HORMONAL REGULATION OF BLOOD GLUCOSE

GLYCEMIA

The term glycemia refers to the concentration of glucose in the blood.

Its normal range spans 70-90 mg/dL (90 mg/dL = 5 mM)

>110 mg/dL	Hyperglycemia
< 70 mg/dL	Hypoglycemia

Glycemia is a good index of glucose metabolism

< 70 mg/dL

Hypoglycemia

- Trembling
- Sweating/chills
- Palpitations
- Hunger
- Altered mental status
- Confusion
- Headache

>110 mg/dL

Hyperglycemia

- Extreme thirst
- Hunger
- Frequent urination
- Fatigue
- Confusion
- Vomiting/nausea
- Abdominal pain

https://www.ncbi.nlm.nih.gov/books/NBK581875/

FACTORS AFFECTING GLYCEMIA

- **Dietary intake**

- **Liver metabolic pathways**

  Consuming glucose: **Glycolysis, Glycogen synthesis, Pentose phosphate pathway, Biosynthesis of lipids (and aminoacids)**

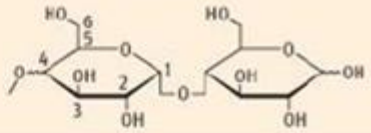
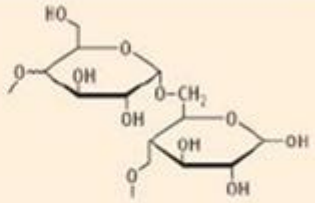
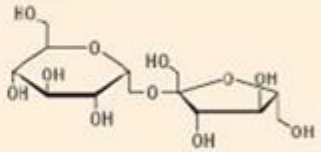
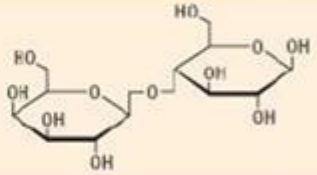
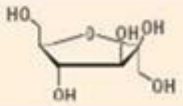
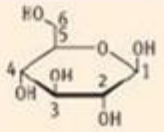
  Producing glucose: **Glycogenolysis, Gluconeogenesis**

- **Metabolic pathways in extrahepatic tissues**

  Consuming glucose: **Glycolysis, Glycogen synthesis**

- **Kidney filtration and reabsorption**

Major dietary carbohydrates

Carbohydrate	Food source	Structure
starch (amylose) [plant]	potatoes, rice, bread, onions	
amylopectin (glycogen) [plant, animal]	potatoes, rice, bread, muscle, liver	
sucrose	desserts, sweets, 'sugar'	
lactose	milk	
fructose	fruits, honey	
glucose	fruits, honey	

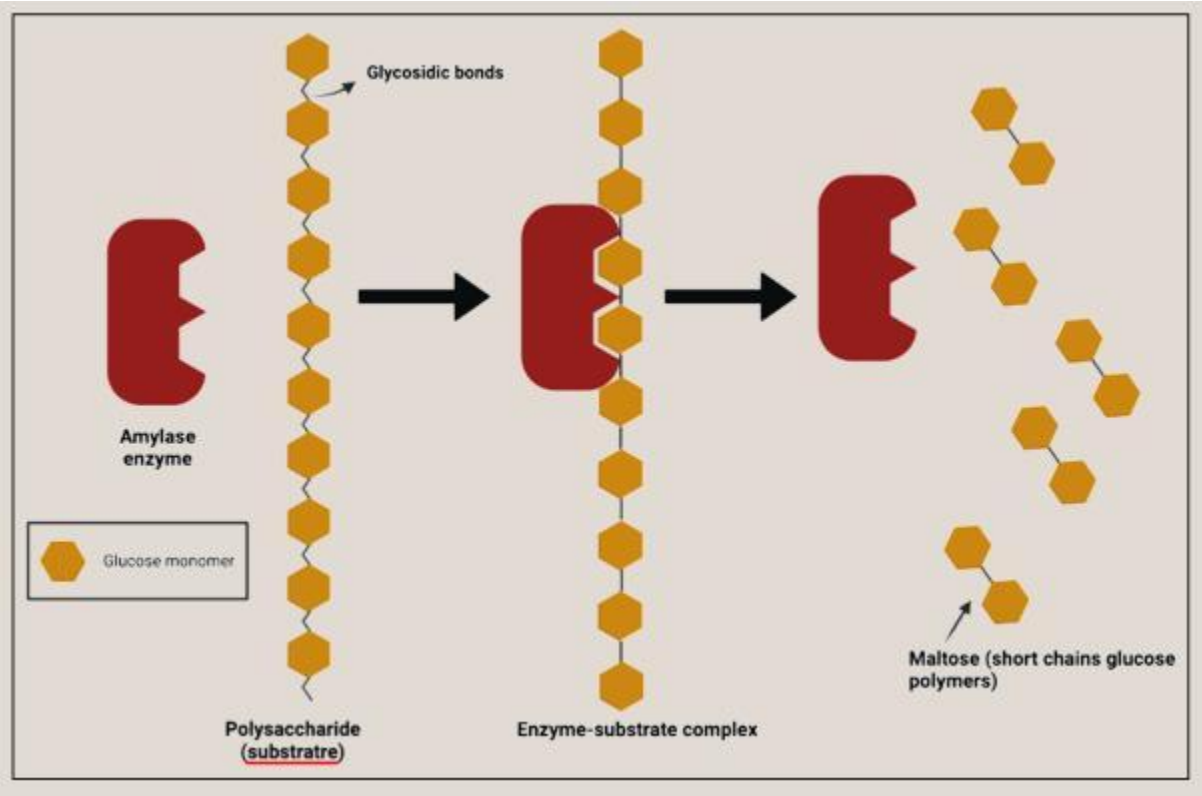
Poly-

Di-

Mono-

saccharides

https://doi.org/10.1016/j.mpaic.2023.07.006

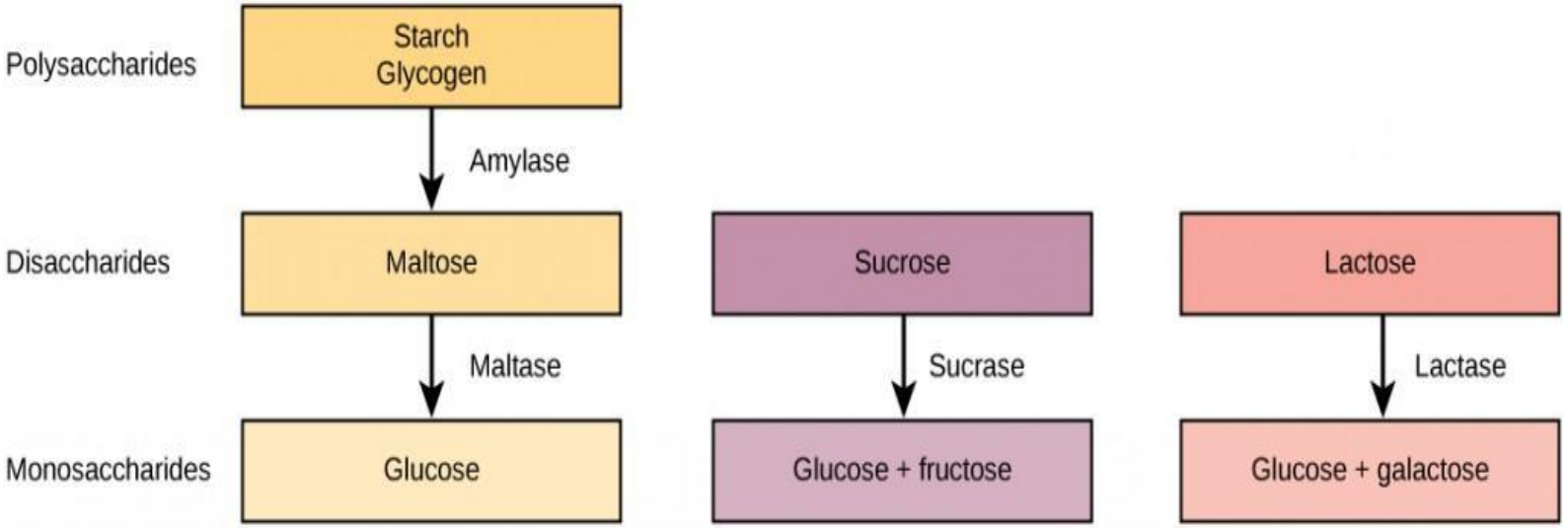


Hydrolysis of long-chain polysaccharides to short chain glucose polymers is carried out by amylases (from salivary glands and pancreas), defined as a group of enzymes that act on α-1,4- and α-1,6-glucosidic bonds present in starch and glycogen

NB: Humans cannot digest β-glycosidic bonds (i.e. cellulose)

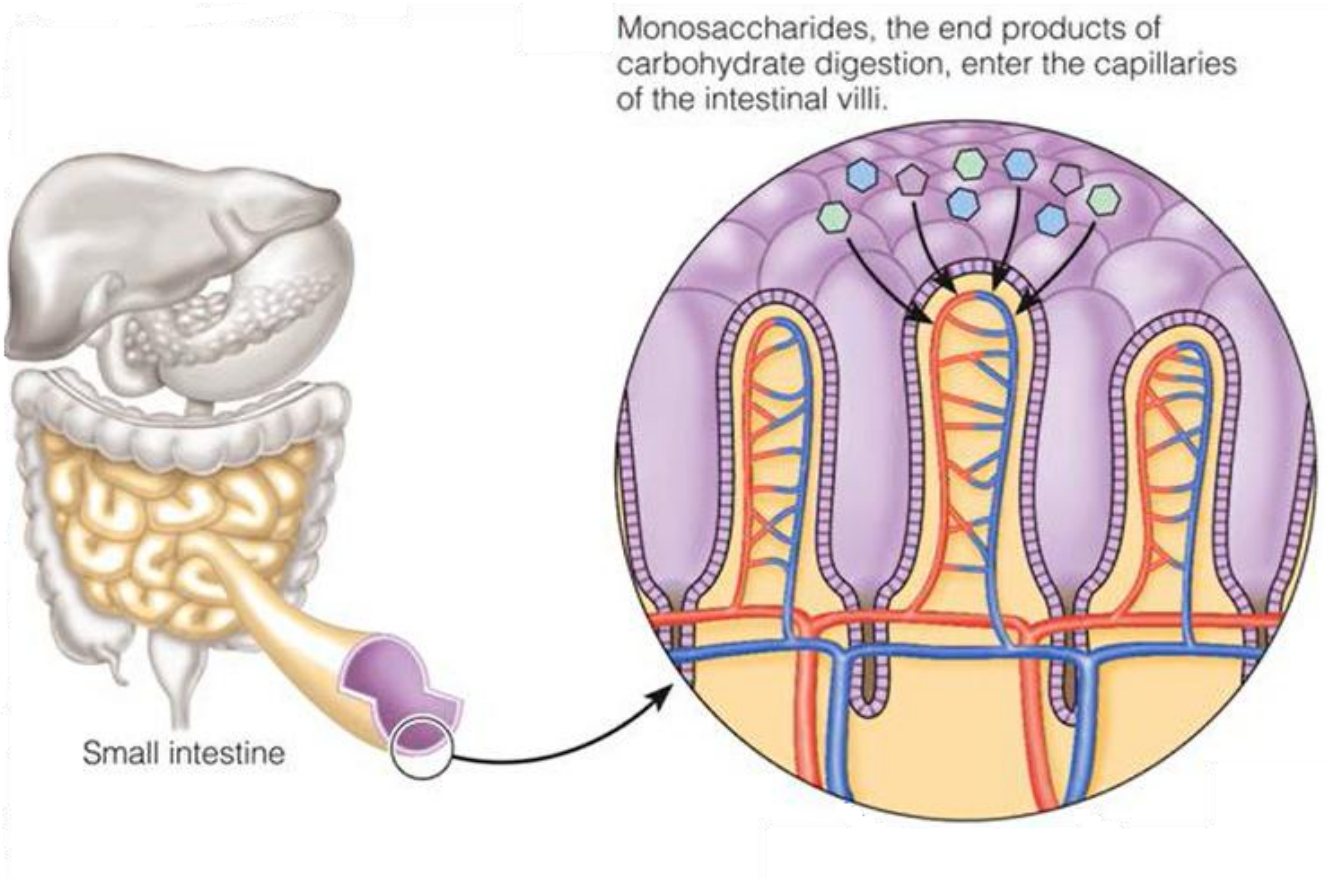
DIGESTION AND INTESTINAL ABSORPTION OF DISACCHARIDES

Disaccharides are broken down into **monosaccharides** by enzymes called maltases, sucrases, and lactases, which are also present in the brush border of the small intestinal wall.

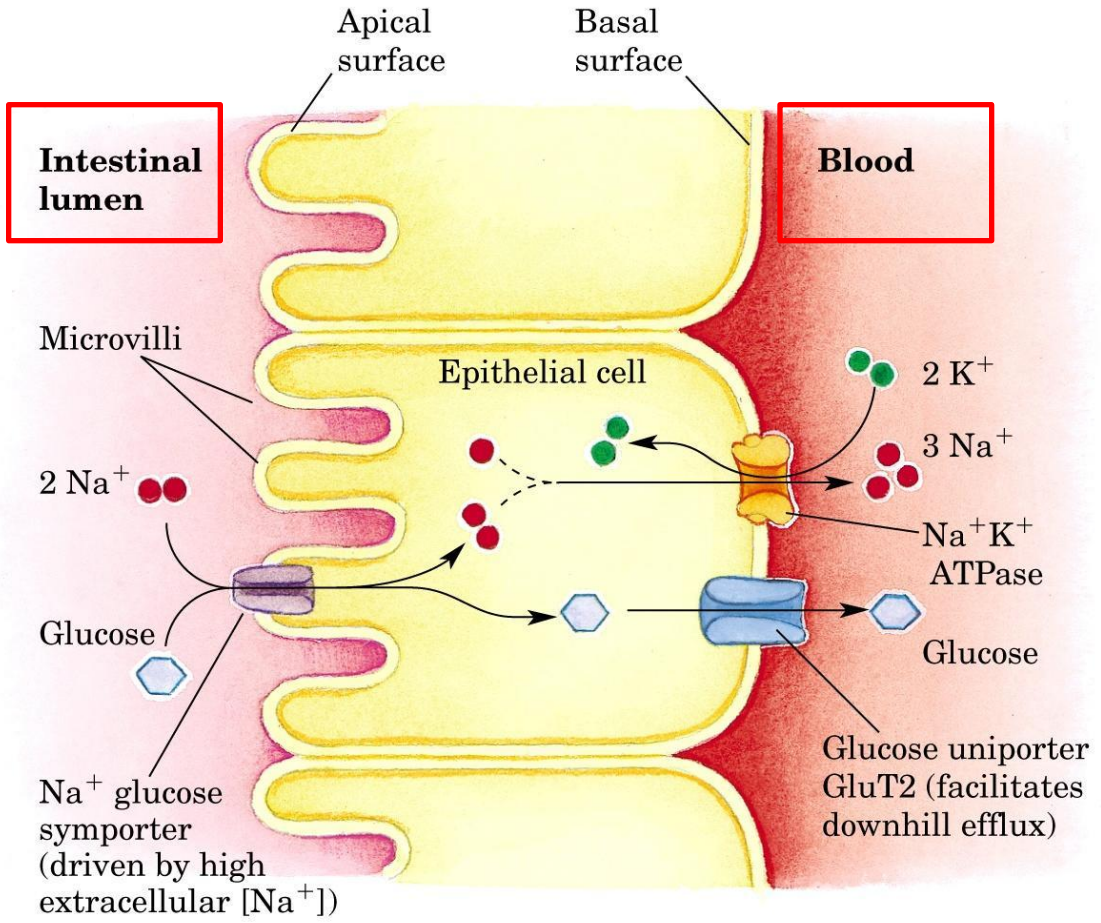


https://opentextbc.ca/biology/chapter/15-3-digestive-system-processes/

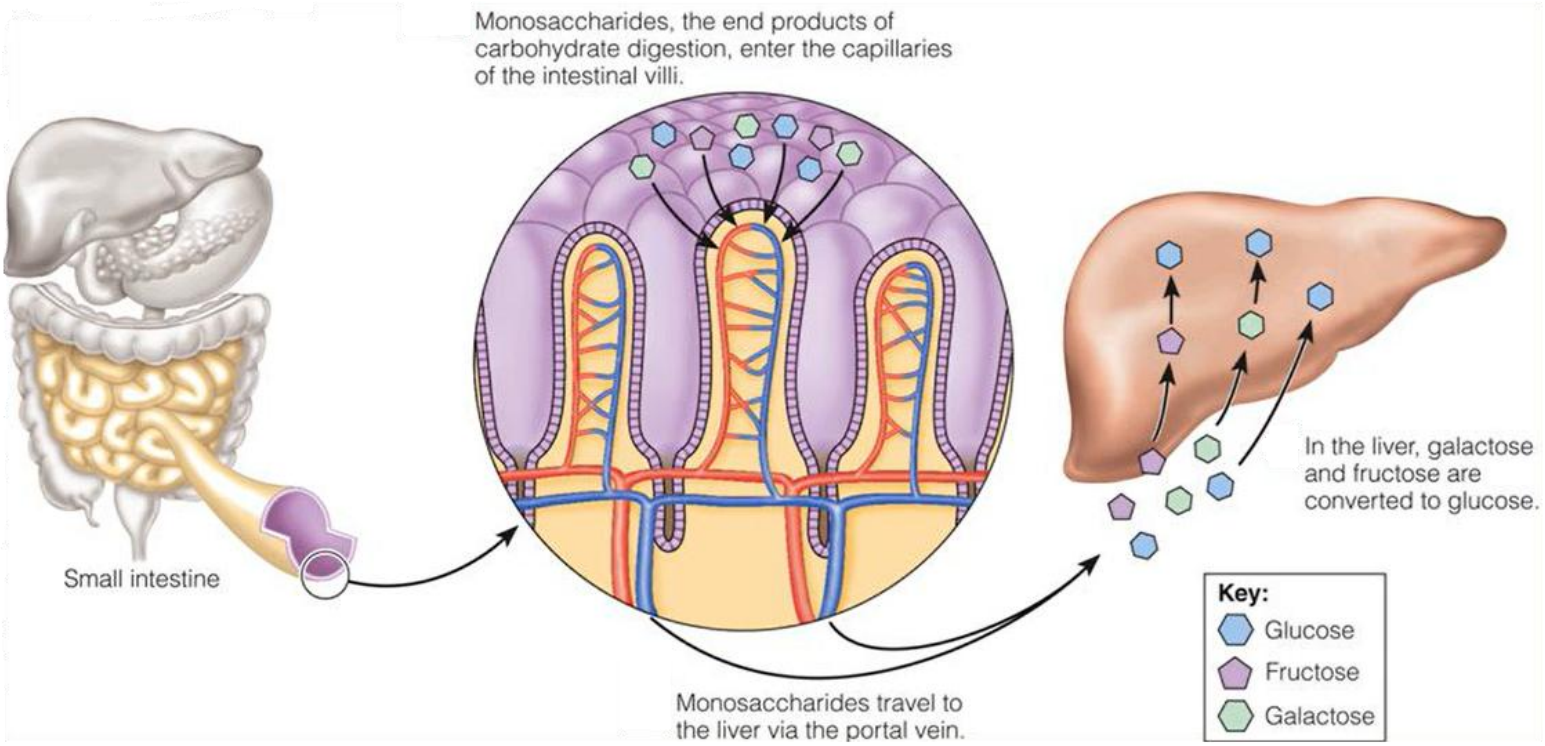
INTESTINAL ABSORPTION OF MONOSACCHARIDES



INTESTINAL ABSORPTION OF MONOSACCHARIDES

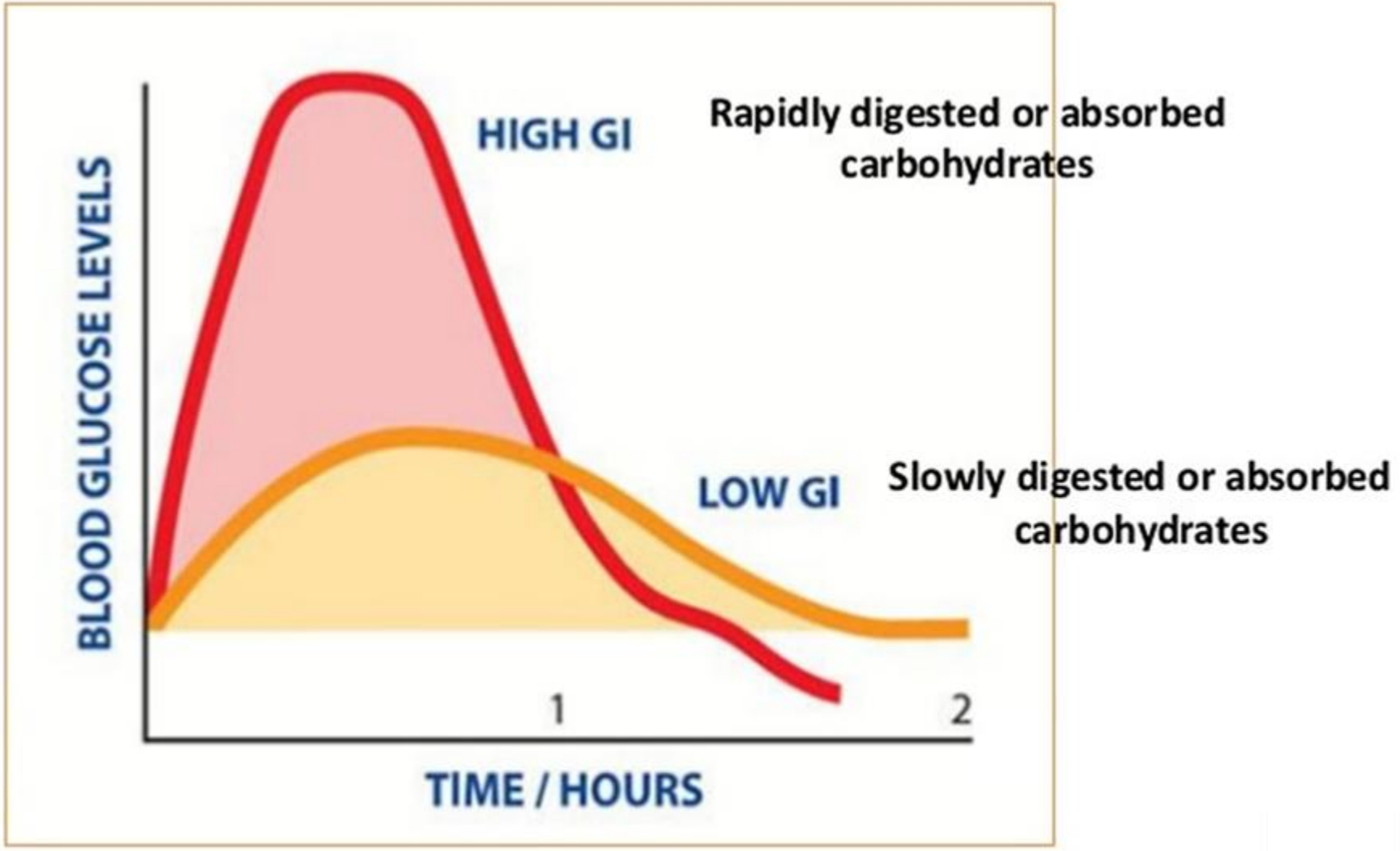


Glycaemic peak after a carbohydrate meal.

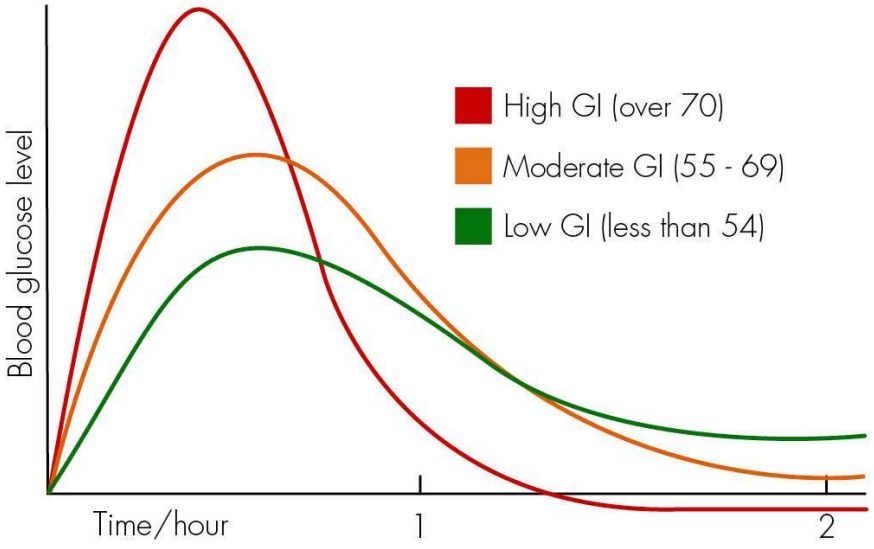


Glucose enters general circulation (glycemic peak).
Glycaemic peak after a carbohydrate meal.
Glycaemic regulation: insulin and glucagon.

Glycemic peak after a carbohydrate meal



The Glycemic Index



Brocolli	10	Canned kidney beans	52	Corn chips	72
Tomatoes	15	Orange juice	52	Watermelon	72
Peach	28	Sweet potato	54	Soda drink	72
Apple	36	Brown rice	54	Honey	73
Chickpeas	42	Sweet corn	55	French fries	76
All bran	42	Banana	56	Doughnut	76
Orange	43	Beetroot	64	White bread	79
Long grain rice	47	Cous cous	65	Cornflakes	84
Green pea	48	Table sugar	65	Baked Potato	85
Oat bran bread	48	Whole wheat bread	68	Dates	100
Carrots	49				

The glycemic index (GI) assigns a numeric score to a food based on how drastically it makes your blood sugar rise. Foods are ranked on a scale of 0 to 100, with pure glucose (sugar) given a value of 100. The lower a food's glycemic index, the slower blood sugar rises after eating that food. In general, the more processed a food is, the higher its GI, and the more fiber or fat in a food, the lower it's GI.

