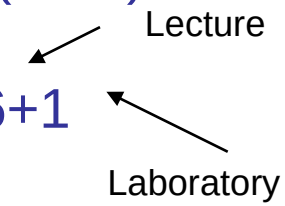
CDL Advances Chemical Studies (ACS)

Metabolic Biochemistry 7 CFU = 6+1



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The control of glycogen synthesis and glycogenolysis are mutually regulated by:

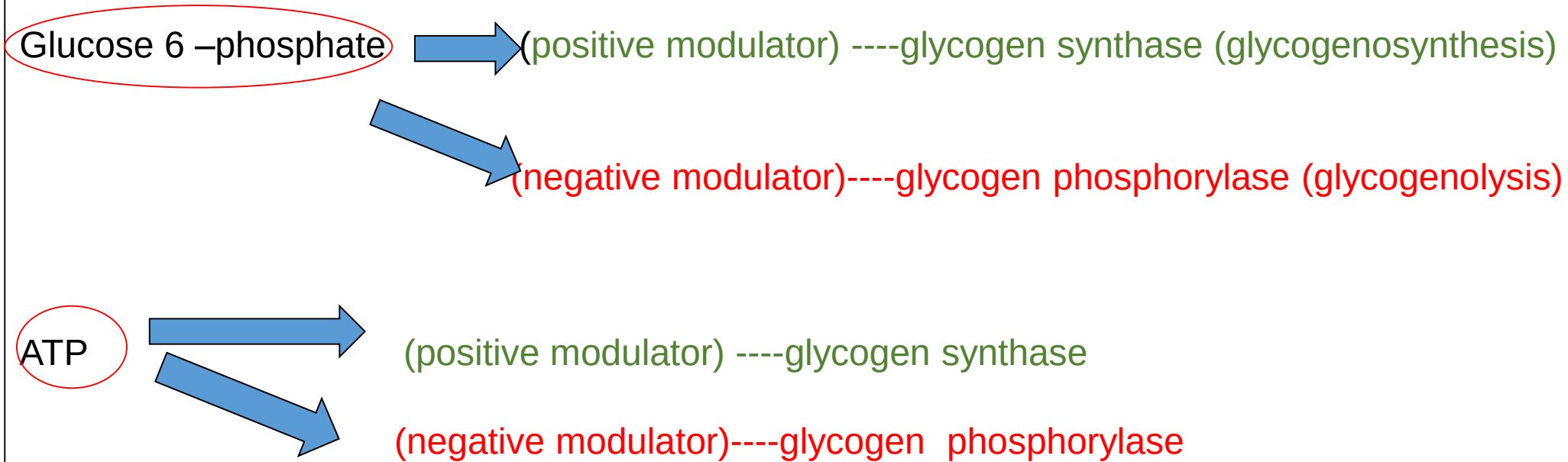
-ALLOSTERIC INTERACTION

-Reversible covalently modification (phosphorilation-dephosphorilation)

-HORMONAL SIGNALS

The control of glycogenosynthesis and glycogenolysis are mutually regulated by:

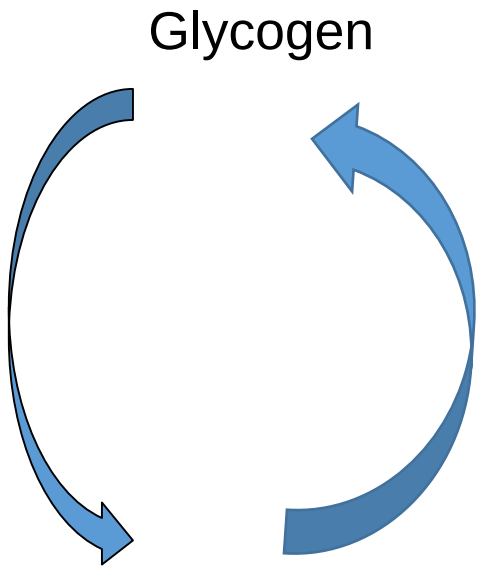
-ALLOSTERIC INTERACTION



ALLOSTERIC INTERACTION

Glucose-6-phosphate is a negative allosteric effector of glycogen phosphorylase
It inhibits its action and consequently glycogenolysis

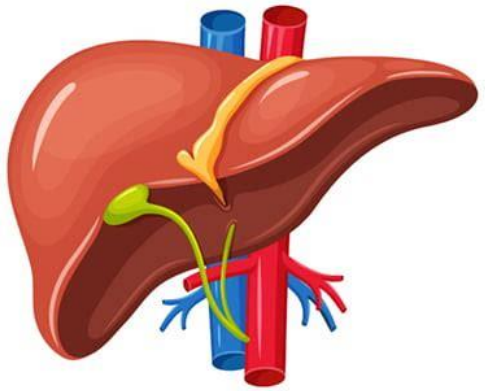
Glucose-6-phosphate is an allosteric effector
Its binding to the allosteric site of glycogen synthase induces an allosteric modification which stabilizes the substrate enzyme binding.



ATP binds at the allosteric site to glycogen phosphorylase.
It causes a conformational change and inhibits its action.

ATP signals the energy state of the cell. ATP binds at the allosteric site to glycogen synthase
It determines a conformational change by stimulating its action.

ALLOSTERIC INTERACTION



LIVER

Glycogen

Glucose 6 –phosphate (+)

Glucose 6 –phosphate (-)

glycogenosynthase

glycogenophosphorylase

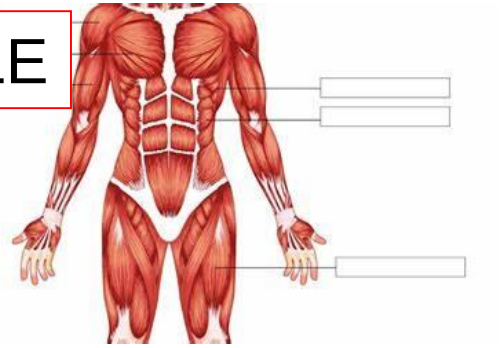
ATP (+)

ATP (-)

Glucose (-)

Glucose 1 –phosphate

MUSCLE



ALLOSTERIC INTERACTION

Glycogen

Glucose 6 –phosphate (+)

Glucose 6 –phosphate (-)

glycogenosynthase

glycogenophosphorylase

ATP (+)

ATP (-)

AMP (+)

Ca^{2+} (+)

Glucose 1 –phosphate

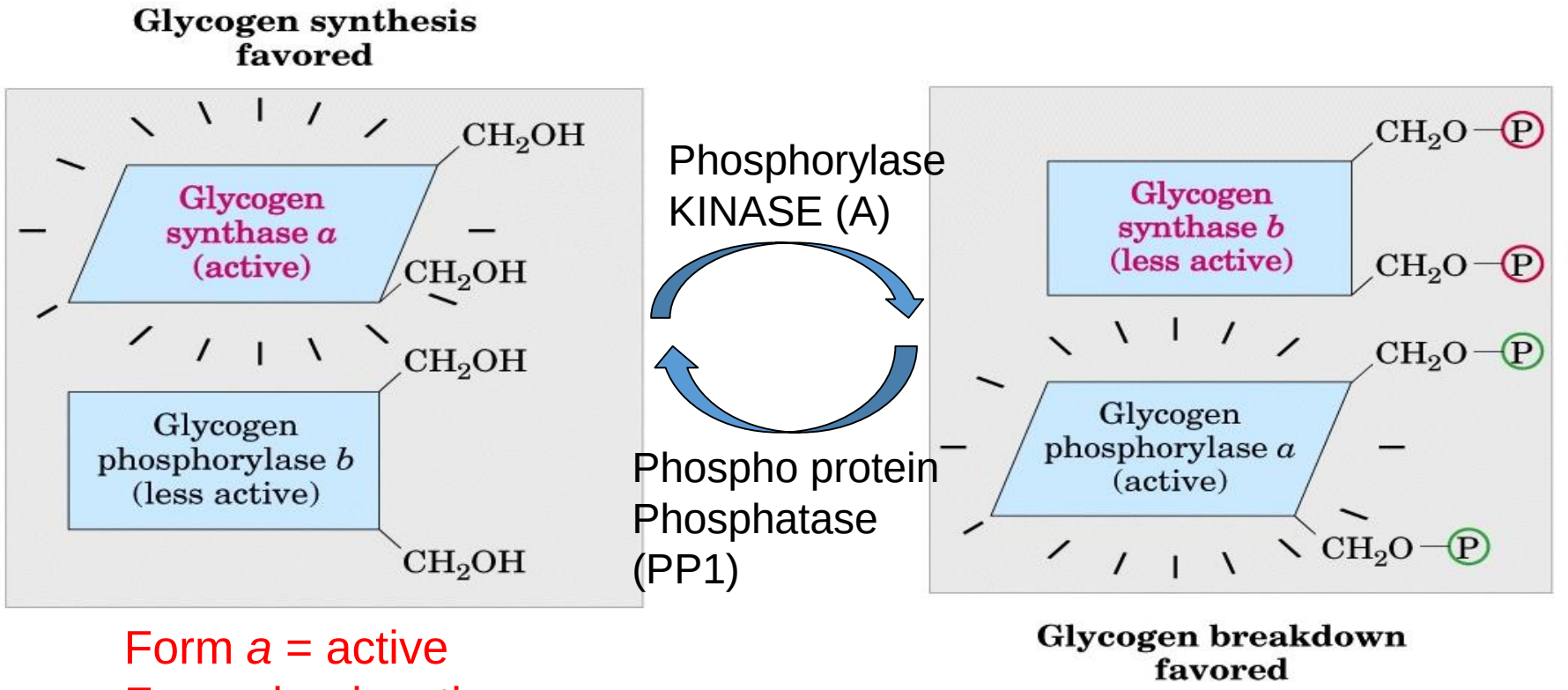
Signals indicating intense muscle activity (Ca^{2+} and AMP) activate phosphorylase to break down glycogen into glucose with glycolysis and obtain ATP

Condition FIGHT or flight

-Reversible covalently modification (phosphorilation-dephosphorylation)

Glycogen synthase and glycogen phosphorylase are two enzymes that can exist in two forms (a) active and (b) inactive

