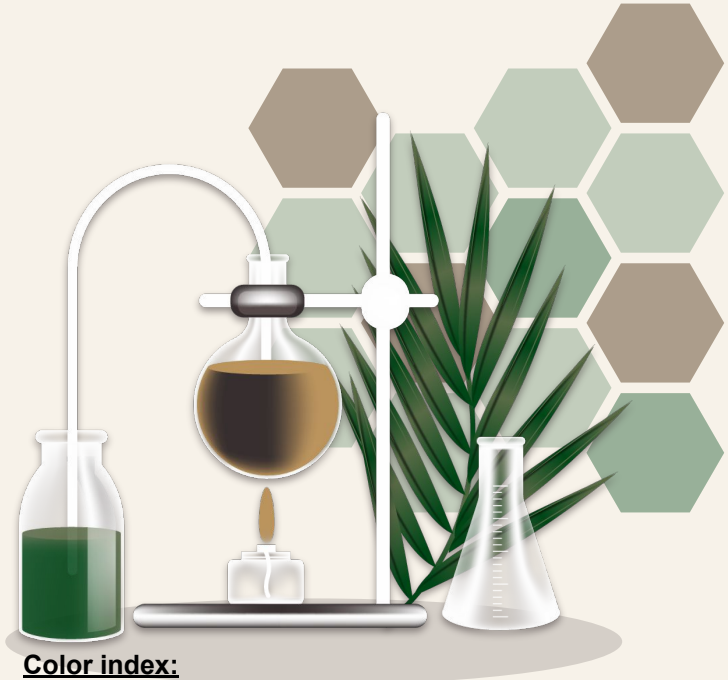
Biochemistry

Glycogen metabolism in muscles



Color index:
-Main text -Girls' slides -Boys' slides
-Important - Dr's notes -Extra

Editing File

Objectives:

Objectives

- The need to store carbohydrates in muscle
- The reason for carbohydrates to be stored as glycogen
- An overview of glycogen synthesis (Glycogenesis)
- An overview of glycogen breakdown (Glycogenolysis)
- Key elements in regulation of both Glycogenesis and Glycogenolysis

Male Doctor : Enzymes names and function are **VERY IMPORTANT** In this lecture .. (Check last Slide in this team)

Note: All slides are important And When you see this star ★ it means MORE IMPORTANT

Location & Functions of Glycogen

When the blood glucose is low, Glycogenolysis starts first Since it's faster than Gluconeogenesis

Location & Functions of Glycogen

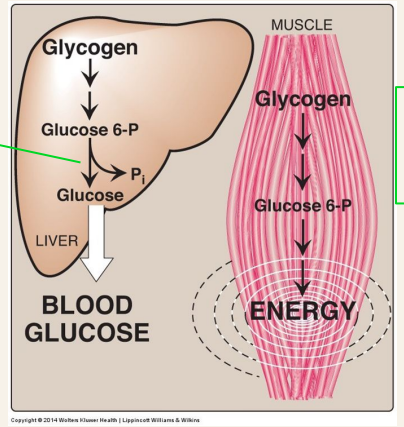
It's very important to understand the function of glycogen in (liver – muscle)

In liver

MALE NOTE : The enzyme in this reaction is : Glucose 6 phosphatase

- 100 g in liver (~ 10% of well-fed liver)
- ★ a source for blood glucose (especially during early stages of fasting)

The major site of storage is the liver



In skeletal muscle

MALE NOTE : There is no Glucose 6 phosphatase in muscles .. instead it goes directly to glycolysis

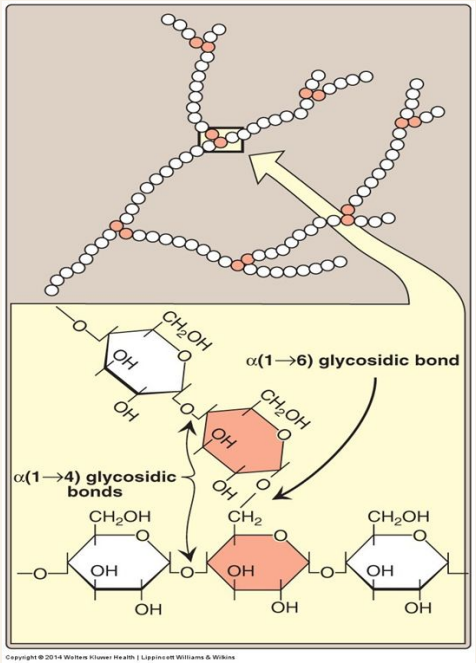
- 400 g in muscles (1–2% of resting muscles weight)
- ★ fuel reserve (ATP) (during muscular exercise)