High blood glucose

Signals the pancreas to secrete insulin into the blood

Insulin

Stimulates:

- Uptake of glucose from the blood into cells
- Storage of glycogen in the liver and muscles
- Conversion of excess glucose into fat for storage

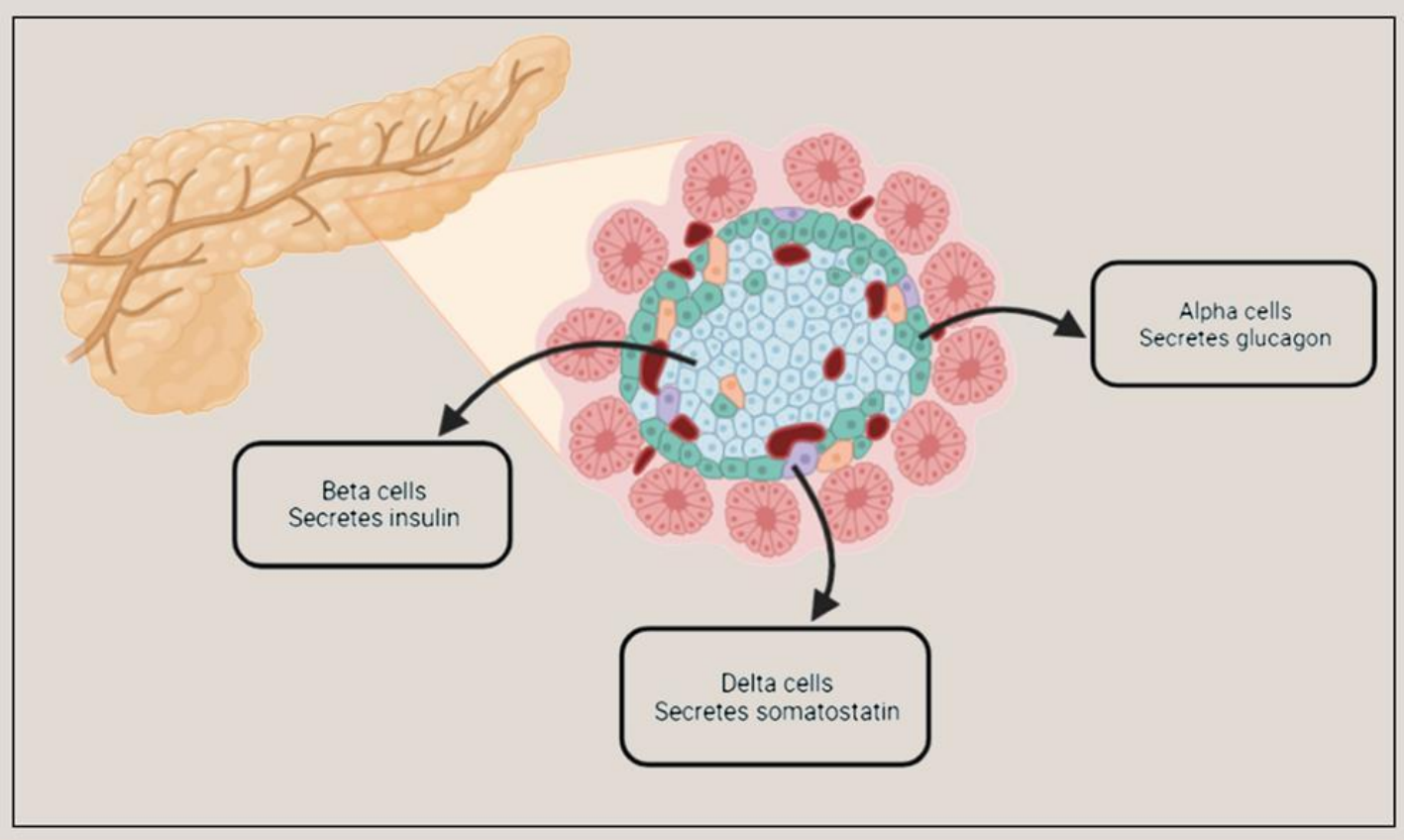
Pancreas

End results

Lower blood glucose

Insulin secretion inhibited

https://doi.org/10.1016/j.mpaic.2023.07.006



The endocrine portion of the pancreas consist of clusters of cells called islets of Langerhans (size range 50–300 μm). Human pancreas has up to two million islets which comprise 1–2% of the pancreatic mass. The islets house five major secretory cell types α, β, δ, F and ε cells.

The α cells produce glucagon and make up 20% of each islet. **Pancreatic β cells comprise the majority of the islet cells, around 65%, and secrete <u>insulin</u>** and amylin (islet amyloid polypeptide; IAPP). δ cells secrete somatostatin and they account for 10% of islet cells. The F cells comprise less than 5% and produces pancreatic polypeptide, whereas the ε cells secrete ghrelin and form 1% of the islet cells.

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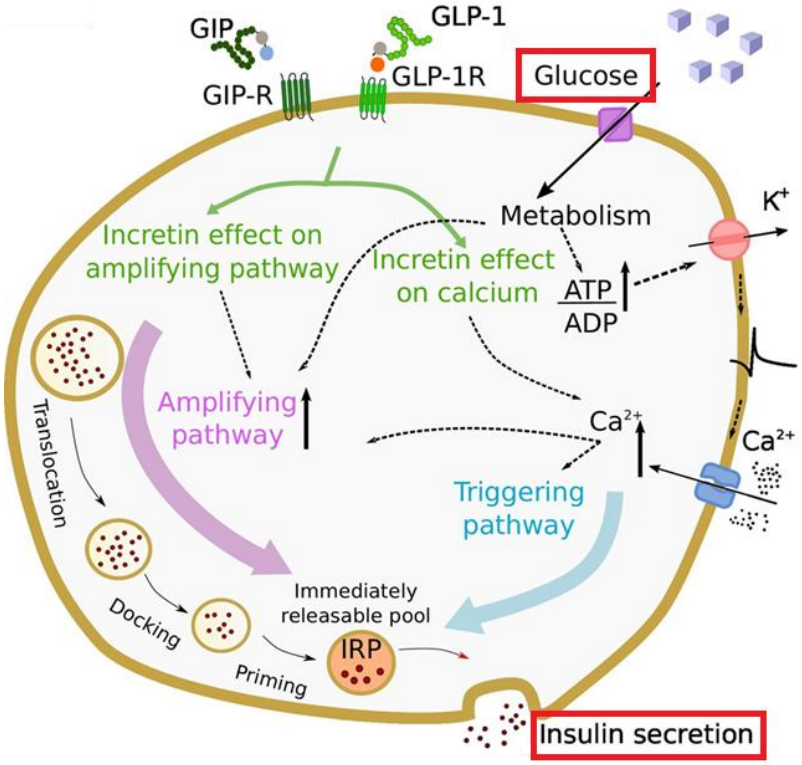
Factors influencing insulin secretion

Stimulatory factors	Inhibitory factors
Raised serum glucose	Low serum glucose
Raised amino acids (arginine, leucine)	Somatostatin
Cortisol	Starvation
Potassium	Diazoxide
Vagal stimulation	α-adrenergic agonists
Glucose-dependent insulinotropic peptide (GIP)	
Sulphonylurea drugs	
β-adrenergic agonists	

High blood glucose

Signals the pancreas to secrete insulin into the blood



The beta-cell senses glucose through its uptake and metabolism rather than via a plasma membrane glucose receptor. Initial beta-cell activation is rapid as it takes less than 2 min for glucose to raise cytosolic calcium signals that trigger insulin granule exocytosis. The link between glucose metabolism and insulin secretion has been termed metabolism-secretion coupling. Mitochondria are essential for this process as they generate metabolic signals, including ATP, that control beta-cell electrical activity and associated calcium signals resulting in insulin exocytosis

https://doi.org/10.1186/s12964-019-0326-6

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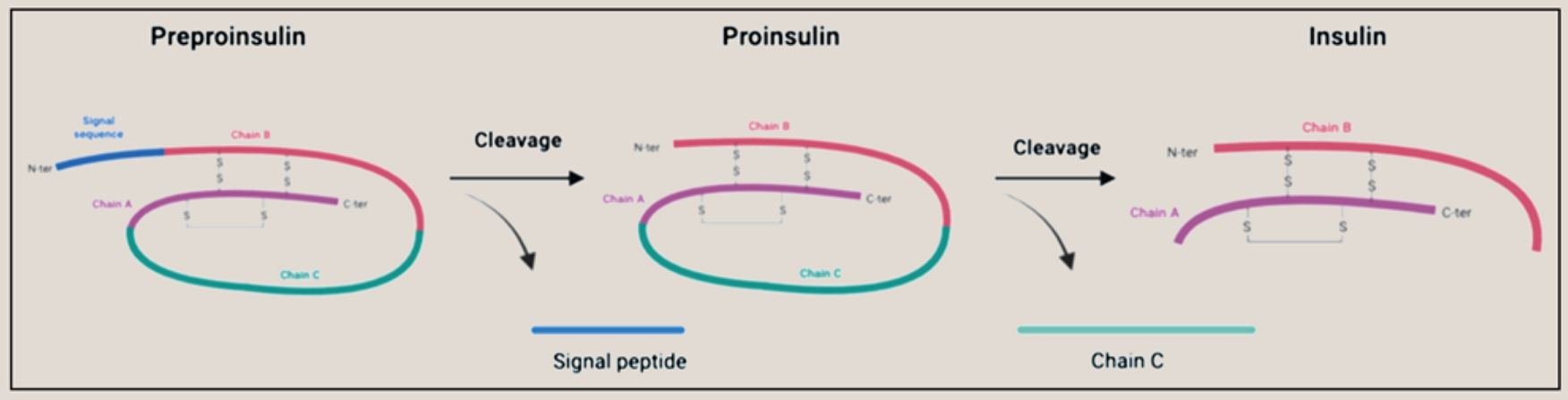
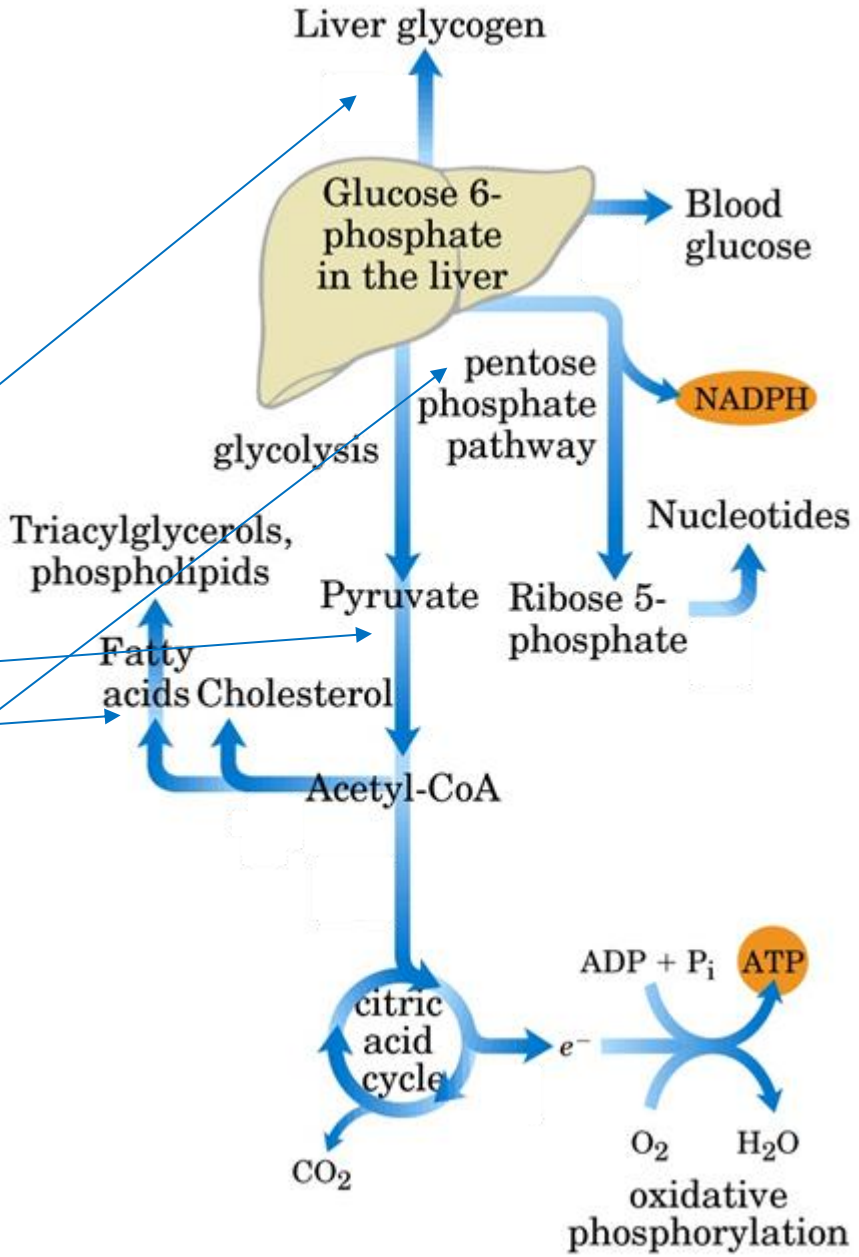


Insulin is synthesized in the ribosomes of RER as preproinsulin. Preproinsulin is cleaved to form proinsulin which is subsequently transported to the Golgi apparatus where further cleaving occurs forming equimolar amounts of insulin and C-peptide packed in secretory granules. The structure of insulin consists of two polypeptide chains (A and B) linked by two disulphide bridges. **Upon stimulation of the β cells, the secretory granules containing insulin,** proinsulin and C-peptide **will undergo exocytosis and be released into the portal circulation**. Insulin is rapidly metabolized by the liver and kidney, resulting in a half-life of 4 minutes. C-peptide does not undergo metabolism and is excreted unchanged by the kidneys. It also has a longer half-life of 30 minutes which makes it a useful biomarker in conditions such as insulinoma, a tumour secreting endogenous insulin resulting in frequent hypoglycaemic symptoms.

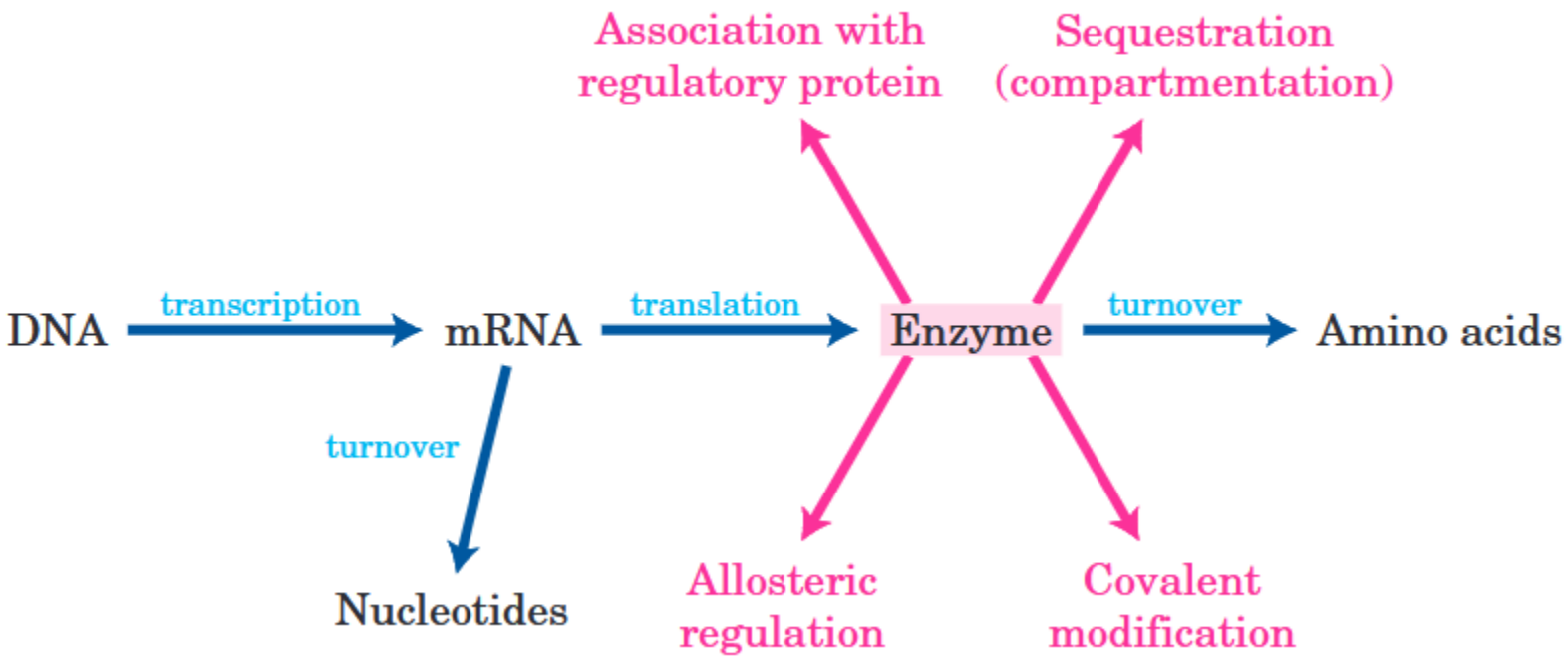
In the liver, insulin activates several pathways consuming glucose:

- Glycogen synthesis,
- Glycolysis,
- Lipid synthesis,
- Pentose phosphate pathway.



Factors that determine the activity of an enzyme.

Blue arrows represent processes that determine the number of enzyme molecules in the cell; red arrows show factors that determine the enzymatic activity of an existing enzyme molecule.



Effect of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (liver)	↑ Glucokinase
↑ Glycolysis	↑ Phosphofructokinase-1
↑ Glycogen synthesis (liver)	↑ Glycogen synthase
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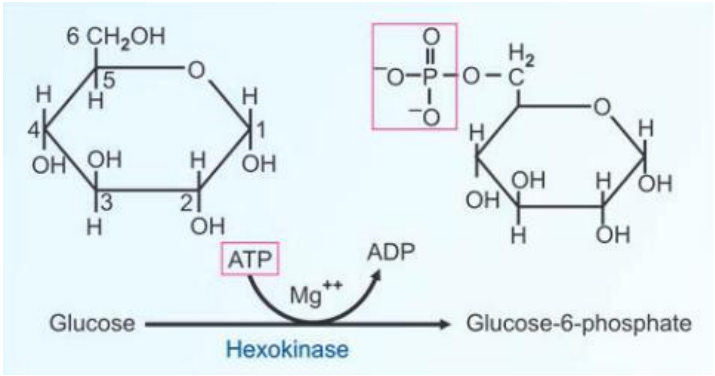


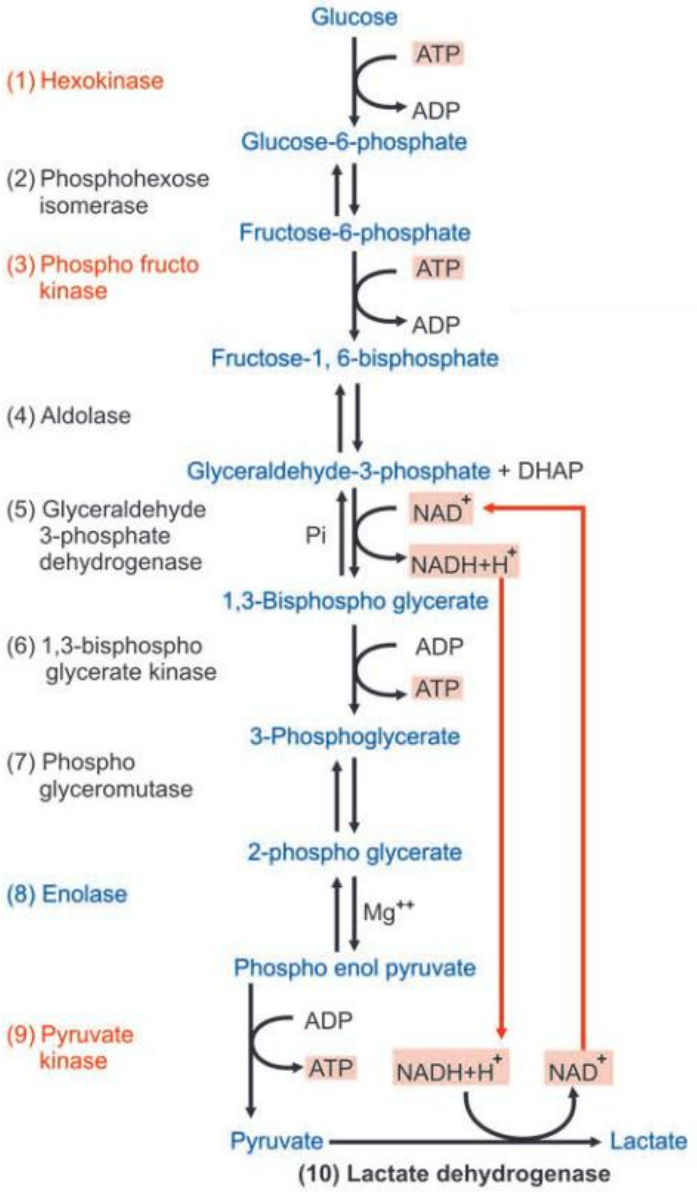
Step 1 of glycolysis (irreversible)
Hexokinase IV = **Glucokinase** (GCK)

GSK occurs only in liver.
It acts only on glucose.

Its Km value = 20 mmol/L (low affinity to substrate).
It acts only when blood glucose is more than100 mg/dL.

Insulin increases GCK gene expression at the transcriptional level

Summary of glycolysis



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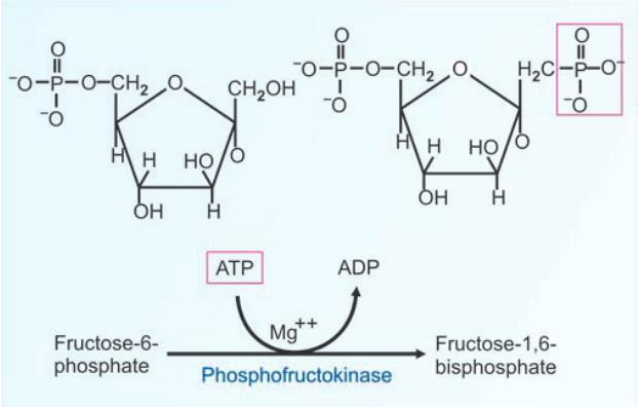
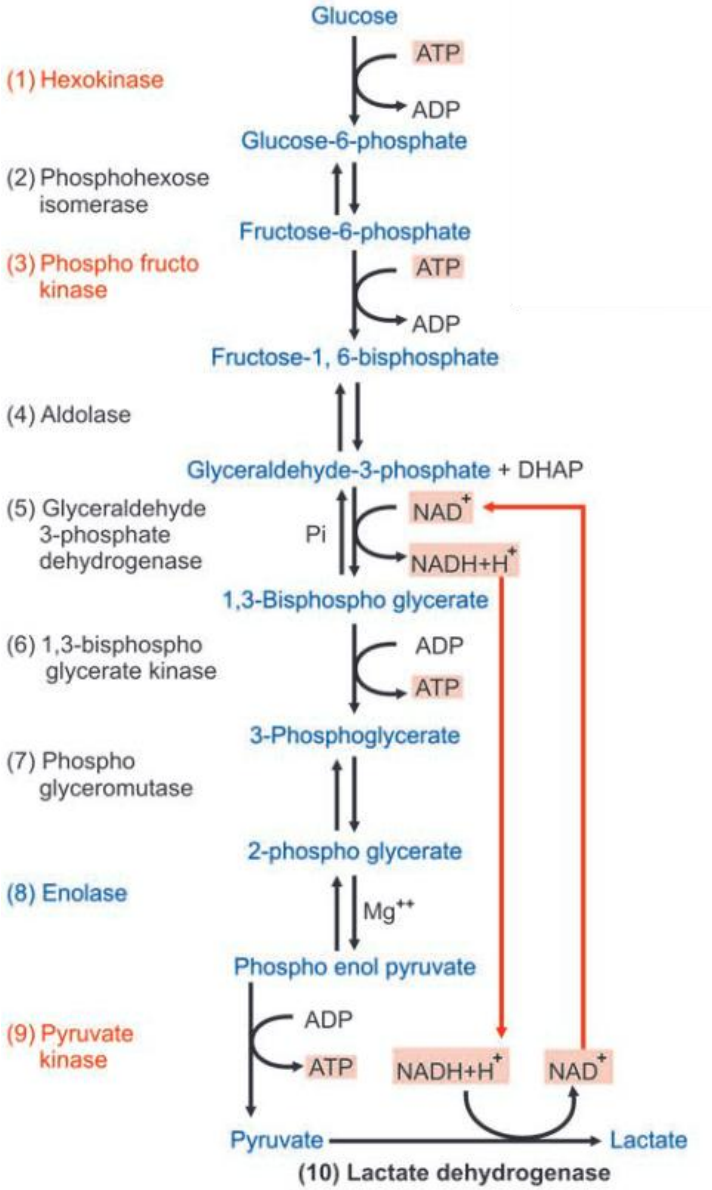


Step 3 of glycolysis (irreversible)
Phosphofructokinase (PFK-1)

A specific isoform of PFK (1) occurs in liver. It acts on fructose-6-phosphate. Allosterically activated by ADP, AMP, or fructose 2,6-bisphosphate, and allosterically inhibited by ATP or citrate.

