Glycogen Metabolism

Bryan Winchester

Biochemistry Research Group
UCL Institute of Child Health at
Great Ormond Street Hospital,
University College London
London, UK.

Great Ormond Street Hospital
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The child first and always

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Overview of Glycogen Function

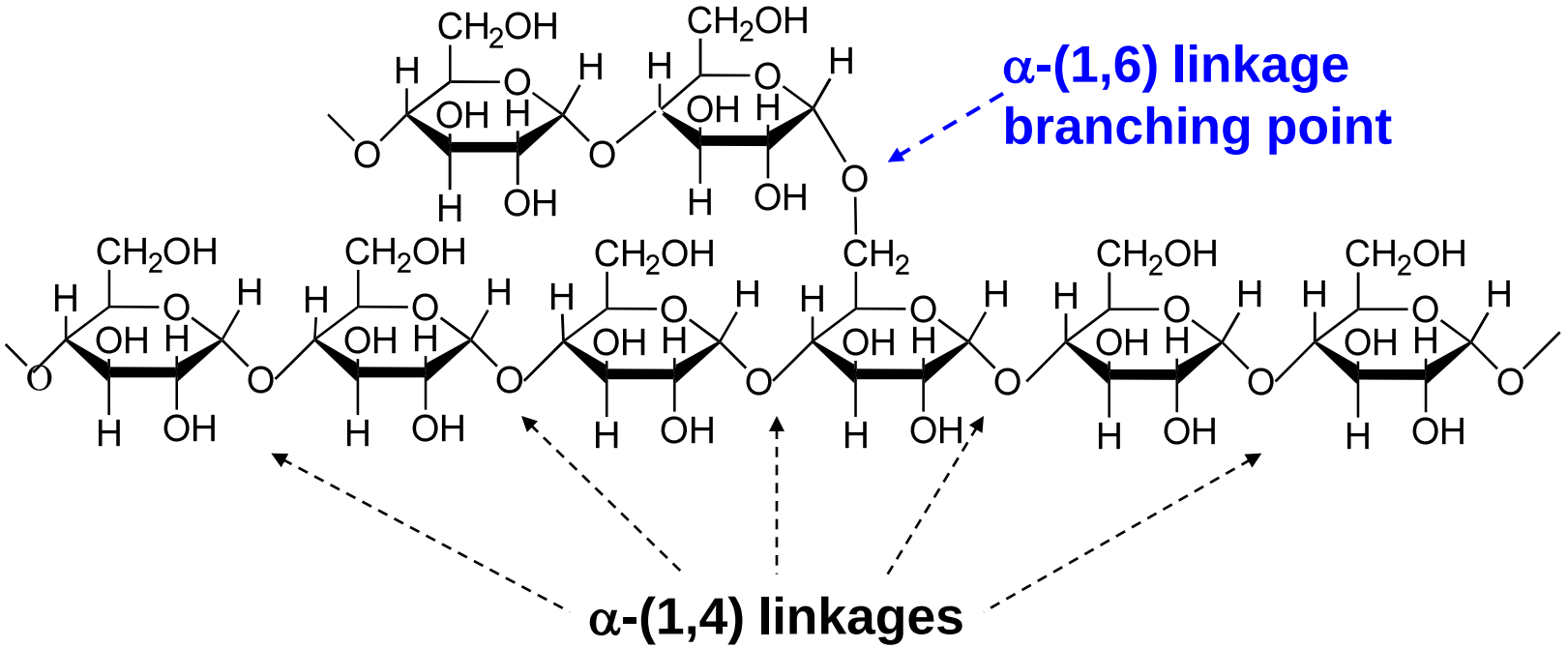
- **Surplus of carbohydrate fuel after meal is conserved as glycogen and fat**
- **Glycogen is the storage form of glucose in mammalian cells**
- **Liver**
  - **After a meal glucose is removed from portal circulation and the excess is stored as glycogen, up to 70g in adult.**
  - **Glycogen acts as a reservoir for regulating blood glucose levels between meals**
  - **Glucose is released from liver glycogen to maintain blood glucose levels, 3.0-5.5 mM, e.g. to supply brain and red blood cells**

