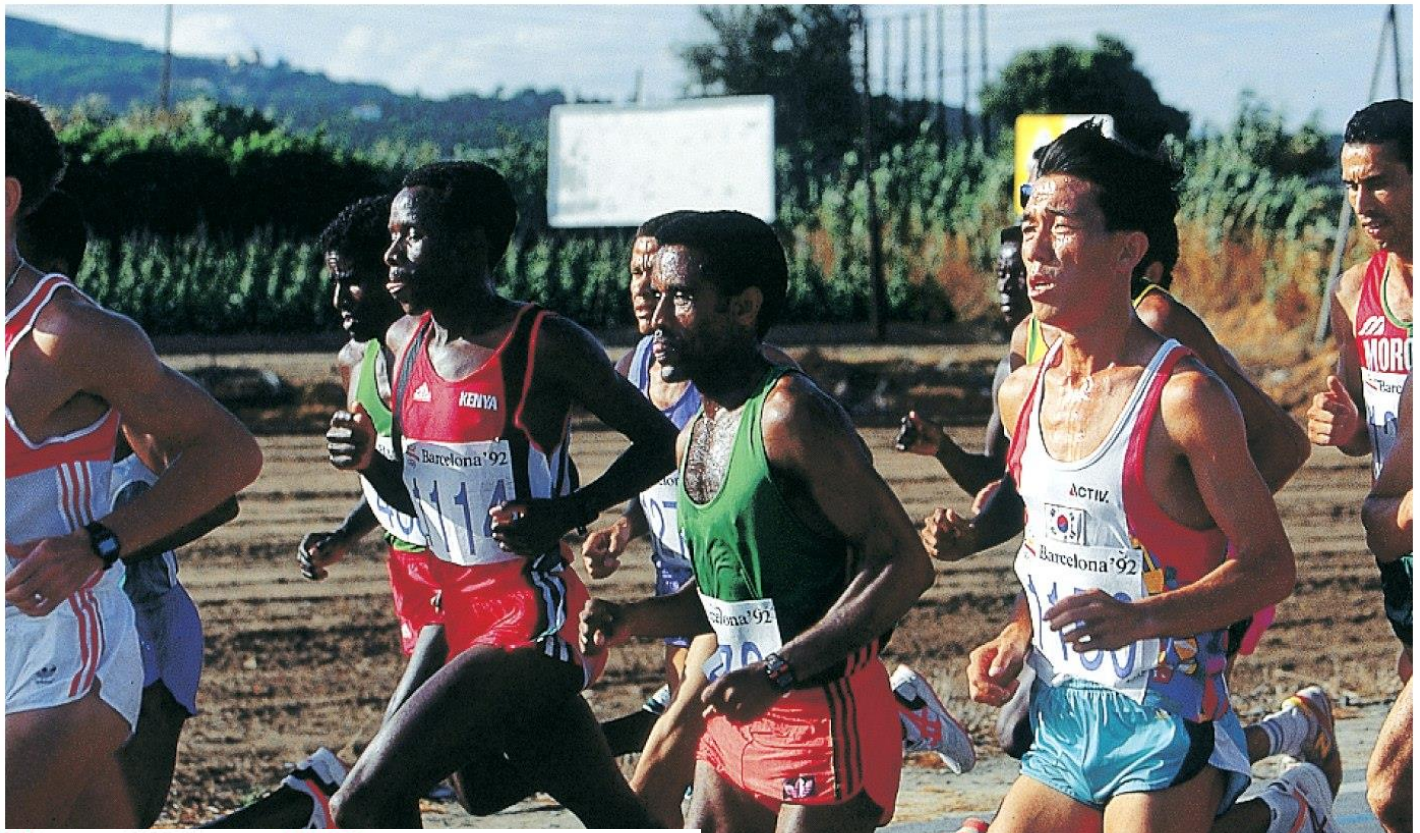
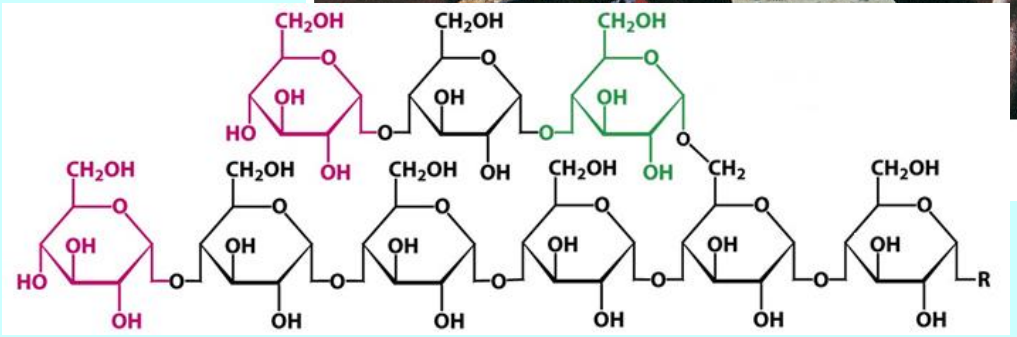
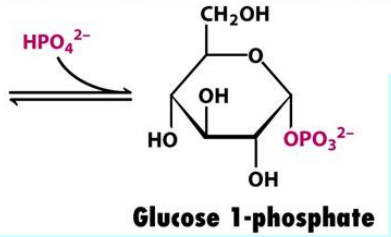
Glycogen Metabolism





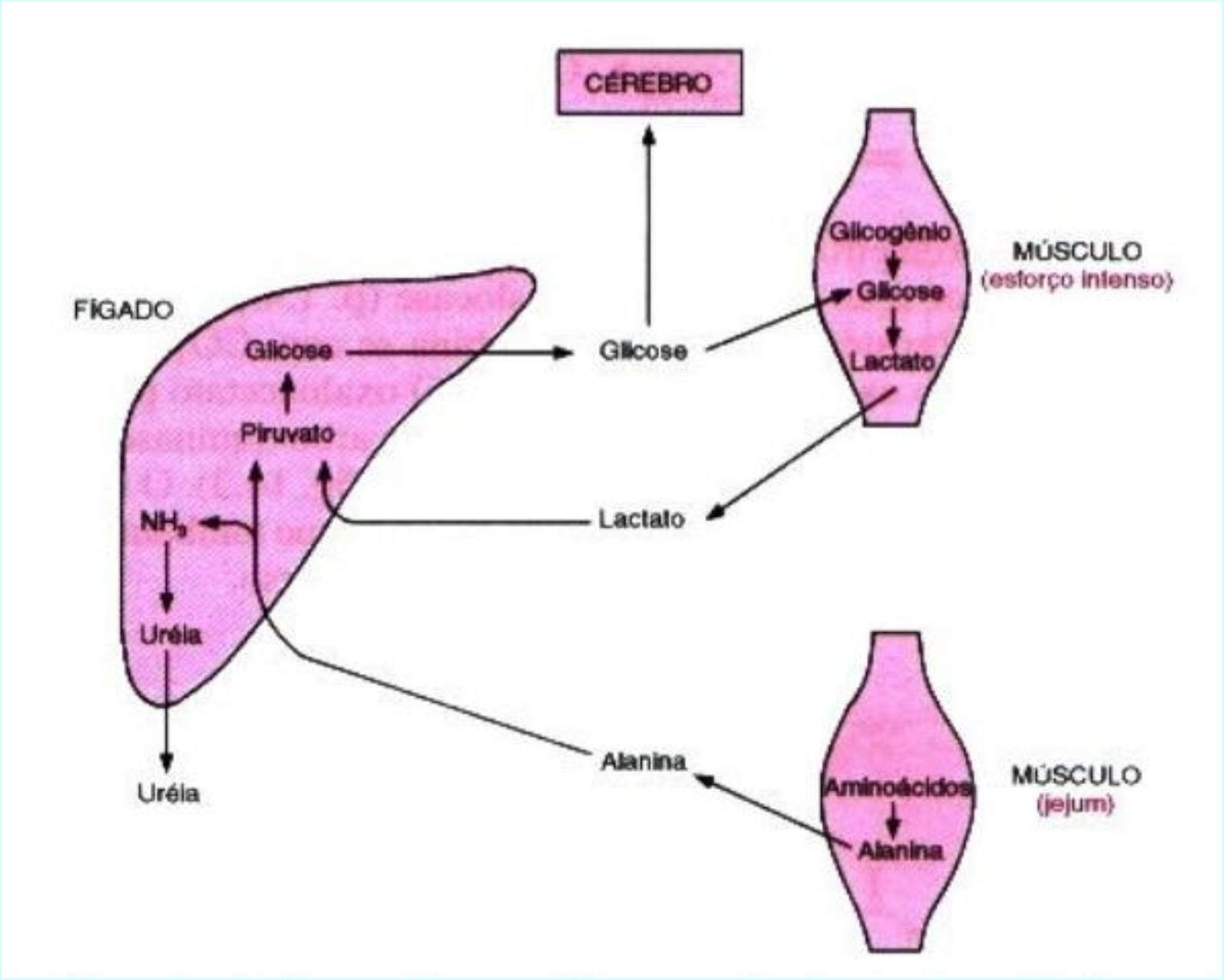


O cérebro consome diariamente 120 g de glicose e as hemácias 30 g

Quadro 14.1 Fonte de energia para diferentes tecidos

Tecido	Composto		
	Glicose	Ácidos graxos	Corpos cetônicos
Cérebro	+		
Hemácias e leucócitos	+		
Medula renal	+		
Retina	+		
Mucosa intestinal	+		
Fígado	+	+	
Adiposo	+	+	
Músculos esqueléticos e cardíaco	+	+	+
Córtex renal	+	+	+

Gliconeogênese: regulação metabólica integrada!



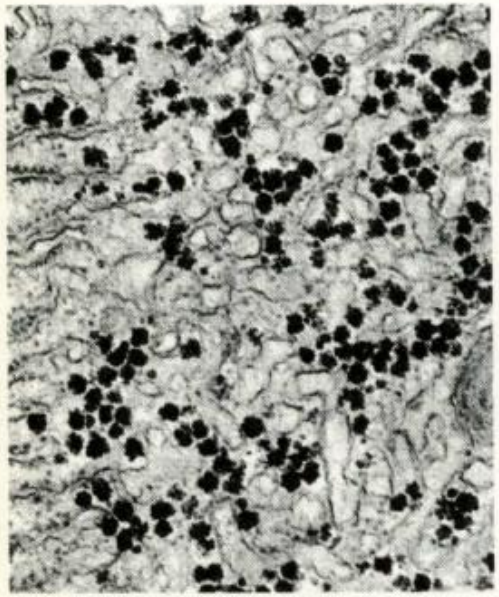
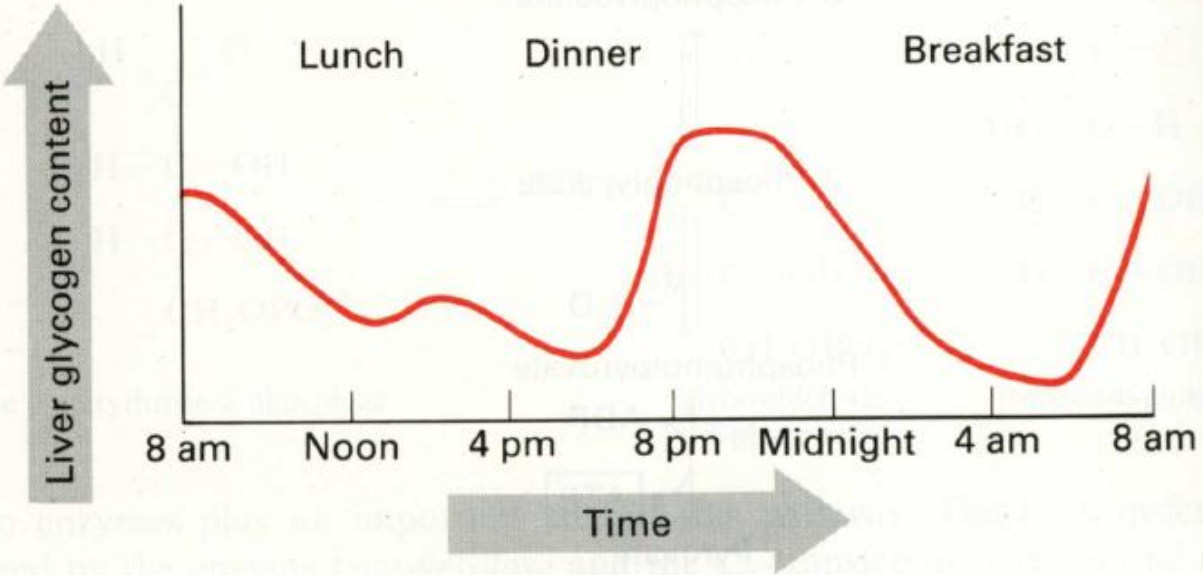
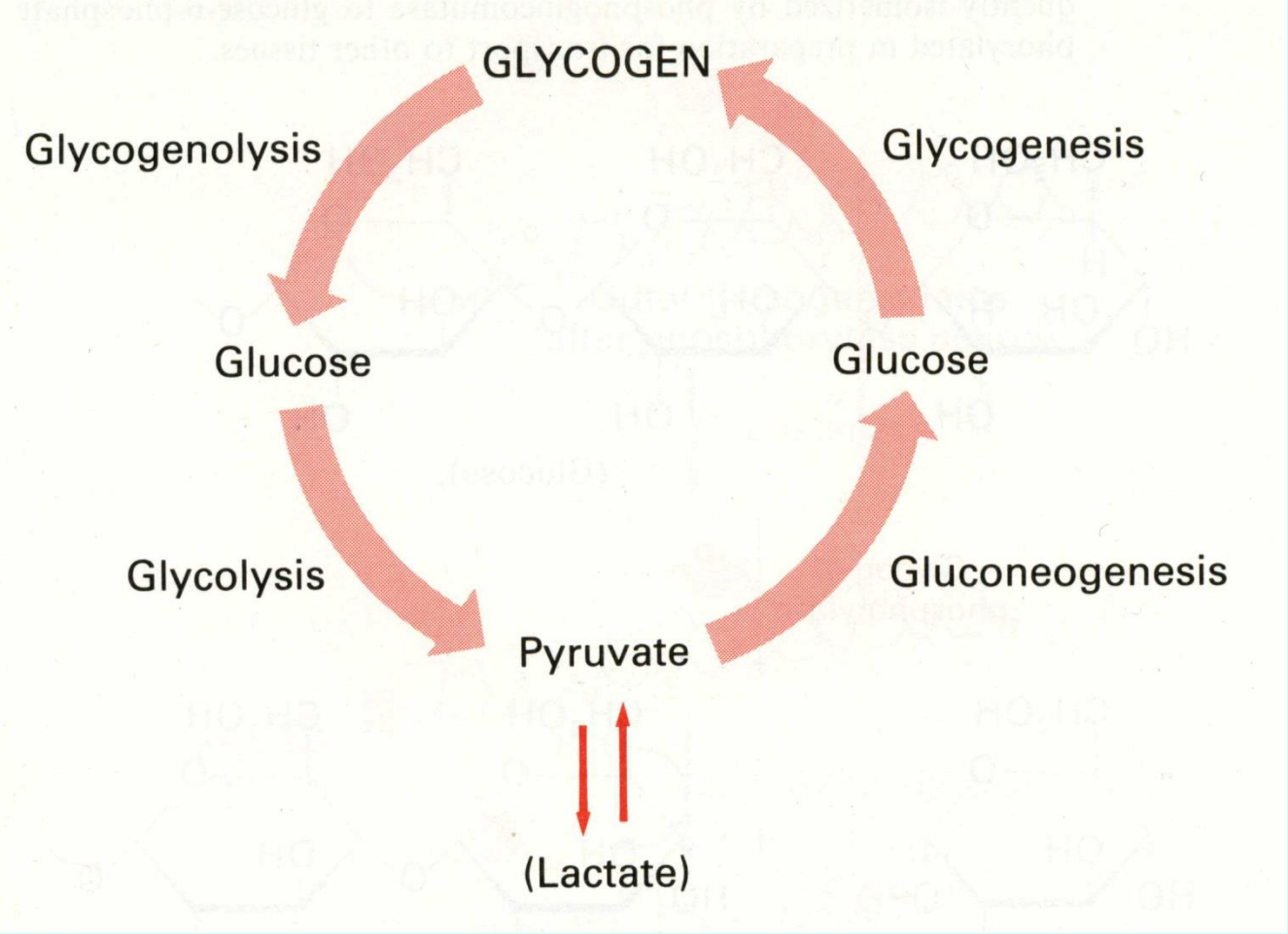


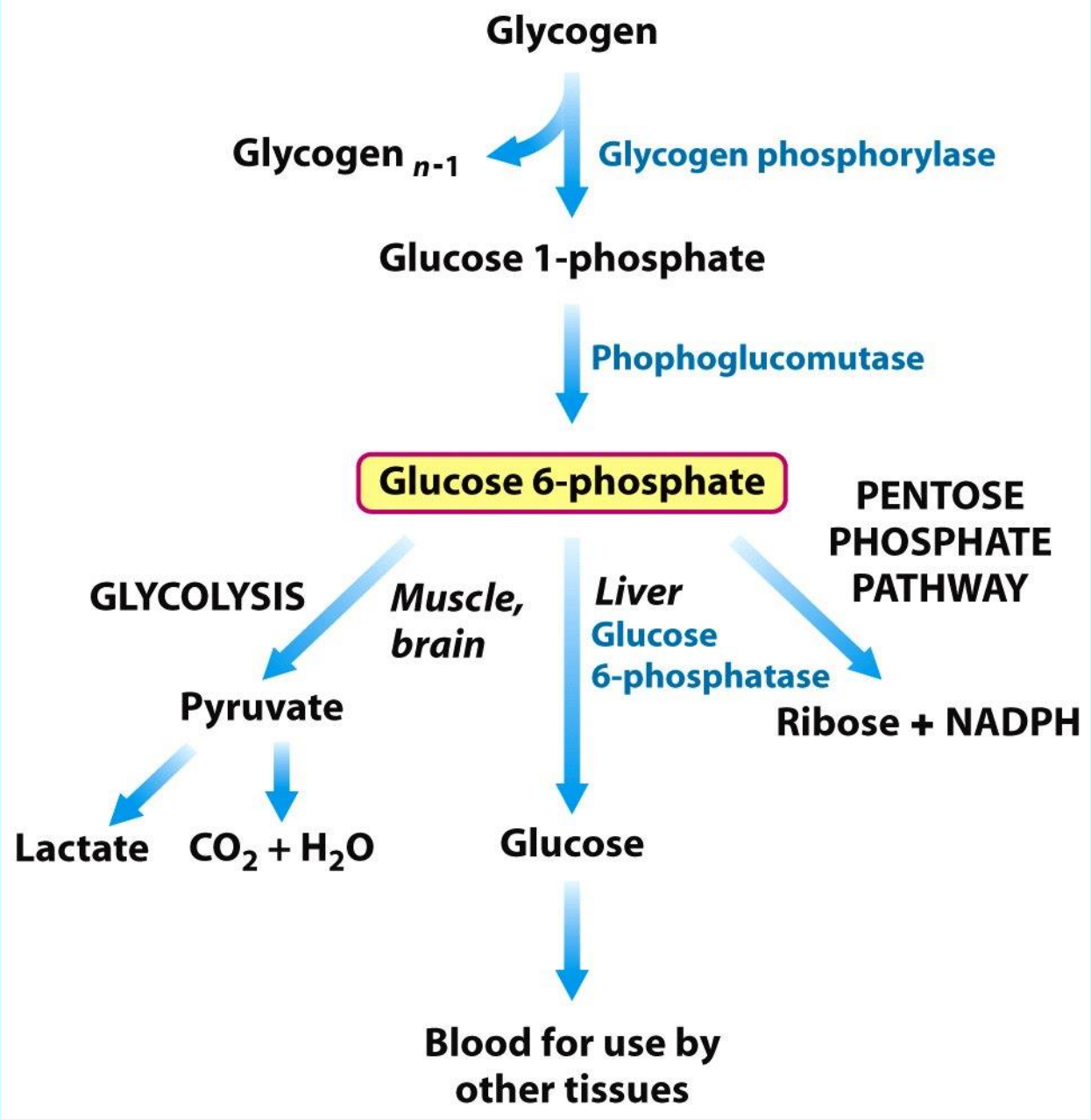
FIGURE 29–9 Electron micrographs showing glycogen granules (darkly stained material) in liver cells.