Insulin increases PFK-1 gene expression at the transcriptional level

Summary of glycolysis



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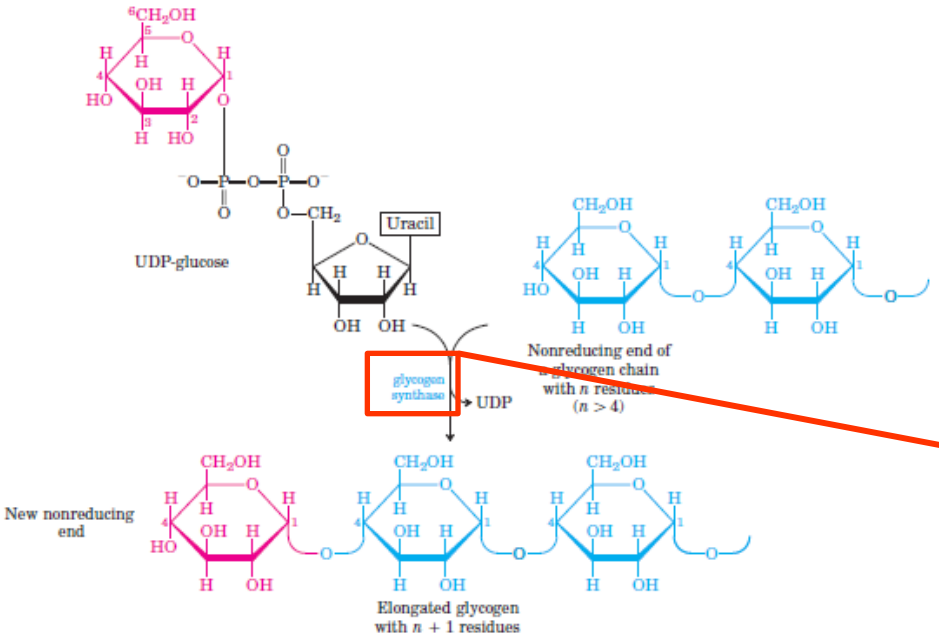
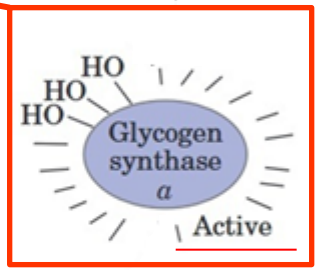
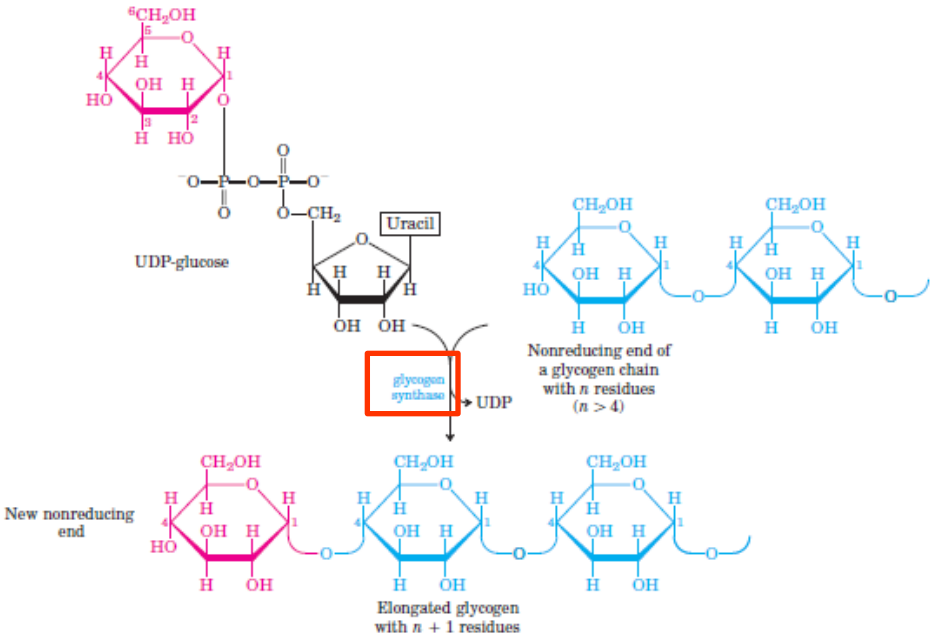




A glycogen chain is elongated by glycogen synthase (GS). The enzyme transfers the glucose residue of UDP-glucose to the nonreducing end of a glycogen branch to make a new (1n4) linkage.



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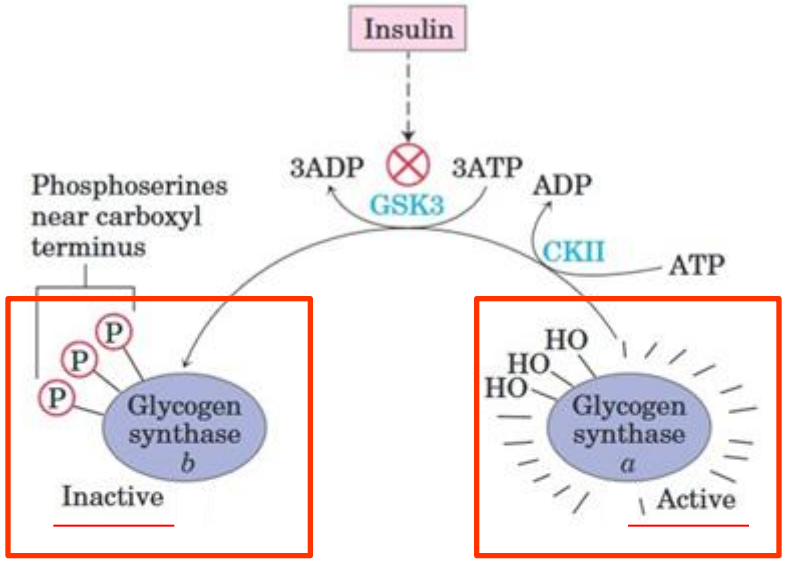
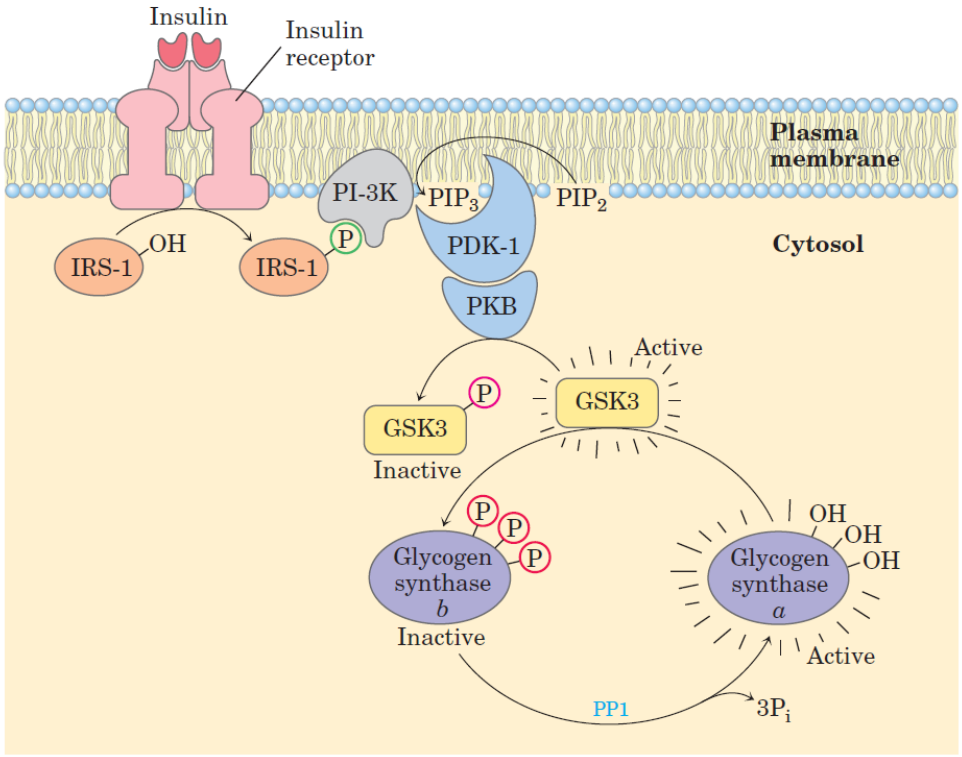
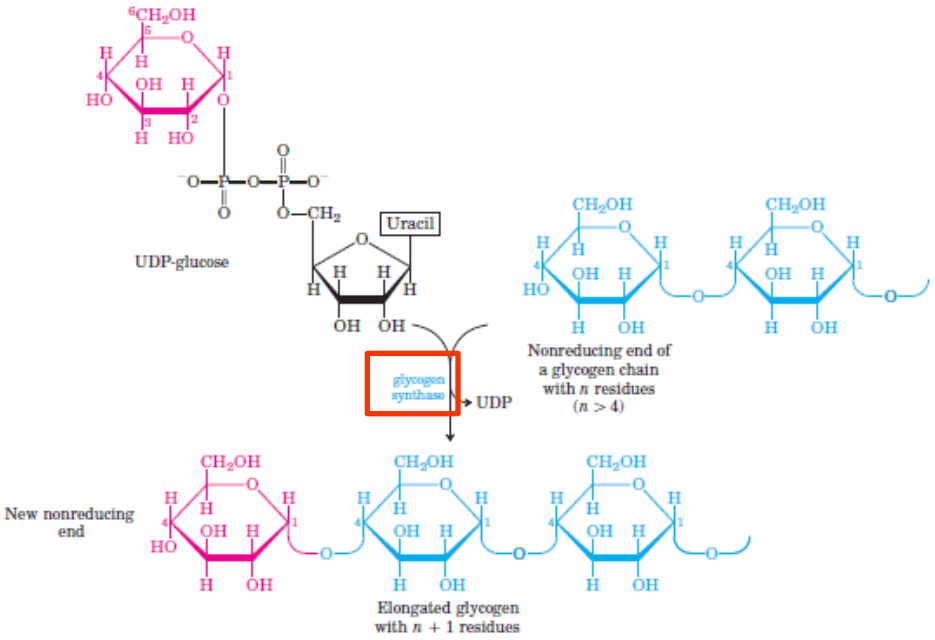
Dephosphorylation = activation of glycogen synthase (GS) follows **inactivation of glycogen synthase kinase (GSK) 3 via insulin-driven phosphorylation**.





Insulin binding to its receptor activates a tyrosine protein kinase in the receptor, which phosphorylates insulin receptor substrate-1 (IRS-1). The phosphotyrosine in this protein is then bound by phosphatidylinositol 3-kinase (PI-3K), which converts phosphatidylinositol 4,5-bisphosphate (PIP_2) in the membrane to phosphatidylinositol 3,4,5-trisphosphate (PIP_3). A protein kinase (PDK-1) that is activated when bound to PIP_3 activates a second protein kinase (PKB), which phosphorylates glycogen synthase kinase 3 (GSK3) in its pseudosubstrate region, inactivating it. The inactivation of GSK3 allows phosphoprotein phosphatase 1 (PP1) to dephosphorylate glycogen synthase, converting it to its active form. In this way, insulin stimulates glycogen synthesis.



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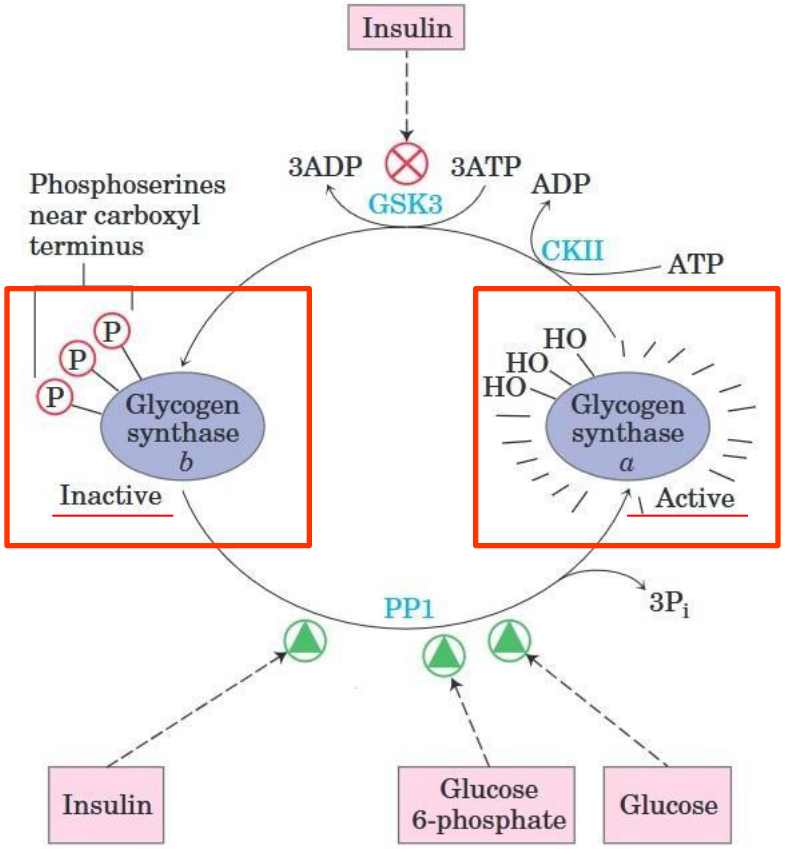
Dephosphorylation = activation of glycogen synthase (GS) follows inactivation of glycogen synthase kinase (GSK) 3 via insulin-driven phosphorylation.

Insulin also promotes glucose-6-phosphate (G-6-P) production, which allosterically activates GS.



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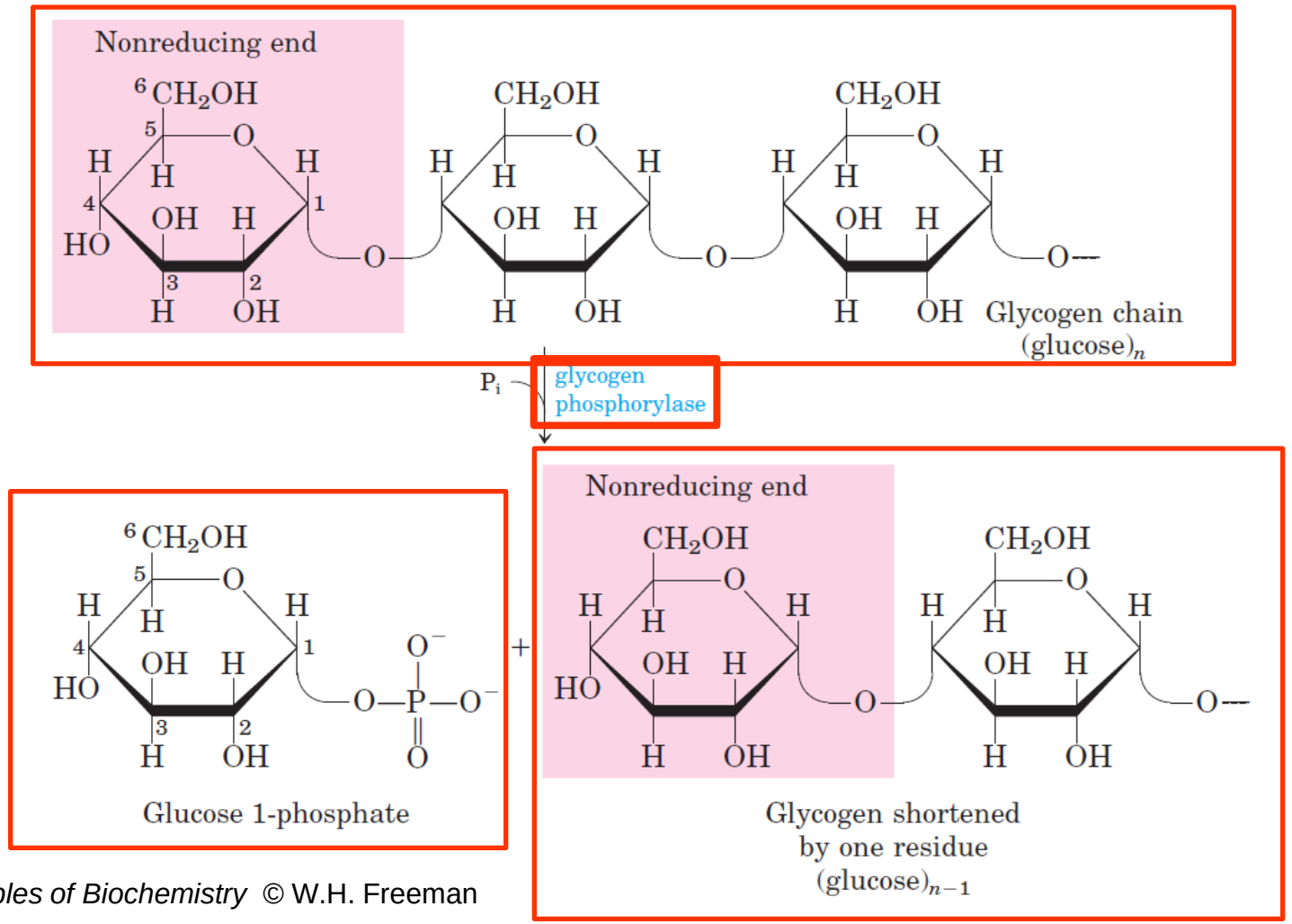
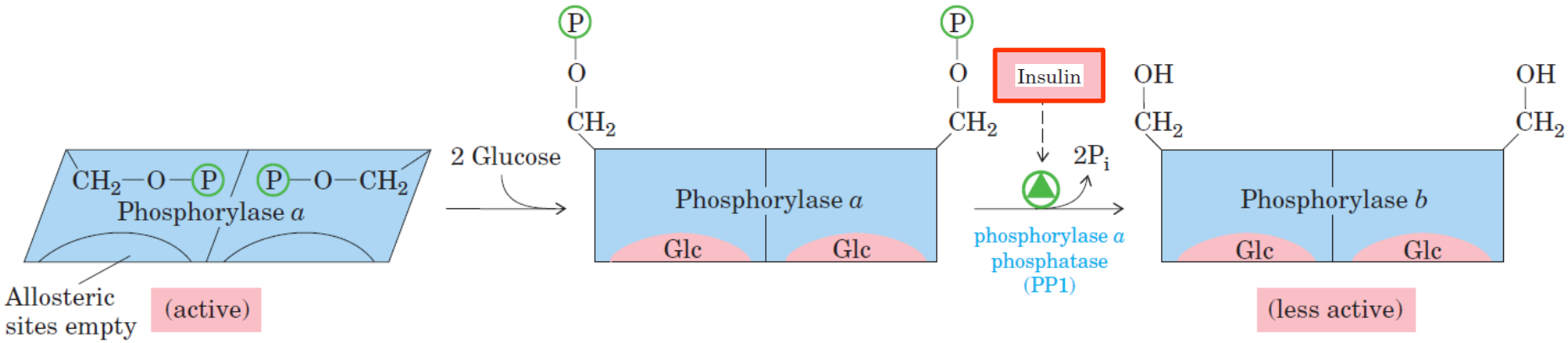
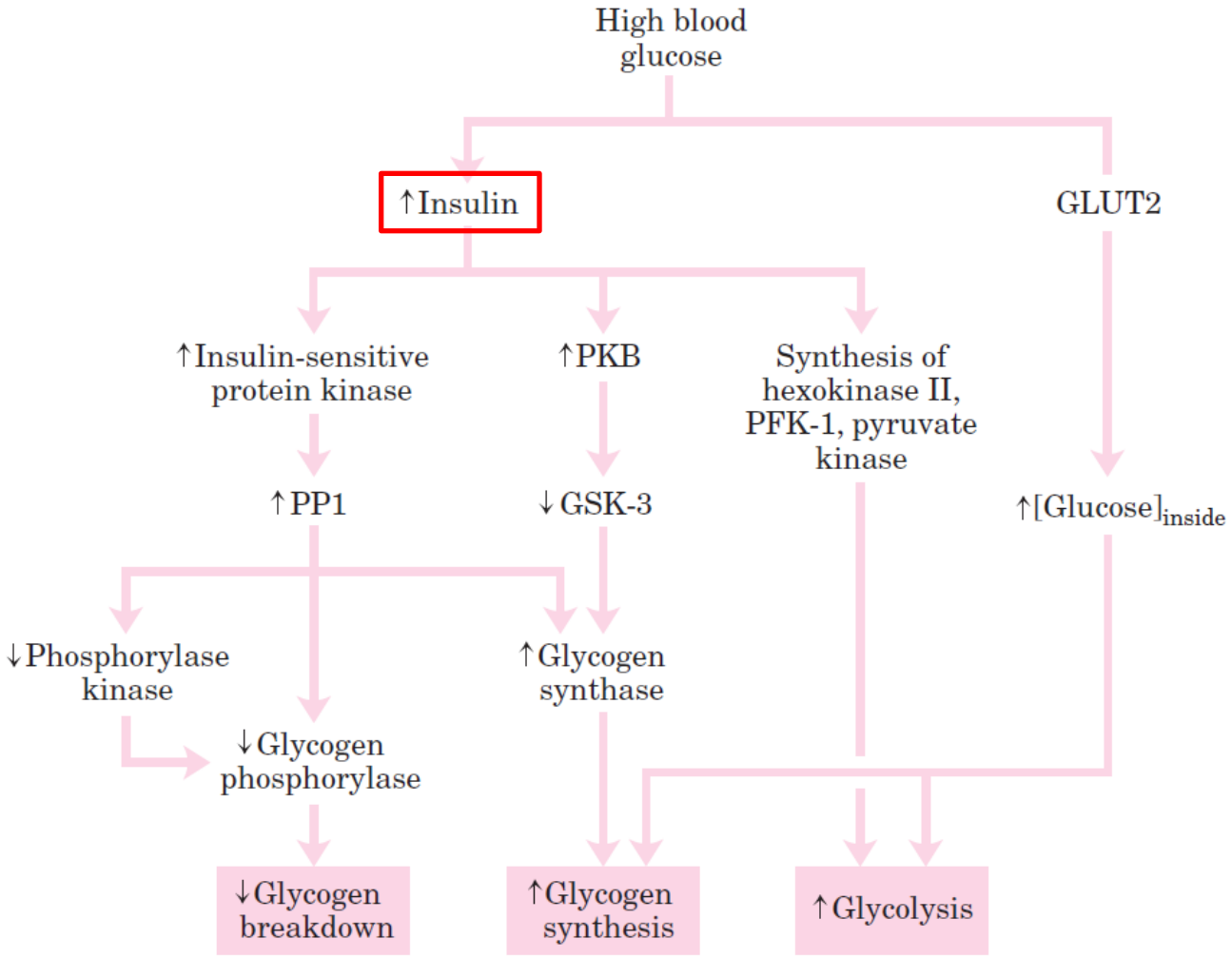
A terminal glucose residue from the nonreducing end of a glycogen chain by **glycogen phosphorylase**





Glucose binding to an allosteric site of the phosphorylase *a* isozyme of liver induces a conformational change that exposes its phosphorylated Ser residues to the action of phosphorylase *a* phosphatase 1(PP1).

