Glycogen Metabolism

Voet & Voet, Chapter 18

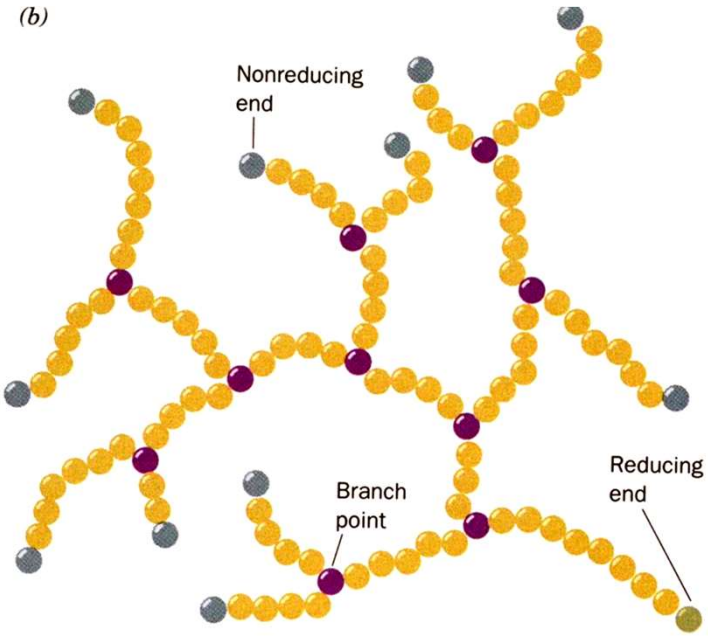
Albert Einstein: "Everything should be made as simple as possible but not simpler"

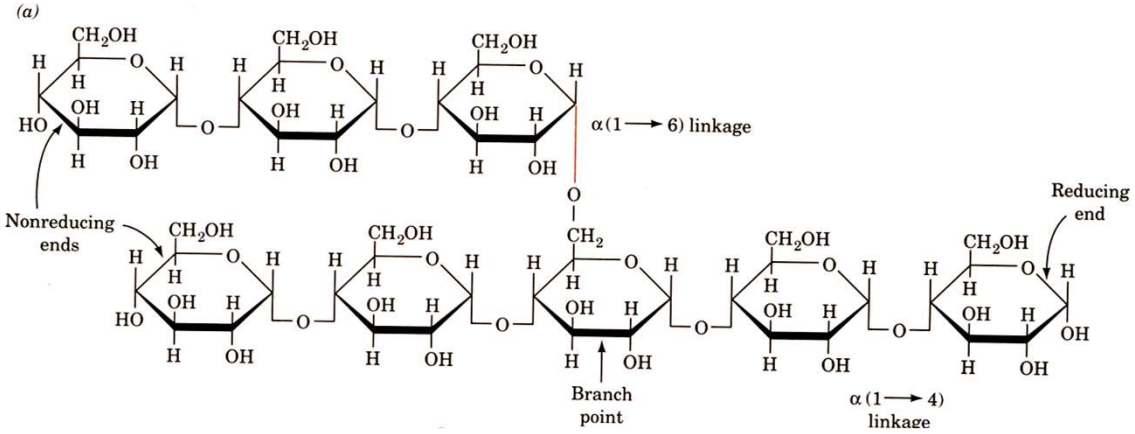
- **Glucose = important fuel (glycolysis, citric aid cycle)**

⇒ needs to be stored to be "ready" for metabolic need

better than fat: rapidly mobilized; can replenish blood glucose; anaerobically metabolized

→ single (BIG) molecules!





- **branches every 8-12 residues**

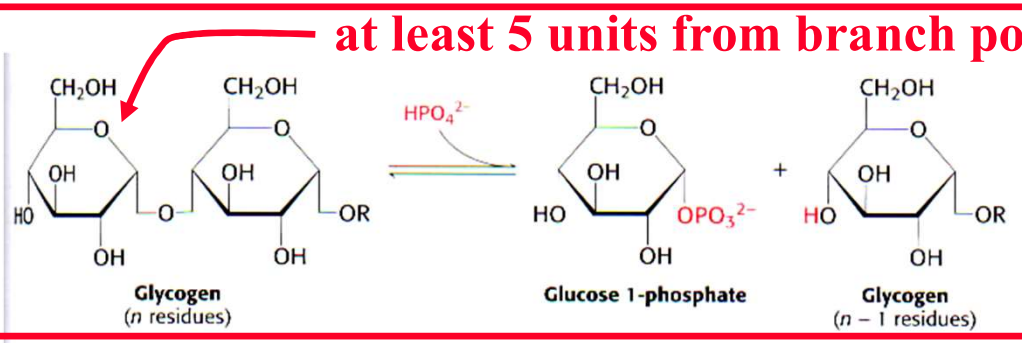
⇒ fast release at every end!

