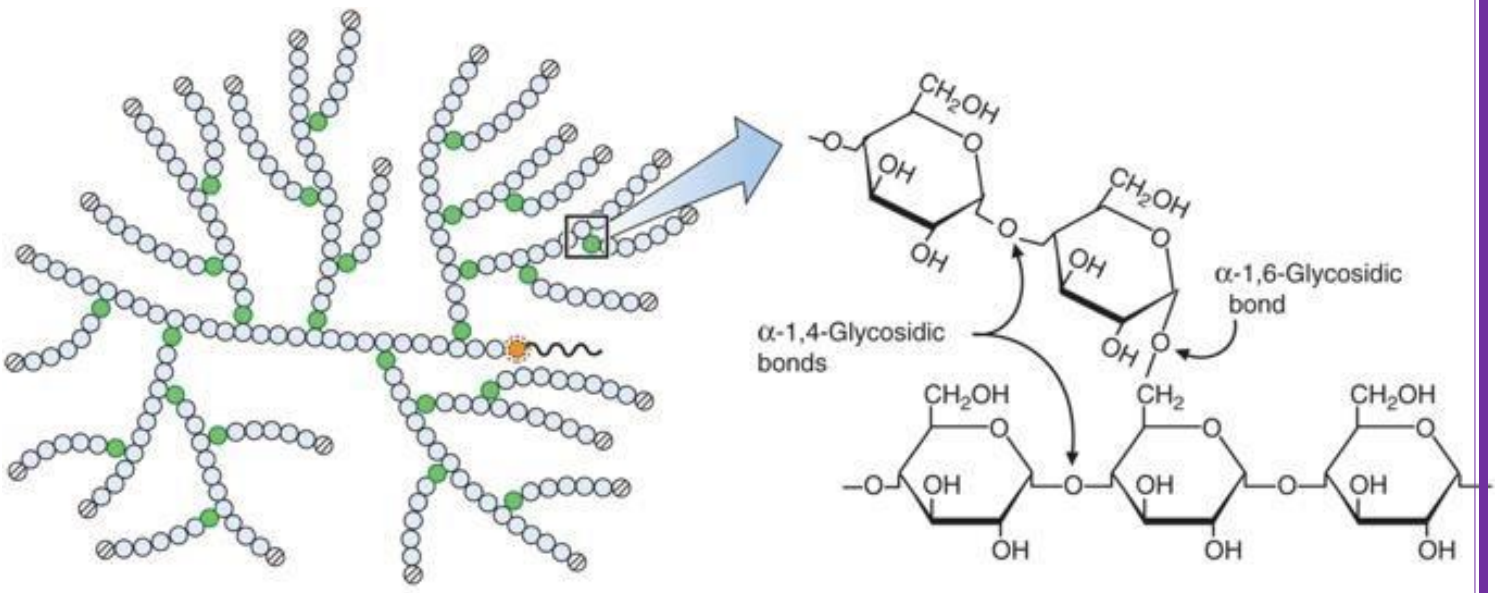
Glycogen Metabolism



The Structure of Glycogen

Glycogen is a highly branched glucose polymer in which the "main chain" is linked by a (α1→4) glycosidic bonds. The polymer also has numerous a (α→1→6) glycosidic bonds, which provide many branch points along the chain fig (1).