This phosphatase converts phosphorylase *a* to phosphorylase *b*, sharply reducing the activity of phosphorylase and slowing glycogen breakdown in response to high blood glucose. **Insulin stimulates PP1 and slow glycogen breakdown.**



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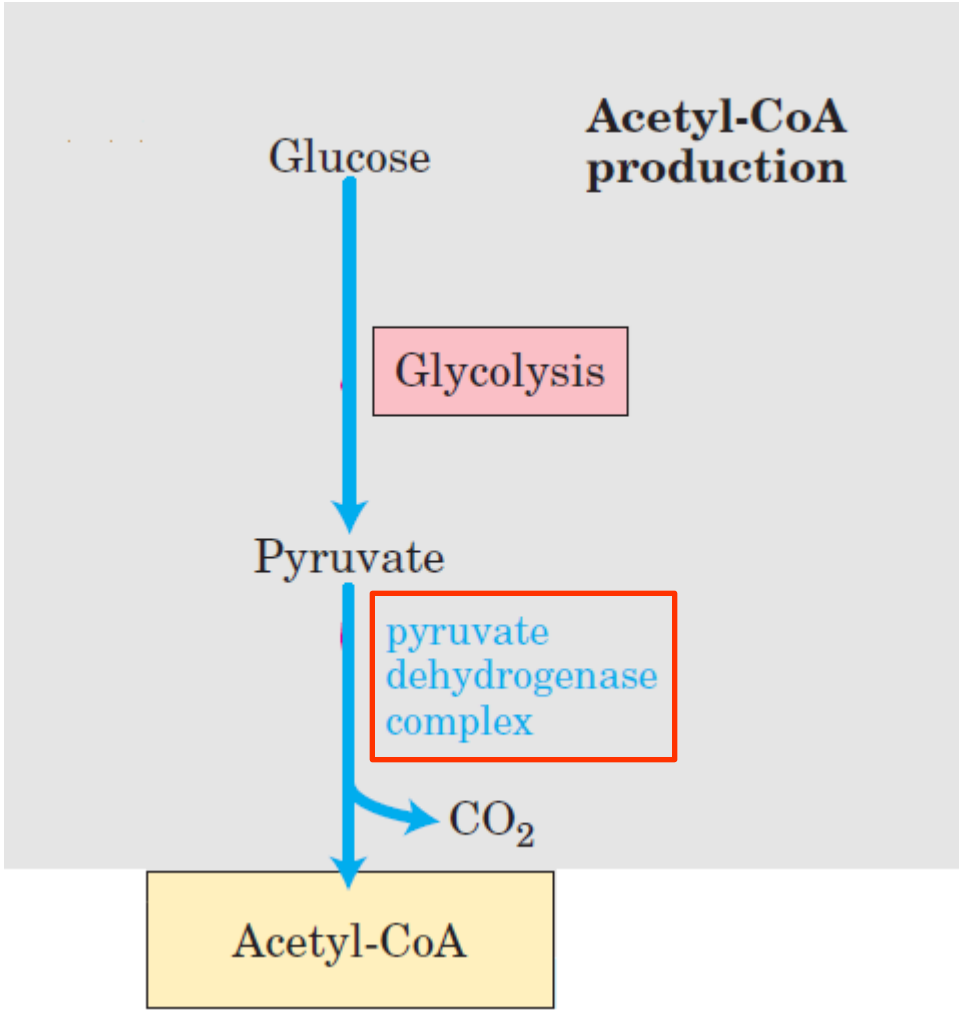
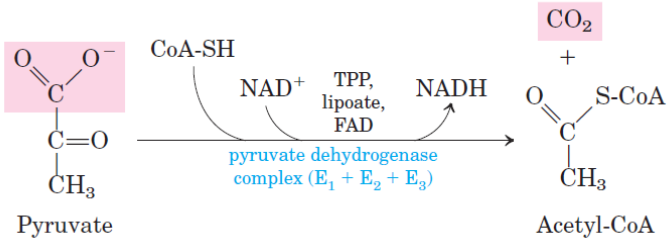
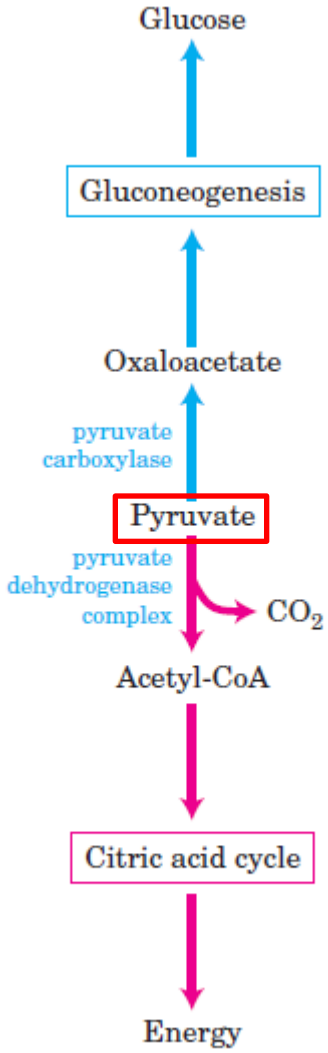


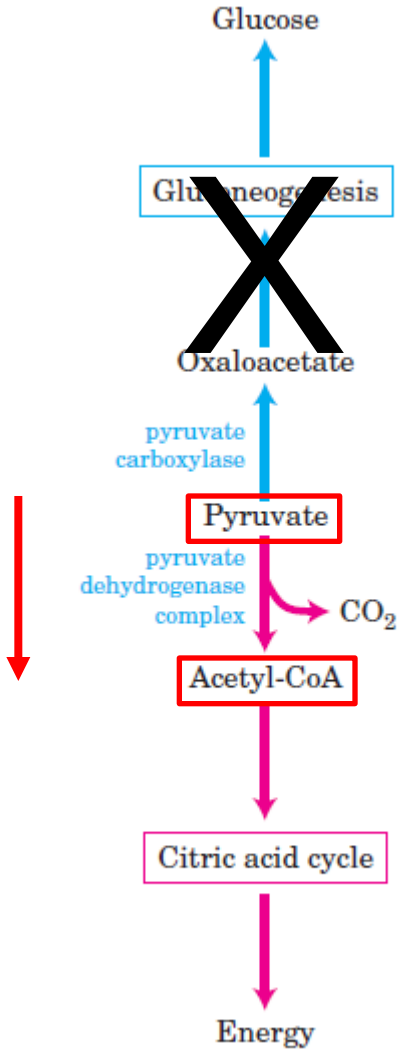
The **pyruvate dehydrogenase (PDH) complex,** a cluster of multiple copies of three enzymes located in the mitochondria of eukaryotic cells, oxidizes pyruvate, (derived from glucose and other sugars by glycolysis), to acetyl-CoA and CO_2



The pyruvate dehydrogenase (PDH) complex undergoes hormonal regulation from insulin.



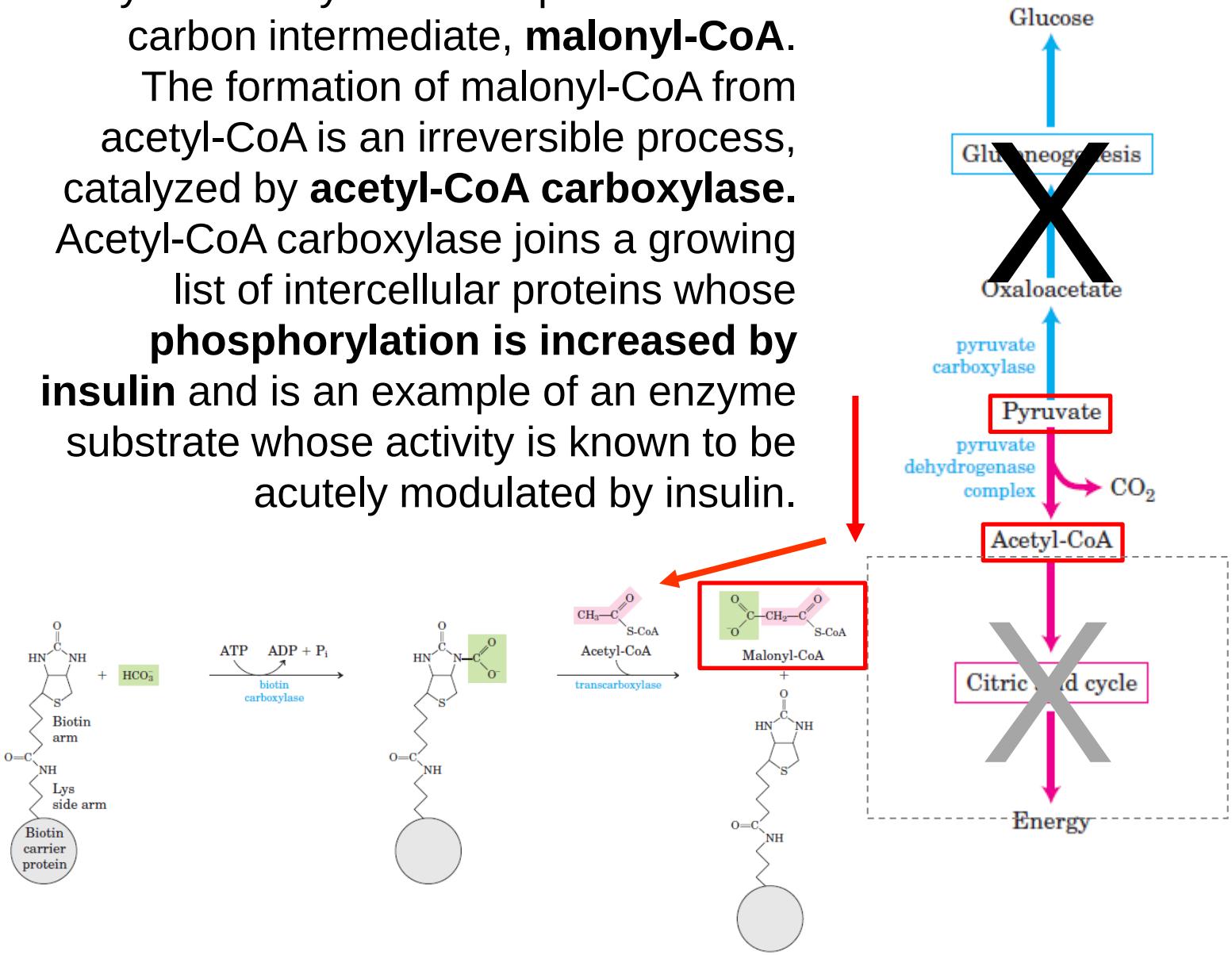
Such regulation does not result from activation of a cAMP-dependent protein kinase, as in many other cases, but it is rather related to changes in **intracellular calcium levels** that **activate a phosphatase. The dephosphorylated form is the active state of PDH**.



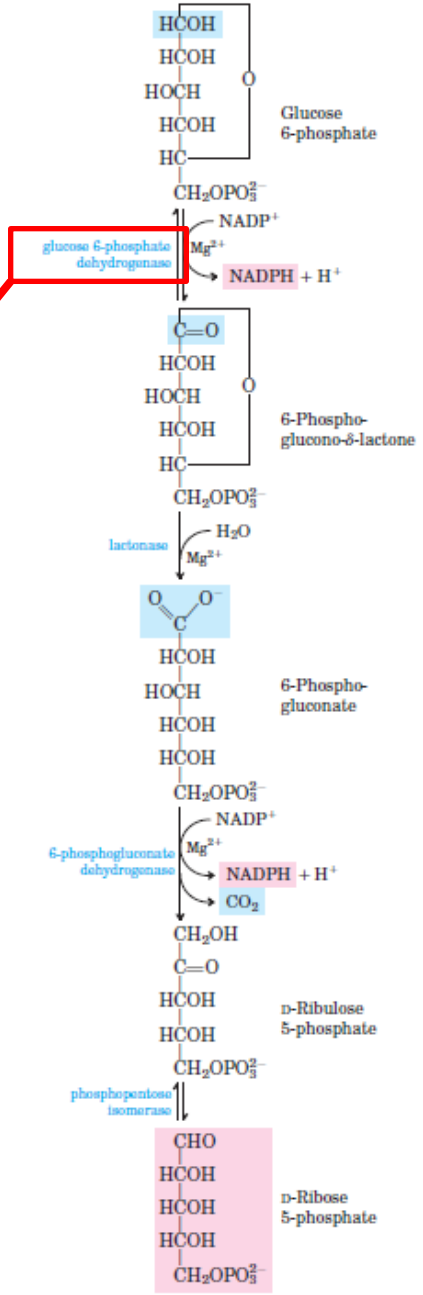
Effect of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

Metabolic effect	Target enzyme
↑ Glucose uptake (liver)	↑ Glucokinase
↑ Glycolysis	↑ Phosphofructokinase-1
↑ Glycogen synthesis (liver)	↑ Glycogen synthase
↓ Glycogen breakdown (liver)	↓ Glycogen phosphorylase
↑ Acetyl-CoA production (liver)	↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase

Fatty acid biosynthesis requires a three-carbon intermediate, **malonyl-CoA**. The formation of malonyl-CoA from acetyl-CoA is an irreversible process, catalyzed by **acetyl-CoA carboxylase.** Acetyl-CoA carboxylase joins a growing list of intercellular proteins whose **phosphorylation is increased by insulin** and is an example of an enzyme substrate whose activity is known to be acutely modulated by insulin.

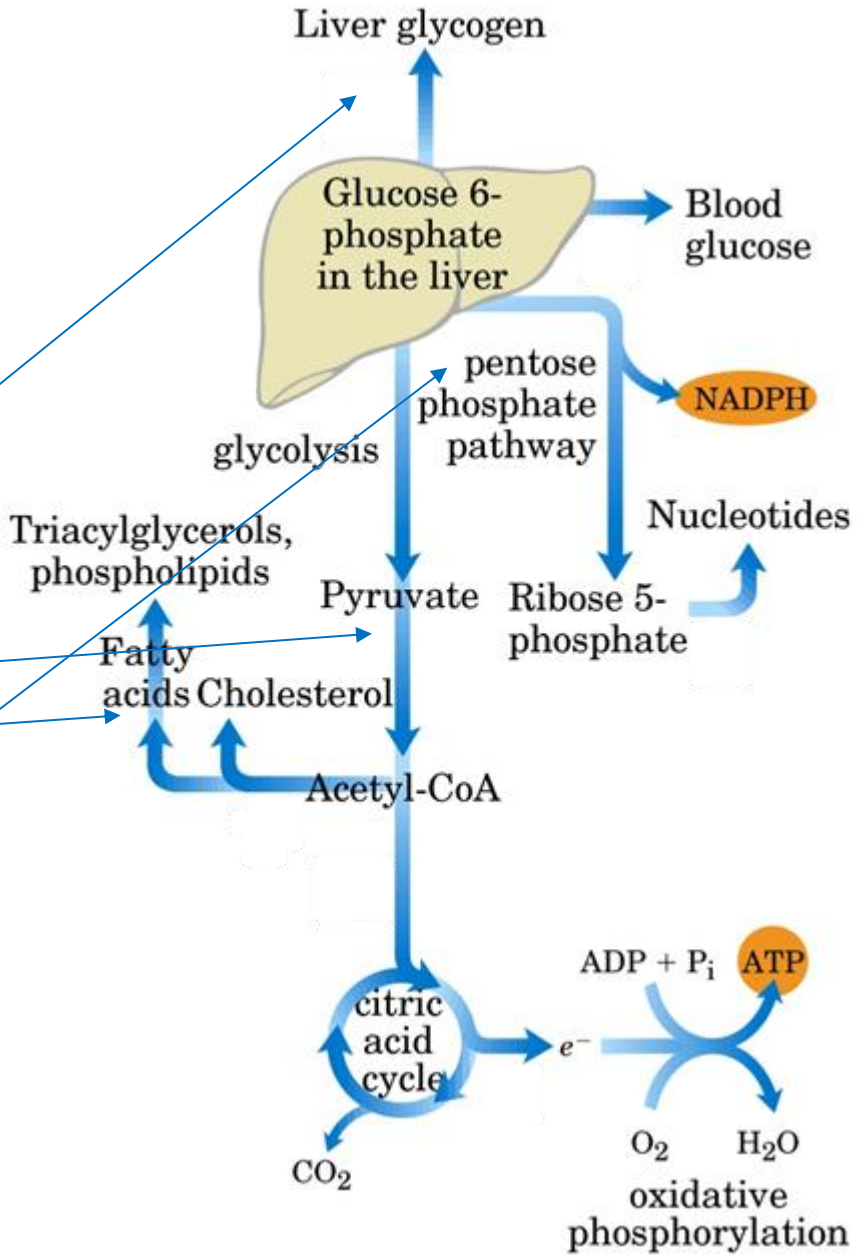


The **Pentose Phosphate Pathway** is a metabolic pathway, parallel to glycolysis, that generates NADPH and pentose, namely ribose 5-phosphate precursor for the synthesis of nucleotides. The first reaction of the pentose phosphate pathway is the oxidation of glucose 6-phosphate (G6P) by **glucose 6-phosphate dehydrogenase (G6PD)** that **is the rate-limiting enzyme of the pentose phosphate pathway**. Thus, regulation of G6PD has downstream consequences for the activity of the rest of the pentose phosphate pathway. **Insulin induces increase in the glucose 6-phosphate dehydrogenase activity, assumed to be due to *de novo* enzyme biosynthesis** involving new RNA production.

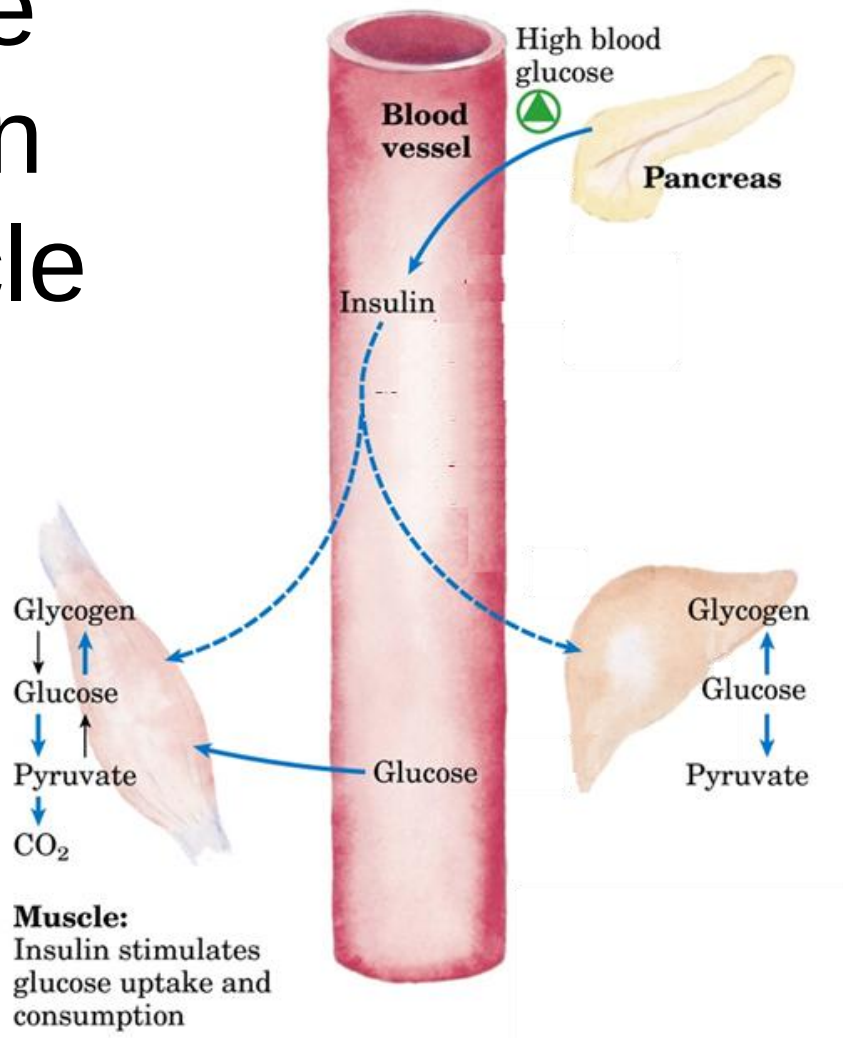


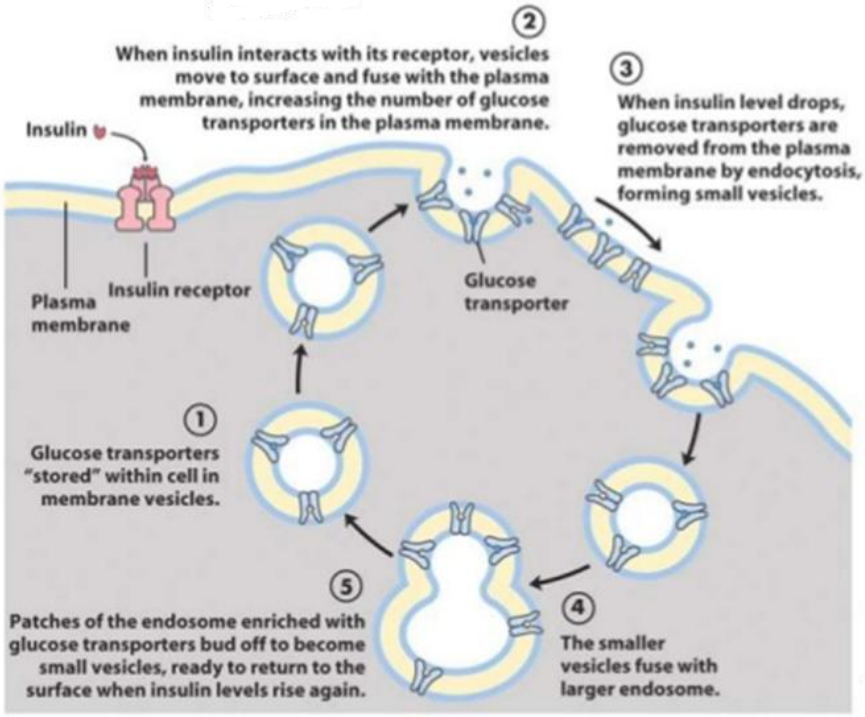
In the liver, insulin activates several pathways consuming glucose:

- Glycogen synthesis,
- Glycolysis,
- Lipid synthesis,
- Pentose phosphate pathway.

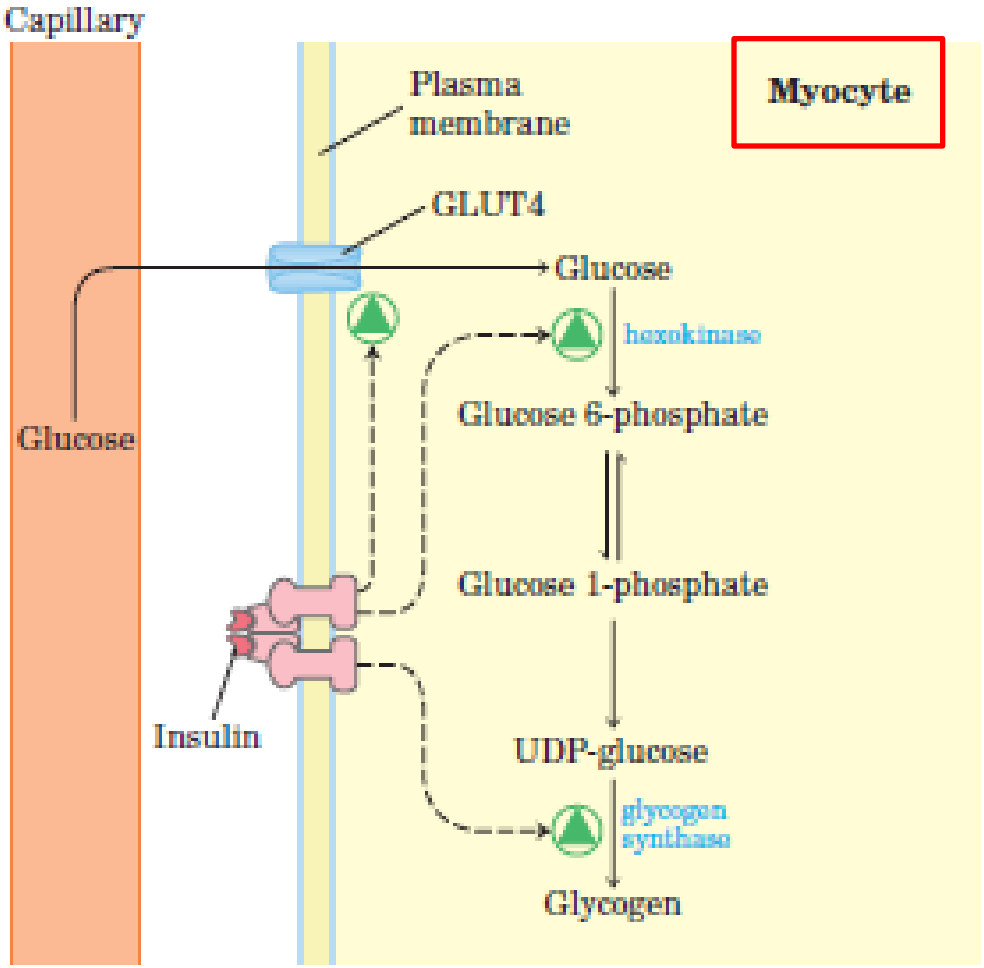


Carbohydrate Metabolism in Skeletal Muscle





The **passive uptake of glucose by muscle and adipose tissue is catalyzed by the GLUT4 transporter**. In the absence of insulin, most GLUT4 molecules are sequestered in membrane vesicles within the cell, but when blood glucose rises, release of insulin triggers GLUT4 movement to the plasma membrane.



