Biochemistry

Title = Metabolism of
Lec no = 9
Done By = Baraa Safi

وقل رب زدني علما

Metabolism of glycogen

Ahmed Salem, MD, MSc, PhD, FRCR

CHO metabolism	*1. Glycolysis* *a. First phase* *b. Second phase* *2.Pentosephosphate pathway* *3.Metabolism of non-glucose sugars* *a.metabolism of fructose.* *b.metabolism of galactose* *c.metabolism of glucuronic acid* 3. Glycogen metabolism a. Glycogen synthesis b. Glycogen breakdown

GLYCOGEN METABOLISM

- Glycogen is the major storage form of carbohydrates in cells
- It is stored in the cytosol as **granules** (all enzymes are cytoplasmic)
- It is present in every cell (but more abundant in liver, muscle):
  - **Muscle glycogen (1-2g/100g; appx 400-500g in total):** provide rapidly available supply of glucose as fuel for glycolysis during contraction (muscle use only)
  - **Liver glycogen (6-10g/100g; appx 100-120g in total):** maintaining blood glucose levels during fasting (for whole body)

Its metabolism involves two processes:

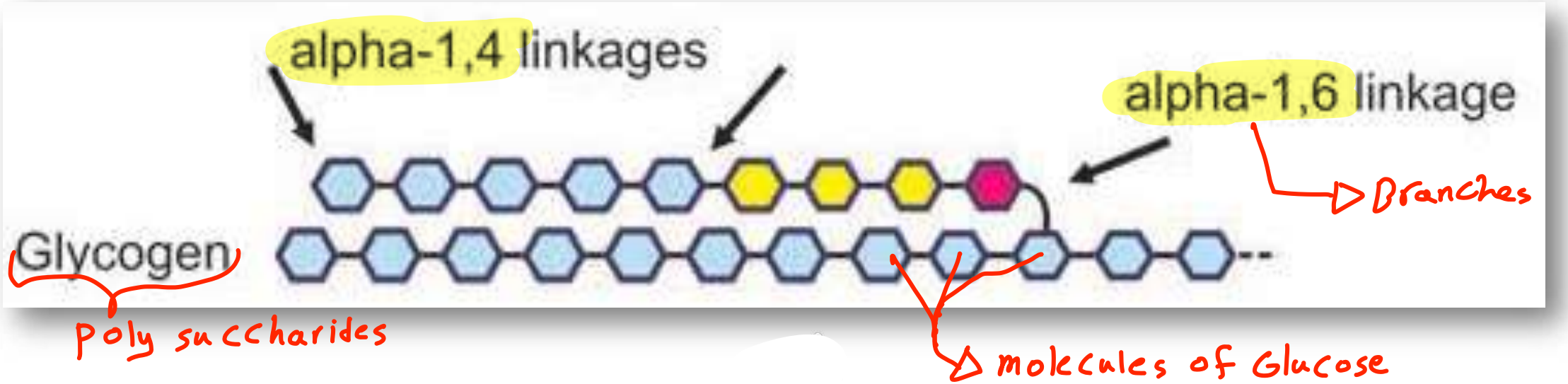
I- Glycogenolysis (Glycogen breakdown)
II- Glycogenesis (Glycogen formation)

في ٣ مخازن في الجسم: 1) (glycogen) 2/ fat 3/ Amino acid

* هاد صحيح كـ (concentration) هو في الـ (muscle) أقل لكنه لما تحسب كمية الـ (glycogen) اللي موجودة بالجسم اللي بالـ (muscle) رح تلاقيها أكثر من اللي بالـ (liver) (400 – 500)

* في فرق بين الـ (glycogen) اللي بالـ (muscle) والـ (liver) :- اللي بالـ (muscle) ثانية مهما بصير حالها (الطاقة بس بستفيد منها الـ (muscle) أما الـ (liver) كريم جدًا لذلك هو بيعطي كل الجسم فبحافظ على مستوى السكر بالدم فبخدم كل الجسم

* (كل الشغلات اللي الها علاقة بالجلايكوجين تتم في الـ (cytoplasm)


alpha-1,4 linkages
alpha-1,6 linkage
Branches
Glycogen
Poly succharides
molecules of Glucose

تكسير الجلايكوجين يتبدأ بعد(4) ساعات من الوجبة ويستمر تقريبا لحد(18) ساعة بعدها بخلص مخزون الجلايكوجين فلازم نفوت بخاصية ثانية عشان نحافظ على مستوى السكر بالدم

Glycogen breakdown (glycogenolysis)

- Starts 4 h after meal (fasting), lasts 12-18h

- Occurs in cytoplasm of cells (except RBCs; does not store glycogen):
  - ***In liver:*** glycogen is hydrolysed to **glucose** to maintain blood glucose level
  - ***In muscle:*** glycogen is hydrolysed to **glucose 6-P** → glycolytic pathway to generate ATP

- Glycogenolysis is catalysed:
  - 1st by ***glycogen phosphorylase*** → glucose 1-P
  - Then by ***debranching enzyme*** → liberate (تحرير) free glucose

Steps of glycogenolysis (enzymes)

