

## **Lecture 3: Glycogen metabolism (Chapter 15)**

**Review: Glycogen breakdown (VVP Ch. 15.1)**

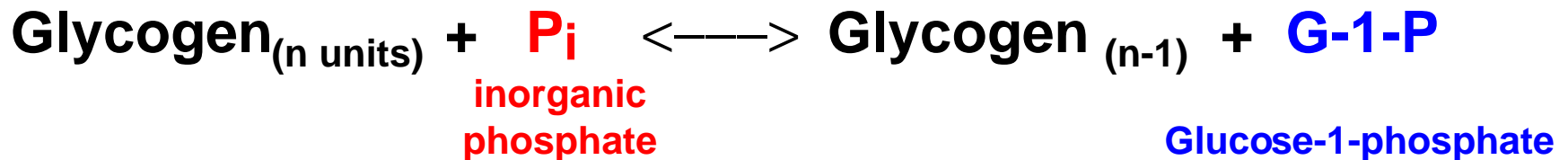
**New: More on Phosphorylase (Ch. 15.1, 15.3)  
Glycogen synthesis (Ch. 15.2)  
Some on regulation (Ch. 15.3)**



**Roll Call!**

# Glycogenolysis (or glycogen breakdown) requires 3 major enzymes:

- 1) **GLYCOGEN PHOSPHORYLASE** (Fig. 15-4; more later)  
(bond cleavage by phosphorolysis)



- 2) **GLYCOGEN DEBRANCHING ENZYME** (Fig. 15-6)

- 3) **PHOSPHOGLUCOMUTASE** (Fig. 15-7):



**G-6-P** has several fates (see Fig 15-1).  
In LIVER, it is hydrolyzed to glucose + **P<sub>i</sub>**  
by **GLUCOSE-6-PHOSPHATASE**.

# GLYCOGEN PHOSPHORYLASE (Review)

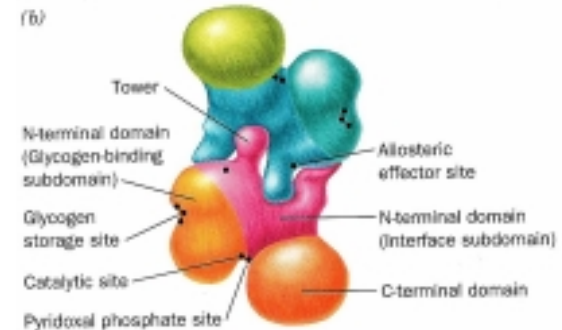
- Is a FAST enzyme.
- Is a dimer of identical 842-residue subunits.
- Removes GLUCOSE UNITS from the NONREDUCING ends of GLYCOGEN.
- Catalyzes the CONTROLLING STEP in glycogen breakdown.
- Only releases units that are 5 or more from the branch (steric hindrance)
- Is regulated by (Fig. 15-5; see Kinemages 14 on the CD with VVP):

## ALLOSTERIC INTERACTIONS—

ATP, G6P & glucose inhibit it;  
AMP activates it.

## COVALENT MODIFICATION —

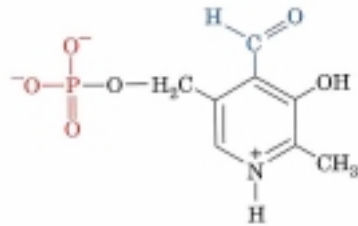
phosphorylation at Ser-14 (Phosphorylase A)—more active  
dephosphorylation (Phosphorylase B )—less active