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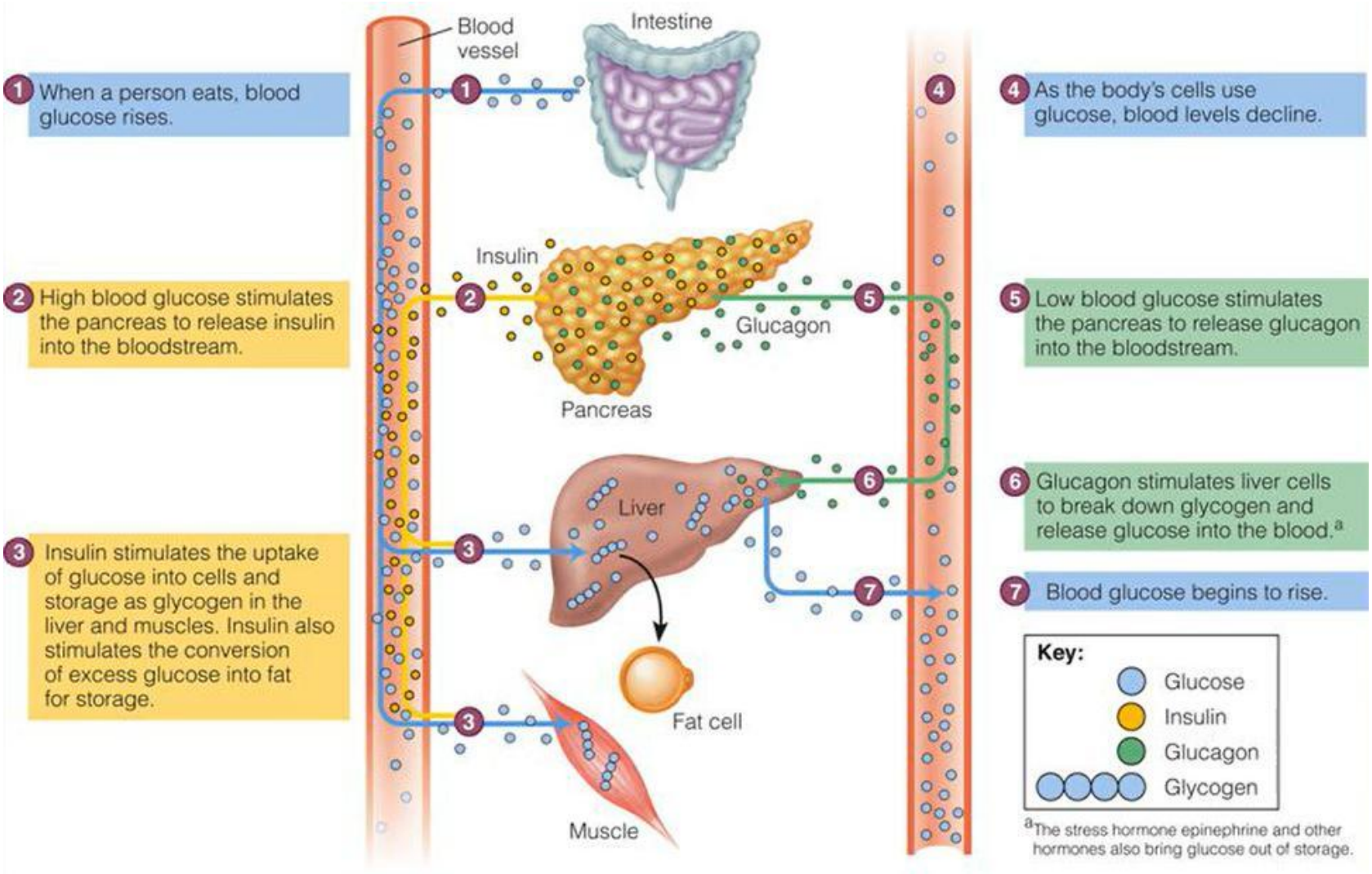
Effect of Insulin on Blood Glucose: Uptake of Glucose by Cells and Storage as Triacylglycerols and Glycogen

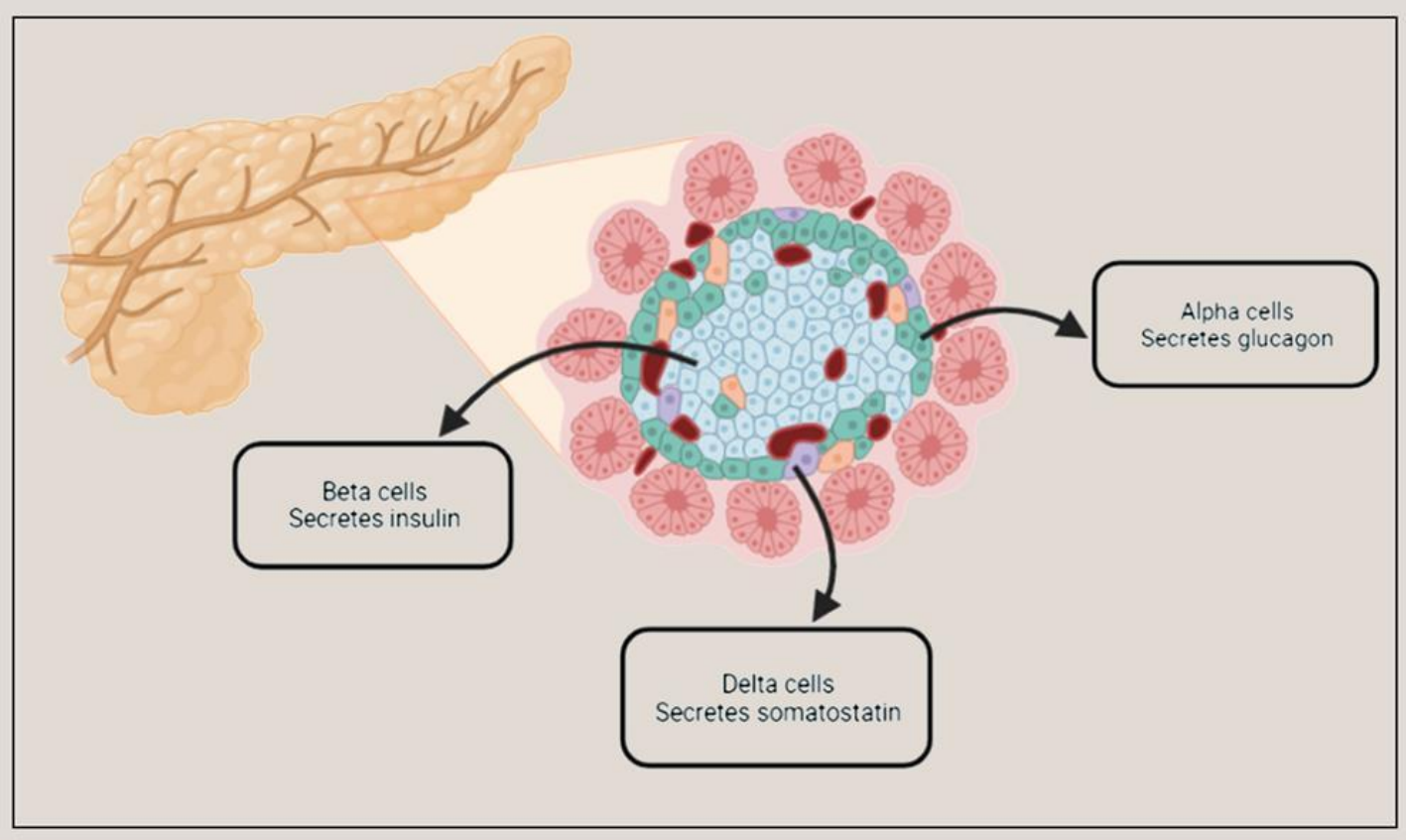
Metabolic effect	Target enzyme
↑ Glucose uptake (muscle)	↑ Glucose transporter
↑ Glucose uptake (liver)	↑ Glucokinase
↑ Glycogen synthesis (liver, muscle)	↑ Glycogen synthase
↓ Glycogen breakdown (liver, muscle)	↓ Glycogen phosphorylase
↑ Glycolysis, acetyl-CoA production (liver, muscle)	↑ Phosphofructokinase-1
	↑ Pyruvate dehydrogenase complex
↑ Fatty acid synthesis (liver)	↑ Acetyl-CoA carboxylase
↑ Triacylglycerol synthesis (adipose tissue)	↑ Lipoprotein lipase

After a carbohydrate-rich meal, insulin activates many pathways that consume glucose (namely: glycolysis, glycogen synthesis, glycolysis, pentose pathway, lipid synthesis…).

During fasting, glucagon activates pathways producing glucose to be released in blood for energy supply (glycogenolysis, gluconeogenesis).

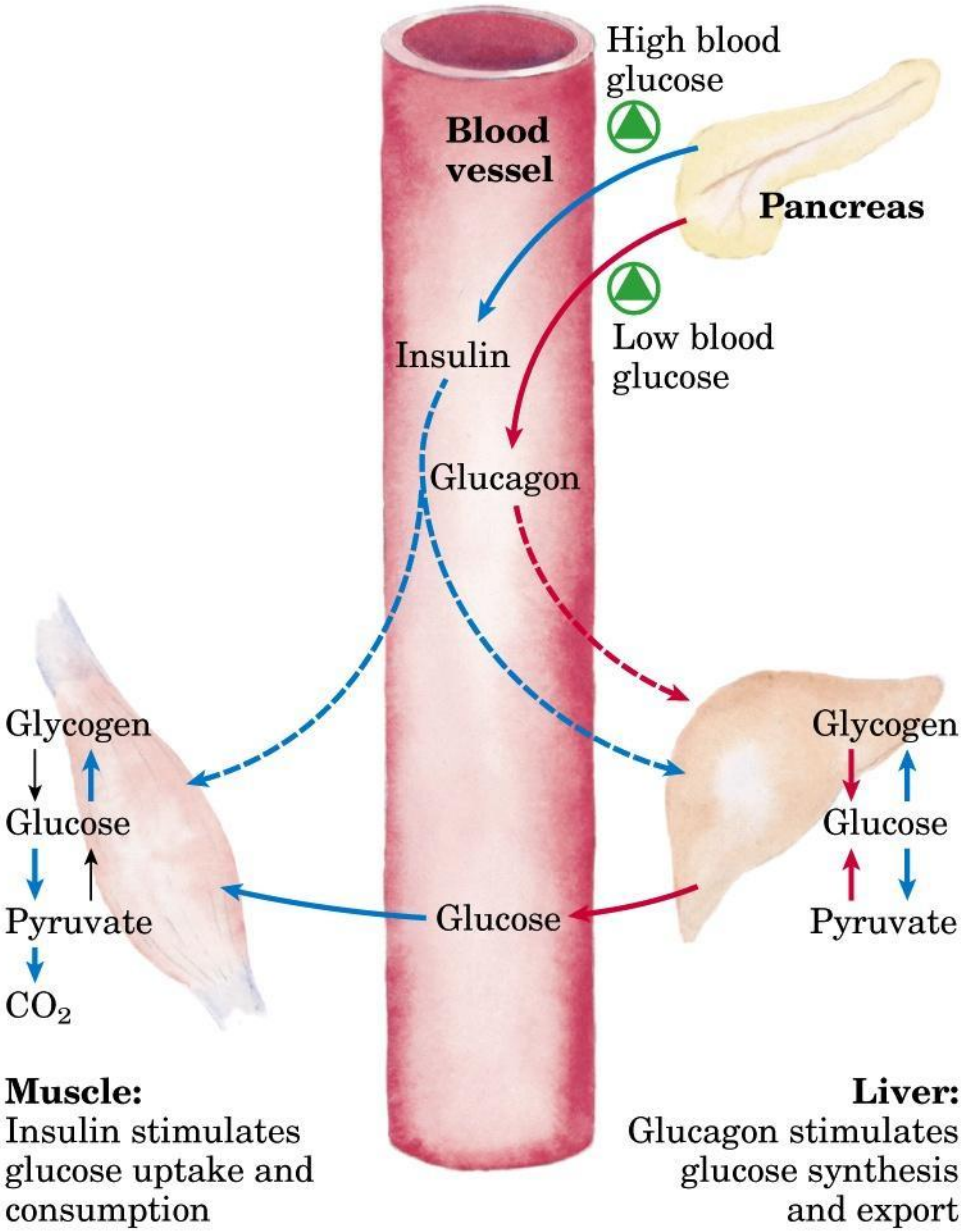


https://doi.org/10.1016/j.mpaic.2023.07.006



The endocrine portion of the pancreas consist of clusters of cells called islets of Langerhans (size range 50–300 μm). Human pancreas has up to two million islets which comprise 1–2% of the pancreatic mass. The islets house five major secretory cell types α, β, δ, F and ε cells.

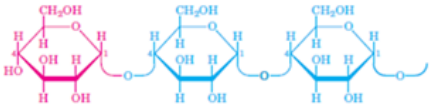
The α cells produce <u>glucagon</u> and make up 20% of each islet. Pancreatic β cells comprise the majority of the islet cells, around 65%, and secrete insulin and amylin (islet amyloid polypeptide; IAPP). δ cells secrete somatostatin and they account for 10% of islet cells. The F cells comprise less than 5% and produces pancreatic polypeptide, whereas the ε cells secrete ghrelin and form 1% of the islet cells.



Fasting
Glucagon actions in the liver

Glycolysis ↓

- Repression of Phosphofructokinase 1



Glycogenolysis ↑

- Activation of glycogenolysis (Glycogen phosphorylase phosphorylated)
- Inhibition of glycogen synthesis (Glycogen synthase phosphorylated)

Gluconeogenesis ↑

Glucogenic Amino Acids, Grouped by Site of Entry

Pyruvate	**Succinyl-CoA**
Alanine	Isoleucine*
Cysteine	Methionine
Glycine	Threonine
Serine	Valine
Threonine	**Fumarate**
Tryptophan*	Phenylalanine*
α-Ketoglutarate	Tyrosine*
Arginine	**Oxaloacetate**
Glutamate	Asparagine
Glutamine	Aspartate
Histidine	
Proline	

Note: All these amino acids are precursors of blood glucose or liver glycogen, because they can be converted to pyruvate or citric acid cycle intermediates. Of the 20 common amino acids, only leucine and lysine are unable to furnish carbon for net glucose synthesis.

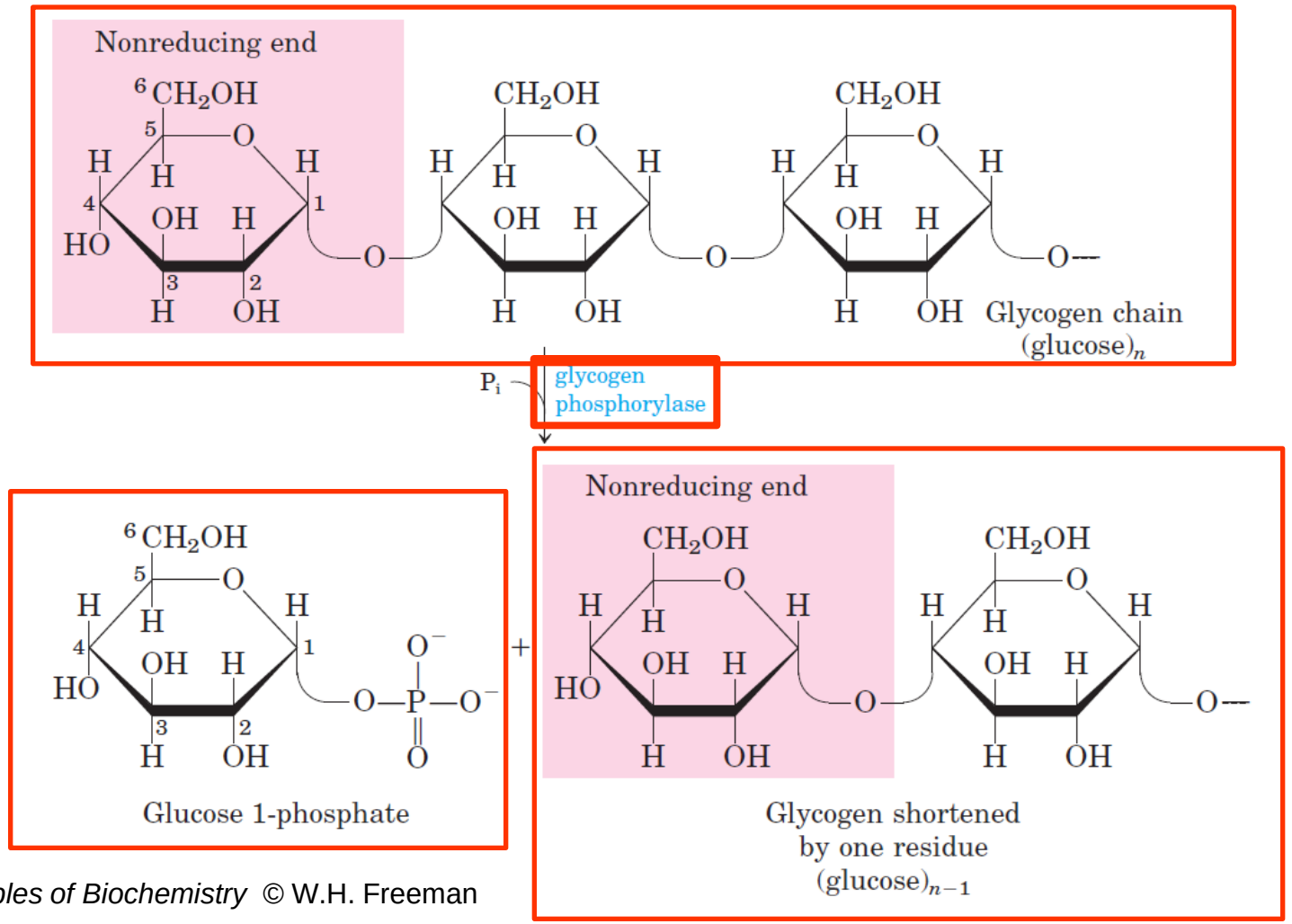
(Fructose 2,6 bisP)

Pathways utilizing AcetylCoA ↓

Effects of Glucagon on Blood Glucose: Production and Release of Glucose By the Liver

Metabolic effect	Effect on glucose metabolism	Target enzyme
↓ Glycolysis (liver)	Less glucose used as fuel in liver	↓ Phosphofructokinase-1
↑ Glycogen breakdown (liver)	Glycogen ⟶ glucose	↑ Glycogen phosphorylase
↓ Glycogen synthesis (liver)	Less glucose stored as glycogen	↓ Glycogen synthase
↑ Gluconeogenesis (liver)	Amino acids, Glycerol, Oxaloacetate ⟶ glucose	↑ Fructose 1,6-bisphosphatase ↓ Pyruvate kinase
↑ Fatty acid mobilization (adipose tissue)	Less glucose used as fuel by liver, muscle	↑ Triacylglycerol lipase

A terminal glucose residue from the nonreducing end of a glycogen chain by **glycogen phosphorylase**

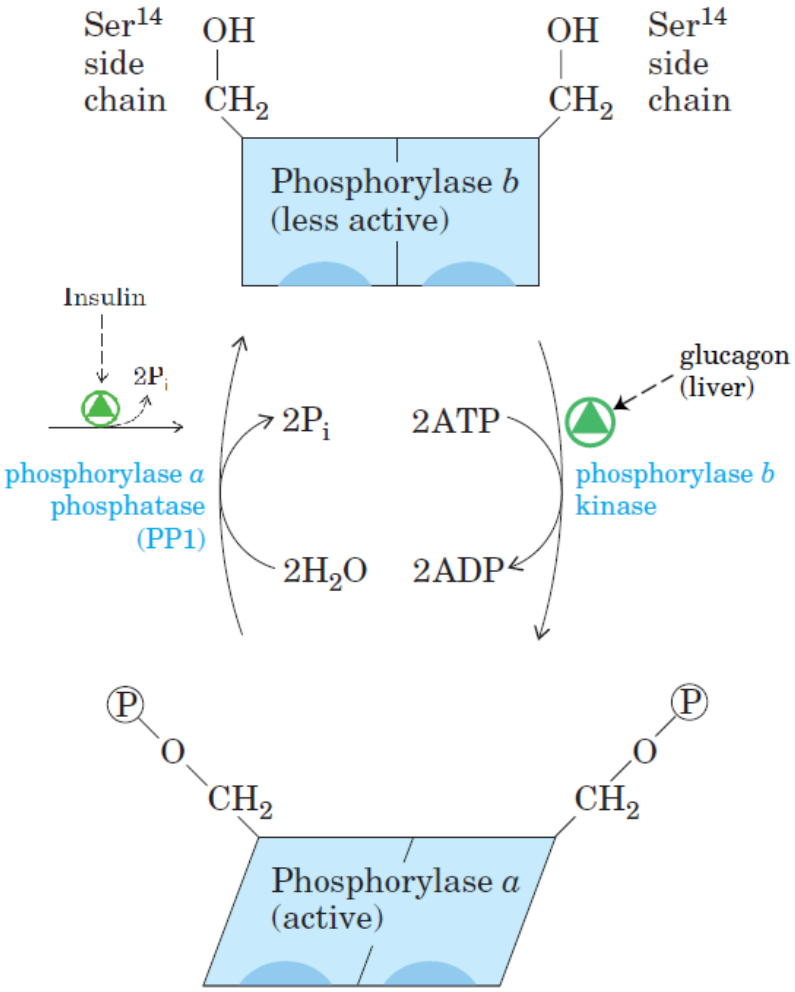


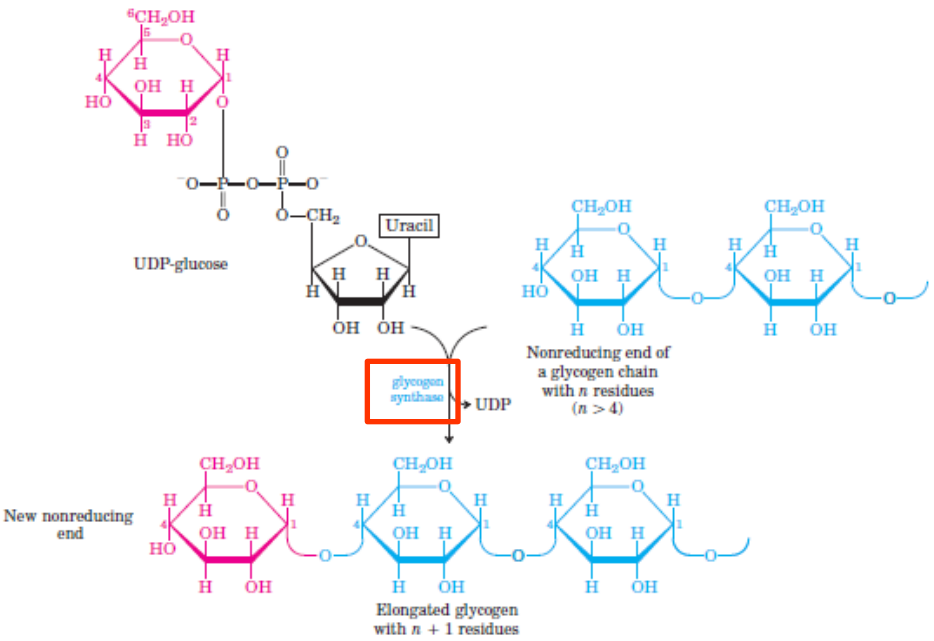
Regulation of muscle glycogen phosphorylase by covalent modification.

In the more active form of the enzyme, phosphorylase *a,* Ser14 residues, one on each subunit, are phosphorylated.

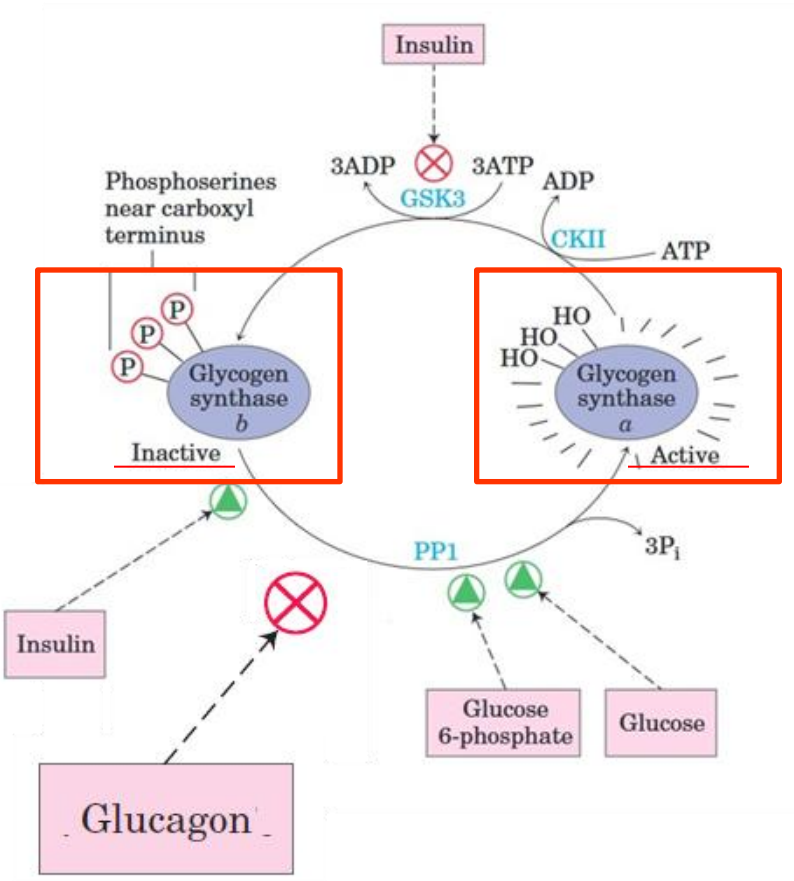
Phosphorylase *a* is converted to the less active form, phosphorylase *b,* by enzymatic loss of these phosphoryl groups, catalyzed by phosphorylase *a* phosphatase (PP1).

Phosphorylase *b* can be reconverted (reactivated) to phosphorylase *a* by the action of phosphorylase *b* kinase.





A glycogen chain is elongated by glycogen synthase (GS). The enzyme transfers the glucose residue of UDP-glucose to the nonreducing end of a glycogen branch to make a new (1n4) linkage.

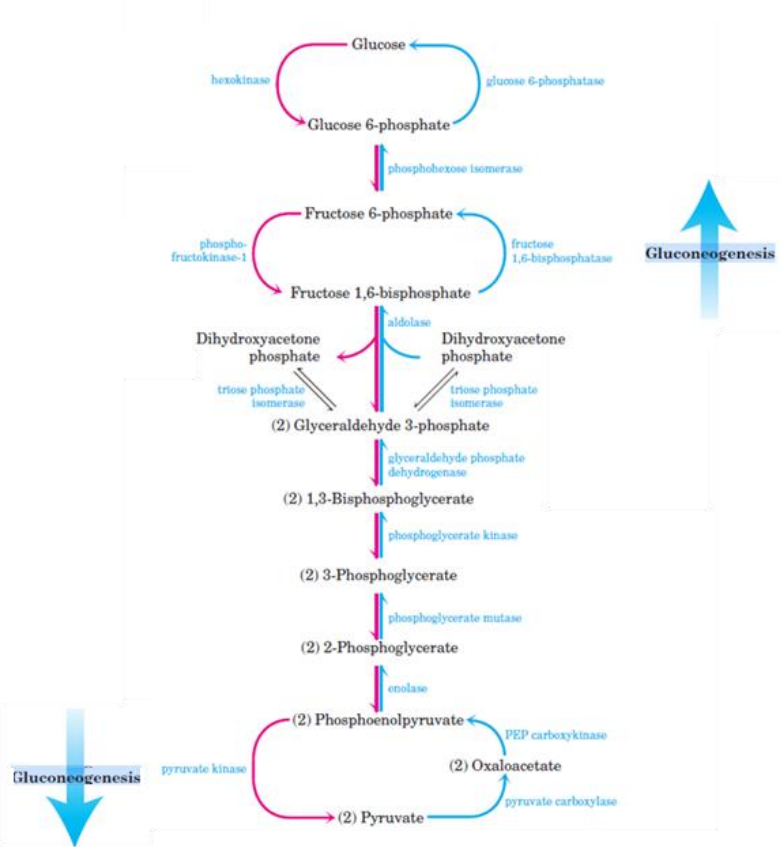


Three irreversible steps in the glycolytic pathway are bypassed by reactions catalyzed by gluconeogenic enzymes:

(1) conversion of pyruvate to PEP via oxaloacetate, catalyzed by pyruvate carboxylase and PEP carboxykinase;

(2) dephosphorylation of fructose 1,6-bisphosphate by FBPase-1;

(3) dephosphorylation of glucose 6-phosphate by glucose 6-phosphatase.