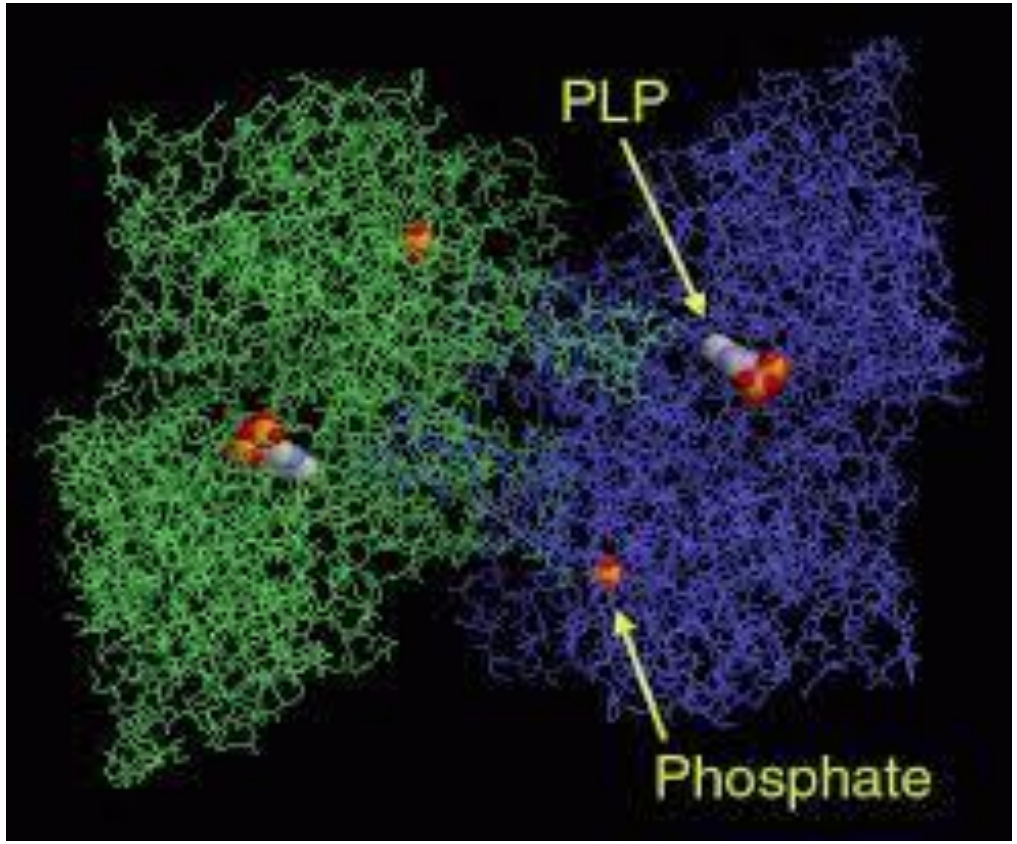
Glycogen synthase is in the active (a) form when it is dephosphorylated, while glycogen phosphorylase is active (a) when it is phosphorylated



Form *a* = active

Forma b = inactive

Glycogen phosphorylase



DIMER

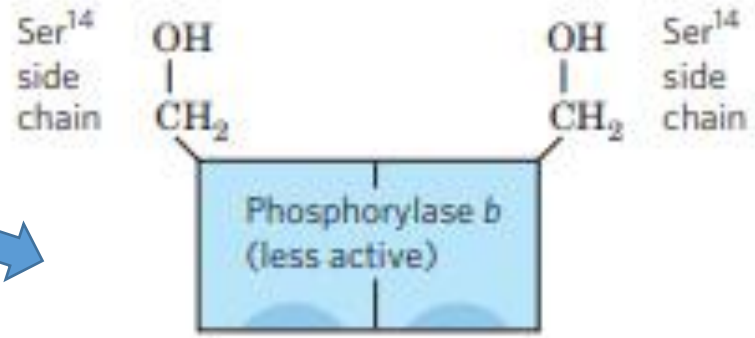
Glycogen → Glucose-1P

Glycogen phosphorylase (called phosphorylase so honored because it was the first phosphorylase to be discovered)

Glycogen → Glucose 1 –phosphate

Two interconvertible forms:

-Glycogen phosphorylase a, (active)
- Glycogen phosphorylase b, (less active)

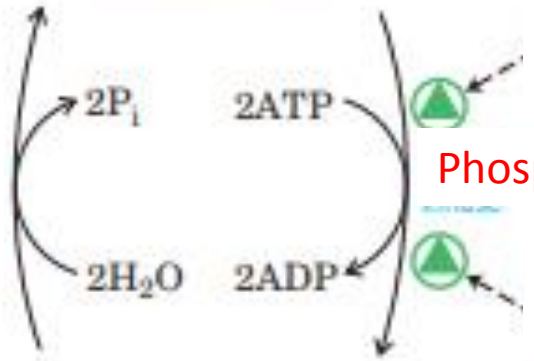


During vigorous muscular activity epinephrine

Actives Phosphorylase b kinase

phosphorylase b,-------→, phosphorylase a.

Phosphorylase a phosphatase (PP1)



Glucagon (liver)

Phosphorylase b kinase

Epinephrine (+)

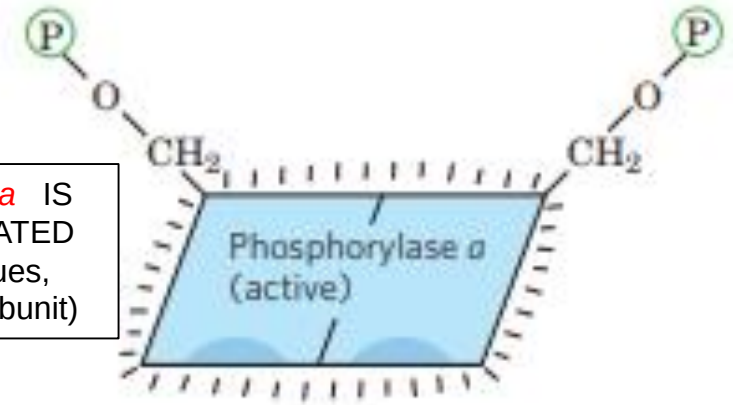
Ca^{2+} (+)

AMP (+)

muscle

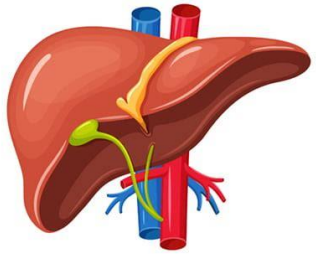
When the muscle returns to rest,

Phosphoprotein phosphatase 1 (PP1)
phosphorylase a, ------→phosphorylase b



Phosphorylase *a* IS PHOSPHORYLATED ON Ser14 residues, (one on each subunit)

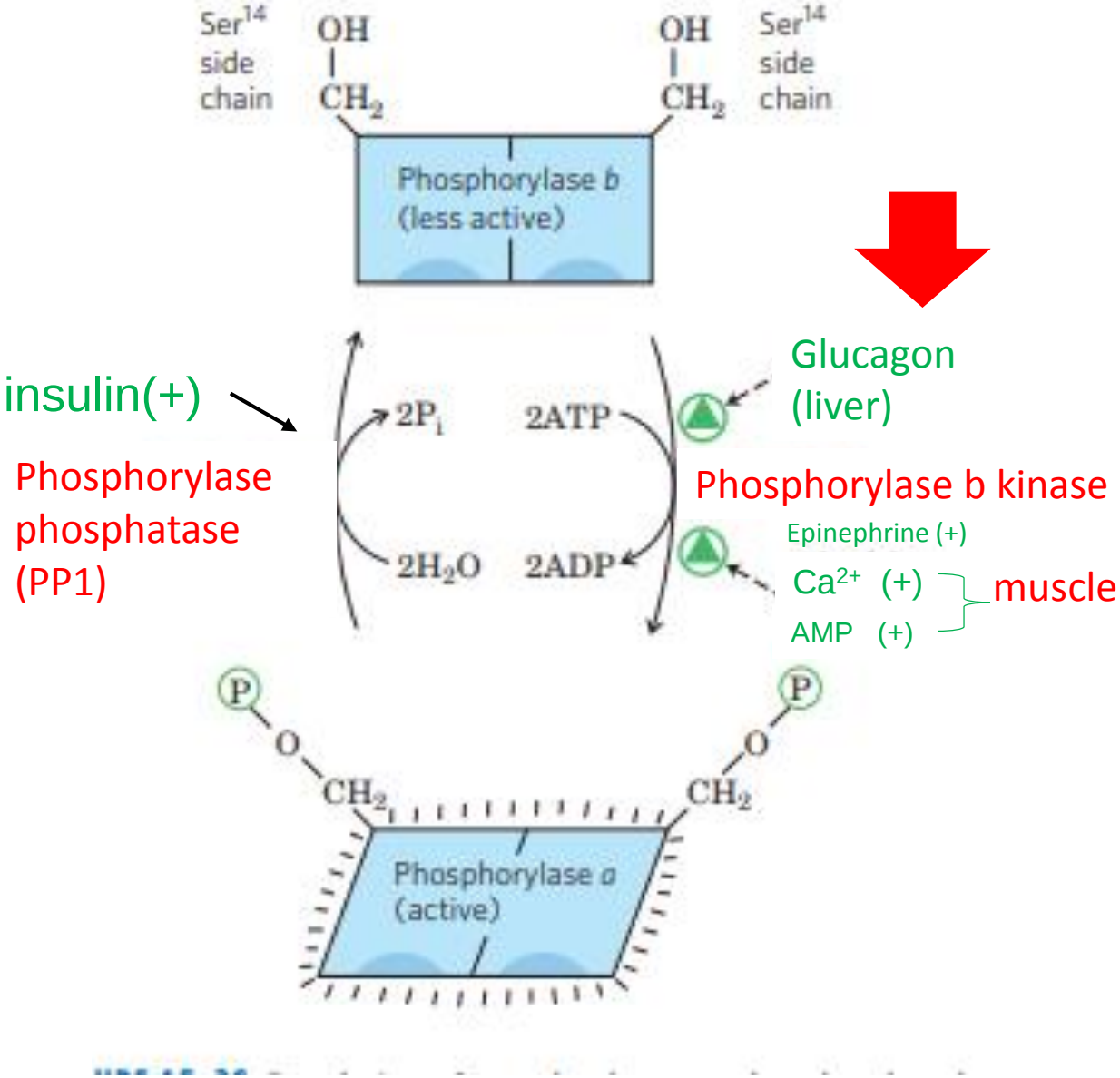
Liver



Glycogen → Glucose 1 –phosphate

Phosphorylase b kinase is responsible for activating phosphorylase b
Activated by glucagon .

Phosphorylase phosphatase (PP1) is responsible for inactivating phosphorylase b
Activated by insulin .



Phosphorylase b kinase

is activated by epinephrine or glucagon through a series of steps.

