15

Bio chemistry

Doctor 2017 | Medicine | JU

◉ Sheet ○ Slides

Done By

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Contributed in the Scientific Correction

shehab

Contributed in the Grammatical Correction

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Doctor

Nayef

Glycogen Metabolism

Sources of Blood Glucose

*** Diet**

- Starch, mono and disaccharides, glucose

- Sporadic, depend on diet

*** Gluconeogenesis**

- Sustained synthesis

- Slow in responding to falling blood glucose level

*** Glycogen**

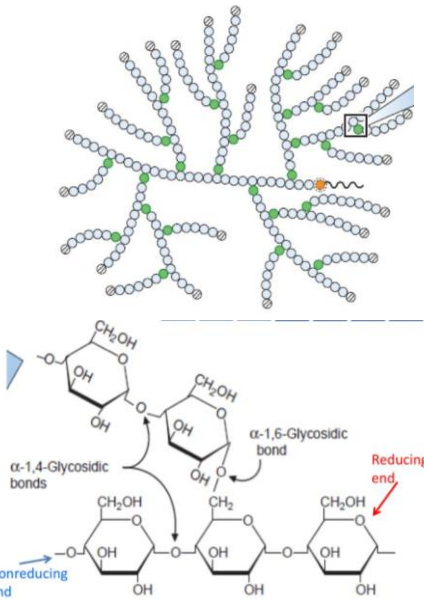
- Storage form of glucose

- Rapid in responding to falling blood glucose and mobilization

- Limited amount

- Important energy source for exercising muscle

Glycogen:

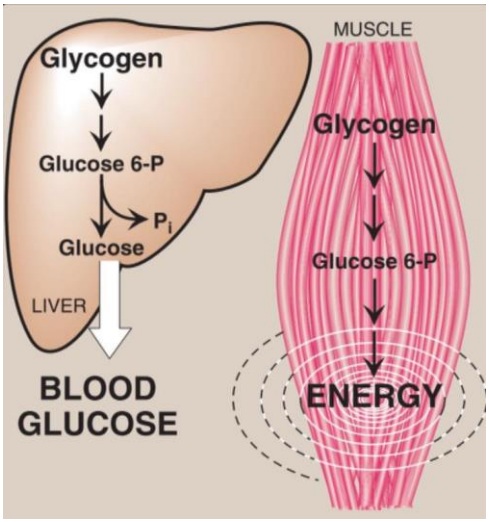


It's an extensively branched homopolysaccharide so that one molecule consists of hundreds of thousands of glucose units- up to M.W. of 100,000,000.

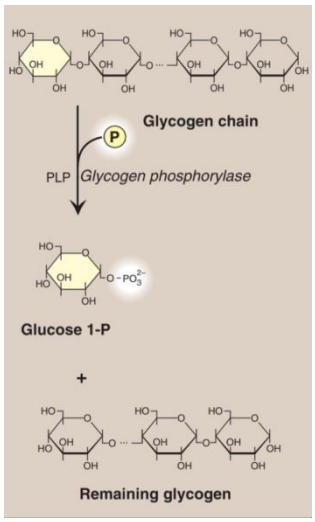
In the linear chains, the glucose residues are connected by α-1,4-glysodic linkages while α-1,6-glysodic bonds create the branching points.

The first glucose residue in the linear chain forms a reducing end (the only reducing end in glycogen), while glucose residues at the end of branches forms non-reducing ends which means that the anomeric carbon isn't free (in fully acetal form). The non-reducing ends are the locations of all glucose addition and removal.

Degradation of glycogen



The main stores of glycogen are found in skeletal muscles and liver. In liver the glycogen is used to maintain the blood glucose concentration while muscle glycogen is used only by the muscle to provide energy for muscle contraction. Glucose-6-phsopate can't cross the membrane and enter the circulation so it must be converted to glucose by glucose-6-phosphatase which is not found in the skeletal muscle.

