Unit2

For internal circulation only

HEXOSE MONOPHOSPHATE PATHWAY

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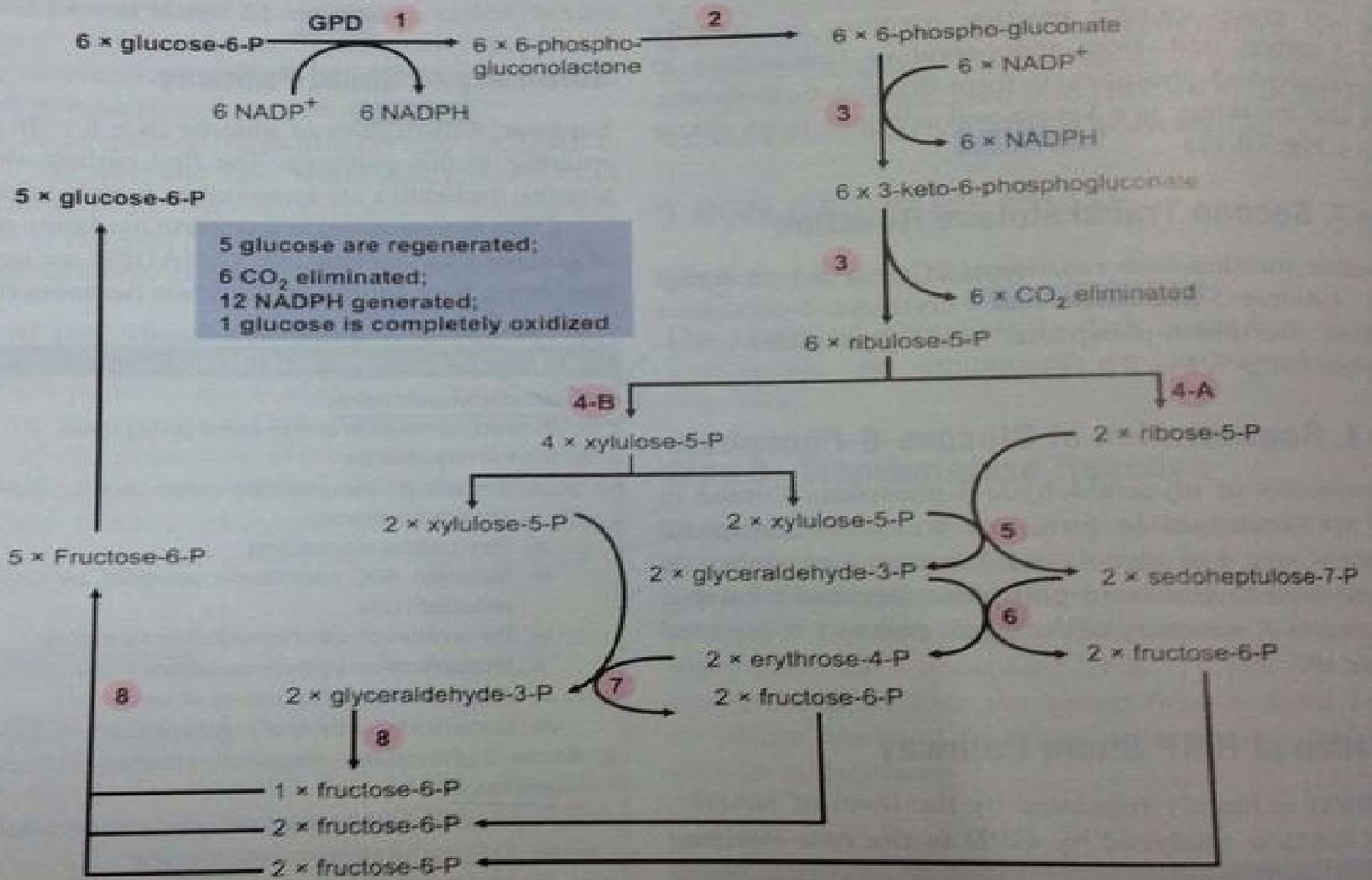
SITE It is located in a cytosol . The tissues such as liver, adipose tissue , adrenal gland ,erythrocytes , testes and lactating mammary gland are highly active in HMP Shunt

