Glycogen metabolism

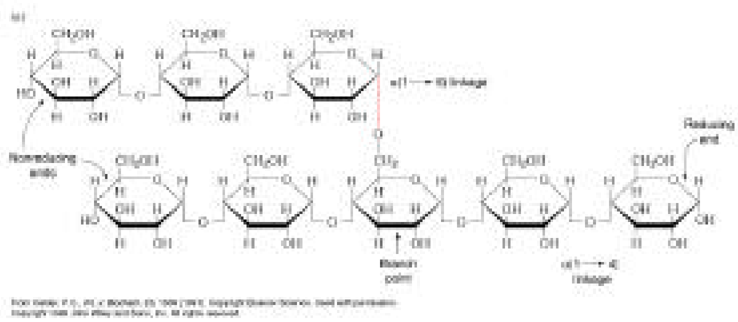
Glycogen review - 1,4 and 1,6 α-glycosidic links
~ every 10 sugars are branched - open helix with many non-reducing ends.
Effective storage of glucose

Glucose storage

Liver glycogen	4.0%	72 g
Muscle glycogen	0.7%	245 g
Blood Glucose	0.1%	10 g

Large amount of water associated with glycogen
- 0.5% of total weight

Glycogen stored in granules in cytosol w/proteins for synthesis, degradation and control
There are very different means of control of glycogen metabolism between liver and muscle



Glycogen biosynthetic and degradative cycle
Two different pathways - which do not share enzymes like glycolysis and gluconeogenesis

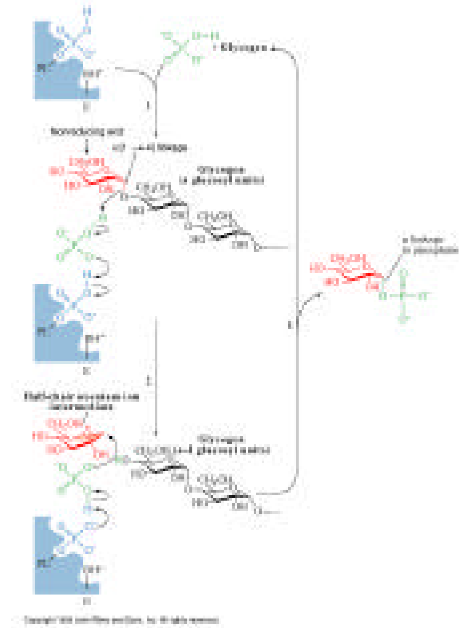
glucose -> glycogen   <u>glycogenesis</u> - biosynthetic
glycogen -> glucose 1-P   <u>glycogenolysis</u> - breakdown

Evidence for two paths
- Patients lacking phosphorylase can still synthesize glycogen
- hormonal regulation of both directions

Glycogenolysis (glycogen breakdown)-
<u>Glycogen Phosphorylase</u> glycogen (n) + Pi -> glucose 1-p + glycogen (n-1)

- Enzyme binds and cleaves glycogen into monomers at the end of the polymer (reducing ends of glycogen)
- Dimmer interacting at the N-terminus.
- rate limiting - controlled step in glycogen breakdown
- glycogen phosphorylase - cleavage of 1,4 α glycosidic bond by Pi NOT H_2O
- Energy of phosphorolysis vs. hydrolysis
  - -low standard state free energy change -transfer potential
  - -driven by Pi concentration
  - -Hydrolysis would require additional step s/ cost of ATP
  - - Think of the difference between adding a phosphate group with hydrolysis
- phosphorylation locks glucose in cell (imp. for muscle)
- Phosphorylase binds glycogen at storage site and the catalytic site is 4 to 5 glucose residues away from the catalytic site.

- Phosphorylase removes 1 residue at a time from glycogen until 4 glucose residues away on either side of 1,6 branch point – stericaly hindered by glycogen storage site
- Cleaves without releasing at storage site
- general acid/base catalysts
- Inorganic phosphate attacks the terminal glucose residue passing through an oxonium ion intermediate.
- cofactor PLP pyridoxal 5'-phosphate
  - Covaliently bound by shiff base
  - Phosphate functional group of PLP acts a an acid/base catalyst
  - Allows the exclusion of water - replaced by Pi



<u>Transferase/debranching enzyme</u>

Finishes what phosphorylase cannot
Two activities on same enzyme

- 1st- transferase - move 4 or 5 sugars from one chain to another
  - Exposes 1,6 branched sugar
- 2nd - debranching - specific cleavage (hydrolysis) of 1,6 branched glucose - giving free glucose

<u>Phosphoglucomutase</u>

glucose 1-P -> glucose 6-P

- mechanism involves phosphoryl shuttle from serine in active site to glucose hydroxyls
- no additional energy required
- equilibrium far to the right

<u>Glucose 6-phosphatase (G-6-Pase)</u>

glucose 6P -> glucose + Pi

- Found mostly in Liver and Kidney NOT Muscle or Brain
- Allows gluconeogenic tissue to supply and glucose for body while muscle and brain keep it for glycolysis

Glycogenesis

<u>UDP glucose transferase</u>

Glucose 1 P + UTP ->UDPglucose + PPi

- UTP acts as a high energy handle for many sugar polymers
- PPi hydrolysis - pulls reaction to right of reaction

<u>Glycogen synthase</u>

UDPglucose -> 1,4 glycogen + UDP

- Highly regulated enzyme of this path
- requires a preexisting primer of glycogen

- Primer is glycogenin enzyme/protein
- Glycogenin glycosylates itself
- Glycogen "core"

· 1,4 glycogen addition until glycogen synthase looses contact with glycogenin core

<u>Branching enzyme</u>

1,4 glycogen -> 1,6 /1,4 glycogen

- once 11 or so glucose residues have been added, transfers 1,4 to another chain in a 1,6 linkage
- transfers about 7 sugar residues

Energy cost of Glycogen synthesis

glucose 6-phosphate -> glucose 1 phosphate

glucose 1-phosphate + UTP -> UDP-Glucose + PPi

PPi + H_20 -> 2 Pi

UDP-glucose + glycogen $_n$ -> glycogen $_{n+1}$ + UDP

<u>ADP + ATP -> UTP + ADP</u>

The cost of storage of glucose in the form of glycogen is very small as compared to the production of ATP from glucose