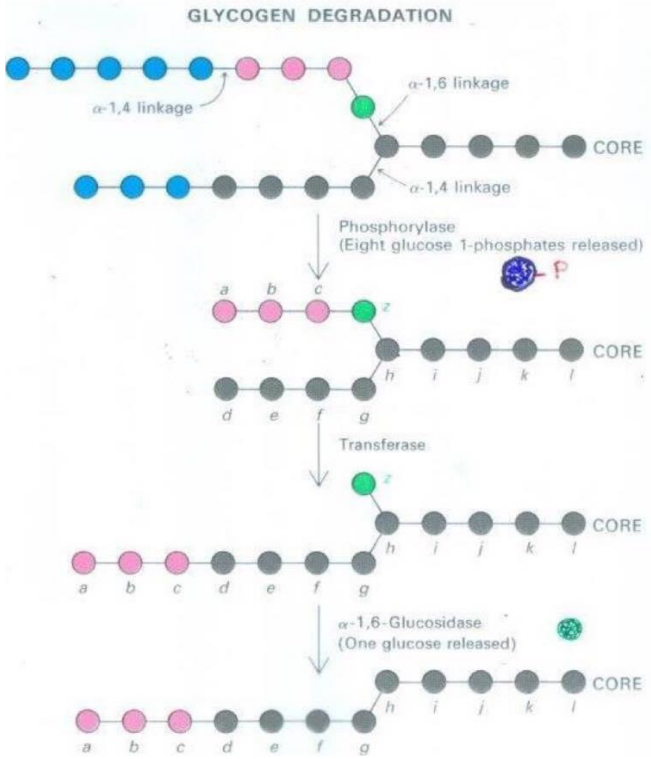


* Glucose given from liver to the blood stream can be generated by 2 ways, either by glycogenolysis or by gluconeogenesis. Both produce glucose 6-P that is converted to glucose by glucose 6-Phosphatase.

-One glucose unit is removed at a time from the non-reducing ends only and is released in the form of glucose 1-phosphate.

Mechanism:

1. **Glycogen phosphorylase** sequentially cleaves the α-1,4-glycosidic bonds between the glucose residues at the non-reducing ends of the glycogen chains (producing glucose 1-P) until four glucose units remain on each chain before a branch point then it stops.



- Glycogen phosphorylase needs a cofactor called pyridoxal phosphate.

2. Branches are removed by the two enzymic activities of a single bifunctional protein (has 2 activities), **the debranching enzyme**.

a) Transferase activity: removes the outer three of the four glucose residues attached at a branch. It next transfers them to the non-reducing end of another chain, lengthening it accordingly. The enzyme works as 4:4

transferase because the same 1,4-glysodic bond that was broken in the first branch is reformed in the other branch.

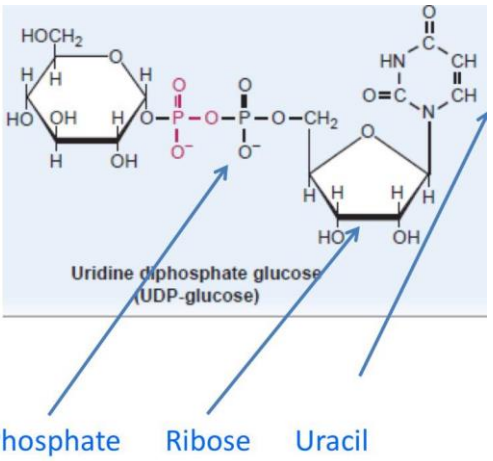
b) α-1,6-glucosidase activity: releases the last residue as free glucose not glucose 1-P.

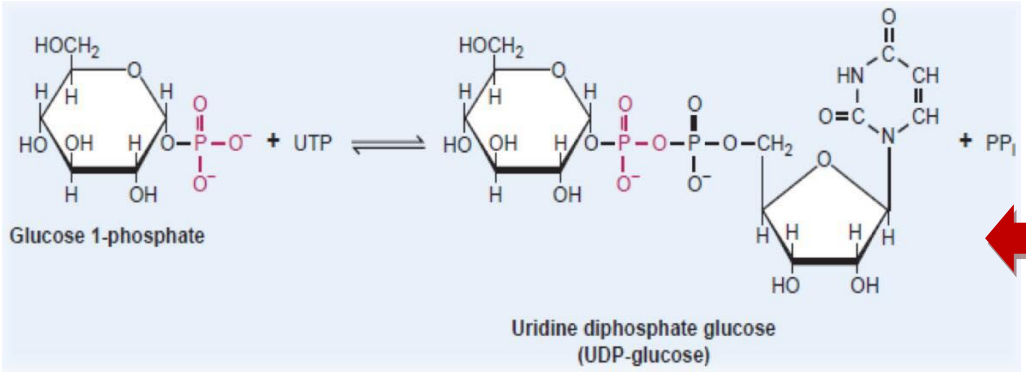
The glucose chain is now available again for degradation by glycogen phosphorylase until four glucose units from the next branch are reached.