How Does the Cell Utilize Glycogen?

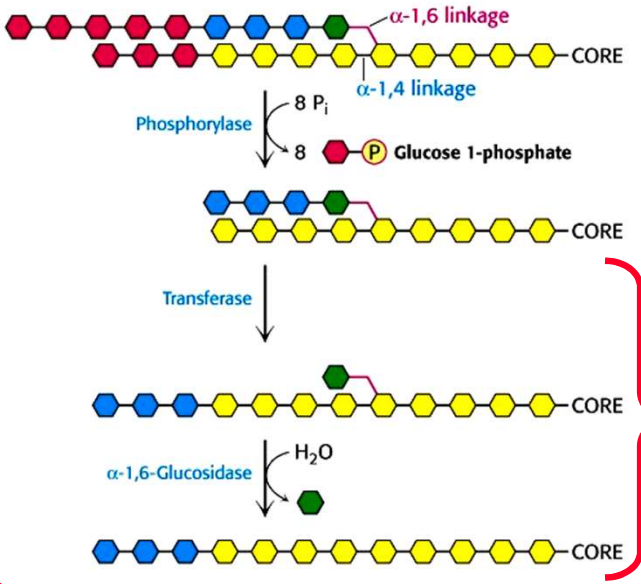
➢ **Glycogen has to be synthesized and degraded in a tightly regulated fashion**

Glycogen Breakdown involves:

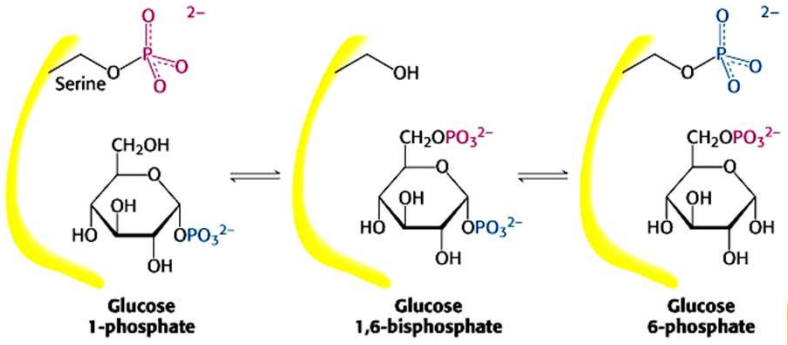
1.) (Glycogen) Phosphorylase



2.) Glycogen debranching enzyme



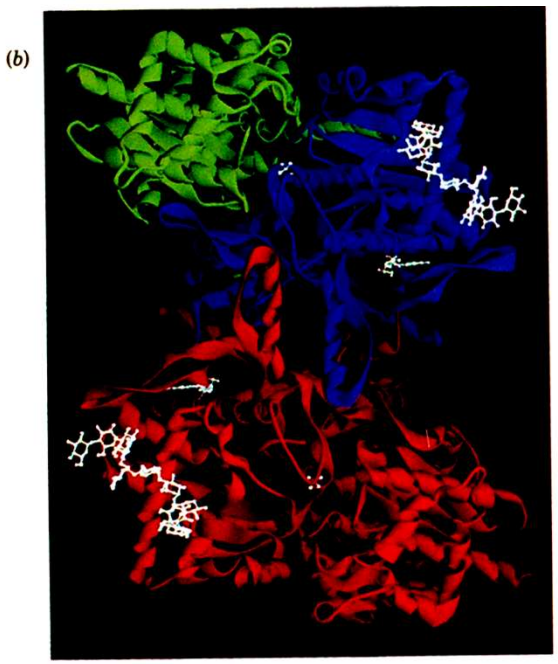
3.) Phosphoglucomutase

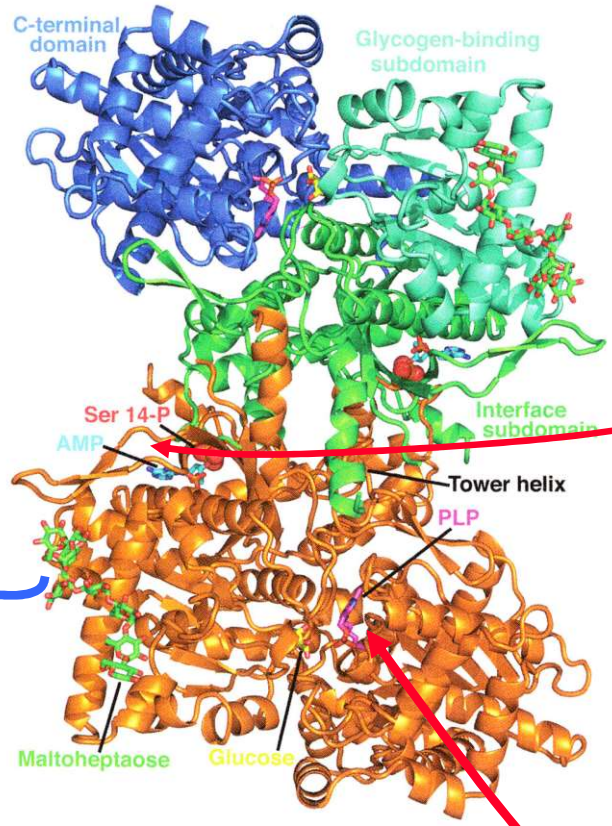


⇒ glycolysis

1.) Glycogen Phosphorylase: The Structure

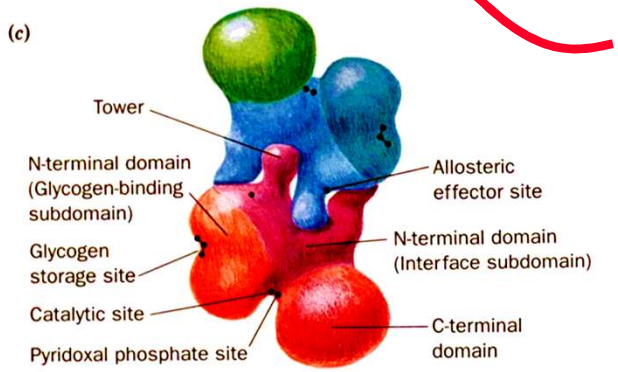
- glycogen storage site
  ⇒ phosphorylase holds on tightly to glycogen
- fits up to 5 glucoses but no branch!
- dimer:





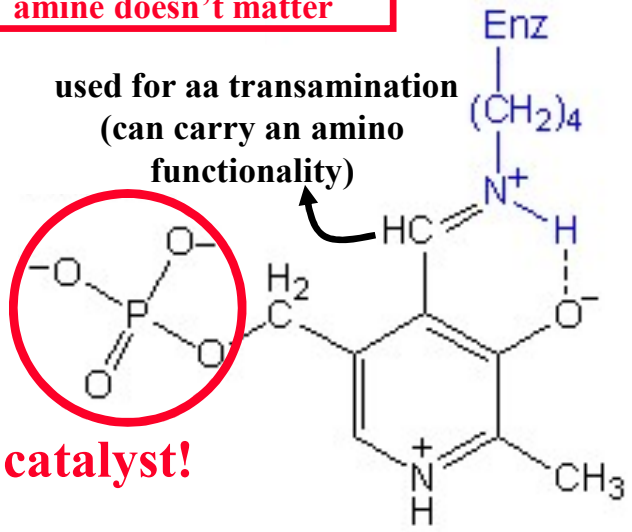
- 842 aa (97 kD)
- <u>two forms:</u>
  phosphorylase a w/ Ser14-phosphoester and phosphorylase b w/o phosphoester

catalytic site



Glycogen Phosphorylase: The Mechanism

BUT: $NaBH_4$ reduction to amine doesn't matter



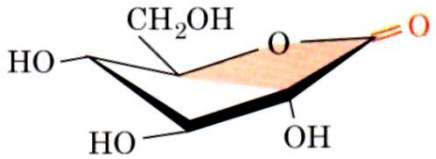
used for aa transamination (can carry an amino functionality)

acid catalyst!

pyridoxal-5-phosphate (Vitamin B_6 derivative)

Evidence:

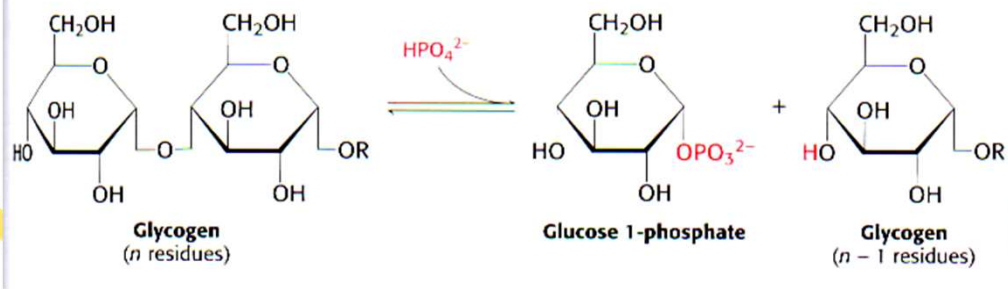
- **Potent inhibitor:**

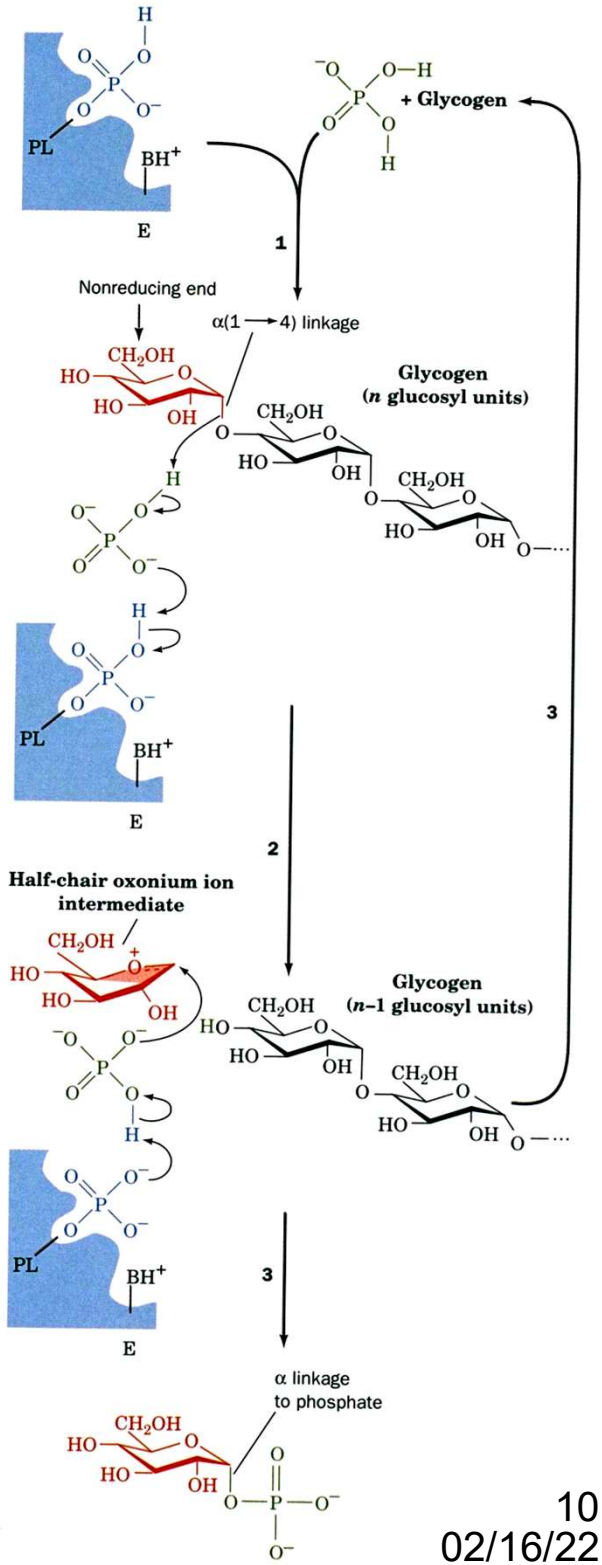


1,5-Gluconolactone

- **Random Bi Bi kinetics (no Ping Pong, no intermediates)**
- **Retention of configuration**