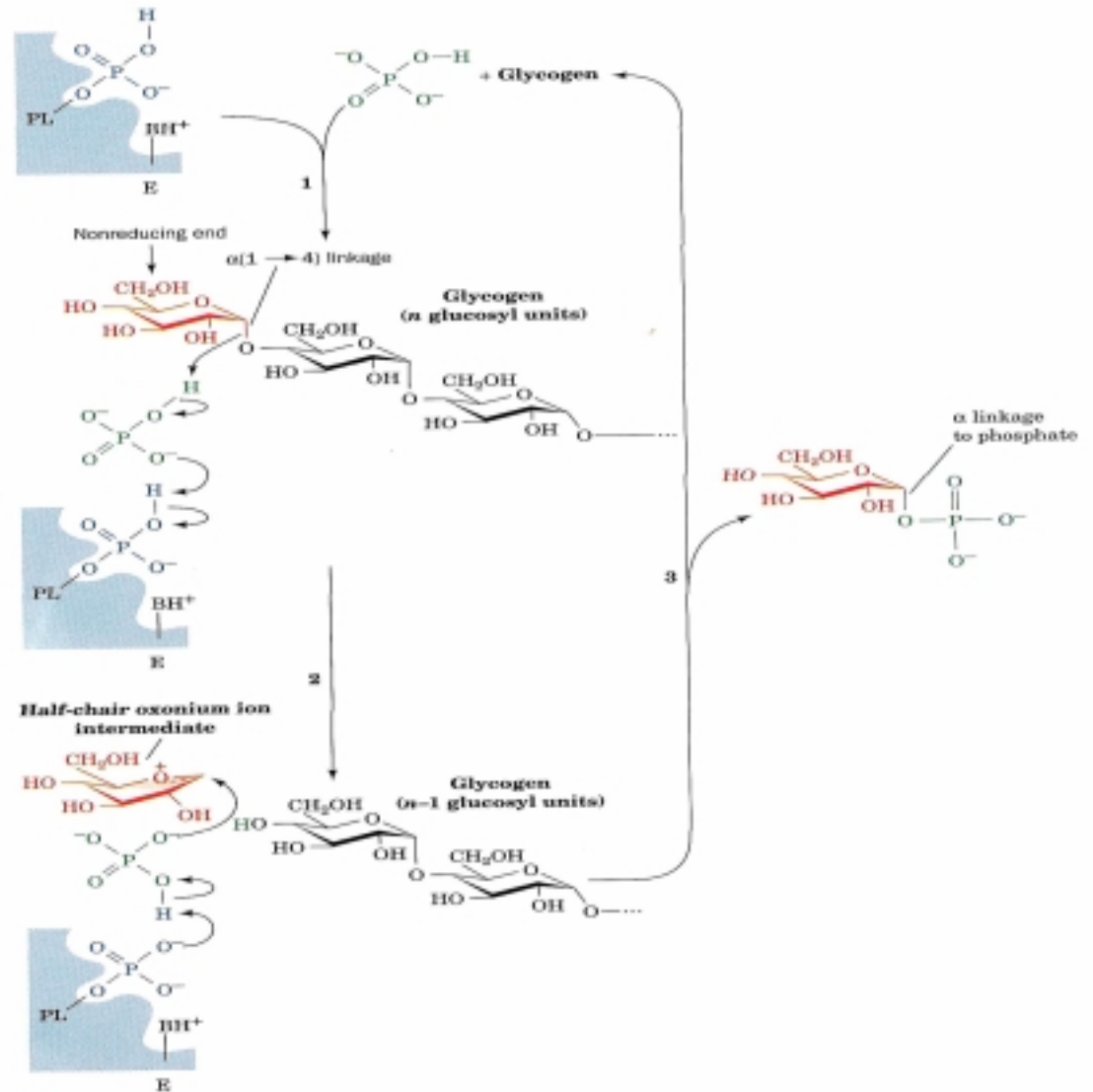
# GLYCOGEN PHOSPHORYLASE (New material)

**Fig. 15-4:**

Phosphorylase has a “random sequential” enzyme mechanism that involves PLP (pyridoxyl-5'-phosphate), a vitamin B6 derivative:

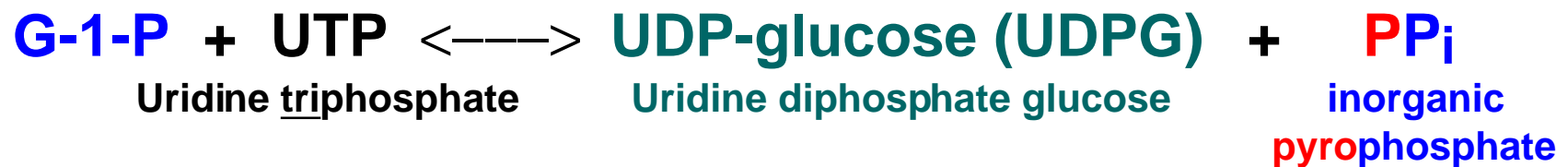


Pyridoxal-5'-phosphate (PLP)



Glycogen SYNTHESIS requires 3 major enzymes, and occurs by a **SEPARATE PATHWAY** from glycogenolysis:

1) UDP-GLUCOSE PYROPHOSPHORYLASE (Fig. 15-9):



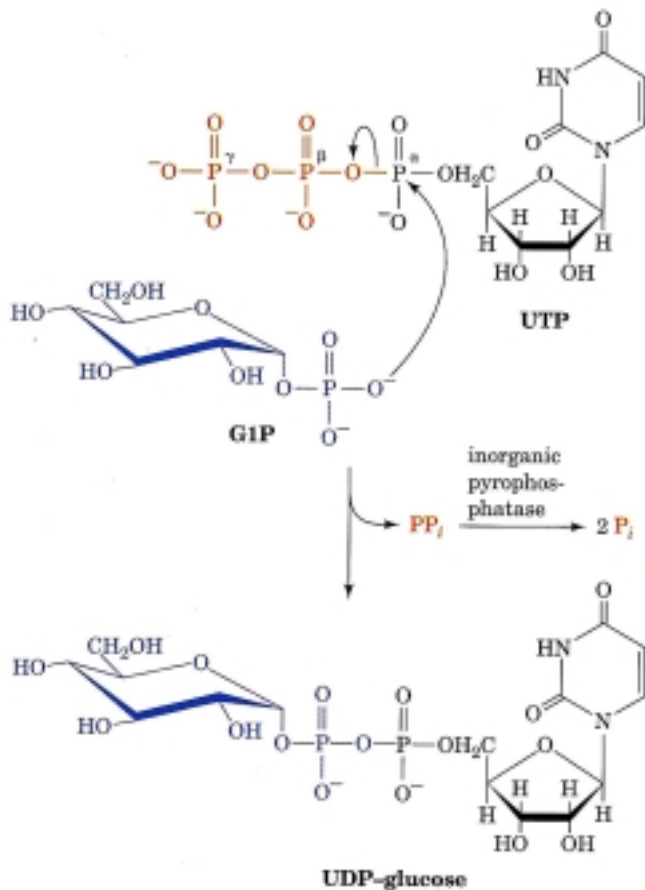
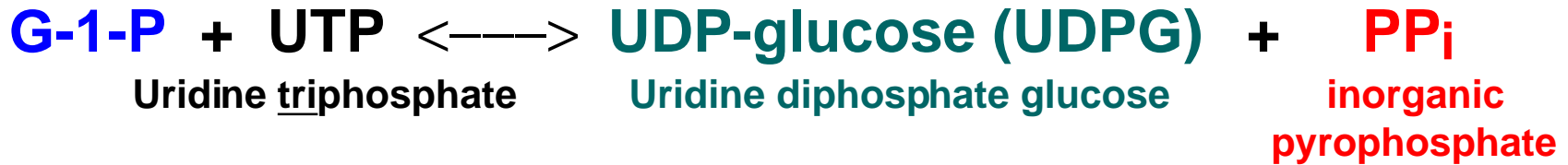
2) GLYCOGEN SYNTHASE (Fig. 15-10):



This reaction must be “primed” by GLYCOGENIN

3) GLYCOGEN BRANCHING ENZYME (Fig. 15-11) or  
AMYLO (1,4→1,6) TRANSGLYCOSYLASE.