FIGURE 29–10 Variation of liver glycogen levels between meals.

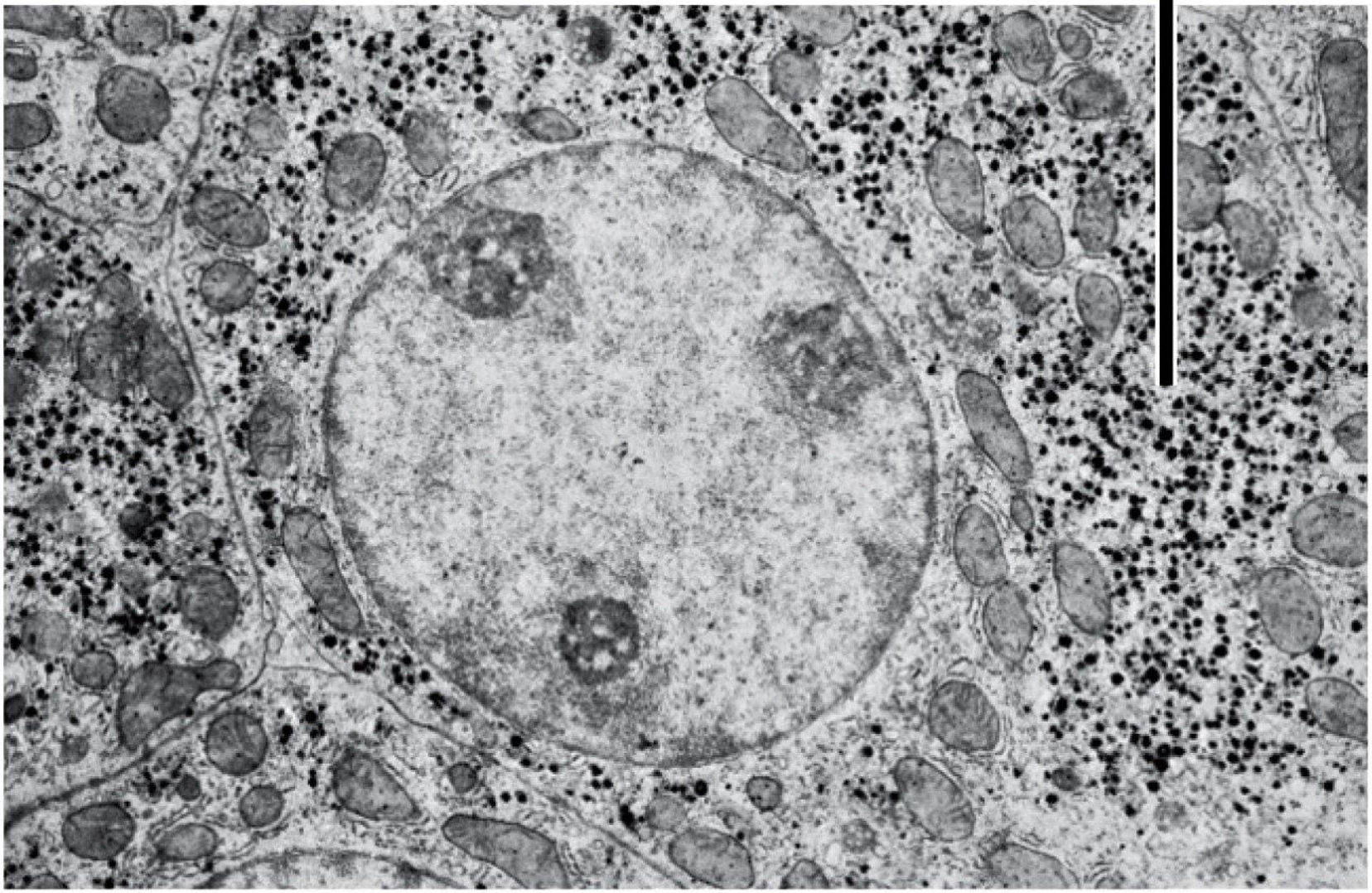


The important pathways of glucose metabolism. Note that the glycogen degradations pathways end in -*lysis*, while the glycogen synthesis pathways end with -*genesis*.




Glycogen
Glycogen $_{n-1}$
Glycogen phosphorylase
Glucose 1-phosphate
Phophoglucomutase
Glucose 6-phosphate
PENTOSE PHOSPHATE PATHWAY
GLYCOLYSIS
Muscle, brain
Liver
Glucose 6-phosphatase
Pyruvate
Ribose + NADPH
Lactate
$CO_2 + H_2O$
Glucose
Blood for use by other tissues

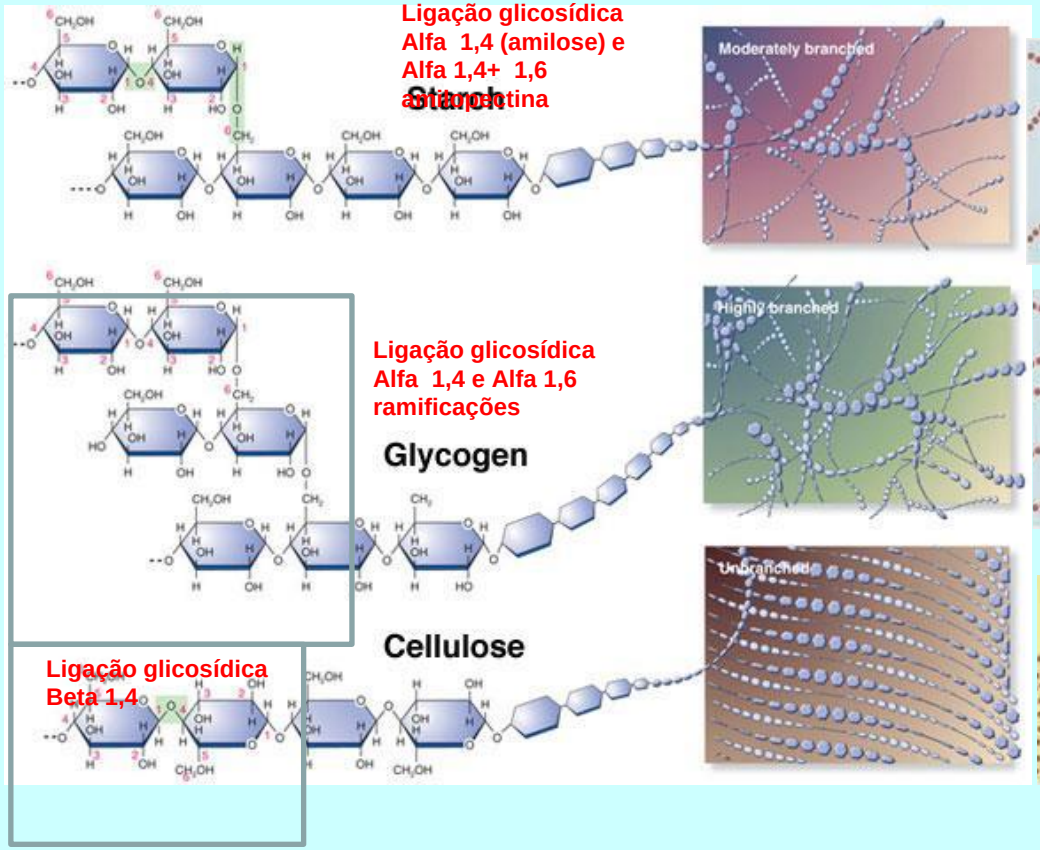
Glycogen granules

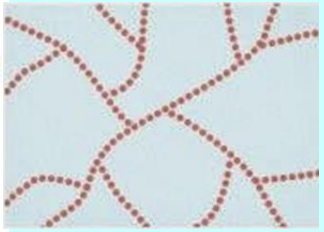


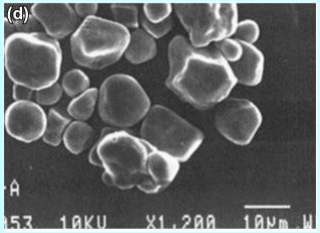
Revisão: polissacarídeos da glicose

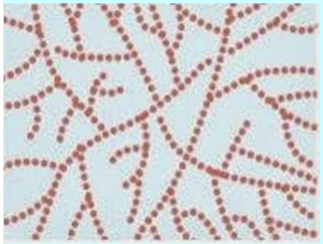
Polissacarídeo	O que é importante saber
Amido 	É um polissacarídeo de reserva energética dos vegetais. As batatas, arroz e a mandioca estão repletos de amido, armazenado pelo vegetal e consumido em épocas desfavoráveis pela planta. O homem soube aproveitar essas características e passou a cultivar os vegetais produtores de amido. Os pães e bolos que comemos são feitos com farinha de trigo, rica em amido. Lembre-se que para o amido ser aproveitado pelo nosso organismo, é preciso digeri-lo, o que ocorre primeiramente na boca e depois no intestino, com adição de água e a participação de catalisadores orgânicos, isto é, substâncias que favorecem ou a
Glicogênio 	É um polissacarídeo de reserva energética dos animais; portanto, equivalente ao amido dos vegetais. No nosso organismo, a síntese de glicogênio ocorre no fígado, a partir de moléculas de glicose. Logo, fígado de boi e fígado de galinha são alimentos ricos em glicogênio.
Celulose 	É o polissacarídeo de papel estrutural, isto é, participa da parede das células vegetais. Poucos seres vivos conseguem digeri-lo, entre eles alguns microrganismos que habitam o tubo digestivo de certos insetos (cupins) e o dos ruminantes (bois, cabras, ovelhas, veados etc.).

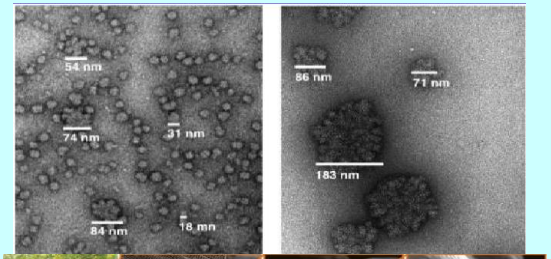
Estrutura dos polissacarídeos de glicose

