Biochemistry

Metabolism

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Glycogen metabolism

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The structure of glycogen

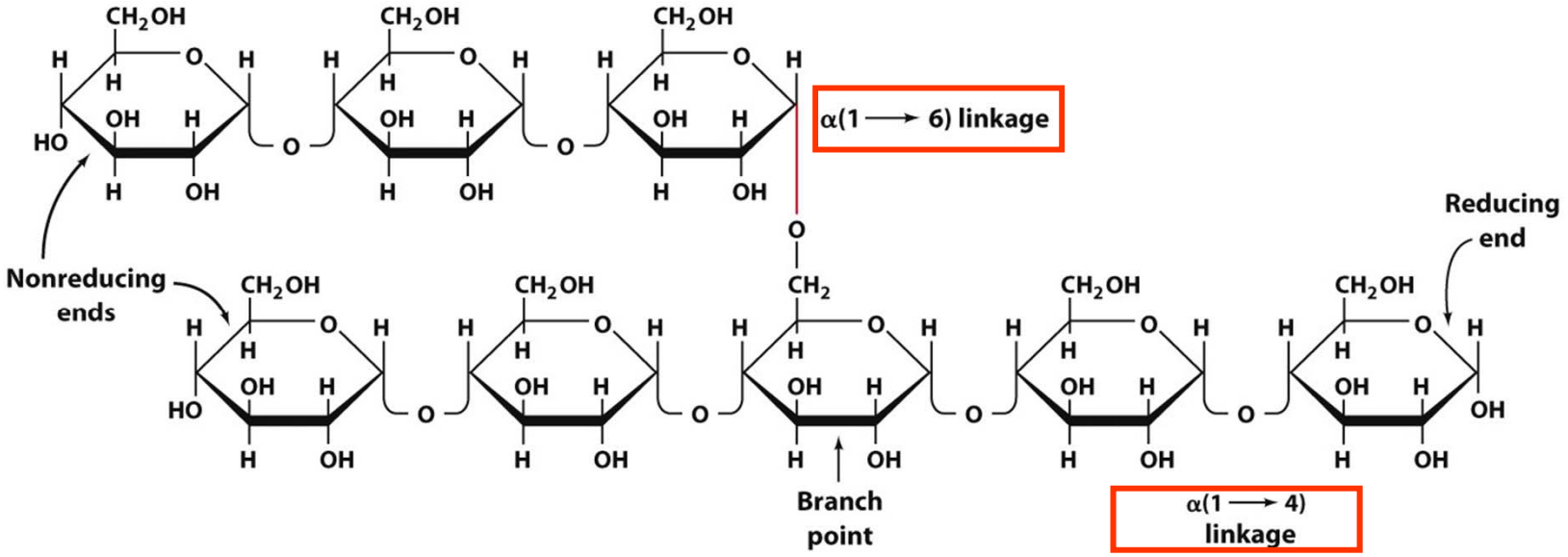

Figure 18-1a

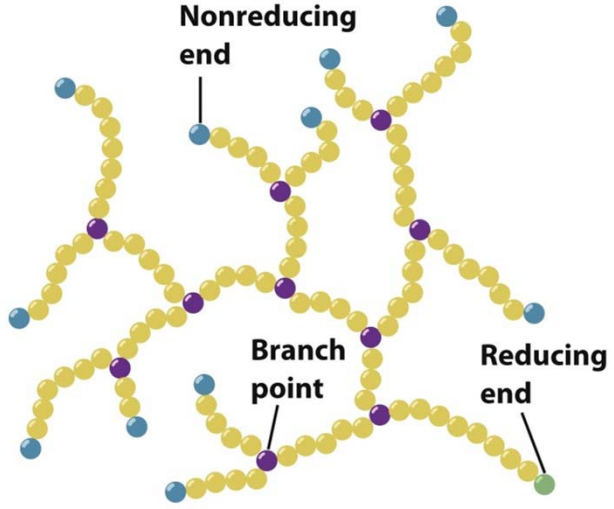

Figure 18-1b

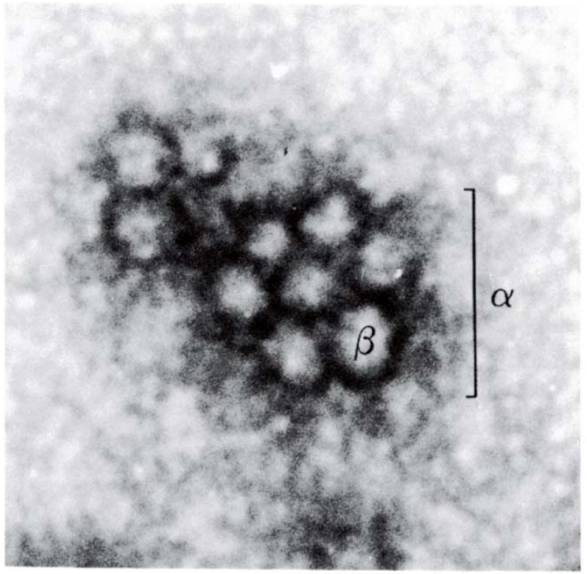

Figure 18-1c
From Calder, P.C., *Int. J. Biochem.* 23, 1339 (1991). Copyright Elsevier Science. Used with permission.

α, glycogen granule

β, glycogen molecule (up to 120,000 glucose residues)

(monomer conc. = 0.4M)
polymer conc. = 10^{-8}M

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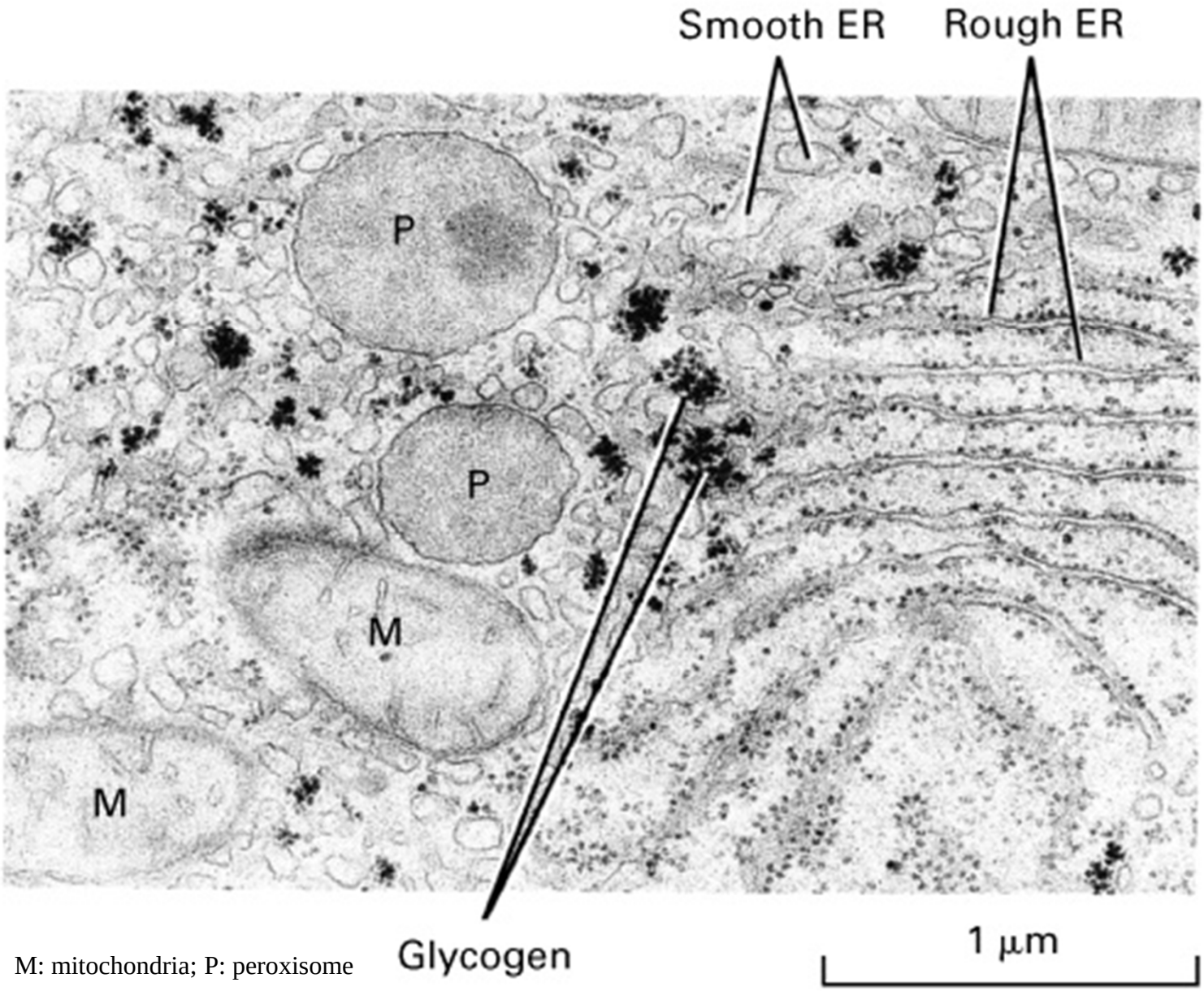
Electron micrograph of rat hepatocyte