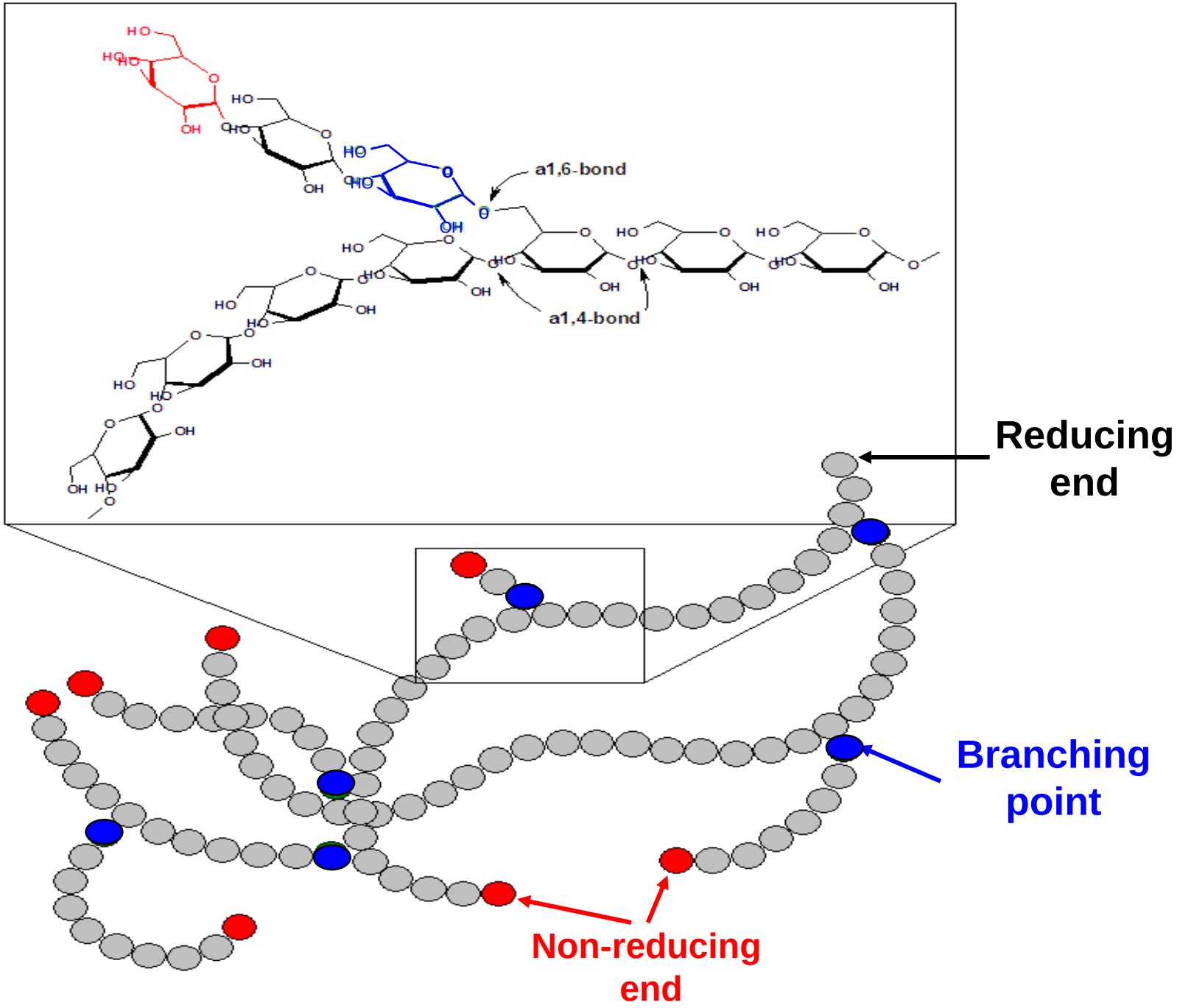
Overview of Glycogen Function

- **Skeletal muscle**
  - **After carbohydrate-rich meal up to 200g of glycogen in skeletal muscle**
  - **Glycogen provides rapid source of glucose in muscle for anaerobic glycolysis and is depleted after strenuous exercise**
  - **Lactate goes to liver for gluconeogenesis**
  - **Muscle takes up glucose from blood to replenish glycogen**
  - **Muscle cannot release glucose into blood so muscle glycogen is only a store for muscle**
- **Cardiac muscle**
  - **Glycogen is utilised for heavy work load**
- **Brain**
  - **Emergency source of glucose in hypoglycaemia or hypoxia**

Structure of Glycogen

- **Glycogen is a homopolymer of glucose, containing up to 55-60,000 glucosyl residues**
- **It consists of linear chains of glucose linked by ⟨–(1,4) glycosidic bonds**
- **The chains are highly branched, with α–(1,6) branch linkages occurring every 8-10 residues.**




a1,6-bond
a1,4-bond
Reducing end
Branching point
Non-reducing end

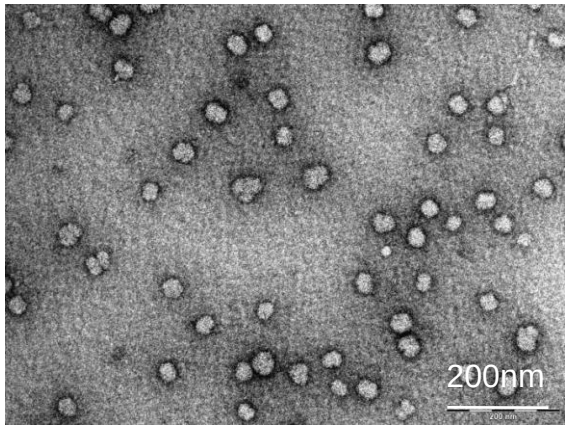
Structure of Glycogen

- **Each glycogen molecule has a dimeric protein, glycogenin covalently attached through the hydroxyl group of a specific tyrosine to the C1 of the first glucose residue at the reducing end of the chain**

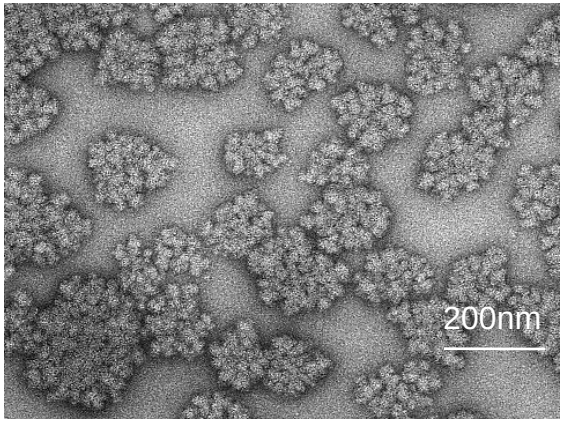
QuickTime™ and a
decompressor
are needed to see this picture.

Structure of Glycogen

- **Glycogen occurs as spherical granules known as beta-particles, 20-50 nm in diameter, except in the liver where the beta-particles aggregate to form rosette-like granules called alpha particles or α-rosettes, which can be up to 200 nm in diameter**
- **Glycogen is found in the cytosol of most cells but is most abundant in liver and muscle**
- **Synthesis and breakdown of glycogen occur in cytosol**