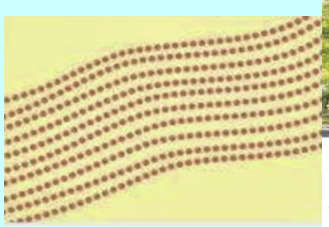


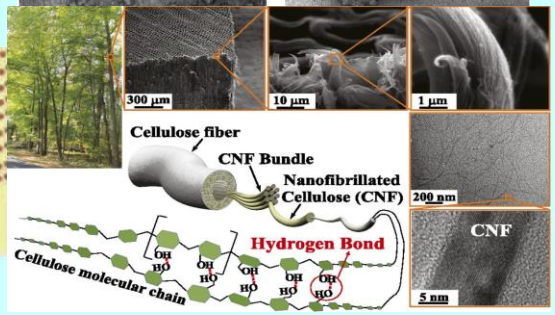




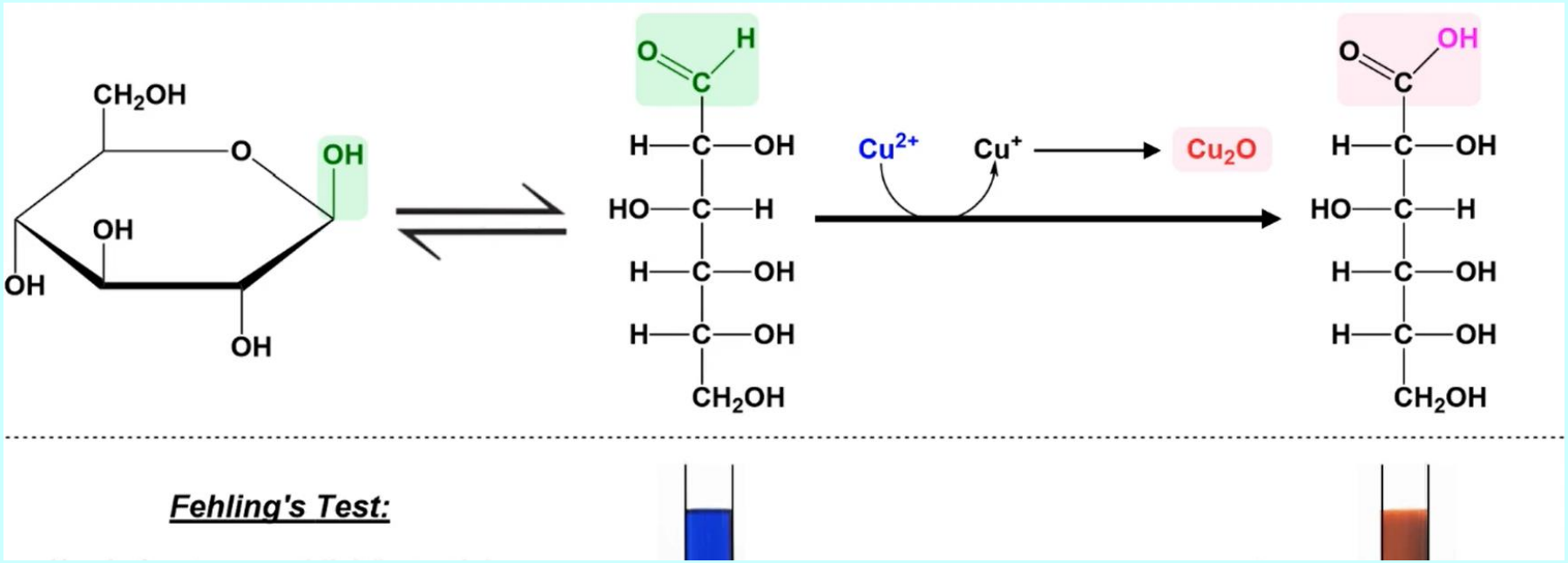




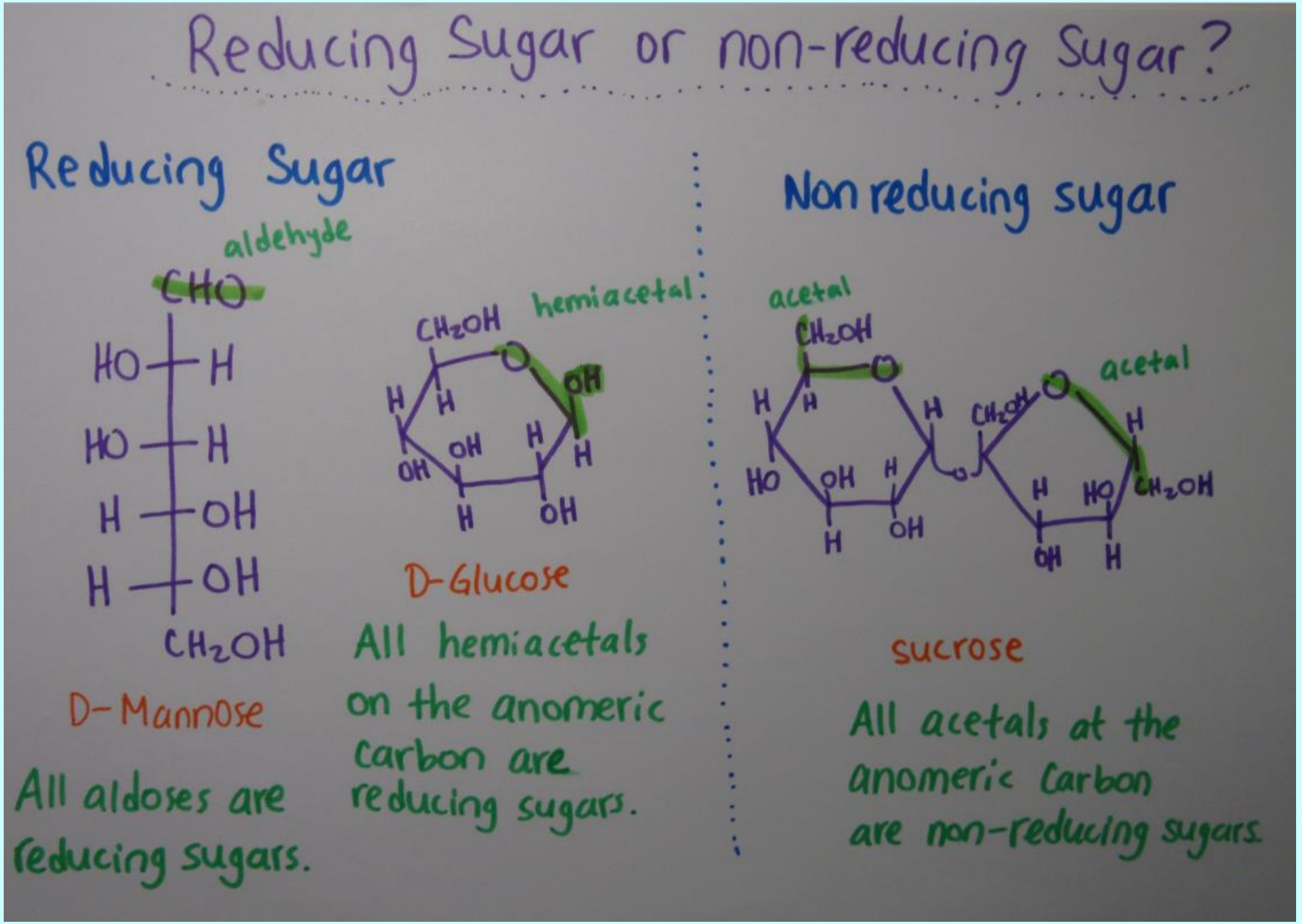




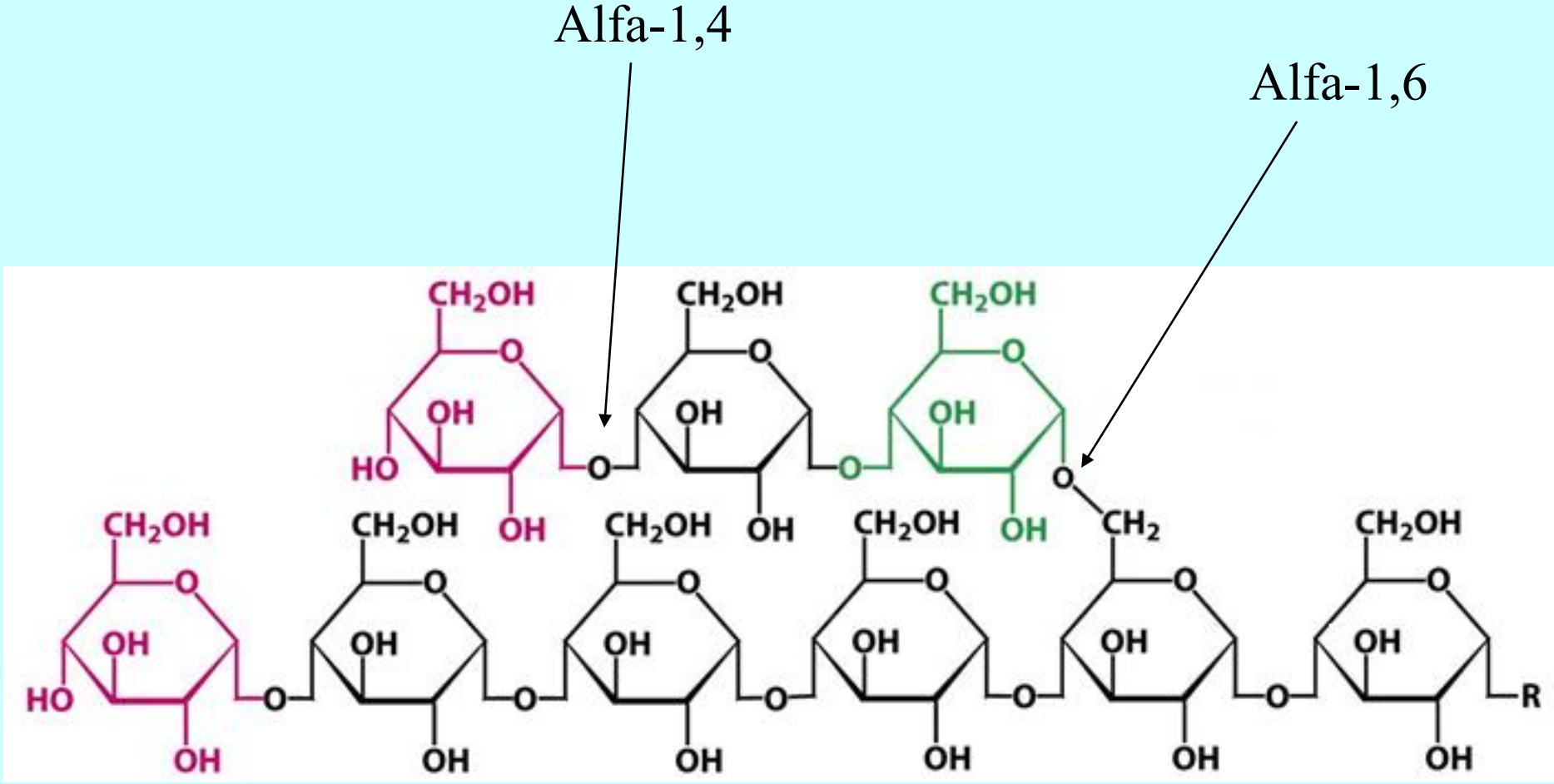
Açúcares redutores: aldeídos ou grupos hemiacetais são oxidados na presença de oxidantes brandos!



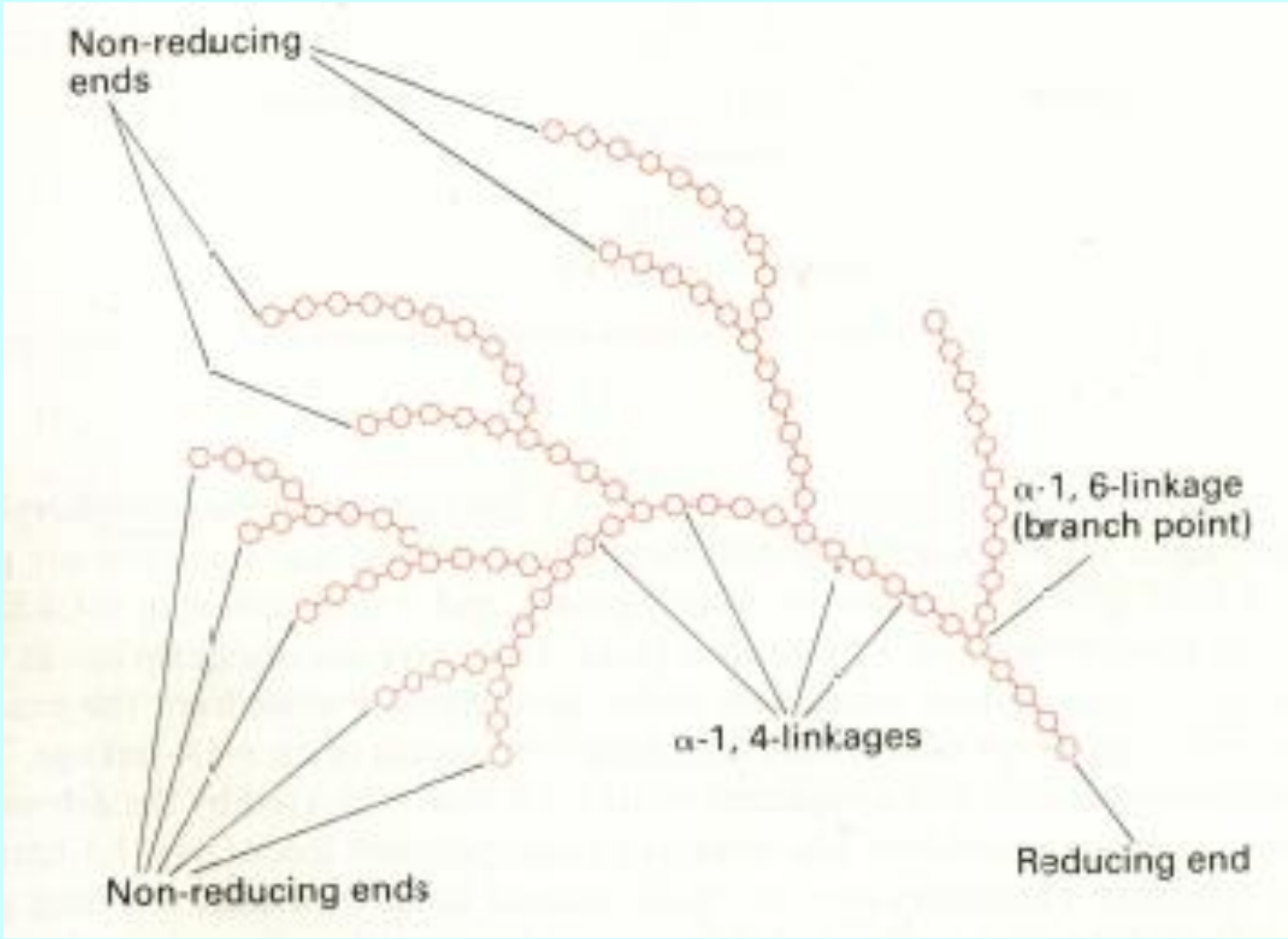
Açúcares redutores e não redutores



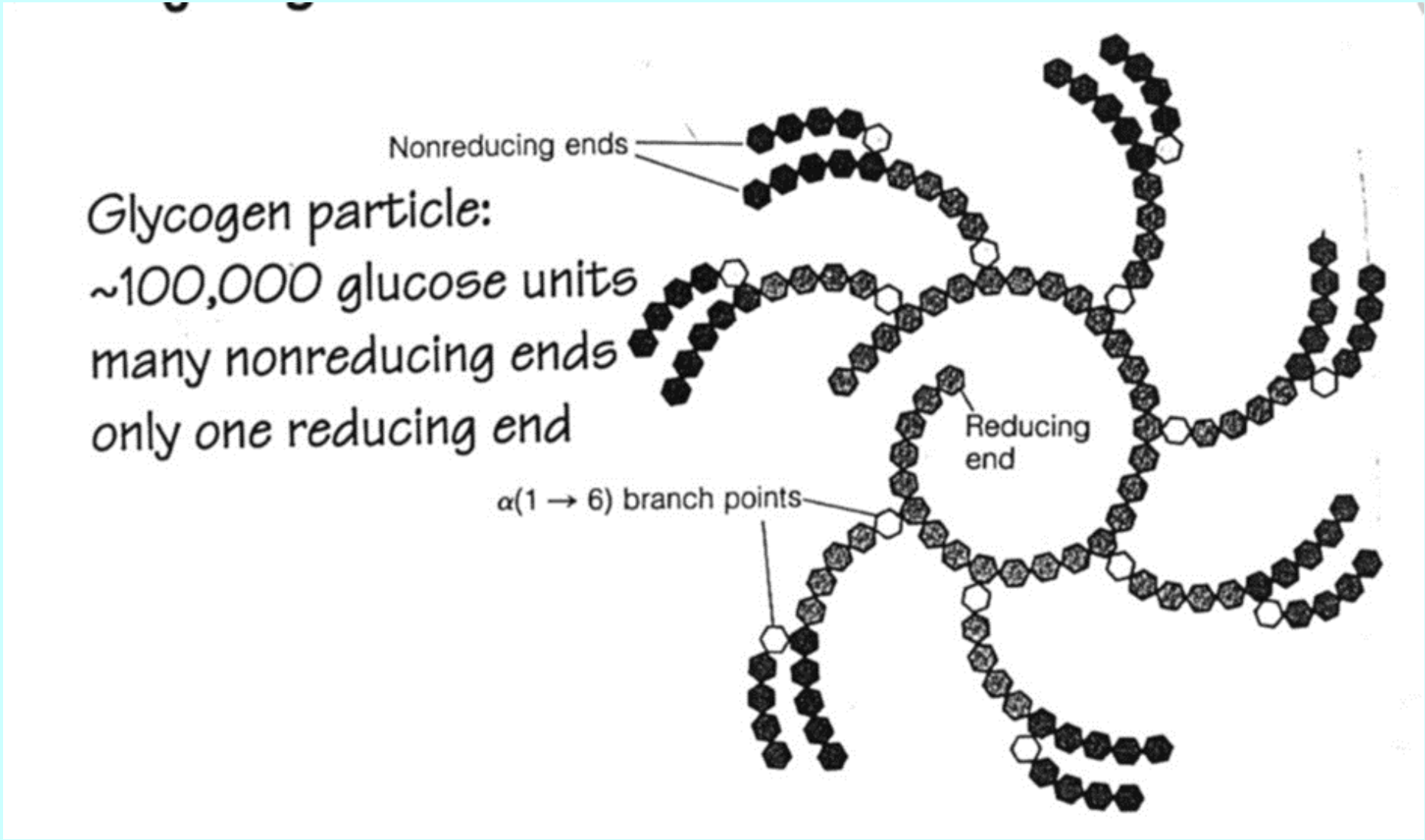
Ligações glicosídicas no glicogênio

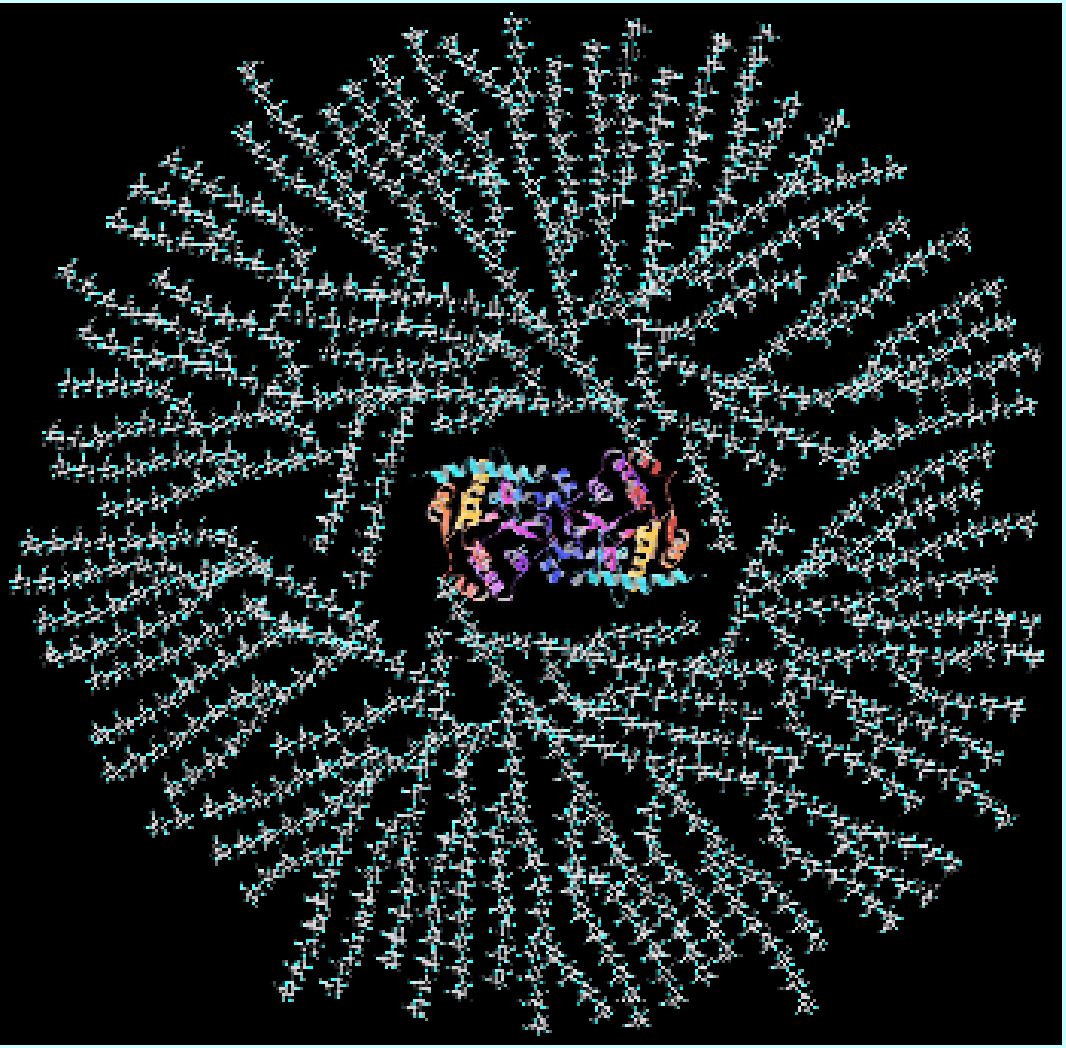


Nomenclatura da estrutura do glicogenio



Estrutura do glicogênio





Grânulo de glicogênio: o glicogênio é uma molécula altamente ramificada no centro da qual há um dímero da proteína glicogenina, que está covalentemente ligada ao polissacarídeo através de um resíduo de tirosina .

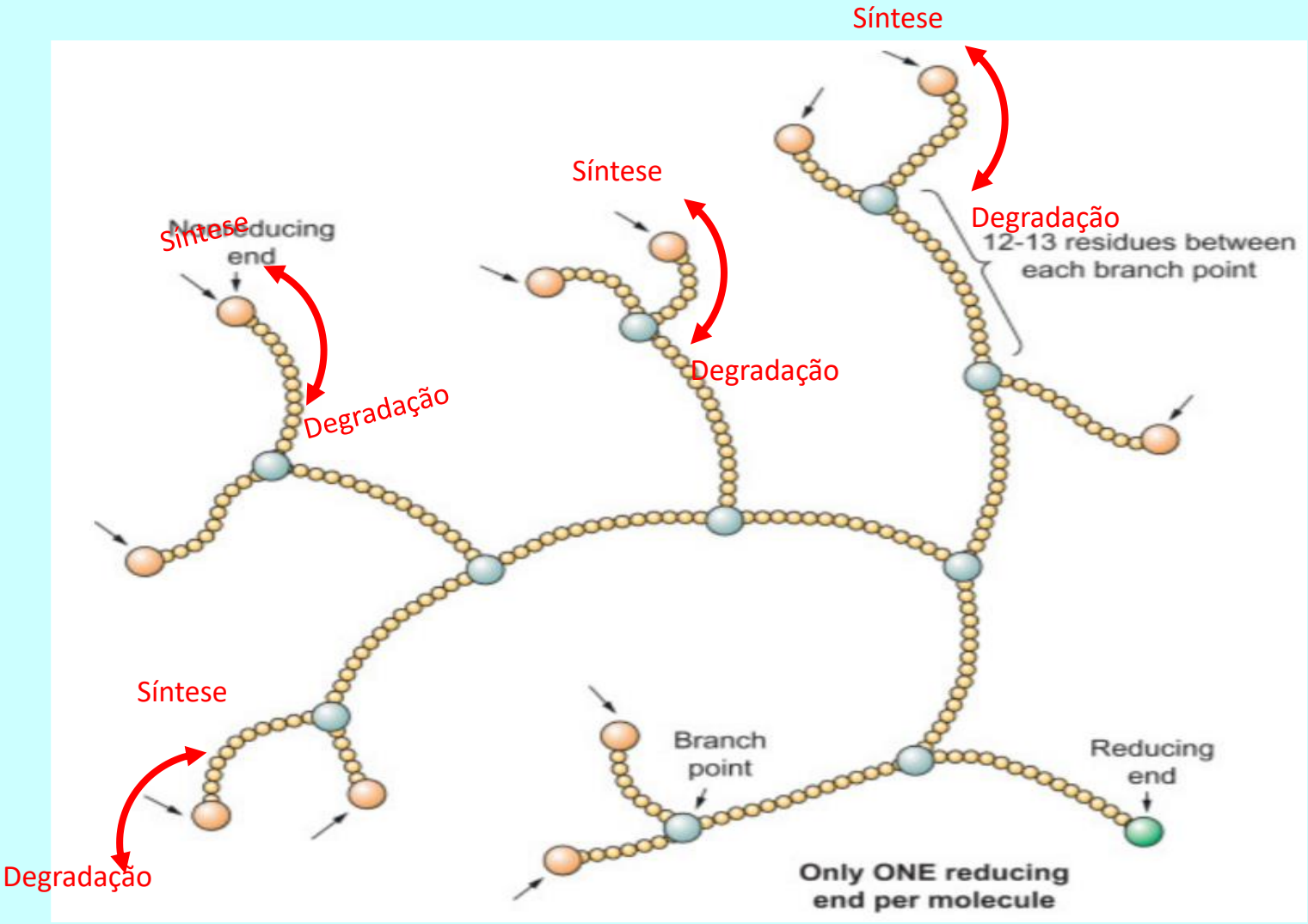
DEGRADAÇÃO DO GLICOGÊNIO

- Quando o organismo está em períodos de jejum, ou no músculo durante atividade intensa, o glicogênio é degradado.