Fasting
Glucagon actions in the liver

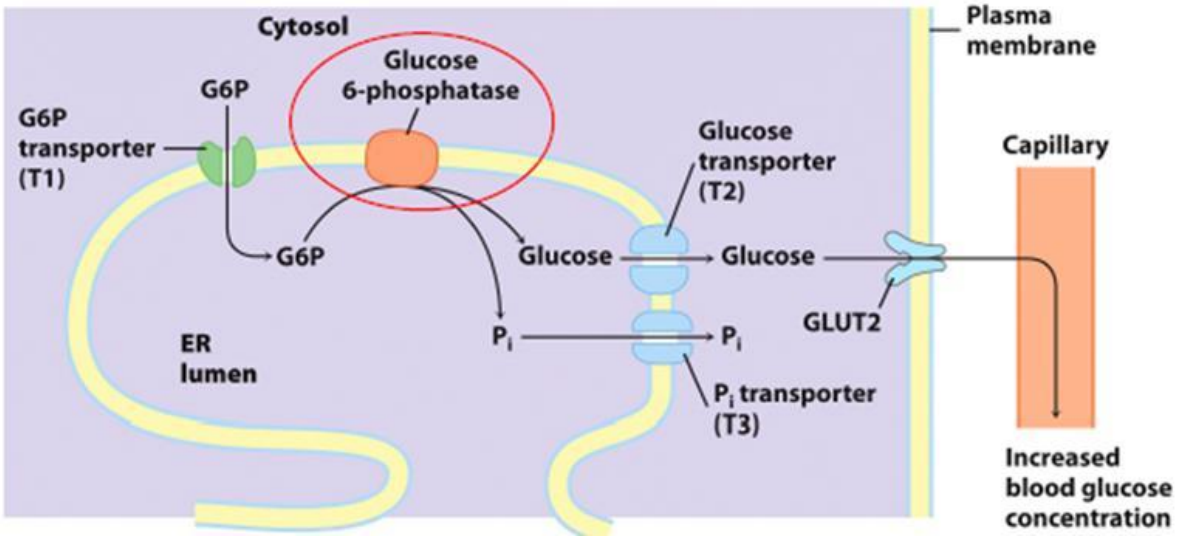
Glycogen

Glycogenolysis

Glucose-6-P

Gluconeogenesis

Aminoacids



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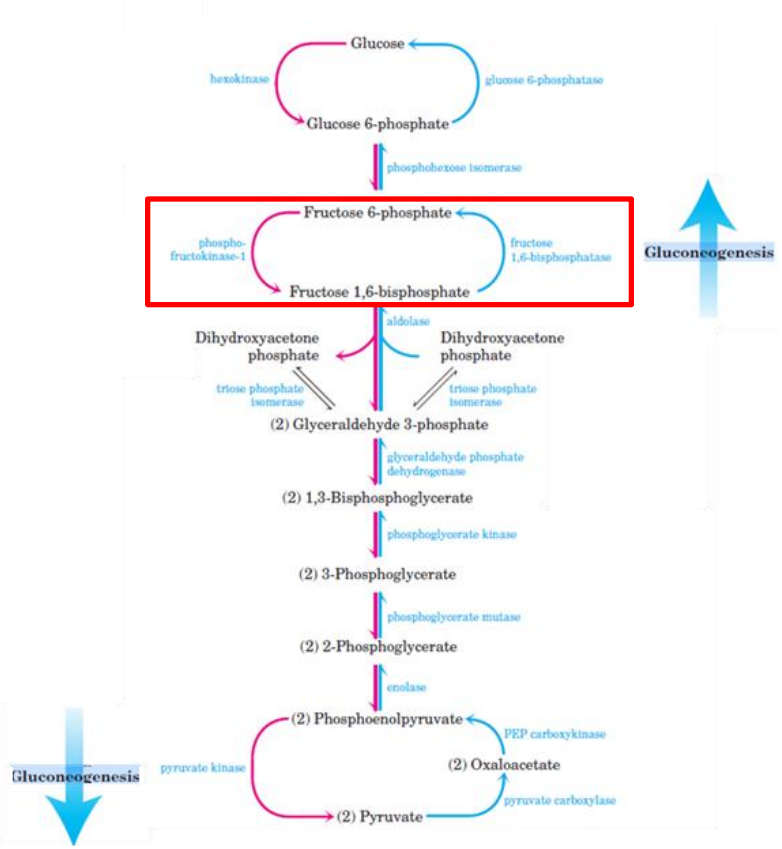
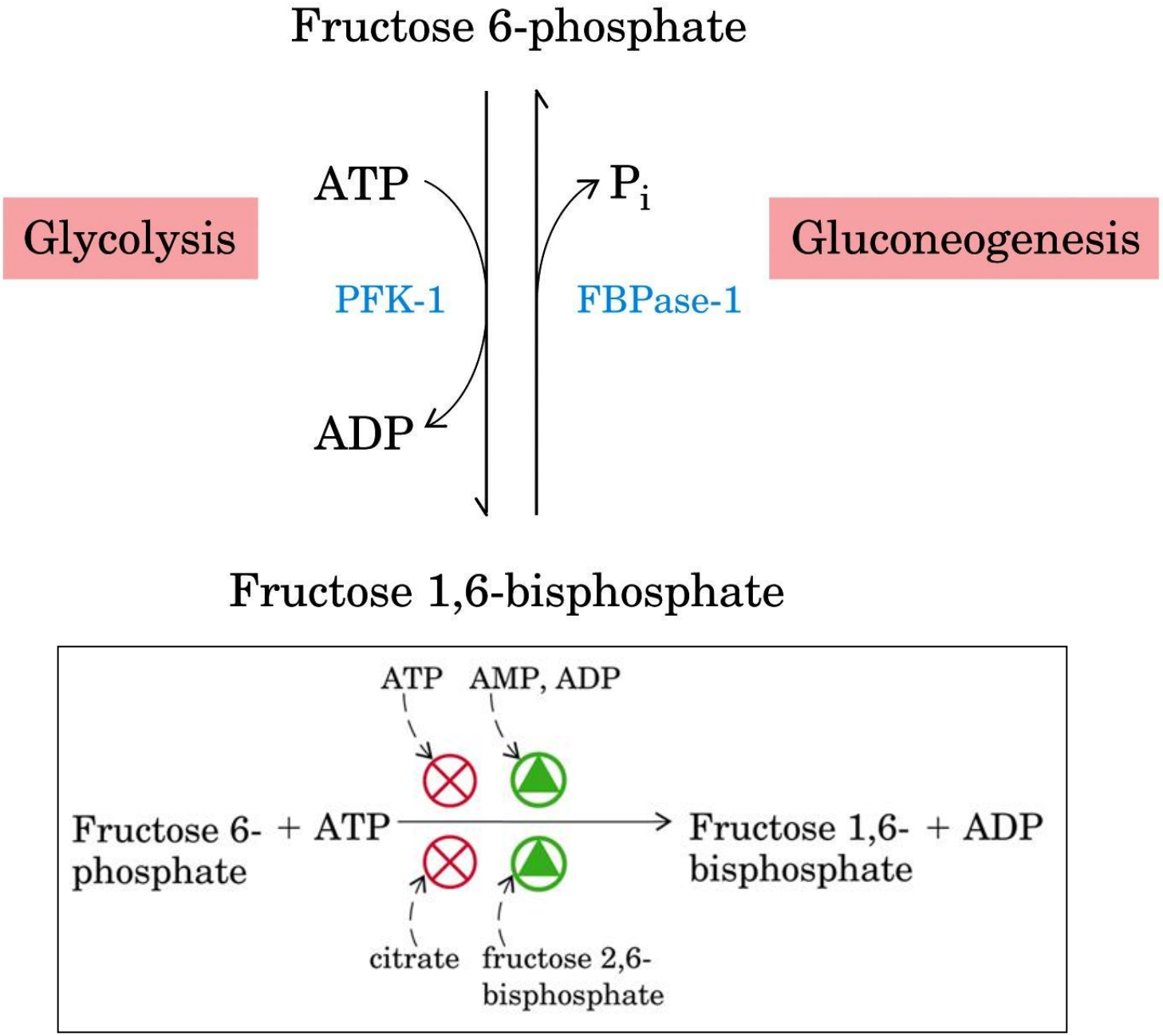
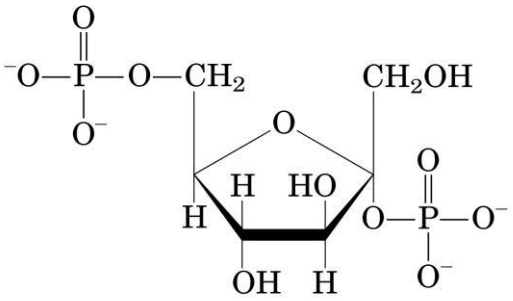
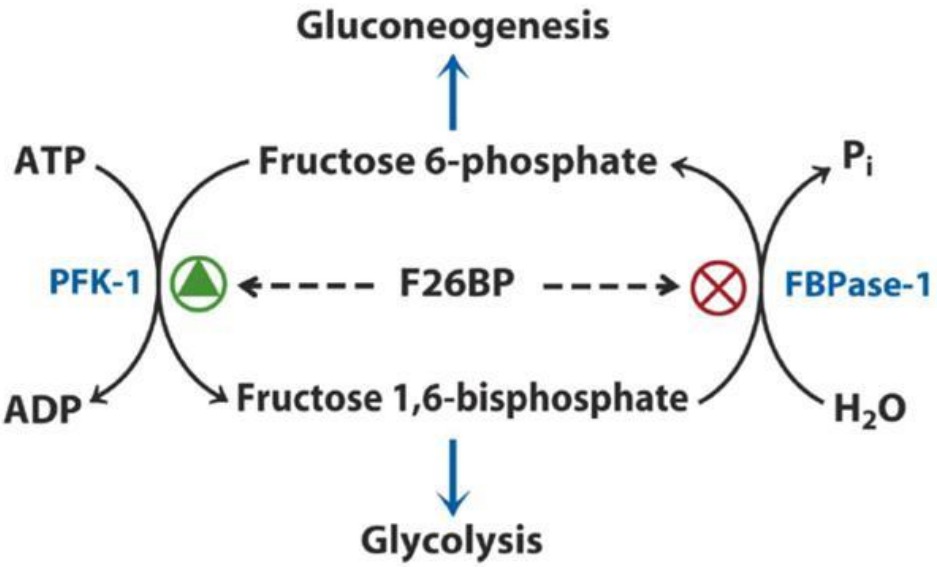


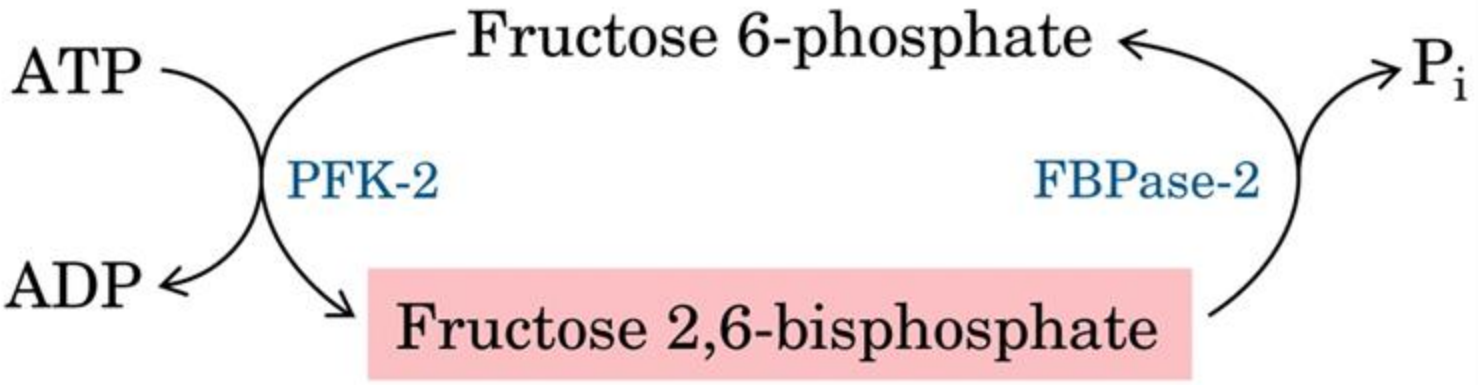






Fructose 2,6-bisphosphate is a potent allosteric:

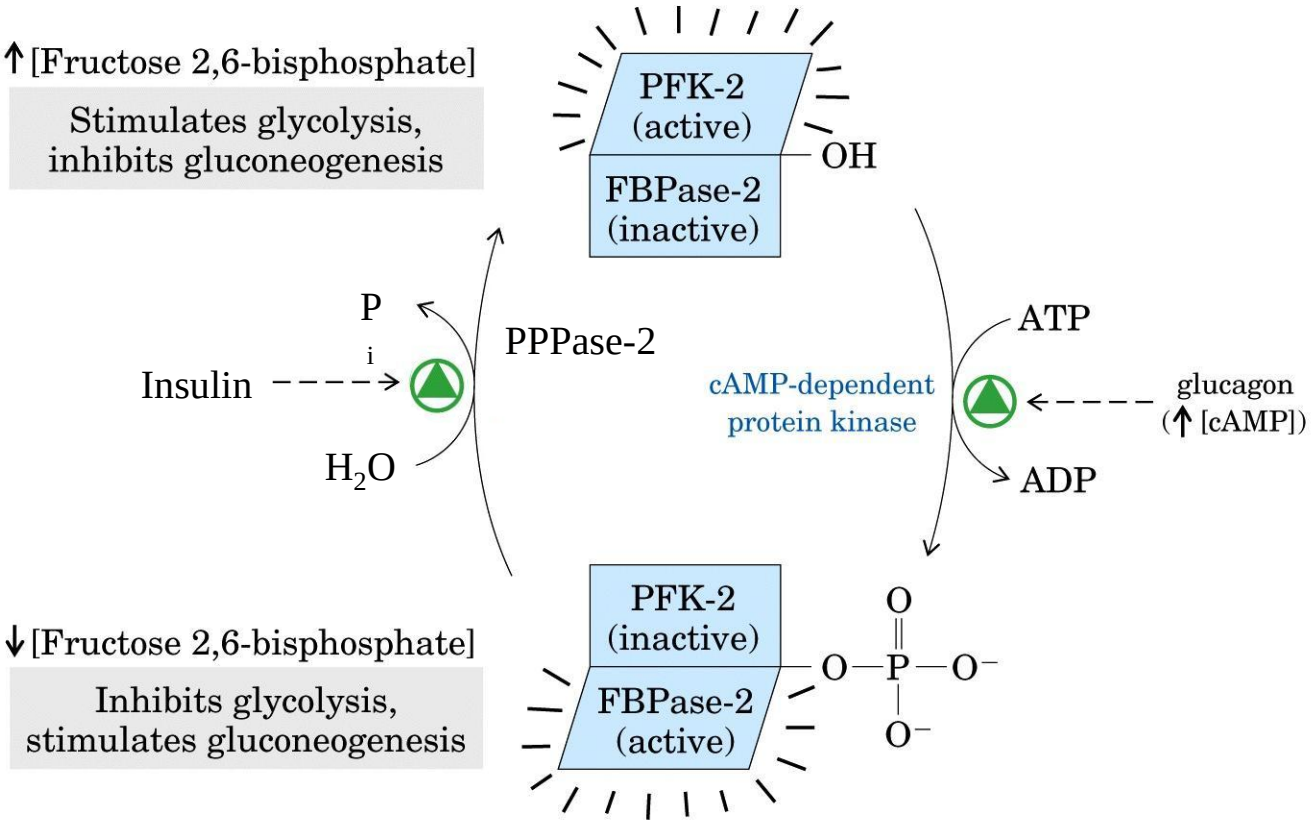
- activator of the key glycolytic enzyme phosphofructokinase-1
- inactivator of the key gluconeogenetic enzyme fructose 1,6-bisphosphatase

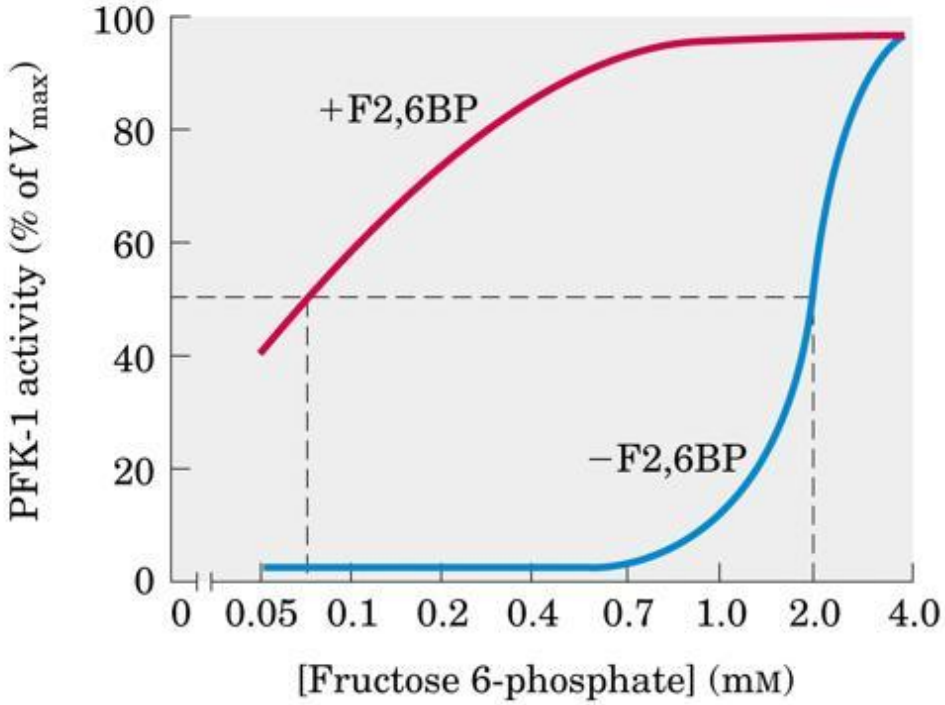


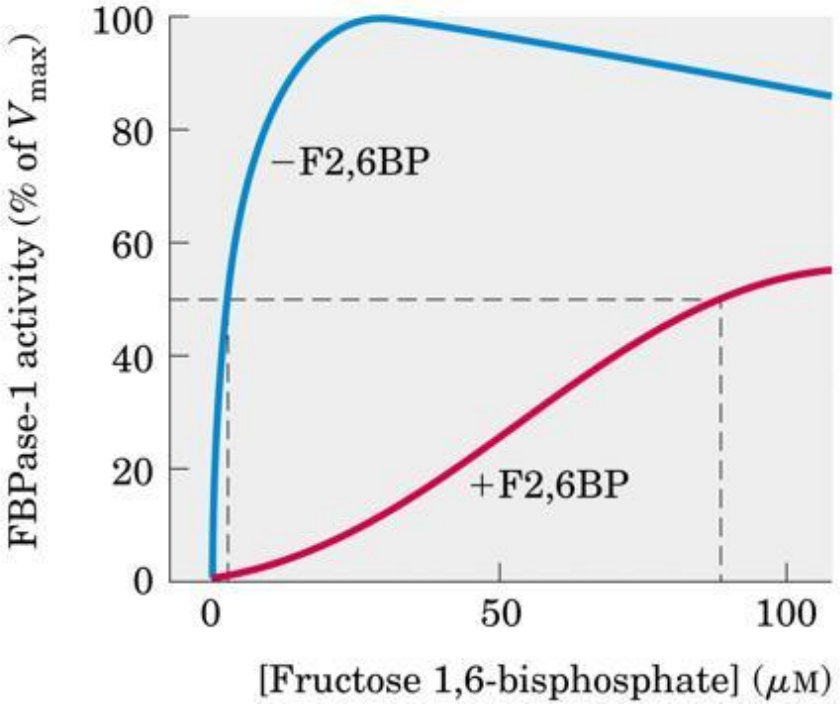
Phosphofructokinase-2 / Fructose 2,6-bisphosphatase (Glycolysis/Gluconeogenesis) are a **bifunctional (tandem) enzyme,** contained in the same protein and regulated by cAMP-Dependent Phosphorylation (by PKA)

Phosphorylation activates FBPase-2 (No F2,6BP)
GLUCAGON

Dephosphorylation activates PFK-2 (High F2,6BP)
INSULIN

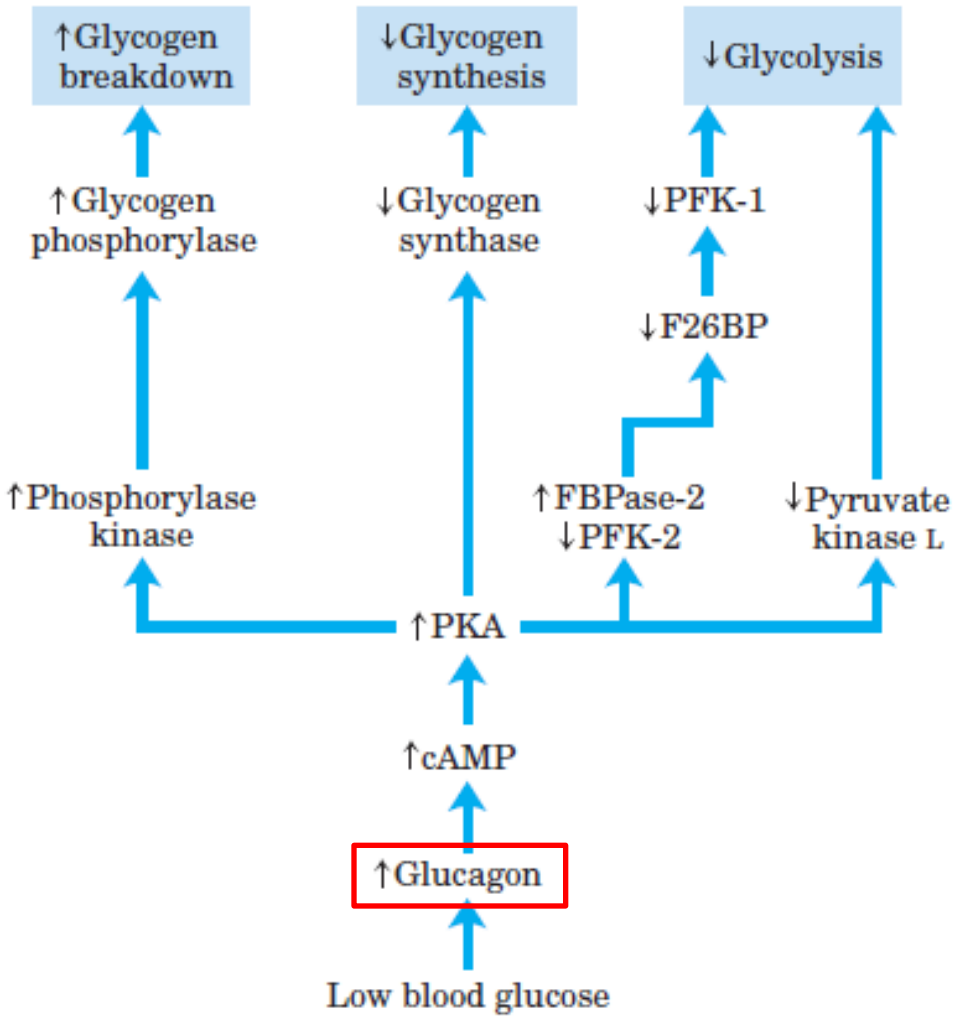



PFK-1 activity (% of V_{max})
100
80
60
40
20
0
+F2,6BP
−F2,6BP
0
0.05
0.1
0.2
0.4
0.7
1.0
2.0
4.0
[Fructose 6-phosphate] (mM)

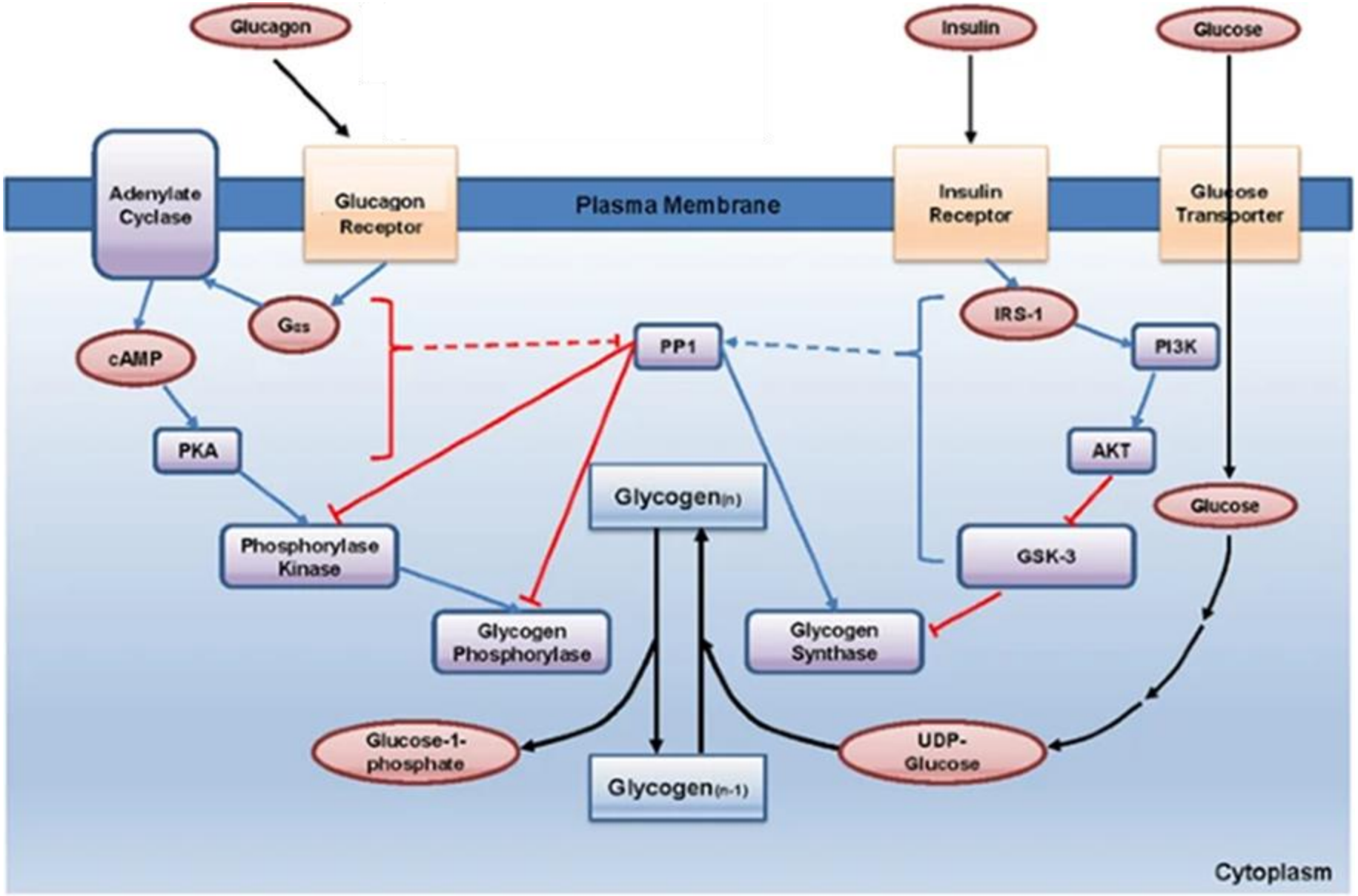

FBPase-1 activity (% of V_{max})
100
80
60
40
20
0
−F2,6BP
+F2,6BP
0
50
100
[Fructose 1,6-bisphosphate] (μM)