In muscles glucose 6-p is converted to energy directly without being converted to glucose first like liver

Structure of Glycogen

- Branched-chain means that it has more than one type of bonds
- a(1-4)bond is the mainly abundant bond in glycogen

Branches (every 8-10 residue) are linked by a(1-6) glycosidic linkage

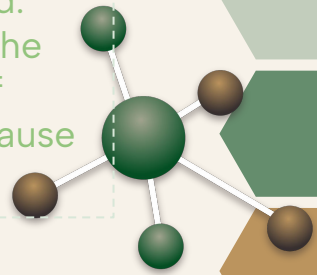


Glycogen is a branched-chain homo-polysaccharide made exclusively from a-D-glucose

Present in the cytoplasm in the form of granules which contain most of the enzymes necessary for glycogen synthesis & degradation

Glucose residues are bound by a(1-4) glycosidic linkage

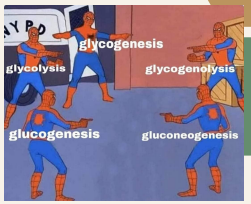
- The orange ones have a(1-6) glycosidic bond. The white ones have a(1-4) glycosidic bond.
- benefit of the branches: the synthesis or degradation of glycogen will be faster because there are many ends



Metabolism of Glycogen in Skeletal Muscle

- first:

Glycogenesis: it is the Synthesis of Glycogen from Glucose



1 **Building blocks:** UDP-GLUCOSE

The glucose is carried by the UDP

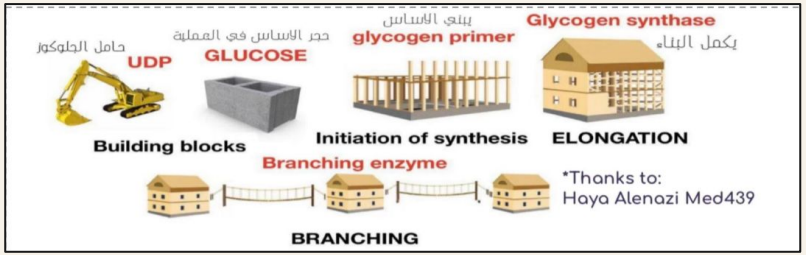
UDP= uridine diphosphate

2 **Initiation of synthesis:** Elongation of pre-existing glycogen fragment OR The use of glycogen primer (glycogenin)

Glycogenin synthesis the primer

3 **ELONGATION by Glycogen synthase:** (for a 1-4 linkages) Glycogen synthase cannot ★ initiate synthesis but only elongates pre-existing glycogen fragment or glycogen primer (glycogenin)

4 **BRANCHING:** Branching enzyme (for a 1-6 linkages)



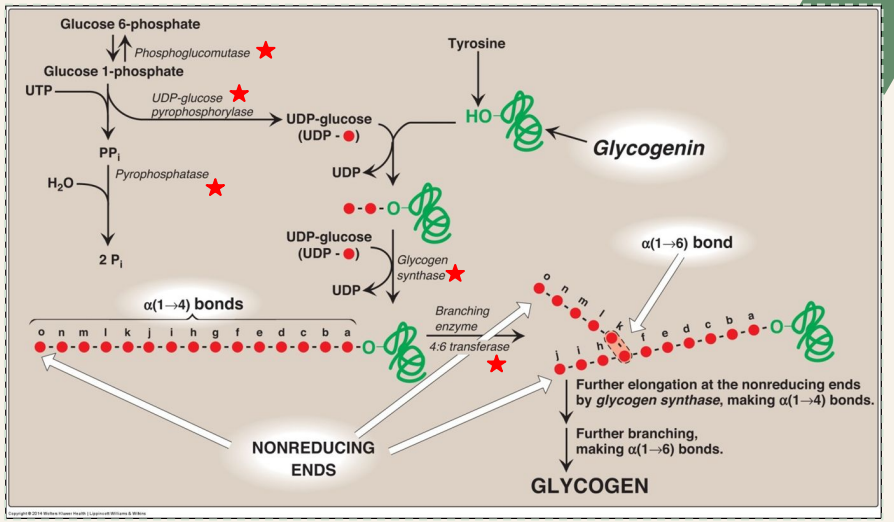
- If there is small fragment remained after a degradation it can be used to initiate the Synthesis of glycogen by elongation
- If not, a glycogenin will initiate the Synthesis by creating the fragments.