1. Glycogen phosphorylase

2. Debranching enzyme (bi-functional)
    A. Glucan transferase
    B. α 1,6 glucosidase

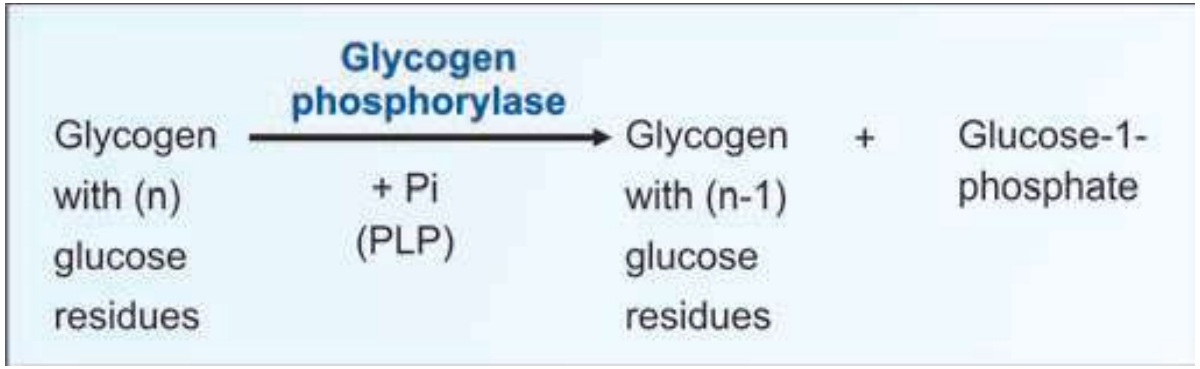
3. Phosphoglucomutase

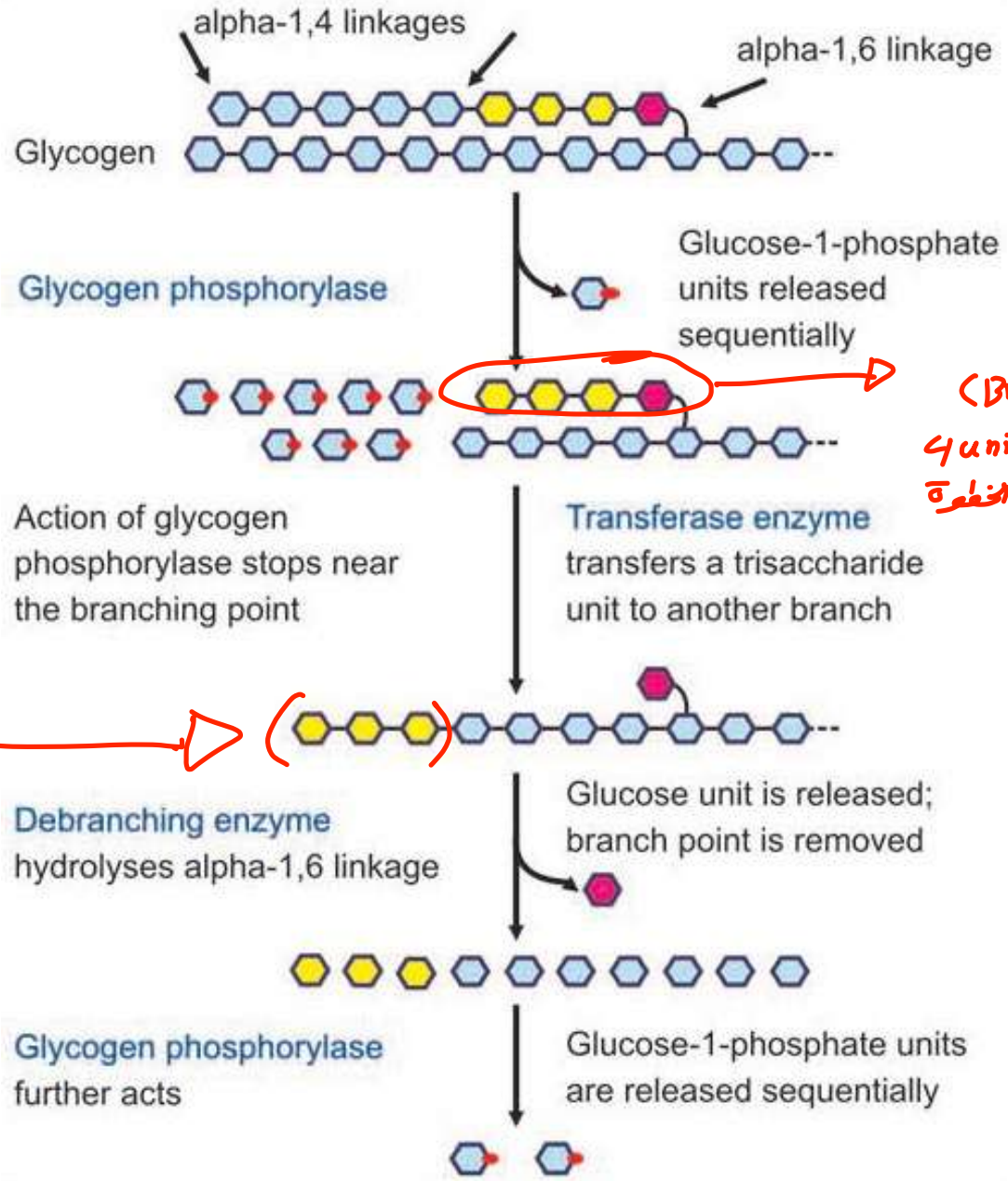
4. Glucose-6 phosphatase

1. Glycogen phosphorylase

- Catalyses release of glucose 1-P from terminal residue of glycogen by adding inorganic phosphate (phosphorolysis)
    - Glycogen phosphorylase contains pyridoxal phosphate as an integral coenzyme

- The action of glycogen phosphorylase stops when 4 glucose residues are left from the branching point

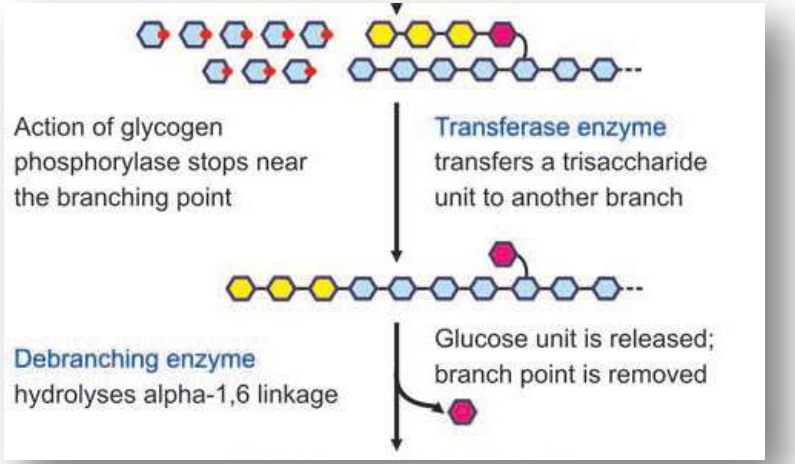




(Branch) ضل
4units تكونه من
هنا نتوقف من الخطوة
الأولى

2. Debranching enzymes

- Glucan transferase
  - It transfers the outer 3 glucose units from the branching point & attaches them to the nearest straight chain
    - This is important to unmask the α 1,6 glucosidic bond at the branching point