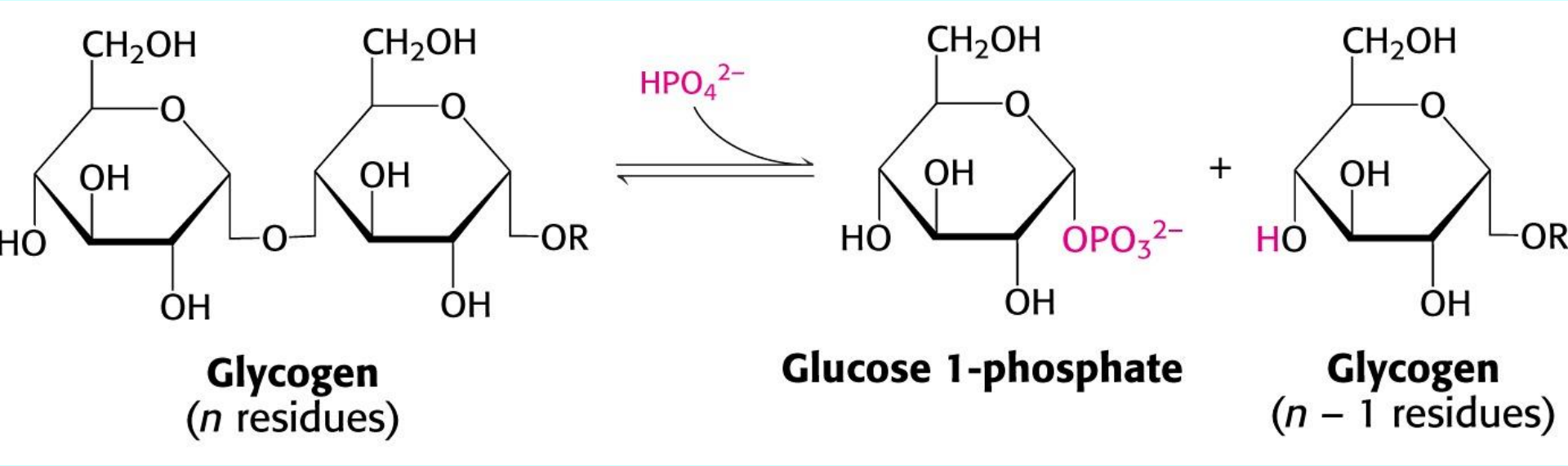
- O glicogênio hepático é degradado produzindo glicose livre, que é exportada para o sangue para manter a glicemia (concentração de glicose sanguínea) nos períodos entre as refeições e jejum noturno.

- No músculo o glicogênio é degradado para fornecer energia para a contração muscular.

A síntese e a degradação do glicogênio ocorrem, respectivamente, através da adição (síntese) e remoção (degradação) sequencial de resíduos de glicose nas extremidades não redutoras do grânulo!

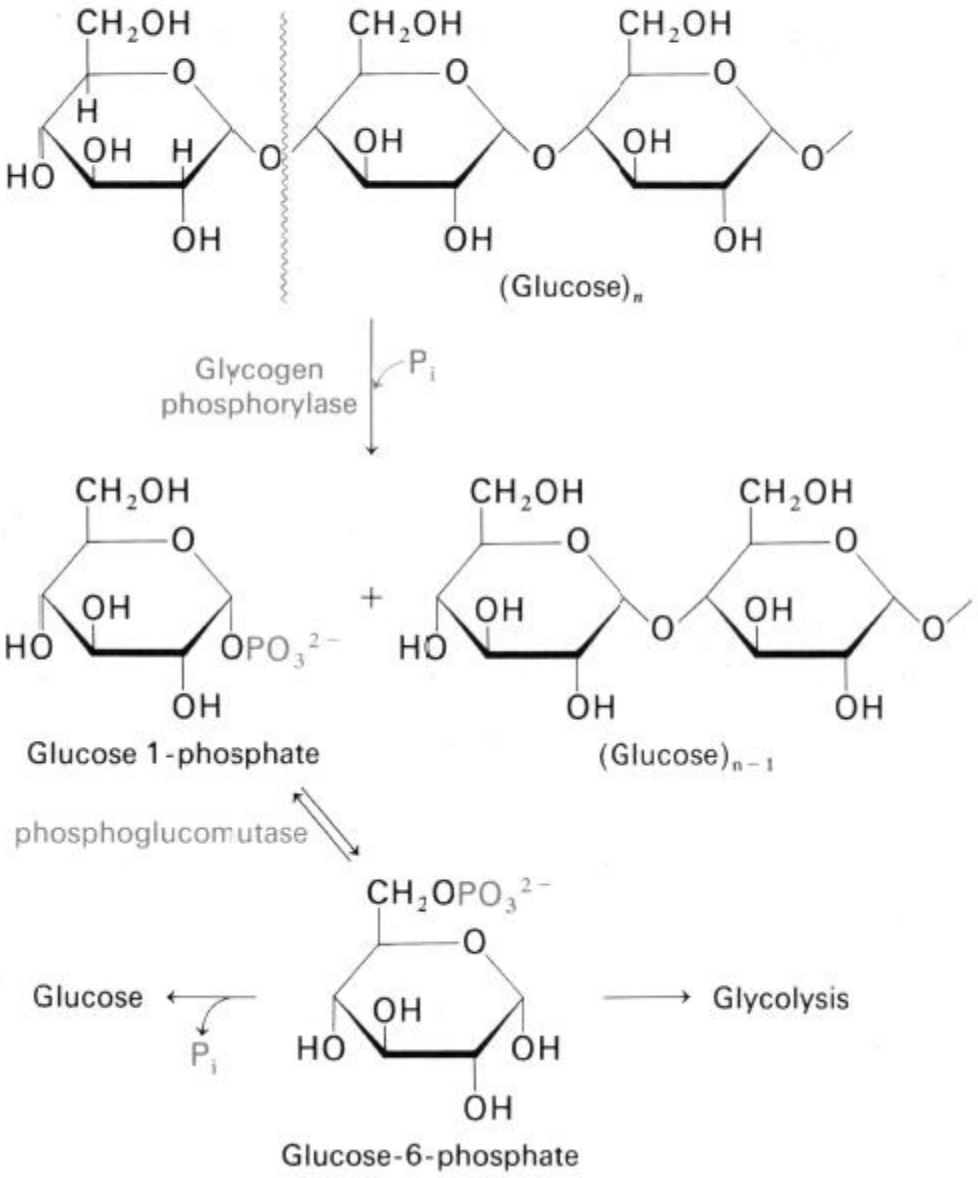


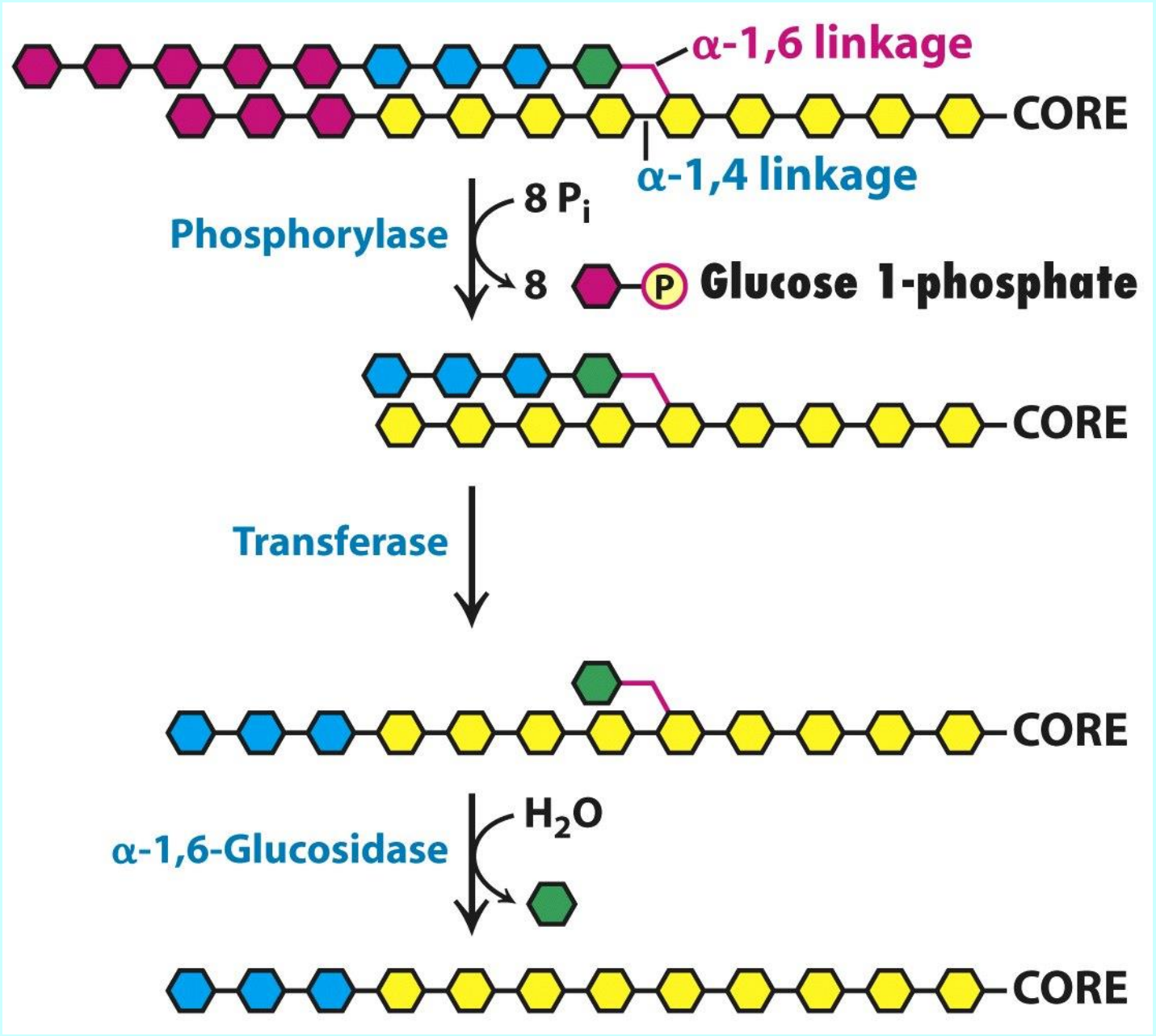
A glicogênio fosforilase catalisa a degradação do glicogênio através da sua fosforilação



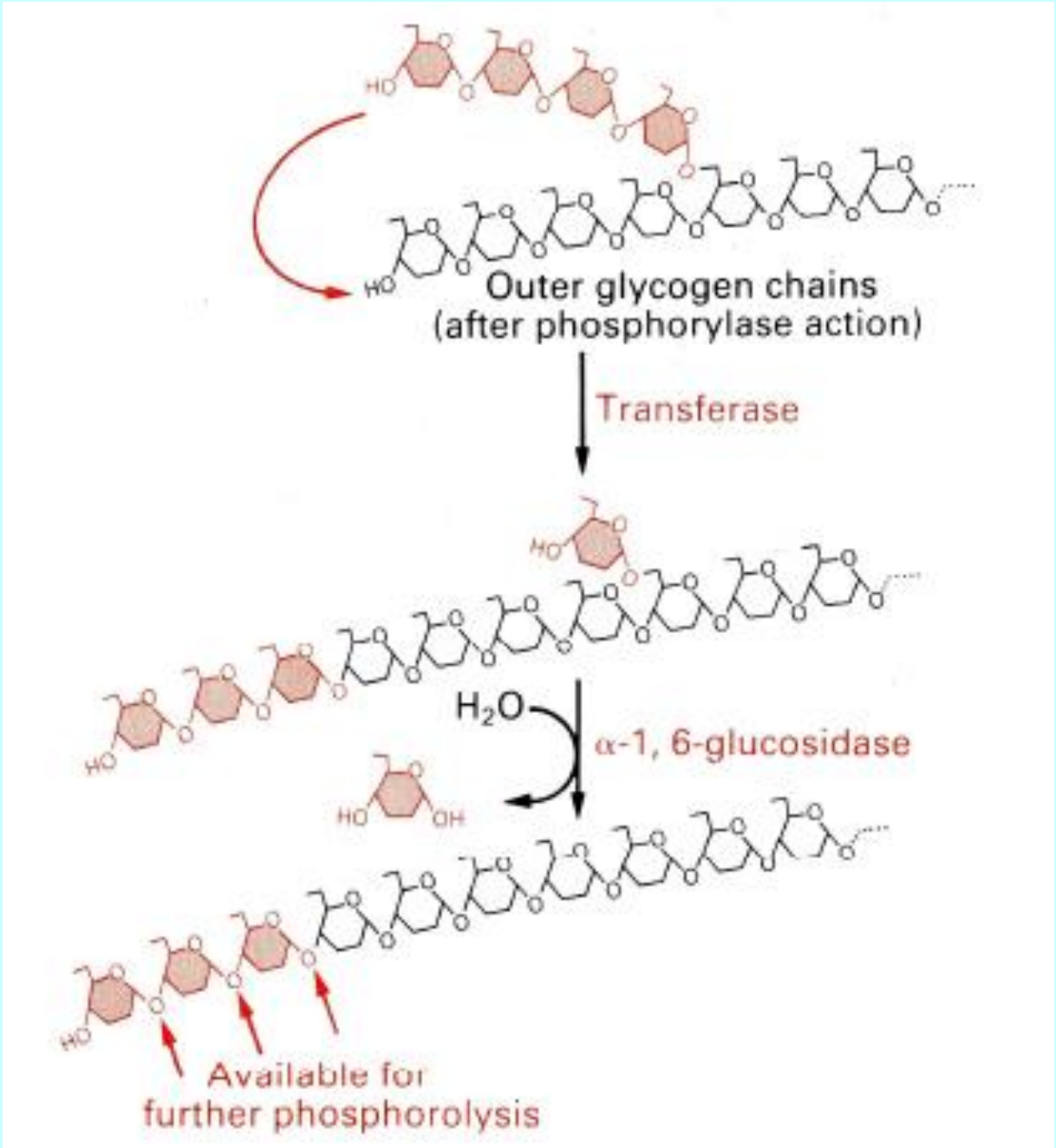
Glicogênio + Pi ⇆ Glicose 1-fosfato + glicogênio
(*n resíduos*) (*n-1 resíduos*)

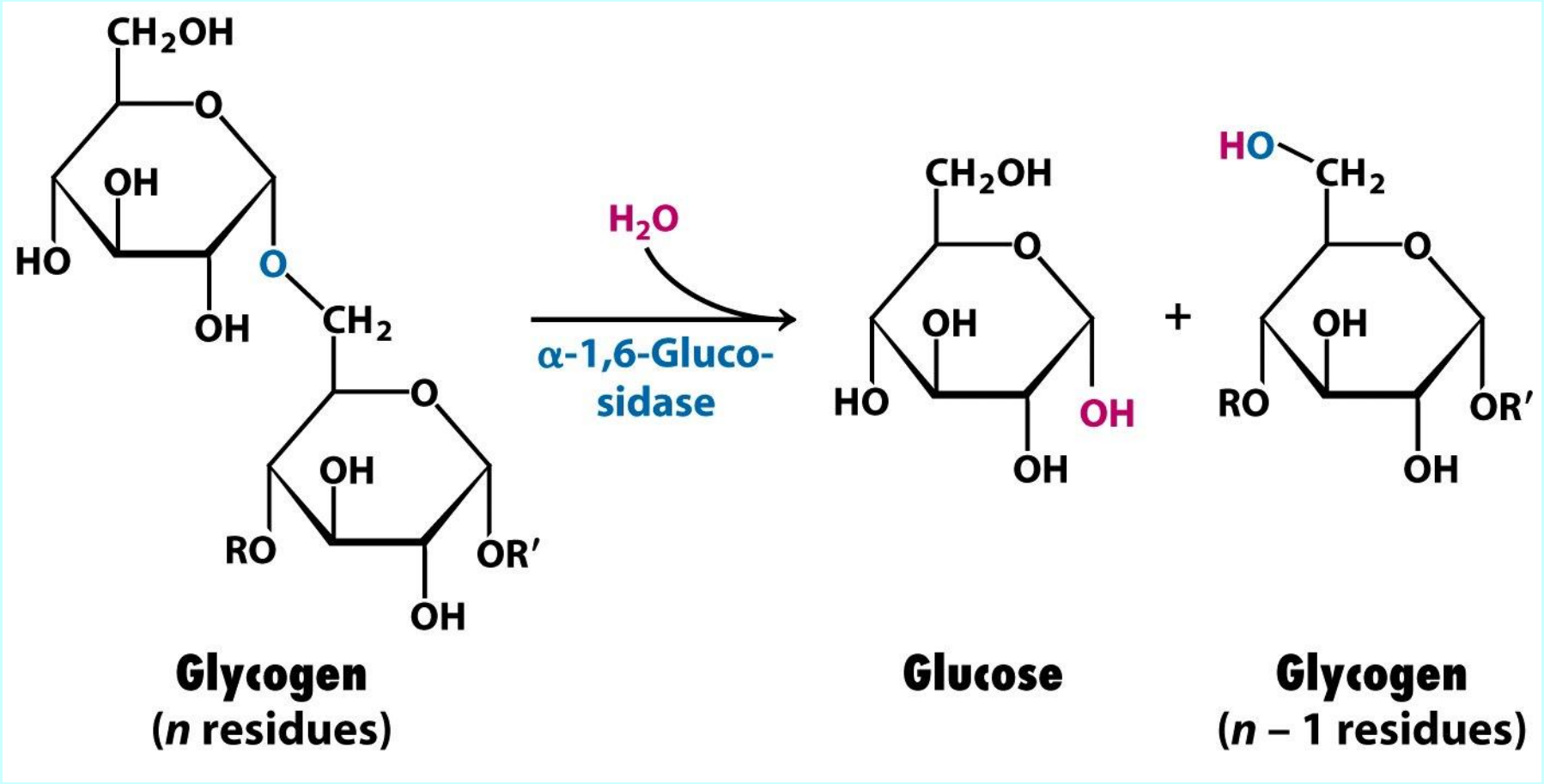
FIGURE 29–13 Glucose monomers are removed from the nonreducing ends of glycogen by the enzyme glycogen phosphorylase, which uses phosphate to split the glycosidic bond, rather than water. The resulting product, glucose-1-phosphate, is subsequently isomerized by phosphoglucomutase to glucose-6-phosphate or dephosphorylated in preparation for transport to other tissues.