Metabolism of Glycogen in Skeletal Muscle

1. G6P will be converted into G1P by phosphoglucomutase
2. adding UDP to G1P (the UDP comes from a UTP) by UDP-glucose pyrophosphorylase the result is (UDP-Glucose)
3. After that There are two possibilities:

A. **there is a pre-existing fragment** Glycogen synthase will keep adding glucose to the fragments to make the polymer by forming a(1-4)bonds

B. **There is no fragment** Glycogenin will act as an enzyme by adding glucose to its tyrosine (num 194) residue (auto glycosylation). After adding couple of residues (5-6 glucose residues) glycogen synthase can start adding more glucose



4. after 8-14 residues the branching starts by branching enzyme (4:6 transferase) to form a(1-6)bonds

Metabolism of Glycogen in Skeletal Muscle

- Second :

Glycogenolysis: Breakdown of Glycogen to Glucose-6-phosphate

1- Shortening of glycogen chain

★- Done by glycogen phosphorylase
- Cleaving of a(1-4) bonds of the glycogen chain producing glucose 1-phosphate
- Glucose 1-phosphate is converted to glucose 6-phosphate by mutase enzyme

2- Removal of branches

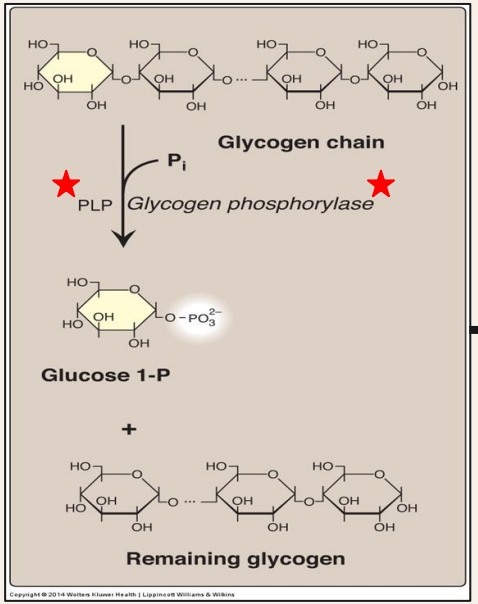
- Done by debranching enzymes (important to know them)
- Cleaving of a(1-6) bonds of the glycogen chain producing free glucose (few)

3- Fate of glucose 6-phosphate (G-6-P)

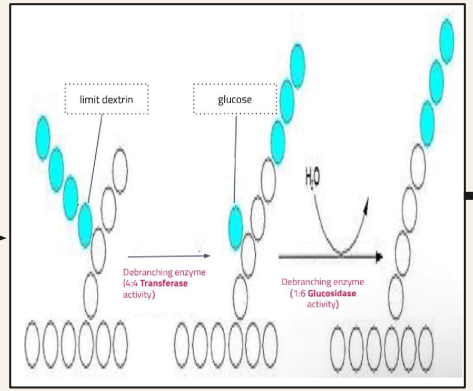
- G-6-P is not converted into free glucose.
- It is used as a source of energy for skeletal muscles during muscular exercise (by anaerobic glycolysis starting from G-6-P)

Metabolism of Glycogen in Skeletal Muscle

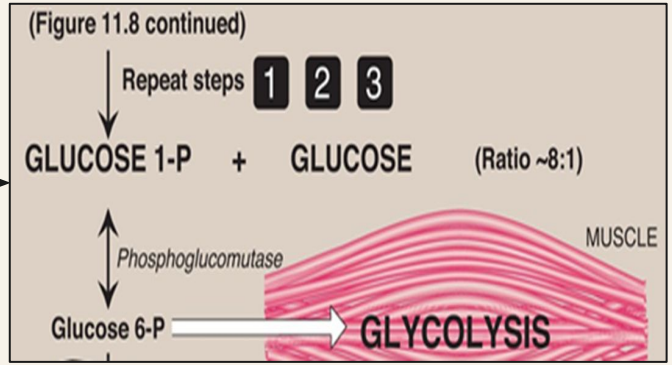
- Second :
  - Glycogenolysis contd..



