP + 2 GTP

Pathway Connections

Oxoalacetate - TCA

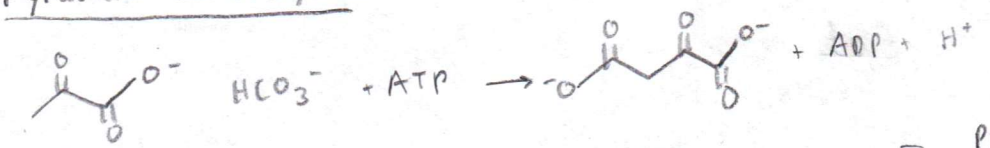
G1P → G6P = skip gluconeogenesis

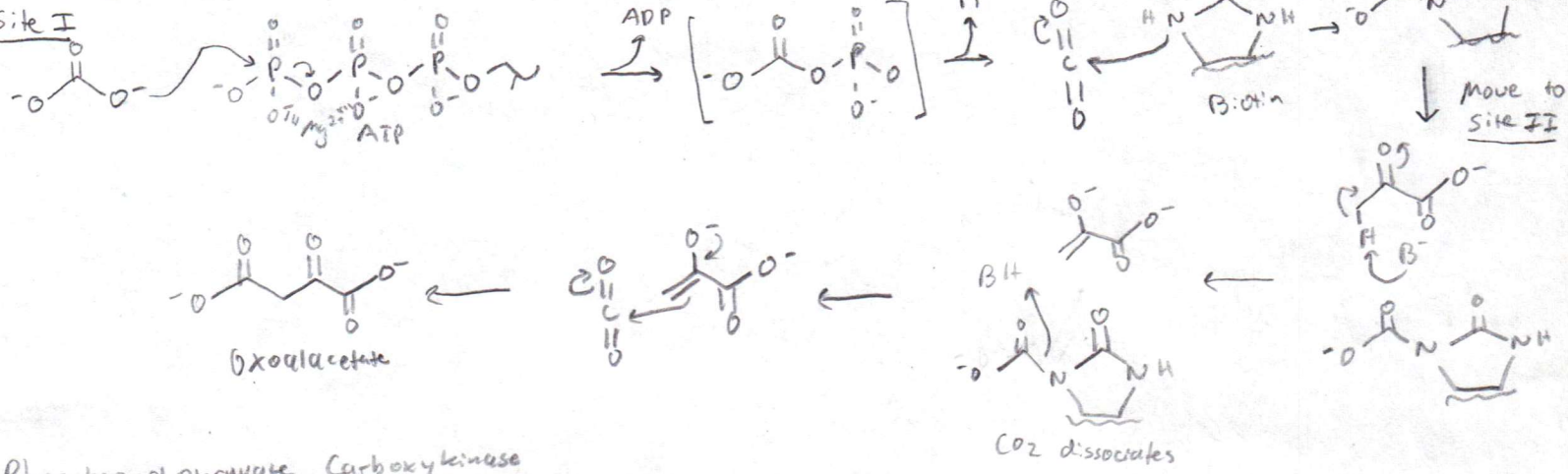
gluconeogenesis is an energy storage process - excess energy stored in glucose to send to other cells or store in glycogen

↳ AMP/ other signals of energy need will inhibit

↳ Citrate/ other signals of excess energy will activate gluconeogenesis

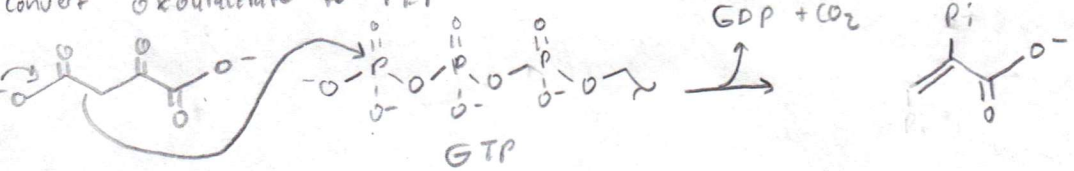
Pyruvate Carboxylase



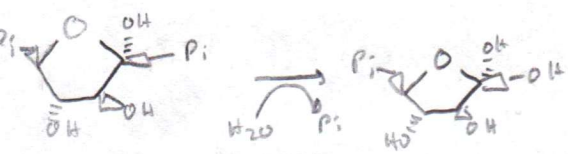


Phosphoenolpyruvate Carboxykinase

convert oxoalacetate to PEP

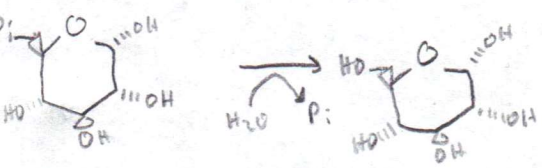


Fructose 1,6 Bisphosphatase



Same as PTM PTPs

Glucose 6 Phosphatase



His grabs Pi, then hydrolize His to regenerate catalyst.