REACTIONS OF THE PATHWAY

1)OXIDATIVE PHASE: G6PD Is an NADP dependent enzyme that converts glucose 6 phosphate to 6 phosphogluconolactone. The latter is then hydrolysed by the gluconolactone hydrolase to 6 phosphogluconate. Next reaction involving the synthesis of NADPH is catalysed by 6 phosphogluconate dehydrogenase to produce 3 keto 6 phosphogluconate which undergoes decarboxylation to give ribulose 5 phosphate.

2) NON OXIDATIVE PHASE: It is concerned with interconversion of three,four ,five and seven carbon monosacchrides. Ribulose 5 phosphate is acted upon by epimerase to produce Xylulose 5 phosphate while ribose 5 phosphate ketoisomerase converts ribulose 5 phosphate to ribose 5 phosphate. The enzyme transketolase catalyse the transfer of two carbon moiety from xylulose 5 phosphate to ribose 5 phosphate to form GA3P and sedoheptulose 7 phosphate.Transketolase is dependent on TPP and Mg ions. Transaldolase brings about transfer of 3 carbon from S7P to GA3P to form fructose 6 phosphate and erythrose 4 phosphate.

Suppose, 6 molecules of glucose enter the HMP shunt pathway:



Enzymes:

1 = Glucose-6-phosphate dehydrogenase (GPD)
2 = Gluconolactone hydrolase
3 = 6-phospho-gluconate dehydrogenase
4A = Isomerase
4B = Epimerase
5 = Transketolase
6 = Transaldolase
7 = Second transketolase
8 = Reversal of glycolysis

Encircled pathway numbers shows the steps referred in the text

REGULATION OF HMP SHUNT

The entry of G6P into HMP pathway is controlled by concentration of NADPH.

#NADPH is inhibitor of G6P DH.

The Synthesis of G6P DH is induced by increased insulin/glucagon after a meal.

SIGNIFICANCE:

HMP Pathway generates two important products

1. Pentose
2. NADPH

IMPORTANCE OF NADPH

#It is required for reductive biosynthesis of fatty acids and steroids.