Epinephrine

Glucagon

Both Activate a GTP-binding protein, G_s

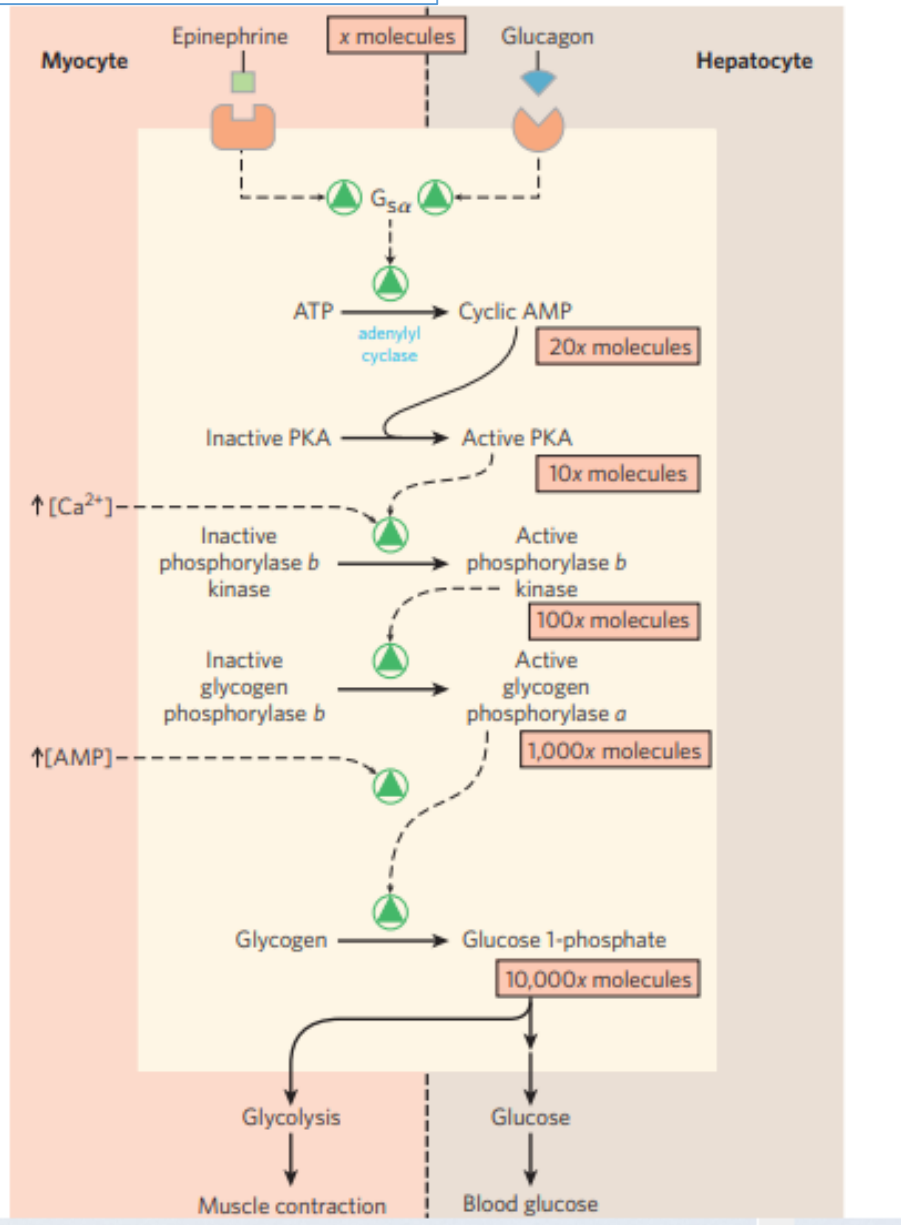
Active G_s triggers a rise in [cAMP], activating PKA.

PKA activates phosphorylase *b* kinase, which then activates glycogen phosphorylase.

cAMP,the second messenger which increases in concentration in response to stimulation by epinephrine (in muscle) or glucagon (in liver).

Epinephrine by binding to specific surface receptors either acting on a myocyte.

Glucagon acting on a hepatocyte

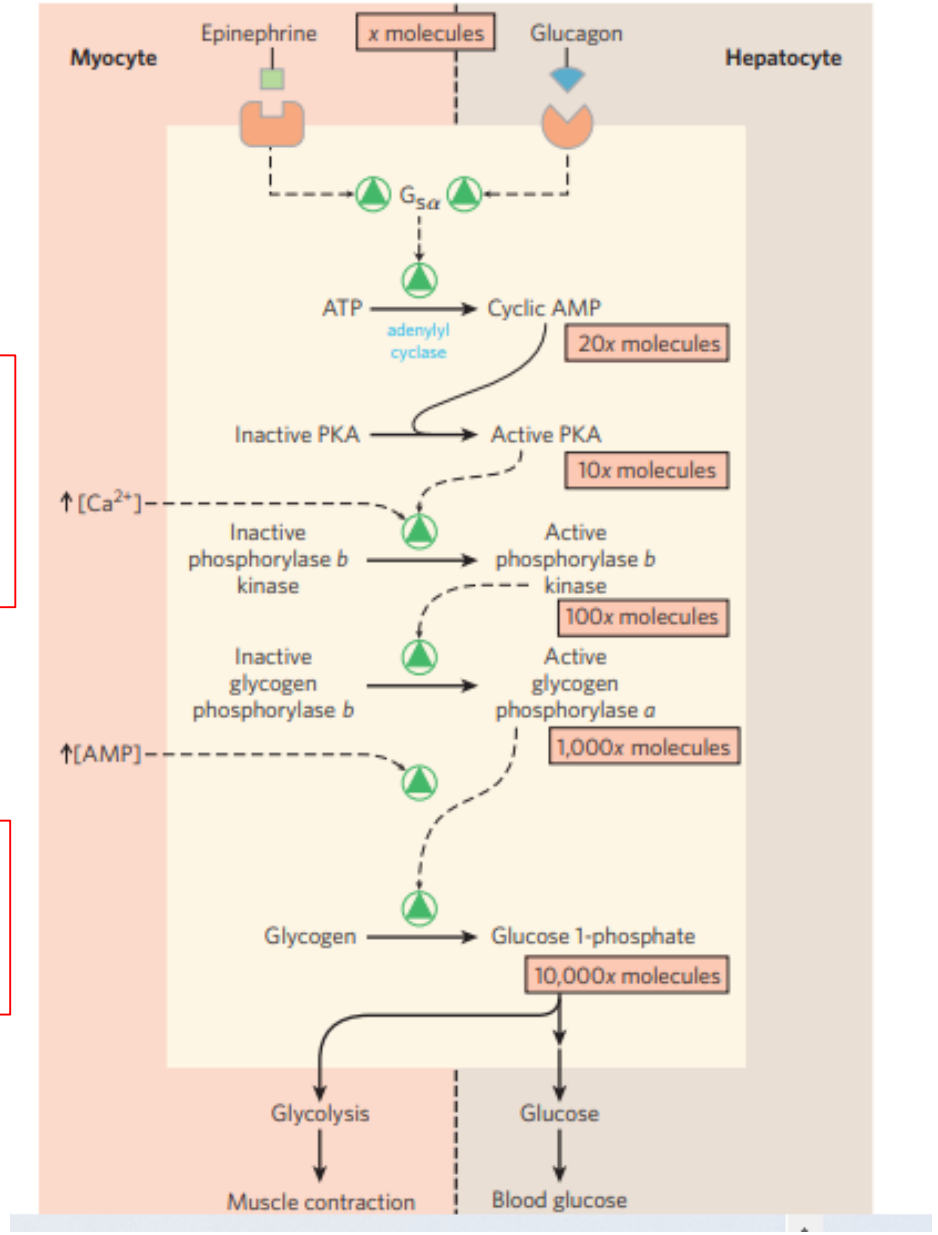


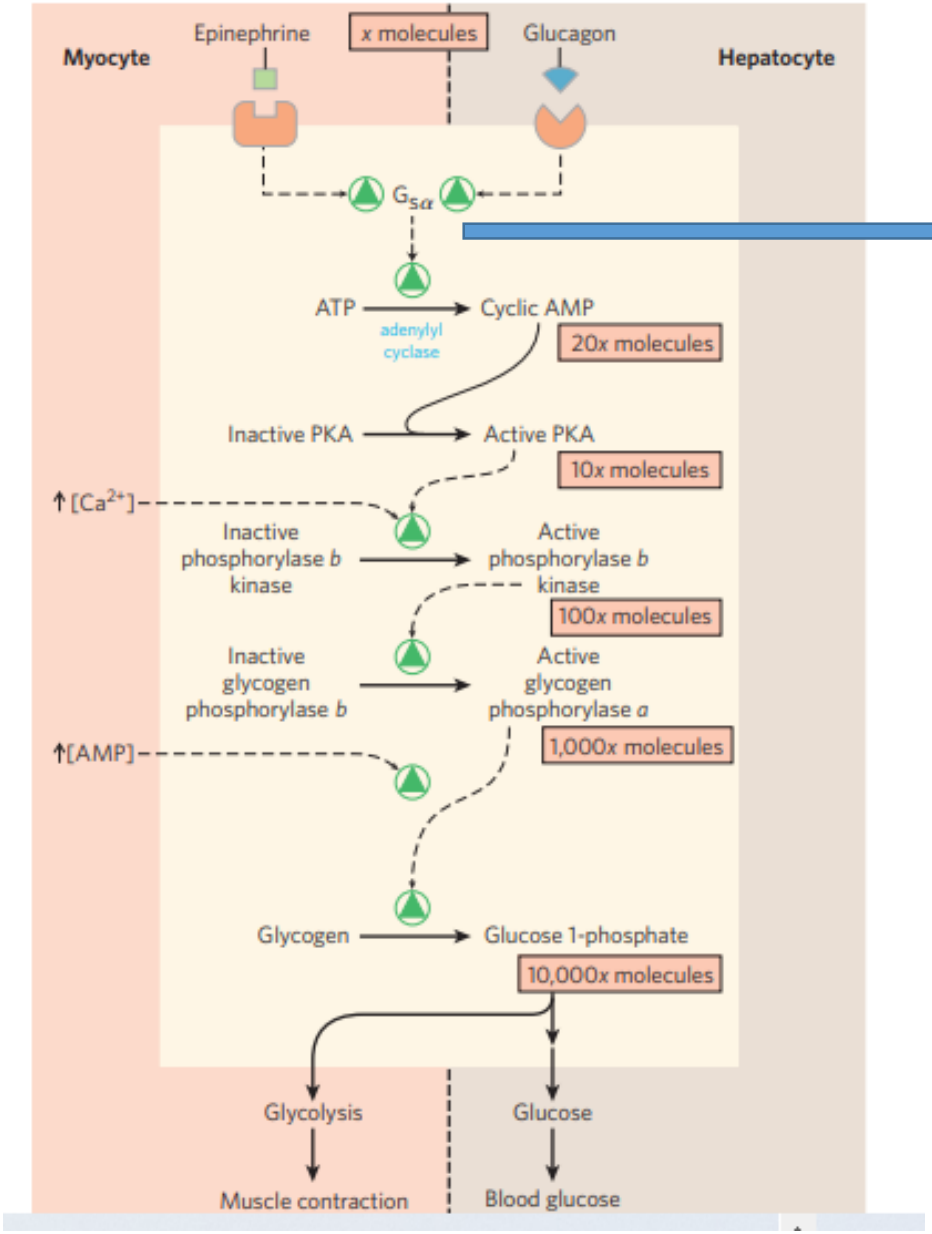
.The resulting breakdown of glycogen provides glucose,

in the myocyte can supply ATP (via glycolysis) for muscle contraction

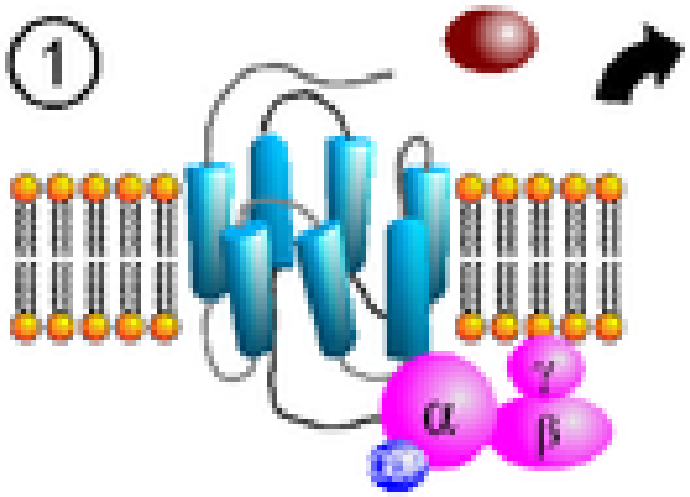
in the hepatocyte is released into the blood to counter the low blood glucose.