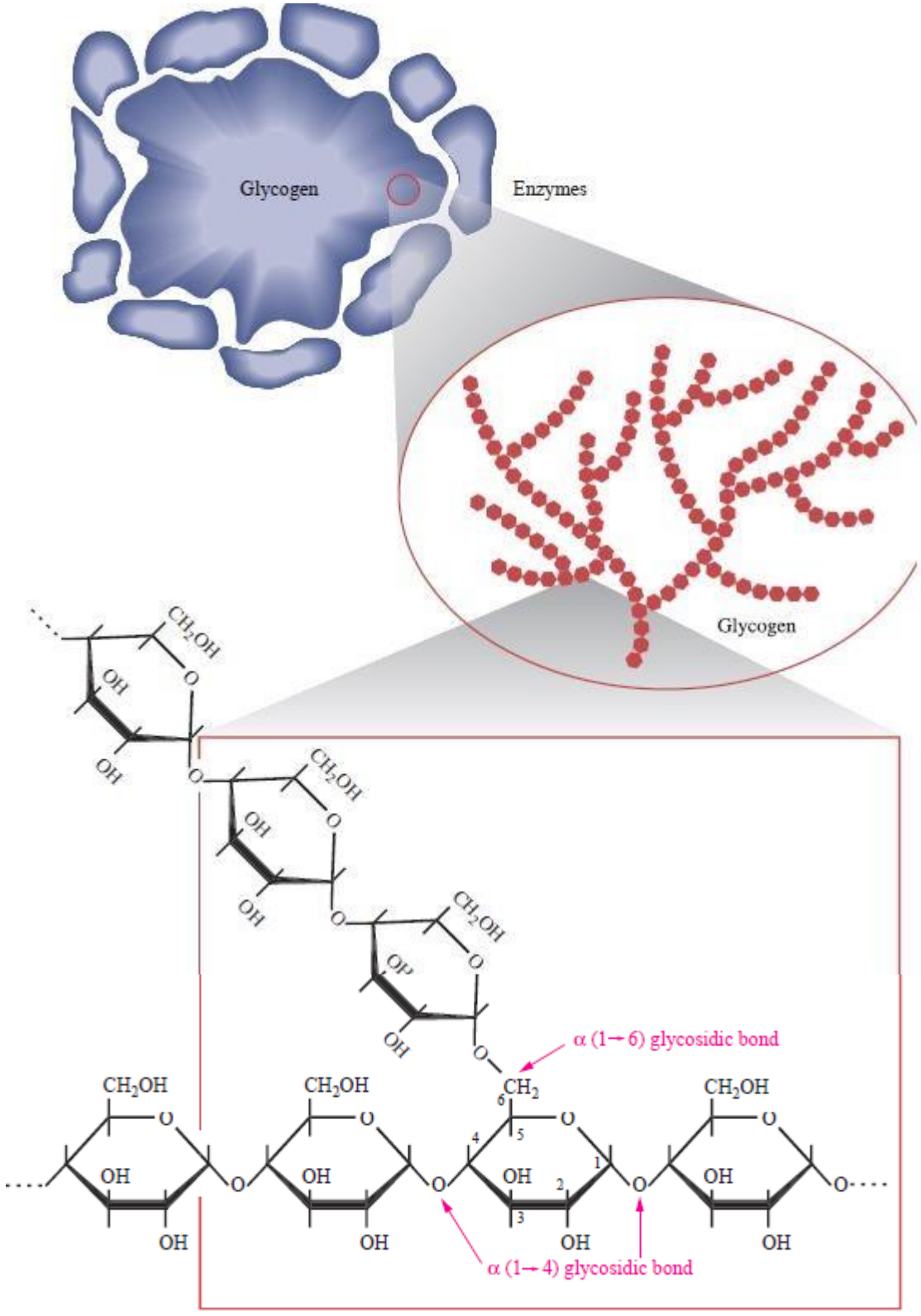


Figure (1) structure of glycogen

Functions of glycogen

Glycogen is the storage form of carbohydrates in humans and animals. It is stored mostly in liver (6-8%) and muscle (1-2%)

In muscles, it is the source of glucose needed for glycolysis.

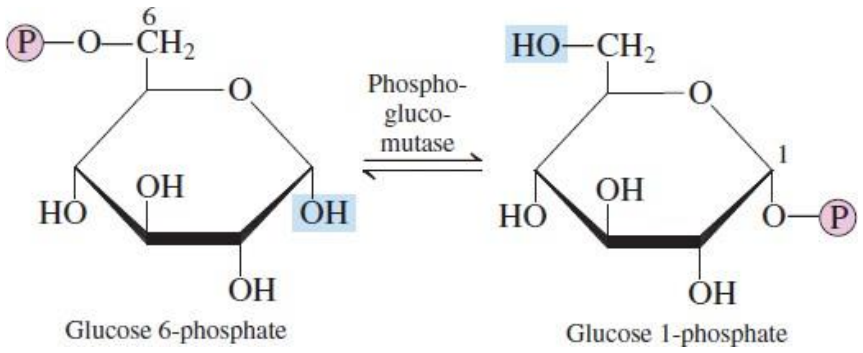
In the liver, it is the source of glucose needed to maintain normal glucose levels in the blood.