- α 1,6 glucosidase
  - This enzyme removes the last glucose residue at the branch point
    - » This glucose residue is released as **free glucose**

- → both these enzymes will together convert the branched chain into a linear one
  - » With removal of branches, phosphorylase can proceed with its action

* الأشياء التي تنتج عن (Glucan transferase) :-

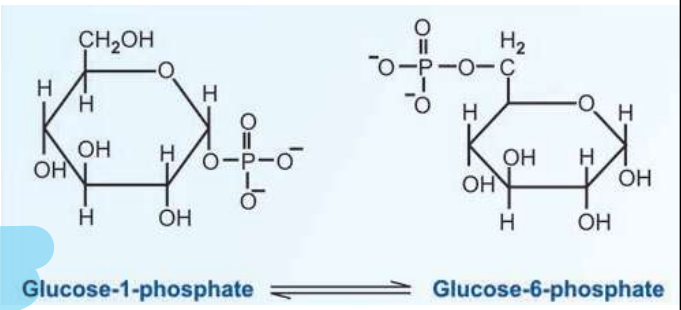
1) بسمح للـ (phosphorelase) أنه يشتغل لأنه نقلت الـ (حلقة) لـ (Chain) قريبة ومستقيمة .

2) بعمل (unmasking) لحبة البلوكوز اللي باللون الأحمر فبسمح للإنزيم الثاني يشتغل ويطلع الـ (free glucose) .

mutase = conversion

(Position) ل (Position) من (phosphate) بنقل

3. Phosphoglucomutase



- This enzyme converts glucose 1-P to glucose 6-P

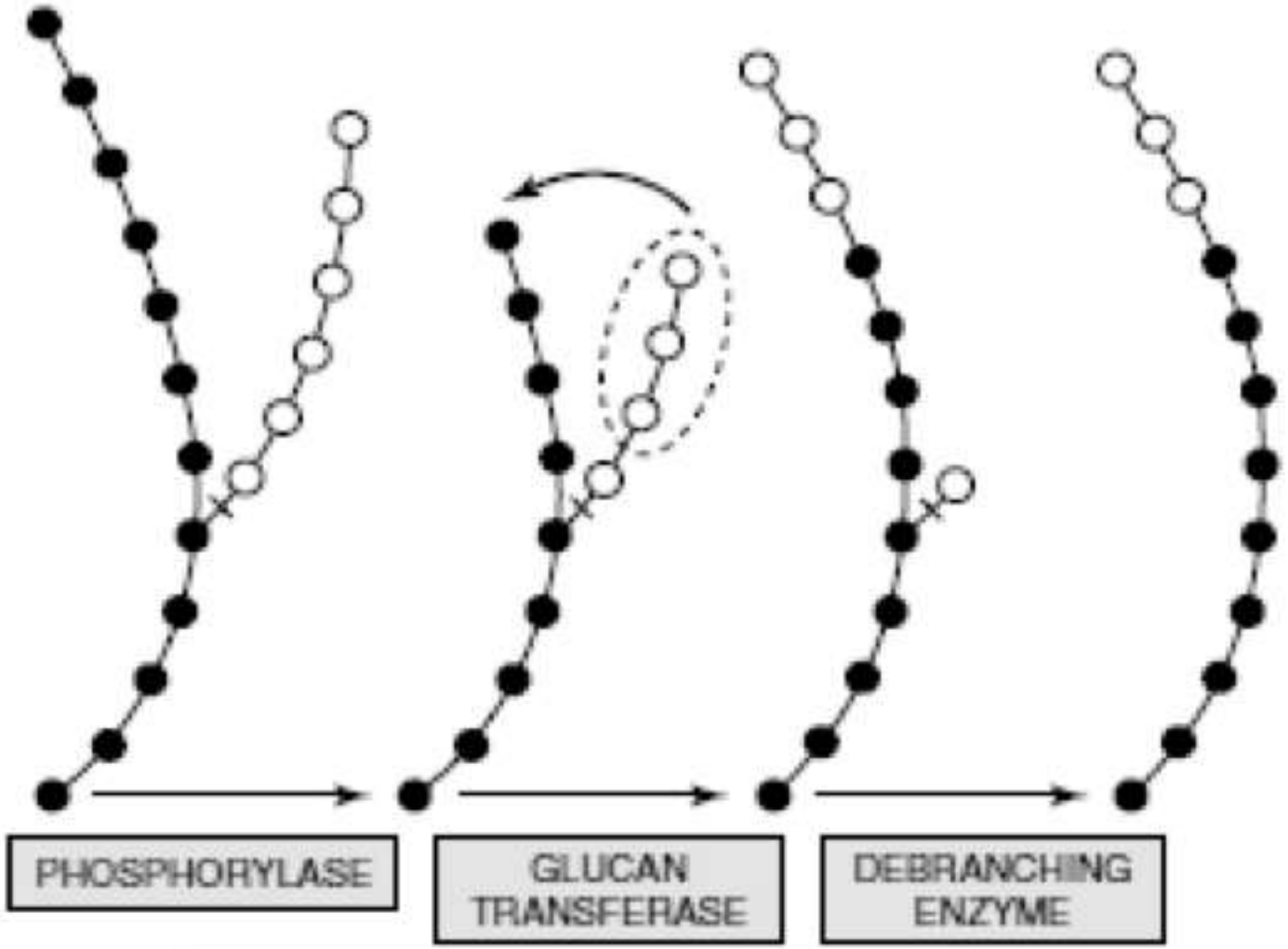
4. Glucose 6-phosphatase

- Converts glucose 6-P to free glucose
  - **It is present mostly in the liver**
  - The product of glycogenolysis is free glucose which is released in the blood
- **Muscle lacks this enzyme:**
  - » Glucose will not be released into blood
  - » Glucose 6-P undergoes glycolysis to produce lactate and ATP for ms contraction