Such cascades effect a large amplification of the initial signal.





Receptors associated with G proteins



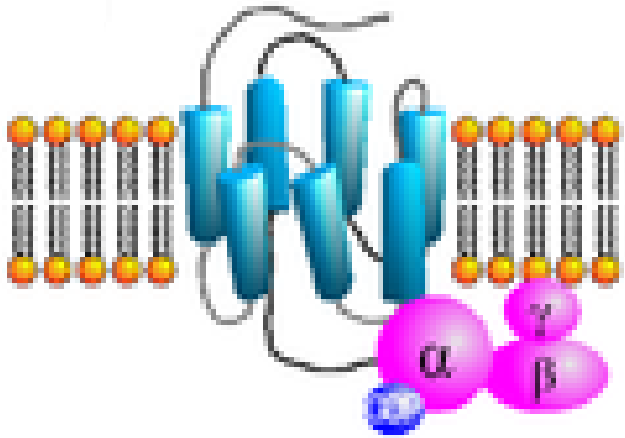
Receptors associated with G proteins

They are receptors of:

- Visual, olfactory and gustatory systems

-Neurotransmitter receptors

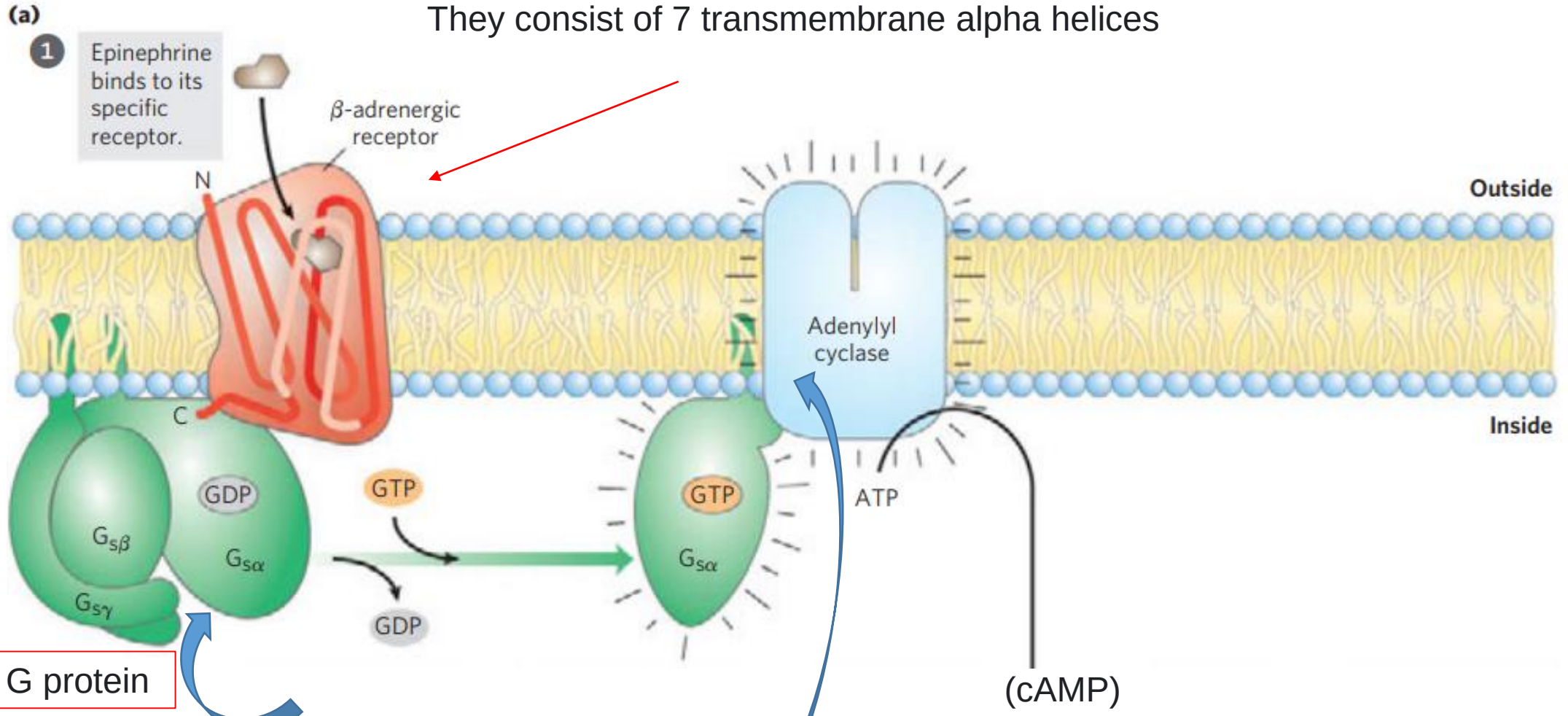
Hormone receptors that control the metabolism of carbohydrates, amino acids and fatty acids



A ligand can have multiple receptors:

- 9 GPCR activated by epinephrine
- 5 GPCR activated by acetylcholine
- 15 activated by serotonin

They consist of 7 transmembrane alpha helices



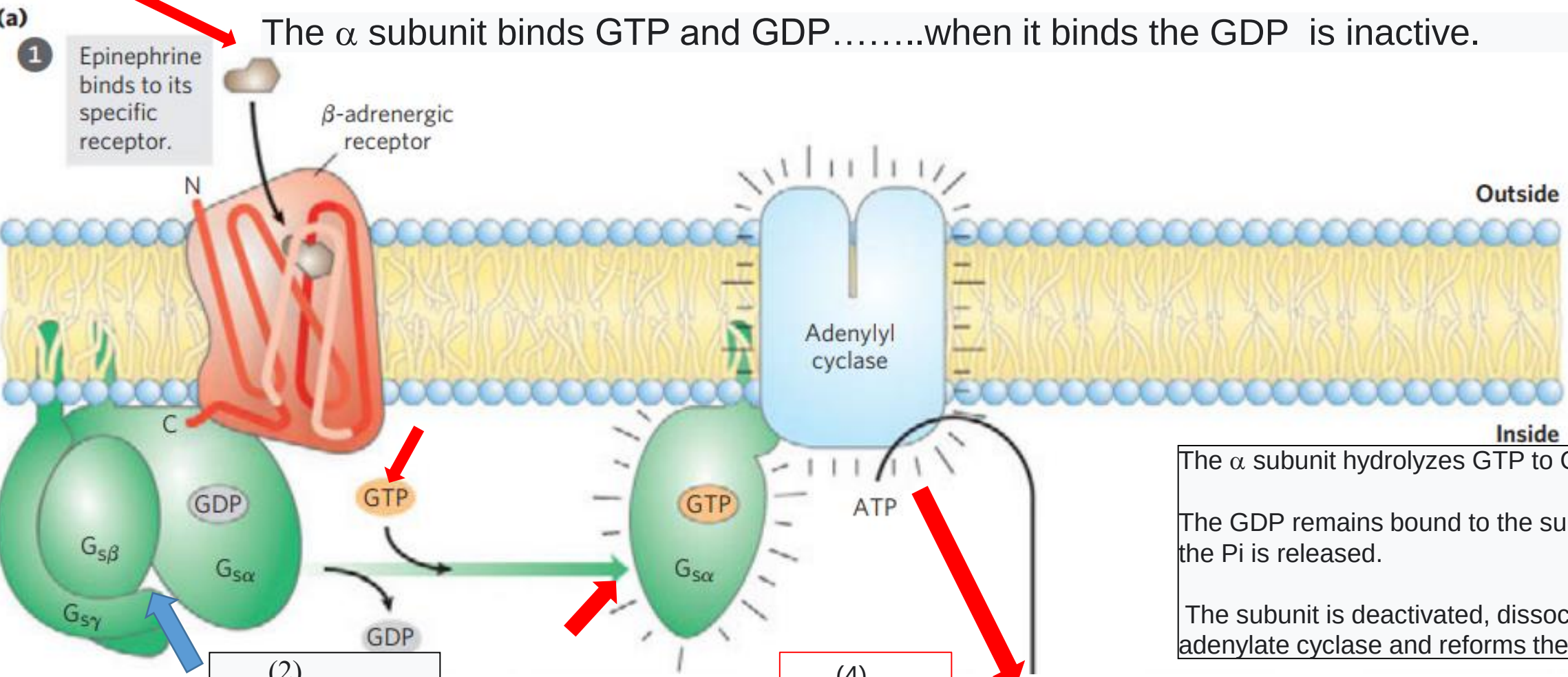
G protein

1 heterotrimeric G protein consisting of three subunits Gα, Gβ, Gγ)

1 membrane-bound effector protein (e-g- adenylate cyclase)

1 second messenger that transfers the signal inside the cell (cAMP)

The α subunit binds GTP and GDP……..when it binds the GDP is inactive.



(2)
α-subunit binds the GTP and it is activated.

(3)
-It dissociates from the β and γ complex, interacts with the effector protein (adenylate cyclase)

(4)
Adenylate cyclase catalyzes the formation of cAMP

cAMP

cAMP actives PKA

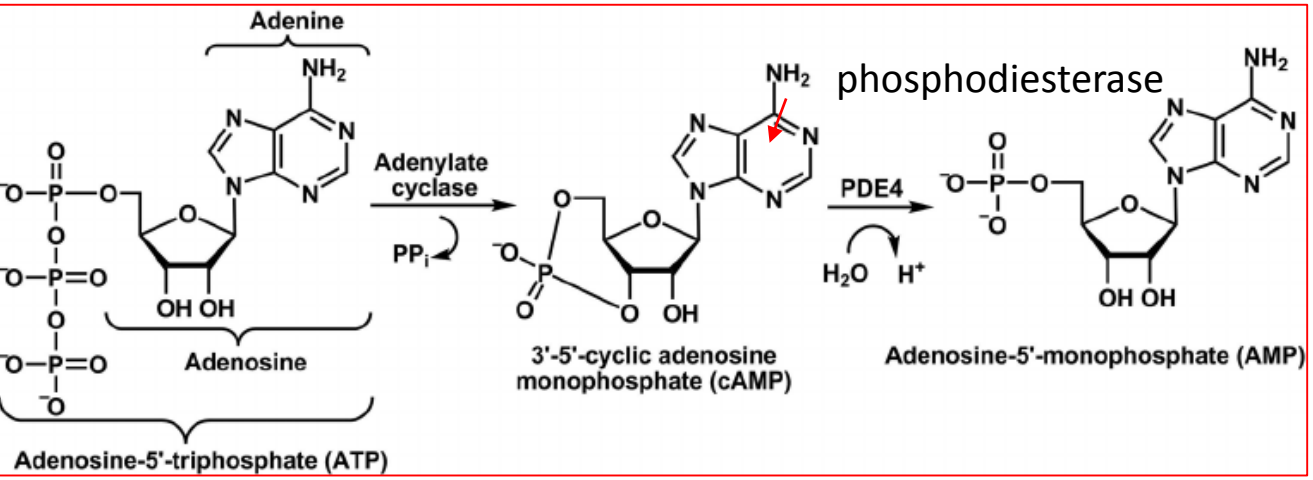
The α subunit hydrolyzes GTP to GDP and Pi.

