بسم الله الرحمن الرحيم

METABOLISM

MID – Lecture 15

Gluconeugenesis & Metabolism of Monosaccharides and disaccharides (Pt.1)

﴿ وَإِن تَتَوَلَّوْا يَسْتَبْدِلْ قَوْمًا غَيْرَكُمْ ثُمَّ لَا يَكُونُوا أَمْثَالَكُم ﴾

اللهم استعملنا ولا تستبدلنا

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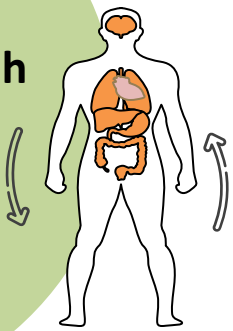

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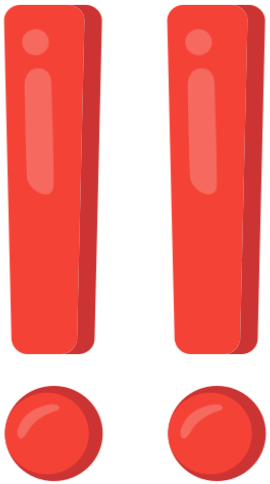
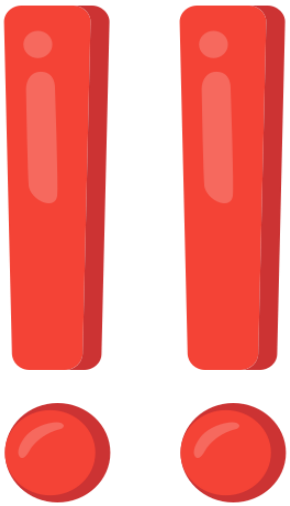
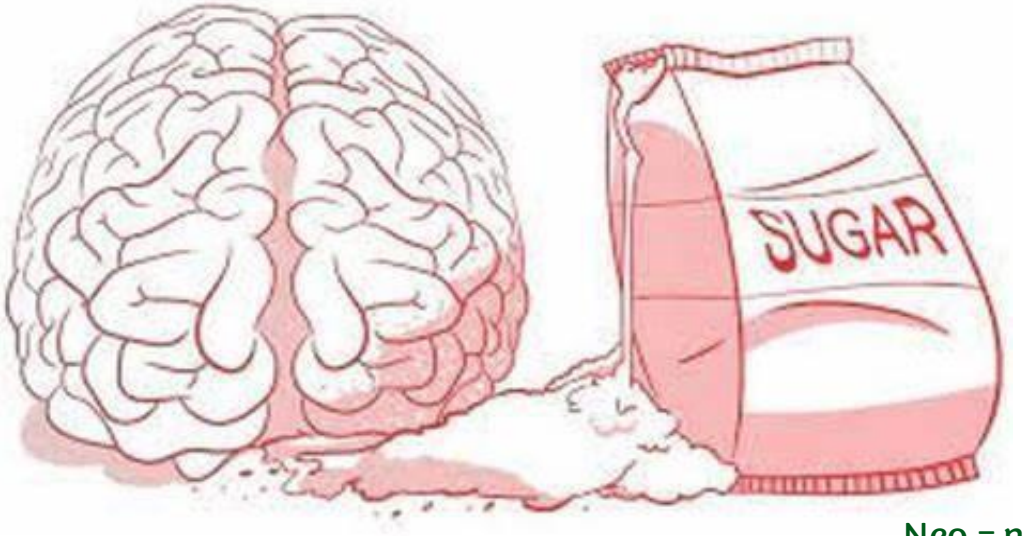
Lecture 15

Previous Lecture Quiz



Quiz Link





Neo = new

Gluconeogenesis

Genesis = generation

(Production of glucose from non- carbohydrate precursors)

Dr. Diala Abu-Hassan

We discussed that it's sustained source of glucose under fasting condition .
During fasting: in the beginning, the source of energy comes from glycogen (but it does not last longer than 24 hours).
Then we shift to gluconeogenesis to provide glucose to the blood to:
maintain blood sugar level + supply brain and other tissues that depend on glucose as a source of energy.

Glucose Synthesis is Required for Survival

(explained in the next two slides)

- Brain is dependent on glucose 120g/day (huge amount of glucose is consumed)
- Body glucose reserve/storage is limited

  ≈ 20 g (extracellular fluid) These compose GAGs, they are dynamic, sugar could be added or removed (+/- 5g) depending on the condition (tissue pressure-function NOT well-fed/ fasting states).

  ≈ 75 g (liver glycogen); enough for 16 hours

  ≈ 400 g (muscle glycogen); for muscle use **only**

  Main source of energy for resting muscle in post-absorptive state
- 70 Kg man has ≈ 15 Kg fat
  - Fatty acids can not be converted to glucose
  - Utilization of FA is increased 4-5 X in prolonged fasting
  - In prolonged fasting; FA ➔ ketone bodies at high rate

Glucose Synthesis is Required for Survival (1)

Body glucose reserve is limited; so why isn't the percentage of stored glucose in the form of glycogen increased?

Large amounts of glycogen can't be stored **because** the amount of energy stored in one gram of sugar is less than energy stored in one gram of fat

(1 gram of sugar = 4 kilocalories, while 1 gram of fat = 9 kilocalories ...Almost double!). > So, it's more efficient to store fat.

- Fat molecules generally are **non-polar** while sugar molecules are **polar**, whenever glucose molecules are stored, they attract H2O molecules and swell and become a gel-like structure so the sugar molecules become larger.
- To store one kilogram of sugar, an additional kilogram of water is attracted, increasing total mass and creating a gel-like appearance.

[So briefly, Sugar (e.g., glucose) is a polar molecule that attracts water due to hydrogen bonding. When sugar is stored or dissolved, it absorbs water, causing it to swell and form a gel-like structure. The process increases the volume and mass of the sugar-water mixture, thus increasing body mass]

Example: A 70 kg man has 15000 grams of fat; how much energy is stored in it?
[REMEMBER 1 gram of fat = 9 kilocalories of energy] so 15000* 9 = 135000 kilocalories .
If the same amount of energy were stored in the form of sugar, how much sugar would be required?
33.75 kg + the H2O that will be attracted, more than double amount!!
(Energy per gram of sugar: 4 kcal/gram. >> Total energy needed: 135,000 kcal.
To find out how many grams of sugar are needed, divide the total energy by the energy per gram of sugar: 135000/ 4)

So it more efficient to store lipids than sugar molecules .

Glucose Synthesis is Required for Survival (2)

- Glycogen acts as a bridge between the well-fed and fasting states. During the early phase of fasting, the body relies on glycogen stores to provide glucose, but this supply is limited.
- As fasting continues, the body shifts to gluconeogenesis to produce glucose not primarily for energy, but mainly to maintain blood sugar levels and supply glucose to cells that depend on it, such as the brain.
- Unlike the brain, tissues like the heart and kidneys do not rely on glucose from gluconeogenesis; they use fatty acids as their primary fuel source during fasting.

There is overlap between processes; before the blood glucose runs out, the body start preparing for gluconeogenesis, which mainly occurs under fast conditions (high level of glucagon hormone)

** Glucagon will bind to its target cells in adipose tissue and activates the degradation of triacylglycerol into glycerol & fatty acids. Fatty acids are carried by albumin (a plasma protein) and distributed to cells so they can be oxidized to produce energy. Glycerol acts as a precursor for gluconeogenesis.

Gluconeogenesis occurs mainly in the liver

(explained in next slides)

Tissues that do not oxidize glc. completely
e.g RBCs
Exercising muscle

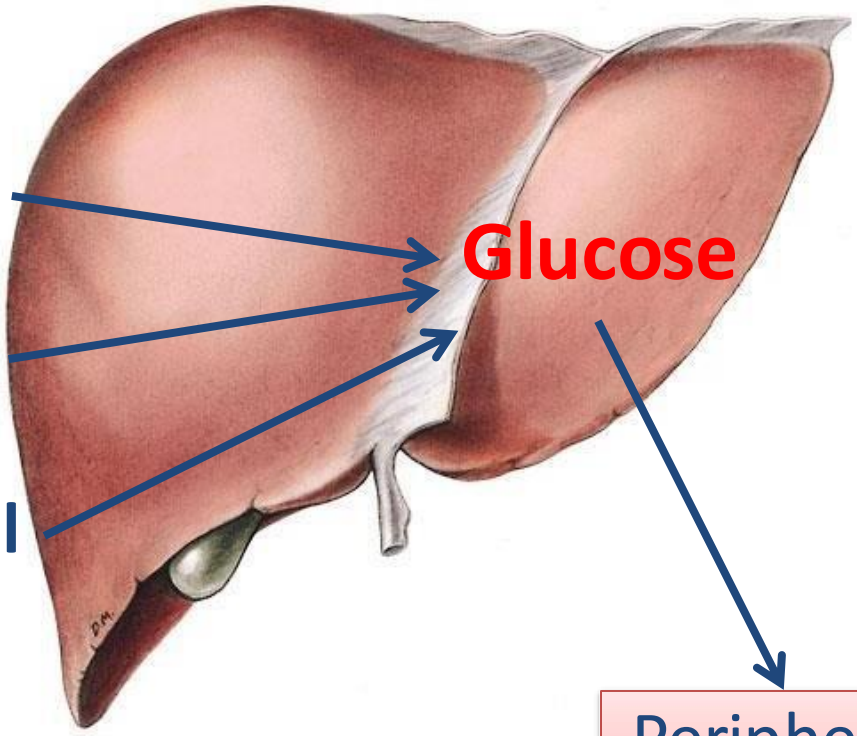
Lactate

Muscle
Glucogenic A.As

Alanine

Glycerol

Adipose tissue



Glucose

Peripheral tissues

Gluconeogenesis occurs mainly in the liver (explanation)

* **Glycerol** is not the only non-carbohydrate precursor for glucose production; **amino acids**, particularly **alanine**, can also serve as important precursors. Many amino acids can be broken down into **pyruvate** (the alpha-keto acid of alanine) or intermediates of the **Krebs cycle**. These **glucogenic amino acids**—majority of amino acids—can be released from muscle cells and used in **gluconeogenesis** to produce glucose.