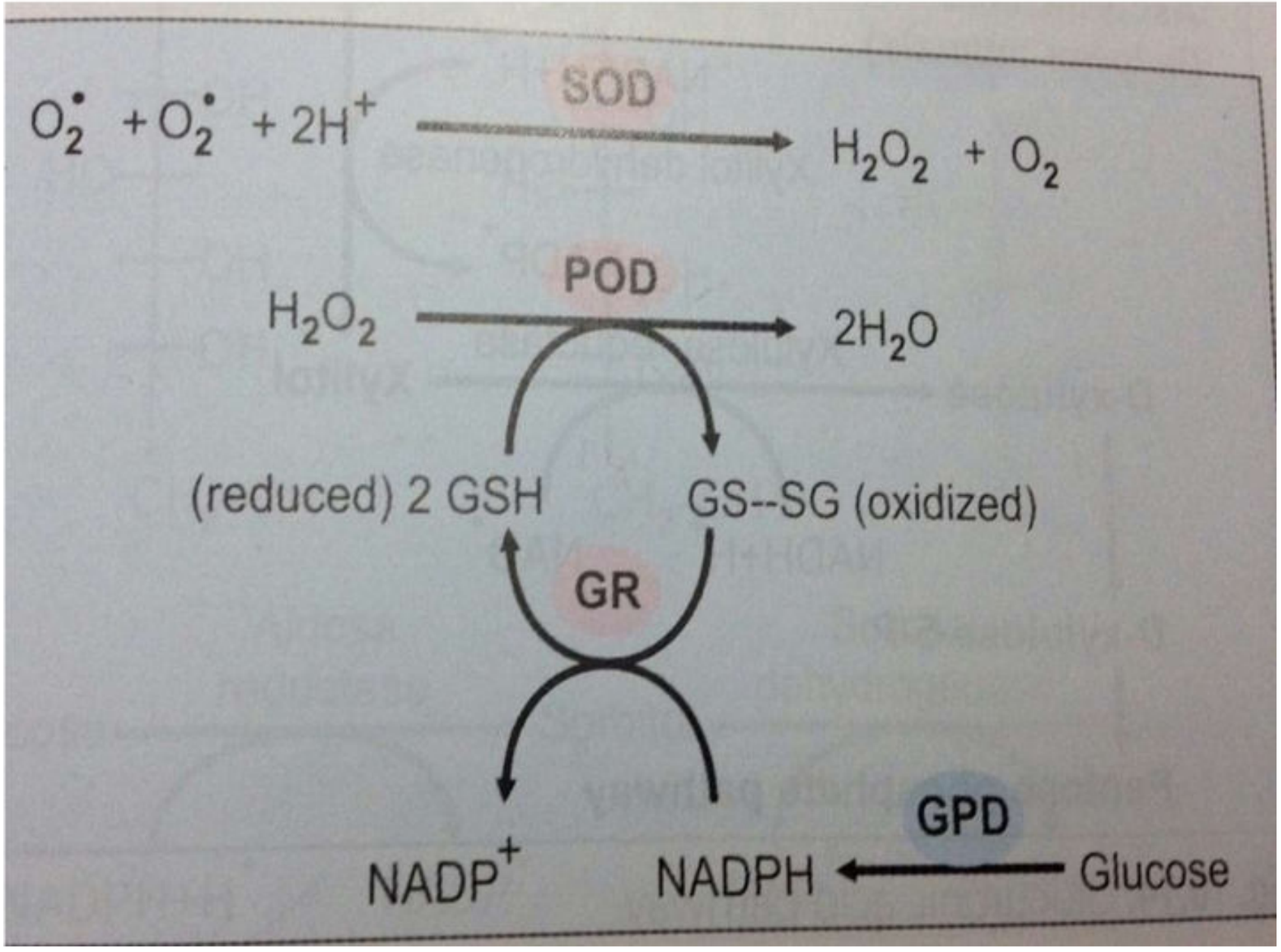
#It is used in synthesis of certain amino acids involving the enzyme Glutamate dehydrogenase.

#Microsomal cytochrome P 450 brings about detoxification of drugs involving NADPH.

#Phagocytosis by WBC requires supply of NADPH.

#NADPH produce in RBC preserve the integrity of RBC membrane.

#GLUTATHIONE:Lipids , proteins and DNA are protected from H_2O_2 by an antioxidant reactions involving NADPH. Glutathione (reduced, GSH) detoxifies H_2O_2, peroxidase catalyses this reaction. NADPH is responsible for regeneration of reduced glutathione from oxidised one.