Glycogenesis

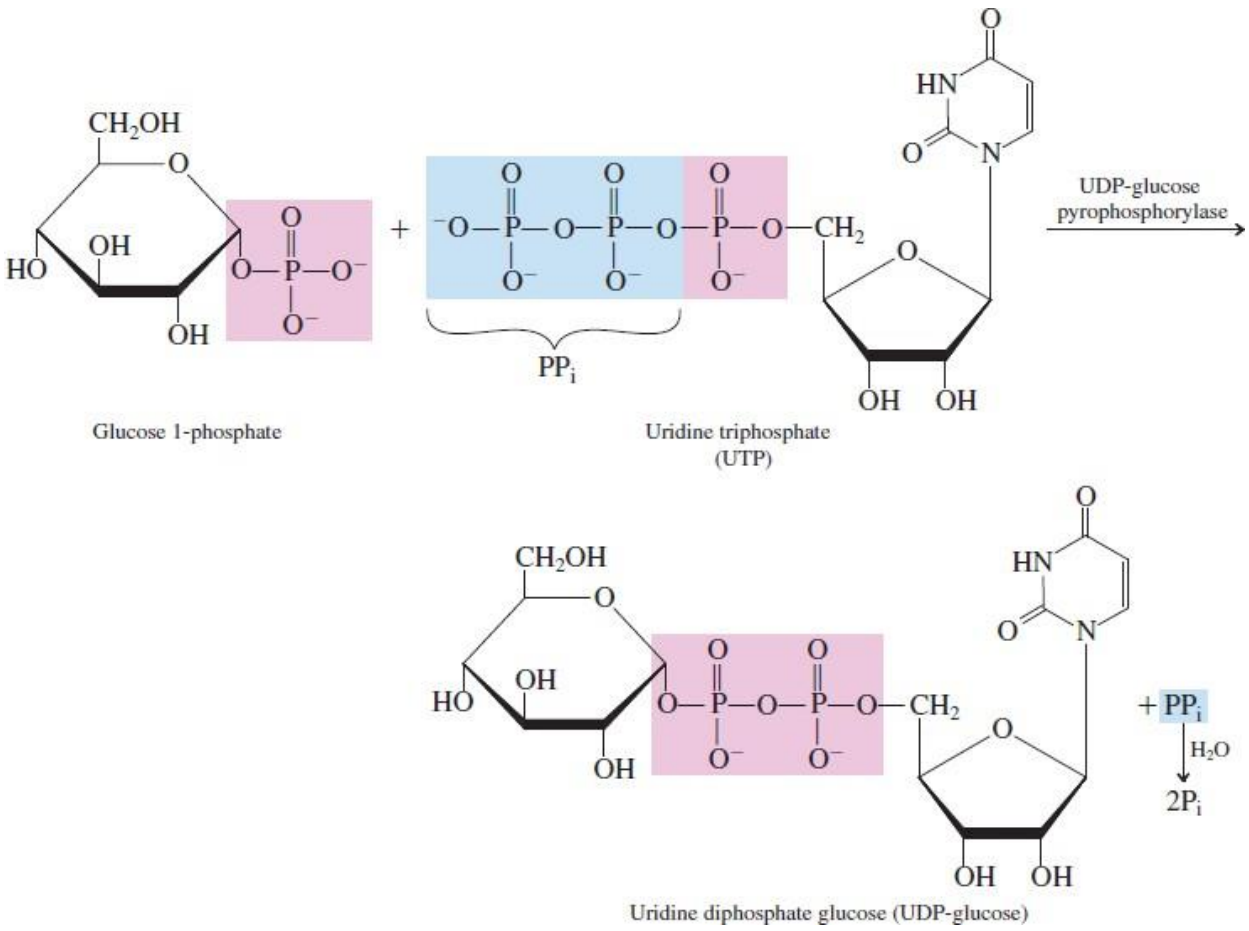
Glycogenesis is the metabolic pathway by which glycogen is synthesized from glucose figure (2). Glycogenesis takes place in the cytosol and requires ATP and UTP, besides glucose.