β-particles from human skeletal muscle



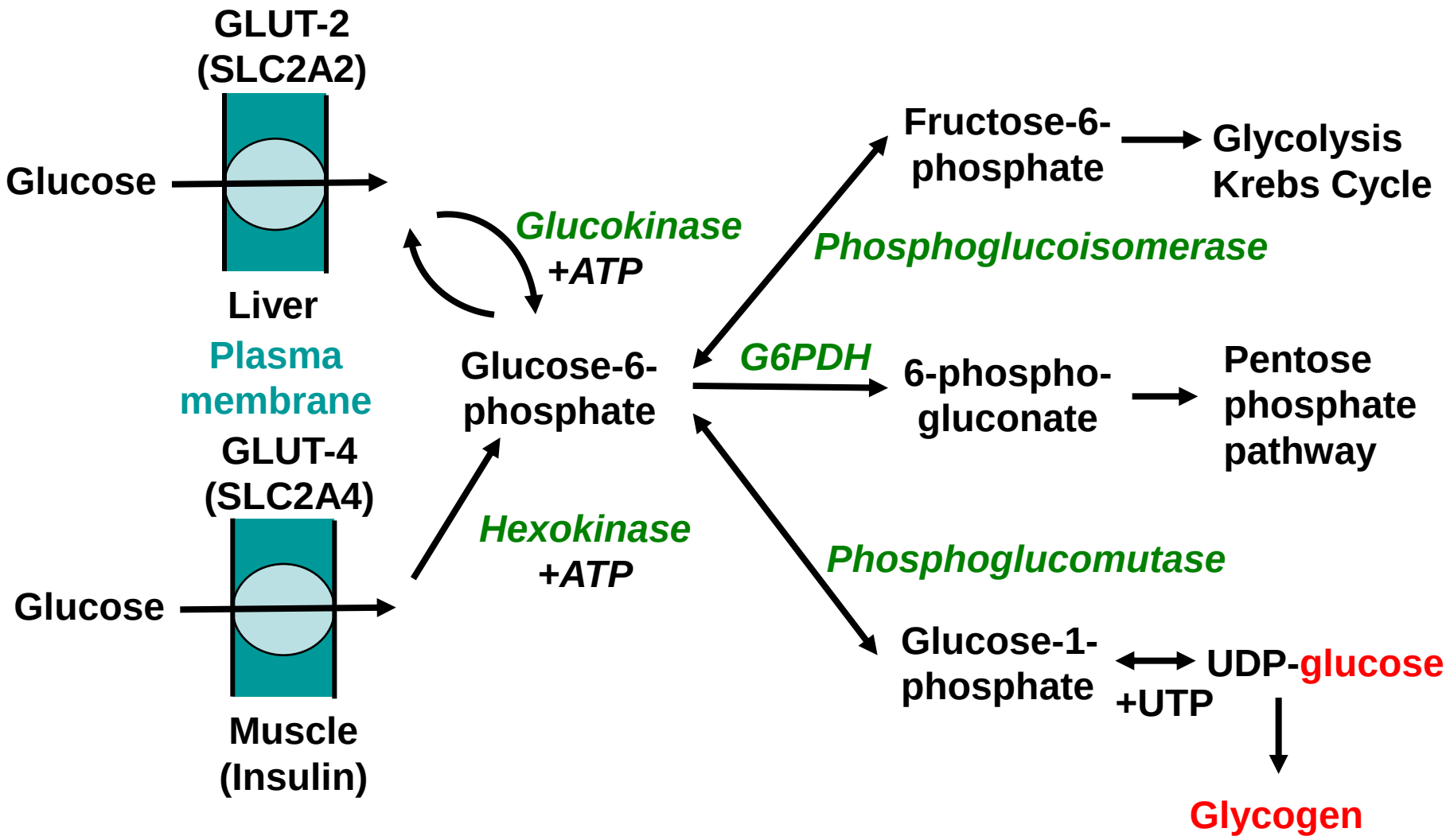
α-particles from rat liver

Courtesy of Dr. David Stapleton, Melbourne

Structure/Function

- **Glycogen is a very compact structure due to the coiling of the polymer chains**
- **This compactness allows large amounts of carbon energy to be stored in a small volume, with little effect on cellular osmolarity**
- **Branching increases solubility and rate at which glucose can be stored and released**
- **Permits rapid mobilisation of glucose in an emergency**

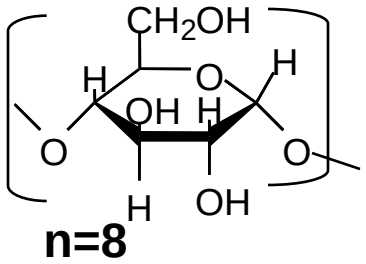
Uptake and Conversion of Blood Glucose to Glycogen: Glycogenosis



G6PDH = Glucose-6-phosphate dehydrogenase

Glycogen Synthesis: Initiation

- **Glycogenin is the primer for glycogen synthesis**
- **It autocatalytically adds glucose to itself from the donor, UDP-glucose, to form a chain of eight α-(1,4)-linked glucose residues**
- **Availability of glycogenin determines number of glycogen particles possible in a cell**
- **The octa-glucosyl glycogenin or existing partially digested glycogen molecules are the templates for the addition of further glucosyl residues catalysed by *glycogen synthase* and the *branching enzyme***



