Glycogen Metabolism

Biochemistry II

By

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DEGRADATION OF GLYCOGEN (GLYCOGENOLYSIS)

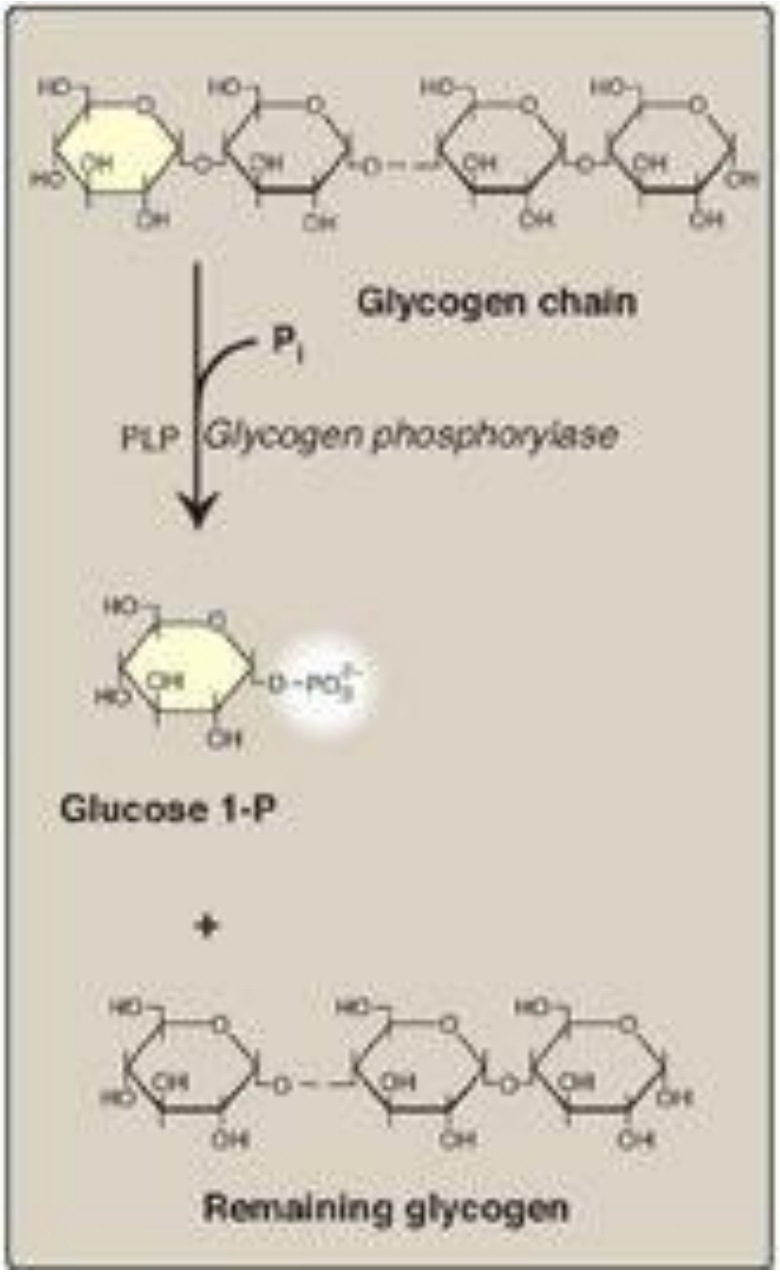
- The degradative pathway that mobilizes stored glycogen in liver and skeletal muscle is
- not a reversal of the synthetic reactions. Instead, a separate set of cytosolic enzymes is required.
- When glycogen is degraded, the primary product is glucose 1-phosphate,
- obtained by breaking α(1→4) glycosidic bonds. In addition, free glucose is released from each α(1→6)–linked glucosyl residue (branch point).