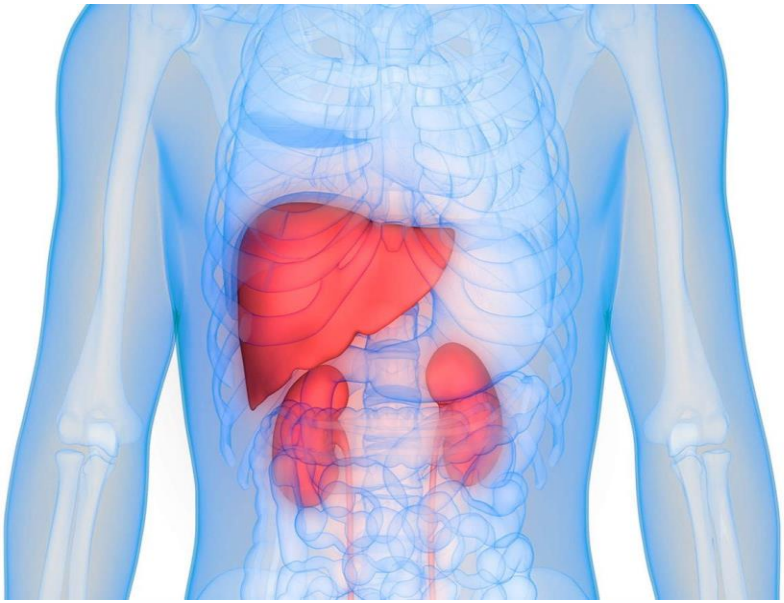
*In addition, **lactate** is another important precursor for gluconeogenesis. It's produced during **anaerobic respiration**, which occurs when oxygen levels decrease, such as:

1. During prolonged exercise. As **muscles** work without sufficient oxygen, they switch to anaerobic metabolism, producing lactate and causing fatigue.
2. It's also found in **RBCs**, which rely on anaerobic metabolism due to the absence of mitochondria. Unlike muscles, RBCs don't experience fatigue because they don't have the fibers that contribute to muscle fatigue.

The lactate produced in muscles and RBCs can be transported to the **liver, where it's converted back into **glucose**, helping to maintain blood glucose levels during periods of intense activity or low oxygen supply.

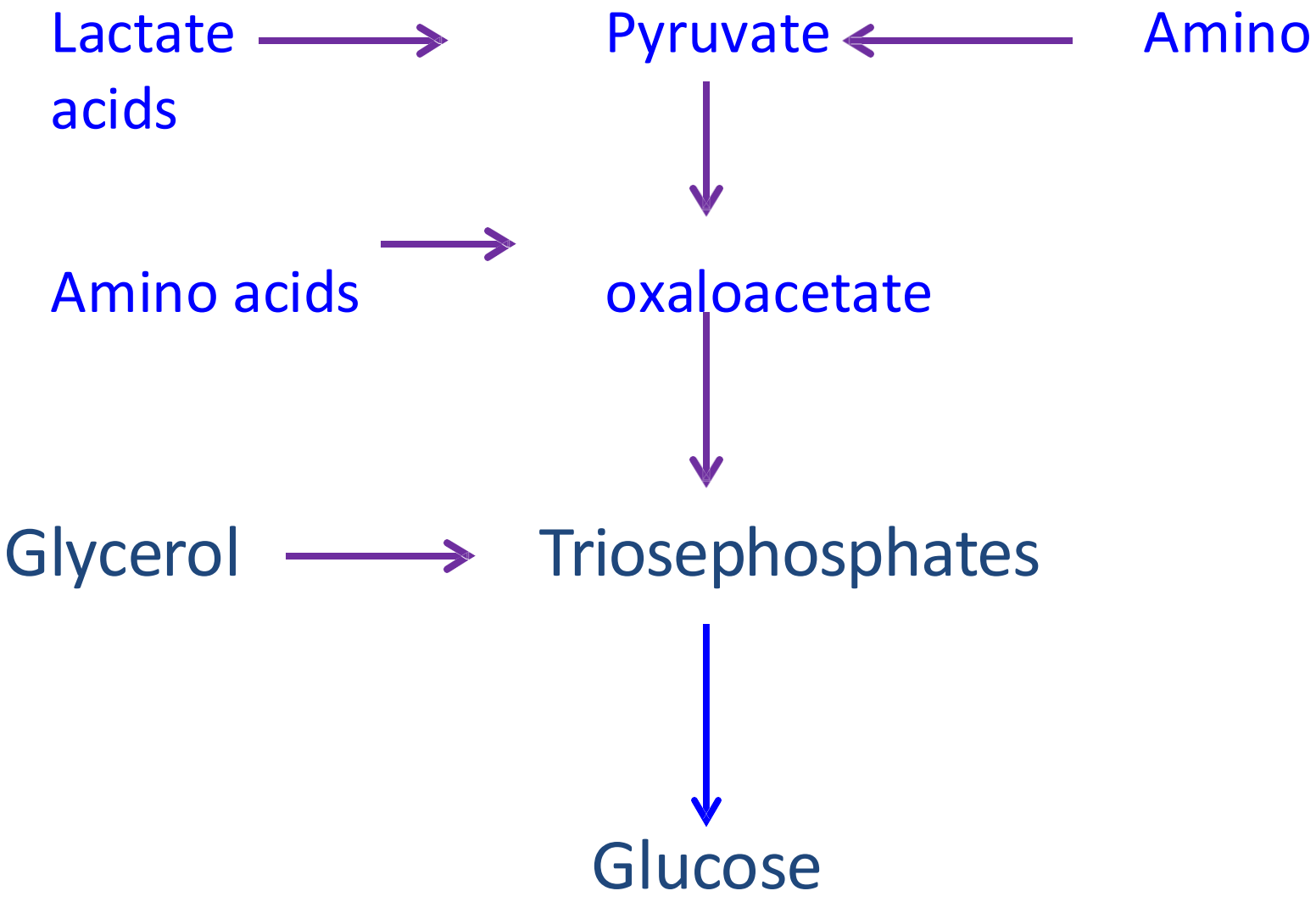
***Glycerol**, **alanine**, and **lactate** are different raw compounds that provide flexibility to the **gluconeogenesis** process. These compounds, derived from various tissues such as **adipose tissue** (glycerol), **muscle** (alanine), and **(RBCs)**(lactate), are transported to the primary sites of gluconeogenesis—mainly the **liver** and sometimes the **kidneys**. The use of different precursors from diverse tissues extends and prolongs the gluconeogenesis process((بتطول لتوصل الكبد, providing a long-term supply of **glucose** to the body, esp. during periods of fasting or prolonged exercise, ensuring a continuous source of energy.

Where and when does gluconeogenesis occur?



- During an overnight fast, ~ 90% of gluconeogenesis occurs in the liver and 10% by the kidneys
- During prolonged fasting kidneys become major glucose-producing organs (40% of total glucose production)
  - the liver continues to work more, but the contribution of the kidneys will increase.

Entrance of substrates into gluconeogenesis



Entrance of substrates into gluconeogenesis

(explanation)

How do these different substrate of precursor molecules enter to gluconeogenesis pathway ?

They enter different stages during the pathway!

- For example: **lactate** is oxidized to **pyruvate**, entering at the beginning of the pathway, as gluconeogenesis essentially reverses glycolysis (which starts with pyruvate and ends with glucose.)
- In the next step, Some **amino acids** once degraded, produce oxaloacetate (which is an intermediate molecule in gluconeogenesis)
- **Glycerol** enters the pathway in the 3rd step as **triose phosphates** (such as **GAP** and **DHAP**) after being phosphorylated and oxidized, due to their structural similarity to these intermediates.

Different points of entry !!

Gluconeogenesis is the opposite of glycolysis BUT

Gluconeogenesis pathway:

**All 7 steps that are reversible in glycolysis will be reversed by the same enzymes. However, irreversible steps are reversed by different enzymes and steps.