Glycogen Synthesis

- Glycogen is synthesized by adding glucose one by one and UDP-Glucose is considered the active donor of glucose units.

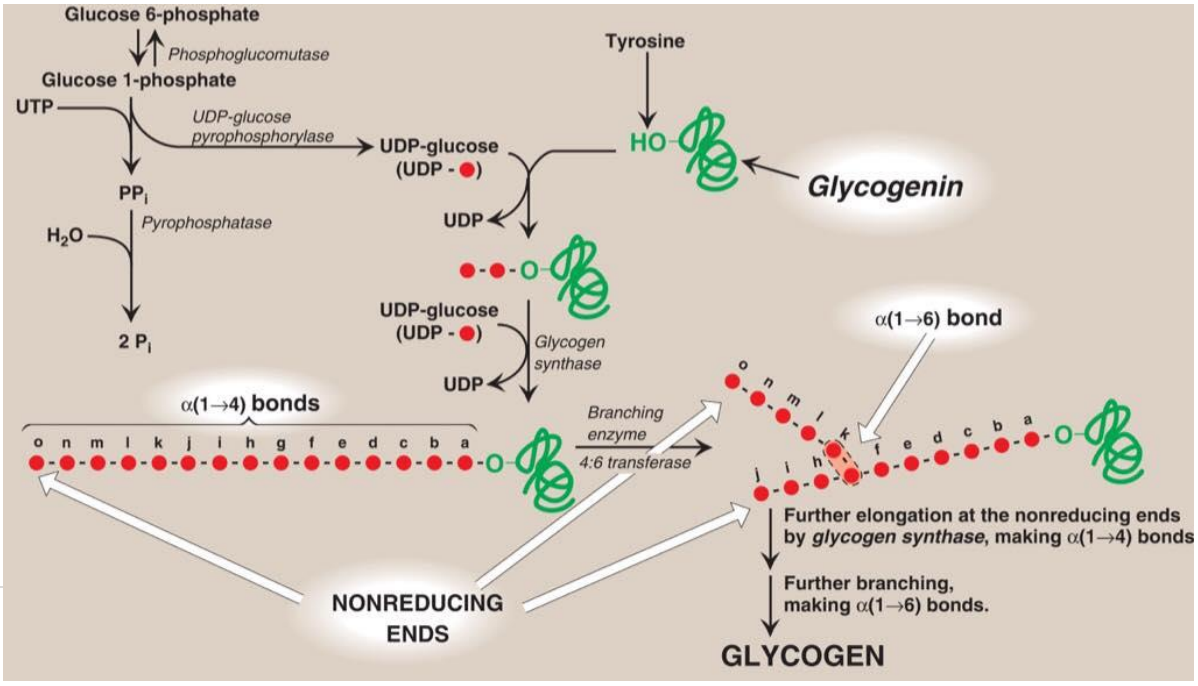
UDP-glucose consists of uracil, ribose, 2 phosphates, and glucose.



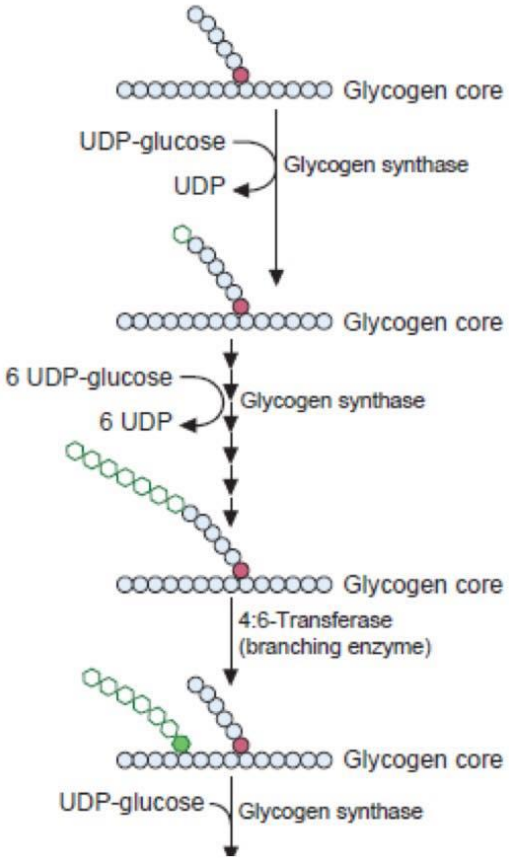


UDP-glucose formation

Mechanism:



1. **Phosphoglucomutase** converts glucose 6-P into glucose 1-P, then glucose 1-P is activated by binding to UTP forming UDP-glucose & pyrophosphate which will be degraded into 2 phosphates by an enzyme called **pyrophosphatase** (this reaction gives energy which ensures that the reaction (G 1-P +UTP>>UDP-glucose+PPi) proceeds in the direction of UDP-glucose production making it irreversible).



2. glycogen synthase makes the 1-4 linkages in glycogen but this enzyme can only add glucose to already existing glycogen (like DNA polymerase 3).

3. If the liver is empty of glycogen, the enzyme needs a primer in order to add glucose molecule.

The primer is made by an enzyme called **Glycogenin** that works on autocatalysis (binds a glucose residue to tyrosine group forming a 9-10 residue chain, then glycogen synthase can work on the primer).

4. Forming branches: **Branching enzyme** removes a chain of six to eight glucose residues from the non-reducing end of the glycogen chain, breaking an 1,4- bond, to another residue on the chain, and attaches it to a non-terminal glucose residue by an 1,6-linkage, thus functioning as a 4:6 transferase.

-The resulting new, non-reducing end, as well as the old non-reducing end from which the six to eight residues were removed can now be further elongated by glycogen synthase.

* Branching enzyme makes branches 8 residues apart.

Energy needed for glycogen synthesis

$$\text{Glucose} + \text{ATP} \longrightarrow \text{Glucose 6-phosphate} + \text{ADP}$$

$$\text{Glucose 6-phosphate} \rightleftharpoons \text{Glucose 1-phosphate}$$

$$\text{Glucose 1-phosphate} + \text{UTP} \rightleftharpoons \text{UDP-Glucose} + PP_i$$

$$PP_i + H_2O \longrightarrow 2P_i$$

$$\text{UDP-Glucose} + \text{Glycogen}_{(n)} \longrightarrow \text{UDP} + \text{Glycogen}_{(n+1)}$$

$$\text{Glc.} + \text{ATP} + \text{UTP} + \text{Glycogen}_{(n)} \longrightarrow \text{ADP} + \text{UDP} + \text{Glycogen}_{(n+1)}$$

Glycogen Storage Diseases:

It's genetic diseases which involves a defect in an enzyme required for the synthesis or degradation of glycogen causing accumulation of excessive amounts of glycogen (the glycogen structure may be normal or abnormal) in one or more tissue. If the affected enzyme is specific for certain type of tissue (there are isoenzymes found in other tissues) the accumulation will be only in that tissue, while the effect will be generalized if there's no isozyme (the enzyme is the same in all type of tissues).

Most of glycogen storage diseases are mild disorders, some are moderate, and some are fatal.

- There are many glycogen storage diseases but we're going to talk about 3 diseases:

1. Glycogen Storage Disease Type I:

Studies showed that 1 from 50000 will have that disease. It is the most common.

It consists of 2 subtypes:

Type Ia: VON GIERKE DISEASE (Glucose 6-Phosphatase deficiency)

Type Ib: Glucose 6-P translocase deficiency (this enzyme moves glucose 6-P to the ER in order to remove the phosphate group)

- These 2 enzymes are found in the liver, kidney and intestine so they will be all affected by this disease causing severe fasting hypoglycemia, progressive renal disease, growth retardation, and delayed puberty.

- In liver, glucose-6-phaspahte doesn't undergo mobilization, so it will be slowly accumulated as glycogen, and its percentage will reach 20%. In addition to accumulation of fats (glucose-6-phospahte> pyruvate> acetyl CoA> fat) leading to Hepatomegaly fatty liver. Glucose-6-phspahte also goes through glycolysis without getting into the blood stream, and the excess amount of pyruvate is converted into lactate causing Hyperlacticacidemia.