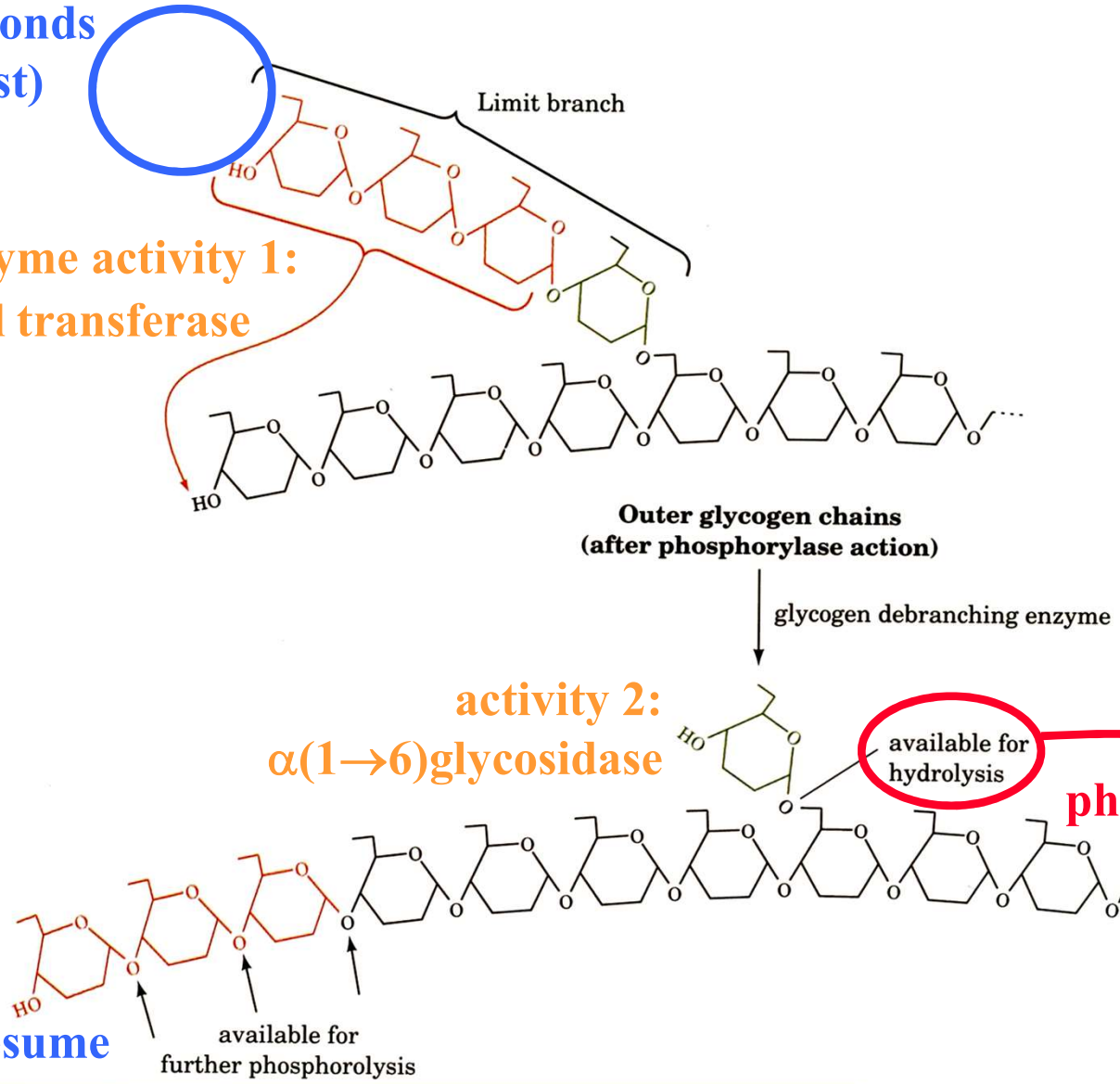
- **Overall:**





2.) Glycogen Debranching Enzyme

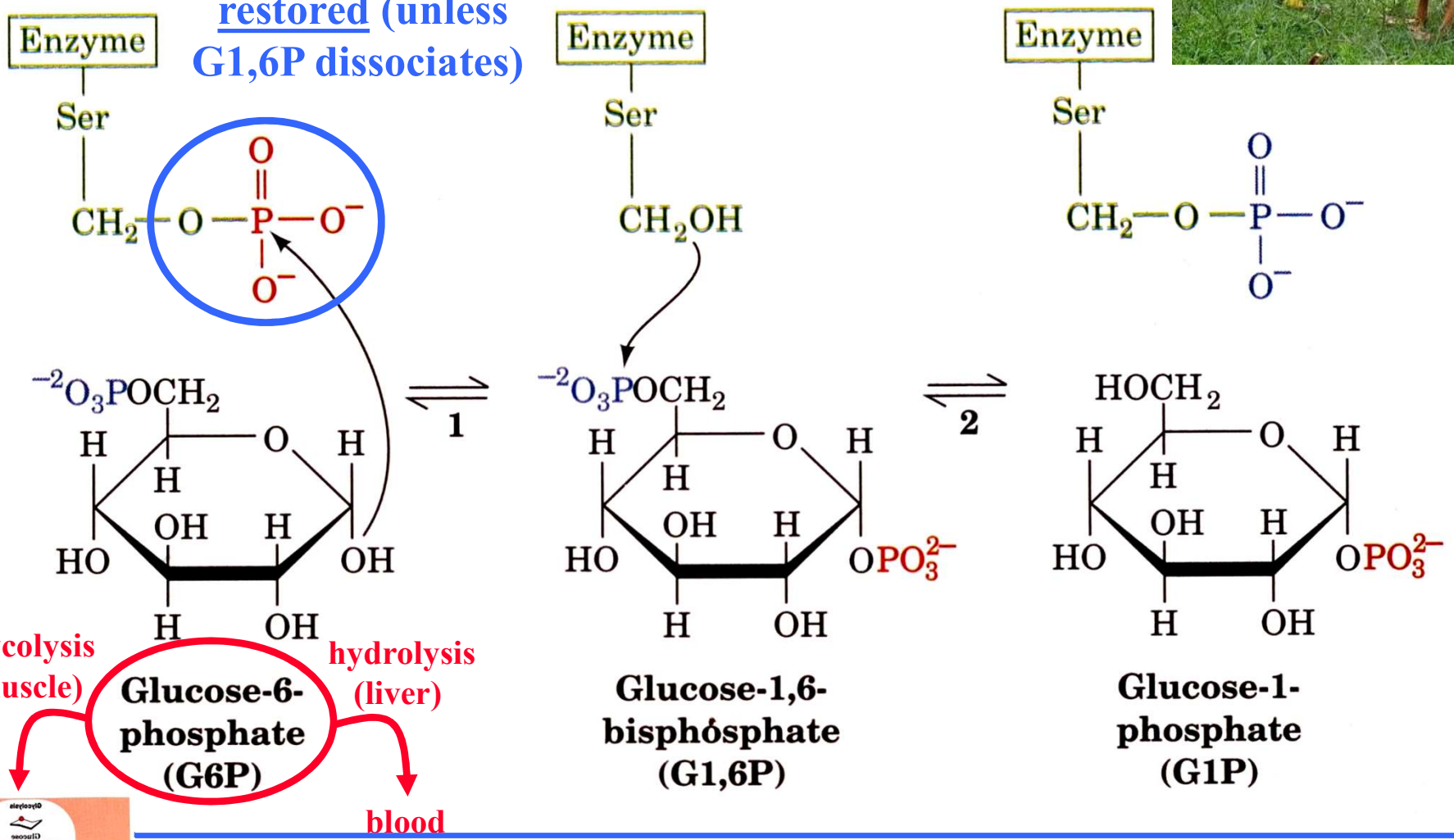
- chewed off by phosphorylase in seconds (muscle is strongest)