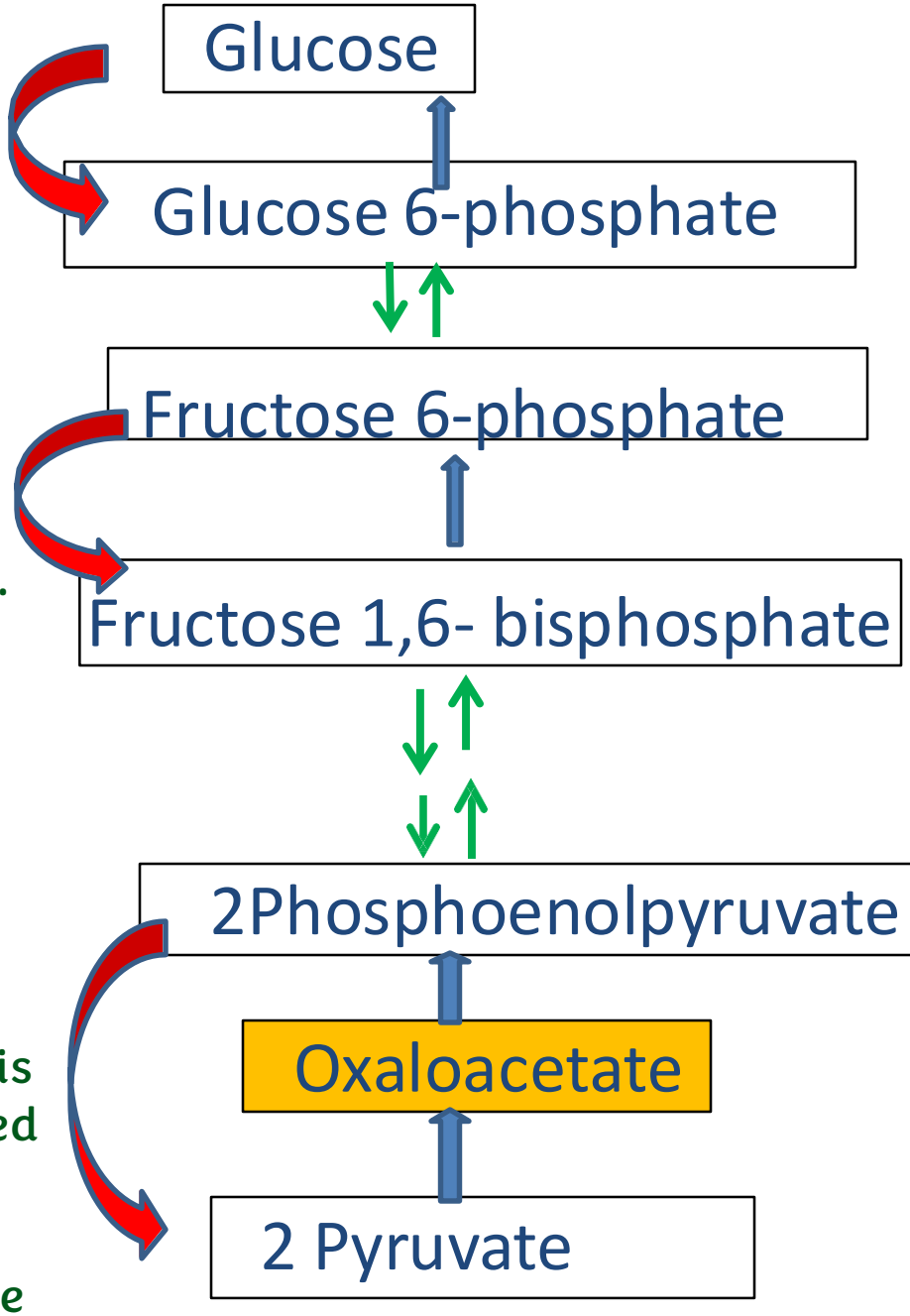
- The process starts with two molecules of pyruvate (3C) to make one glucose molecule.

Recall that:

PEP is converted to pyruvate by pyruvate kinase (an irreversible step), To reverse this, two steps are required:

1) From pyruvate to OAA.
2) From OAA to PEP –> Then it enters reversible steps...

F6P to F1,6P conversion by PK1 in glycolysis is **irreversible.** So, a **different enzyme** is needed to remove phosphate from carbon number one to make F6P. Another enzyme will be used (phosphatase) to produce glucose at the last step.

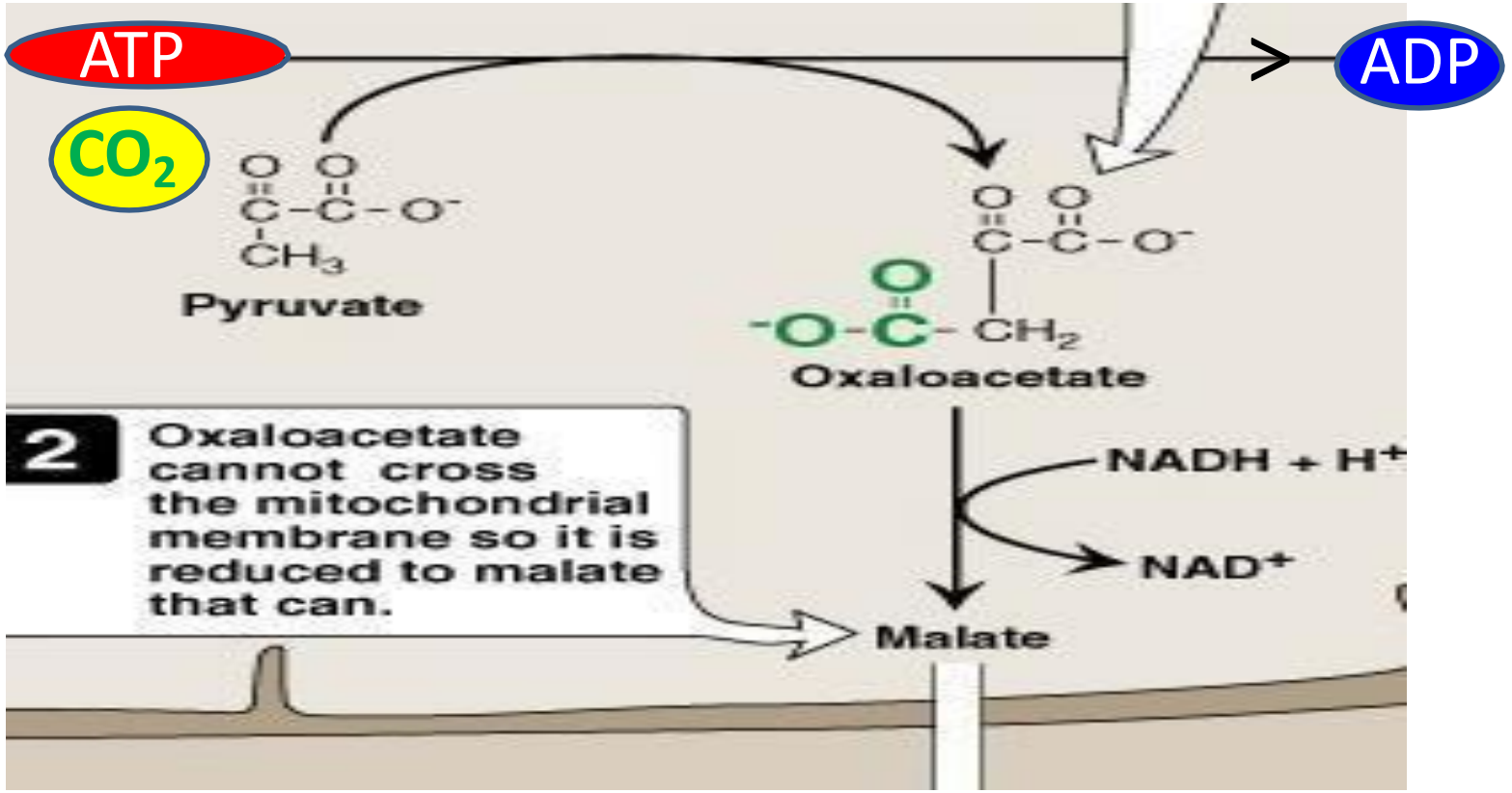


Reversing the irreversible steps

1. From pyruvate to phosphoenolpyruvate (PEP)

Carboxylation of Pyruvate Produces Oxaloacetate (OAA)

- By pyruvate carboxylase
- In mitochondria
- Allosterically activated by Acetyl CoA

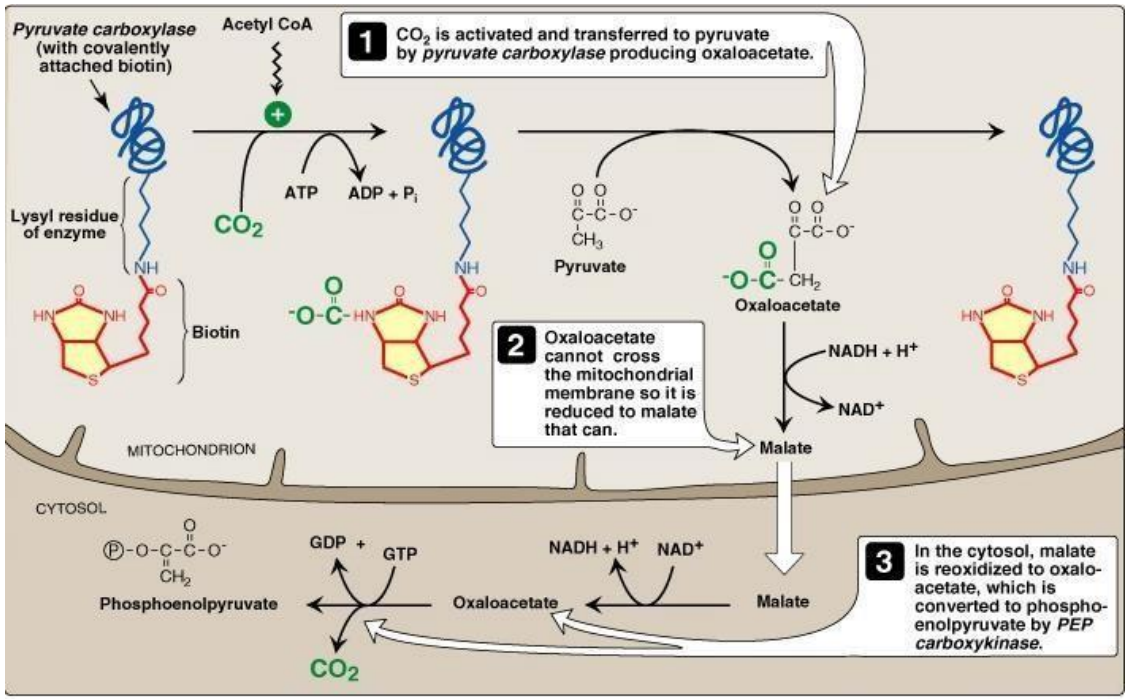


Carboxylation of Pyruvate Produces Oxaloacetate (OAA)