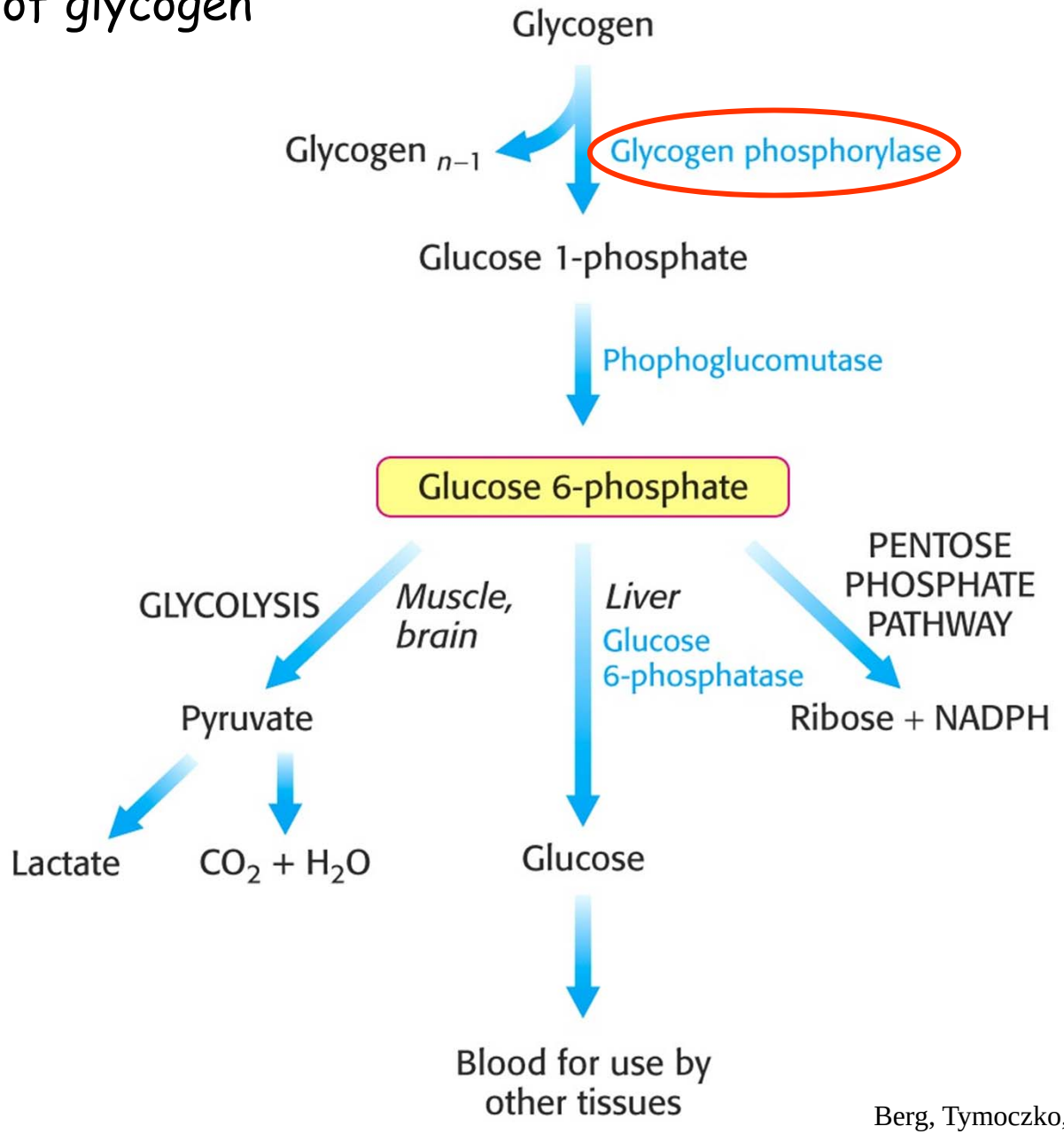


M: mitochondria; P: peroxisome

carbohydrate rich meal:
glycogen = 5-10% of liver net weight
12-18 h fasting: liver essentially glycogen free

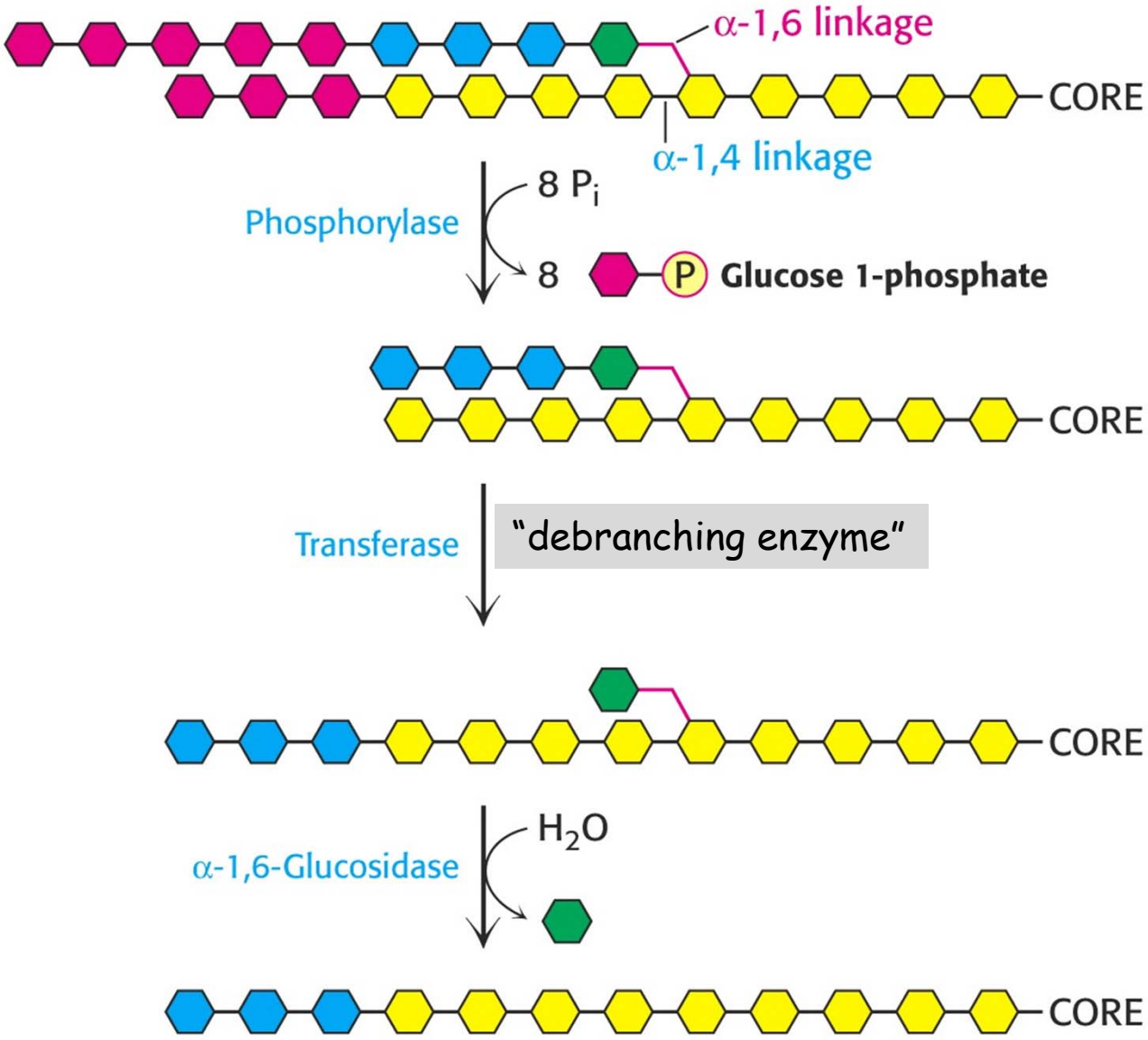
glycogen amount never exceeds 1% of muscle net weight