Regulation

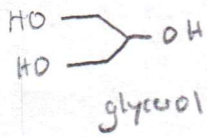
AMP - activate PFK
inhibit F1,6PPhosphatase
- indicate low energy levels

Citrate - inhibit PFK
- activate F1,6PPatase
- buildup of TCA due to max velocity = burn less glucose, make more

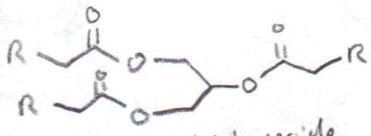
Pi
glyconolysis activated via glycogen phosphorylase ^ PTM

glyconeogenesis - inactivate glycogen synthase during glyconolysis
w/ ser → ser-Pi

Fatty Acid Metabolism



glycerol


triglyceride

Pathway Connections

SCoA → TCA
NADH / $FADH_2$ → ETC
} ~ 100 ATP

FA Breakdown Energy

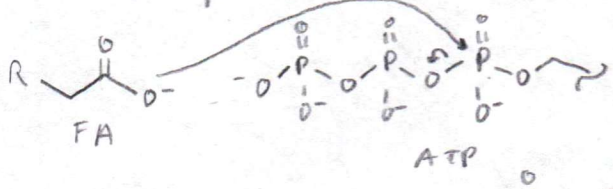
Acetyl-CoA = 1 ATP Directly TCA
↳ 3 NADH
↳ 1 $FADH_2$
} TCA

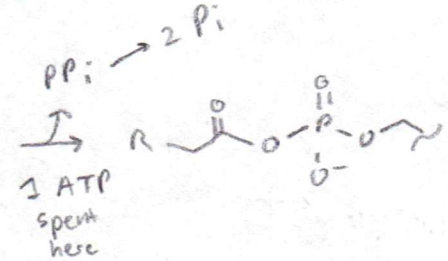
Each 2 carbon cleavage
↳ 1 NADH
↳ 1 $FADH_2$

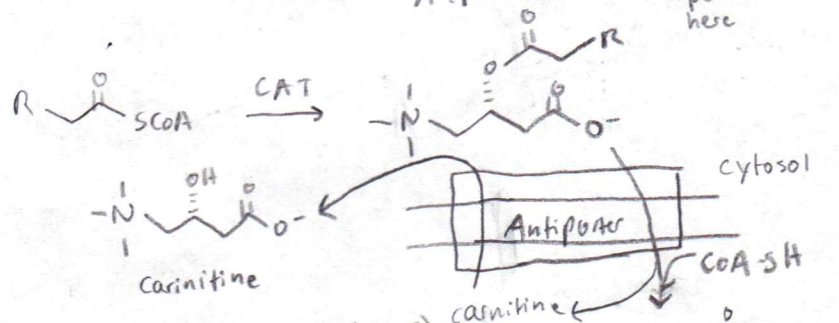
Account for -2 ATP for AMP FA activation conversion AMP → ADP
Another ATP to rebuild AMP

FA Breakdown

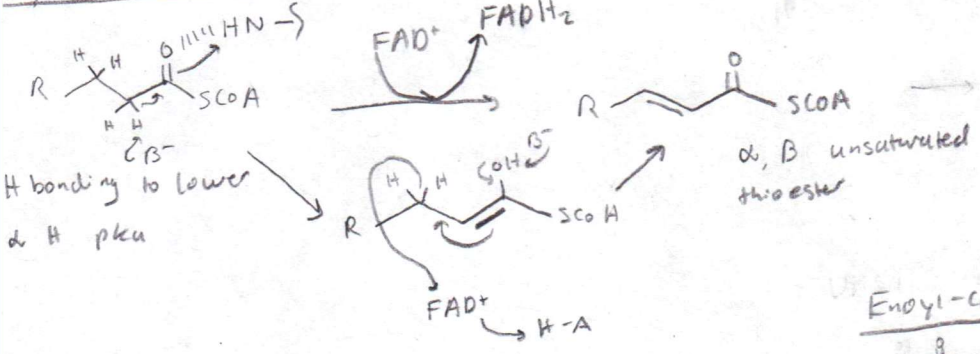
Convert FA → Acetyl-CoA
- Produce NADH / $FADH_2$ and acetyl-CoA for TCA
- Breakdown 2 carbons at a time
- 2n carbon FA yields n acetyl CoA and breakdown process occurs n-1 times