- Gluconeogenesis starts with Pyruvate molecules as they are the final products of glycolysis. Firstly, pyruvate is converted to phosphoenolpyruvate (PEP).
- Pyruvate doesn't come from glycolysis (why would glucose be broken down only to reform it again!) Rather, it comes from different sources as mentioned (mainly from glucogenic amino acids -alanine)
- Pyruvate (3C) (located in the mitochondria) will be carboxylated to oxaloacetate (4C) in a carboxylation reaction with the need of **CO_2 molecule**, enzyme (**Pyruvate carboxylase**), **biotin** as a coenzyme and **ATP molecule** as all carboxylation reactions need energy.
- Pyruvate carboxylase (with covalently bound biotin) brings CO_2 molecule and binds it to biotin
- CO_2 is activated and transferred to pyruvate by pyruvate carboxylase, producing oxaloacetate (ATP molecule is consumed)

From OAA to PEP

- Enzyme is found in both cytosol and mitochondria
- The generated PEP in the mitochondria is transported to the cytosol by a specific transporter
- The PEP that is generated in the cytosol requires the transport of OAA from the mitochondria to the cytosol



From OAA to PEP

- Oxaloacetate is formed in the **mitochondria.**
- To finish the gluconeogenesis reaction (specifically the reversible steps catalysed by the same enzymes in glycolysis which are present in the cytosol) , Oxaloacetate has to be transported to the cytosol .
- The problem is that oxaloacetate doesn't have a specific transporter, so it is reduced to malate by malate dehydrogenase (and NADH is oxidized to NAD+)
- Malate has a specific transporter, so it can exist out of the mitochondria to the cytosol.
- After that , malate is oxidized to oxaloacetate in the cytosol by the cytosolic malate dehydrogenase (and NAD+ is reduced to NADH)
- Now , oxaloacetate (4C) is in the cytosol, so it is converted to phosphoenolpyruvate (3C) with the loss of a CO2 molecule in a decarboxylation reaction. At the same time, phosphorylation reaction takes place , with the consumption of a GTP molecule (a source of energy and a phosphate group)
- This step is catalysed by **phosphoenolpyruvate carboxykinase**
- PEP can be produced in the mitochondria as well , and it can be transported to the cytosol by a specific transporter.

Reversing the reversible steps

- Since PEP is produced, the last step is reversed.
- Now , the backward reactions in the reversible steps of glycolysis are going to take place by the same enzymes used in glycolysis.

- So, phosphoenolpyruvate (PEP) is converted to 2-phosphoglycerate (2PG) by Enolase
- 2-phosphoglycerate (2PG) to 3-phosphoglycerate (3PG) by Phosphoglycerate mutase
- 3-phosphoglycerate (3PG) to 1,3-bisphosphoglycerate (1,3BPG) by Phosphoglycerate kinase
- 1,3-bisphosphoglycerate (1,3BPG) to glyceraldehyde-3-phosphate (G3P) by Glyceraldehyde 3-phosphate dehydrogenase
- Glyceraldehyde-3-phosphate (G3P) is isomerized to dihydroxyacetone phosphate (DHAP) by Triose phosphate isomerase
- Glyceraldehyde-3-phosphate (G3P) and dihydroxyacetone phosphate (DHAP) are combined to form fructose- 1,6-bisphosphate (F1,6BP) by Aldolase

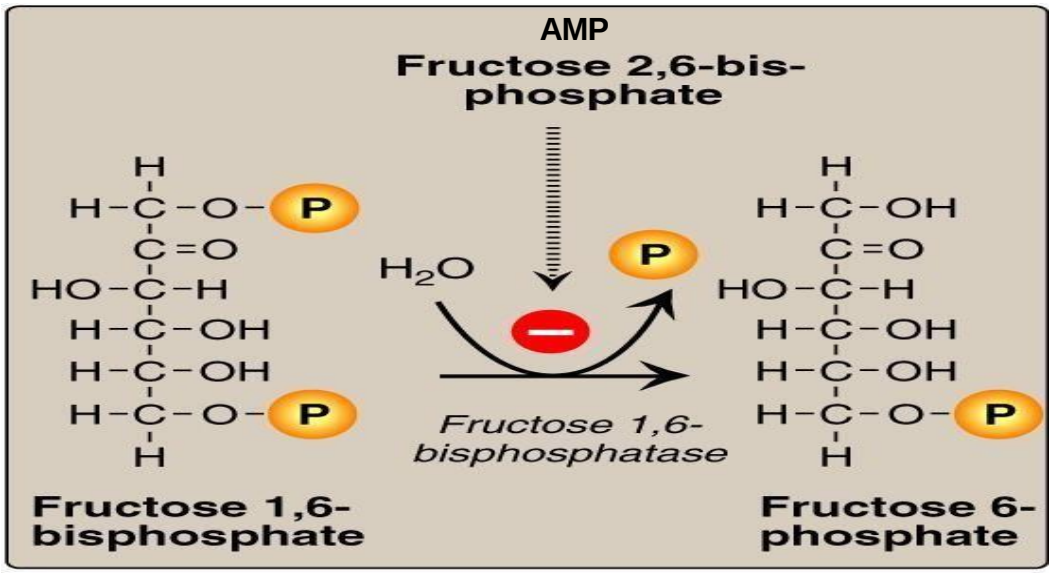
Reversing the irreversible steps

2. From fructose-1,6-bisphosphate to fructose-6-phosphate

Dephosphorylation of fructose 1,6-bisphosphate

- This reaction bypasses the irreversible phosphofructokinase-1 reaction

- This step is reversed in a single rxn by Fructose 1,6-bisphosphatase to produce Fructose-6-phosphate (the reverse of phosphofructokinase-1 rxn)
- Notice that the enzymes involved in the reverse reactions are regulated in the opposite manner with the same allosteric regulators.
- AMP and Fructose 2,6-bisphosphare are positive allosteric regulators for phosphofructokinase 1 , however they are negative allosteric regulators for Fructose 1,6-bisphosphatase
- Fructose 1,6-bisphosphatase acts as a switch enzyme between glycolysis and gluconeogenesis
- Now , Fructose-6-phosphate is isomerized to Glucose-6-phosphate by phosphoglucose isomerase (reversible step)

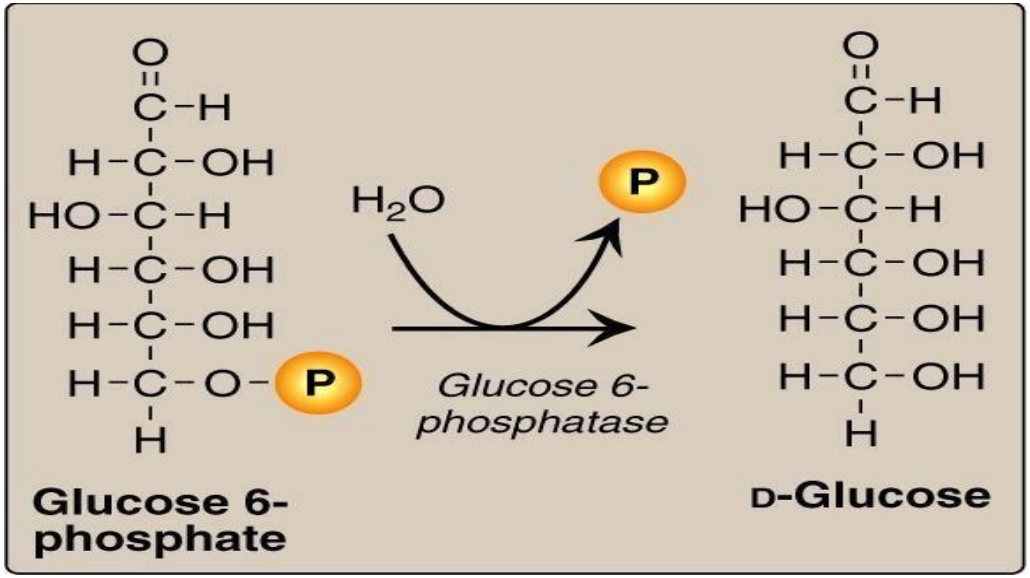


Reversing the irreversible steps

3. From glucose-6-phosphate to glucose

Dephosphorylation of glucose 6- phosphate

- **Bypasses the irreversible hexokinase reaction**
- **Only in liver and kidney**
- **Glucose 6-phosphate translocase is needed to transport G-6-P across the ER membrane**



Glucose 6-phosphatase in Endoplasmic Reticulum (ER)

Hint: Muscle lacks glucose 6-phosphatase, and therefore muscle glycogen cannot be used to maintain blood glucose levels.