Utilization of glycogen



Berg, Tymoczko, Stryer: Biochemistry

The strategy of glycogen breakdown



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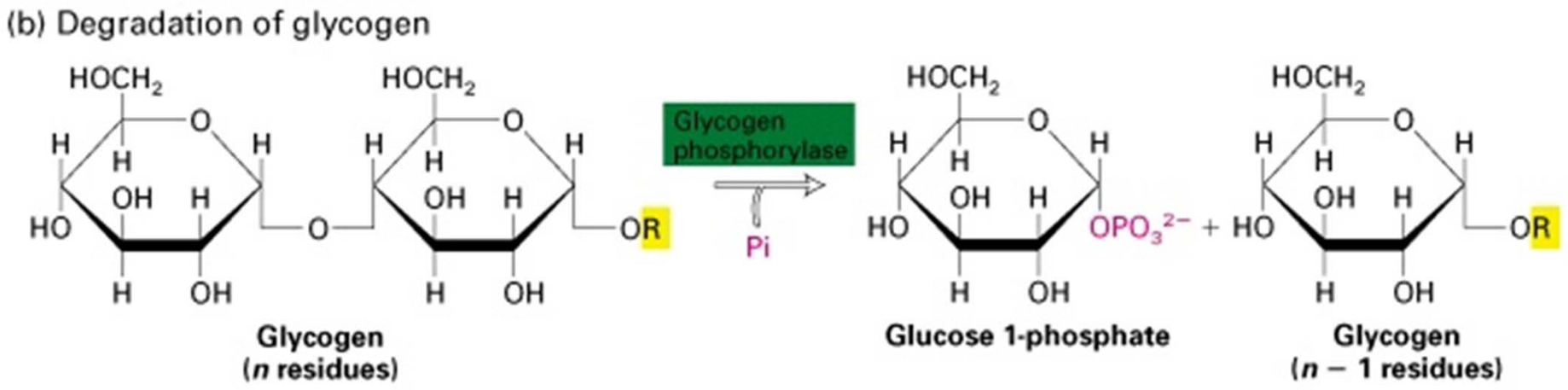
Glycogen phosphorylase catalyzes the phosphorolytic cleavage of an
∝ 1,4 glycosidic linkage generating glucose-1-phosphate



✓ rate-limiting for glycogen breakdown
catalyses velocity >> "debranching enzyme"

✓Highly regulated:

✓covalent modification: phosphorylation of serine

✓ allosteric modulators:
(of the b form) ATP, G6P – inhibiting, AMP, calcium – stimulating
(of the a form) glucose - inhibiting

The reaction mechanism of glycogen phosphorylase

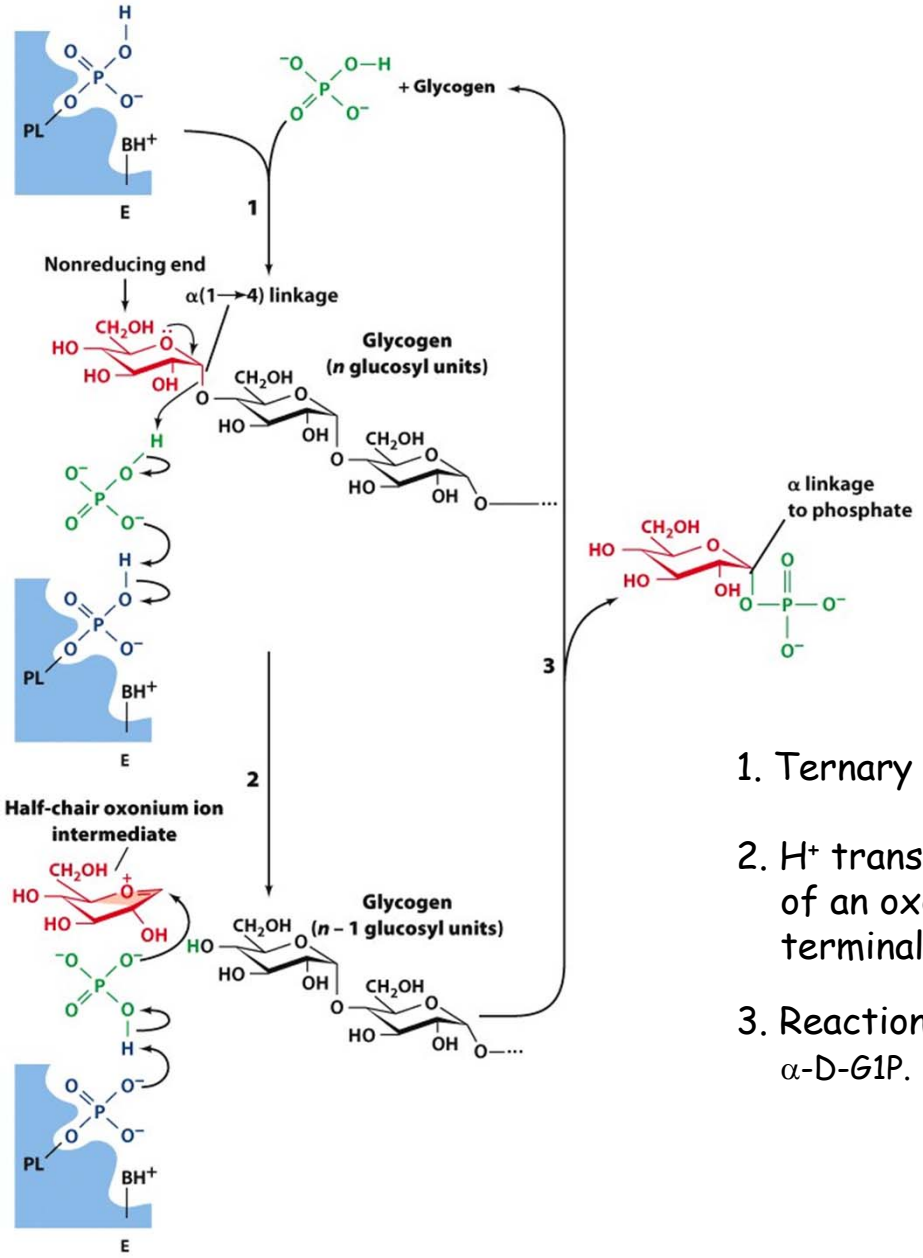
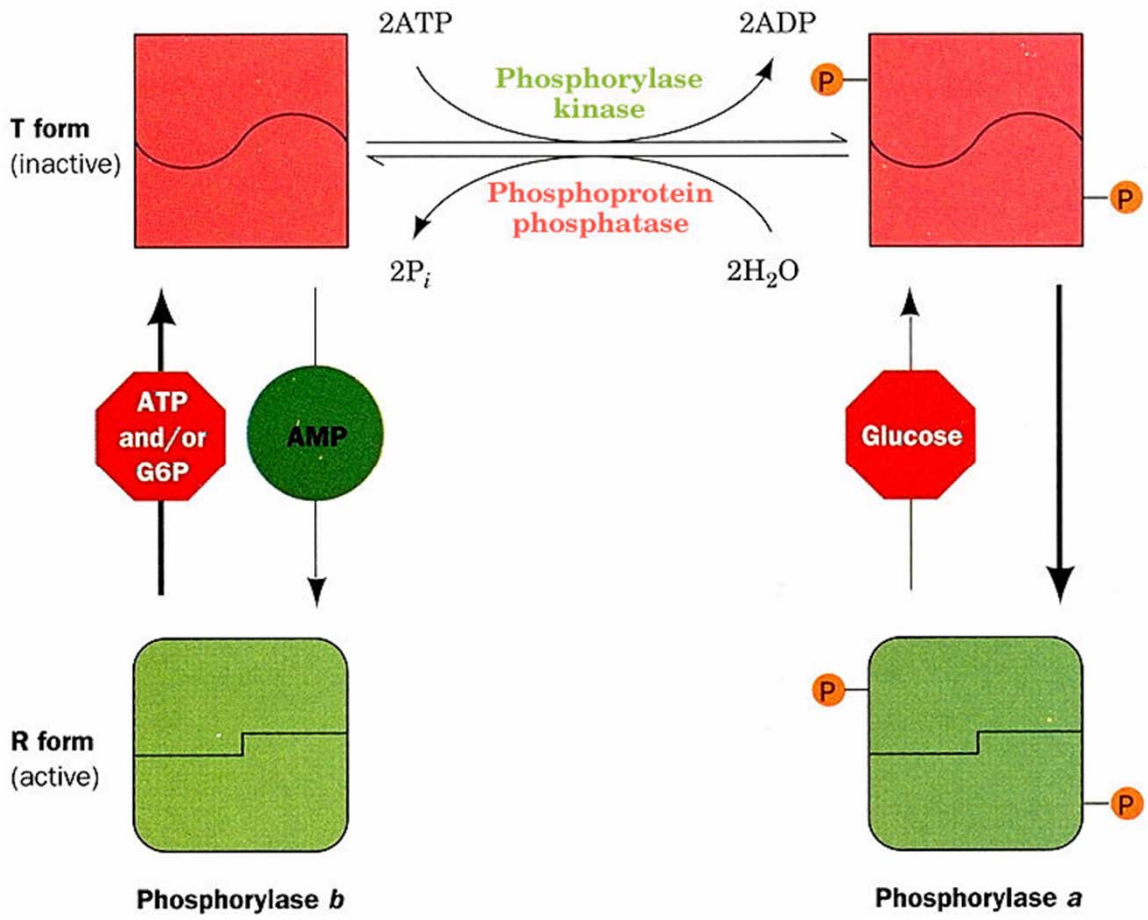


Figure 18-3

PL: Pyridoxal phosphate
BH^+: Lys-residue

1. Ternary complex formation
2. H^+ transfer from PLP to P_i facilitates formation of an oxonium ion intermediate from the terminal glucosyl residue and acid catalysis by P_i.
3. Reaction of P_i with the oxonium ion to generate α-D-G1P.