Energy yield (anaerobic):

- Glucosyl unit derived from glycogen → 3 ATP
- Glycolysis starts from glucose → 2 ATP

* أنت لوجايب (Glucose molecule) من (Glycogen) رح تعطيك (3ATP) ولكنه لو مبلش من (Glucose) مش عنه طريق السبب أنه مهوني بتبلش منه (2ATP). رح ينتج عندنا (Glycogen) (Glucose-6-P)


PHOSPHORYLASE
GLUCAN TRANSFERASE
DEBRANCHING ENZYME

(Glycogen) بناء

GLYCOGENESIS

* تكوين (Glycogen) من أو إلى (glucose) المكونة الأساسية تاعه أو (hexoses)

- It is the formation of glycogen from glucose or other hexoses

- It occurs in the cytosol of cells (except RBCs) especially in *liver* & *muscles*

- **Importance:** Storage of excess glucose, or other hexoses taken in food

Steps of glycogenesis

uracil diphosphate glucose

1. Activation of glucose + formation of UDP glucose*

جلوكوز متأكتن بسمحلنا أنه هو يكونه ال (Building blocks) لل (Glycogen)

2. Addition of glucosyl residues

نضيف (glucose molecules) للمركب تاعنا

3. Formation of branches

*UDP glucose: uracil diphosphate glucose → nucleotide sugar made from pyrophosphate group, pentose sugar ribose, glucose, and nucleobase uracil

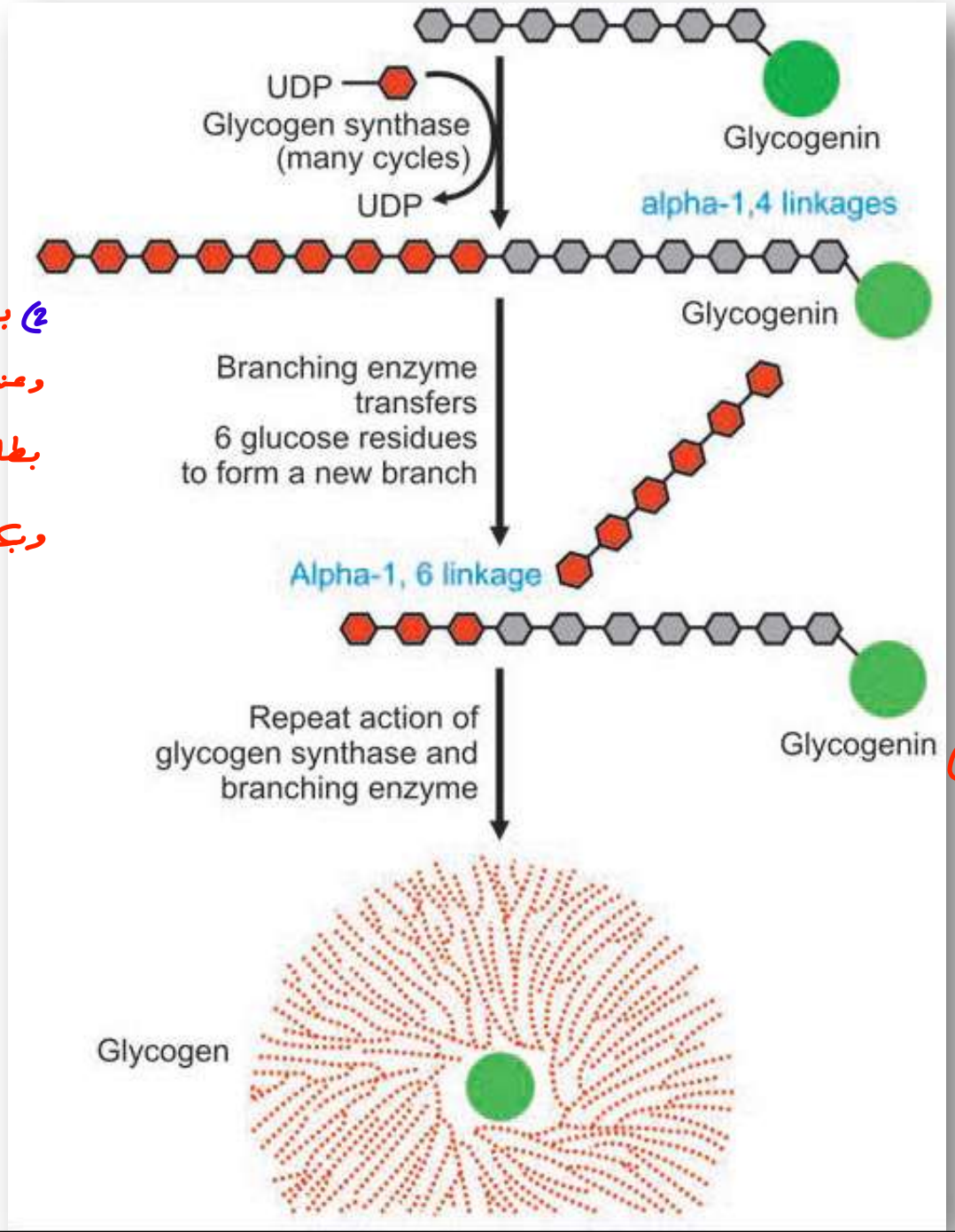
- involved in formation of glycoproteins
- glycogen precursor
- nucleotide sugar metabolism

صورة في (3) شغلات:

1) محتاج اشي اسمه (Glycogen primer) آو (Glycogenen) هذا بروتين بنبني منه خلاله البلايكوجين

2) بغوت على هذا البلا يكوجينين (UDP glucose) وعنطريت انزيم اسمه (Glycogen synthase) بطلع الـ (UDP) لبرا وبضل الـ (Glucose) بغوت وبكبرلك الـ (Glycogen)

3) بعدهيك بصير تيجيني (Branches) ففي عندنا (Branching enzyme) واللي بسحولة بنقلك (glucose unit) عشان يصلك (Branch) جديدة



G → Glucokinase (liver) / Hexokinase (muscle) → G-6-P → phosphoglucomutase → G-1-P → G-1-P uridyl transferase (UTP, PPi) → UDPG

1. Formation of UDP glucose:

- Glucose is phosphorylated to G-6-P by **glucokinase** (liver) or hexokinase (muscle)

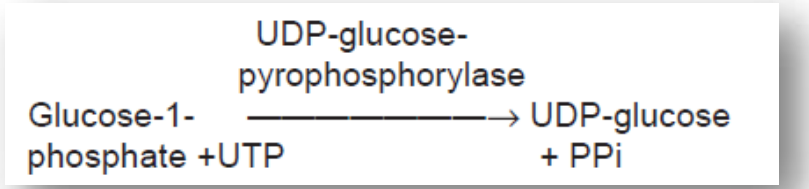
(سؤال بالإمتحان)

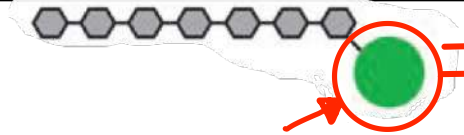
- G-6-P is then converted to G-1-P by **phosphoglucomutase**

- **G-1-P uridyl transferase** catalyzes formation of UDP-G from G-1-P and UTP with liberation of pyrophosphate (irreversible reaction)

  بيدخل حر — PPi

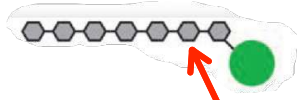
  - UDP glucose is called ***activated glucose*** and serves as a **glucose donor** for glycogen synthesis





= (Glycogenin) = (Glycogen primer) على (U-D-P-G) هو نه بدنا نضيف ا *

2. Addition of glucosyl residues



(بروتين ماسك به (oligosaccharide chain) هي حقيقة تمثل شكل الـ (Glycogen) ولكنه أبسط)

- **Glycogen primer:** oligosaccharide chain linked by α1,4 glucosidic links attached to *protein-CHO nucleus* called **glycogenin**

Glycogenin

  - Glycogen primer may be an old incompletely broken glycogen molecule or a newly formed glycogen primer

(تكسرت من زمانه) (تكونت من جديد)

  - **Glycogenin** can undergo autoglycosylation (i.e. bind glucose to its tyrosine residue via OH group)
  - **Glycogenin** binds more glucose units in form of UDPG one by one through α1,4 glucosidic links → up to 8 units (primer)

- → Glycogen synthase (key enzyme) transfers more activated glucose units from UDPG to the end of glycogen primer (and UDP is removed)
  - This repeats until about 12 glucose residues are added

- لحد هنا في (Branch) ٧

(UDP) وبديله (glucose) بضيف منها حبات (UDP-G) يعني بجيب *

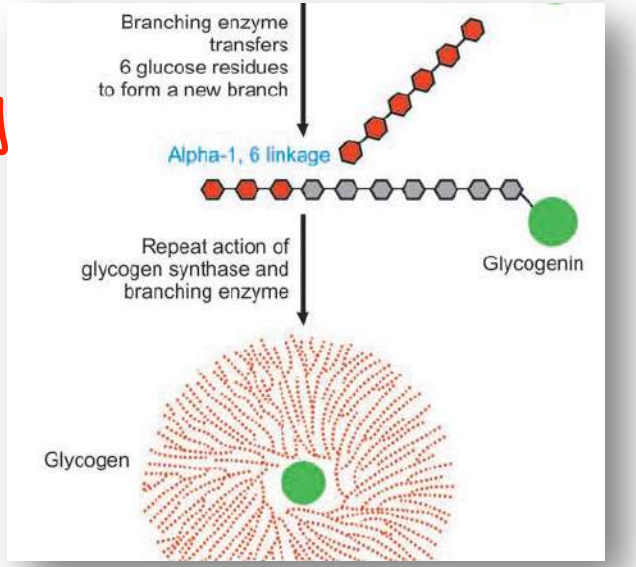
3. Formation of branches

*أهمية الـ (Branches):
- بتحافظ على الـ (stability)
- بتخليك عندك امكانية تخزين كمية (Glycogen) بمساحة أصغر