Dephosphorylation of glucose 6- phosphate

- Glucose-6-phosphate must be dephosphorylated to glucose by Glucose-6-phosphatase
- This enzyme is not present in the muscles
- This enzyme is present in the ER lumen as a soluble protein , so glucose-6-phosphate has to be transported to the ER lumen where the dephosphorylation reaction is going to take place.
- Glucose-6-phosphatase cannot pass through GLUTs or SGLT (bcz glucose is phosphorylated), so it needs a translocase to be transported
- When glucose is produced in the ER lumen , it needs to be transported back to the cytosol by GLUT 7 (which is present in gluconeogenic tissues like liver and kidney)
- Then Glucose can exit the hepatocytes or kidney cells through other types of GLUTs like GLUT 2 (of course not GLUT 4 because there is no insulin in fasting conditions)

Energy requirements of gluconeogenesis

- Glycolysis produces energy, so its reverse pathway is expected to consume energy.
- Gluconeogenesis is an anabolic pathway [large molecules (glucose) are produced from smaller molecules (2 pyruvate molecules)] although it occurs under fasting conditions.
- Generally, anabolic pathways are inactive during fasting, but this pathway is essential and is not considered a major anabolic pathway.

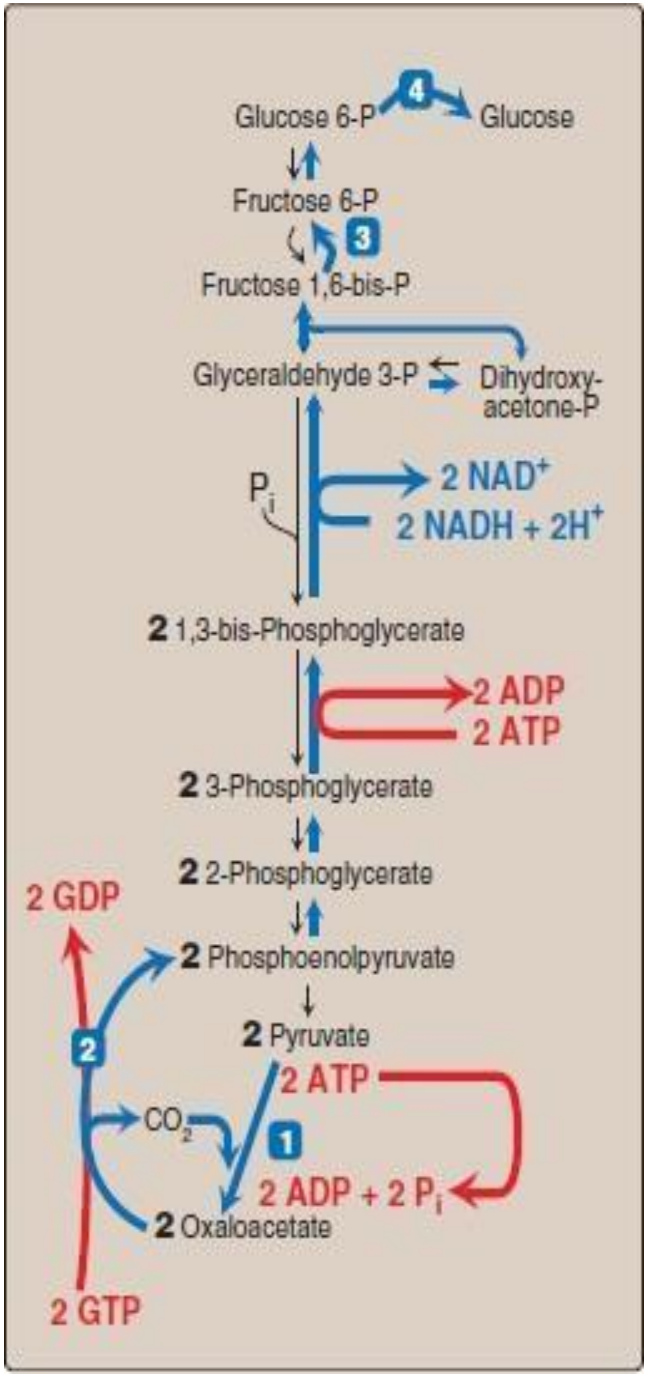
- The first step (the carboxylation reaction) needs ATP molecule for each Pyruvate molecule -> 2 ATP molecules are needed bcz it's repeated twice per glucose produced

- The second step (catalysed by carboxykinase) needs a GTP molecule for each malate molecule -> 2 GTP molecules are needed

- The fifth step (3-Phosphoglycerate to 1,3-bisphosphoglycerate) consumes 2 ATP molecules

- Dephosphorylation reactions in the last steps don't produce any energy (phosphate group is utilized in other reactions)

- FOR EACH GLUCOSE MOLECULE PRODUCED <u>6 ATP</u> MOLECULES ARE NEEDED (APPROXIMATELY)



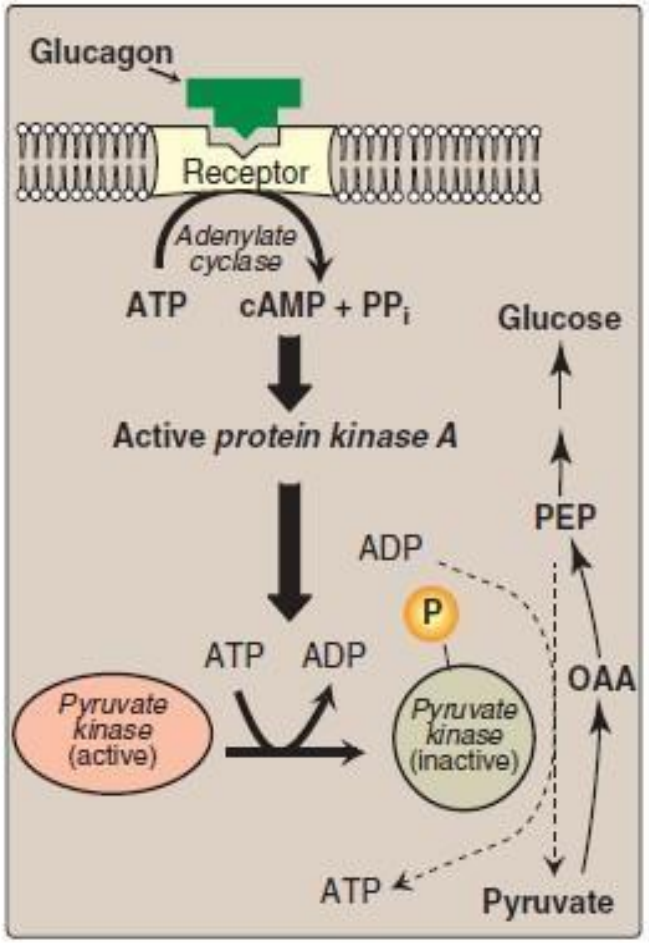
Regulation of gluconeogenesis

Mainly by :

- **The circulating level of glucagon :**
- ✓ **Glucagon lowers the level of fructose 2,6-bisphosphate , resulting in activation of fructose 1,6- bisphosphatase and inhibition of PFK- 1**
- ✓ **Inhibition of pyruvate kinase**
- ✓ **Glucagon increases the transcription of the gene for PEP-carboxykinase**

- **The availability of gluconeogenic substrates**

- **Slow adaptive changes in enzyme activity due to an alteration in the rate of enzyme synthesis or degradation (or both)**



Regulation of gluconeogenesis

HORMONAL REGULATION (mainly glucagon)

- When the level of glucagon (the fasting hormone) is increased, it binds to the GPCR on the target cells which then activates adenylyl cyclase to produce cAMP which activates protein kinase A (PKA).
- Protein kinase A has many targets :

✓ The bifunctional enzyme : PKA phosphorylates the bifunctional enzyme phosphofructokinase-2/fructose-2,6-bisphosphatase. This activates the FBPase-2 , decreasing fructose-2,6-bisphosphate levels, which inhibits glycolysis (by decreasing PFK-1 activity) and promotes gluconeogenesis (by relieving inhibition on fructose-1,6-bisphosphatase).

✓ Pyruvate kinase: Protein kinase A phosphorylates Pyruvate kinase and inhibits it resulting in inhibition of glycolysis (to prevent the reverse pathway of gluconeogenesis from occurring at the same time)

✓ Glycogen synthase : inhibited to stop glycogen synthesis in fasting conditions .

✓ Glycogen phosphorylase kinase : activated to increases glycogen degeneration .

- Glucagon also affects the transcription factors. It enters the nucleus, binds to a certain sequence of the DNA, and activates gene expression of target genes (the gene for PEP carboxykinase which catalyses step 2), to increase its transcription and activate glyconeogenesis.