The control of the homodimeric glycogen phosphorylase:
a.) covalent modification: Ser-phosphorylation
b.) allosteric modulators: of the b-form: AMP, calcium - activators
ATP, G6P - inhibitors
of the a-form: glucose - inhibitor



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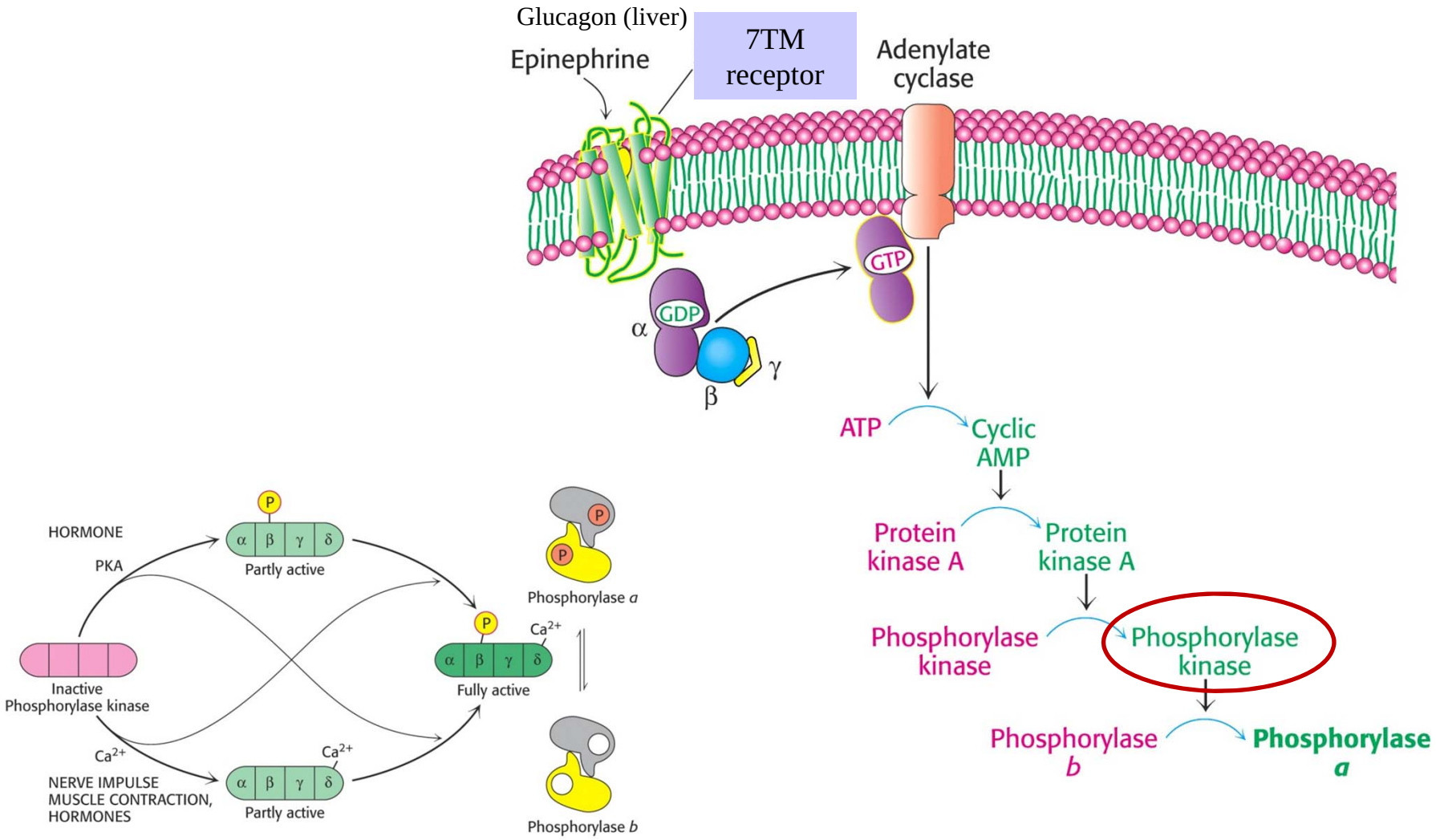
c.) the hormonal regulation of glycogen phosphorylase



Activation of phosphorylase kinase

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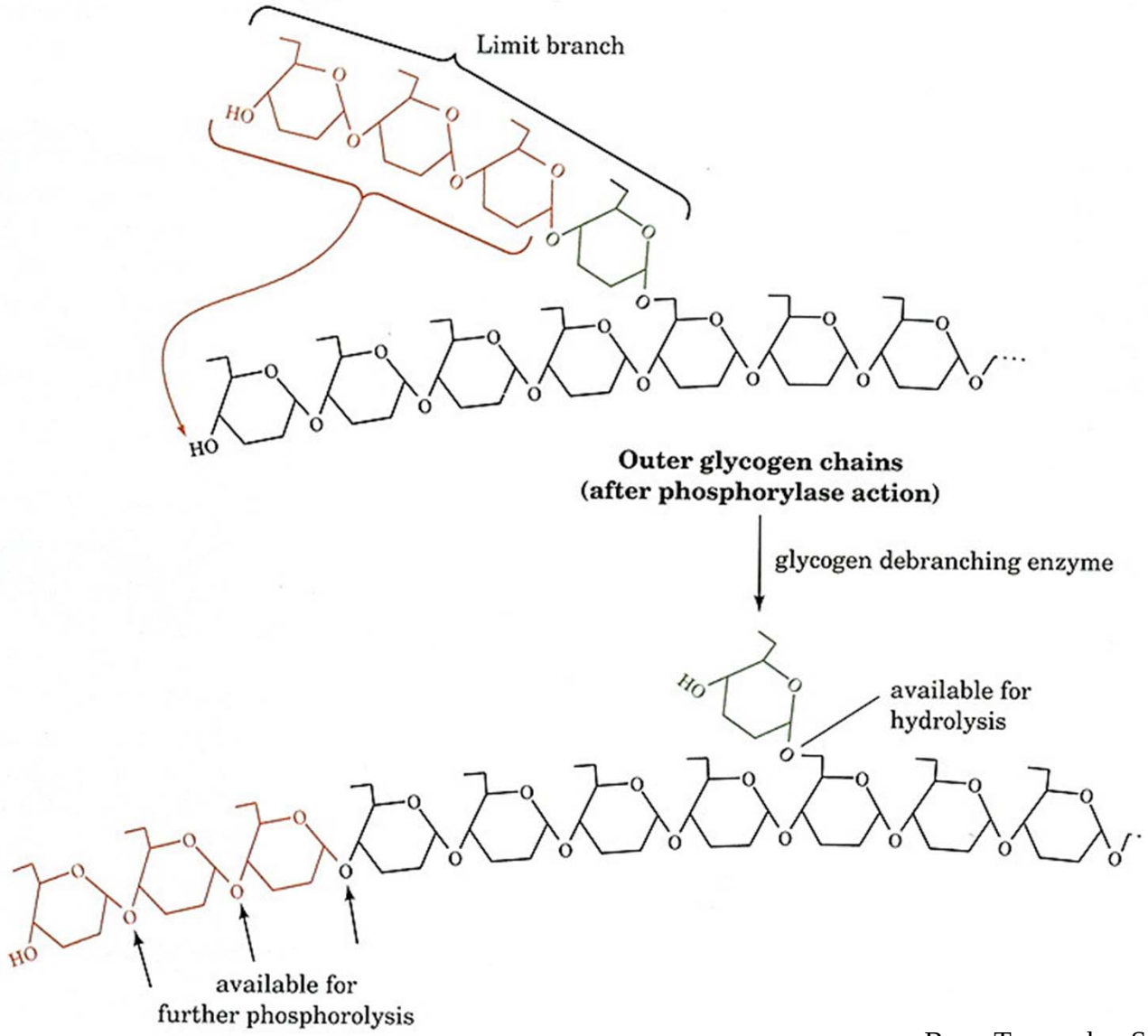
Glycogen debranching is catalyzed by: $\propto$1,4 $\rightarrow$ $\propto$1,4 glucosyltransferase and amylo 1,6-glucosidase