Tyrosine-194

QuickTime™ and a
decompressor
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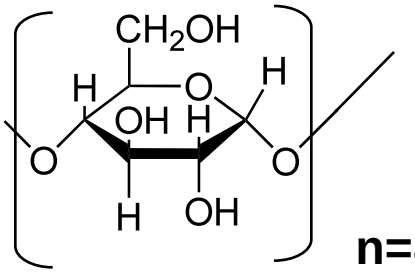
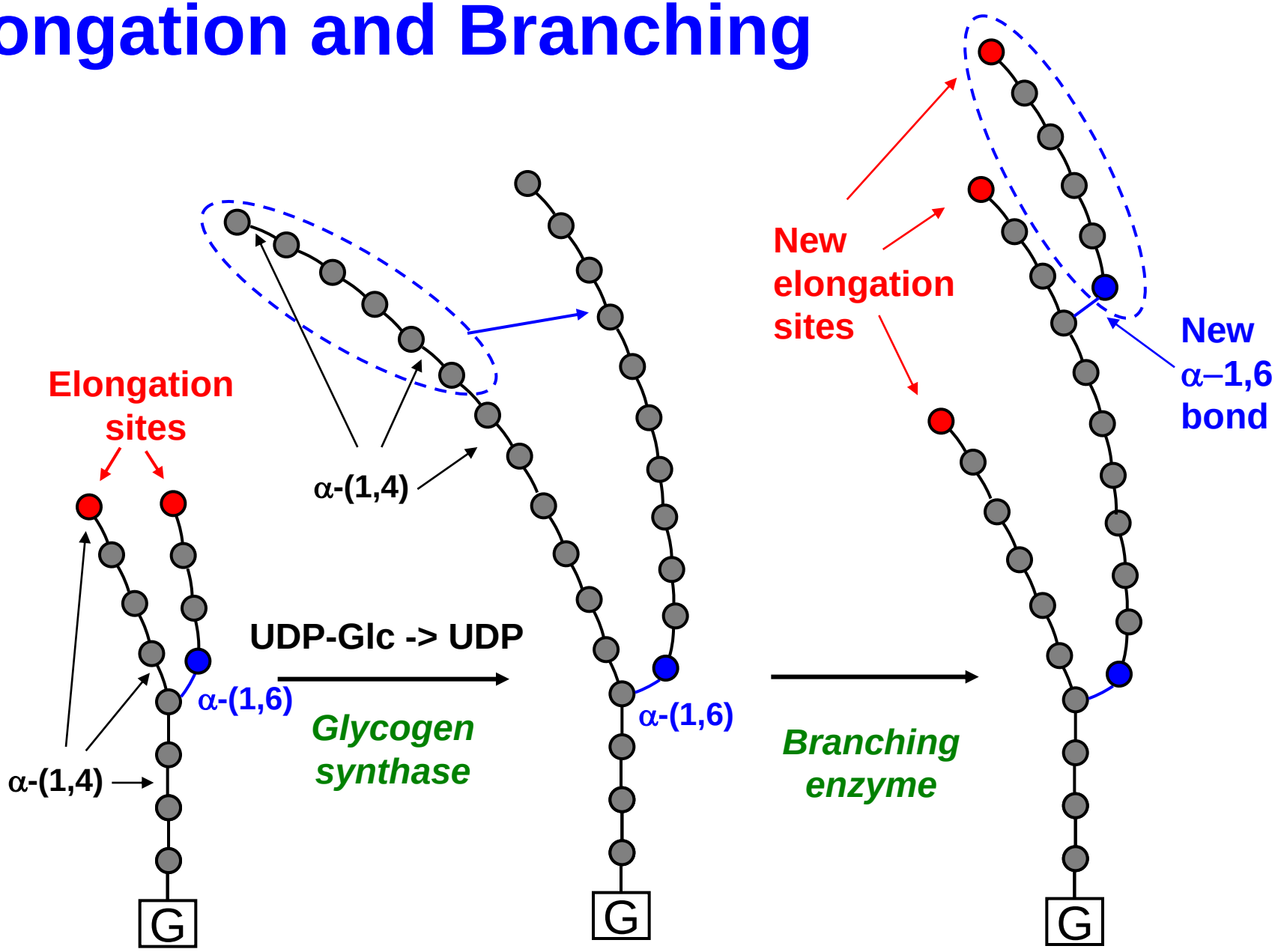


Tyrosine-194

Elongation and Branching



G = rest of glycogen molecule

Energy Cost of Glycogen Synthesis

UDP-glucose is formed from glucose-1-phosphate:

Glucose-1-phosphate + UTP → UDP-glucose + PP_i

PP_i + H_2O → 2 P_i

Overall:

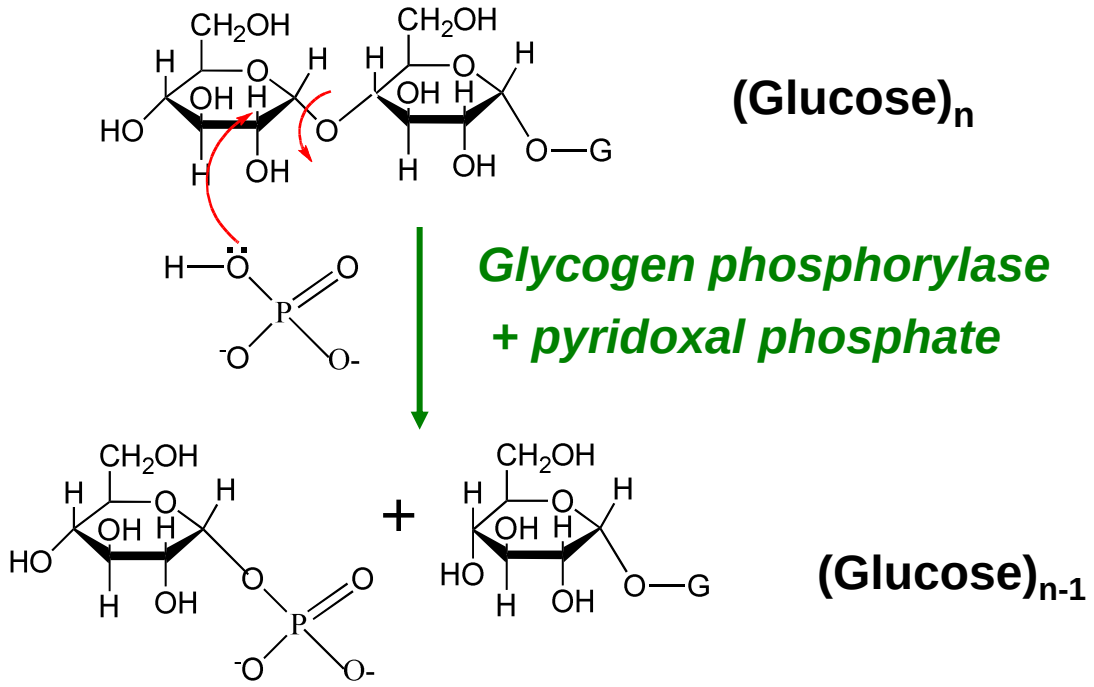
Glucose-1-phosphate + UTP → UDP-glucose + 2 P_i

Spontaneous hydrolysis of the ~P bond in PP_i (P~P) drives the overall reaction

Cleavage of PP_i is the only energy cost for glycogen synthesis (<u>one</u> ~P bond per glucose residue)