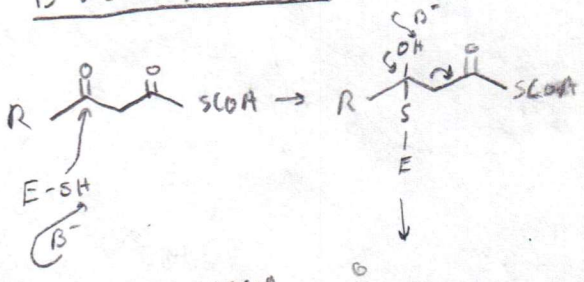




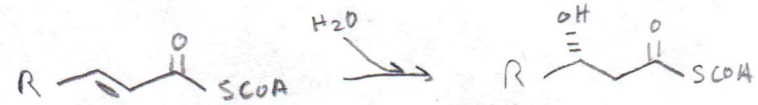
Acyl-CoA Dehydrogenase (step 1)



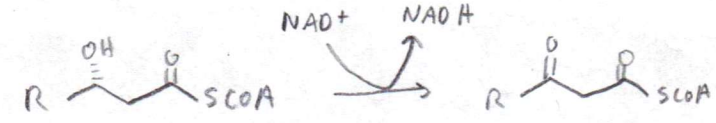
β-ketoacyl Thiolase (step 4)



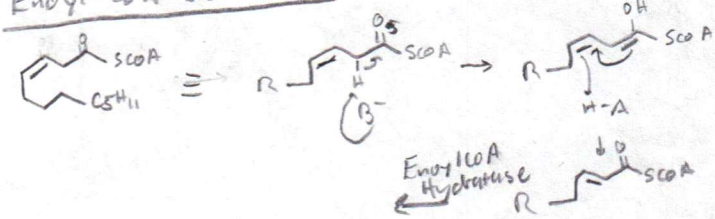
Enoyl-CoA Hydratase (step 2)



Hydroxyacyl-CoA Dehydrogenase (step 3)



Enoyl-CoA Isomerase



Odd Numbered FA yields propionyl-CoA

1) Propionyl carboxylase - Biotin mech to add CO_2
2) methylmalonyl-CoA Epimerase - Racemization
3) methylmalonyl-CoA Mutase - make succinyl CoA for TCA