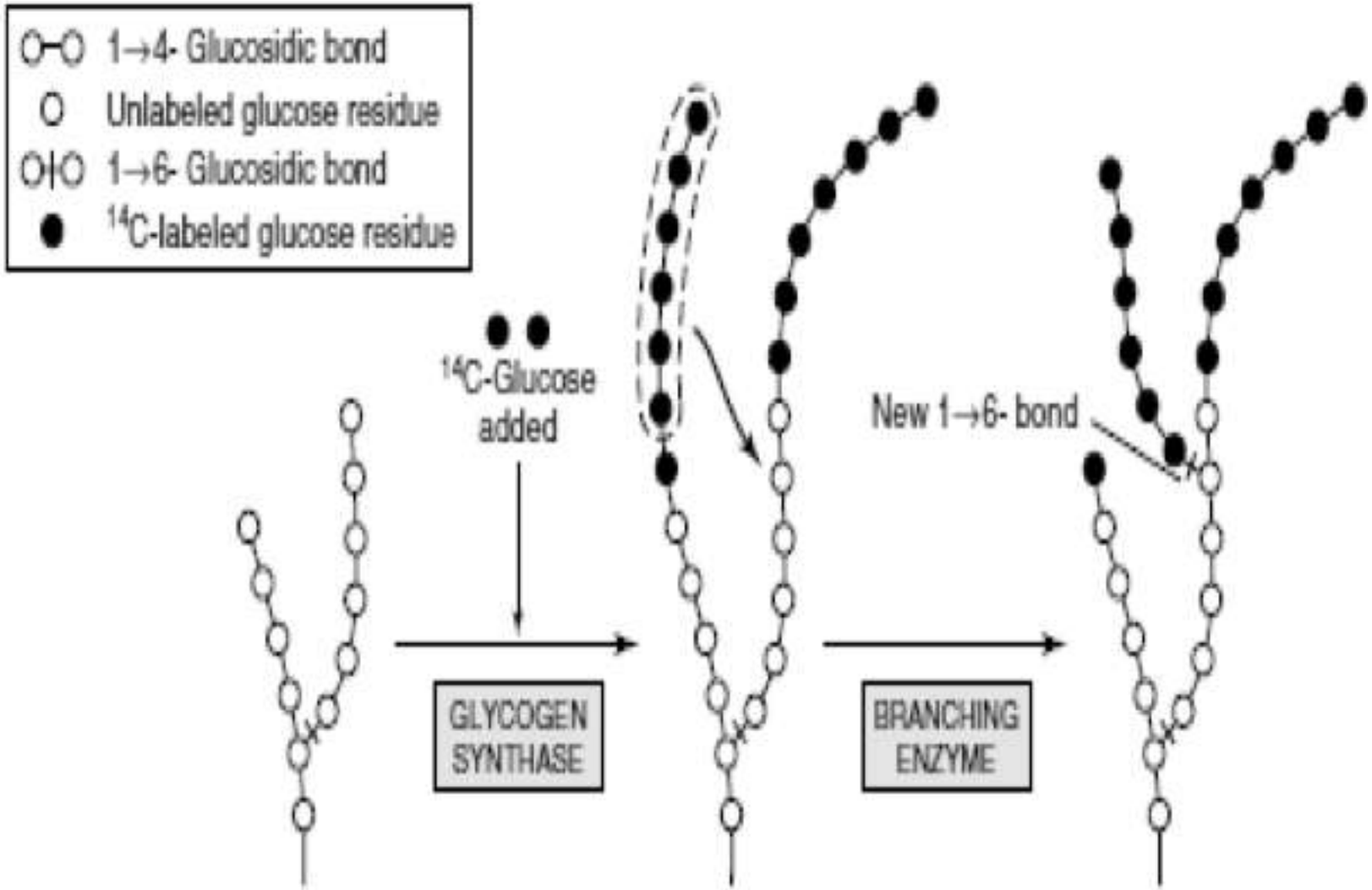
- When chain length is 11-12 residues:
  - A **branching enzyme** (AKA amylo 1,4 → 1,6 transglucosidase) transfers a block of 6-8 glucose units from the end of glycogen to C6 of glucose:
    - Creating a new α-1, 6-glucosidic bond
    - A new branch appears on which glycogen synthase can act again

بنقل

لهيك أضيف (Branch) بقلل طول السلسلة فبسمح لـ (glycogen synthase) أنه يعمل مجدداً



The combined action of glycogen synthase and branching enzyme → a highly branched glycogen structure


1→4- Glucosidic bond
Unlabeled glucose residue
1→6- Glucosidic bond
14C-labeled glucose residue
14C-Glucose added
GLYCOGEN SYNTHASE
New 1→6- bond
BRANCHING ENZYME

Biological impotence of branching

- Makes glycogen more stable
- Increases number of ends → increases number of sites accessible to glycogen synthase (**amplifying cascade**)
- Increase sites of breaking attacks by phosphorylase → facilitating glycogen breakdown

Regulation of glycogen metabolism

- Principle enzymes controlling this are:
  - Glycogen synthase
  - Phosphorylase

Reciprocally regulated

تحكم متعاكس

لـ لو واحد منهم (inhibited) الثاني يكون (activated) و بالعكس

- They are controlled by:
  - Allosteric control
  - Covalent modification

Regulation of glycogen metabolism

- Allosteric control (عن طريق الـ (Allosteric site): حسب حاجتك)
  - Glycogen synthase
    - Stimulated by glucose 6-P & ATP
    - Inhibited by glycogen (product)
  - Glycogen phosphorylase
    - Stimulated by AMP
    - Inhibited by glucose & ATP

ما بنا أصلاً نحس

كم معنا الطاقة الي نعرفها

Regulation of glycogen metabolism

- Covalent modification (more/less active) موجودين بطريقتين (*، *) أنه لازم تفهم عشان تفهمه

  – Glycogen synthase: active in ***dephosphorylated*** form

  – Glycogen phosphorylase: active in ***phosphorylated*** form

  – Covalent modification of these enzymes is through hormones that act through the 2nd messenger cAMP

  – Glycogen synthase exists in 2 forms (interconverted by specific enzyme):
    – Less active phosphorylated form (glycogen synthase b)
    – More active ***dephosphorylated*** form (glycogen synthase a)

  – Glycogen phosphorylase exists in 2 forms:
    – Less active ***dephosphorylated*** form (phosphorylase b)
    – More active phosphorylated form (phosphorylase a)

بعد ما تاكل ويكون كمية (Glucose) كبيرة

* الأنسولين ما بحب يشوف كميات كبيرة بالدم فبطلع من البنكرياس وبعمل (dephosphorylation)