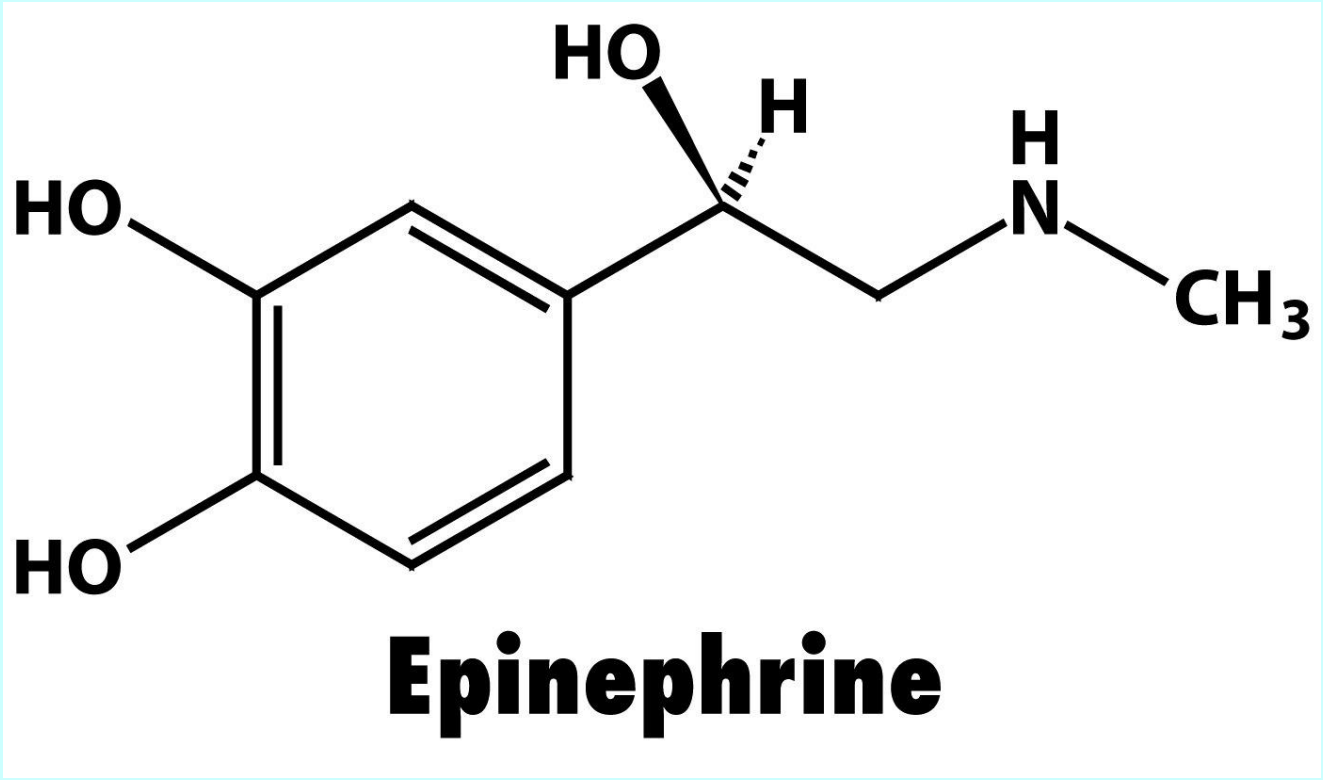



α-1,6 linkage
CORE
α-1,4 linkage
Phosphorylase
8 P_i
8
P
Glucose 1-phosphate
CORE
Transferase
CORE
α-1,6-Glucosidase
H_2O
CORE

Processo de desramificação de glicogênio

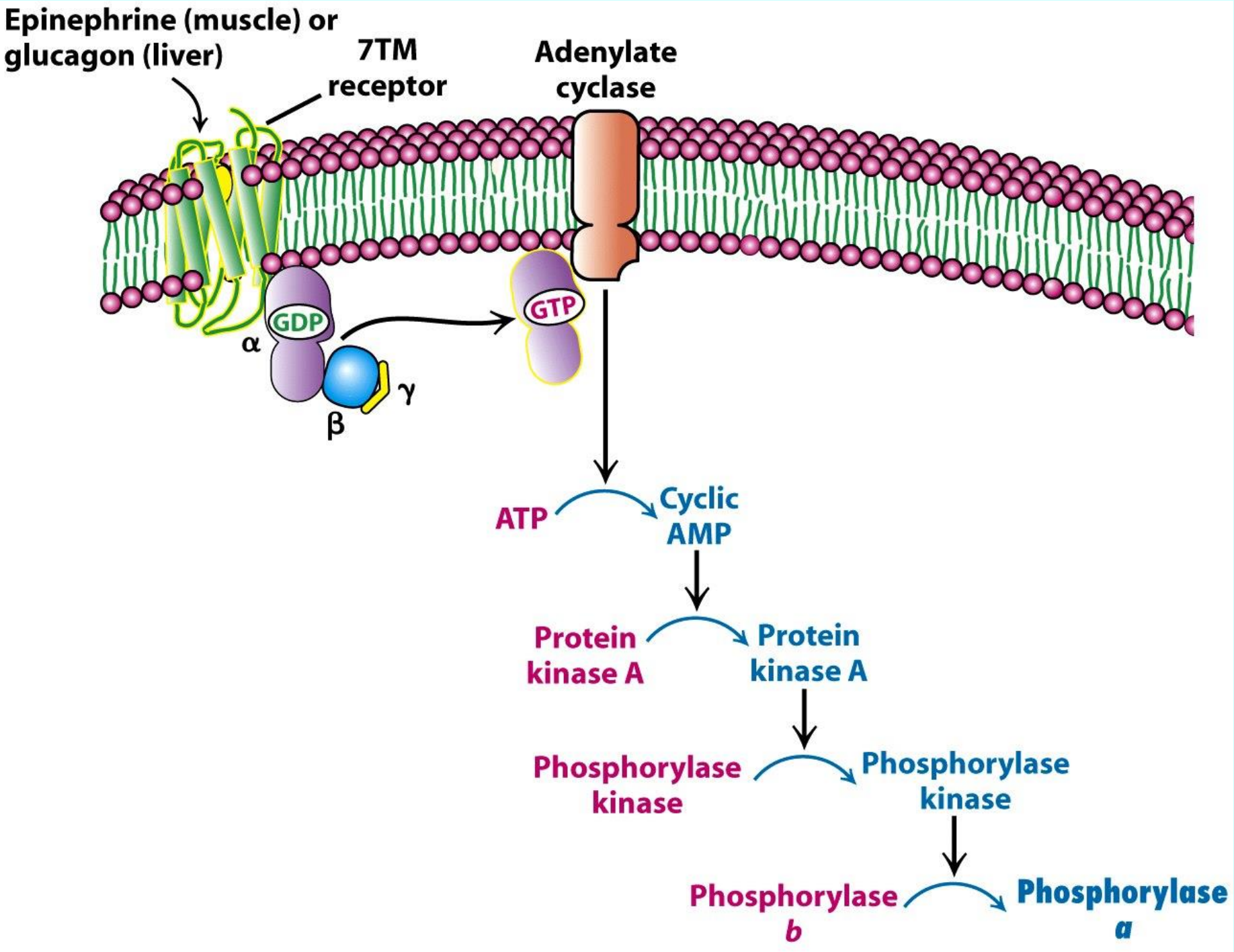


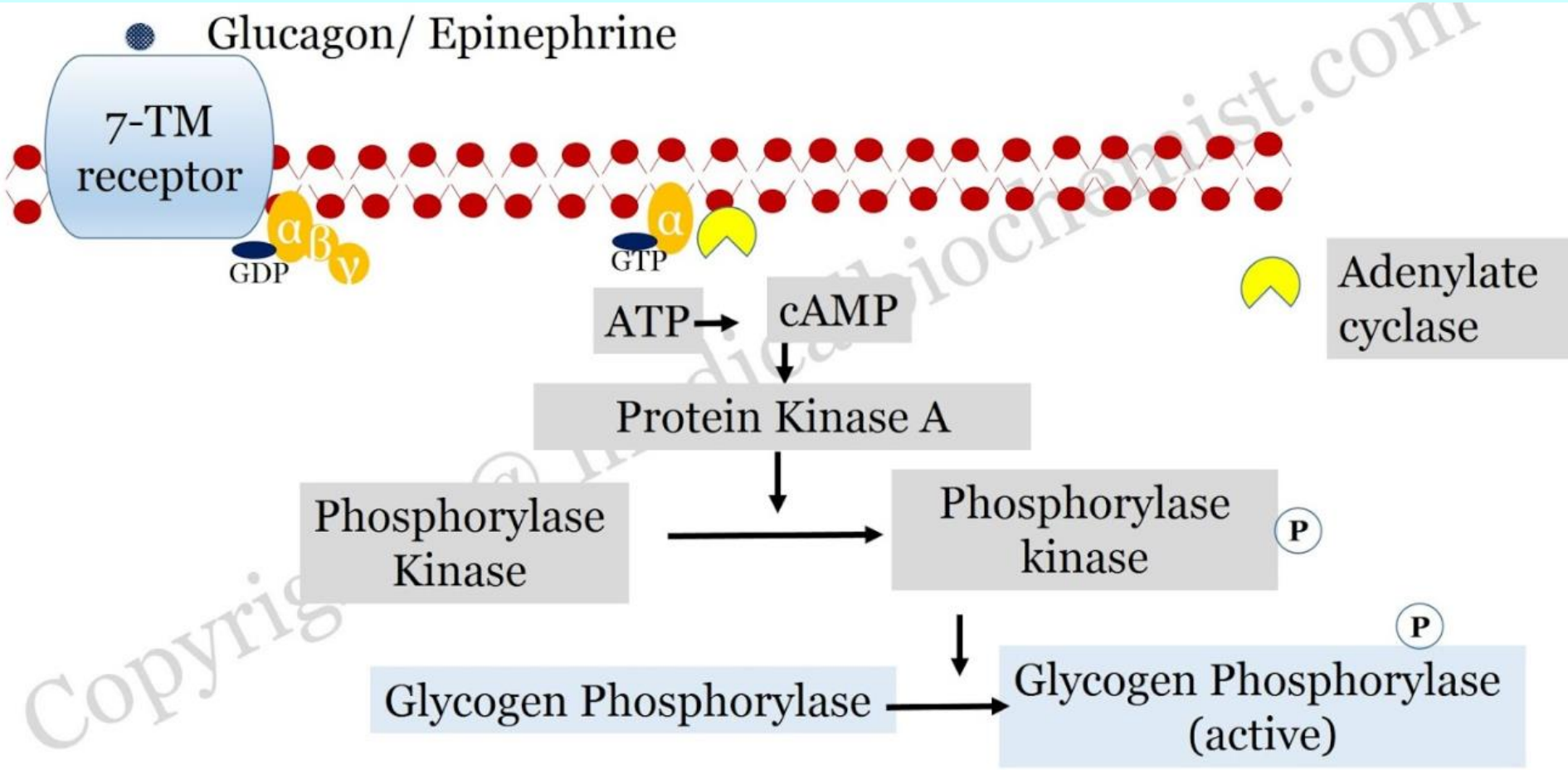

CH2OH
O
OH
HO
O
OH
CH2
O
OH
RO
OR′
OH
H2O
α-1,6-Gluco-
sidase
CH2OH
O
OH
HO
OH
OH
+
HO
CH2
O
OH
RO
OR′
OH
Glycogen
(n residues)
Glucose
Glycogen
(n – 1 residues)



(β-phenylethylamine)

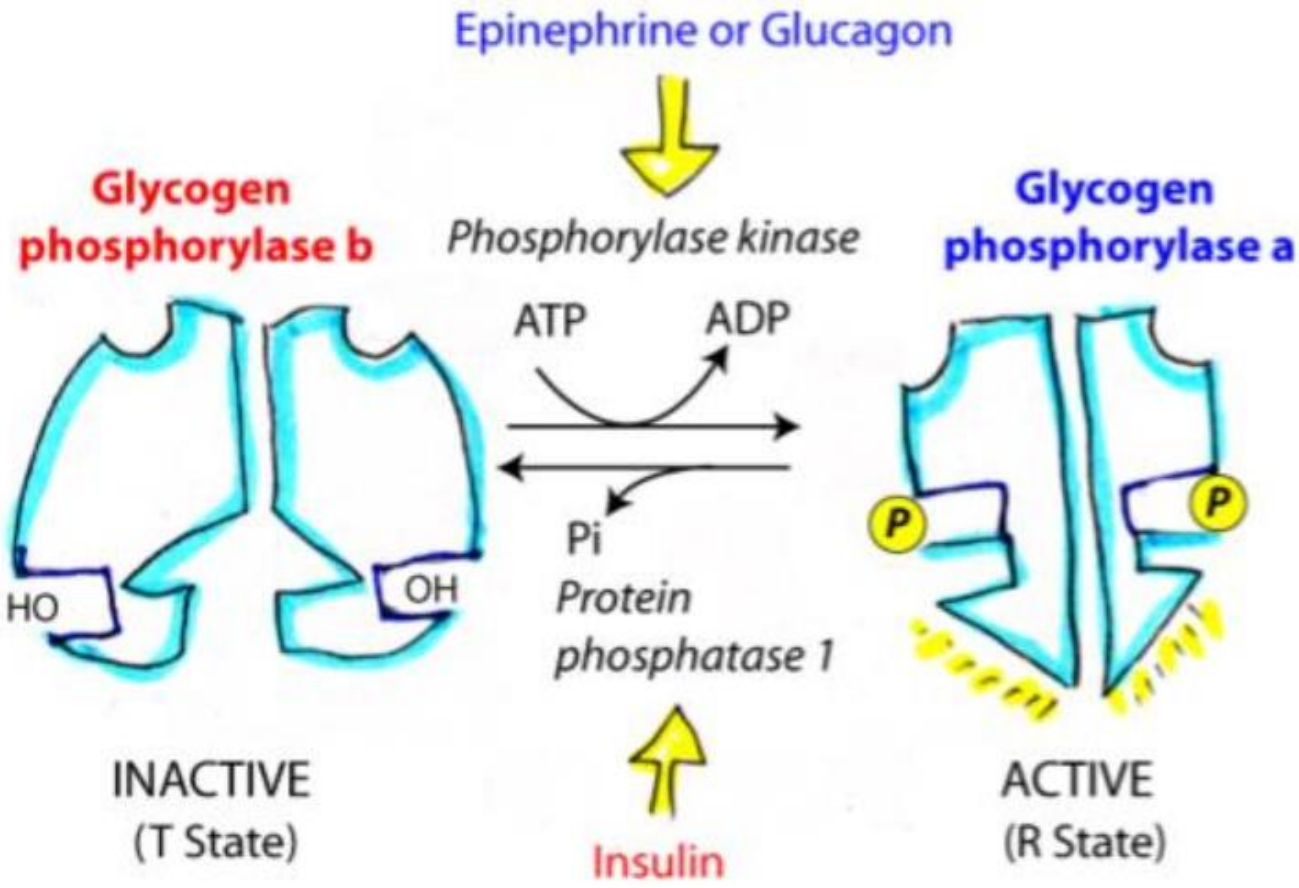

5
10
+H3N–His–Ser–Glu–Gly–Thr–Phe–Thr–Ser–Asp–Tyr–
15
20
–Ser–Lys–Tyr–Leu–Asp–Ser–Arg–Arg–Ala–Gln–
25
29
–Asp–Phe–Val–Gln–Trp–Leu–Met–Asn–Thr–COO−
Glucagon


Epinephrine (muscle) or glucagon (liver)
7TM receptor
Adenylate cyclase
GDP
GTP
α
β
γ
ATP
Cyclic AMP
Protein kinase A
Protein kinase A
Phosphorylase kinase
Phosphorylase kinase
Phosphorylase b
Phosphorylase a