Regulation of gluconeogenesis

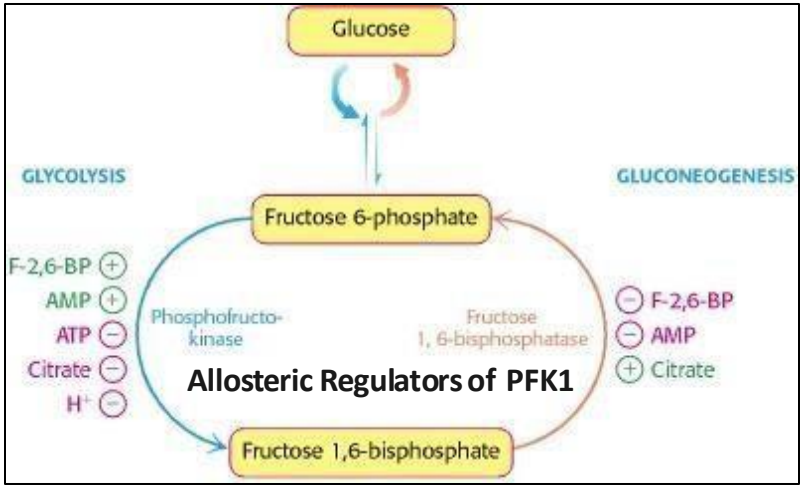
- **The availability of gluconeogenic substrates :**

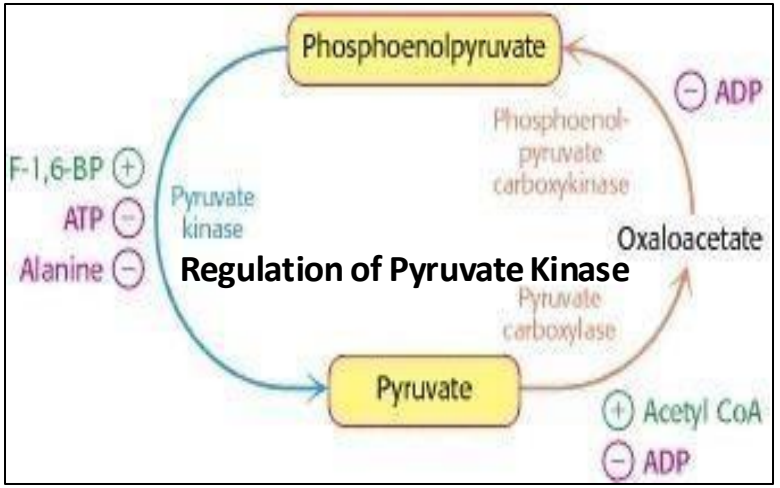
- **Gluconeogenic substrates come from other tissues and cells , so they need to be transported to the liver and kidney where gluconeogenesis takes place .**

- **Slow adaptive changes in enzyme activity due to an alteration in the rate of enzyme synthesis or degradation (or both) :**

- **Synthesis of enzymes, increasing their concentrations, and decreasing their degradation all affect gluconeogenesis and regulate it**

Regulation of gluconeogenesis





- **Fructose 1,6-bisphosphatase is :**

✓ **Inhibited by Fructose 2,6-bisphosphate that's produced by the bifunctional enzyme. On the other hand, Fructose 2,6-bisphosphate activates glycolysis (phosphofructokinase 1)**

✓ **Inhibited by AMP (indicator of low energy) because gluconeogenesis needs energy**

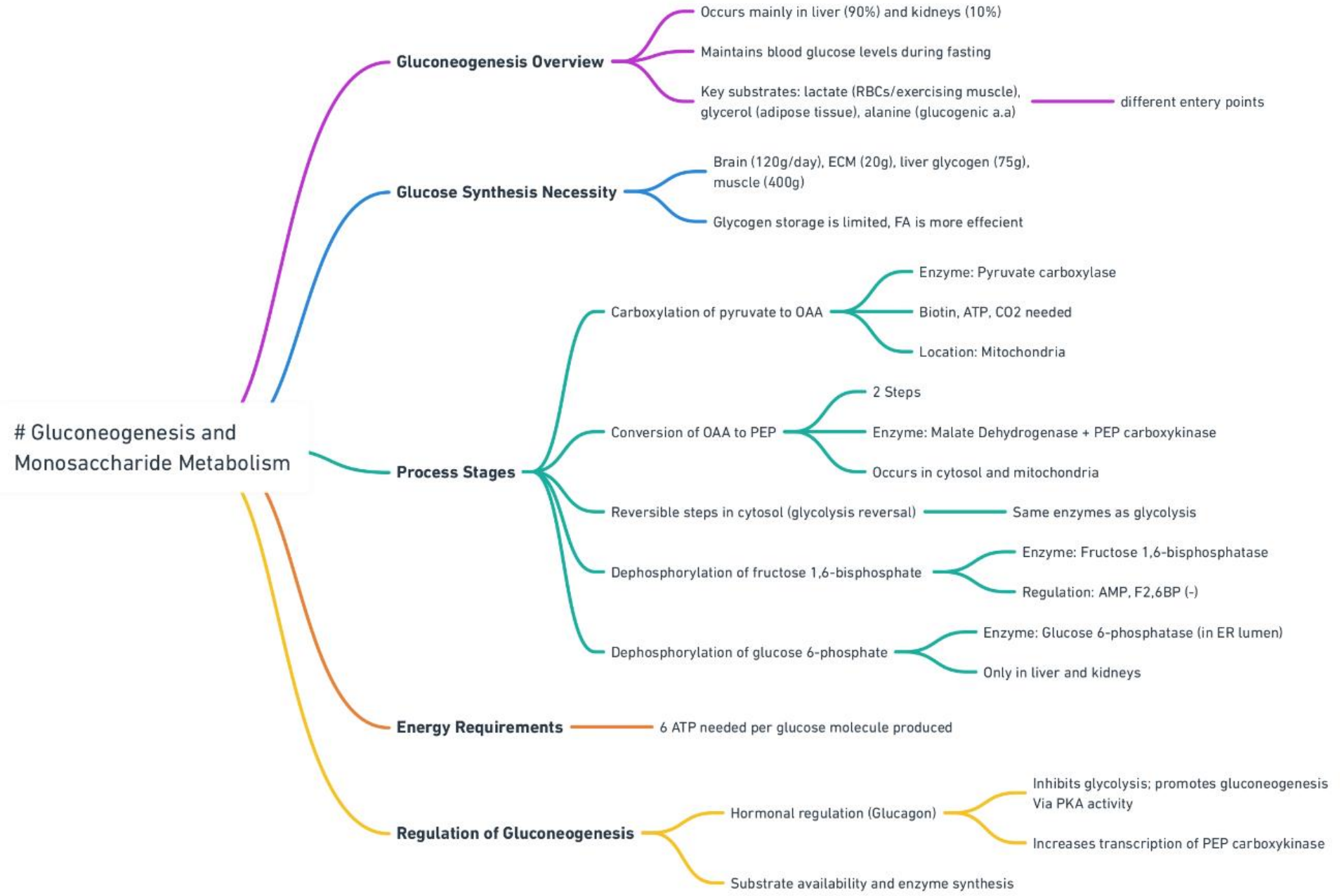
✓ **Activated by Citrate as it indicates active Krebs Cycle (because of the Acetyl Co-A that comes from degradation of fatty acids) , so energy is produced to activate this pathway**

- **Pyruvate carboxylase is :**

✓ **Activated by high concentration of Acetyl CoA (which comes from degradation of fatty acids under fasting conditions) .**

✓ **Inhibited by ADP for the reason mentioned**

- **Phosphoenolpyruvate carboxykinase is inhibited by ADP for the reason mentioned**


Gluconeogenesis and Monosaccharide Metabolism
Gluconeogenesis Overview
Occurs mainly in liver (90%) and kidneys (10%)
Maintains blood glucose levels during fasting
Key substrates: lactate (RBCs/exercising muscle), glycerol (adipose tissue), alanine (glucogenic a.a)
different entery points
Glucose Synthesis Necessity
Brain (120g/day), ECM (20g), liver glycogen (75g), muscle (400g)
Glycogen storage is limited, FA is more effecient
Process Stages
Carboxylation of pyruvate to OAA
Enzyme: Pyruvate carboxylase
Biotin, ATP, CO2 needed
Location: Mitochondria
Conversion of OAA to PEP
2 Steps
Enzyme: Malate Dehydrogenase + PEP carboxykinase
Occurs in cytosol and mitochondria
Reversible steps in cytosol (glycolysis reversal)
Same enzymes as glycolysis
Dephosphorylation of fructose 1,6-bisphosphate
Enzyme: Fructose 1,6-bisphosphatase
Regulation: AMP, F2,6BP (-)
Dephosphorylation of glucose 6-phosphate
Enzyme: Glucose 6-phosphatase (in ER lumen)
Only in liver and kidneys
Energy Requirements
6 ATP needed per glucose molecule produced
Regulation of Gluconeogenesis
Hormonal regulation (Glucagon)
Inhibits glycolysis; promotes gluconeogenesis Via PKA activity
Increases transcription of PEP carboxykinase
Substrate availability and enzyme synthesis

The body utilizes each type of monosaccharide for specific purposes depending on its characteristics.

Remember that

Metabolism of Monosaccharides and Disaccharides

Summarizing some side talk before we start the new topic:

{وَكُلُواْ وَٱشۡرَبُواْ وَلَا تُسۡرِفُوٓاْۚ إِنَّهُۥ لَا يُحِبُّ ٱلۡمُسۡرِفِينَ}

Dr. Diala Abu-Hassan, DDS, PhD

Fructose Metabolism

- 10% of the daily calorie intake.

However, this is not a constant percentage and can vary depending on your diet type.

- Sources: sucrose, Fruits, honey, high-fructose corn syrup.

High-fructose corn syrup, which contains a mixture of fructose and glucose, is commonly used as a sweetener in many processed foods. However, its health effects have been widely debated.

- Entry into cells is not insulin dependent.

Unlike glucose, which can enter cells through insulin-dependent transporters like GLUT4, fructose uptake is insulin-independent by GLUT5 mainly.

- Does NOT promote the secretion of insulin.

The primary purpose of fructose metabolism is to generate energy.

Glucose increases blood sugar levels and insulin secretion, while **fructose** is metabolized in the liver without significantly impacting blood sugar directly, but excessive fructose intake can have long-term negative effects on metabolism and insulin sensitivity, so the effect of fructose on blood sugar level is debated upon.