During fed state

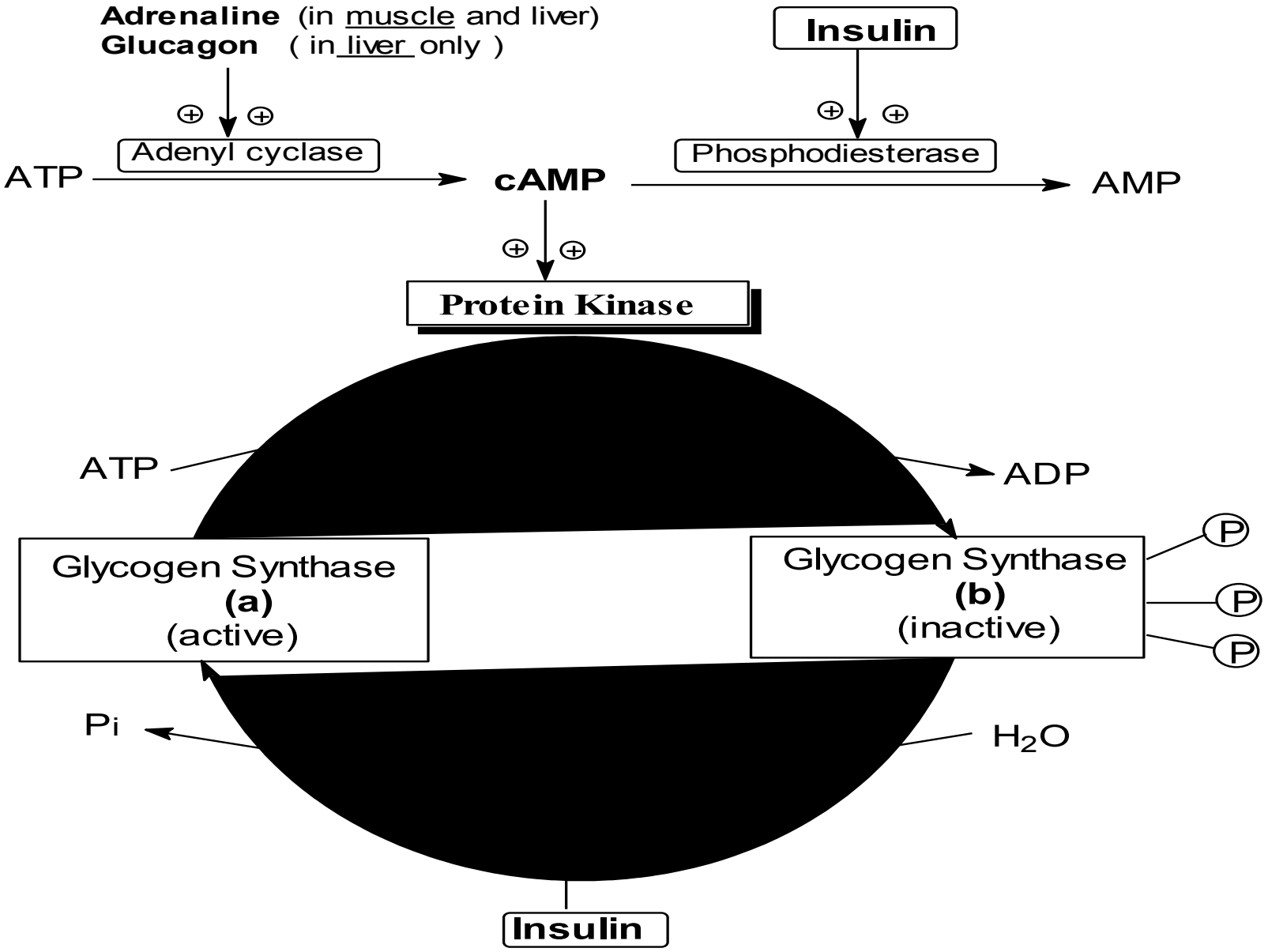
- Insulin dephosphorylates both glycogen synthase and glycogen phosphorylase via 2 mechanisms:
  - Activation of phosphodiesterase enzyme → inactivates cAMP to AMP → inhibits protein kinase
    (Phosphorelation) هاد اللي بعمل
  - Activation of phosphatase enzyme which removes P:
    - » Dephosphorylation of glycogen synthase → its activation → GLYCOGENESIS
    - » Dephosphorylation of glycogen phosphorylase → its inactivation → inhibition of glycogenolysis

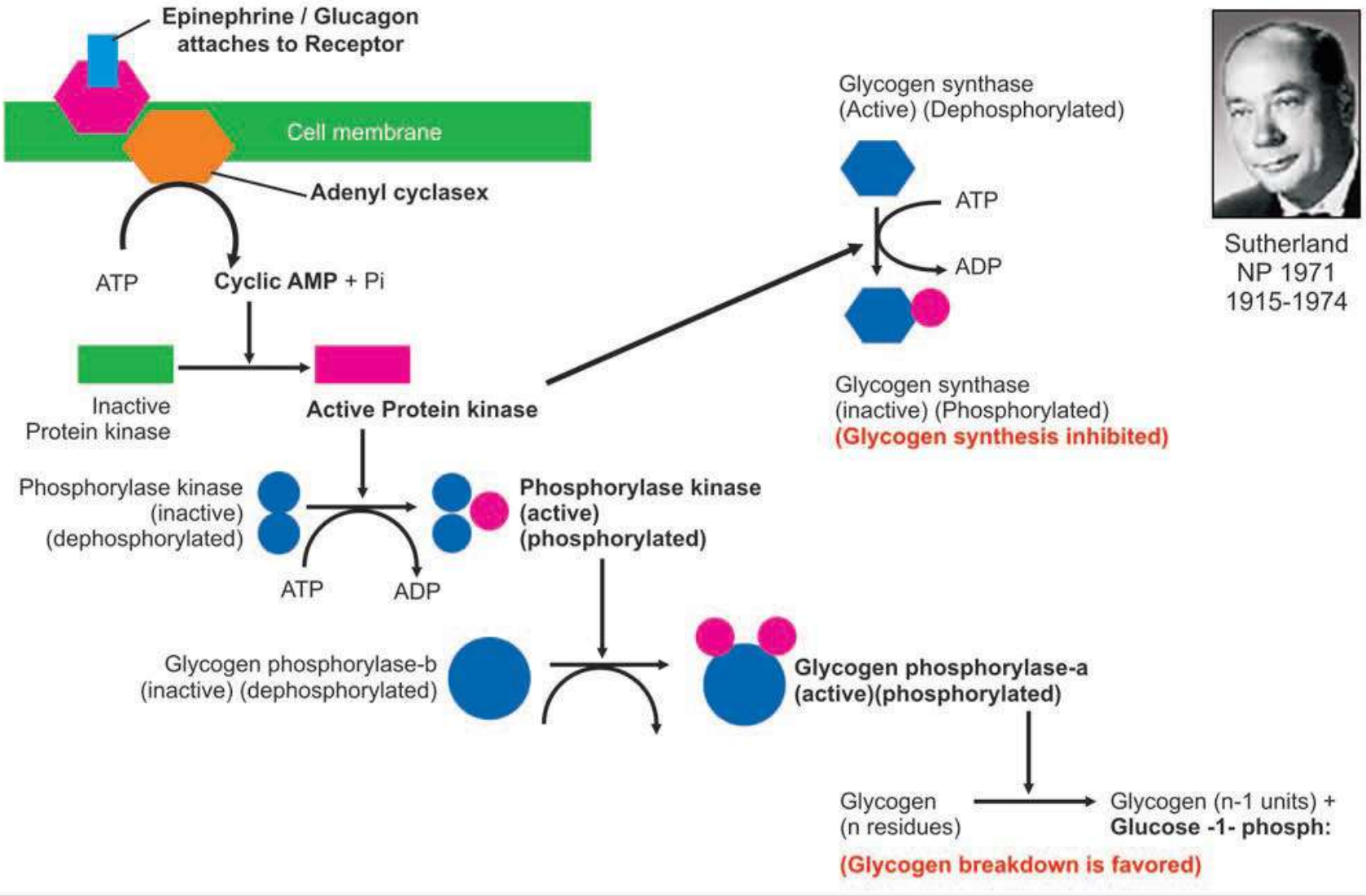
(الشخص وهو صائم محتاج يحافظ على مستوى السكر بالدم عنه طريق تكسير ال (Glycogen)