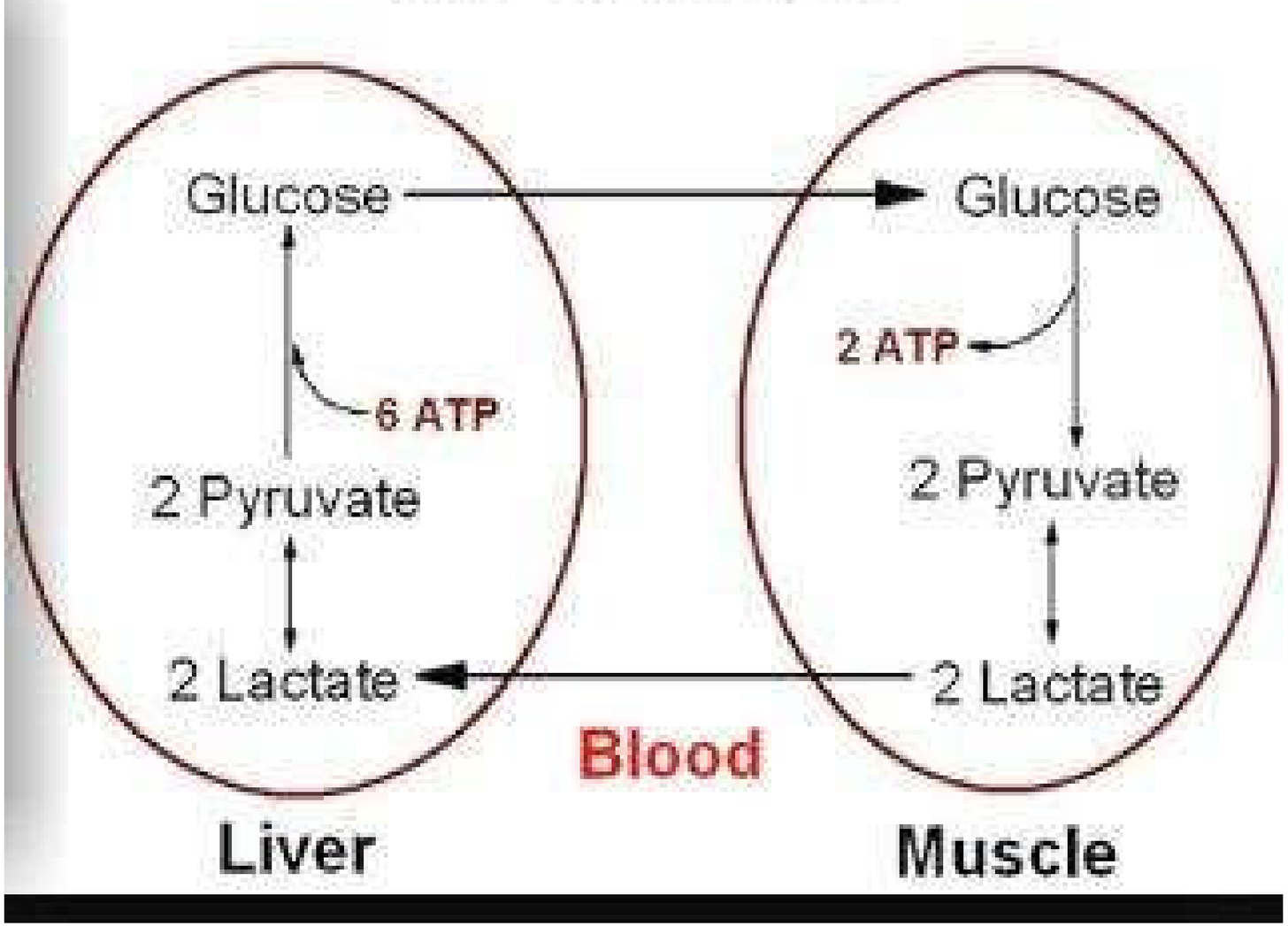

$O_2^{\bullet} + O_2^{\bullet} + 2H^+$
SOD
$H_2O_2 + O_2$
H_2O_2
POD
$2H_2O$
(reduced) 2 GSH
GS--SG (oxidized)
GR
$NADP^+$
NADPH
GPD
Glucose

G6P DH deficiency causes Hemolytic Anemia: Mutations cause deficiency of G6P DH with consequent impairment of NADPH. Detoxification of H2O2 is inhibited and cellular damage results- Lipid peroxidation leads to RBC membrane breakdown and hemolytic anemia.

CORI CYCLE (GLUCONEOGENESIS FROM LACTATE)

Lactate produced by skeletal muscles is a major precursor for gluconeogenesis. Lactate or pyruvate produced in muscle cannot be utilized for the production of glucose due to the absence of certain enzymes(G6Pase and F16BPase).Therefore lactate is carried from the muscle through blood to liver where it is oxidized to pyruvate. Pyruvate so produced is converted to glucose by gluconeogenesis.