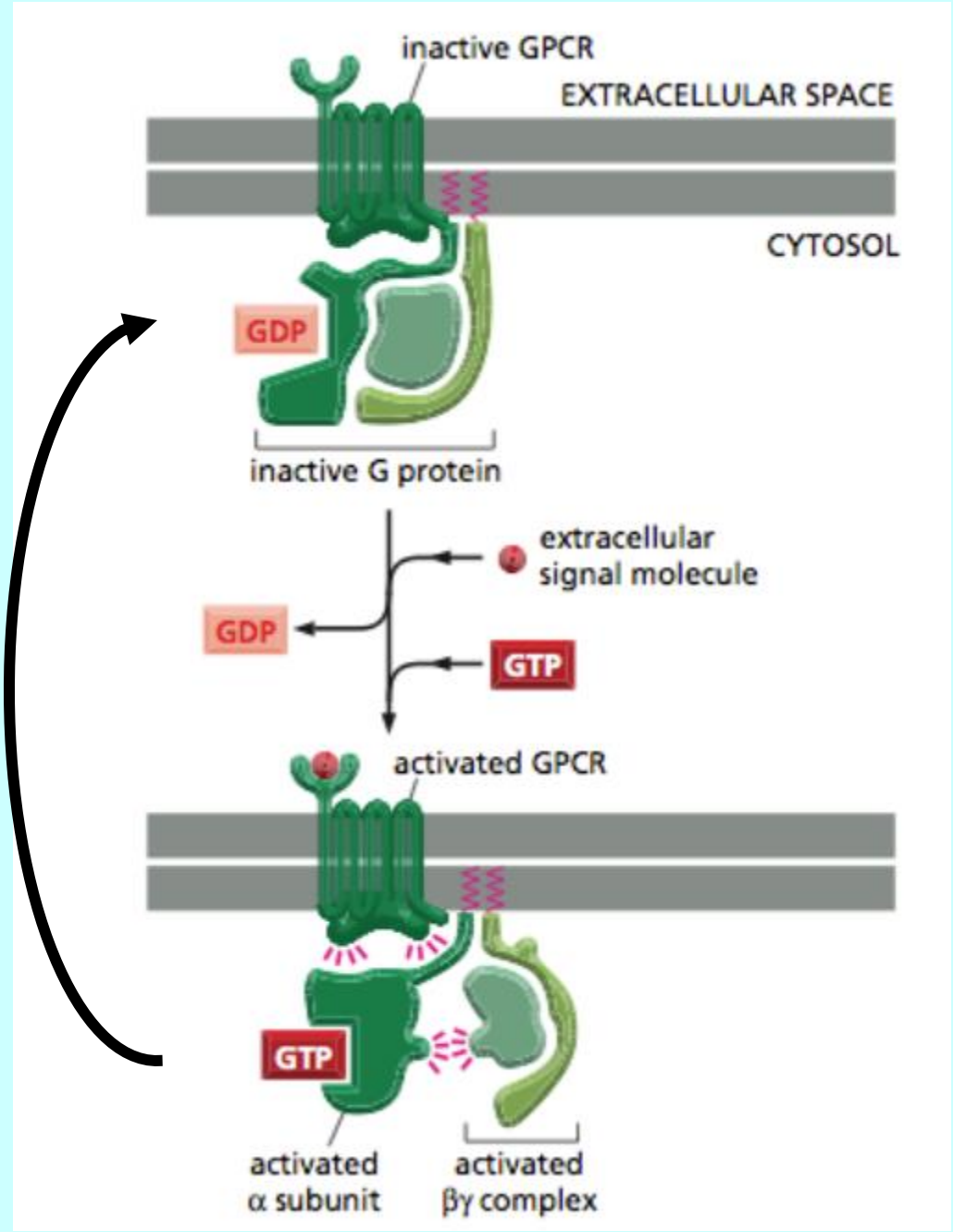

Glucagon/ Epinephrine
7-TM receptor
α
β
γ
GDP
α
GTP
Adenylate cyclase
ATP
cAMP
Protein Kinase A
Phosphorylase Kinase
Phosphorylase kinase
P
P
Glycogen Phosphorylase
Glycogen Phosphorylase (active)

Regulation of Glycogen Phosphorylase Activity

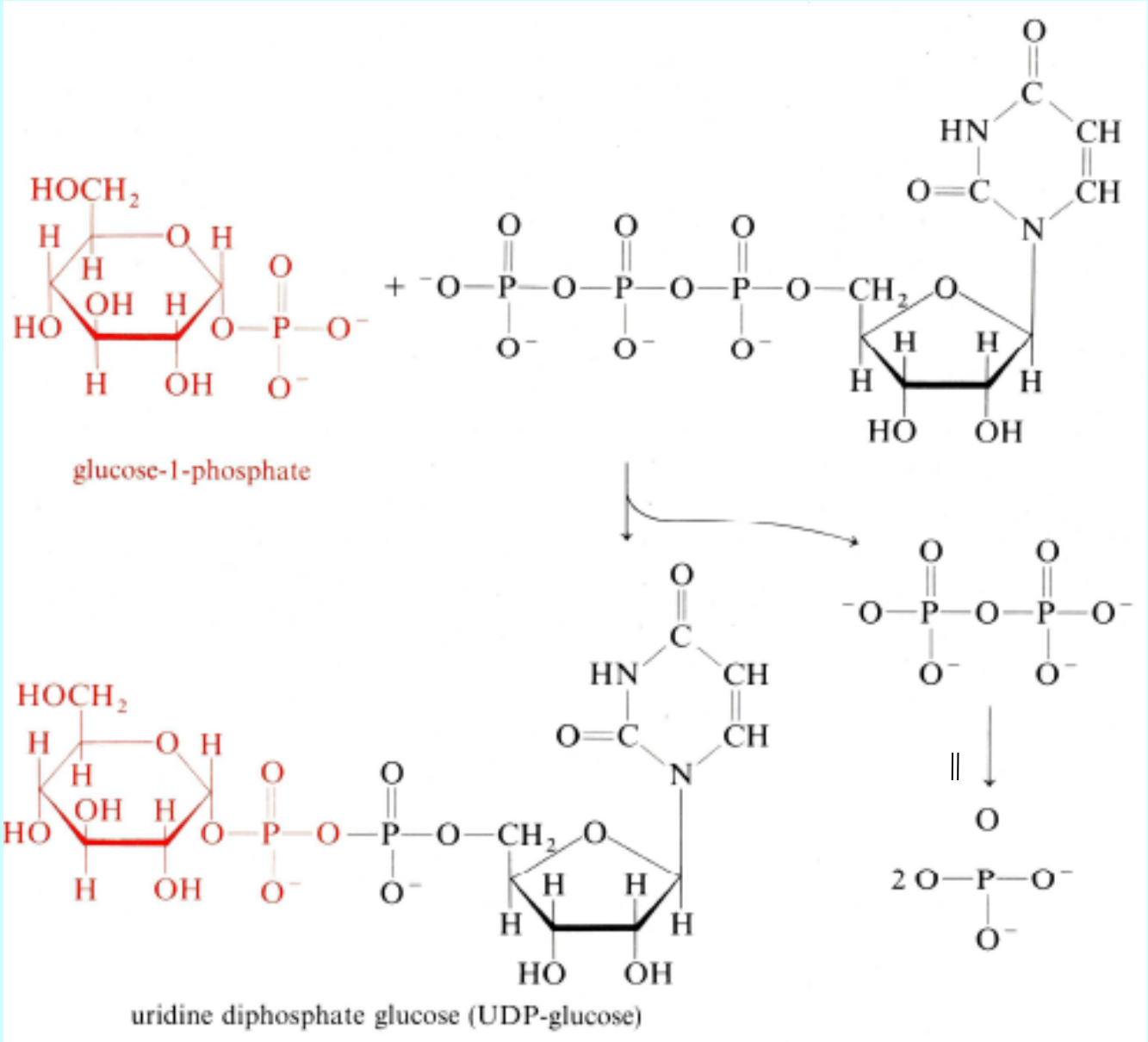
The enzyme responsible for phosphorylating glycogen phosphorylase b to activate it, is **phosphorylase kinase** which is a downstream target of glucagon and epinephrine signaling.

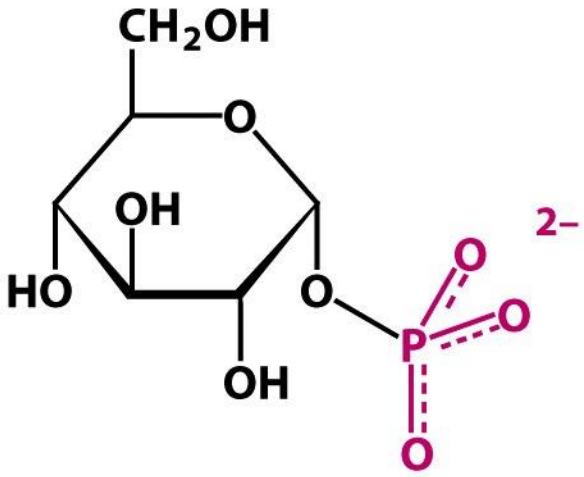


Atividade GTPasica



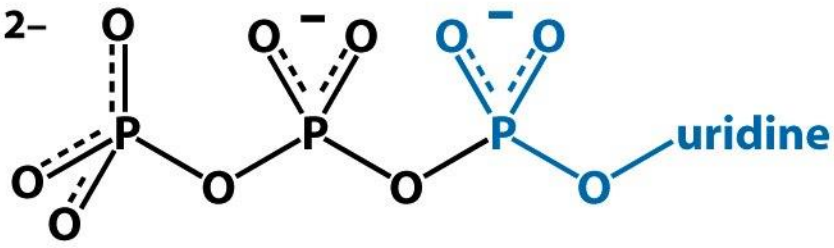
A síntese de glicogênio começa com a ativação da glicose-1-P em UDP-glicose