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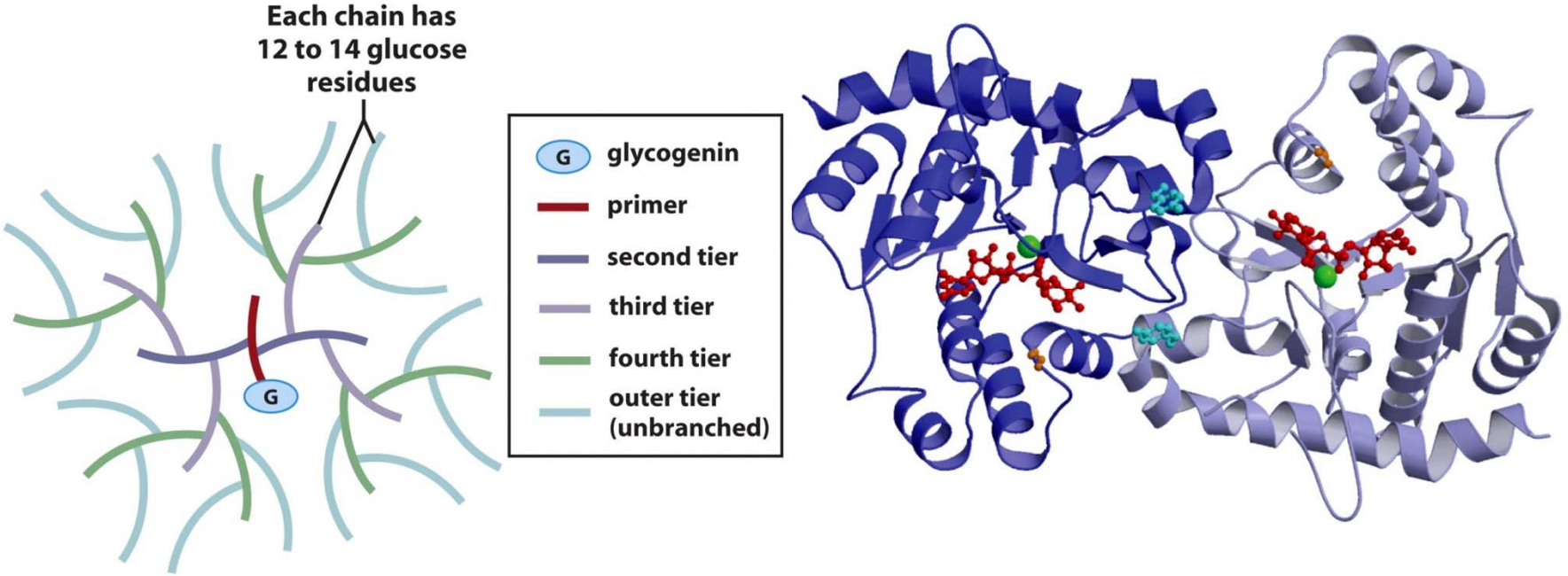
Glycogenin and the structure of the glycogen particle

Glycogenin initiates glycogen synthesis (*primes the initial sugar residues in glycogen)*

here: the dimeric protein from human muscle tissue



UDP-Glc

Tyr

Asp

Mn^{2+}

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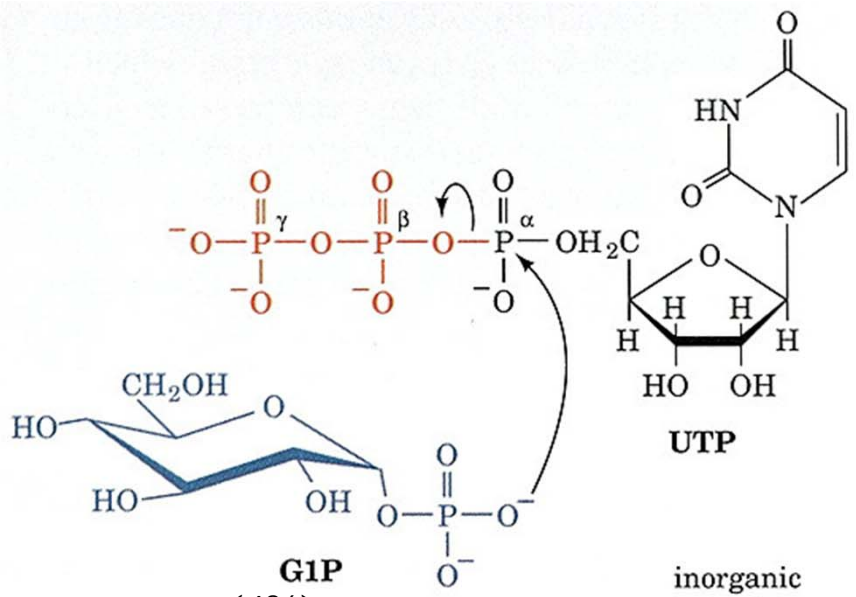
UDP-Glc, the substrate of glycogen synthase is generated by the activation of glucose (G1P) with UTP

Phosphoglucomutase

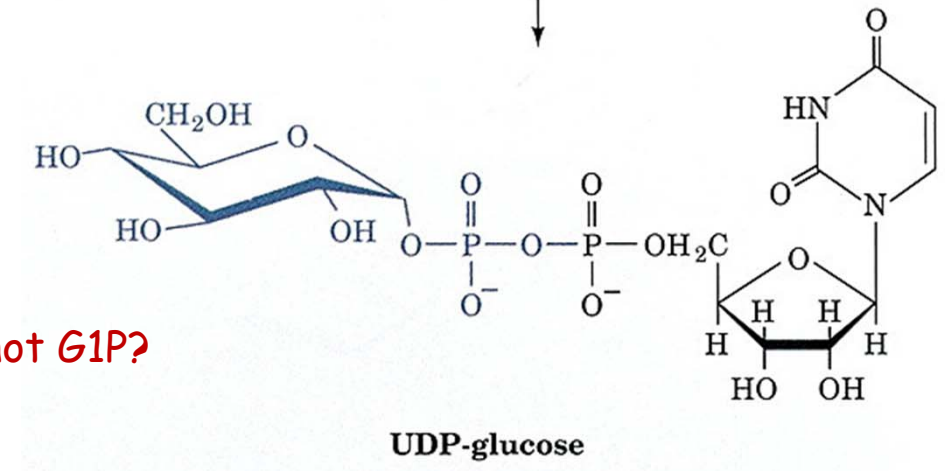
G6P → G1P

(96%) (4%)



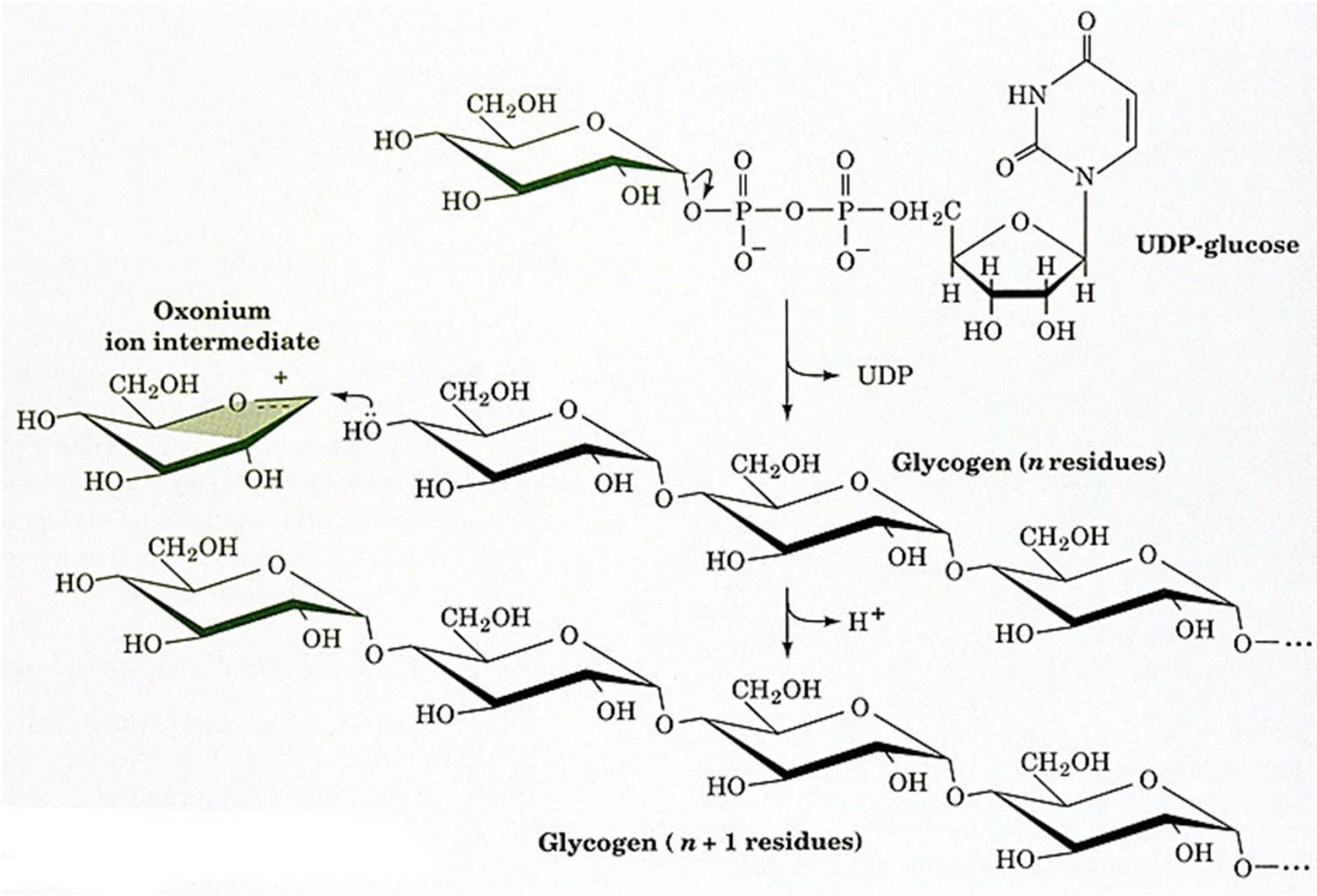
UDP-Glucose Pyrophosphorylase

PP_i → (inorganic pyrophosphatase) → $2P_i$



Why UDP-Glc and not G1P?