Shortening of chains

- Glycogen phosphorylase sequentially cleaves the α(1→4) glycosidic bonds between
- the glucosyl residues at the nonreducing ends of the glycogen chains by simple

phosphorolysis (producing glucose 1-phosphate) until four glucosyl units remain on each chain before a branch point.

- Phosphorylase contains a
- molecule of covalently bound pyridoxal phosphate that is required as a coenzyme.
- The resulting structure is called a limit dextrin, and phosphorylase cannot degrade it any further.


Glycogen chain
P_i
PLP
Glycogen phosphorylase
Glucose 1-P
+
Remaining glycogen

Removal of branches

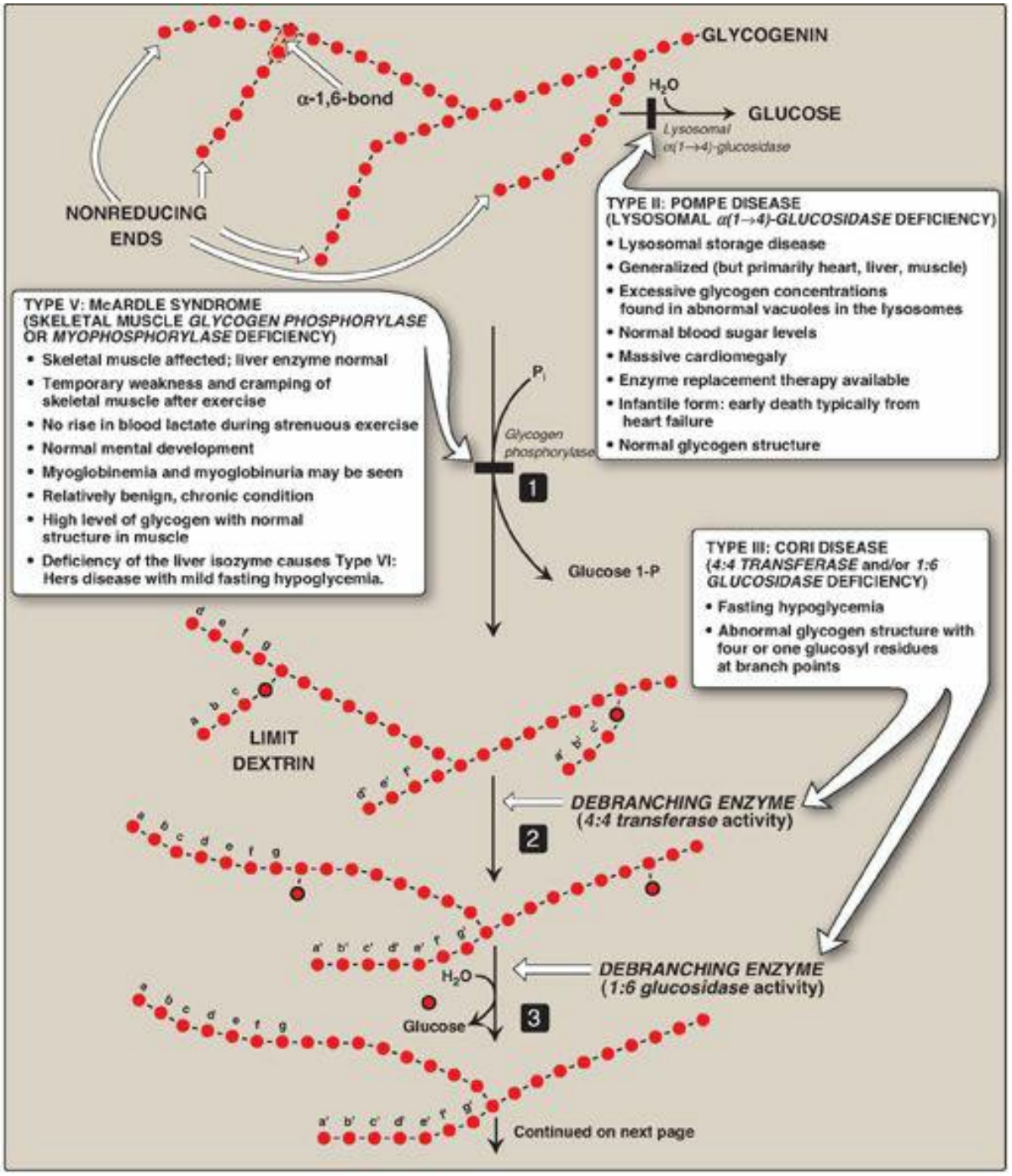
- Branches are removed by the two enzymic activities of a single bifunctional protein,
- the 1st debranching enzyme, oligo-α(1→4)→α(1→4)-glucantransferase activity removes the outer 3 of the 4 glucosyl residues