Glycogen Breakdown: Glycogenolysis

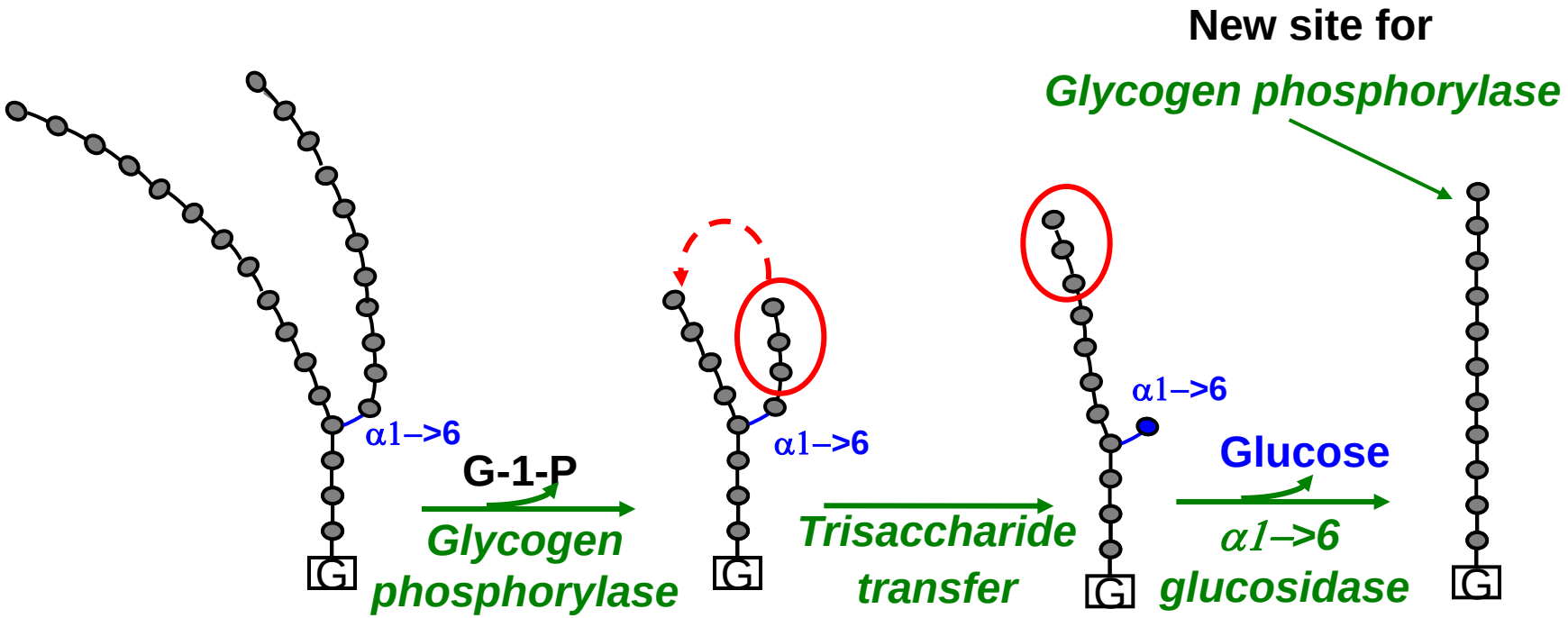
- **The primary step in the breakdown of glycogen is the phosphorolytic cleavage of the α1->4 glycosidic bonds, catalysed by the enzyme *glycogen phosphorylase***



N.B. Not free glucose

Glycogen Breakdown: Debranching

- ***Glycogen phosphorylase*** **removes glucose residues until the distance from a branching point is 4 glucose residues when another enzyme the** ***debranching enzyme*** **takes over**
  Two activities: ***trisaccharide transfer, α1–>6 glucosidase***



Glycogen Breakdown

- **The combined activities of *glycogen phosphorylase* and the dual activities of the *debranching enzyme, trisaccharide transfer and α1–>6 glucosidase,* lead to the complete breakdown of glycogen to predominantly glucose-1-phosphate and a little free glucose**

- **The only free glucose generated results from the hydrolysis of the branching α1–>6 glucosidic linkage by the *debranching enzyme***

- **The reaction catalysed by *phosphoglucomutase* is reversible**

  Glucose-1-phosphate ⇌ Glucose-6-phosphate

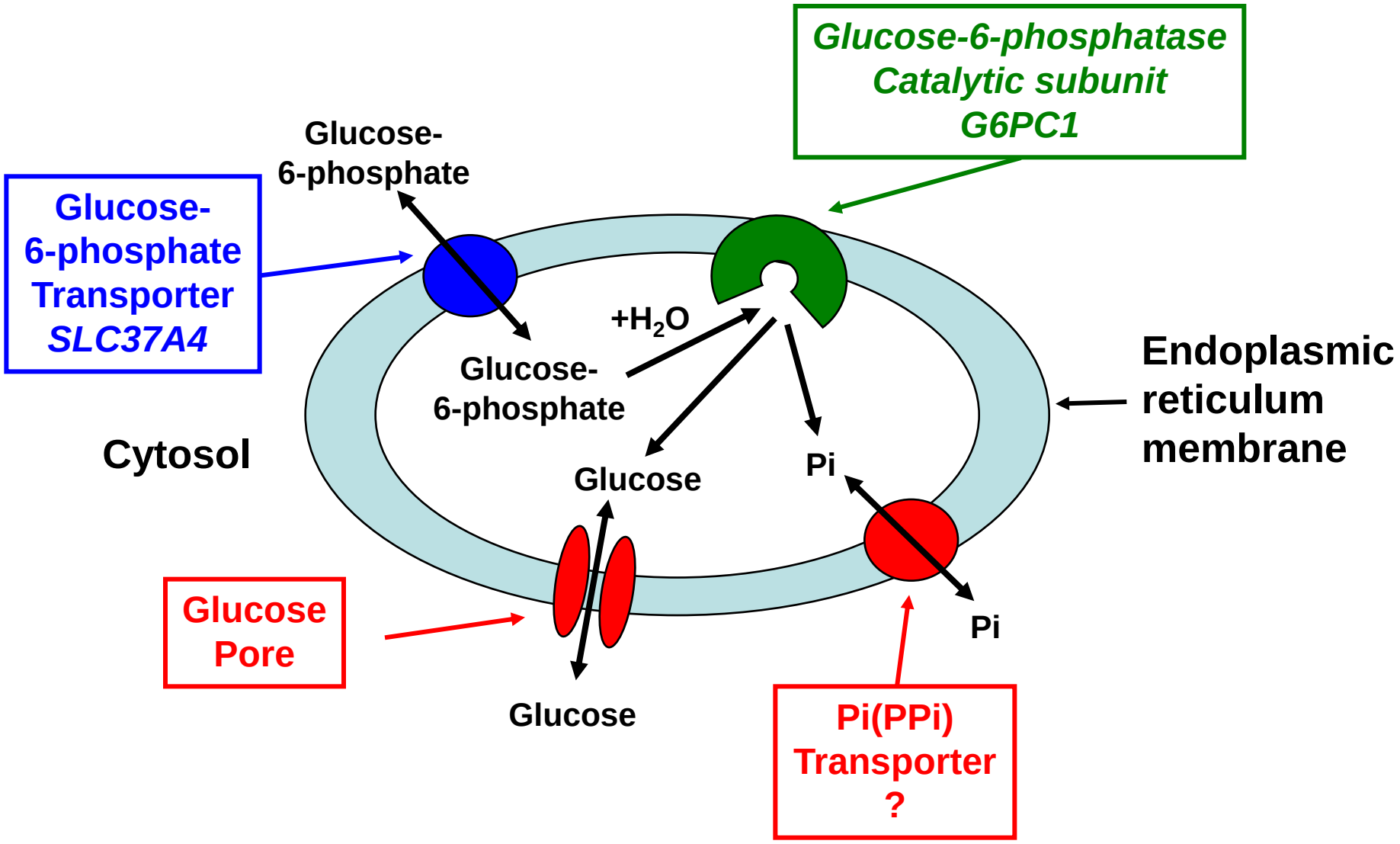
- **In liver and kidney but not muscle, glucose is produced by *glucose -6-phosphatase***