# 1) UDP-GLUCOSE PYROPHOSPHORYLASE (Fig. 15-9):



The  $\Delta G^\circ$  of this reaction is nearly ZERO, but the **PP<sub>i</sub>** formed is hydrolyzed to 2 **P<sub>i</sub>** (orthophosphate) in a highly EXERGONIC reaction the the omnipresent enzyme, **INORGANIC PYROPHOSPHATASE**. Therefore, the overall reaction is also highly exergonic:

	$\Delta G^\circ$ (kJ/mol)
<b>GIP + UTP</b> $\rightleftharpoons$ <b>UDPG + PP<sub>i</sub></b>	~ 0
<b>H<sub>2</sub>O + PP<sub>i</sub></b> $\longrightarrow$ <b>2 P<sub>i</sub></b>	- 33.5
<b>GIP + UTP</b> $\rightleftharpoons$ <b>UDPG + 2 P<sub>i</sub></b>	- 33.5
<b>OVERALL</b>	

**UDPG is a HIGH ENERGY compound that can donate GLYCOSYL units to the growing glycogen chain. No further energy is required for glycogen synthesis.**

### **IMPORTANT GENERAL NOTE:**

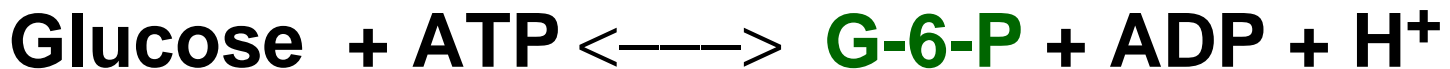
**The cleavage of a nucleoside triphosphate (NTP) to form  $PP_i$  is a common synthetic strategy. The free energy of  $PP_i$  hydrolysis (by inorganic pyrophosphatase) can be utilized together with the free energy of NTP hydrolysis to drive an otherwise endergonic reaction to completion. (We will see this over and over and over this semester!)**

Where did **GIP** come from for this reaction?

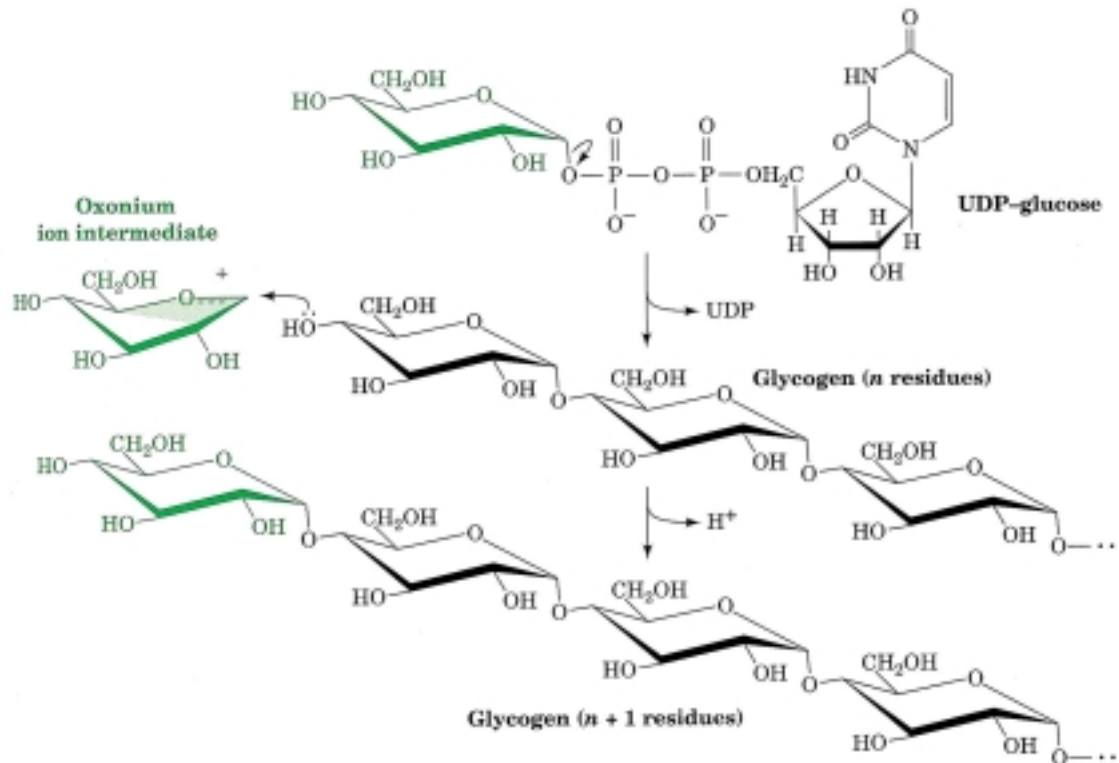
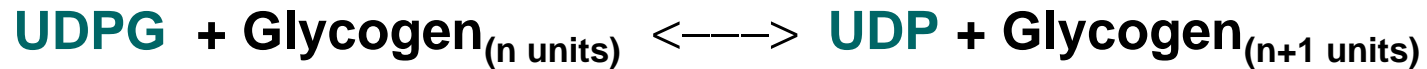
1) Phosphoglucomutase is reversible:



2) HEXOKINASE (in glycolysis) and GLUCOKINASE (in liver—helps maintain blood glucose levels):



## 2) GLYCOGEN SYNTHASE MECHANISM (Fig. 15-10):



The glycosyl unit of UDPG is transferred to the C(4)-OH on one of the non-reducing ends of glycogen, forming an  $\alpha(1\rightarrow4)$  glycosidic bond. Note that this step makes  $\alpha$ -amylose, not the branched structure of glycogen.

The  $\Delta G^{\circ}$  for this reaction is  $-13.7 \text{ kJ/mol}$ , making this reaction spontaneous (exergonic) under the same conditions that glycogen breakdown is exergonic. Therefore, the rates of the two reactions must be independently and tightly controlled.

**For each molecule of GIP that is converted to glycogen, one molecule of UTP is hydrolyzed to UDP + P<sub>i</sub>.**

**The UTP is replenished by the enzyme  
NUCLEOSIDE DIPHOSPHATE KINASE:**



**(UTP hydrolysis is energetically equivalent to ATP hydrolysis.)**

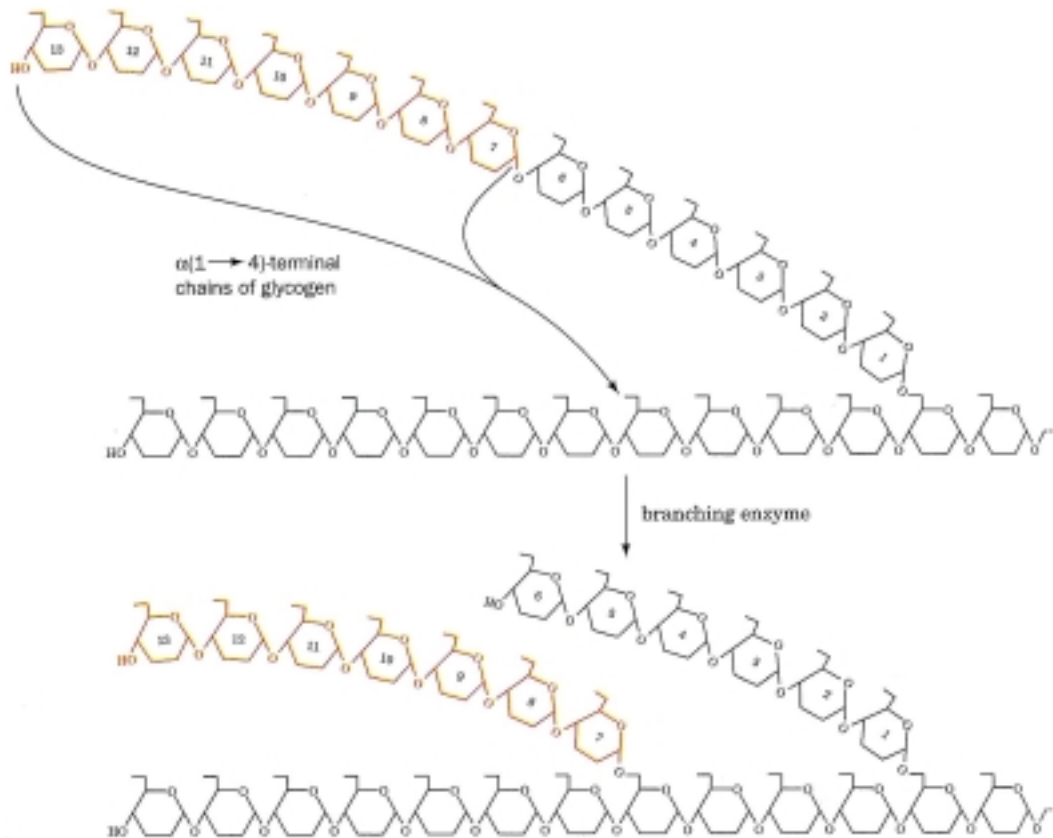
## **GLYCOGENIN and Glycogen “Priming”**