((Note: Glycogen percentage in the liver is 10% while in muscles it's 1-2% which equals 400 grams in muscles))

- Glucose 6-P enters through a pathway (Pentose phosphate pathway) that forms ribose 5-P which is a precursor for synthesis of purine nucleotides causing hyperuricemia (which will be explained later on this semester).

- Normal glycogen structure; increased glycogen stored.

*** Treatment: Nocturnal gastric infusions of glucose or regular administration of uncooked cornstarch every 3 hours even at night.**

2. Glycogen Storage Disease Type V (Muscle glycogen phosphorylase deficiency)- (McArdle syndrome)

- Only muscle is affected because this isozyme is located in muscles.

- It has mild effects which involve <u>weakness and cramping of muscle after exercise.</u>

(Note: muscle glycogen won't be affected much by fasting because it's there to give the muscle its own energy while exercising.)

- There will be no increase in [lactate] during exercise.

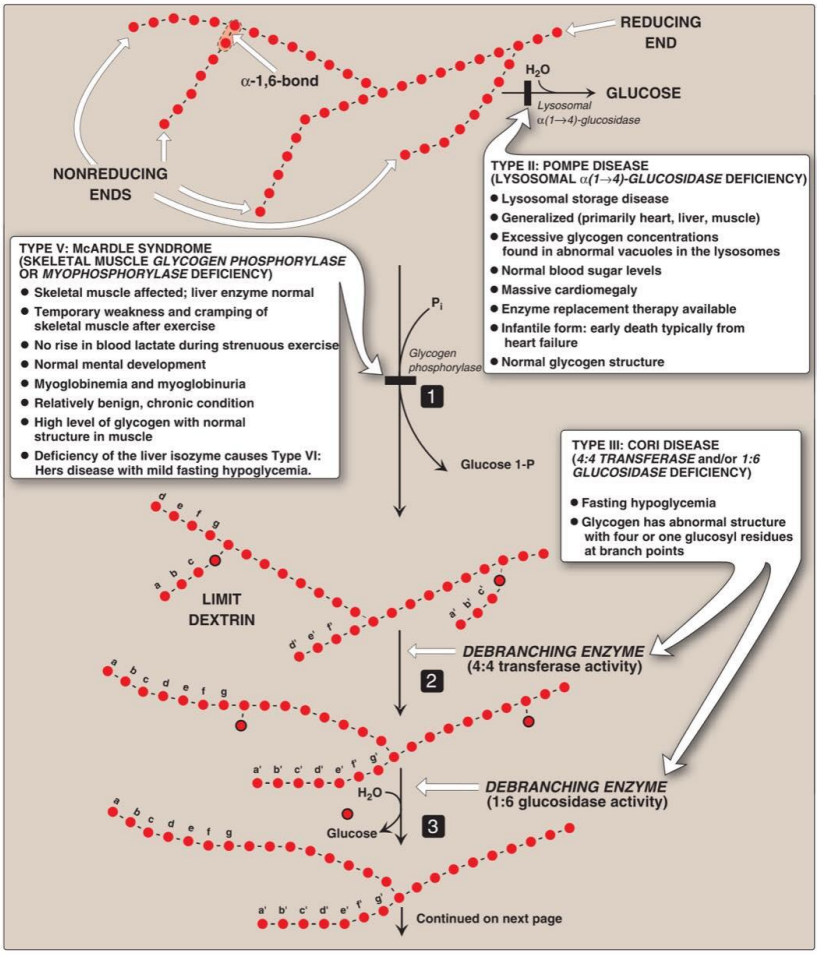
3. Glycogen Storage Disease Type II (Lysosomal α-1,4- glucosidase deficiency) ➔ POMP Disease

-Affects degradation of glycogen in the lysosomes which degrades almost 3% of glycogen.