The GDP remains bound to the subunit and the Pi is released.

The subunit is deactivated, dissociates from adenylate cyclase and reforms the trimer

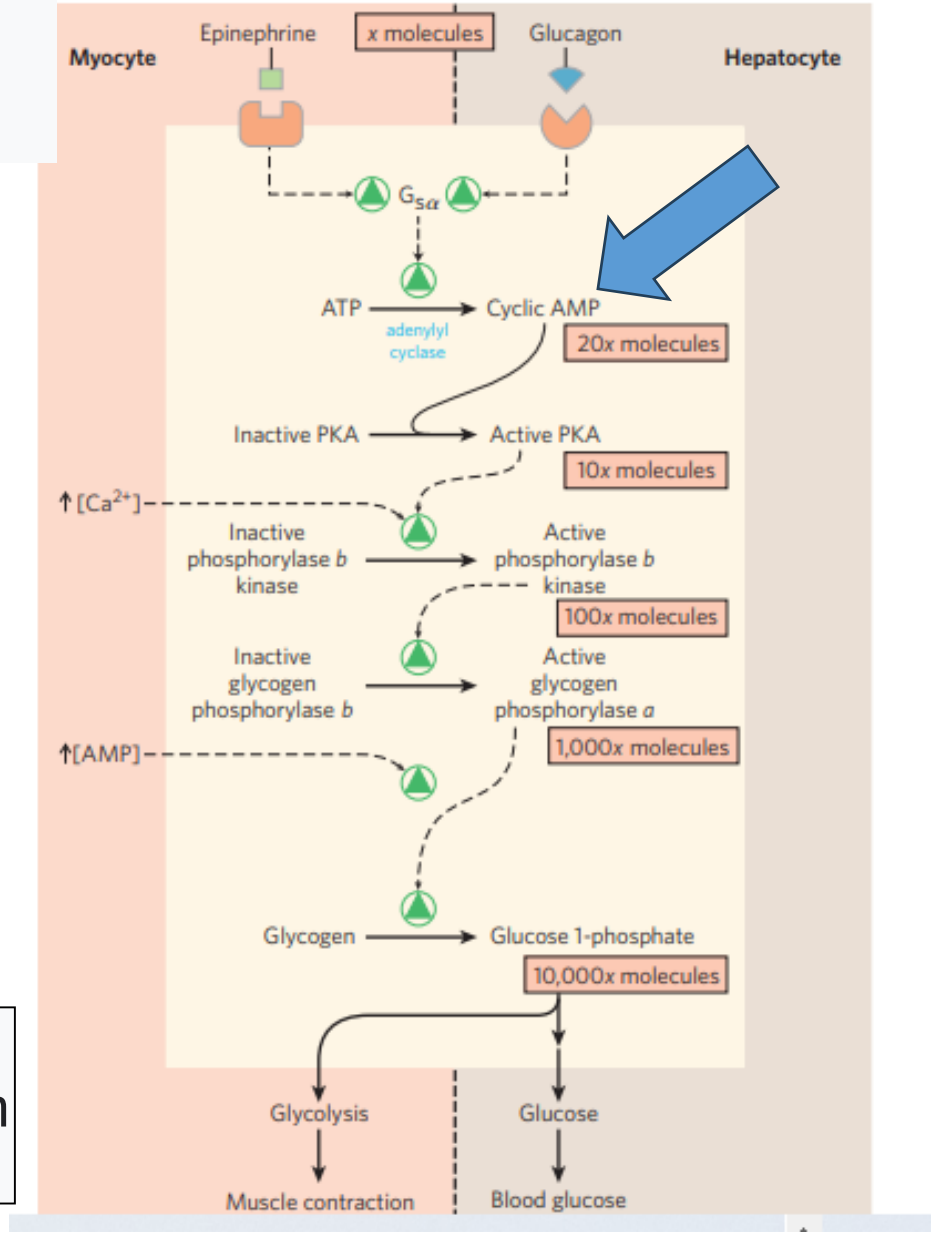
cAMP

It is synthesized from ATP by the action of adenylate cyclase (enzyme linked to the plasma membrane)

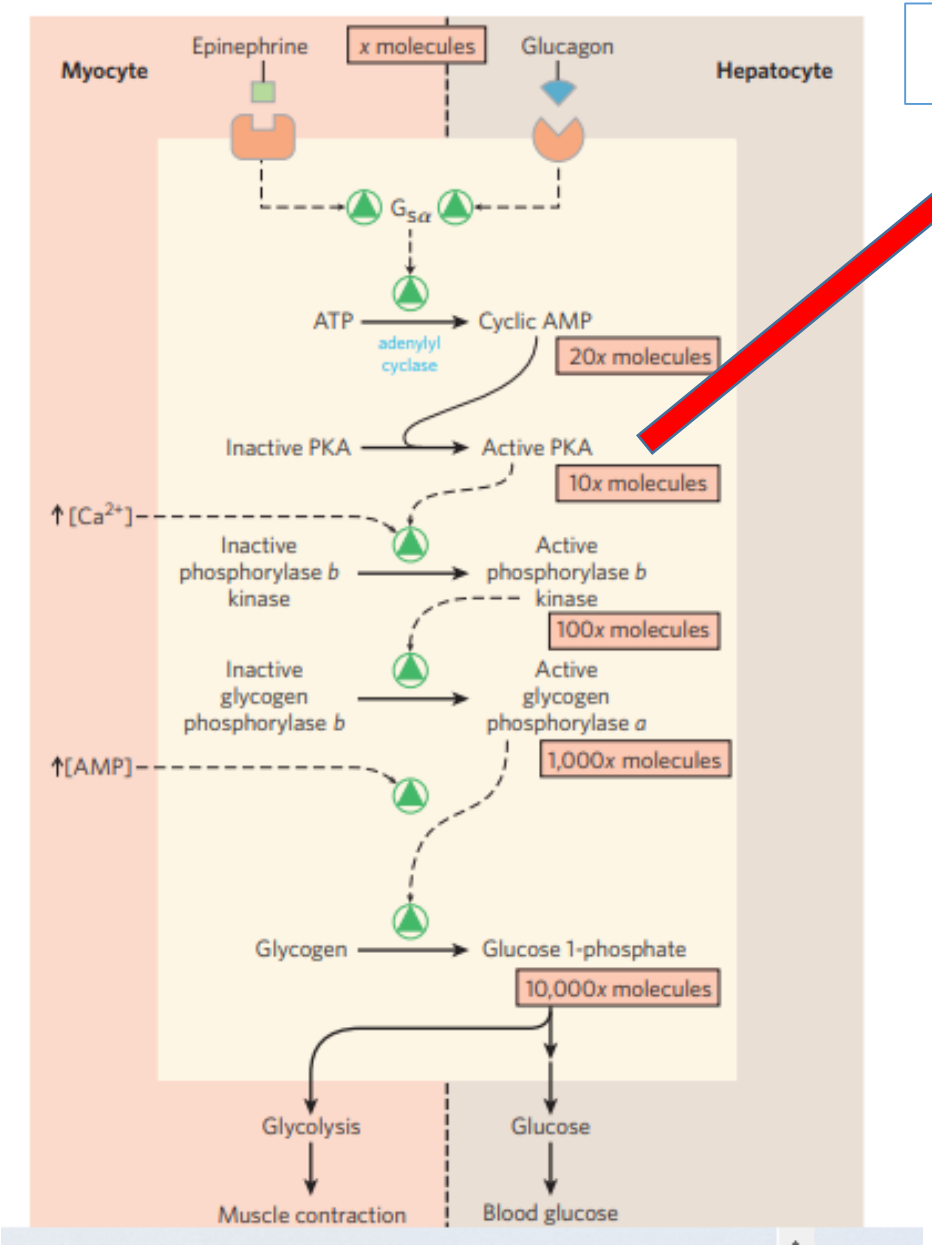


The messages of the first messengers (hormones) on the cell surface are transmitted inside the cell by the cAMP (2 messenger)

cAMP is involved in many signal transduction pathways mediated by different hormones (not just hormones involved in glucose metabolism)



Caffeine and theophylline (drug) inhibit phosphodiesterase



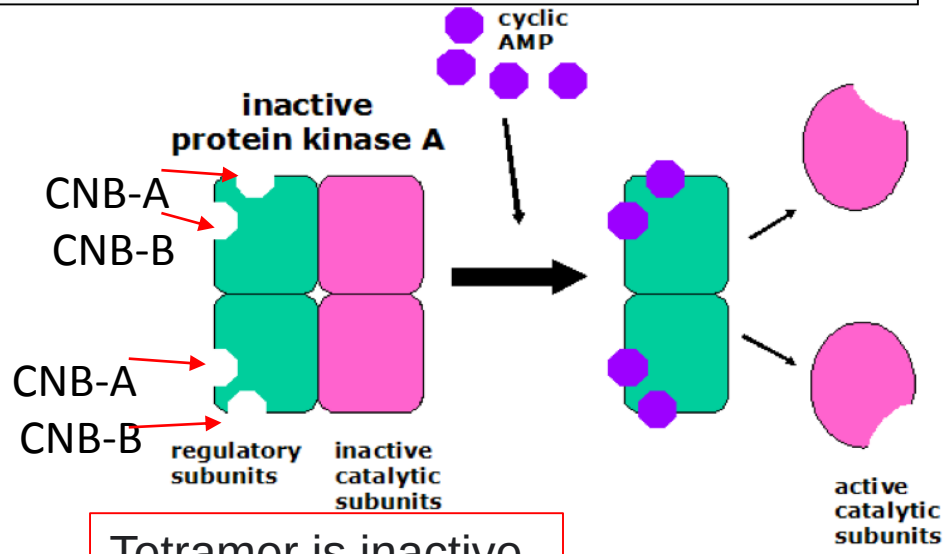
Protein kinase A (PKA)

phosphorylates different target proteins in different tissues

Structure

2 regulatory subunits (R)
2 catalytic subunits (C)

Each subunit has two sites for cAMP



Tetramer is inactive

R subunits dissociate from the C subunits and the protein kinase is activated

allosterically activated by Cyclic AMP (cAMP)

The binding of cAMP to both sites causes a conformational change

Hormonal regulation

Epinephrine.

In muscle activates glycolysis to sustain muscle contraction for the fight-or-flight

Glucagon

In liver activates glycogen breakdown, counters the low blood glucose and release glucose.

These different roles are reflected in subtle differences in the regulatory mechanisms in muscle and liver.

The glycogen phosphorylases of liver and muscle are isozymes, encoded by different genes and differing in their regulatory properties.