attached at a branch.

- It next transfers them to the nonreducing end of another chain, lengthening it accordingly. Thus, an α(1→4) bond is broken and an α(1→4) bond is

made, and the enzyme functions as a 4:4 transferase.

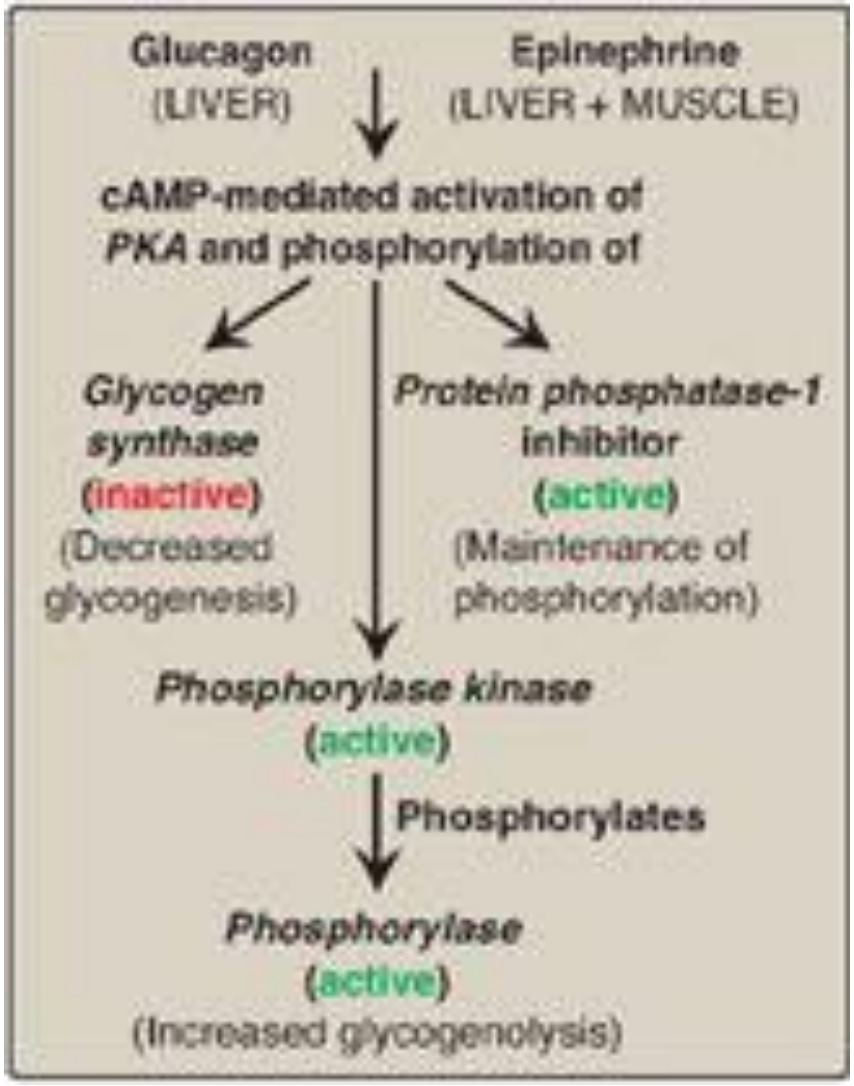
- the remaining glucose residue attached in an α(1→6) linkage is removed hydrolytically by amylo-α(1→6)-glucosidase activity, releasing free glucose. The glucosyl chain is now available again for degradation by glycogen phosphorylase until four glucosyl units in the next branch are reached.