Fructose metabolism occurs through two main pathways:

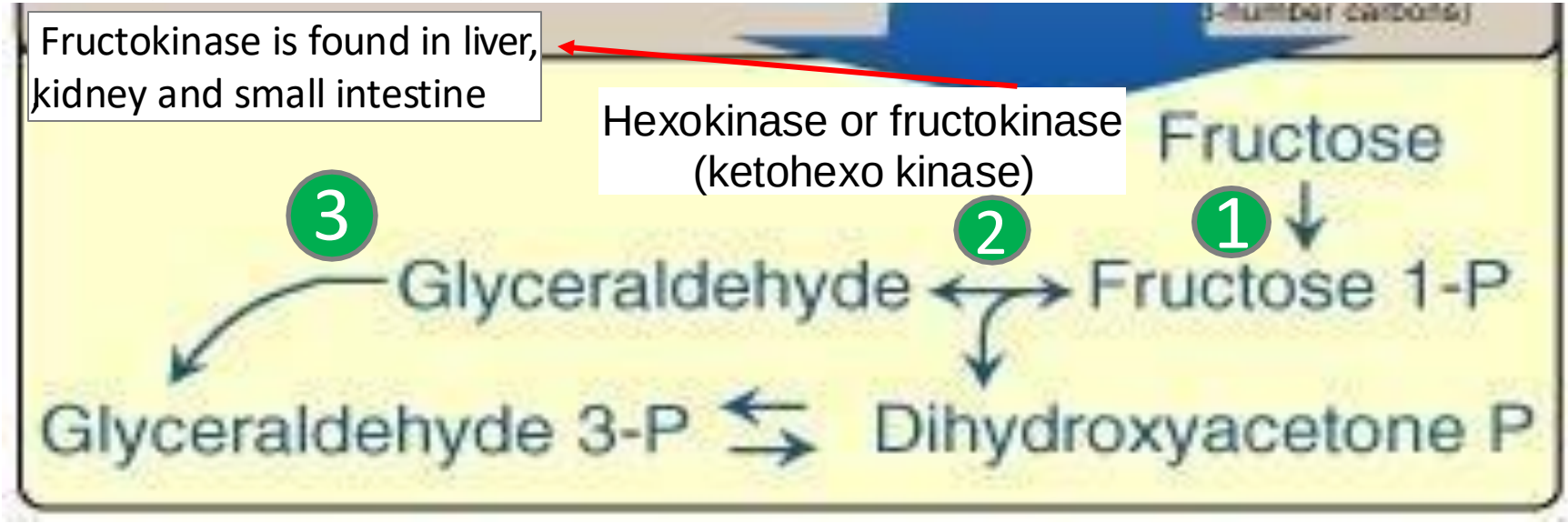
1. Fructose-specific pathway (Fructose metabolism in the liver):

1. **Fructose phosphorylation**: Fructose is first phosphorylated by fructokinase (also called ketohexokinase) to form fructose-1-phosphate.
2. **Cleavage**: Fructose-1-phosphate is then split by aldolase B into two three-carbon molecules: Dihydroxyacetone phosphate (DHAP) & Glyceraldehyde.
3. **Conversion to glycolytic intermediates**:

· **Glyceraldehyde** must be phosphorylated to glyceraldehyde-3-phosphate (G3P) to join glycolysis (by glyceraldehyde kinase.)

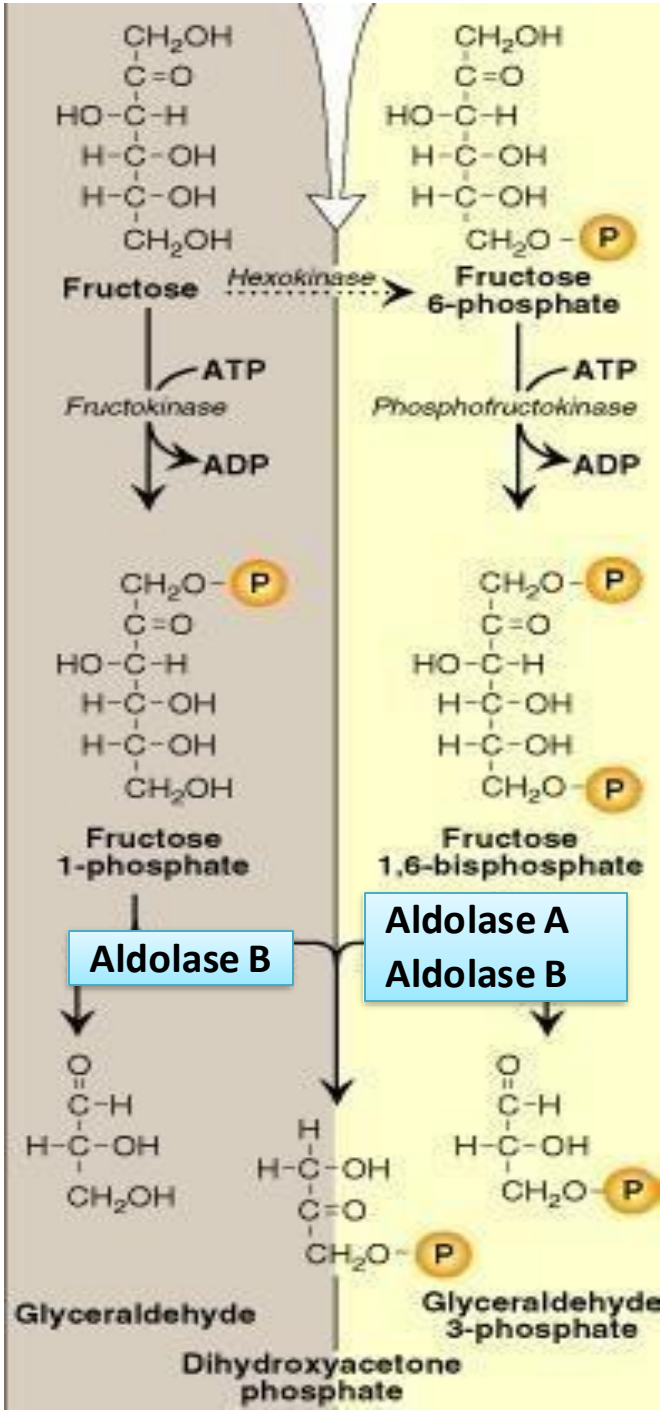
· Both **DHAP** and **G3P** can then enter the **glycolytic pathway.**

2. Non-specific, general pathway. See the next slide for explanation.



2. Non-specific, general pathway:

- **Hexokinase** phosphorylates fructose directly to form **fructose-6-phosphate (F6P)**, bypassing the second step of glycolysis (the isomerization).
- **Phosphofructokinase 1** then phosphorylates **F6P** to form **fructose-1,6-bisphosphate**.
- **Aldolase** (either A or B isoform) cleaves it into **glyceraldehyde-3-phosphate (G3P)** and **dihydroxyacetone phosphate (DHAP)**.



Fructose Metabolism

1. The specific pathway.

The specific pathway is more favorable because it bypasses the PFK-1 step, which is a rate-limiting step (very slow) in glycolysis, allowing for faster and more efficient fructose metabolism.

2. The non-specific pathway.

Hexokinase affinity to fructose is low

- The rate of fructose metabolism is more rapid than that of glucose because the trioses formed from fructose 1-phosphate bypass *phosphor fructokinase-1-P* the major rate-limiting step in glycolysis.

Human expresses three forms of aldolase

Aldolase B

- Works in both the specific and non-specific pathways.
- Liver, kidney, small intestine.
- Substrate Fruc. 1 phopsphate Also Fruc. 1,6 bisphospate.