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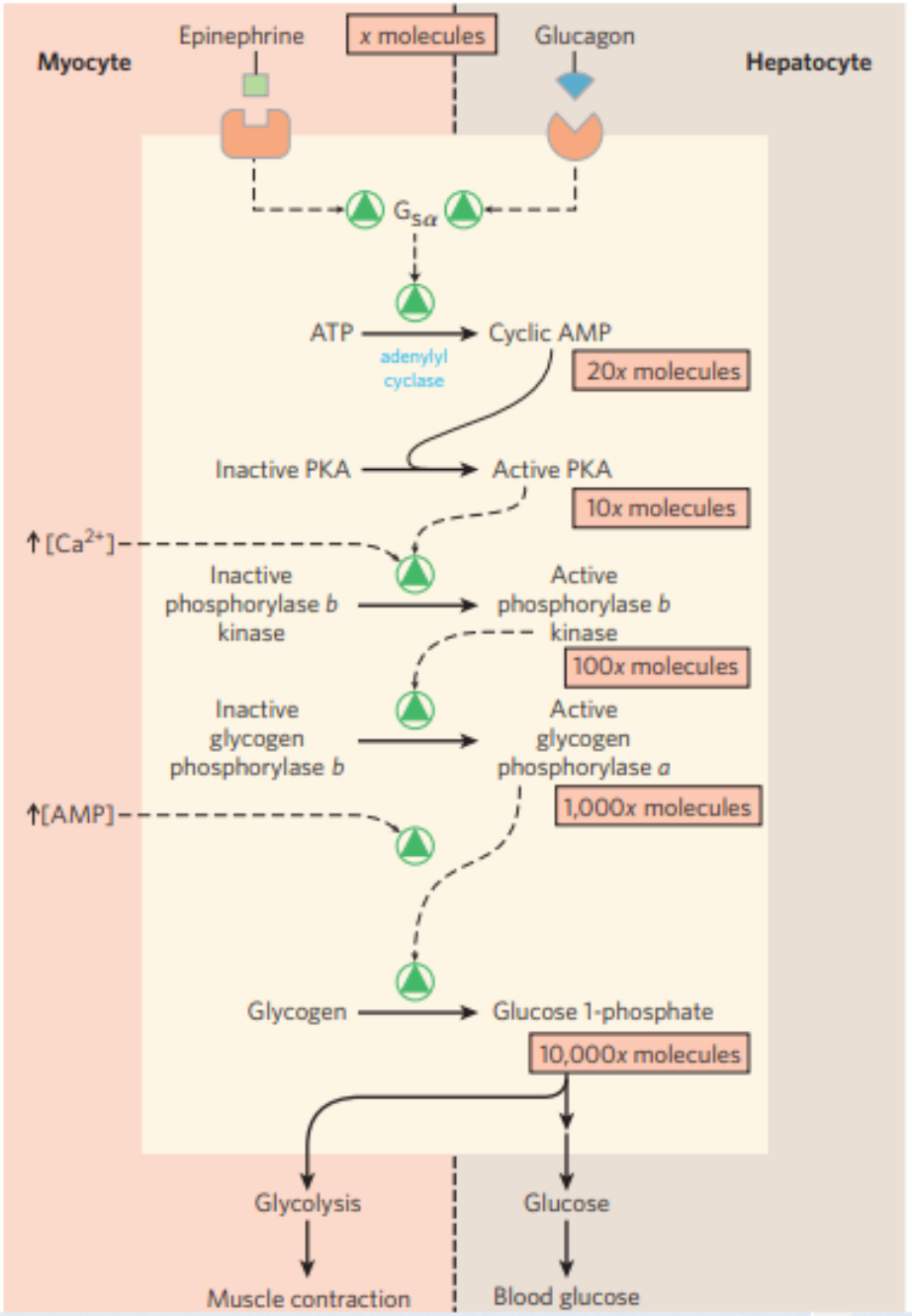


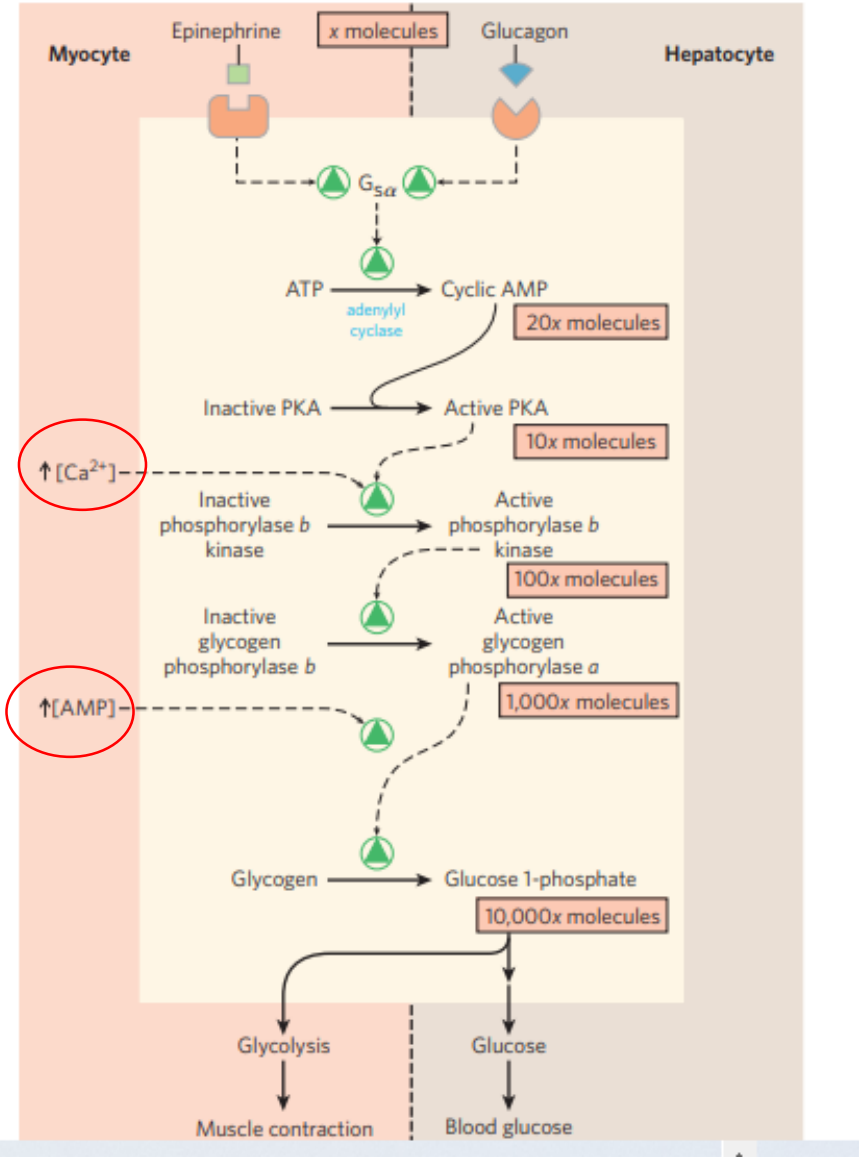
Muscle

Allosteric regulation occurs only in the muscle

Regulation of phosphorylase by covalent modification are two allosteric control mechanisms:

1) Ca2+: the signal for muscle contraction, binds to and activates phosphorylase b kinase, promoting conversion of phosphorylase b to the active a form.
Ca2+ binds to phosphorylase b kinase through its subunit, which is calmodulin.

2) AMP, which accumulates in vigorously contracting muscle as a result of ATP breakdown,
AMP binds to and activates phosphorylase,



RESULT:
INCREASED release of glucose 1-phosphate from glycogen.

When ATP levels are adequate

ATP blocks the allosteric site to which AMP binds, inactivating glycogeno phosphorylase.

LIVER

glycogen phosphorylase regulation

Regulated hormonally and allosterically.

(phosphorylation/dephosphorylation)

Low blood glucose level → glucagon

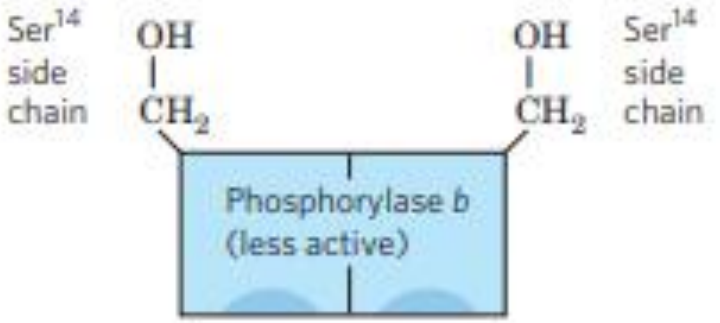
activates phosphorylase b kinase,

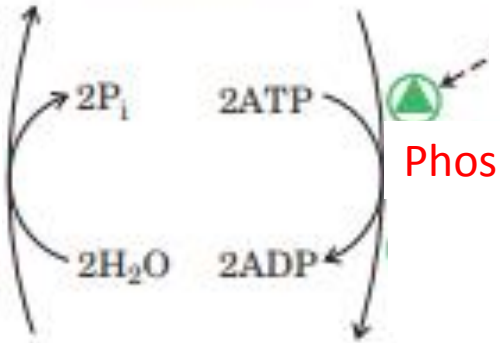
release of glucose into the blood.

When blood glucose levels return to normal,

Glucose enters hepatocytes and binds to an inhibitory allosteric site on phosphorylase a.

This binding also produces a conformational change that exposes the phosphorylated Ser residues to PP1 that dephosphorylates enzyme

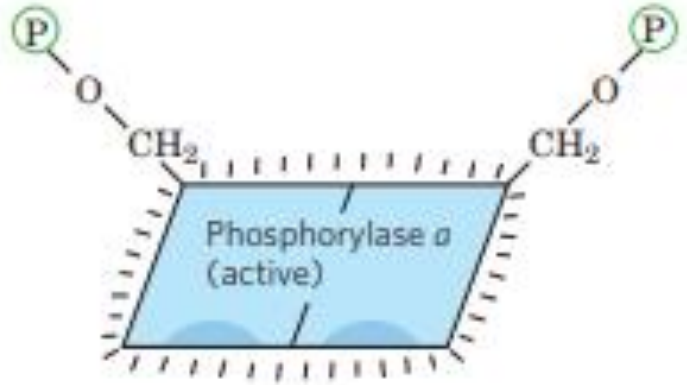




Glucagon (liver)