Glycogenesis involves three reactions (steps).

Step 1: **Isomerization:** *Formation of Glucose 1-phosphate.* The starting material for this step is not glucose itself but, rather, glucose 6-phosphate (available from the fi rst step of glycolysis).



Step 2: **Activation:** *Formation of UDP-glucose.* Glucose 1-phosphate from Step 1 must be activated before it can be added to a growing glycogen chain. The activator is the high-energy compound UTP (uridine triphosphate). A UMP is transferred to glucose 1-phosphate, and the resulting PPi is hydrolyzed to 2Pi.



Step 3: **Linkage to Chain:** *Glucose Transfer to a Glycogen Chain*. The glucose unit of UDP-glucose is then attached to the end of a glycogen chain called a "primer" (A small fragment of pre-existing glycogen to initiate glycogen synthesis).

$$\underset{}{\text{UDP-glucose}} + \underset{\text{Glycogen chain}}{(\text{glucose})_n} \xrightarrow{\text{Glycogen synthase}} \underset{\text{Glycogen with an additional glucose unit}}{(\text{glucose})_{n+1}} + \text{UDP}$$

the UDP produced in (Step 3) is converted back to UTP. The conversion reaction requires ATP.

$$\text{UDP} + \text{ATP} \longrightarrow \text{UTP} + \text{ADP}$$

[Note] Adding a single glucose unit to a growing glycogen chain requires the investment of two ATP molecules: one in the formation of glucose 6-phosphate and one in the regeneration of UTP.

Glycogenolysis

Glycogenolysis *is the metabolic pathway by which glucose 6-phosphate is produced from glycogen.* This process does not require UTP or UDP molecules as in glycogenesis fig (2).

Glycogenolysis is a two-step process rather than a three-step process.

Step1: ***Phosphorolysis:*** *Formation of Glucose-1-phosphate.* The enzyme glycogen phosphorylase effects the removal of an end glucose unit from a glycogen molecule as glucose 1-phosphate.

$$\underset{\text{Glycogen}}{(\text{Glucose})_n} + P_i \xrightarrow[\text{Phosphorylase}]{\text{Glycogen}} \underset{\text{Glycogen with one fewer glucose unit}}{(\text{glucose})_{n-1}} + \text{glucose 1-phosphate}$$

Step 2: ***Isomerization:*** *Formation of Glucose 6-phosphate.* The enzyme phosphoglucomutase catalyzes the isomerization process whereby the phosphate group of glucose 1-phosphate is moved to the carbon 6 position.

$$\text{Glucose 1-phosphate} \underset{\text{mutase}}{\overset{\text{Phosphogluco-}}{\rightleftharpoons}} \text{glucose 6-phosphate}$$