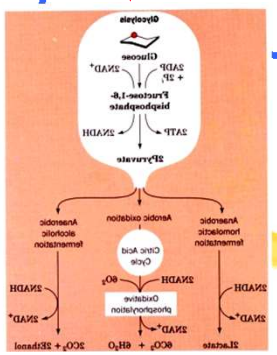


debranching enzyme activity 1: α(1→4)glycosyl transferase

- phosphorylase can resume (after lag)

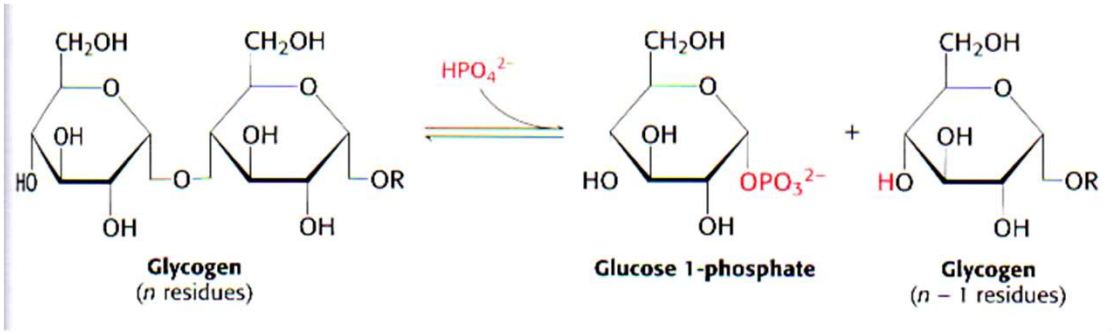
3.) Phosphoglucomutase





➢ **Similar to phosphoglycerate mutase**

Energetics of Glycogen Phosphorylation



$$\Delta G' = \Delta G^{0}' + RT \ln \frac{[\text{glycogen}_{n-1}][\text{G1P}]}{[\text{glycogen}_{n}][\text{P}_i]}$$ **and ΔG^{0}' = + 3.1 kJ/mol**

$\Rightarrow \Delta G' = 0$ (with $[\text{glycogen}_{n-1}] = [\text{glycogen}_{n}]$) for $\dfrac{[\text{G1P}]}{[\text{P}_i]} = \dfrac{1}{3.5}$