The Cori Cycle



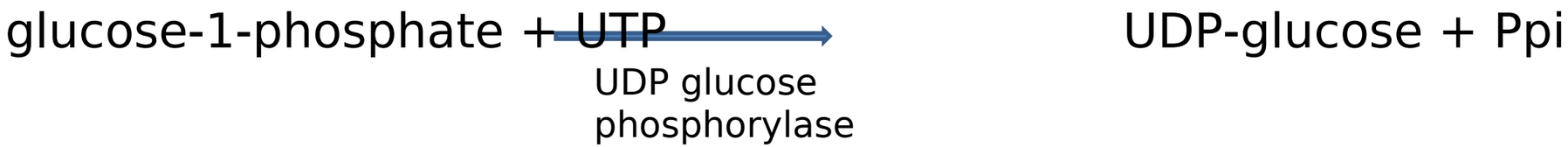
Glycogen synthesis (Glycogenesis)

- Glycogen is the storage form of carbohydrates in the human body.
- The major sites of storage are liver and muscle.
- Glycogenesis is the synthesis of glycogen from blood glucose for storage in the body.

The various steps involved are:-

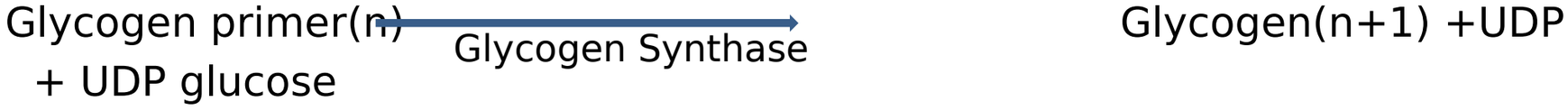
- **ACTIVATION OF GLUCOSE**

  UDP glucose is formed from glucose-1-phosphate and UTP by the enzyme UDP-glucose pyrophosphorylase.



Glycogen Synthase

- Glucose moiety from UDP glucose is transferred to glycogen primer(glycogenin).
- Primer is essential to accept glycosyl unit. It is made up of protein-carbohydrate complex



- In next step, activated glucose units are added by the enzyme glycogen synthase. The glucose unit is added to the non reducing(outer) end

of the primer to form an alpha-1,4 glycosidic linkage and UDP is liberated.