  Glucose-6-phosphate + H_2O ⟶ Glucose + Pi

  ↓

  Blood

Action of Glucose-6-phosphatase in Liver



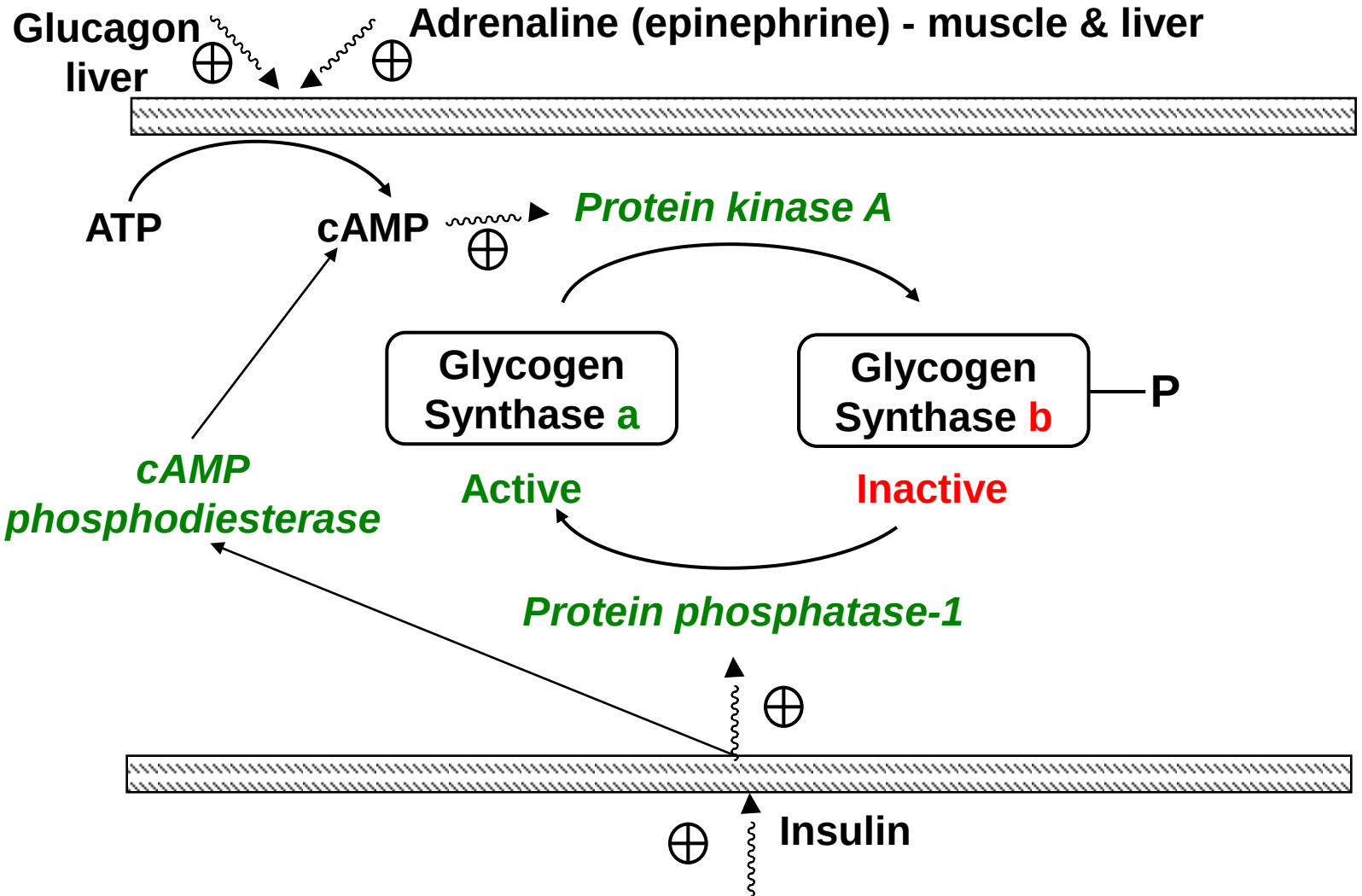
Regulation of Glycogen Metabolism

- **The synthesis and breakdown of glycogen are spontaneous and if unregulated would form a "futile cycle" costing one ~P per cycle**

- ***Glycogen synthase*** **and** ***glycogen phosphorylase*** **are reciprocally regulated by allosteric mechanisms and covalent modification, phosporylation and dephosphorylation, to prevent this situation**

Covalent Regulation of *Glycogen Synthase*

- ***Glycogen synthase*** **exists in two forms**
  - **Active dephosphorylated form a and inactive phosphorylated form, b**