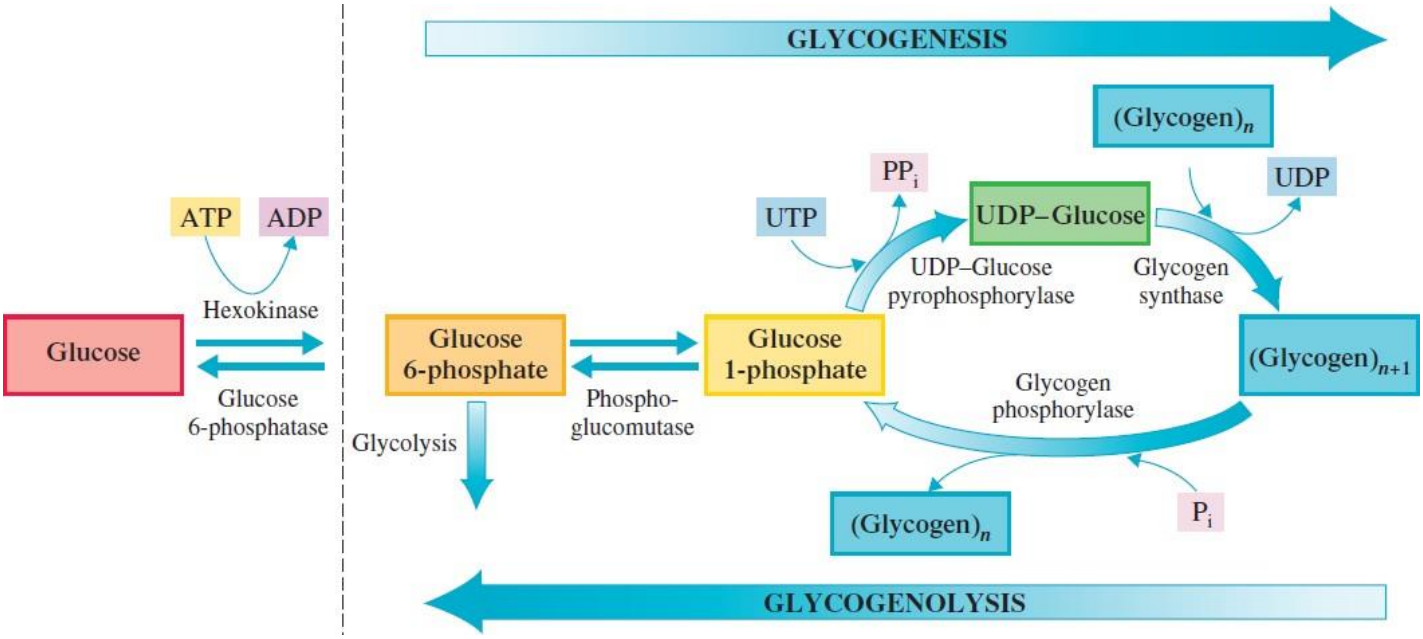


Figure (2) The processes of glycogenesis and glycogenolysis contrasted

Glycogen storage disease

is a metabolic disorder caused by enzyme deficiencies affecting either glycogen synthesis or glycogen breakdown, typically in muscles and/or liver cells.

GSD has two classes of cause: genetic and acquired.

Genetic GSD is caused by any inborn error of metabolism (genetically defective enzymes) involved in these processes.

In livestock, acquired GSD is caused by intoxication with the alkaloid castanospermine.

There are seven common types of GSD:

- Type (1) von Gierke's disease
- Type (2) Pompe’s disease
- Type (3) Cori’s disease (or Forbe’s disease)
- Type (4) Anderson’s disease
- Type (5) McArdle’s disease
- Type (6) Hers' disease

- Type (7) Tarui's disease

The table below summarize the types of glycogen storage diseases with their characteristic features.

Type	Name	Enzyme defect	Organ(s) involved	Characteristic features
I	von Gierke's disease (type I glycogenosis)	Glucose 6-phosphatase	Liver, kidney and intestine	Glycogen accumulates in hepatocytes and renal cells, enlarged liver and kidney, fasting hypoglycemia, lactic acidemia; hyperlipidemia; ketosis; gouty arthritis.
II	Pompe's disease	Lysosomal α-1,4 glucosidase (acid maltase)	All organs	Glycogen accumulates in lysosomes in almost all the tissues; heart is mostly involved; enlarged liver and heart, nervous system is also affected; death occurs at an early age due to heart failure.
III	Cori's disease (limit dextrinosis, Forbe's disease)	Amylo α-1,6-glucosidase (debranching enzyme)	Liver, muscle, heart, leucocytes	Branched chain glycogen accumulates; liver enlarged; clinical manifestations are similar but milder compared to von Gierke's disease.
IV	Anderson's disease (amylopectinosis)	Glucosyl 4-6 transferase (branching enzyme)	Most tissues	A rare disease, glycogen with only few branches accumulate; cirrhosis of liver, impairment in liver function.
V	McArdle's disease (type V glycogenosis)	Muscle glycogen phosphorylase	Skeletal muscle	Muscle glycogen stores very high, not available during exercise; subjects cannot perform strenous exercise; suffer from muscle cramps; blood lactate and pyruvate do not increase after exercise; muscles may get damaged due to inadequate energy supply.
VI	Her's disease	Liver glycogen phosphorylase	Liver	Liver enlarged; liver glycogen cannot form glucose; mild hypoglycemia and ketosis seen.
VII	Tarui's disease	Phosphofructokinase	Skeletal muscle, erythrocytes	Muscle cramps due to exercise; blood lactate not elevated; hemolysis occurs.