Insulin → PPPase 2a → Tandem enzyme dephosphorylated = kinase → Fructose-2,6-bisP → PFK+ → Glycolysis +

Glucagon → cAMP → PKA → Tandem enzyme phosphorylated = phosphatase → no Fructose 2,6 bisP → FBPase + → Gluconeogenesis +



Regulation of glucose metabolism from a liver-centric perspective



https://doi.org/10.1038/emm.2015.122

High blood glucose		Low blood glucose
Signals the pancreas to secrete insulin into the blood		Signals the pancreas to secrete glucagon into the blood
Insulin Stimulates: • Uptake of glucose from the blood into cells • Storage of glycogen in the liver and muscles • Conversion of excess glucose into fat for storage	 Pancreas	**Glucagon** Stimulates: • Breakdown of glycogen from the liver • Release of glucose into the blood
End results Lower blood glucose Insulin secretion inhibited		**End results** Raised blood glucose Glucagon secretion inhibited

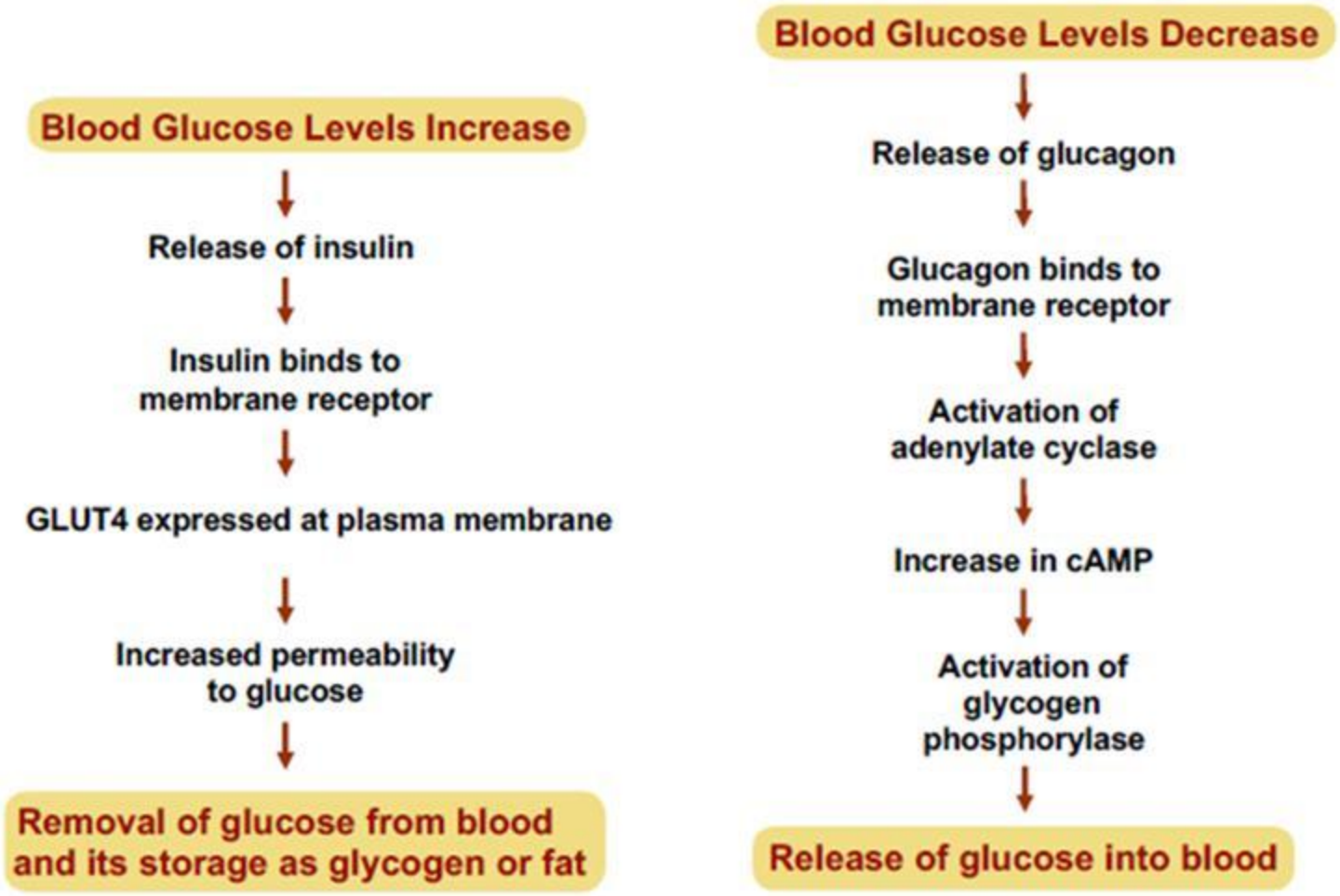
Insulin and glucagon

Glucokinase
Glucose-6-Pase

Glycogen synthase
Glycogen phosphorylase

Phosphofructokinase
Fructose-1,6-BPase

Summary

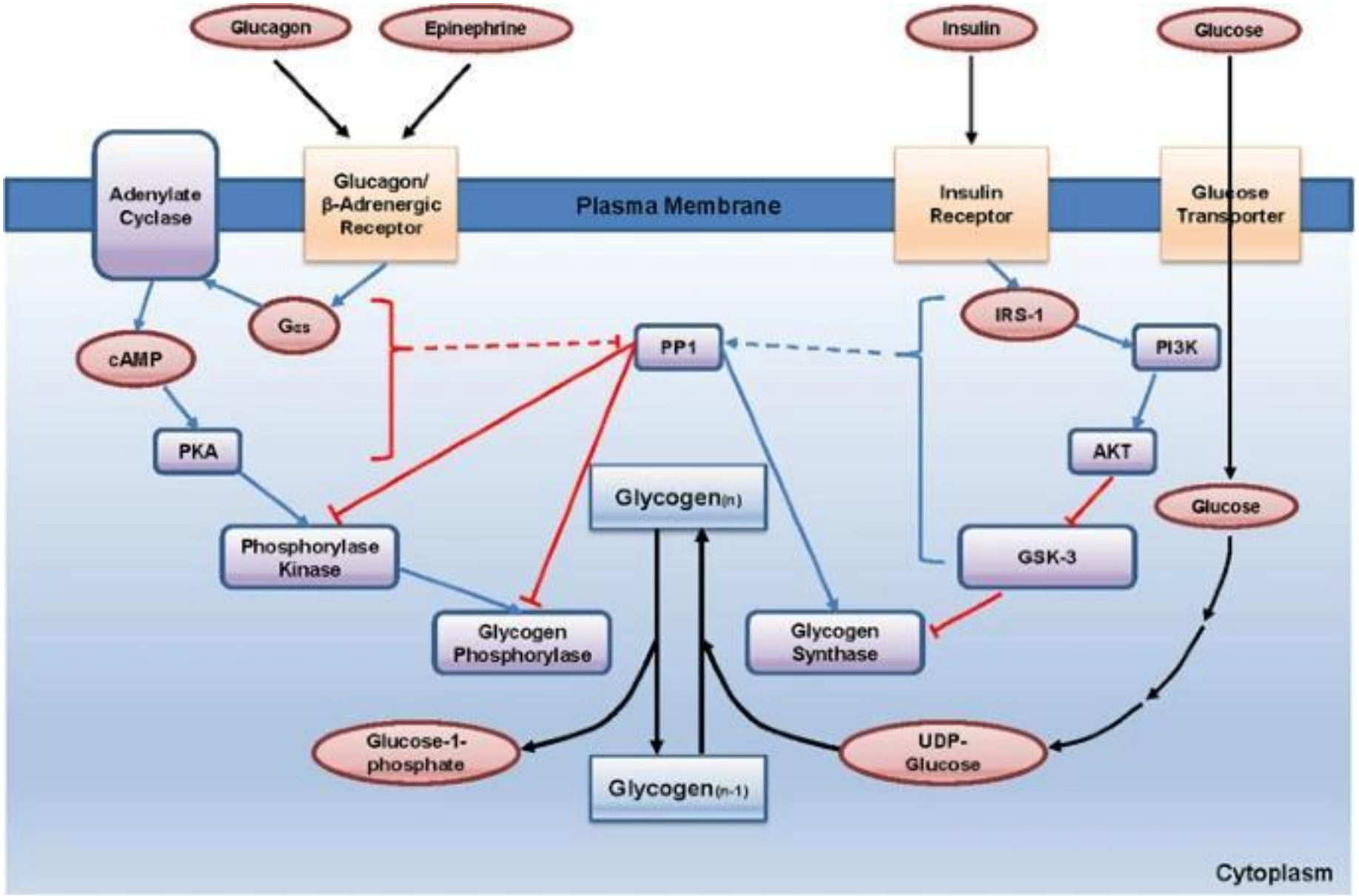

Blood Glucose Levels Increase
Release of insulin
Insulin binds to membrane receptor
GLUT4 expressed at plasma membrane
Increased permeability to glucose
Removal of glucose from blood and its storage as glycogen or fat
Blood Glucose Levels Decrease
Release of glucagon
Glucagon binds to membrane receptor
Activation of adenylate cyclase
Increase in cAMP
Activation of glycogen phosphorylase
Release of glucose into blood

Other Hormones affecting Glycemia

Insulin: Pancreatic β Cells
Tyrosine kinase Receptors

Glucagon: Pancreatic α Cells
G-protein-associated Receptors

Adrenaline: Adrenal Medulla
G-protein-associated Receptors



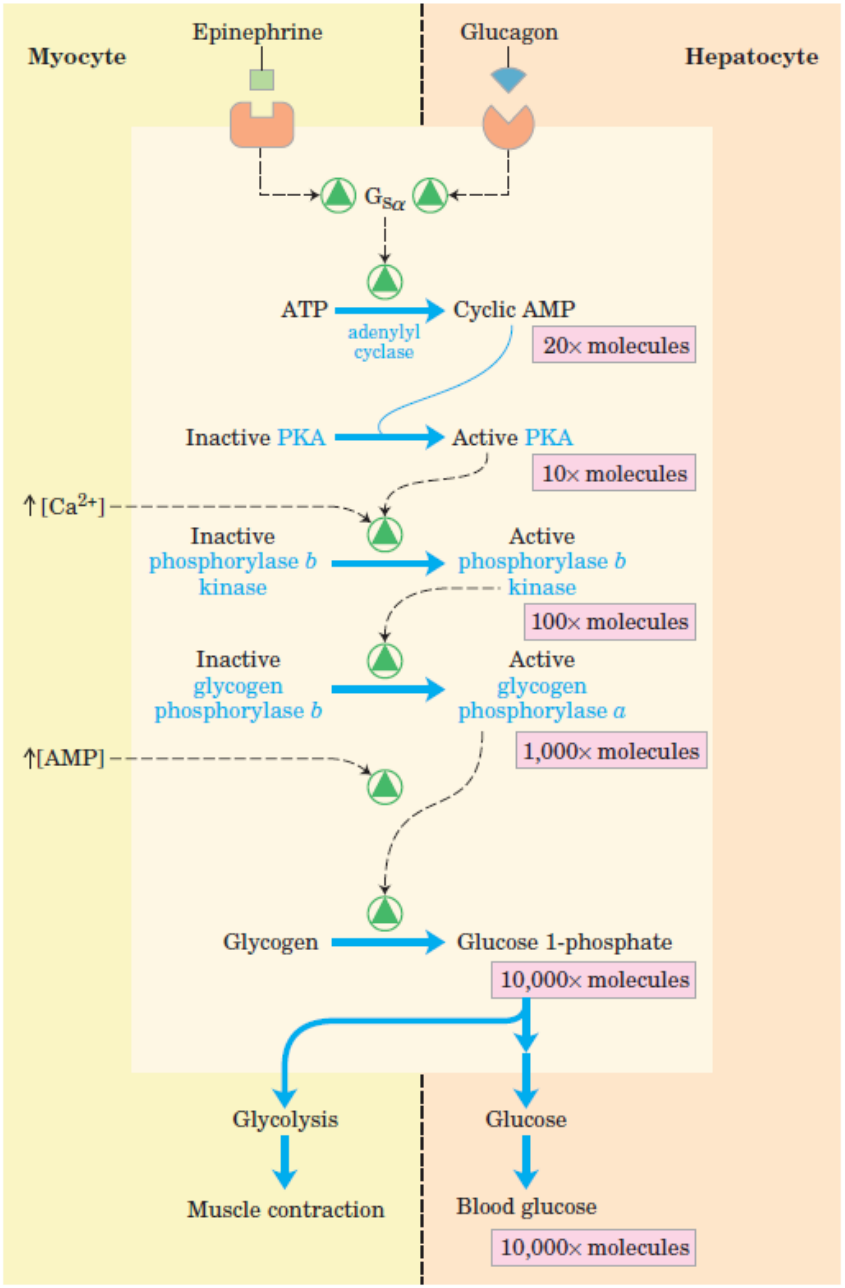
https://doi.org/10.1038/emm.2015.122

REMEMBER!

Skeletal muscle lacks

- glucagon receptors
- glucose-6-phosphatase
- gluconeogenesis

Amplification of hormone-stimulated signal transduction



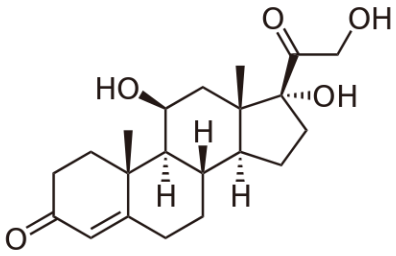
Other Hormones affecting Glycemia

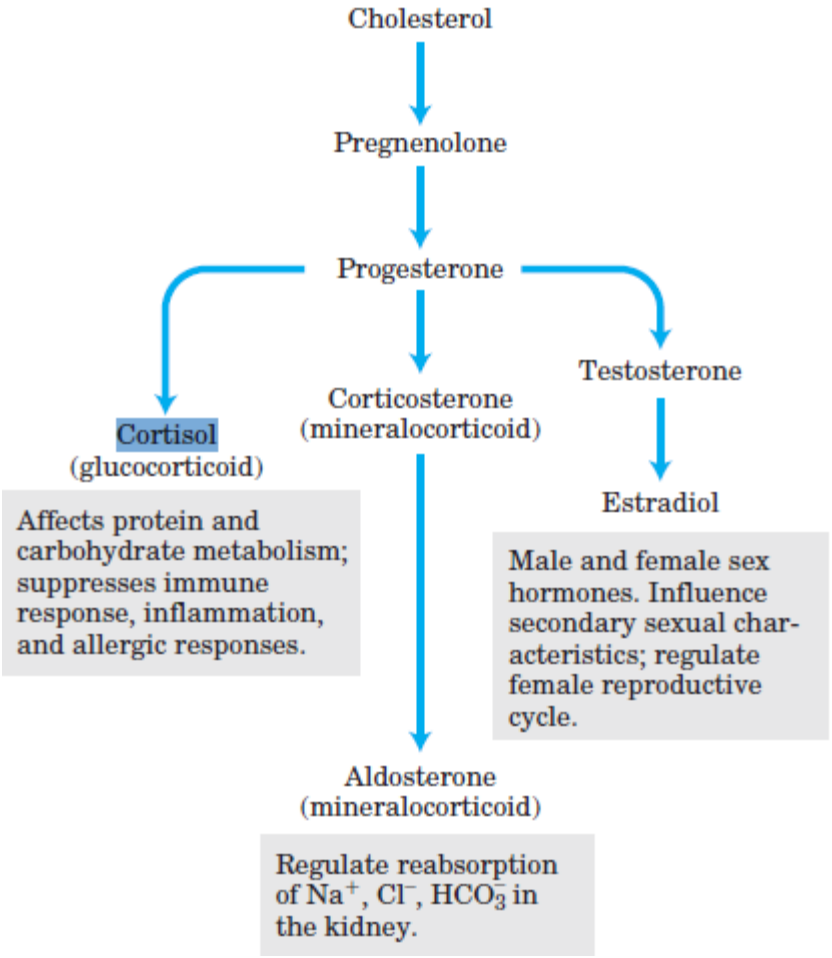
Insulin: Pancreatic β Cells
Tyrosine kinase Receptors

Glucagon: Pancreatic α Cells
G-protein-associated Receptors

Epinephrine: Adrenal Medulla
G-protein-associated Receptors

Cortisol: Zona Fasciculata of Adrenal Cortex
Cytoplasmic Receptors

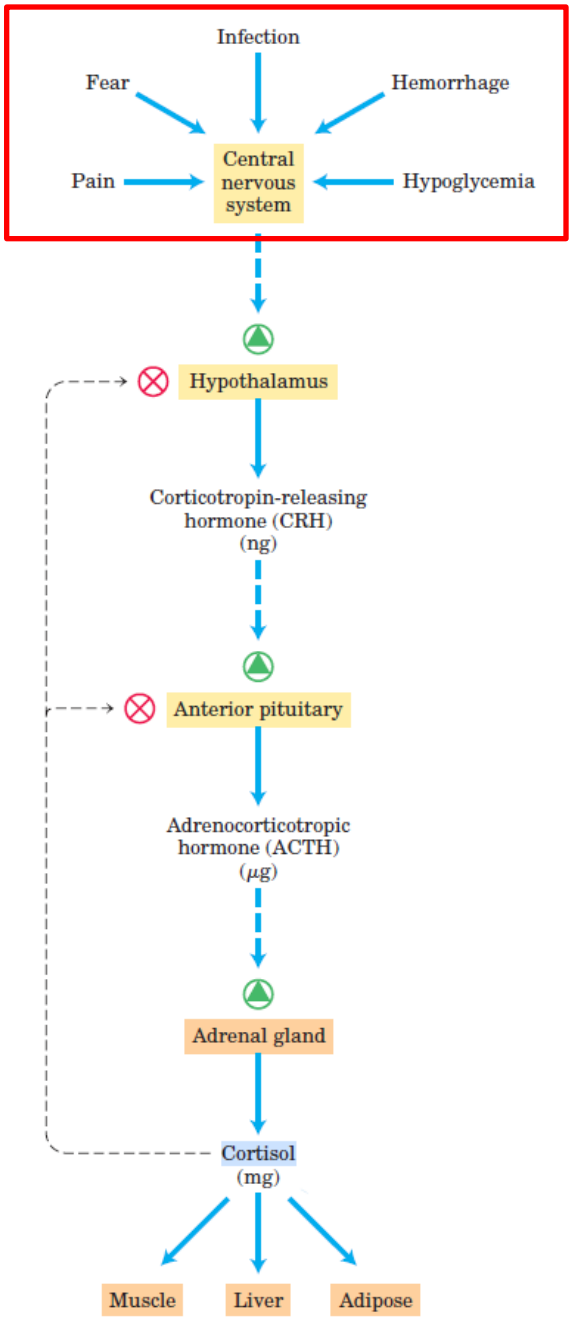




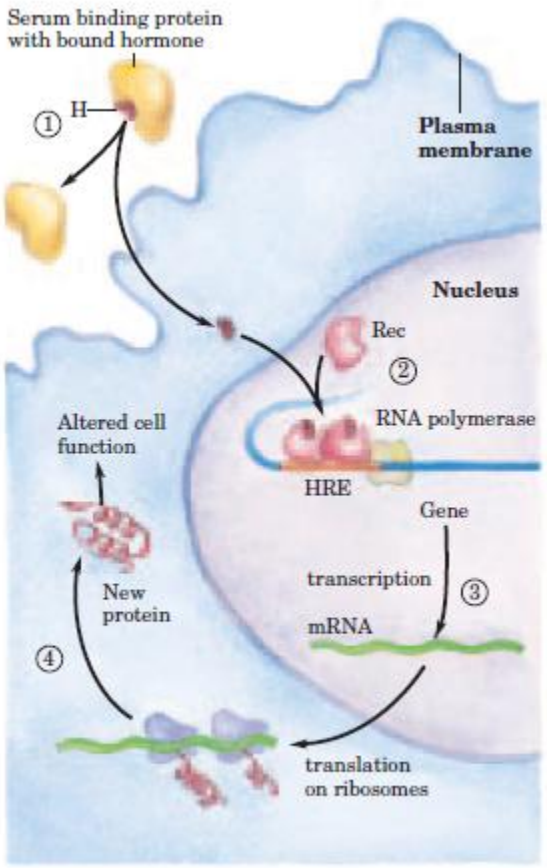
In liver, cortisol increases the rate of gluconeogenesis
Cortisol decreases glucose uptake by muscle

= **hyperglycemia**

Unlike other types of hormones, steroid hormones do not have to bind to plasma membrane receptors. Instead, they can interact with intracellular receptors that are themselves transcriptional transactivators. Steroid hormones (e.g. cortisol), too hydrophobic to dissolve readily in the blood, travel on specific carrier proteins from their point of release to their target tissues. In the target tissue, the hormone passes through the plasma membrane by simple diffusion and binds to its specific receptor protein in the nucleus. The hormone-receptor complex acts by binding to highly specific DNA sequences called hormone response elements (HREs), thereby altering gene expression.



The steroid hormone-receptor complex acts by binding to highly specific DNA sequences called hormone response elements (HREs), thereby altering gene expression.



① Hormone (H), carried to the target tissue on serum binding proteins, diffuses across the plasma membrane and binds to its specific receptor protein (Rec) in the nucleus.

② Hormone binding changes the conformation of Rec; it forms homo- or heterodimers with other hormone-receptor complexes and binds to specific regulatory regions called hormone response elements (HREs) in the DNA adjacent to specific genes.

③ Binding regulates transcription of the adjacent gene(s), increasing or decreasing the rate of mRNA formation.

④ Altered levels of the hormone-regulated gene product produce the cellular response to the hormone.

Physiological effects of low blood glucose in humans

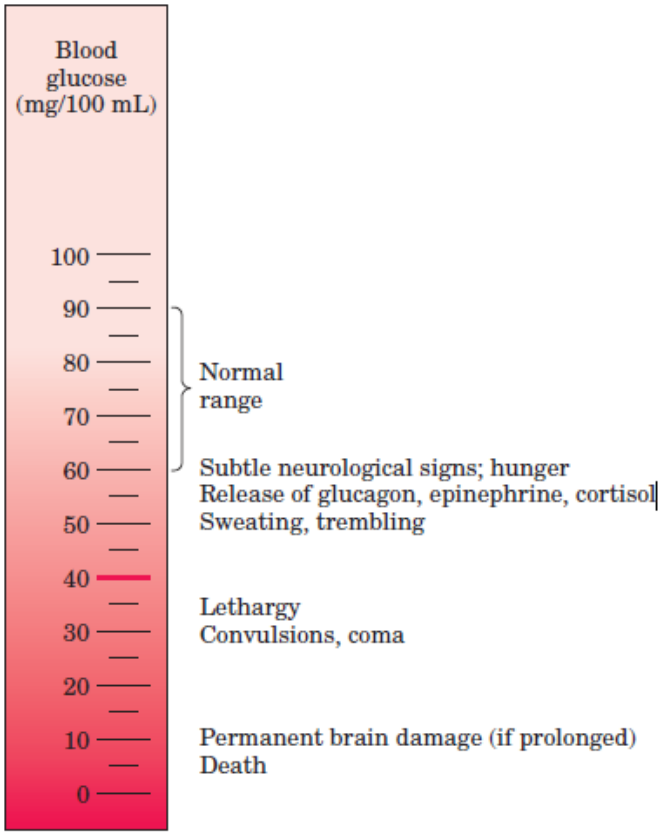
The minute-by-minute adjustments that keep the blood glucose level near 4.5 mM involve the combined actions of insulin, glucagon, epinephrine, and cortisol on metabolic processes in many body tissues, but especially in liver, muscle, and adipose tissue.