The glycogen phosphorylase combined with pyridoxal phosphate (cofactor)



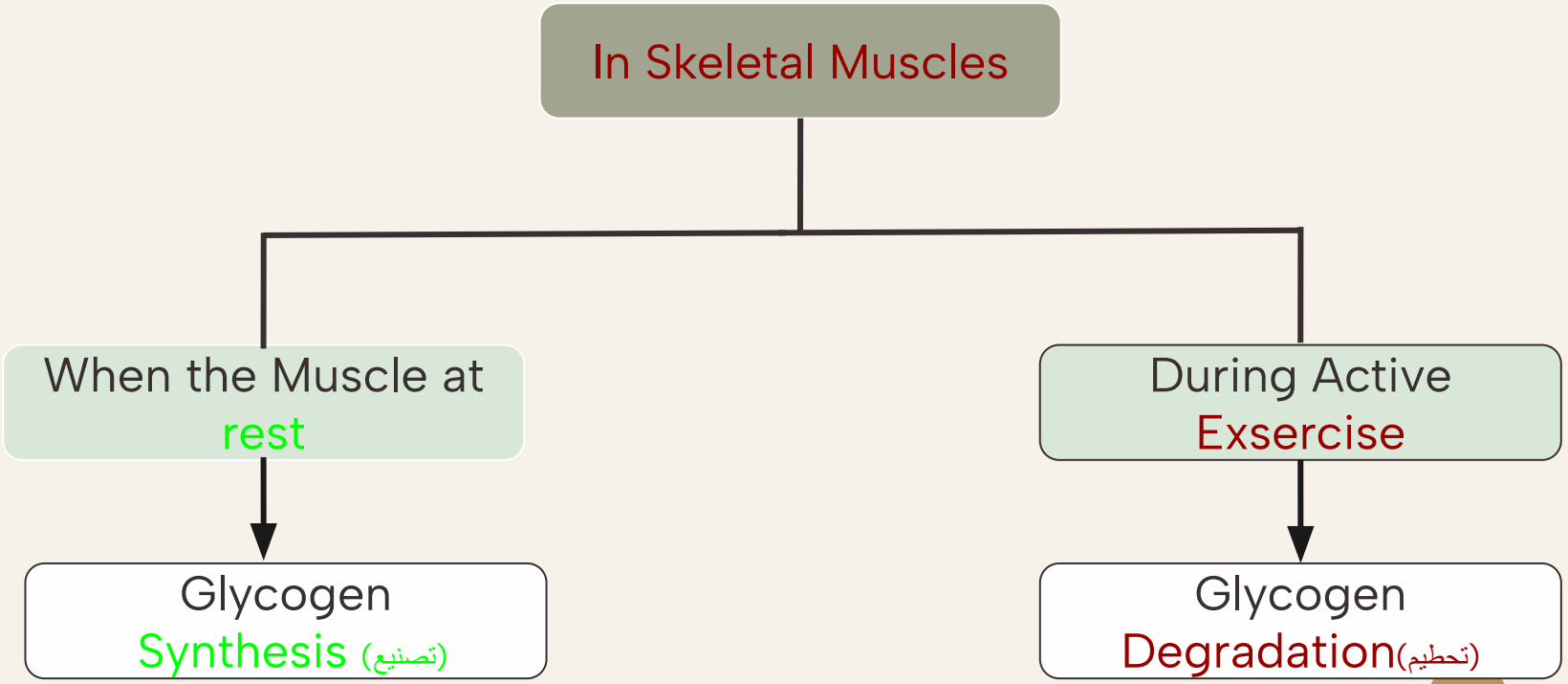
4:4 transferase: transfers three glucose residues from glycogen branch to a nearby branch.
1:6 Glucosidase: will release free glucose (important enzymes)



don't mix between:
(4:6 transferase) glycogenesis
(4:4 transferase) glycogenolysis