Reaction catalyzed by glycogen synthase



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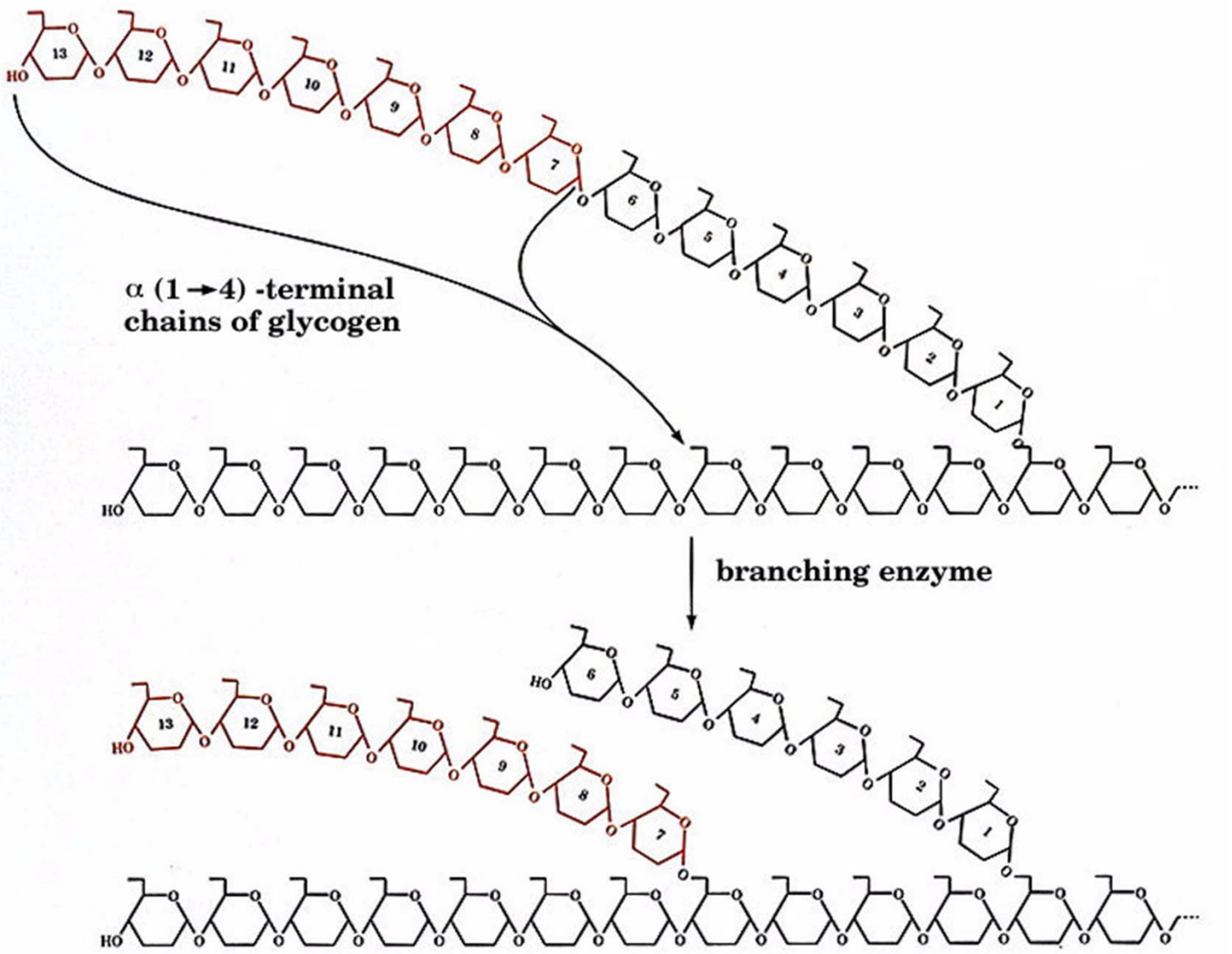
The branching of glycogen is catalyzed by amylo-1,4→1,6 transglycosylase



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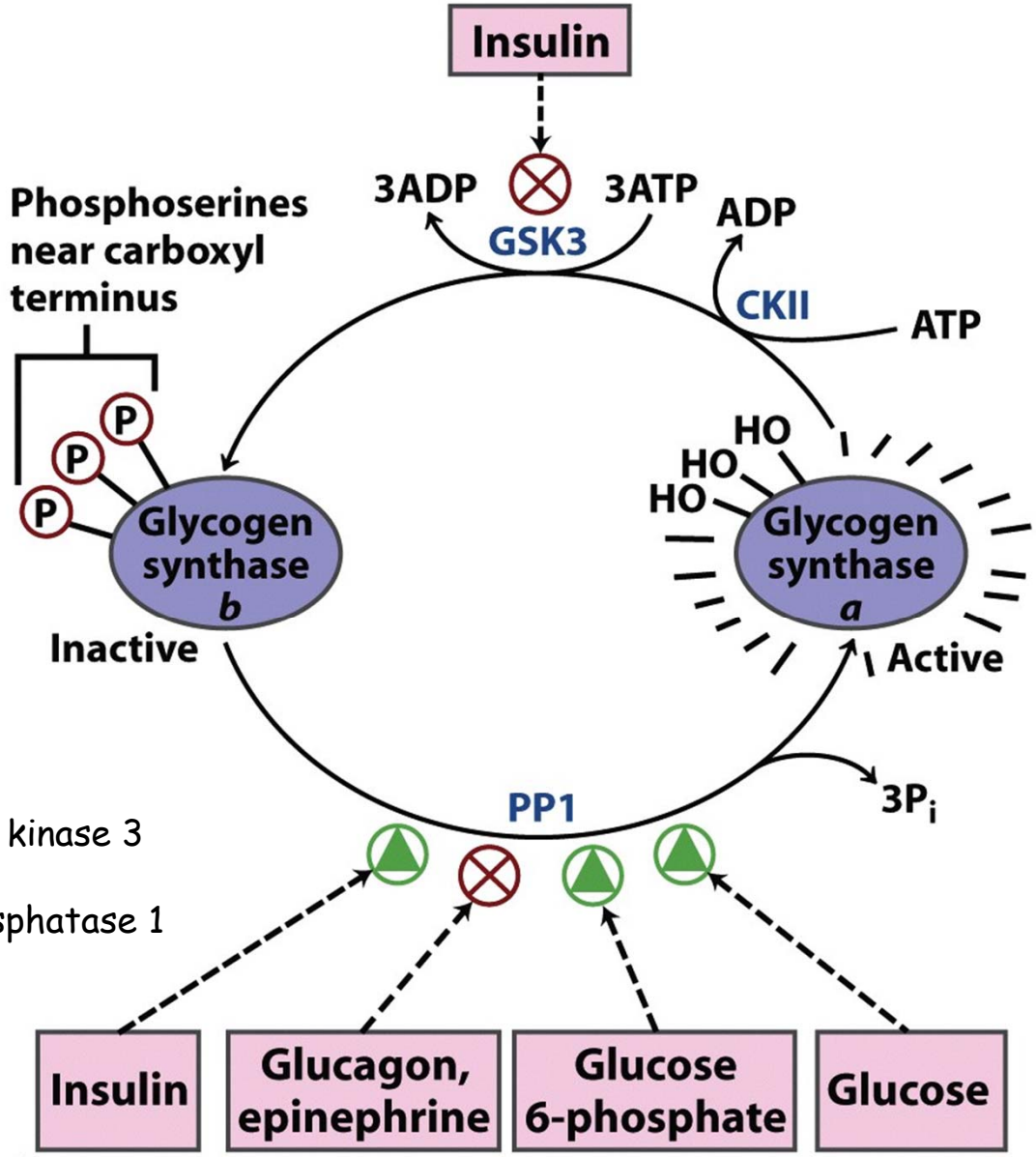
Glycogen synthase activity is under the control of covalent modifications