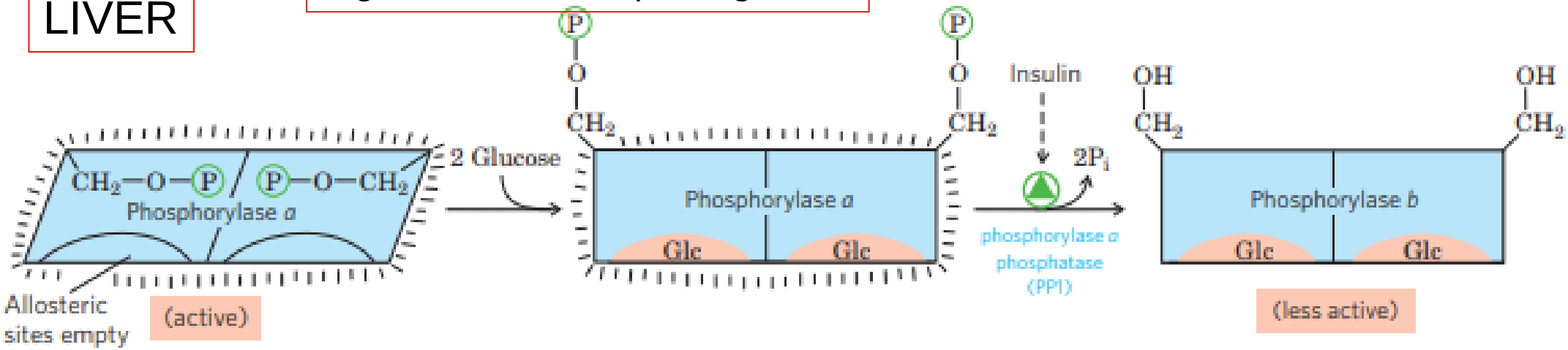
Phosphorylase b kinase

Phosphorylase a phosphatase (PP1)

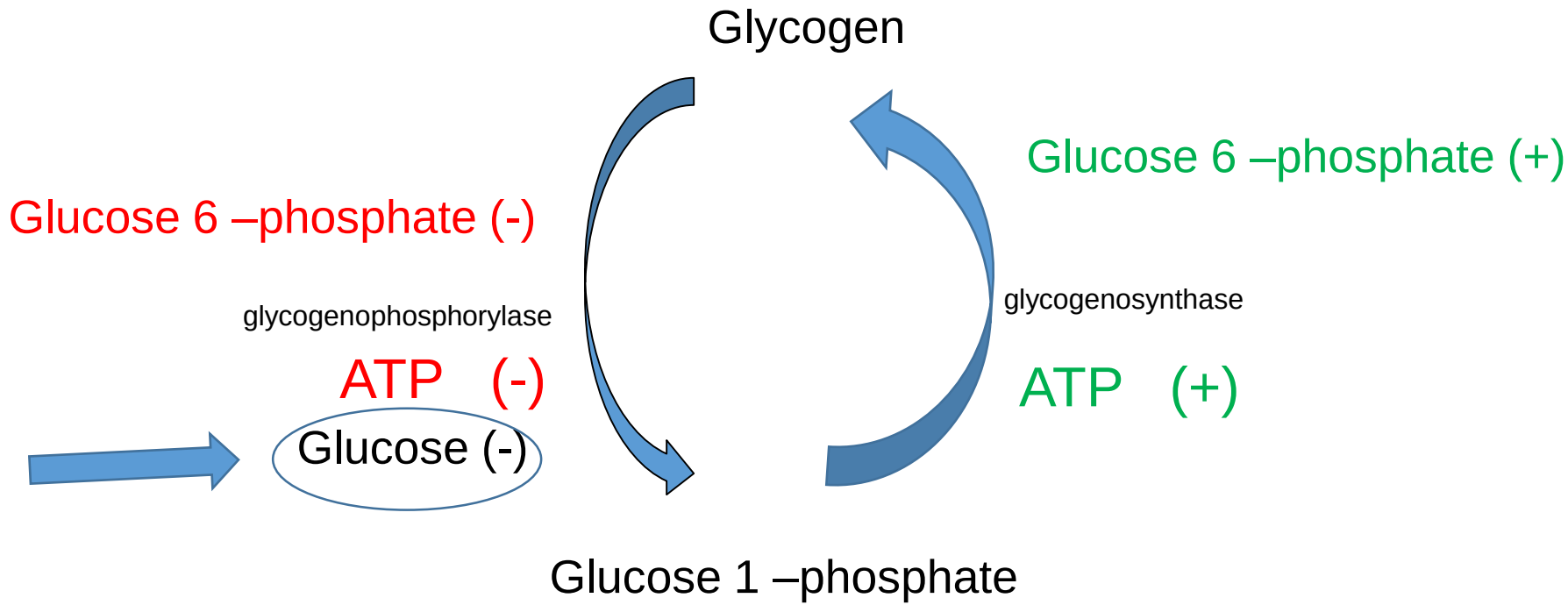


LIVER

Regulated allosterically from glucose

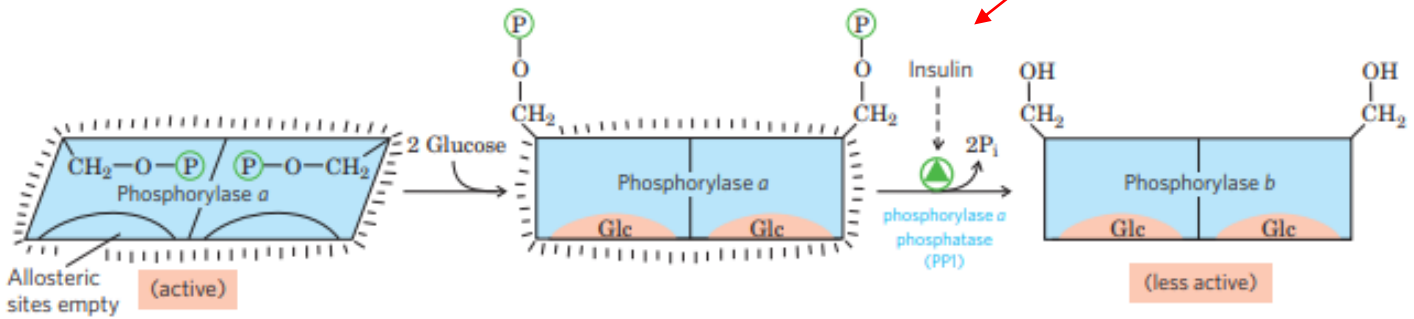


The allosteric site for glucose allows liver glycogen phosphorylase to act as its own glucose sensor and to respond appropriately to changes to blood glucose.



LIVER

INSULIN

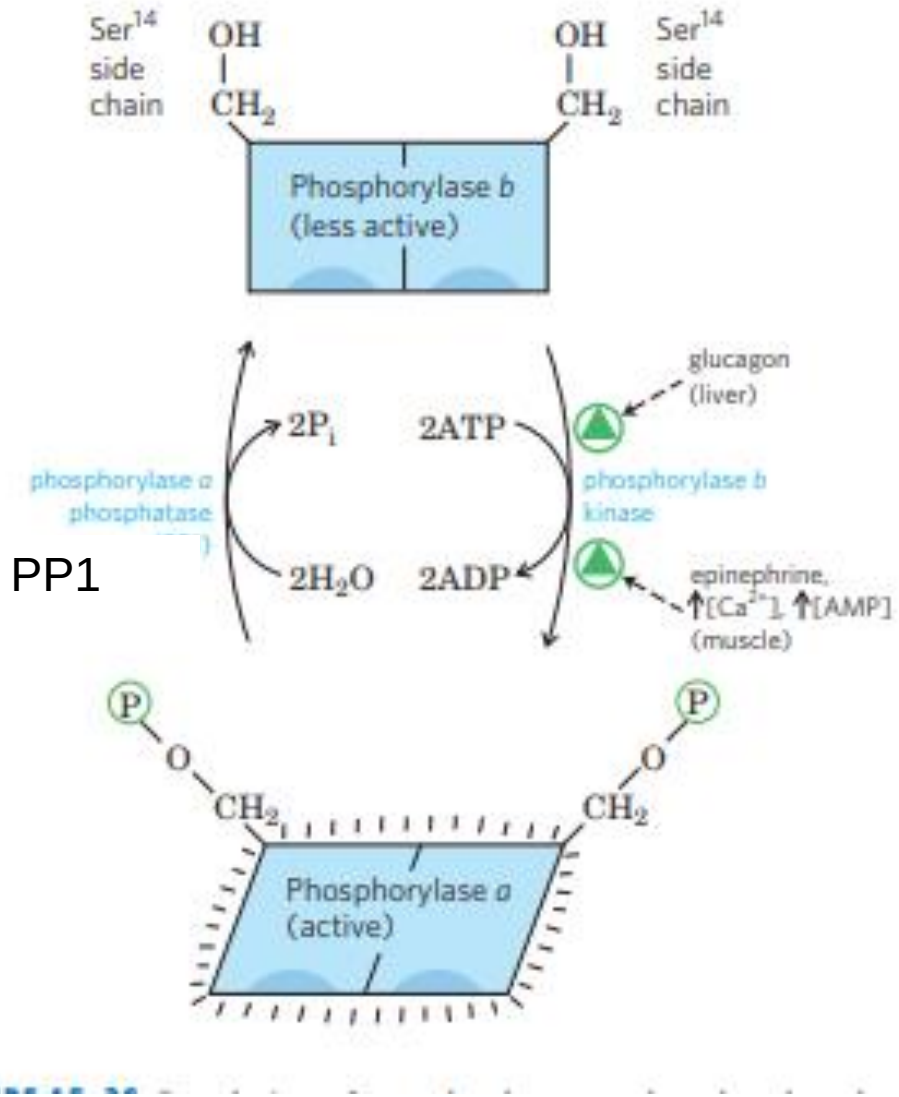


Insulin activates PP1

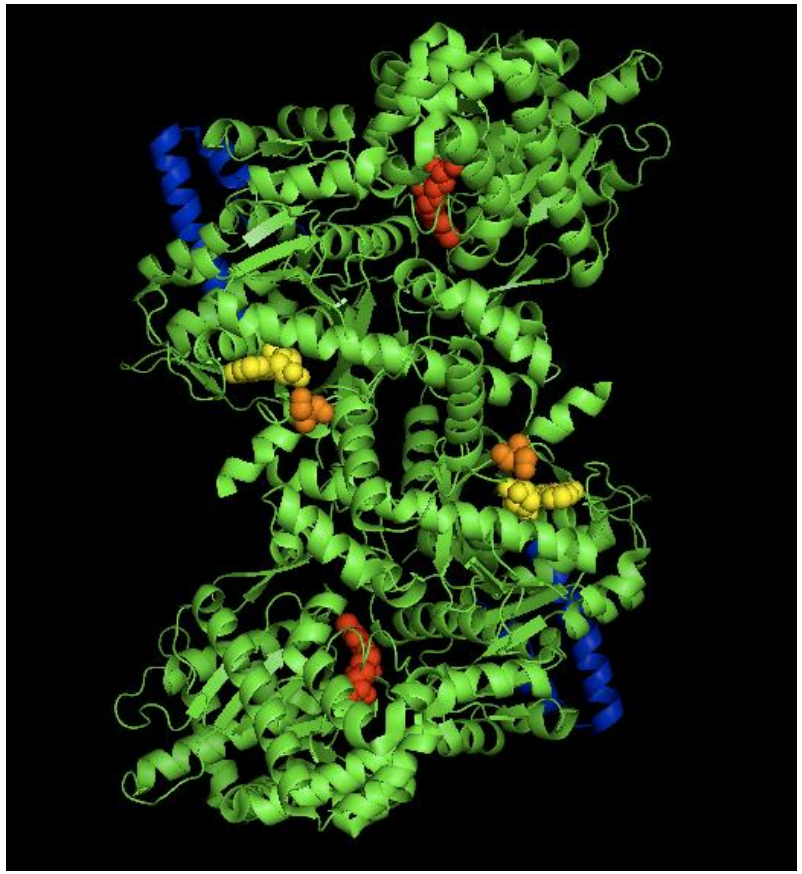
glycogen phosphorylase (inactivated)

increase glycogeno synthesis

PP1



Glycogen synthase



Glycogen synthase

Effects of GSK3

Glycogen Synthase Kinase 3

Glycogen synthase a (active) has three Ser residues near its carboxyl terminus.