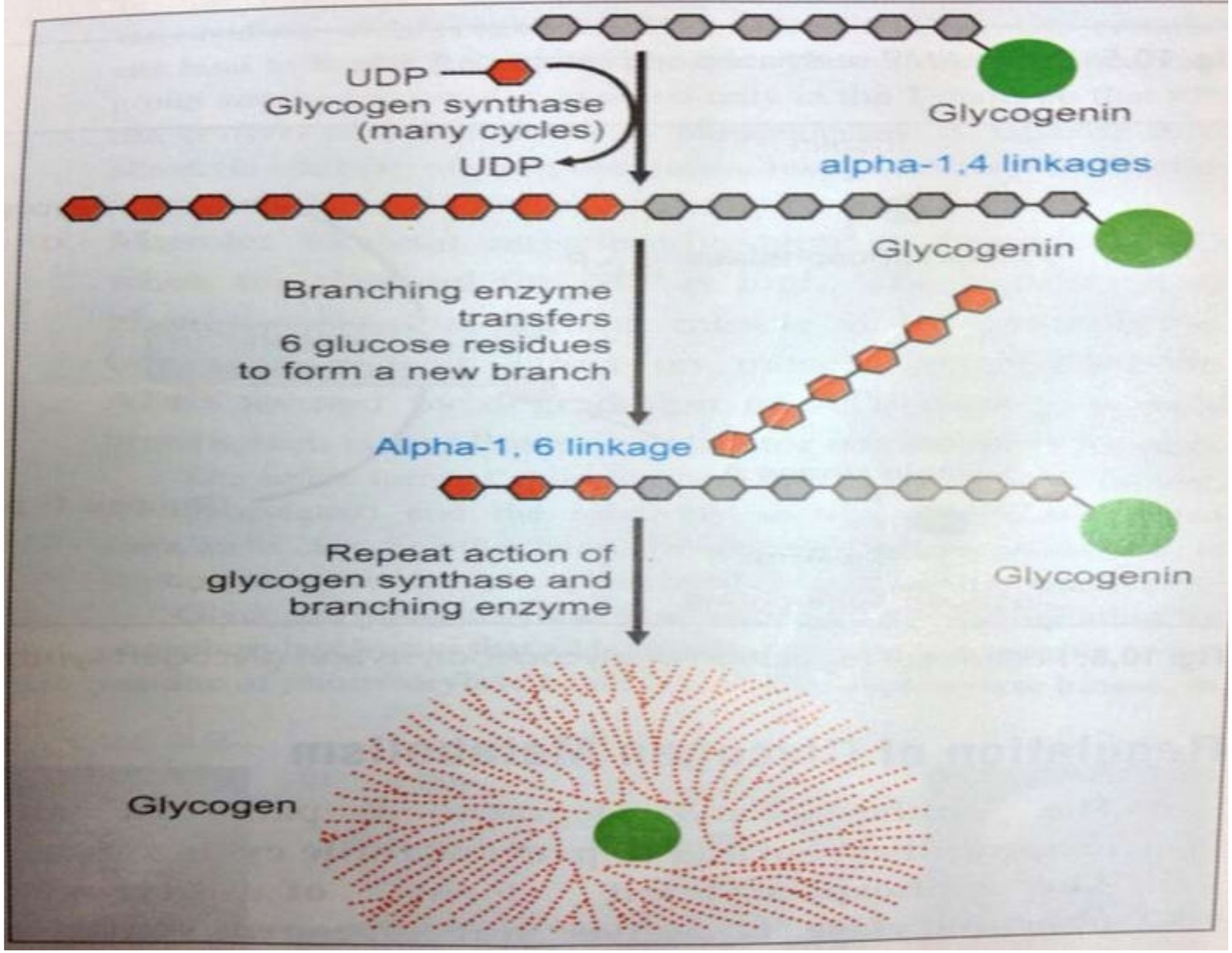
BRANCHING ENZYME

- This enzyme creates alpha-1,6 linkage.
- When the chain is lengthened to 11-12 glucose residues, the branching enzyme will transfer a block of 6 to 8 glucose residues from this chain to another site on the growing molecule. This enzyme **amylo-[1,4] [1,6]-transglucosidase** forms alpha-1,6 linkage.