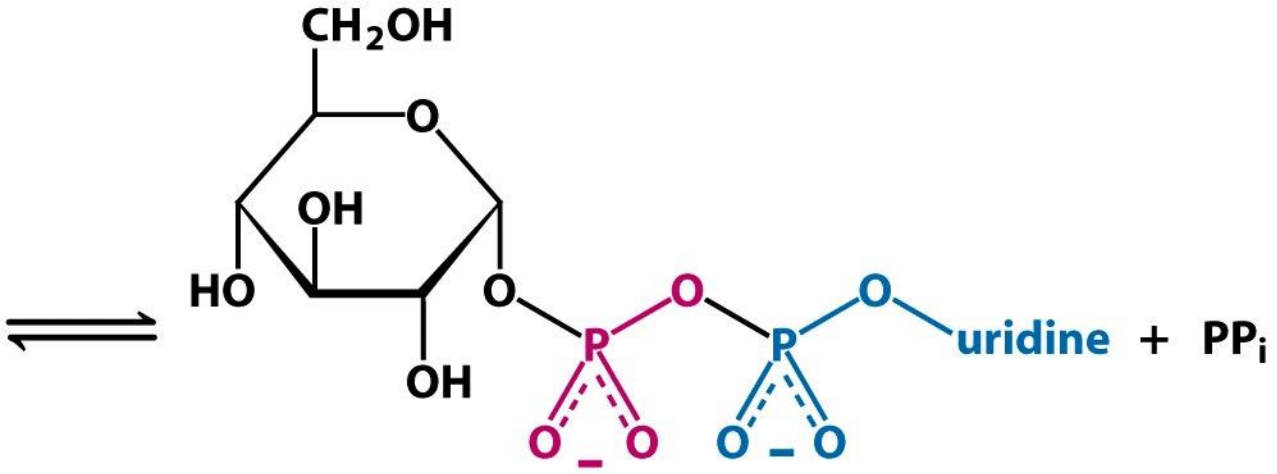


Glucose 1-phosphate

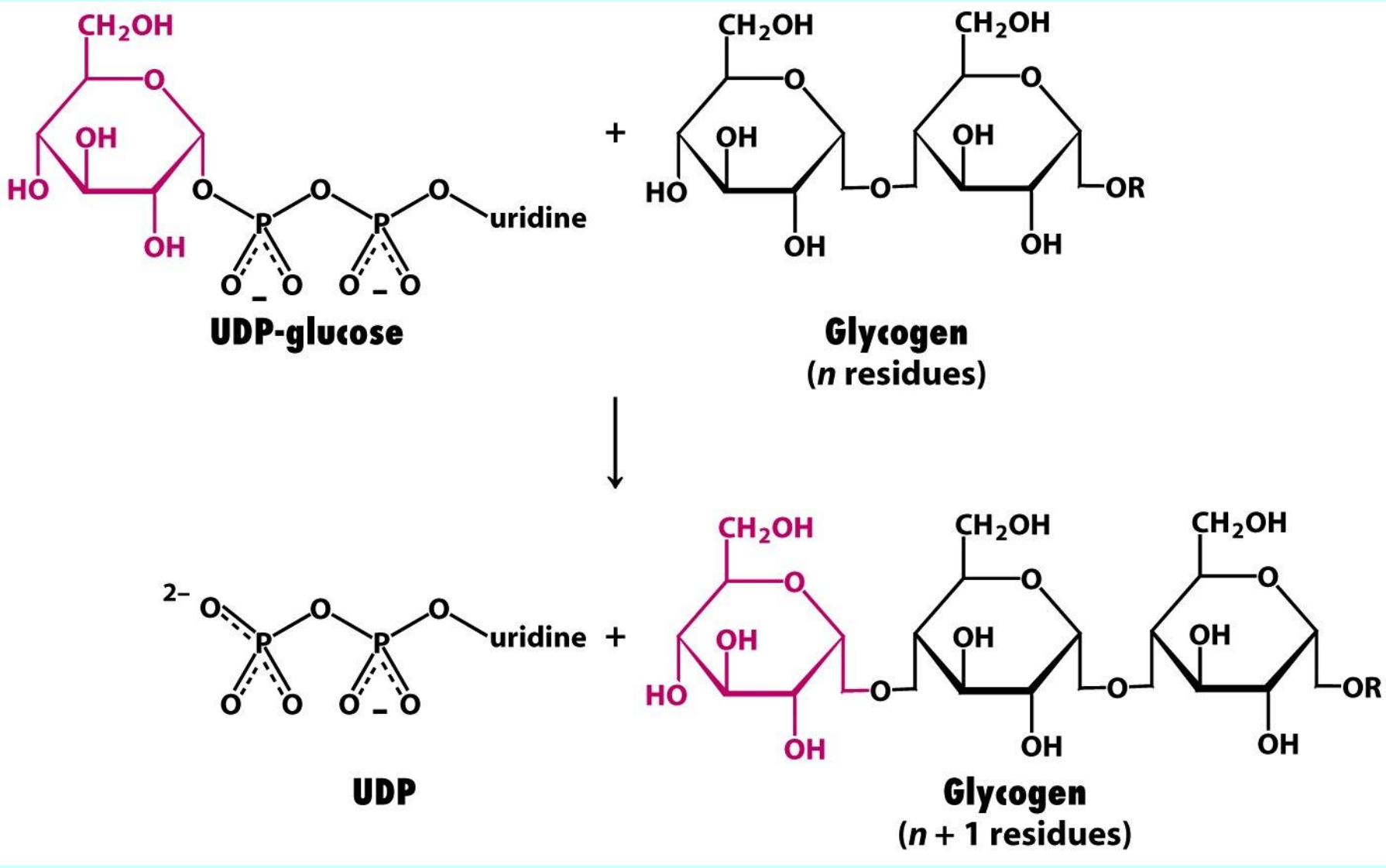
+



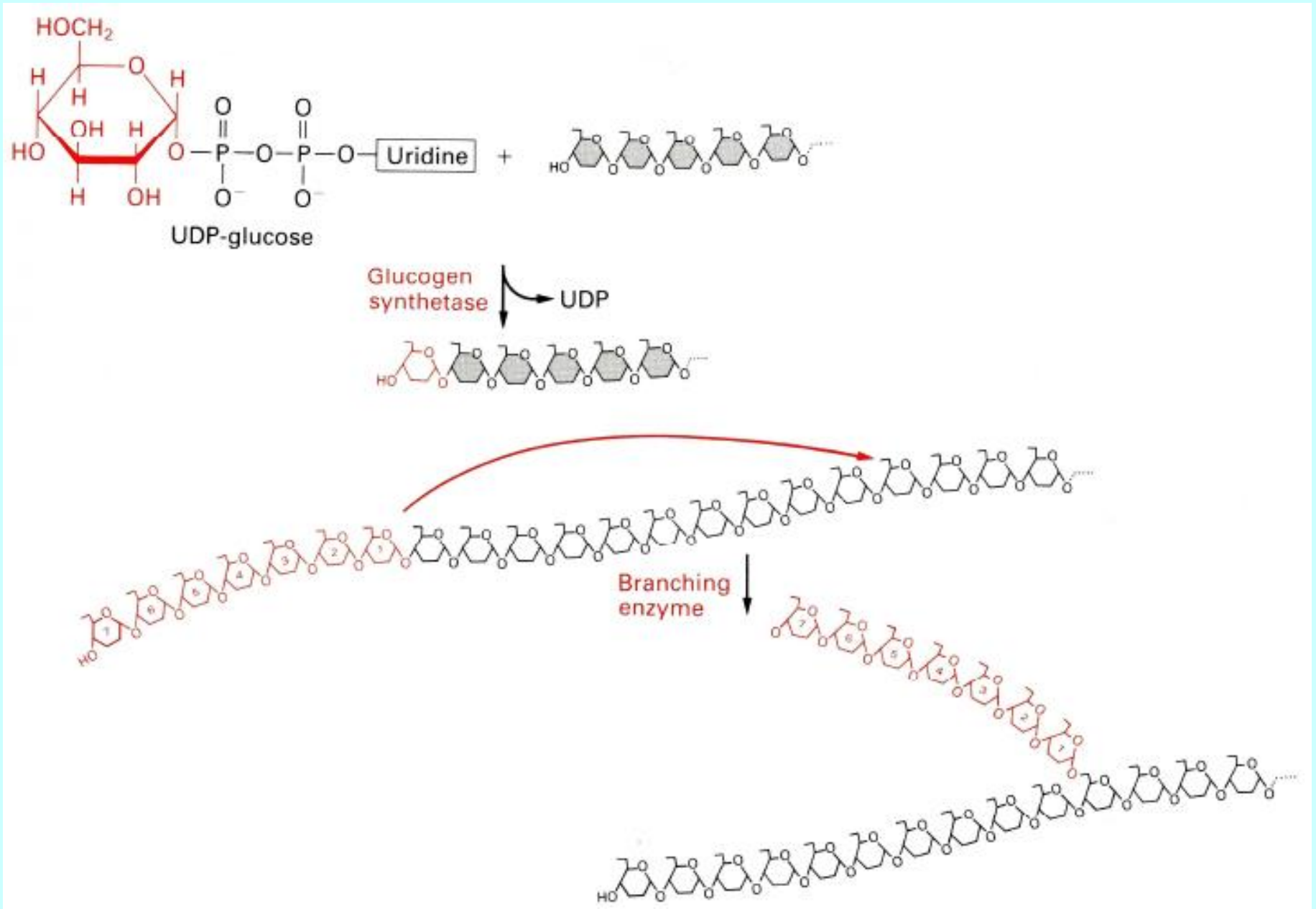
UTP

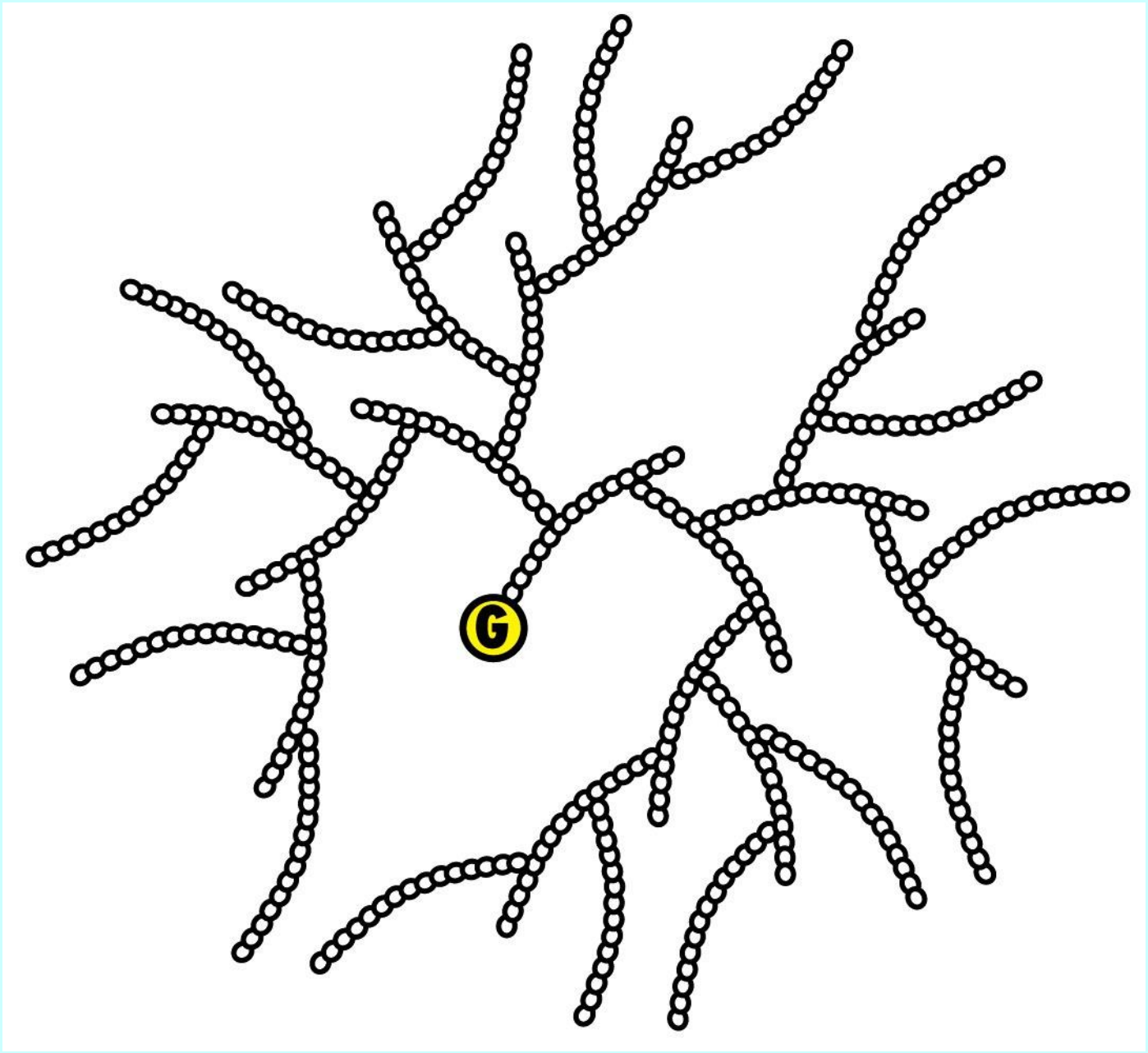


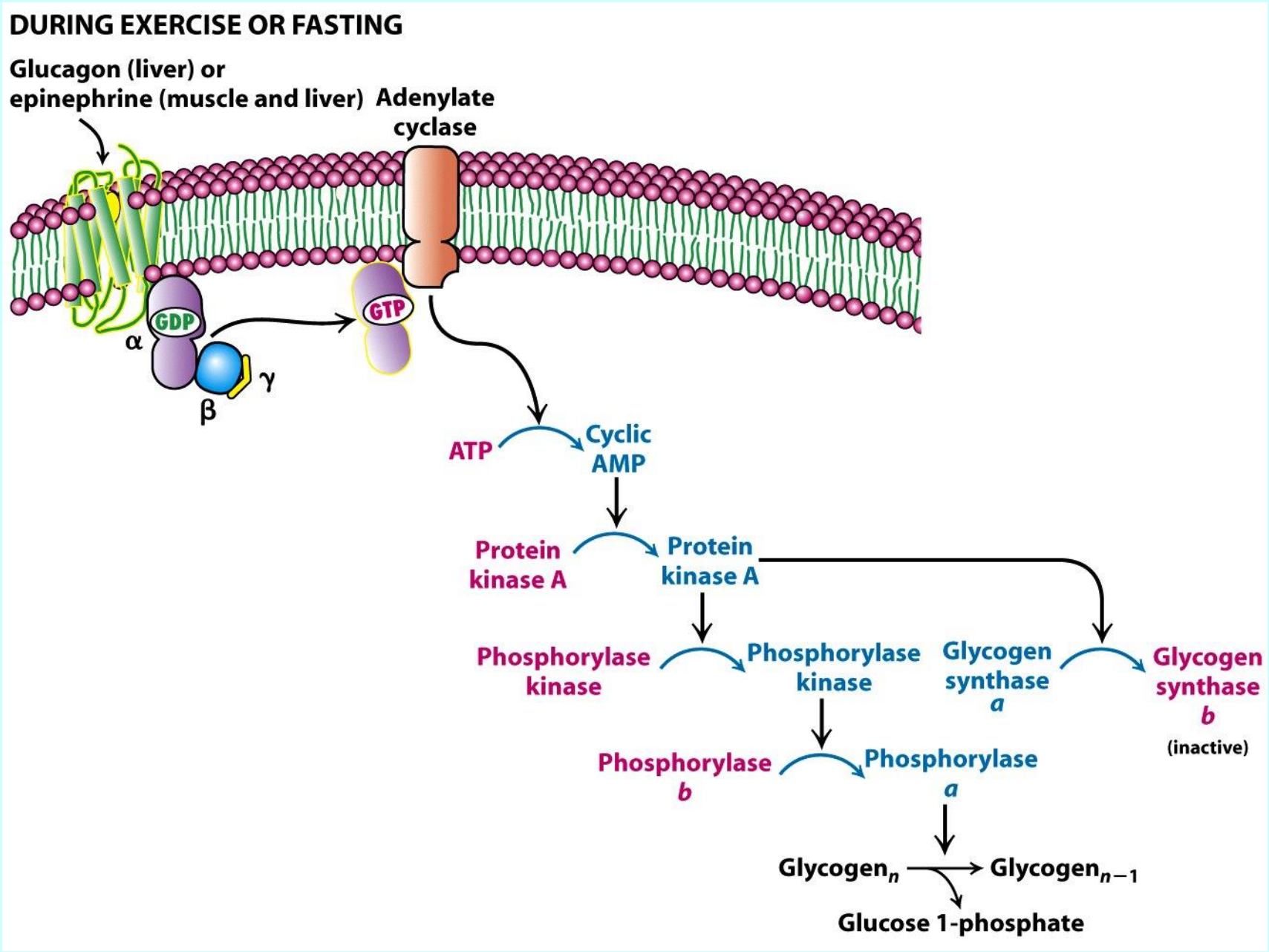
UDP-glucose

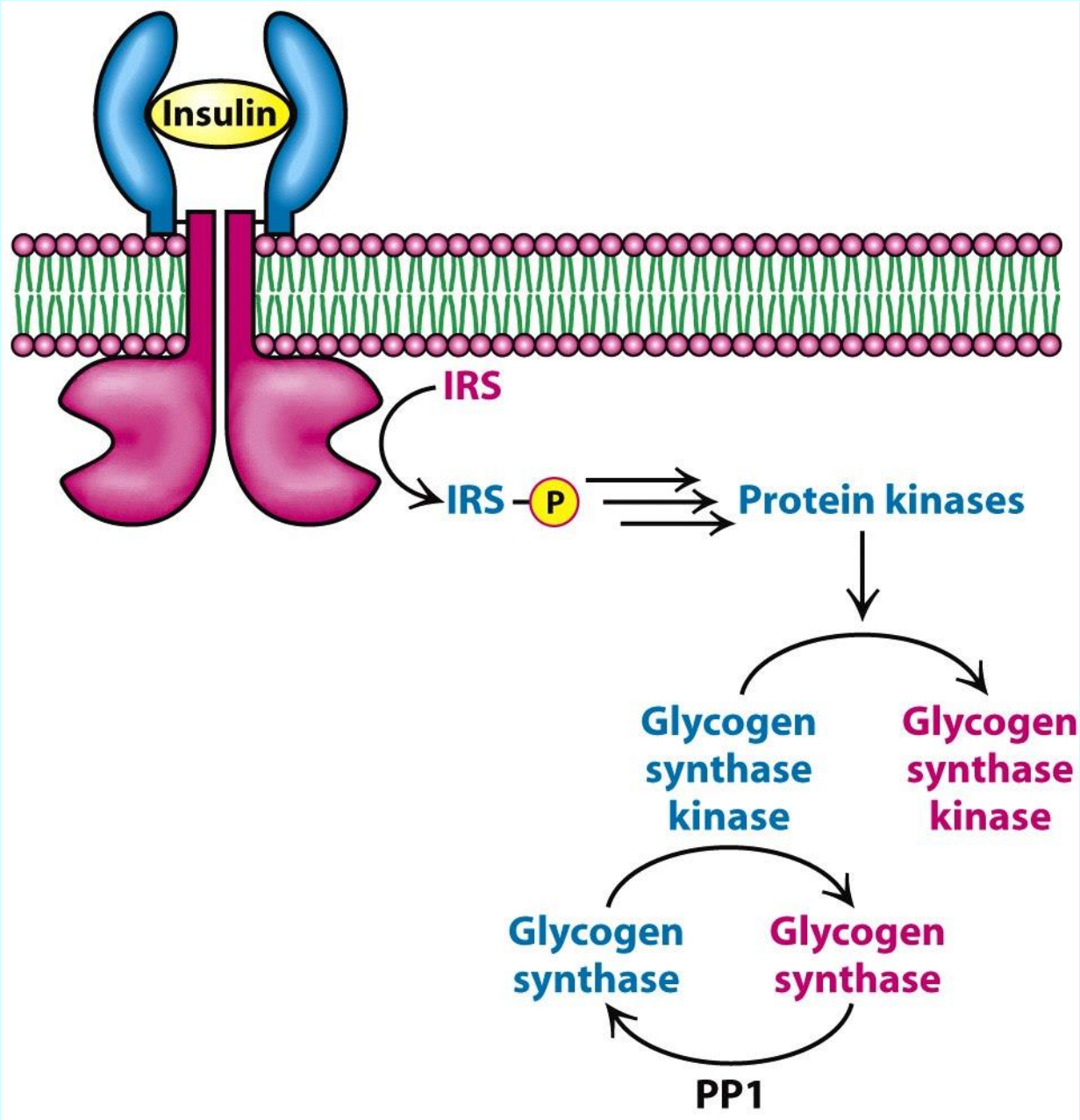

CH2OH
O
OH
HO
OH
O
P
O
P
O
uridine
O
O
O
O
UDP-glucose
+
CH2OH
O
OH
HO
OH
O
CH2OH
O
OH
OR
OH
Glycogen
(n residues)
2–
O
P
O
P
O
uridine
O
O
O
O
UDP
+
CH2OH
O
OH
HO
OH
O
CH2OH
O
OH
O
CH2OH
O
OH
OR
OH
Glycogen
(n + 1 residues)

Síntese de glicogênio: alongamento e ramificação

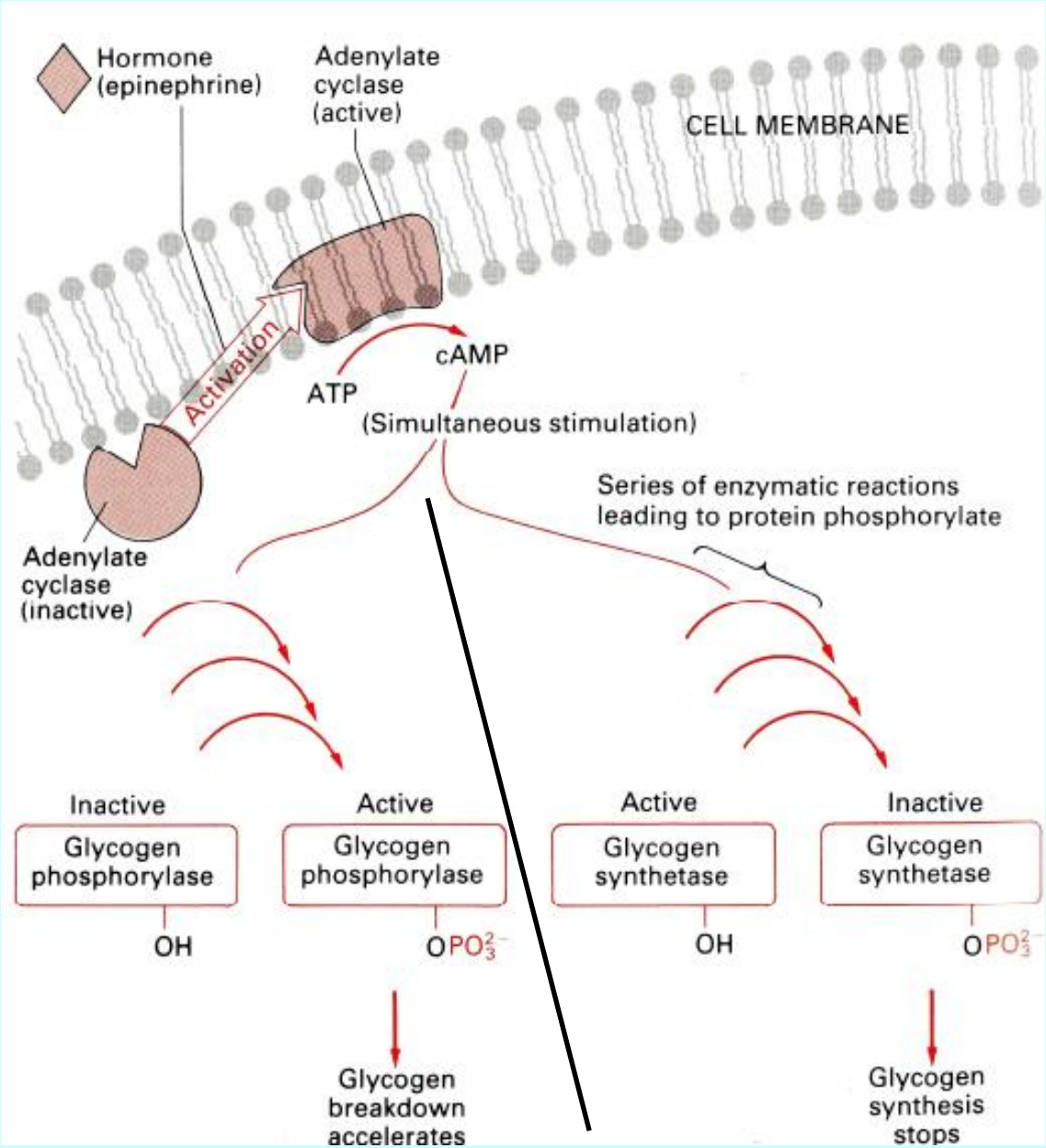


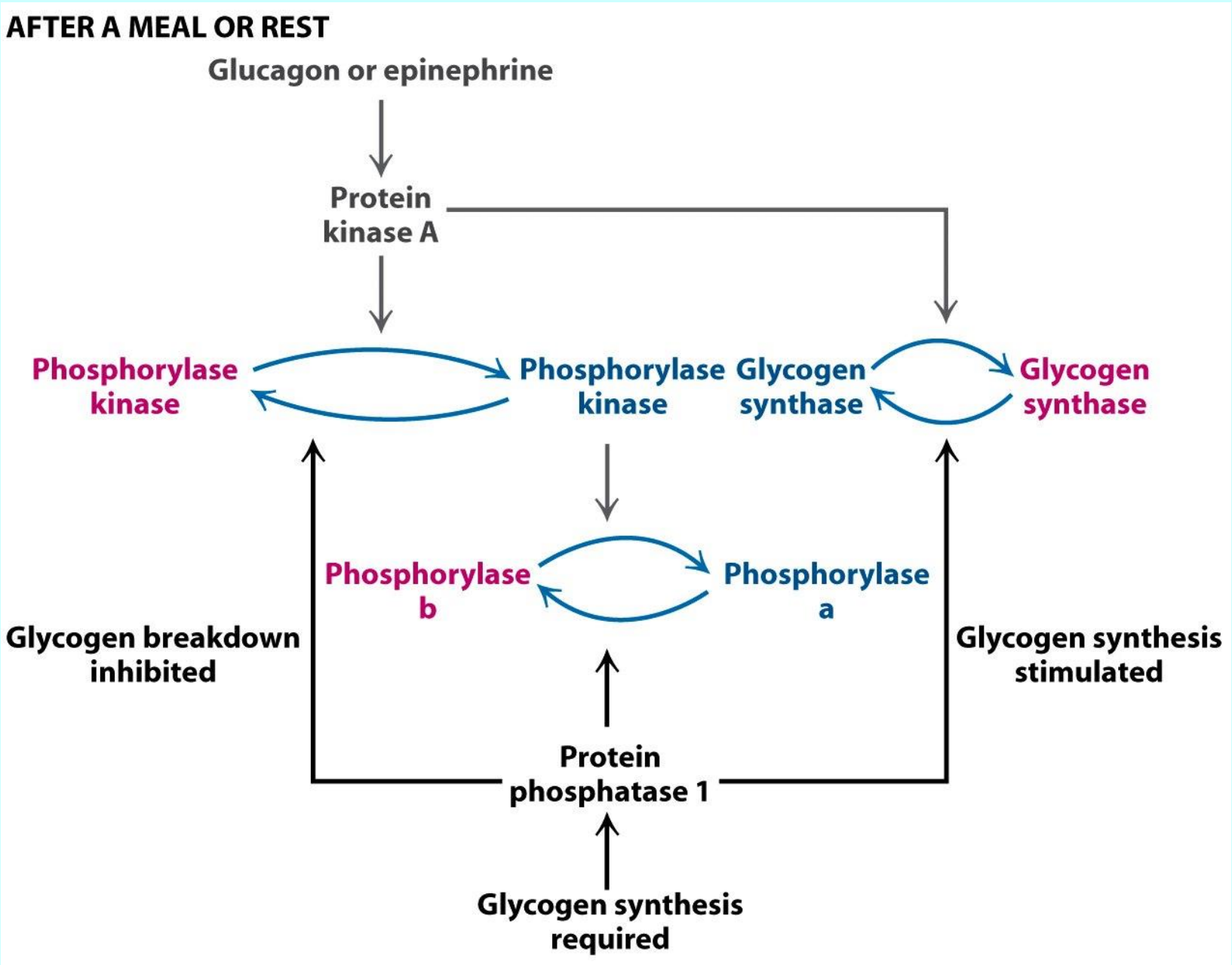

G


DURING EXERCISE OR FASTING
Glucagon (liver) or
epinephrine (muscle and liver)
Adenylate
cyclase
GDP
GTP
α
β
γ
ATP
Cyclic
AMP
Protein
kinase A
Protein
kinase A
Phosphorylase
kinase
Phosphorylase
kinase
Glycogen
synthase
a
Glycogen
synthase
b
(inactive)
Phosphorylase
b
Phosphorylase
a
Glycogen$_n$
Glycogen$_{n-1}$
Glucose 1-phosphate