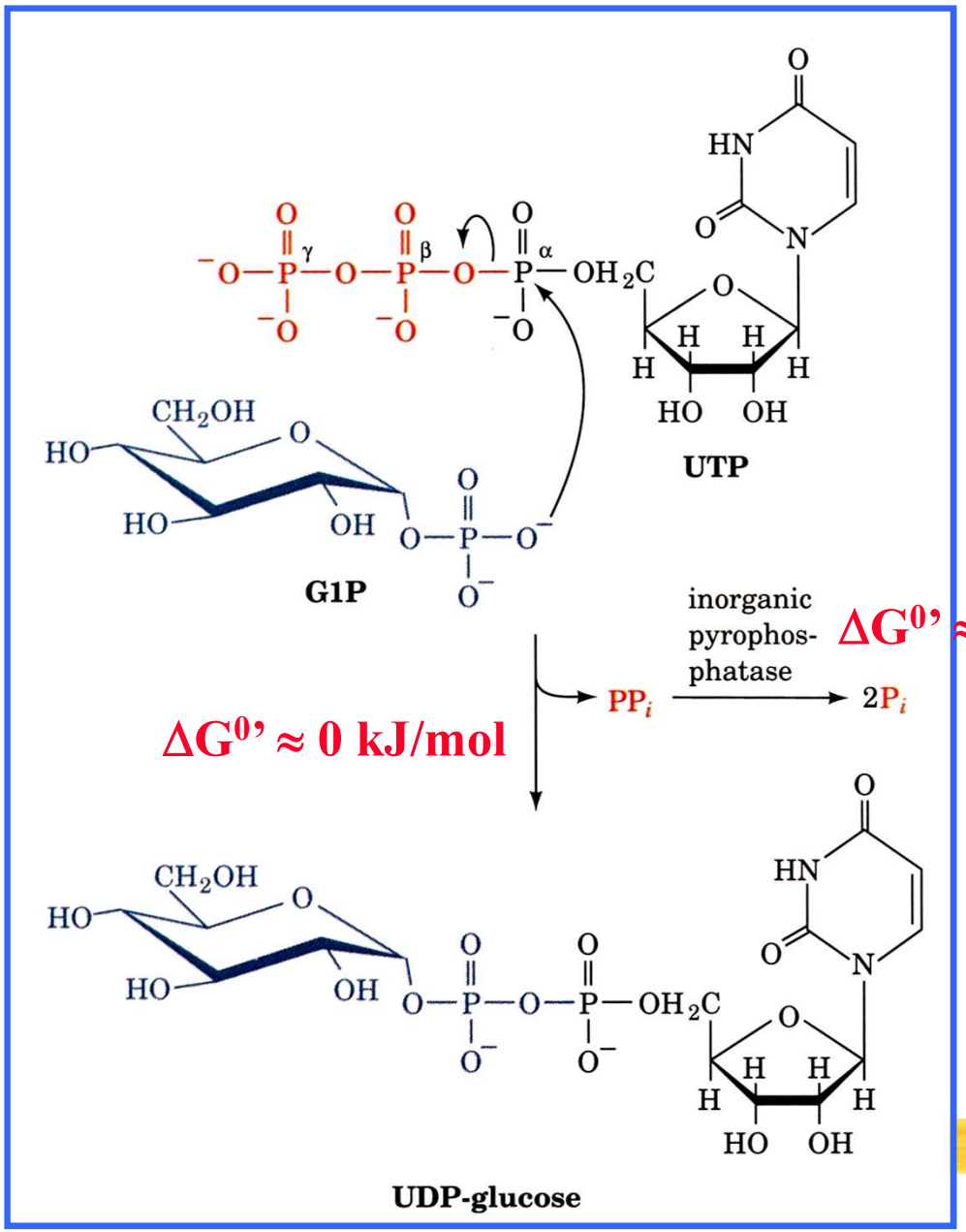
in cell: $\dfrac{[\text{G1P}]}{[\text{P}_i]} = \dfrac{1}{30}$ to $\dfrac{1}{100}$ **$\Rightarrow \Delta G' = -5$ to -8 kJ/mol** **exergonic**

Biosynthetic and degradative pathways are different!

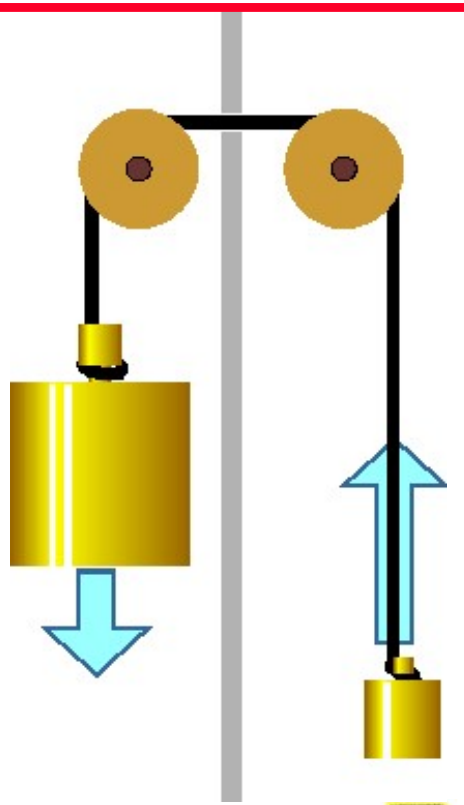
- **Both pathways can be independently regulated**
- **Both pathways can be active at similar concs.**