**Glycogen synthesis can only occur by extending an already existing  $\alpha$  (1 $\rightarrow$ 4)-linked glucan chain.**

**Therefore, how can it get started in the first place?**

**Answer: The first step in glycogen synthesis is the attachment of a glucose residue to the -OH group on Tyr-194 of GLYCOGENIN. This attachment step is done by the enzyme TYROSINE GLUCOSYLTRANSFERASE. Glycogenin then autocatalytically extends the glucan chain by up to 7 residues long (also donated by **UDPG**). Glycogen synthase can then attach glucose residues to this glycogen “primer”. Each molecule of glycogen is associated with ONE molecule each of glycogenin and glycogen synthase.**

### 3) GLYCOGEN BRANCHING ENZYME (Fig. 15-11) or AMYLO (1,4→1,6) TRANSGLYCOSYLASE:



Breaks  $\alpha(1 \rightarrow 4)$  glycosidic bonds and forms  $\alpha(1 \rightarrow 6)$  linkages. Transfers terminal chain segments of about 7 residues to the C(6)-OH groups of glucose residues. Each transferred segment must come from a chain of at least 11 residues, and the attachment point must be at least 4 residues away from another branch point. Segment can be moved to the same or a different chain.

**Note: Not to be confused with Glycogen Debranching Enzyme!**

**Control of glycogen metabolism is very complex. It involves:**

- **allosteric regulation of both GS & GP**
- **substrate cycles**
- **enzyme-catalyzed covalent modification of both GS & GP**
- **covalent modifications are under hormonal control in the body, through their own enzymatic cascades**

**In LIVER: Glycogen metabolism is ultimately controlled by GLUCAGON — a 29 AA-long polypeptide hormone that is secreted from the pancreas into the blood (liver cells have glucagon receptors).**

**In MUSCLES (and various other tissues): Is controlled by adrenal hormones, EPINEPHRINE (adrenalin) and NOREPINEPHRINE (noradrenalin).**

**These hormones act at cell surfaces to stimulate ADENYLATE CYCLASE, thus increasing [cAMP], which acts inside cells as a ‘second messenger’ for the hormones. Cells have many cAMP-dependent PROTEIN KINASES whose activities increase upon cAMP binding. (Reminder: Kinases catalyze the transfer of phosphoryl groups between ATP and other molecules, proteins in this case.)**

**Liver maintains blood [glucose] at ~5 mM; if it drops to half of this, a coma results. Upon blood [glucose] decrease, the liver releases glucose to the blood; glucose triggers pancreas to release glucagon, which causes increase [cAMP] in liver, which stimulates glycogen breakdown. Glucose diffuses freely out of liver cells, causing an increase in blood [glucose]. High blood [glucose] causes release of INSULIN from the pancreas to the blood. The rate of glucose TRANSPORT across many cell membranes increases in response to insulin.**