GSK3: glycogen synthase kinase 3
CKII: casein kinase II
PP1: phosphoprotein phosphatase 1

Figure 15-37
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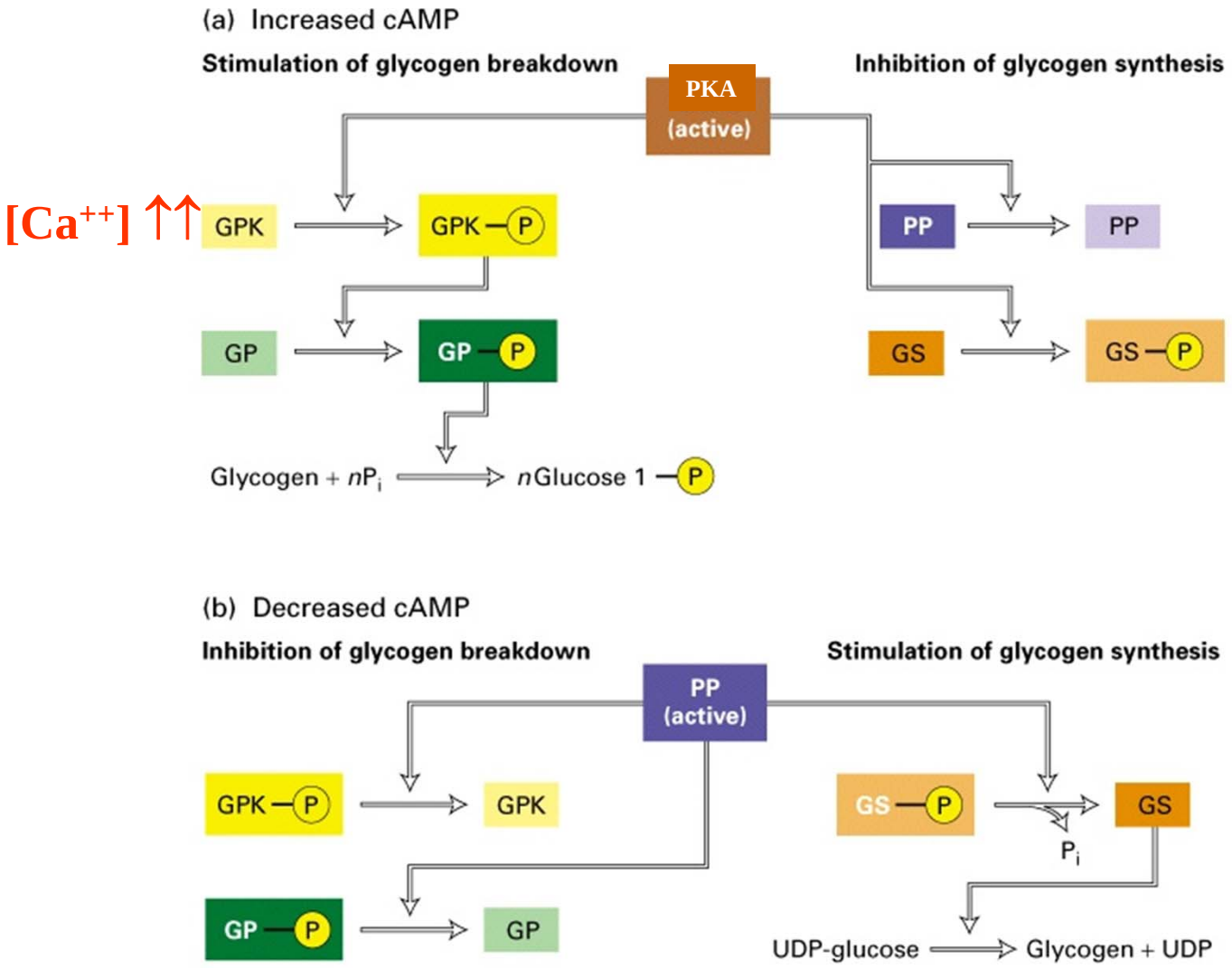
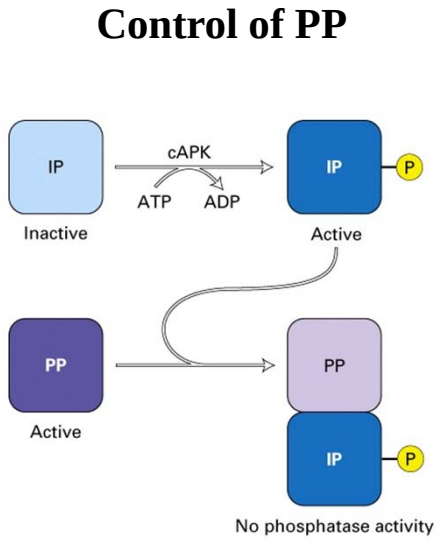
Coordinated regulation of glycogen turnover by cAMP (in liver and muscle)





Lodish et al. Molecular Cell Biology

Glycogen targeting protein G_M is one of a family of proteins that bind other proteins (including PP1) to glycogen particles.

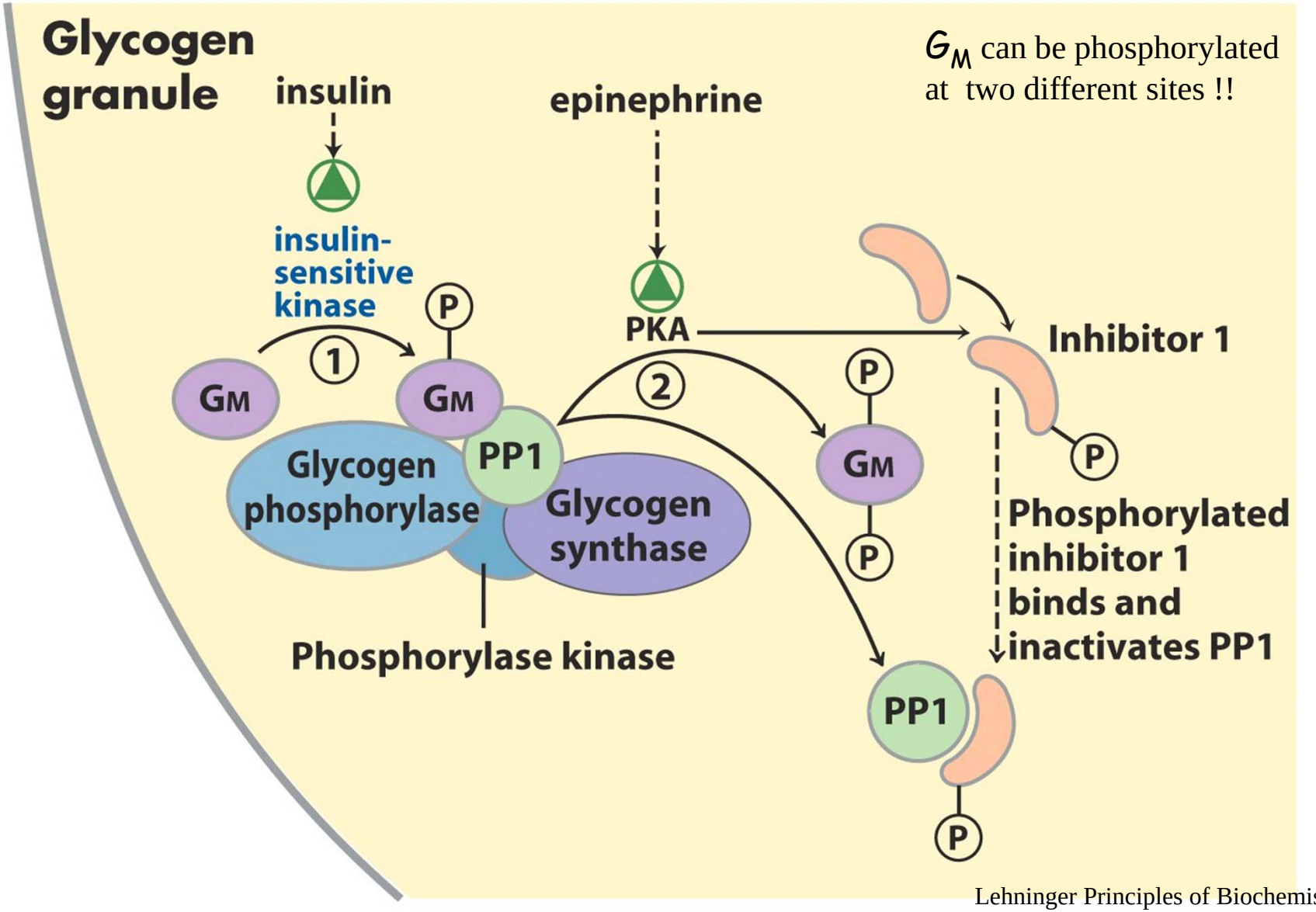


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TABLE 21.1 Glycogen-storage diseases

Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
II Pompe disease	α-1,4-Glucosidase (lysosomal)	All organs	Massive increase in amount; normal structure.	Cardiorespiratory failure causes death, usually before age 2.
III Cori disease	Amylo-1,6-glucosidase (debranching enzyme)	Muscle and liver	Increased amount; short outer branches.	Like type I, but milder course.
IV Andersen disease	Branching enzyme (α-1,4 ⟶ α-1,6)	Liver and spleen	Normal amount; very long outer branches.	Progressive cirrhosis of the liver. Liver failure causes death, usually before age 2.
V McArdle disease	Phosphorylase	Muscle	Moderately increased amount; normal structure.	Limited ability to perform strenuous exercise because of painful muscle cramps. Otherwise patient is normal and well developed.
VI Hers disease	Phosphorylase	Liver	Increased amount.	Like type I, but milder course.
VII	Phosphofructokinase	Muscle	Increased amount; normal structure.	Like type V.
VIII	Phosphorylase kinase	Liver	Increased amount; normal structure.	Mild liver enlargement. Mild hypoglycemia.

Note: Types I through VII are inherited as autosomal recessives. Type VIII is sex linked.

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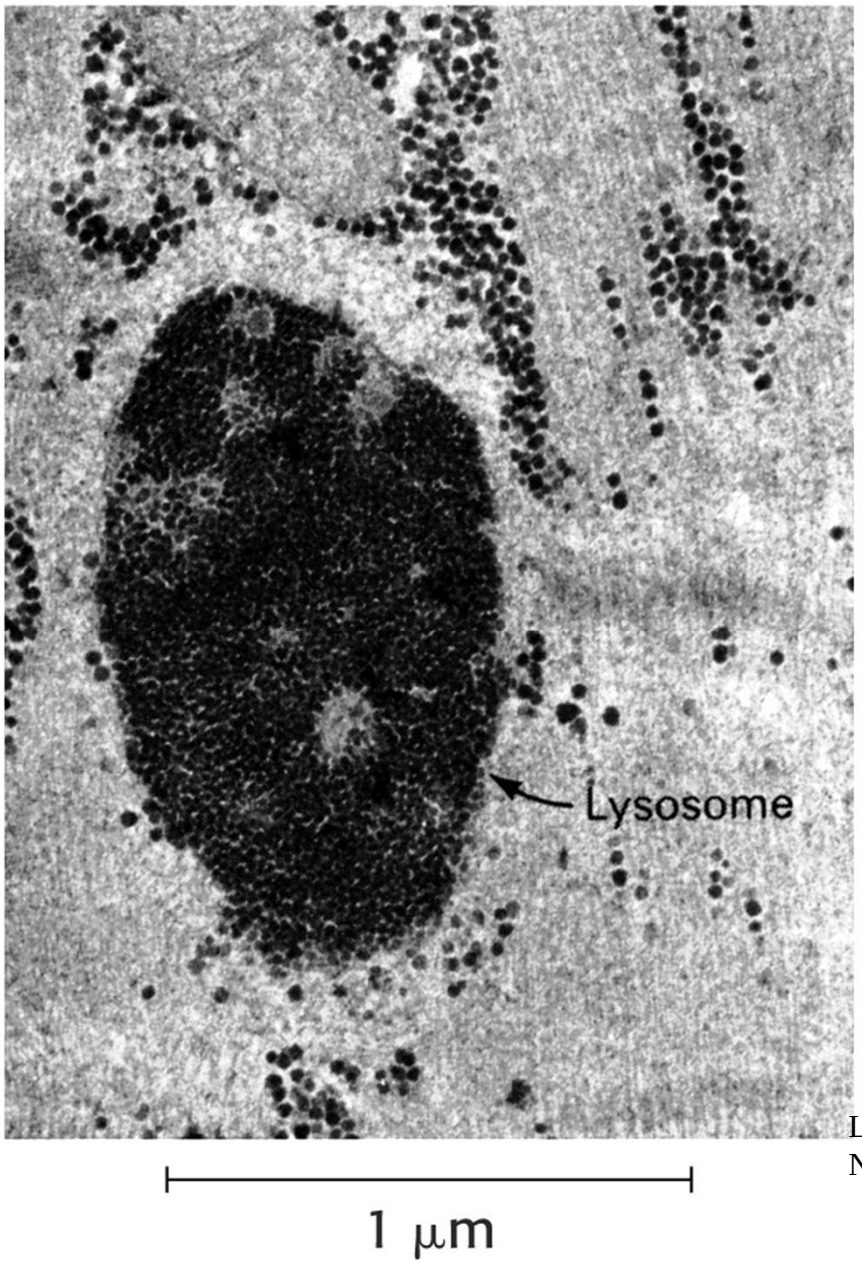
Pompe disease: lysosomal storage of glycogen is fatal



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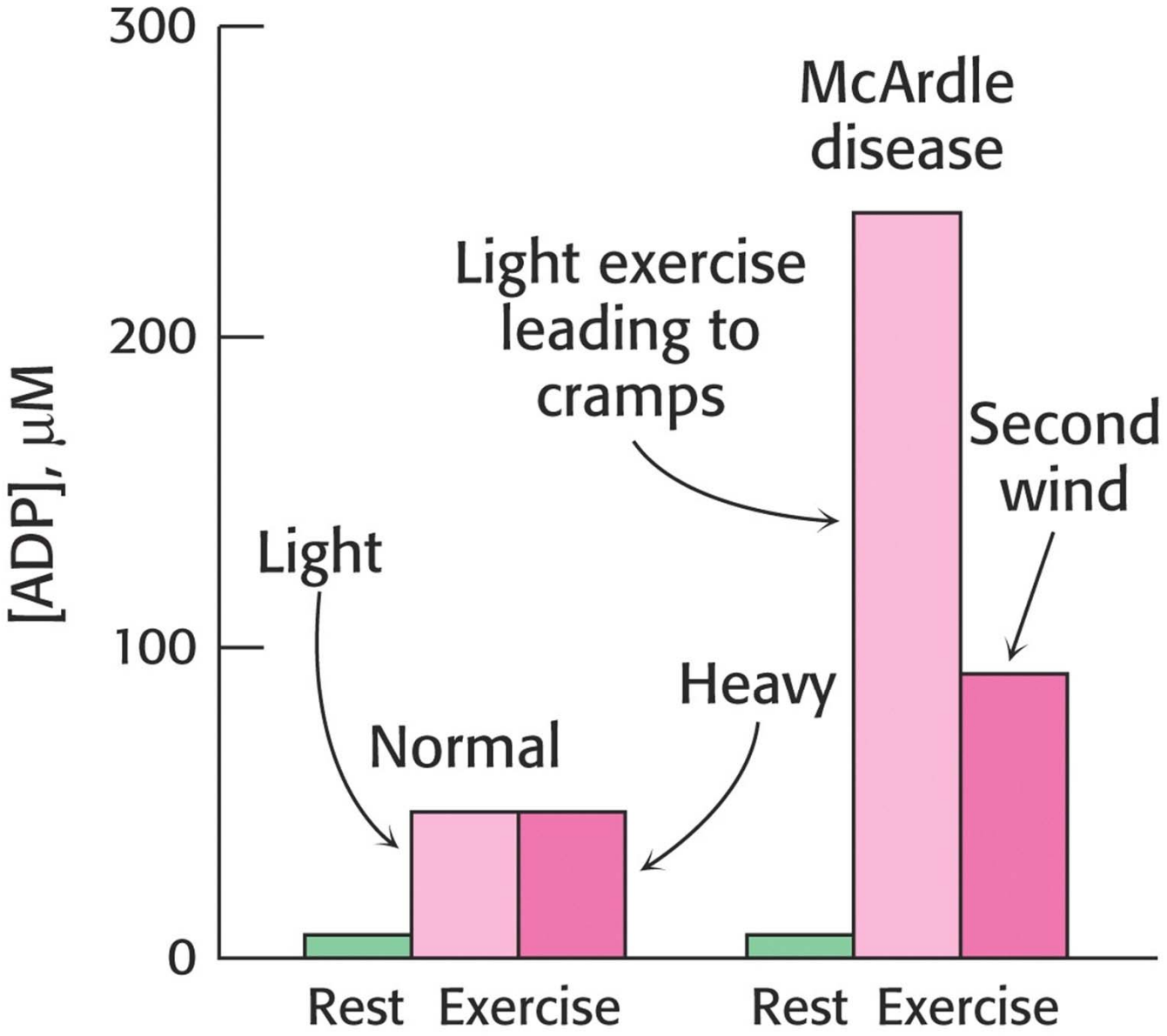

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