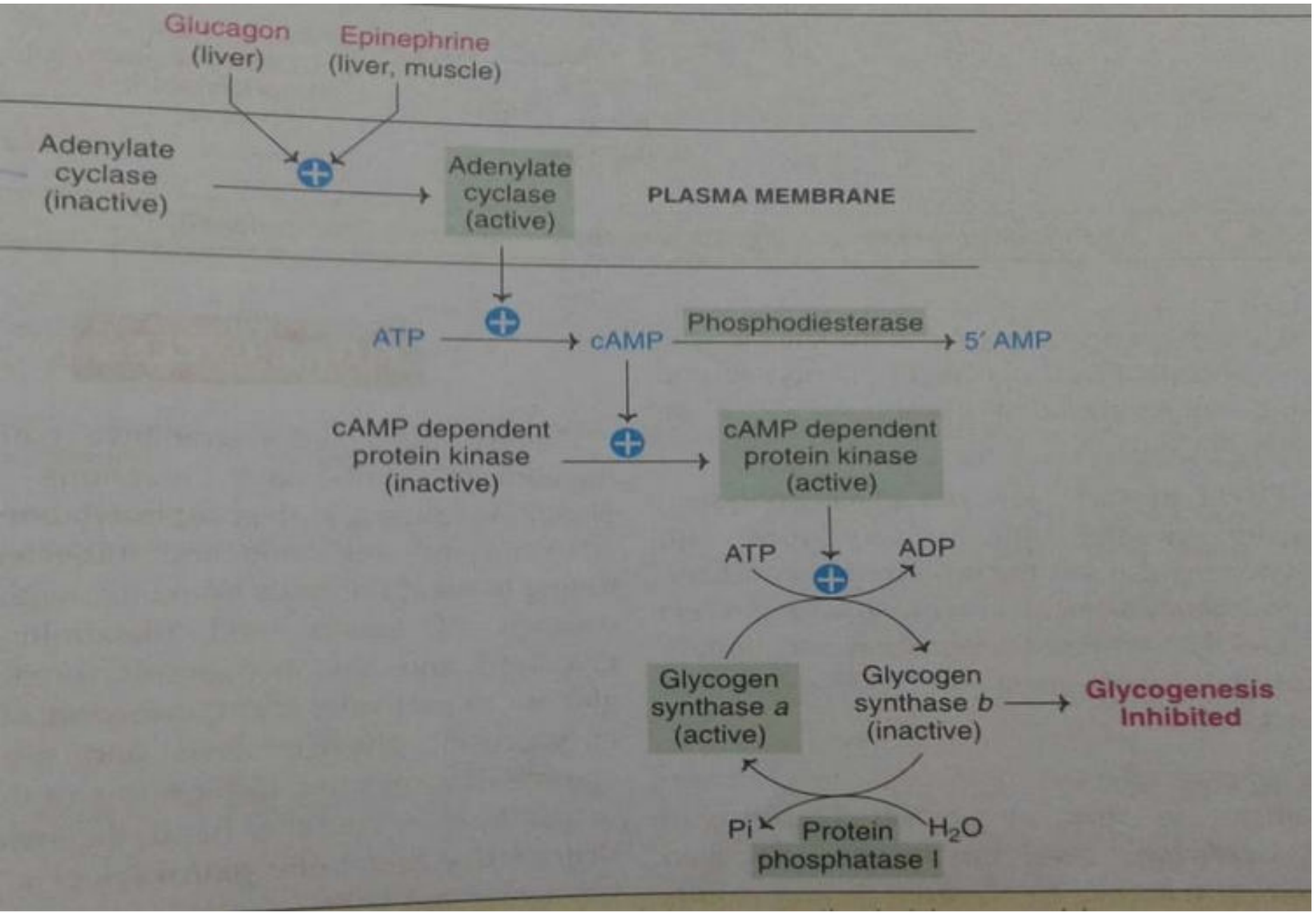
- To this newly created branch, further glucose units can be added in alpha-1,4 limkage by glycogen synthase.

Important points

- The key enzyme for glycogenesis is glycogen synthase, the activity of which is decreased by glucagon and epinephrine but is enhanced by insuli, under the stimulus of hyperglycemia.
- Glycogen synthase enzyme becomes inactive on phosphorylation.
- The covalent modification of this enzyme is by a cyclic AMP mediated cascade.


UDP
Glycogen synthase
(many cycles)
UDP
Glycogenin
alpha-1,4 linkages
Glycogenin
Branching enzyme
transfers
6 glucose residues
to form a new branch
Alpha-1, 6 linkage
Glycogenin
Repeat action of
glycogen synthase and
branching enzyme
Glycogen

Regulation of glycogenesis



GLYCOGEN STORAGE DISEASES

The metabolic defects concerned with the glycogen synthesis and degradation are collectively reffered to as glycogen storage diseases. These disorders are characterised by deposition of normal or abnormal type of glycogen in one or more tissues.

VON GIERKE’S DISEASE(TYPE1)

This disorder results invarious boochemical manifestations

1.fasting hypoglycemia:due to the defect in the enzyme glucose 6 phosphate enough glucose is not released from the liver

2.lactic acidemia:glucose is not synthesised from the lactate produced in the muscle and liver. Therefore lactate level in the blood increases.

3.hyperlipidemia:there is the blockade in a gluconeogenesis hence more fat is mobilised to meet energy requiremenats of the body.

4.hyperuricemia:elevated plsma levels of uric acid are often seen.

POMPE’S DISEASE(TYPE2):

1.It is due to the defect of enzyme lysosomal a-1,6 glucosidase.
2.All the organs are involved.
3.glucogen accumlates in lysosome in almost all the tissues,heart is mostly involved,enlarged liver nd heart,death occurs at an early age due to heart failure,nervous system is also affected.