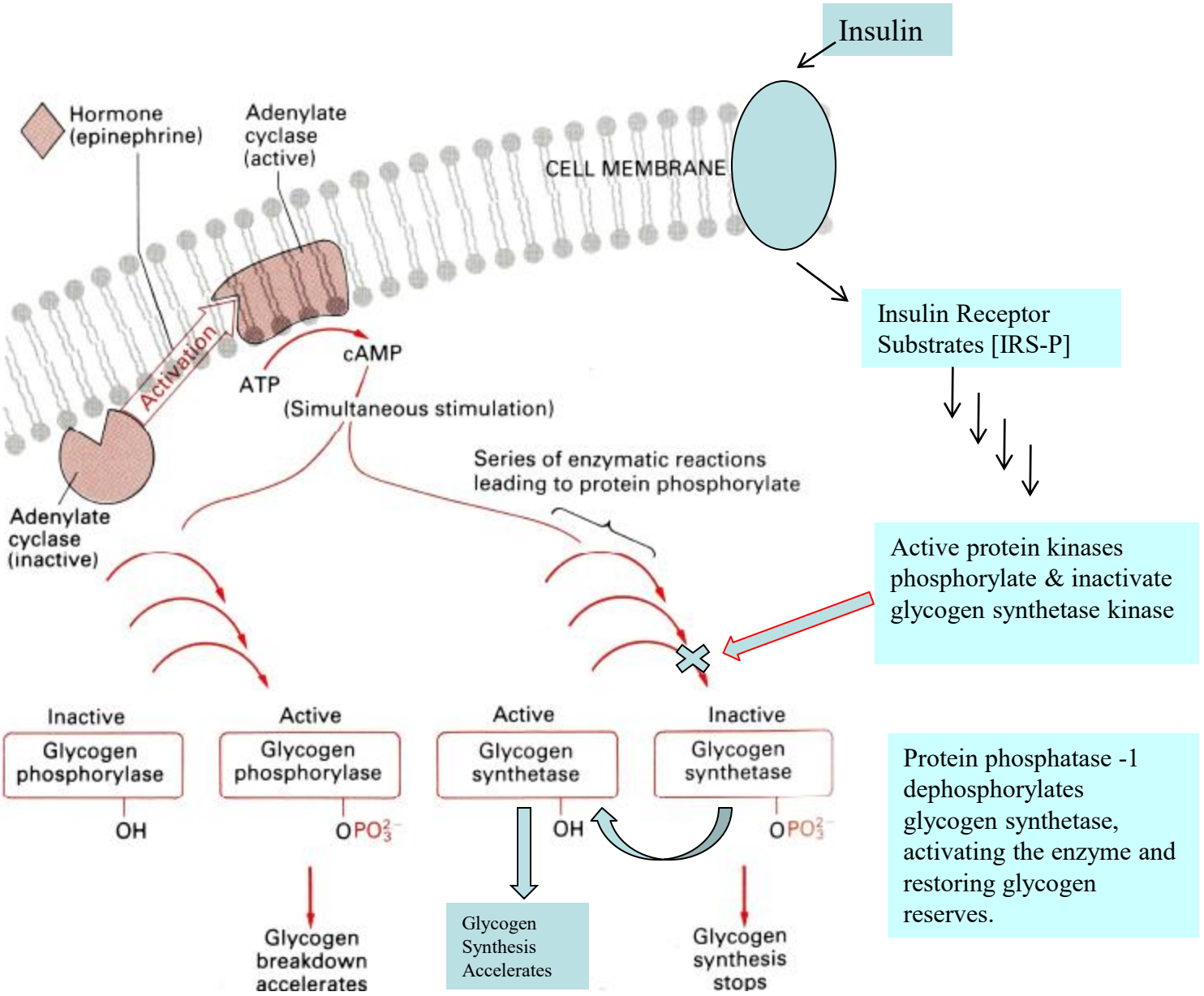

Insulin
IRS
IRS
P
Protein kinases
Glycogen synthase kinase
Glycogen synthase kinase
Glycogen synthase
Glycogen synthase
PP1

Regulação hormonal do metabolismo do glicogênio




AFTER A MEAL OR REST
Glucagon or epinephrine
Protein kinase A
Phosphorylase kinase
Phosphorylase kinase
Glycogen synthase
Glycogen synthase
Phosphorylase b
Phosphorylase a
Glycogen breakdown inhibited
Glycogen synthesis stimulated
Protein phosphatase 1
Glycogen synthesis required

Hormonal regulation of Glycogen Metabolism



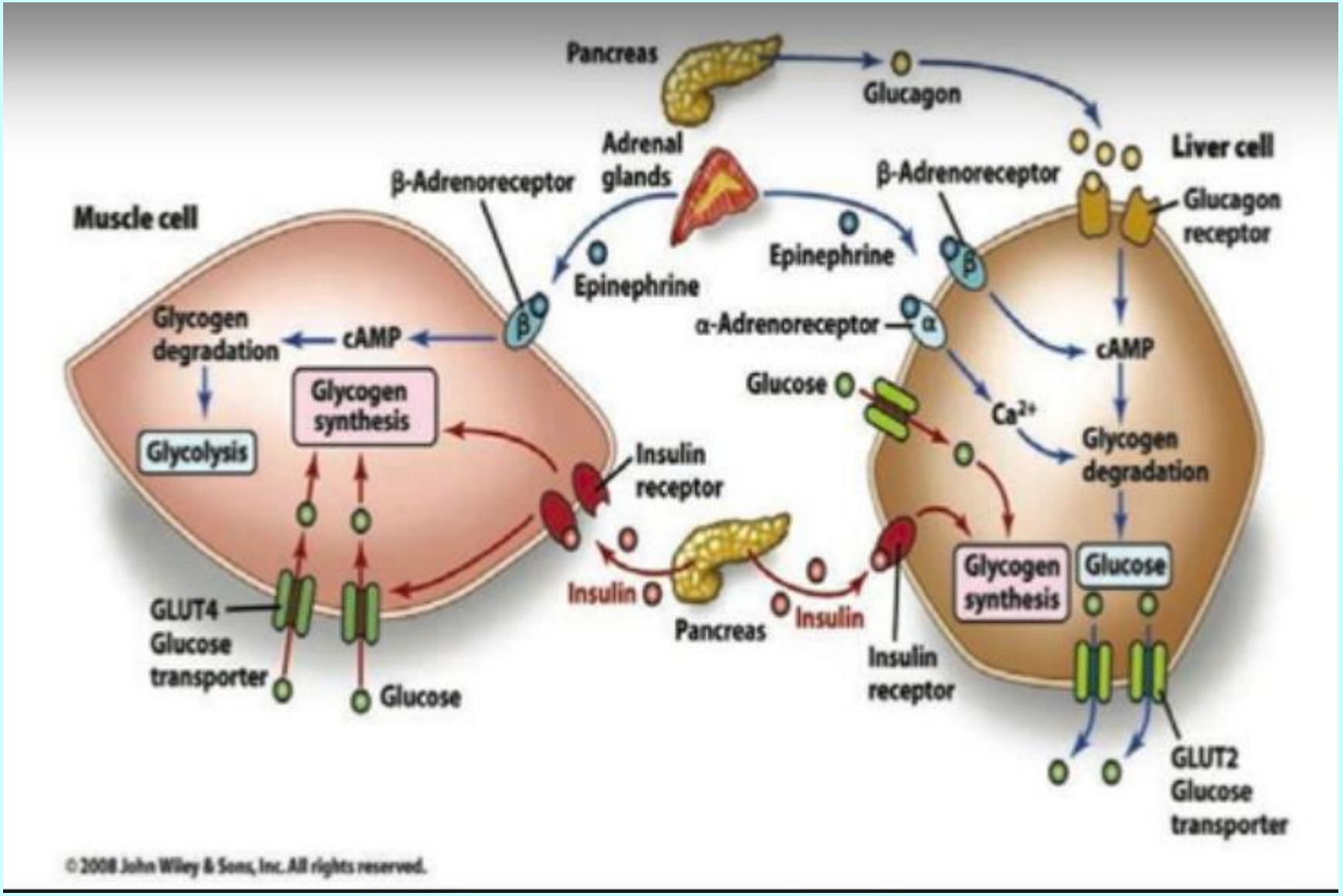

Pancreas
Glucagon
Adrenal glands
Liver cell
β-Adrenoreceptor
β-Adrenoreceptor
Glucagon receptor
Muscle cell
Epinephrine
Epinephrine
Glycogen degradation
cAMP
α-Adrenoreceptor
cAMP
Glucose
Glycogen synthesis
Ca2+
Glycolysis
Glycogen degradation
Insulin receptor
Insulin
Pancreas
Insulin
Glycogen synthesis
Glucose
GLUT4 Glucose transporter
Glucose
Insulin receptor
GLUT2 Glucose transporter
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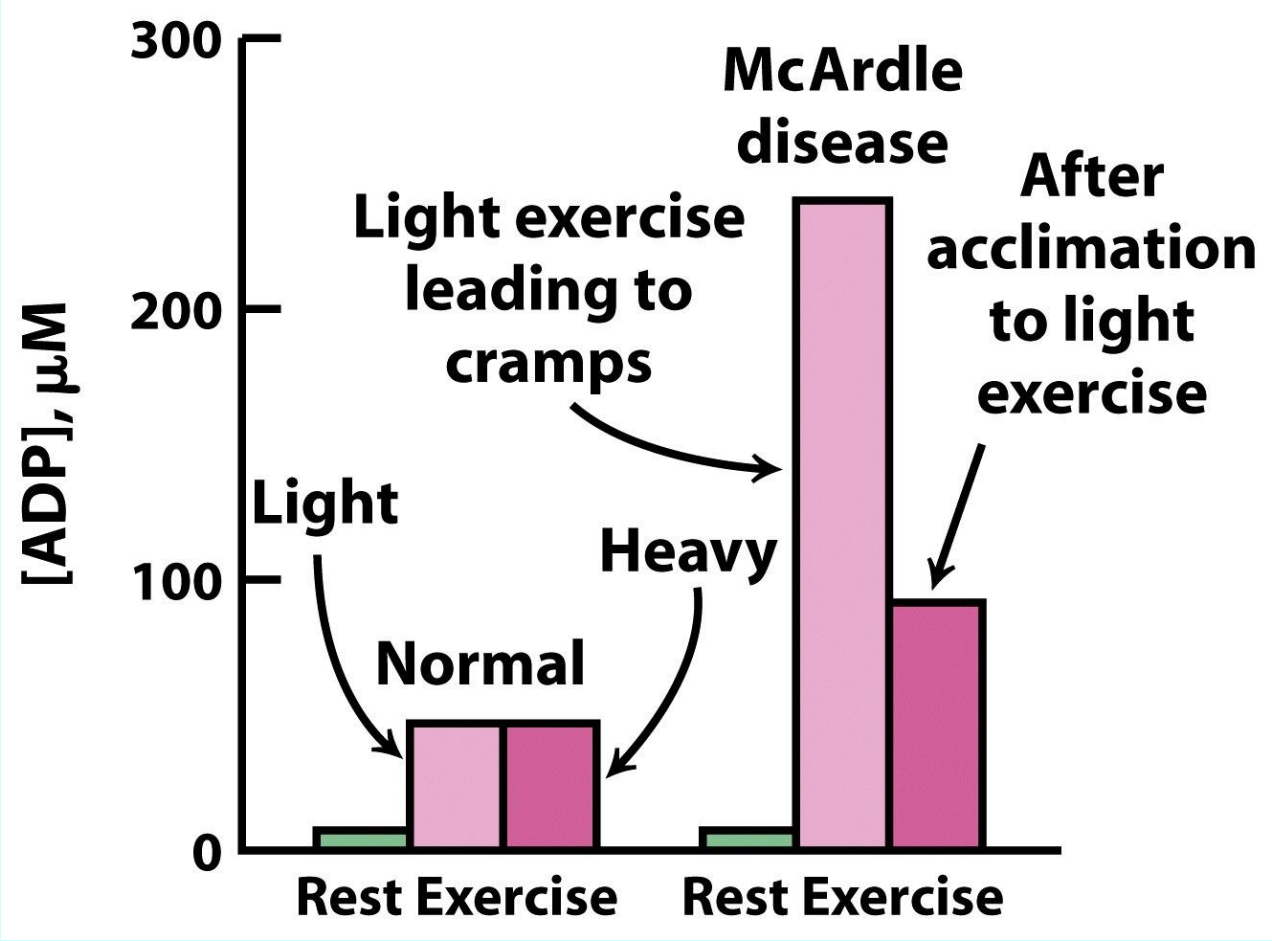
TABLE 21.1 Glycogen-storage diseases

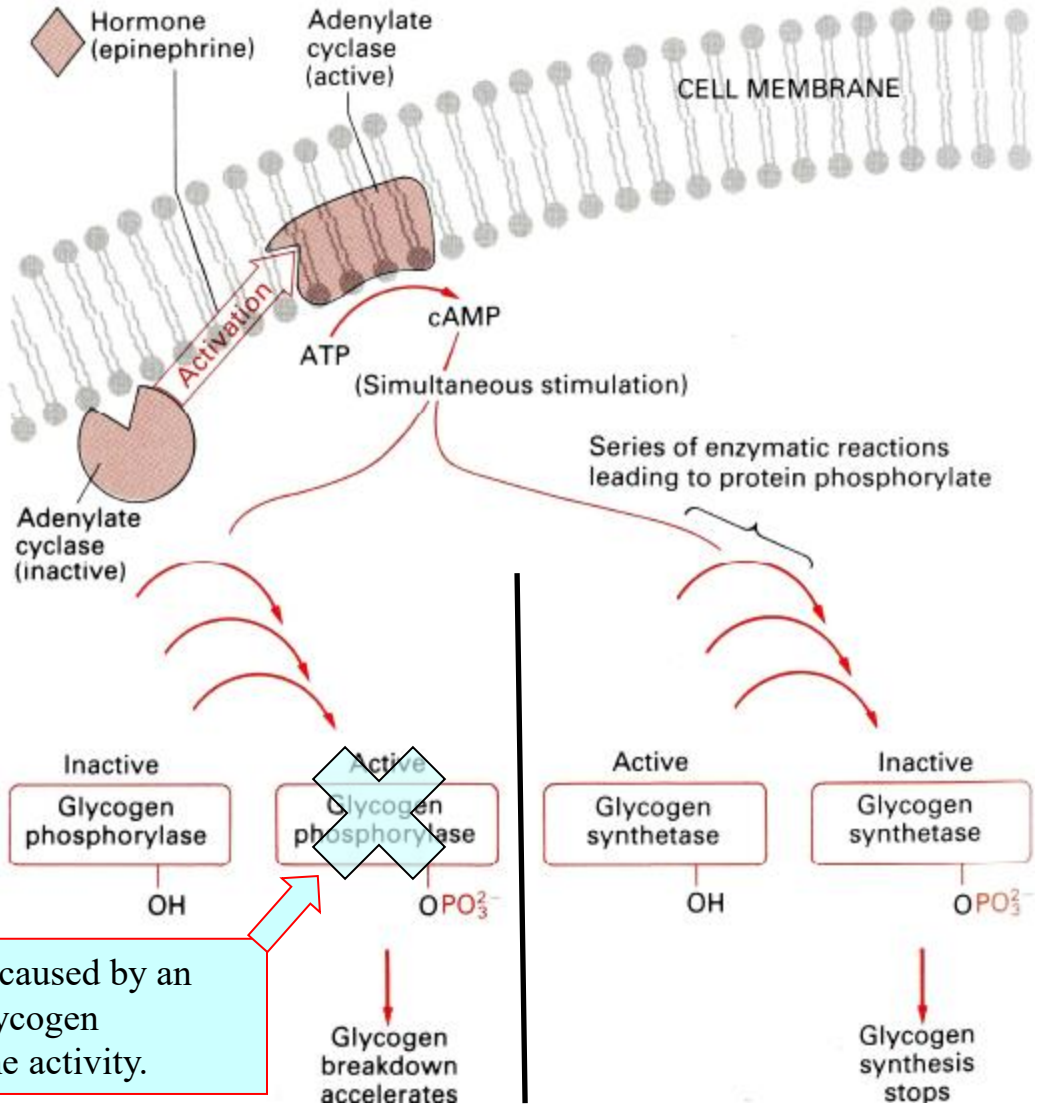
Type	Defective enzyme	Organ affected	Glycogen in the affected organ	Clinical features
I Von Gierke disease	Glucose 6-phosphatase or transport system	Liver and kidney	Increased amount; normal structure.	Massive enlargement of the liver. Failure to thrive. Severe hypoglycemia, ketosis, hyperuricemia, hyperlipemia.
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.

Estudos de ressonância magnética (RMN-31P) mostram níveis elevados de ADP em células musculares de pacientes com doença de McArdle

A causa da Síndrome de McArdle é um gene defeituoso que produz uma enzima chamada glicogênio fosforilase





McArdles' disease is caused by an absence of muscle glycogen phosphorylase enzyme activity.

Subsequently, glycolytic activity slows and ADP accumulates. Creatine phosphate is hydrolyzed during strenuous exercise, yielding a more alkaline environment in muscle cells.