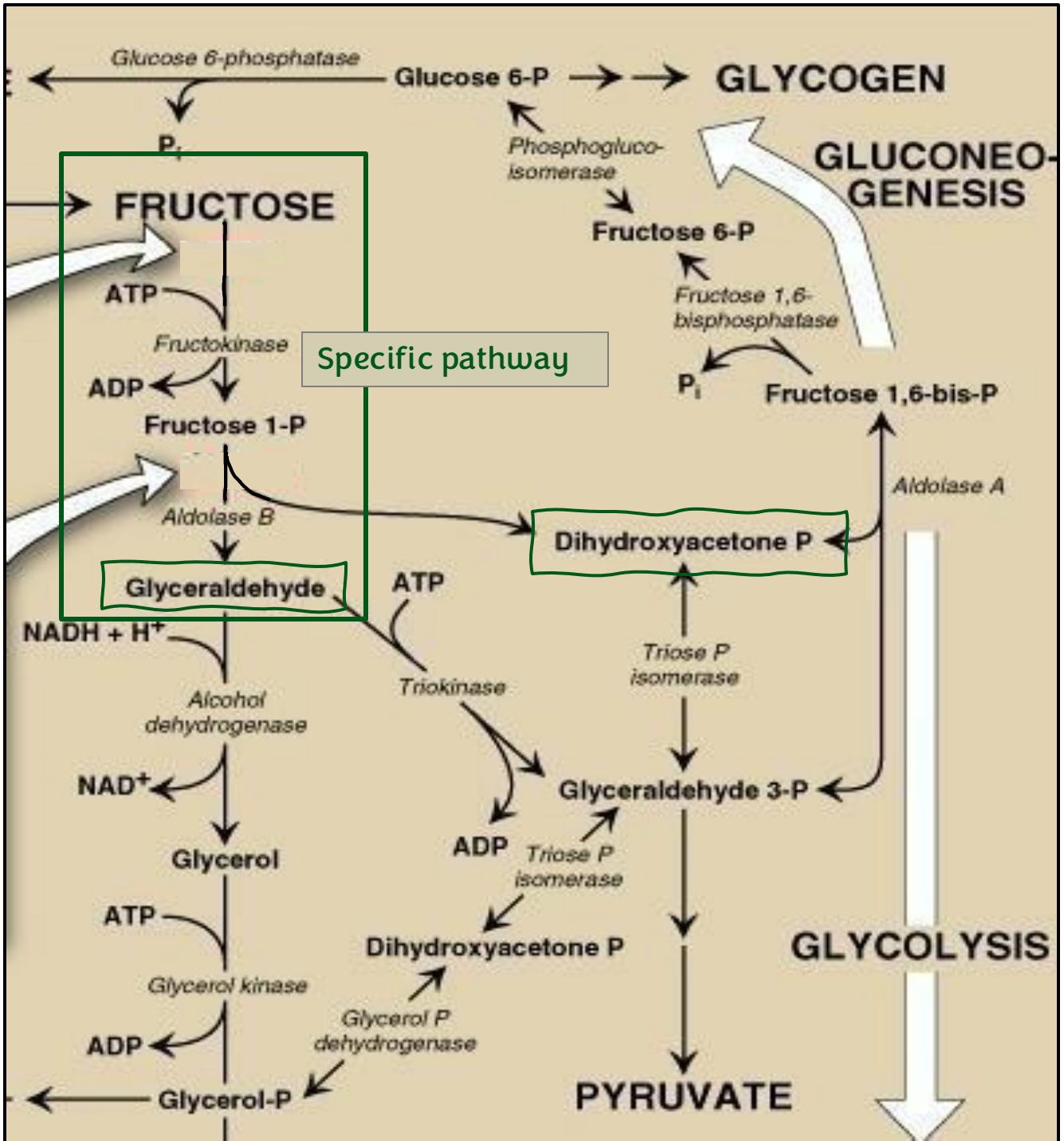
Aldolase A

- Works only in non-specific pathway.
- In most tissues.
- Substrate Fruc. 1,6 bisphospate Not Fruc. 1 phpsphate.

because it interacts with glycolysis.

↓activity➔ fructose intolerance

We will cover this later, but it is a condition where the body is unable to properly digest fructose, often leading to symptoms like bloating, abdominal pain, and diarrhea.



Fructose Metabolism and Interaction with other Pathways

For clarification, please refer to the next slide.

The **specific pathway** can interact with different metabolic pathways through its intermediates:

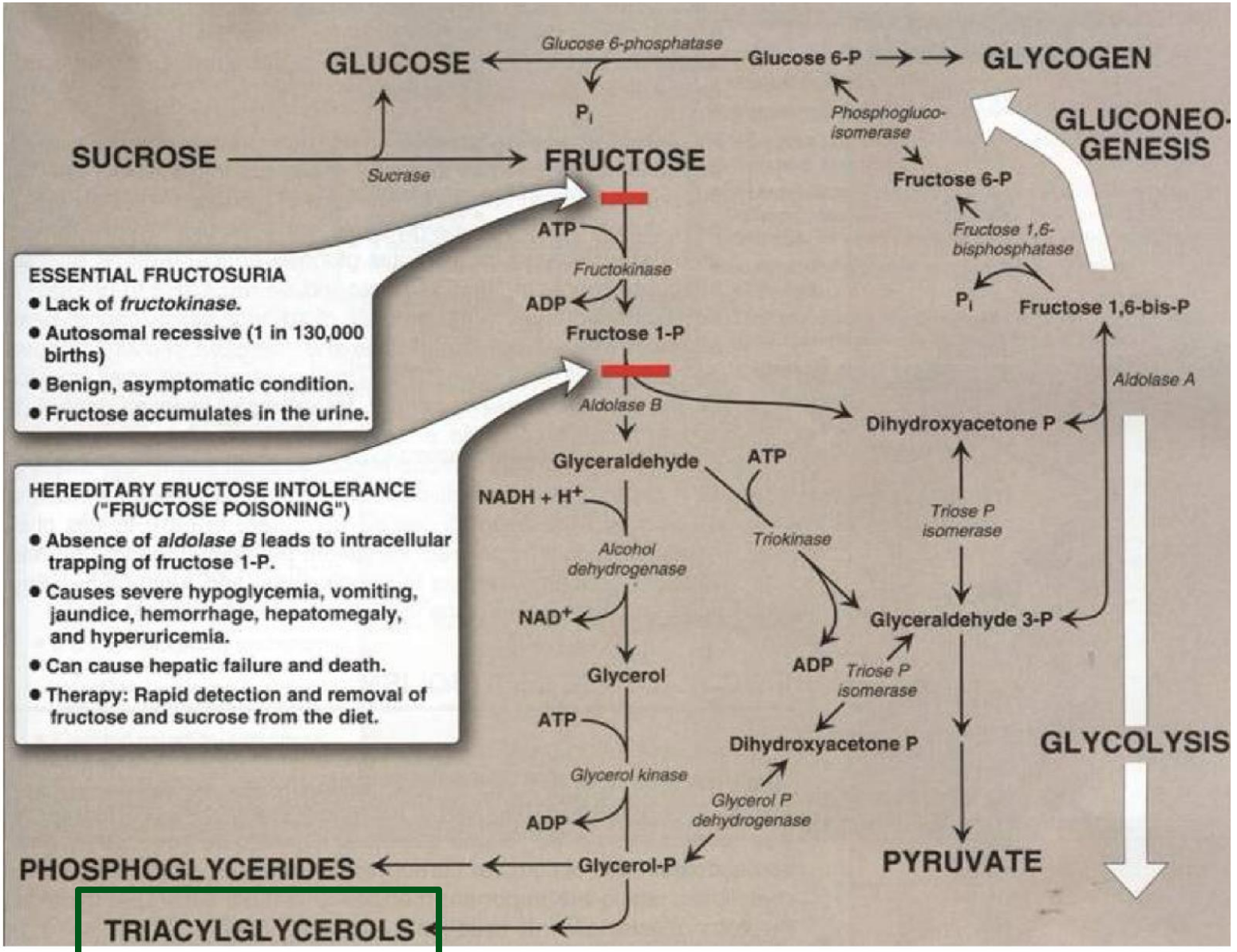
- **Dihydroxyacetone phosphate (DHAP)** can interact with both **gluconeogenesis** and **glycolysis etc**.

- **Glyceraldehyde** can be processed in two main ways:

1. **Phosphorylation by triokinase** using ATP to convert it to glyceraldehyde-3-phosphate, which then interacts with glycolysis or gluconeogenesis.

2. Alternatively, glyceraldehyde can undergo a **longer pathway**:
   - First, it is reduced by **alcohol dehydrogenase** to form **glycerol**.
   - Then, **glycerol** is phosphorylated by **glycerol kinase** to form **glycerol phosphate**, which is subsequently oxidized to **DHAP** and then isomerized to **G3P**.

3. Glyceraldehyde can also be used to build **triacylglycerols** (fats). That's why when you eat sugar, it can lead to weight gain, because it interacts with lipid synthesis promoting fat storage.



الحمدُ للهِ العظيمِ وكَفَى مُصلّيًا عَلَى الرَّسُولِ المُصطَفَى
سُبحانكَ اللهمَّ وبحمدِك، أشهدُ أنْ لا إلهَ إلَّا أنتَ، أستغفِرُكَ وأتوبُ إليكَ.

For any feedback, scan the code or click on it.

Corrections from previous versions:

Versions	Slide # and Place of Error	Before Correction	After Correction
V0 → V1			
V1 → V2			

Additional Resources:

رسالة من الفريق العلمي:

Reference Used:
(numbered in order as cited in the text)

1. Lippincott Biochemistry 7th Ed. Chapter 10 (Gluconeogenesis)
2. Lippincott Biochemistry 7th Ed. Chapter 12 (Monosaccharide and Disaccharide Metabolism)
3. …

Extra References for the Reader to Use:

1. Gluconeogenesis by Dirty Medicine YT Video
2. Fructose Metabolism by Dirty Medicine YTV
3. Gluconeogenesis by Sketchy YTV
4. Other

كتبَ سلمان الفارسيّ إلى أبي الدرداء: "أما بعد، فإنك لا تنال ما تُريد إلّا بترك ما تشتهي، ولن تبلغ ما تأمُل، إلَّا بالصَّبر على ما تكره، فَلْيكُن قولك ذكرًا، وصمتك فكرًا، ونظرك عبرة، واعلم أن أعجزَ الناس من أتبع نفسَه هواها وتمنى على الله، وأن أكْيَسهم من أتعب نفسه وعمل لما بَعد الموت" ♡.

- سبحان الله وبحمده، سبحان الله العظيم
- لا إله إلا أنت سبحانك إني كنت من الظالمين
- {رَبِّ إِنِّي لِمَا أَنْزَلْتَ إِلَيَّ مِنْ خَيْرٍ فَقِيرٌ}
- اللهم ثبت الأقدام وسدد الرمي

﴿ إِنَّ الَّذِينَ اتَّقَوْا إِذَا مَسَّهُمْ طَائِفٌ مِنَ الشَّيْطَانِ تَذَكَّرُوا فَإِذَا هُمْ مُبْصِرُونَ ﴾

تذكَّروا ولم يقل ذكروا إشارةً إلى أن الغفلة يطردها التذكر والاعتبار؛ لأن الذكر ميدانه اللسان والتذكر ميدانه القلب.