During fasting state

- Glucagon (in liver) & epinephrine (in liver & muscle):
  - Activate a membrane receptor (G protein) → activates adenyl cyclase (a membrane linked enzyme) → converts ATP to cAMP
  - cAMP activates cAMP dependent protein kinase → phosphorylates (inactivates) glycogen synthase → inhibits glycogensis
    - Activation of protein kinase → activate phosphorylase kinase enzyme → stimulation of glycogen phosphorylase → glycogenolysis

تكسير


Adrenaline (in muscle and liver)
Glucagon (in liver only)
Insulin
Adenyl cyclase
Phosphodiesterase
ATP
cAMP
AMP
Protein Kinase
ATP
ADP
Glycogen Synthase
(a)
(active)
Glycogen Synthase
(b)
(inactive)
P
P
P
Pi
H2O
Insulin


Epinephrine / Glucagon
attaches to Receptor
Cell membrane
Adenyl cyclasex
ATP
Cyclic AMP + Pi
Inactive
Protein kinase
Active Protein kinase
Phosphorylase kinase
(inactive)
(dephosphorylated)
ATP
ADP
Phosphorylase kinase
(active)
(phosphorylated)
Glycogen phosphorylase-b
(inactive) (dephosphorylated)
Glycogen phosphorylase-a
(active)(phosphorylated)
Glycogen
(n residues)
Glycogen (n-1 units) +
Glucose -1- phosph:
(Glycogen breakdown is favored)
Glycogen synthase
(Active) (Dephosphorylated)
ATP
ADP
Glycogen synthase
(inactive) (Phosphorylated)
(Glycogen synthesis inhibited)
Sutherland
NP 1971
1915-1974

Allosteric regulation in muscle exercise:

- Muscle phosphorylase is allosterically activated by AMP → glycogenolysis
  - (muscle exercise) بزید بال
- AMP is increased during muscular exercise and allosterically inhibited by:
  - ATP & G-6-P because their elevated levels indicate that the cell is not in need of more energy and there is no need to breakdown glycogen.

During muscle exercise:
↑ release of Ca from sarcoplasmic reticulum → activates glycogen phosphorylase → glycogenolysis

Induction and repression of the key enzyme:

- Carbohydrate feeding → induce insulin → ↓ synthesis of key enzyme (**repression**) so glycogenolysis is inhibited.

- Fasting → ↓ insulin and ↑ anti-insulin which increase synthesis of key enzyme (**induction**) so glycogenolysis is stimulated.

(لا يوجد امتحانه ميد أو فاينال نخلوا منه هذا الجدول)

Glycogen storage diseases

Inborn errors of glycogen metabolism

Classified into different types according to the deficient enzyme

Type	Disease Name	Defective enzyme	Glycogen levels	Glycogen structure	Principal tissue affected
I	Von Gierke's disease	Glucose-6-phosphatase (G6pase)	High	Normal	Liver, kidney
II	Pompe's disease	α-1,4 Glucosidase	Very high	Normal	All organs
III	Cori's Forbes' disease	Debranching enzyme	High	Short outer branches	Liver, Heart, Muscle
IV	Andersen's disease	Branching enzyme	Normal	Long outer branches	Liver, Spleen, Muscle
V	McArdle's disease	Muscle Phosphorylase	High	Normal	Muscle
VI	Hers' disease	Liver Phosphorylase	High	Normal	Liver
VII	Tarui's disease	Phosphofructokinase	High	Normal	Muscle
VIII	Hepatic phosphorylase kinase deficiency	Phosphorylase kinase	High	Normal	Liver

Most common

(بس العضلات تتأثر)

Characteristic feature

I: Fasting hypoglycaemia (not responding to adrenaline), hepatomegaly

II: early death before 2 years

III: mild fasting hypoglycaemia

IV: hepatosplenomegaly, mild hypoglycaemia, results in synthesis of straight chain glycogen only

V: exercise intolerance, painful muscle cramps during exercise

(تشنجات)