FA Biosynthesis

- Use NADPH instead of NADH

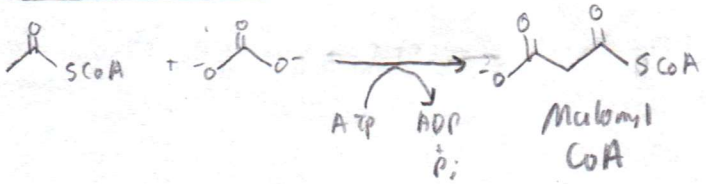
Goal - Run thiolase in reverse

to link malonyl-CoA w/ FA/acetyl-CoA

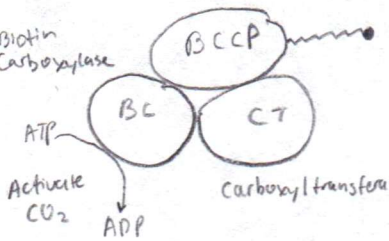
To do this, need to make malonyl-CoA

Malonyl-CoA creation in FA synthase

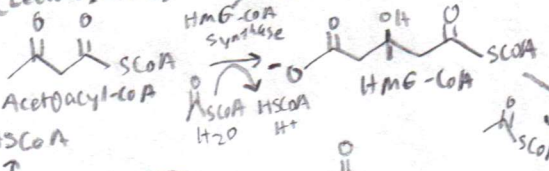
Biotin Carboxylase

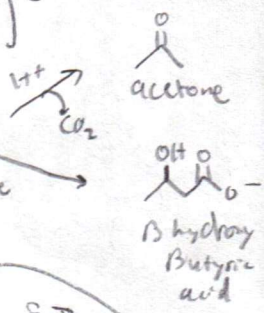


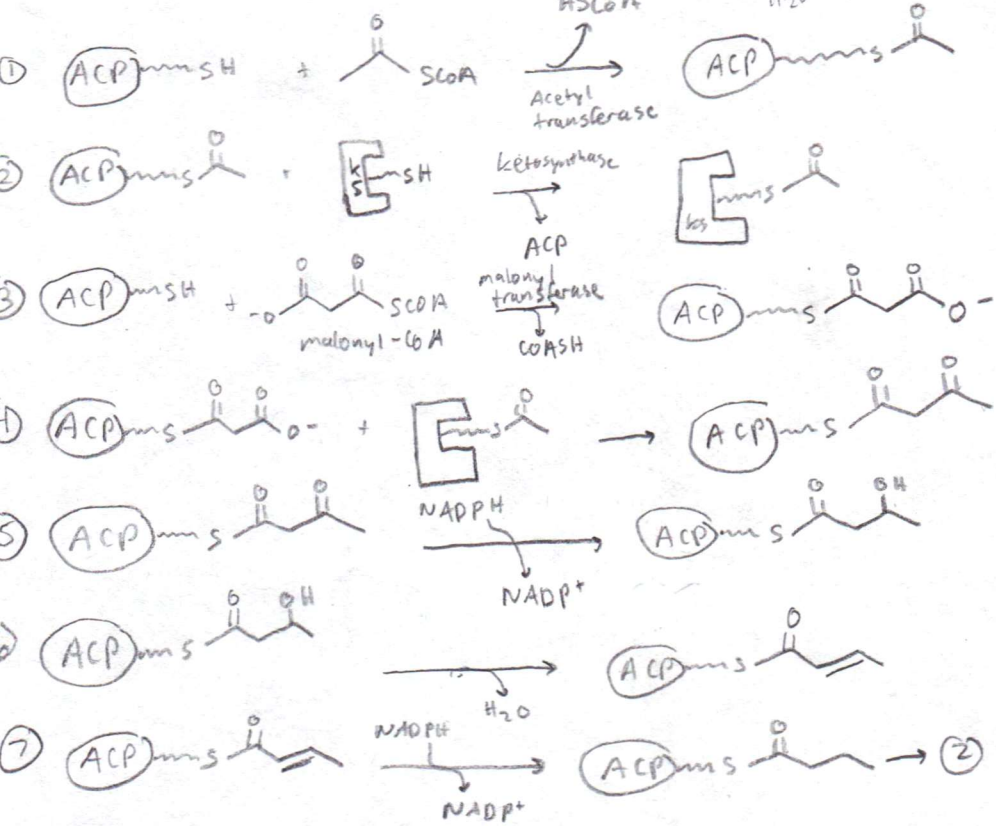
Normally biotin mechanism



Alternate ketone Body (Lecture NOTES)







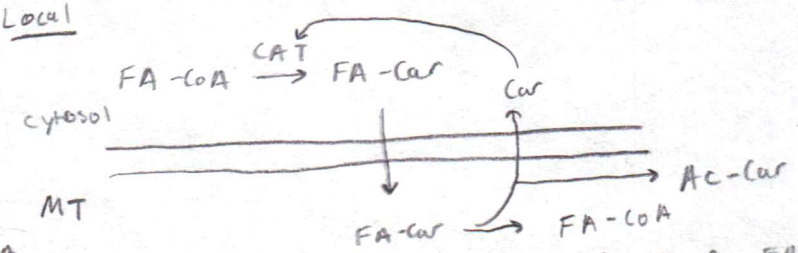
1 → (2 → 3 → 4 → 5 → 6 → 7)$_6$ → 8

for palimitic acid

Avoid protons being grabbed by malonyl-CoA

FA Regulation

Local



Excess acetyl-CoA = send out of MT for FA synthesis

Le Chatlier - control carnitine levels to control intake

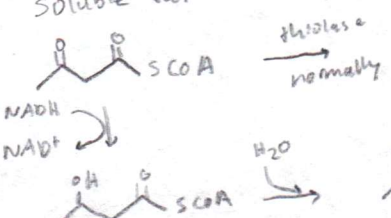
↳ tie up w/ Ac-Car = ↓ Breakdown

citrate = TCA backups store acetyl-CoA as FA

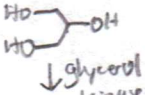
Global

FA's not soluble = difficult to transport

Soluble but - FA that can move in body



Needed to prevent enzyme that just hydrolyzed any thioester (Lecture)

TAG → 3FA + 

↓ glycerol kinase

↓ glycerol 3-phosphate dehydrogenase

DHAP

triglyceride

FA