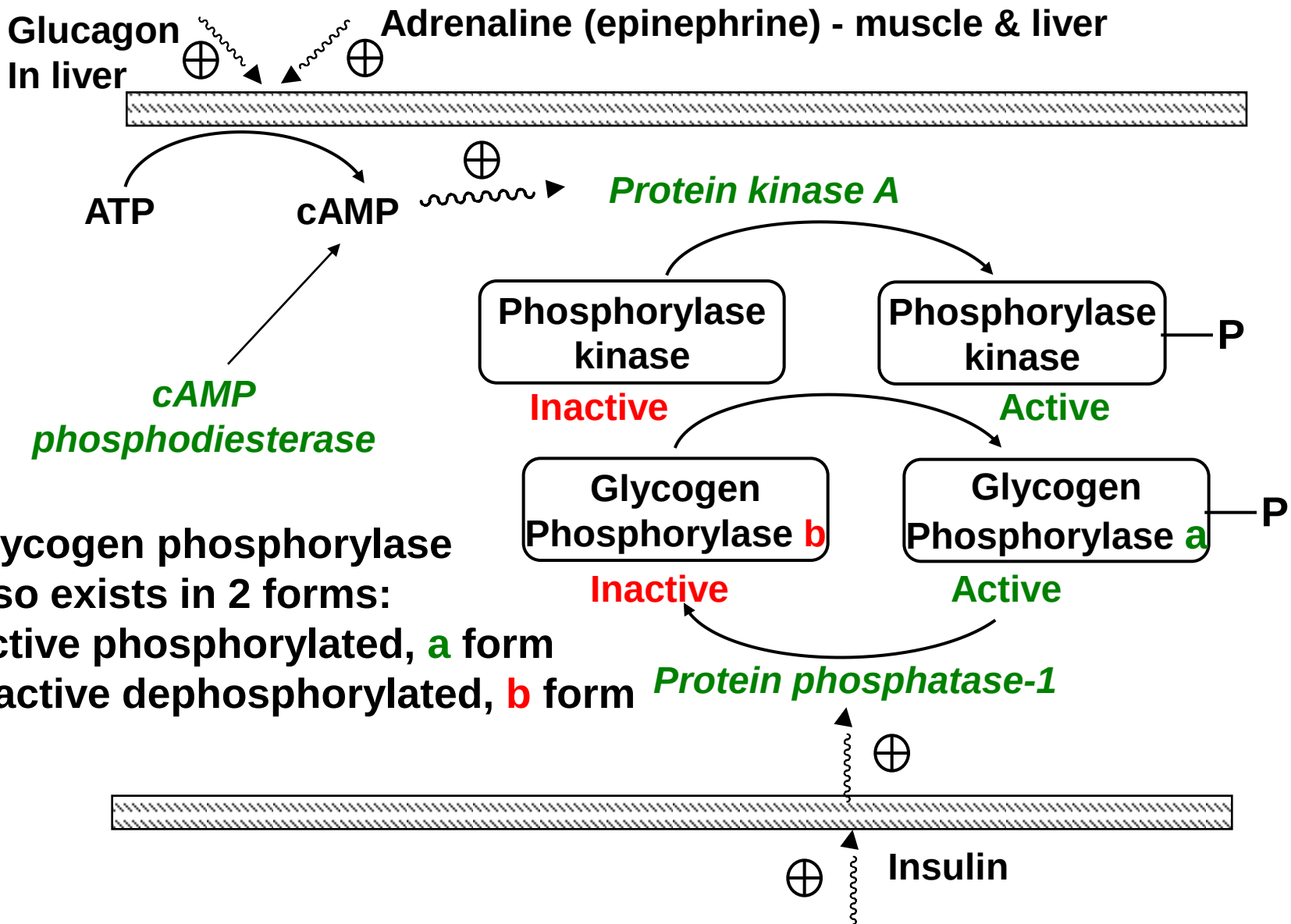
Allosteric Regulation of Glycogen Synthase

- **Allosteric regulation is the regulation of an enzyme's activity by the binding of an effector molecule at a site other than the active site. It can be positive or negative**

- **The inactive phosphorylated form, b, of *glycogen synthase* is allosterically activated by glucose-6-phosphate**

- **High blood glucose leads to high intracellular glucose-6-phosphate and thence to formation of glycogen through activation of *glycogen synthase***

Covalent Regulation of Glycogen Phosphorylase



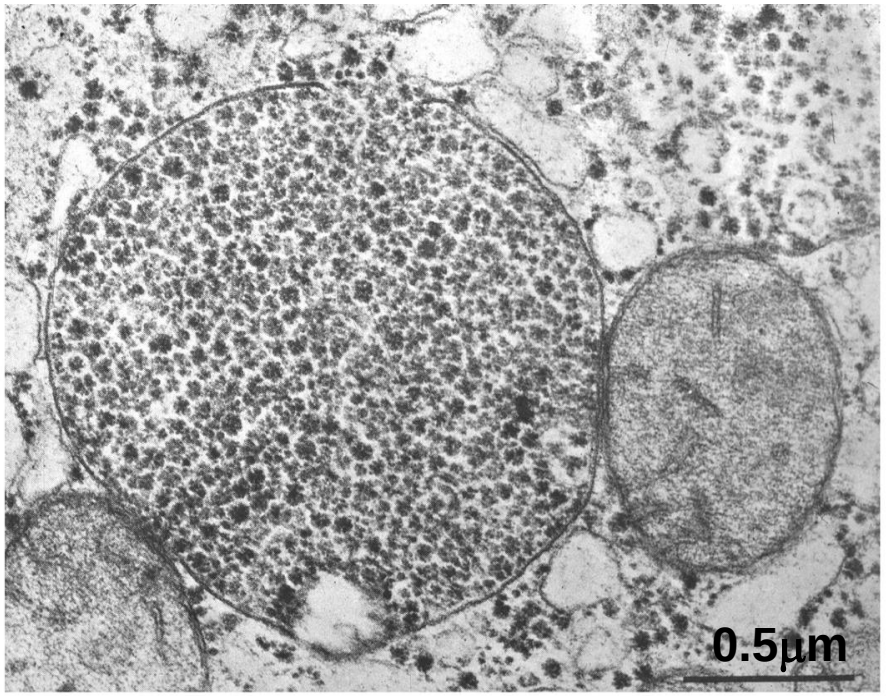
Glycogen phosphorylase also exists in 2 forms:
Active phosphorylated, a form
Inactive dephosphorylated, b form