Glycogen Synthesis Must Take another Route

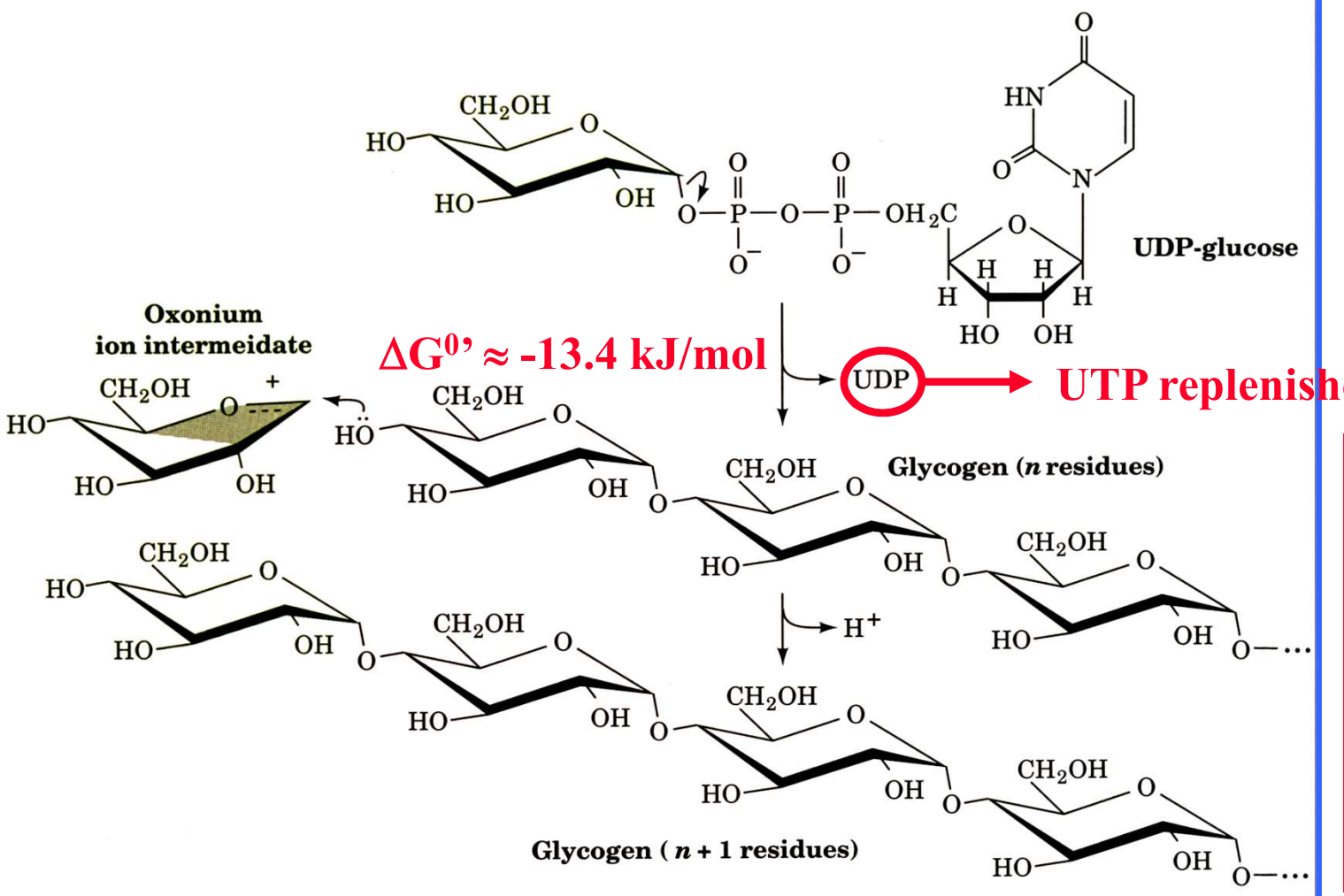
1.) UDP-Glucose Pyrophosphorylase



$\Rightarrow$ **Overall exergonic**



2.) Glycogen Synthase

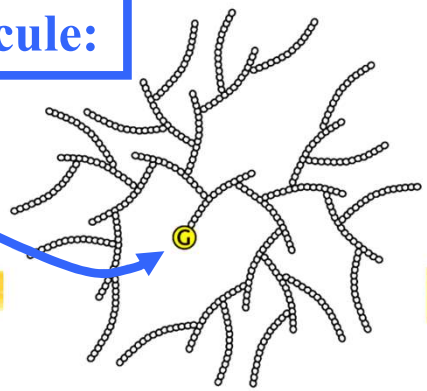


Overall loss of 1 UTP → UDP + P_i

BUT this is ONLY a loss of 3% of the overall energy stored in 1 glucose molecule!

Priming a glycogen molecule:

1 Glycogenin/granule for first 7 glucoses



3.) Glycogen Branching Enzyme

- Transfer for branching is exergonic
- Transfer for debranching would be endergonic

⇒ Hydrolysis instead!