Regulation of Glycogen Metabolism

Synthesis & degradation of glycogen are tightly regulated



Regulation of Glycogen Metabolism

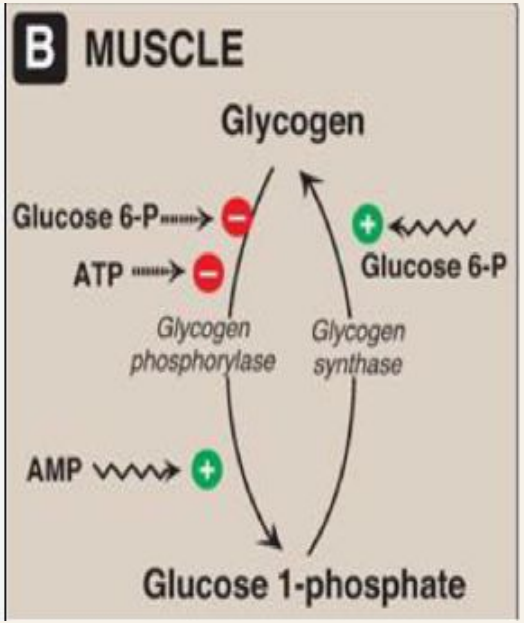
IMPORTANT SLIDE

★ Regulation occurs by 2 mechanisms :
1- Allosteric regulation 2- Hormonal regulation (Covalent modification)

MALE DOCTOR : This may come in SAQ (:

1- Allosteric regulation

Glycogen phosphorylase (Glycogenolysis) الإنزيم الأساسي في الهدم	Glycogen synthase (Glycogenesis) الإنزيم الأساسي في البناء
Activators : AMP, Ca+2	Activators : Glucose 6-p
Inhibitors : ATP, Glucose 6-p	Inhibitors : ــــــ



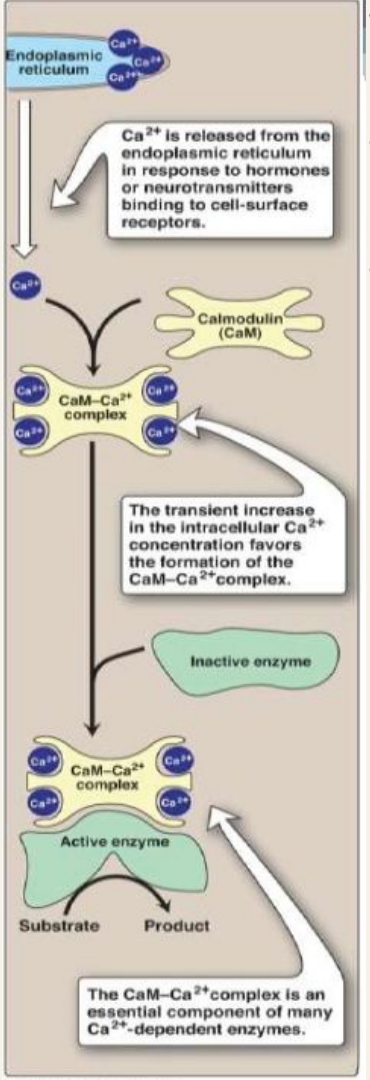
Extra
السلايدة هذي لازم تفهمونها قبل الحفظ ، عندنا عمليتين تتم في الجلايكوجين (هدم وبناء) وكل عملية لها انزيم مسؤول عنها ، فمثلا : في الهدم فيه إنزيم وظيفته يهدم ويطلع لنا جلكوز(phosphorylase) وفي البناء إنزيم ثاني وظيفته يأخذ جلكوز ويبني منه جلايكوجين (synthase) ، وكل إنزيم منهم له مواد تساعد على تفعليه عشان يقوم بدوره ومواد تثبطه ، فمثلا عندنا انزيم الهدم (phosphorylase) وظيفته انه يهدم جلايكوجين ويطلع جلكوز، والجلكوز نحوله بعدين إلى طاقة ATP لذلك إذا صارت عندنا كمية وفيرة من الطاقة ما نحتاج الإنزيم يشتغل فيروح الATP بدوره ويثبط عمل إنزيم الهدم فبالتالي يثبط عملية تكسير الجلايكوجين

Regulation of Glycogen Metabolism

1	Increase of calcium during muscle contraction
2	Formation of Ca+2- calmodulin complex.
3	Activation of Ca+2-dependent enzymes, e.g, Glycogen phosphorylase

Extra :

في حالة انقباض العضلات يزيد مستوى الكالسيوم ويرتبط مع calmodulin ويفعل انزيم Glycogen phosphorylase اللي بدوره يسوي degradation لأن العضلة في حالة active exercise نفس ما ذكرنا قبل