Allosteric Regulation of Glycogen Phosphorylase

- **Genetically distinct forms in liver and muscle**
- **It is a dimer that exists in "relaxed" (active) & "tense" (inhibited) conformations**
- **It is sensitive to allosteric effectors that are indicators of energy state of cell**
- **Muscle *phosphorylase* is sensitive to AMP, ATP & glucose-6-phosphate**
  - **AMP (increases when ATP is depleted) stimulates *phosphorylase b* promoting the relaxed conformation.**
  - **ATP & glucose-6-phosphate inhibit *phosphorylase b*, promoting the tense conformation. Binding sites overlap that of AMP.**
  - **Glycogen breakdown is inhibited when ATP and glucose-6-phosphate are abundant**
- **Liver *phosphorylase a* (active form) is inhibited by glucose**
  - **Binding of glucose increases affinity for *protein phosphatase-1* and hence inactivation**

Lysosomal Glycogen Metabolism

The accumulation of glycogen in tissues from patients with glycogen storage disease type 2 (Pompe disease) with a deficiency of *acid α-glucosidase* indicates that some glycogen is turned over in lysosomes

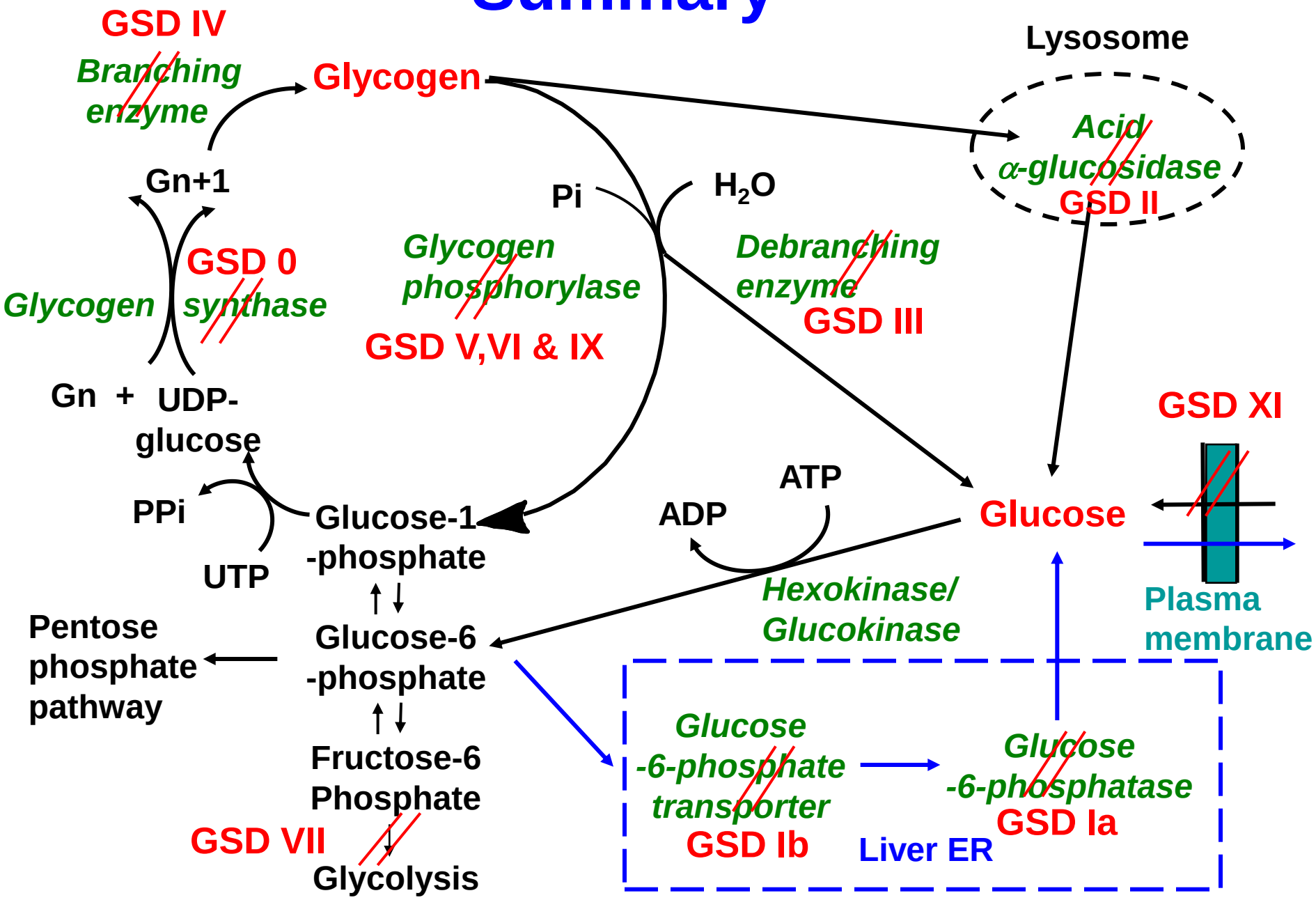


Liver parenchymal cell showing lysosome containing α-particles of glycogen (Courtesy of Dr. F van Hoof)

Function

- **Serendipitous imbibing of cytosol by lysosomes?**
- **Actively transported into lysosomes?**
- **Cellular function for glucose generated in lysosomes?**

Summary


GSD IV
Branching enzyme
Glycogen
Lysosome
Acid α-glucosidase
GSD II
Gn+1
Pi
H2O
Glycogen
GSD 0
synthase
Glycogen phosphorylase
GSD V,VI & IX
Debranching enzyme
GSD III
Gn + UDP-glucose
GSD XI
PPi
UTP
Glucose-1-phosphate
ATP
ADP
Glucose
Hexokinase/
Glucokinase
Plasma membrane
Pentose phosphate pathway
Glucose-6-phosphate
Fructose-6 Phosphate
GSD VII
Glycolysis
Glucose-6-phosphate transporter
GSD Ib
Glucose-6-phosphatase
GSD Ia
Liver ER