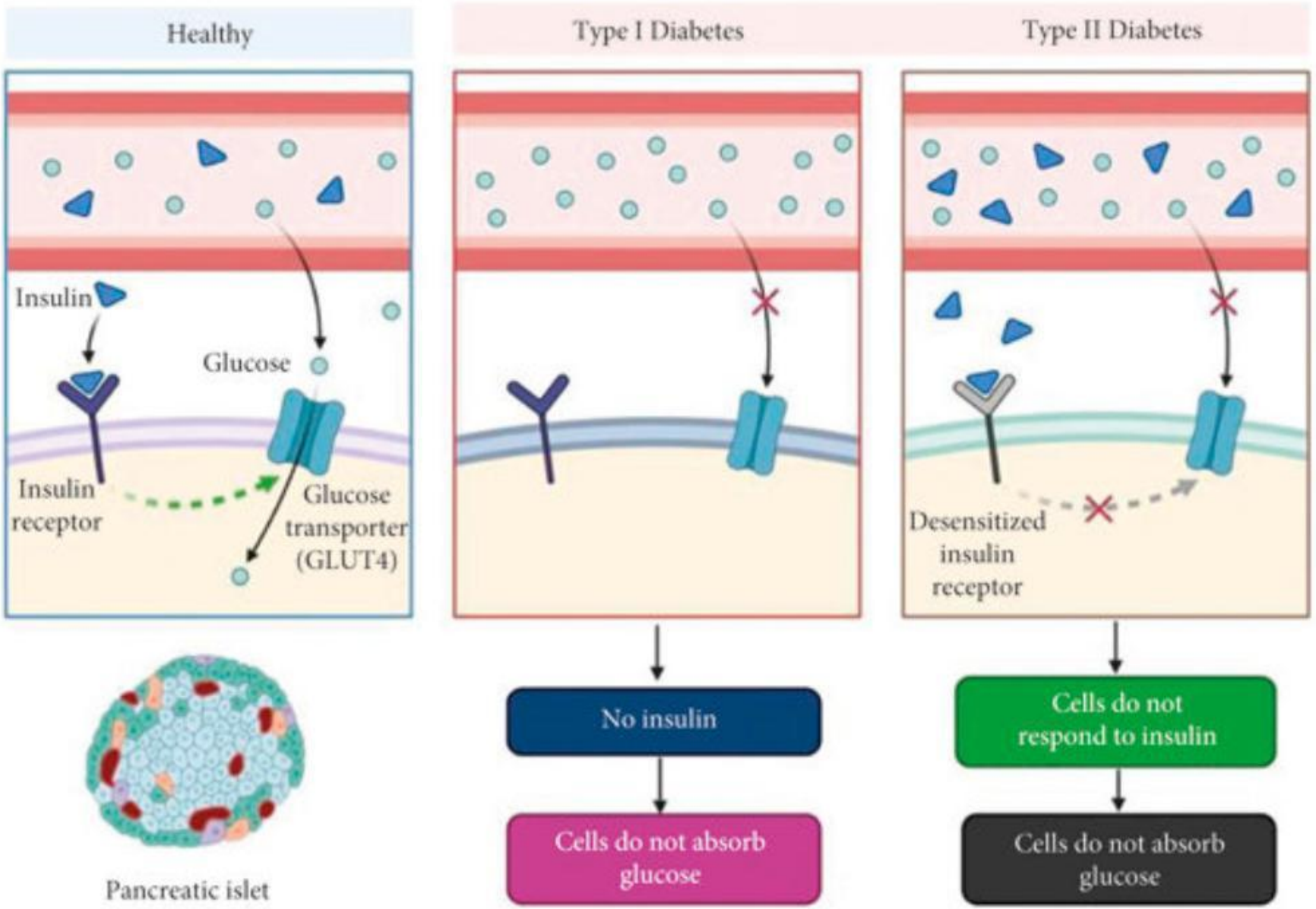
Insulin signals these tissues that blood glucose is higher than necessary; as a result, cells take up excess glucose from the blood and convert it to the storage compounds glycogen and triacylglycerol.

Glucagon signals that blood glucose is too low, and tissues respond by producing glucose through glycogen breakdown and (in liver) gluconeogenesis and by oxidizing fats to reduce the use of glucose.

Epinephrine is released into the blood to prepare the muscles, lungs, and heart for a burst of activity.
Cortisol mediates the body's response to longer-term stresses.
Regulations happens during three normal metabolic states: well-fed, fasted, and starving.

Derangements in the signaling pathways that control glucose metabolism produce diabetes mellitus.



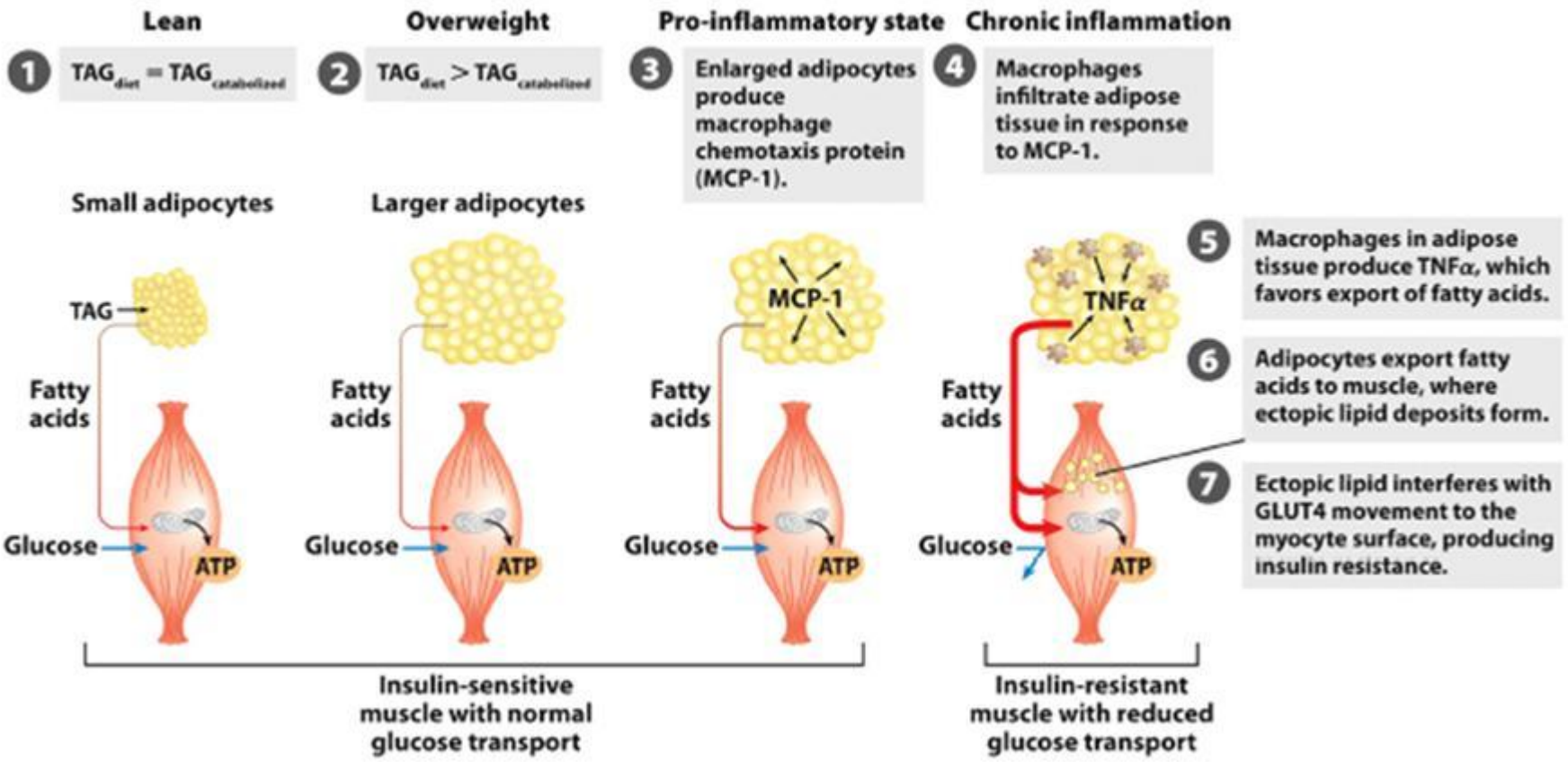


doi:10.1155/2022/5649156

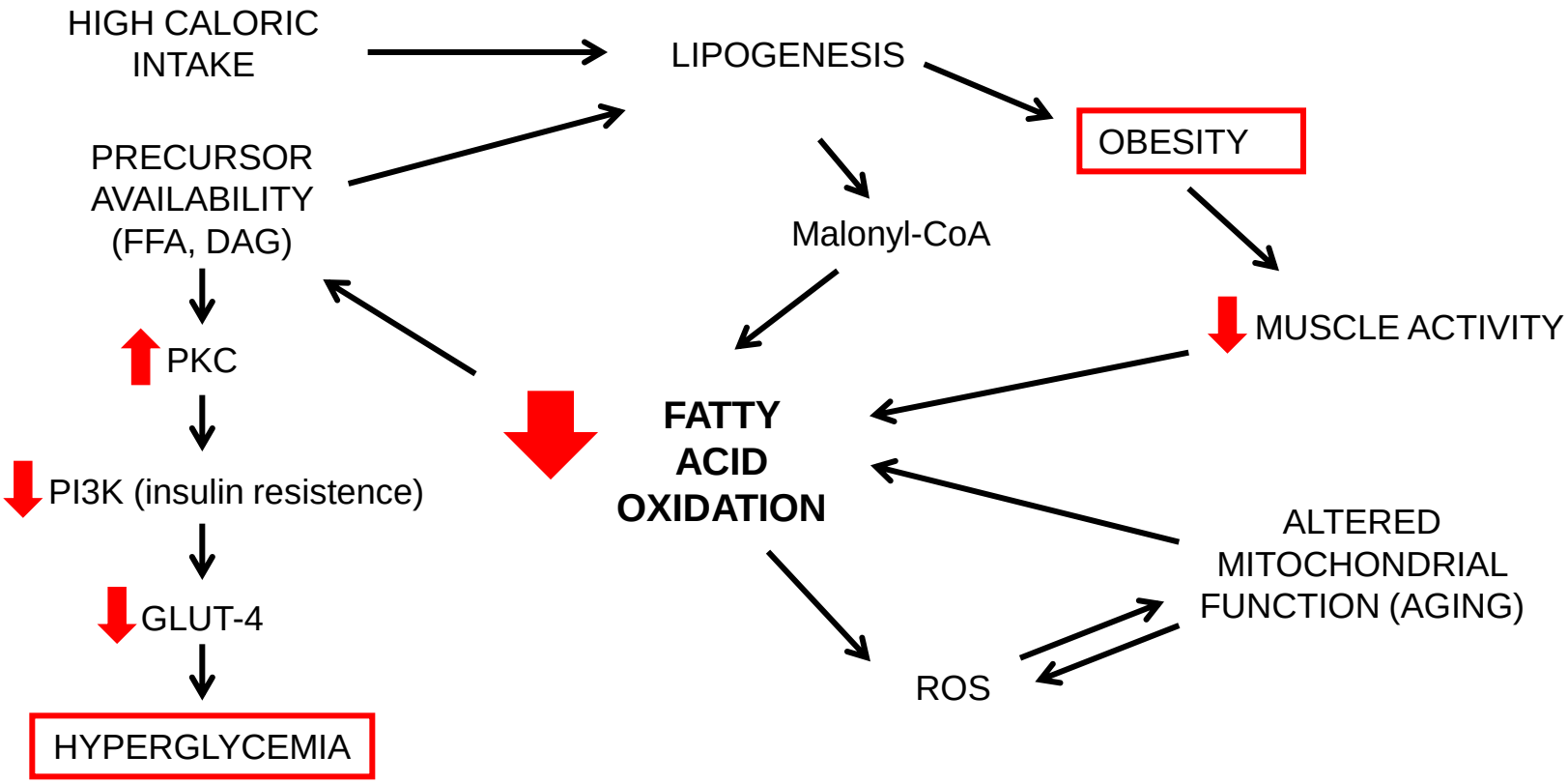
Type II diabetes

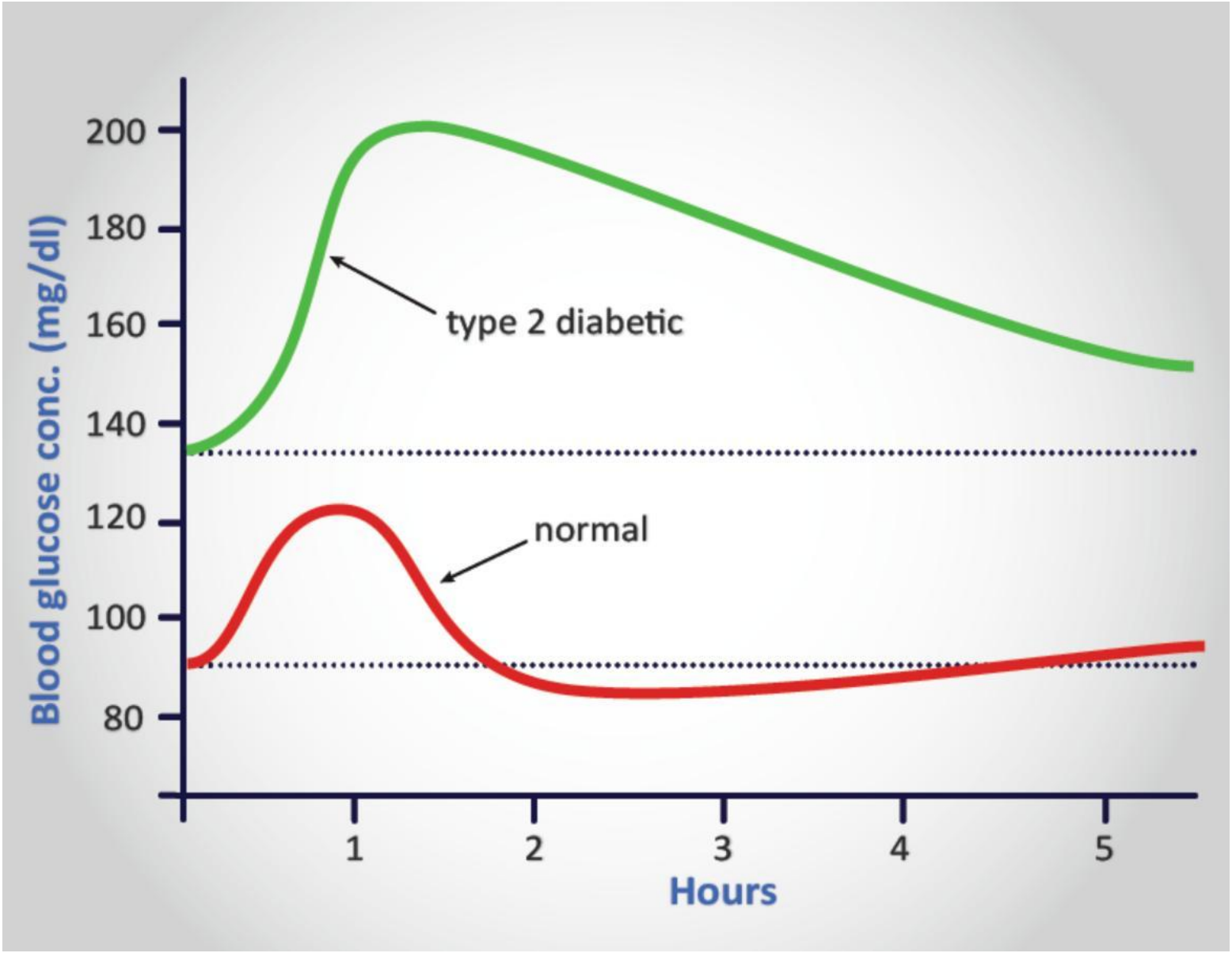
- Usually develops after age 40.
- Often develops in individuals who are overweight or obese.
- The disease often goes undiagnosed for awhile.
- The early stages are reversible.

How excess in fat causes insulin resistance and type II diabetes



Obesity and type II diabetes



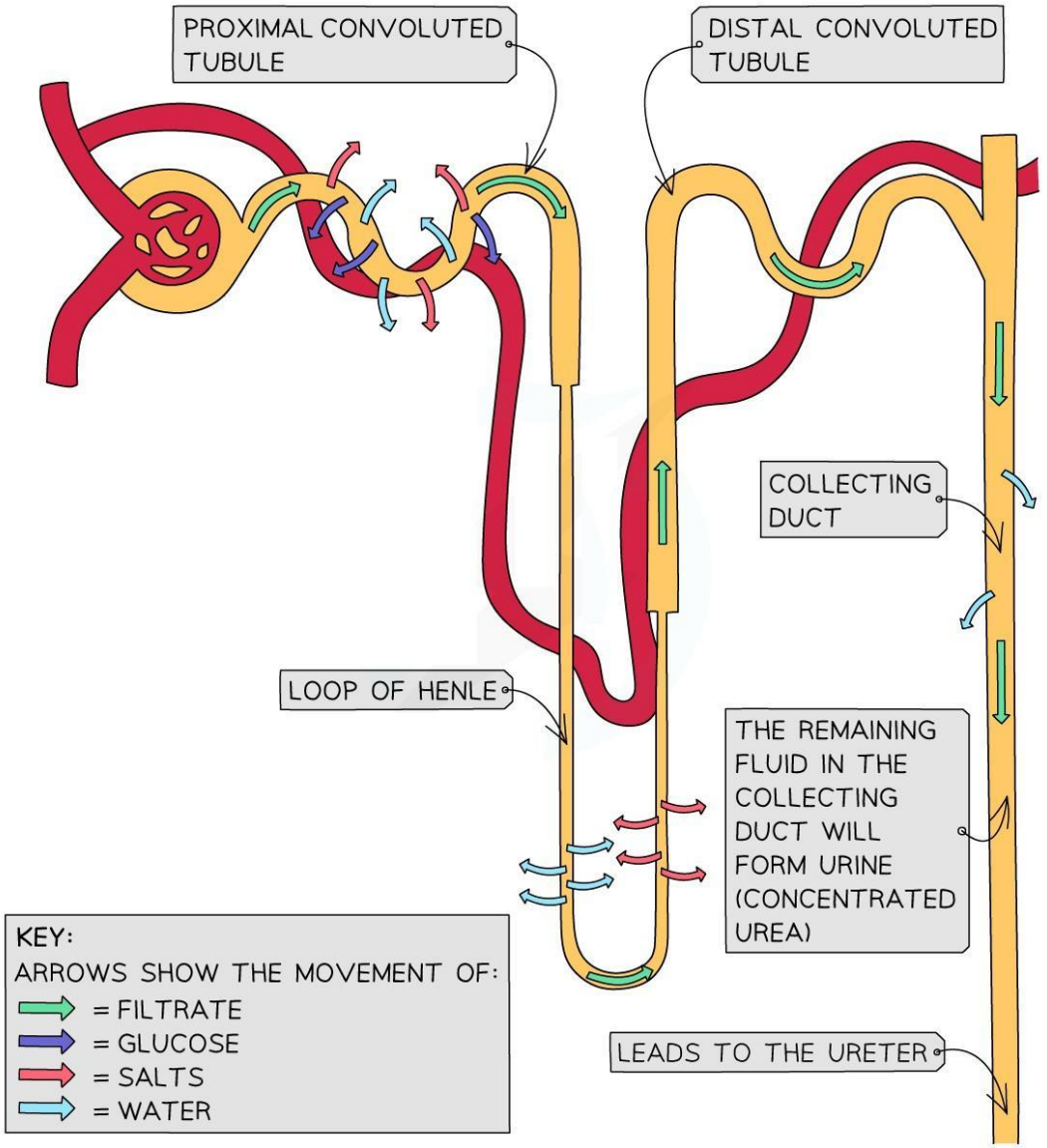


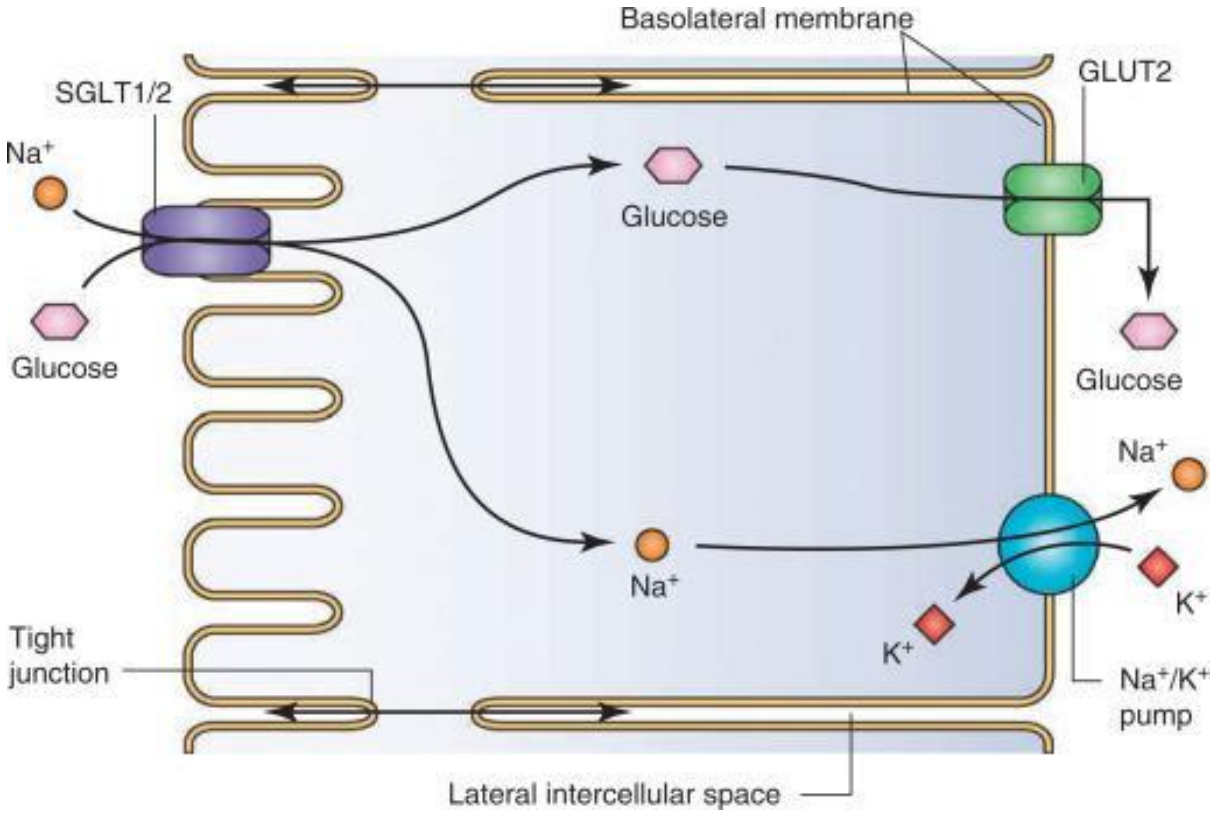
https://themedicalbiochemistrypage.org/diabetes-type-1-and-type-2/

DIABETES COMPLICATIONS

- Peripheral Neuropathy
- Retinopathy (blindness)
- Nephropathy
- Peripheral Vasculopathy (diabetic foot, gangrene)
- Coronaropathy (heart infarction)
- Brain vasculopathy (stroke)
- Sexual disturbances (male impotence)

In physiological conditions glucose is absent in urine



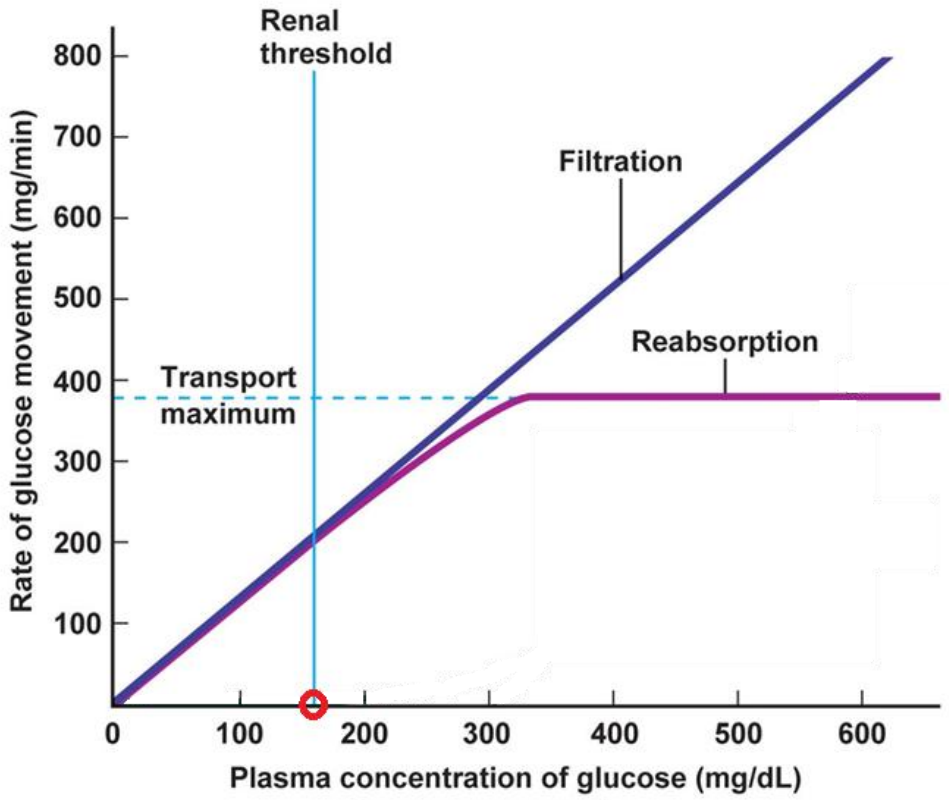


Kidney glucose reabsorption is effected by two sodium-dependent glucose cotransporter (SGLT) proteins. SGLT2, situated in the S1 segment, is a low-affinity high-capacity transporter reabsorbing up to 90% of filtered glucose. SGLT1, situated in the S3 segment, is a high-affinity low-capacity transporter reabsorbing the remaining 10%

doi:10.1038/ki.2010.509

Tubular reabsorption increases linearly with filtered load as a part of glomerulotubular balance.

When reabsorption reaches the tubular capacity (T_m glucose), glucose starts appearing in the urine.



doi:10.1038/ki.2010.509

Glycosuria = glucose presence in urine

In defects of tubular reabsorption of glucose (with normal glycemia)

In diabetes mellitus