IMPORTANT SLIDE

Regulation of Glycogen Metabolism

2- Hormonal regulation By Epinephrine

Muscle Contraction → Epinephrine Release → In skeletal muscle

Epinephrine / Receptor binding

G protein coupled receptor

cAMP

Enzyme phosphorylation

EXTRA : باختصار بسيط عند انقباض العضلة يفرز الإبنفرين اللي بدوره يروح لل skeletal muscle ويرتبط مع GPCR مما ينتج عنه إنتاج cAMP وبعلم أن الحركة اللي صارت إنقباض وزي ما قلنا قبل أن الانقباض يعني exercise والناتج يكون glycogen degradation لذلك يروح يسوي فسفرة للانزيم ال phosphorylase ويخليه فعال ، والعكس مع انزيم synthase

Glycogen synthase
Inactive form

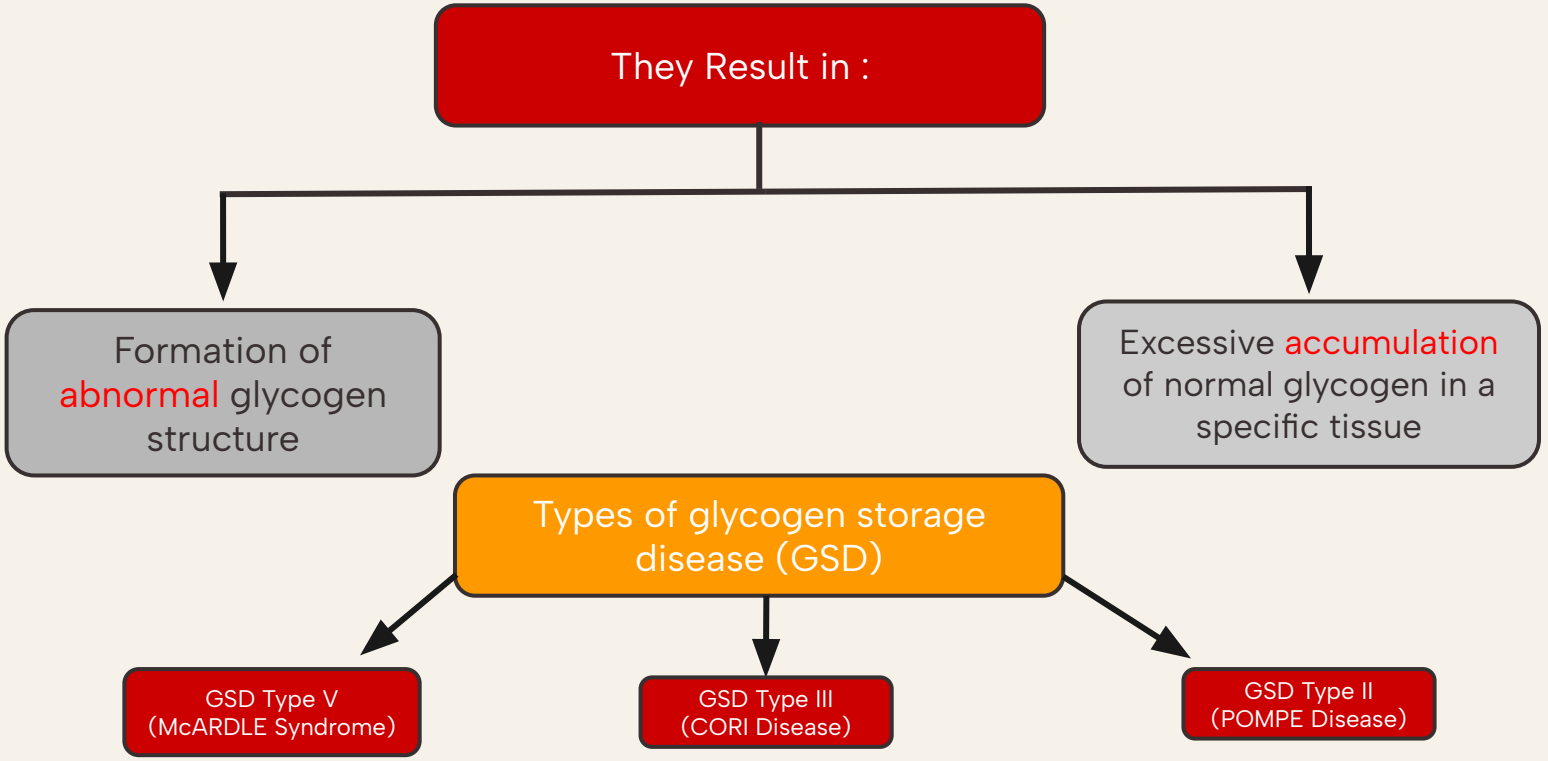
Inhibits Glycogenesis

Glycogen phpsphorylase
Active form

Stimulate Glycogenolysis

Glycogen Storage Disease (GSD)

Definition: A group of genetic diseases that result from a defect in an enzyme required for glycogen synthesis or degradation.