-Excessive glycogen will accumulate in abnormal vacuoles in the lysosomes in several tissues including liver, heart and muscle causing <u>massive cardiomegaly and early death from heart failure.</u>

-Normal blood sugar, normal glycogen structure

<u>This is the type of glycogen storage disease that is fatal.</u>



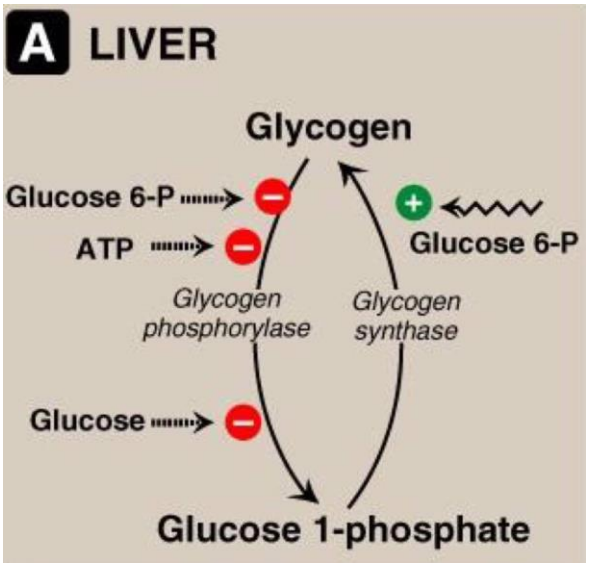
Regulation of glycogen synthesis & degradation:

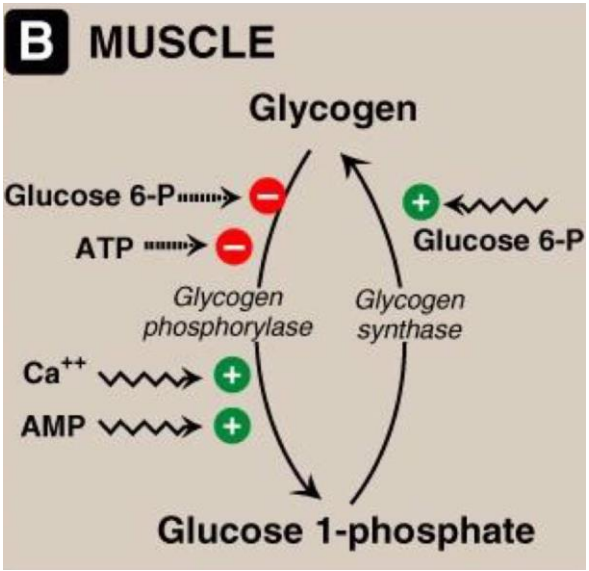
Regulation can be rapid (allosteric regulation) and can be slow (neurotransmitters and hormones).

In the well-fed state, glycogen synthase in both liver and muscle is allosterically activated by glucose 6-phosphate which is present in elevated concentrations. In contrast, glycogen phosphorylase is allosterically inhibited by glucose 6-phosphate, as well as by ATP, a high-energy signal in the cell.

In liver, but not muscle, non-phosphorylated glucose is also an allosteric inhibitor of glycogen phosphorylase.

Ca+2 & AMP activates Glycogen phosphorylase in muscles (this will be our next topic).





** Recall allosteric regulation that was previously mentioned in sheet 13 & 14 for glycolysis and gluconeogenesis:

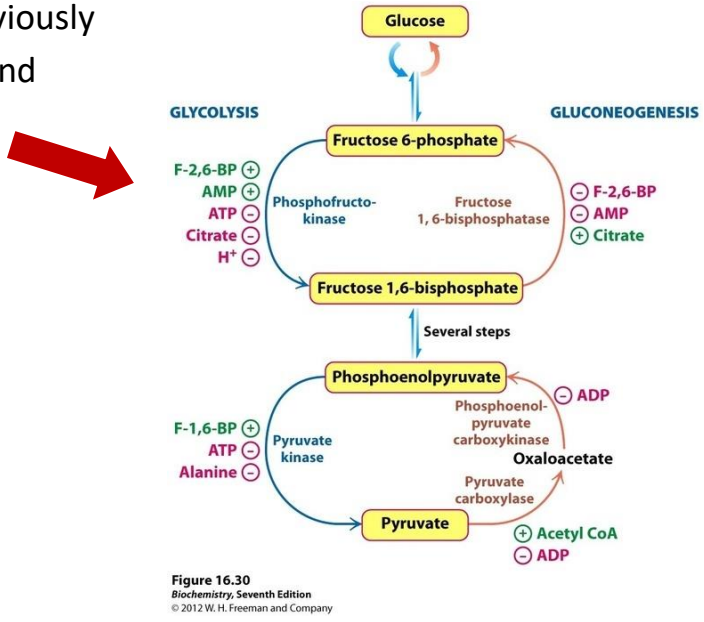


Figure 16.30
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GOOD LUCK :)