GLYCOGENIN
α-1,6-bond
NONREDUCING ENDS
H_2O
GLUCOSE
Lysosomal α(1→4)-glucosidase
TYPE II: POMPE DISEASE (LYSOSOMAL α(1→4)-GLUCOSIDASE DEFICIENCY)
• Lysosomal storage disease
• Generalized (but primarily heart, liver, muscle)
• Excessive glycogen concentrations found in abnormal vacuoles in the lysosomes
• Normal blood sugar levels
• Massive cardiomegaly
• Enzyme replacement therapy available
• Infantile form: early death typically from heart failure
• Normal glycogen structure
TYPE V: McARDLE SYNDROME (SKELETAL MUSCLE GLYCOGEN PHOSPHORYLASE OR MYOPHOSPHORYLASE DEFICIENCY)
• Skeletal muscle affected; liver enzyme normal
• Temporary weakness and cramping of skeletal muscle after exercise
• No rise in blood lactate during strenuous exercise
• Normal mental development
• Myoglobinemia and myoglobinuria may be seen
• Relatively benign, chronic condition
• High level of glycogen with normal structure in muscle
• Deficiency of the liver isozyme causes Type VI: Hers disease with mild fasting hypoglycemia.
P_i
Glycogen phosphorylase
1
Glucose 1-P
TYPE III: CORI DISEASE (4:4 TRANSFERASE and/or 1:6 GLUCOSIDASE DEFICIENCY)
• Fasting hypoglycemia
• Abnormal glycogen structure with four or one glucosyl residues at branch points
LIMIT DEXTRIN
DEBRANCHING ENZYME (4:4 transferase activity)
2
DEBRANCHING ENZYME (1:6 glucosidase activity)
H_2O
Glucose
3
Continued on next page

REGULATION OF GLYCOGENESIS AND GLYCOGENOLYSIS

- Because of the importance of maintaining blood glucose levels, the synthesis and
- degradation of its glycogen storage form are tightly regulated. In the liver, glycogenesis
- accelerates during periods when the body has been well fed, whereas glycogenolysis
- accelerates during periods of fasting.

- In skeletal muscle, glycogenolysis occurs during
- active exercise, and glycogenesis begins as soon as the muscle is again at rest.
- Regulation of glycogen synthesis and degradation is accomplished on two levels. First,
- glycogen synthase and glycogen phosphorylase are hormonally regulated (by
- phosphorylation/dephosphorylation) to meet the needs of the body as a whole.


Glucagon
(LIVER)
Epinephrine
(LIVER + MUSCLE)
cAMP-mediated activation of
PKA and phosphorylation of
Glycogen synthase
(inactive)
(Decreased glycogenesis)
Protein phosphatase-1 inhibitor
(active)
(Maintenance of phosphorylation)
Phosphorylase kinase
(active)
Phosphorylates
Phosphorylase
(active)
(Increased glycogenolysis)

- **glycogen synthase** is **activated** by
- **glucose 6-phosphate**, but **glycogen phosphorylase** is inhibited by **glucose 6- phosphate** as well as by **ATP**.
- In the liver, glucose also serves an an allosteric inhibitor of glycogen phosphorylase. The **Ca2+** released from the endoplasmic
- reticulum in muscle during exercise and in liver in response to epinephrine **activates phosphorylase kinase** by
- binding to the enzyme's **calmodulin** subunit. This
- allows the enzyme to activate **glycogen phosphorylase**, thereby causing glycogen degradation.
- **AMP** activates glycogen phosphorylase in muscle.

Reference

- Lippincott’s
- Illustrated Reviews:
- Biochemistry
- Sixth Edition