MALE DOCTOR : FOR Every disease you must know
1- The cause
2- The names and types

Glycogen Storage Diseases
GSD Type V (McArdle Syndrome)

Caused by : Deficiency of 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 isoenzyme causes Type VI : (Hers Disease) with mild fasting Hypoglycemia

MALE DOCTOR : YOU Should know the difference between the enzyme in the liver and skeletal muscle (they cause different diseases)

Glycogen Storage Diseases
GSD Type II (POMPE DISEASE)

Caused by : Lysosomal **α (1-4) GLUCOSIDASE DEFICIENCY**

MALE DOCTOR : THE STARS ARE MORE IMPORTANT But you should know the rest also

- 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.

Glycogen Storage Diseases
GSD Type III (CORI Disease)

Caused by : (4:4 transferase and/or 1:6 glucosidase deficiency)

MALE DOCTOR DID not focus on this slide but you should know it just in case

- Fasting hypoglycemia.
- Abnormal glycogen structure with 4 or 1 glycosyl residues at branch points.

IMPORTANT SLIDE

Important Enzymes in This lecture

Enzyme	Function	Important Characters :
Glucose 6 phosphatase (male doctor said it in lecture)	Converts Glucose 6 phosphate to glucose	Not found in muscles
Glycogen synthase	Elongates pre-existing glycogen fragment or glycogen primer	CANNOT INITIATE SYNTHESIS BY ITSELF ★
Phosphoglucomutase	Converts Glucose 6 phosphate to Glucose 1 phosphate	Changes the phosphate group location
UDP- Glucose pyrophosphorylase	Combines UTP with Glucose 1 phosphate	The result is the BUILDING BLOCK of glycogen(UDP-Glucose)
4:6 transferase	Branching enzyme that transfer a group of residues Which has 1-4 bonds and branch it at 1-6	Works in Glycogenesis
4:4 transferase	Debranching enzyme That transfer LIMIT DEXTRIN from 1-4 to 1-4	Works in Glycogenolysis
Glycogen phosphorylase	Cleaving of α (1-4) bonds of glycogen producing glucose 1 phosphate	Pyridoxal phosphate (PLP) is an important Cofactor
1:6 Glucosidase	Debranching enzyme	The only enzyme that gives us free glucose
Lysosomal α (1-4) glucosidase	Removes about 1-2% of the excess glycogen in the body to maintain its normal range	Deficiency In type II POMPE DISEASE

Multiple choice questions

1

..... cannot initiate synthesis but only elongates pre-existing glycogen

A) Glycogenin | B) 1:6 Glucosidase | C) Glycogen synthase

2

The Shortening of glycogen chain is done by which of the following enzymes

A) glycogenin | B) 1:6 Glucosidase | C) Glycogen phosphorylase

3

What does the Glucose 6 phosphate do as an allosteric regulator:

A) Inhibits glycogenesis | B) Activate glycogen phosphorylase | C) Inhibits Glycogenolysis

4

After muscle contraction epinephrine is released which causes :

A) Stimulate Glycogenesis | B) Inhibit Glycogenolysis | C) Stimulate Glycogenolysis

5

Caused by : Lysosomal α (1-4) GLUCOSIDASE DEFICIENCY

A) Type II | B) Type V | C) Type VI

MCQ Answers : 1C / 2C / 3C / 4C / 5A

SAQs

Question:
Mention two mechanisms of glycogen regulation with an example of each ?

Question:
Mention two enzymes that work in allosteric regulation of glycogen and their functions ?

Answers of SAQs:

Q1/ 1- Allosteric regulation : ATP

2- Hormonal regulation (Covalent modification) : Epinephrine

Q2/ –**Glycogen synthase : Elongates pre-existing glycogen fragment or glycogen primer**

Glycogen phosphorylase : Cleaving of α (1-4) bonds of glycogen producing glucose 1 phosphate

Meet our Team

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