Phosphorylated by GSK3 (glycogen synthase kinase 3)

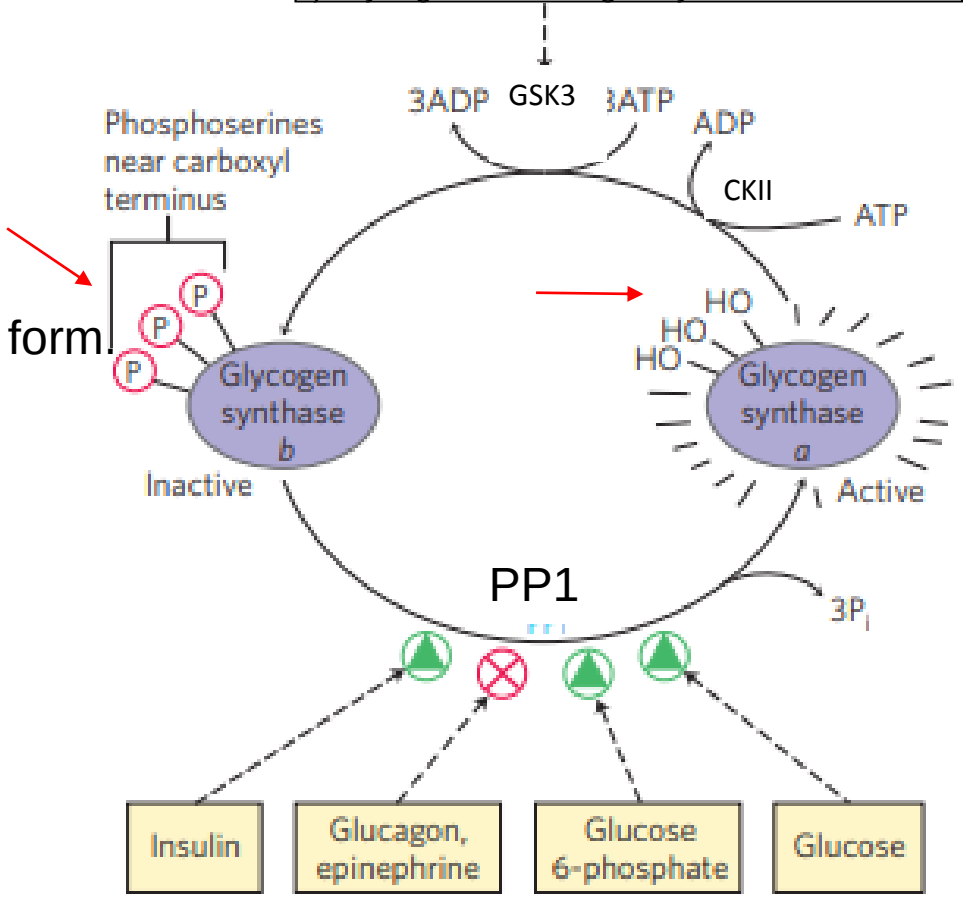
Glycogen synthase from (a) form is converted to the inactive (*b*) form.

Glycogenosynthesis is ensured by the intervention of three enzymatic activities:

1) UDP-glucose pyrophosphorylase

2) Glycogen synthetase (or synthase)

3) Glycogen branching enzyme



GSK3 requires prior phosphorylation of glycogenosynthase by casein kinase (CKII).

Liver

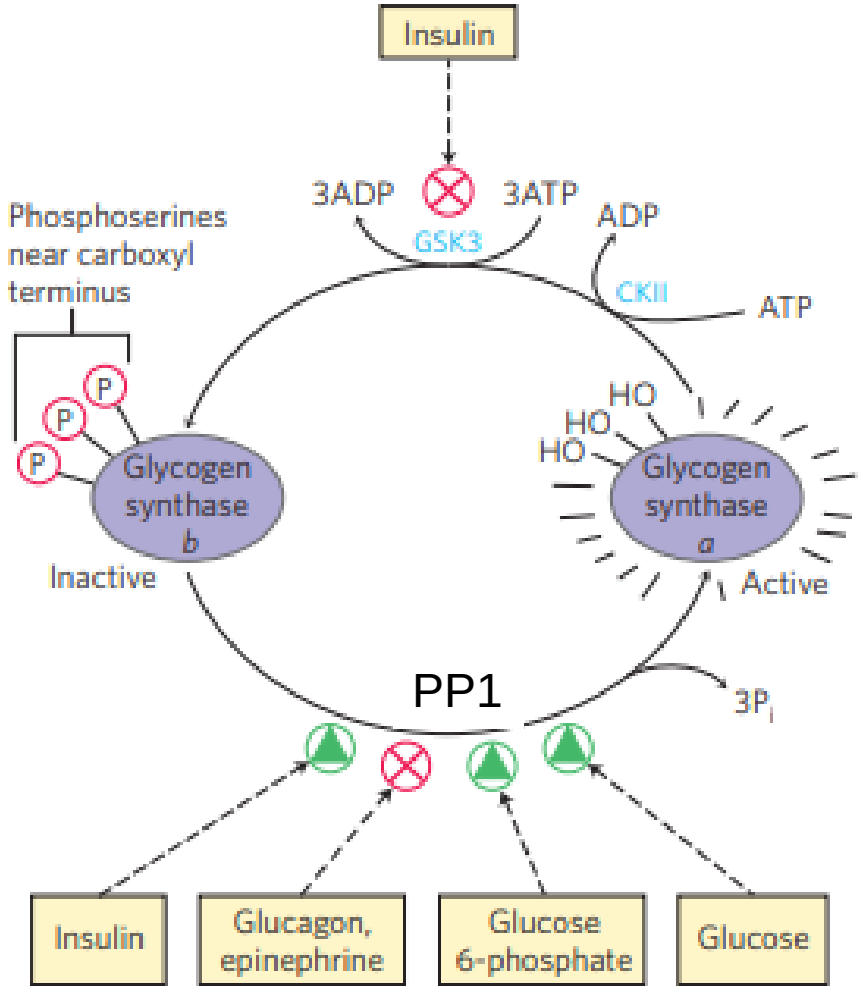
Regulated hormonally and allosterically.

Conversion of glycogen synthase b to the active form is promoted by PP1, which is bound to the glycogen particle.

PP1 removes the phosphoryl groups from the three Ser residues

Glucose 6-phosphate binds to an allosteric site of glycogen synthase b, making the enzyme a better substrate for dephosphorylation by PP1 and causing its activation.

Glucose 6-phosphate acts as sensor. (similarly to glucose for glycogen phosphorylase)



Muscle

A different phosphatase may have the role played by PP1 in liver, activating glycogen synthase by dephosphorylating it

LIVER

INSULIN

blocks the activity of GSK3

Blocks
Glycogen synthase *b*

activates PP1

RESULT

Actives glycogenosynthesis

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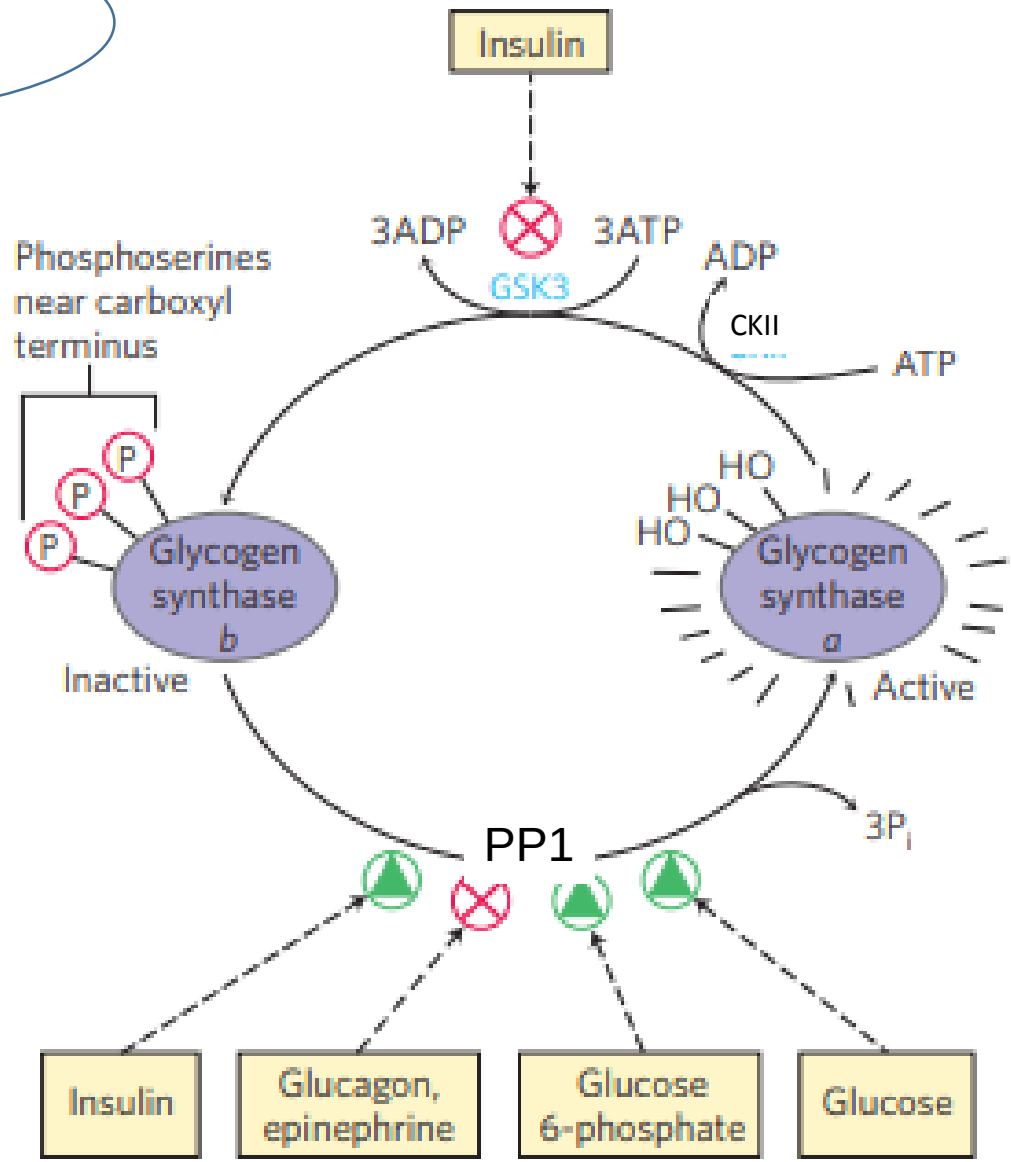
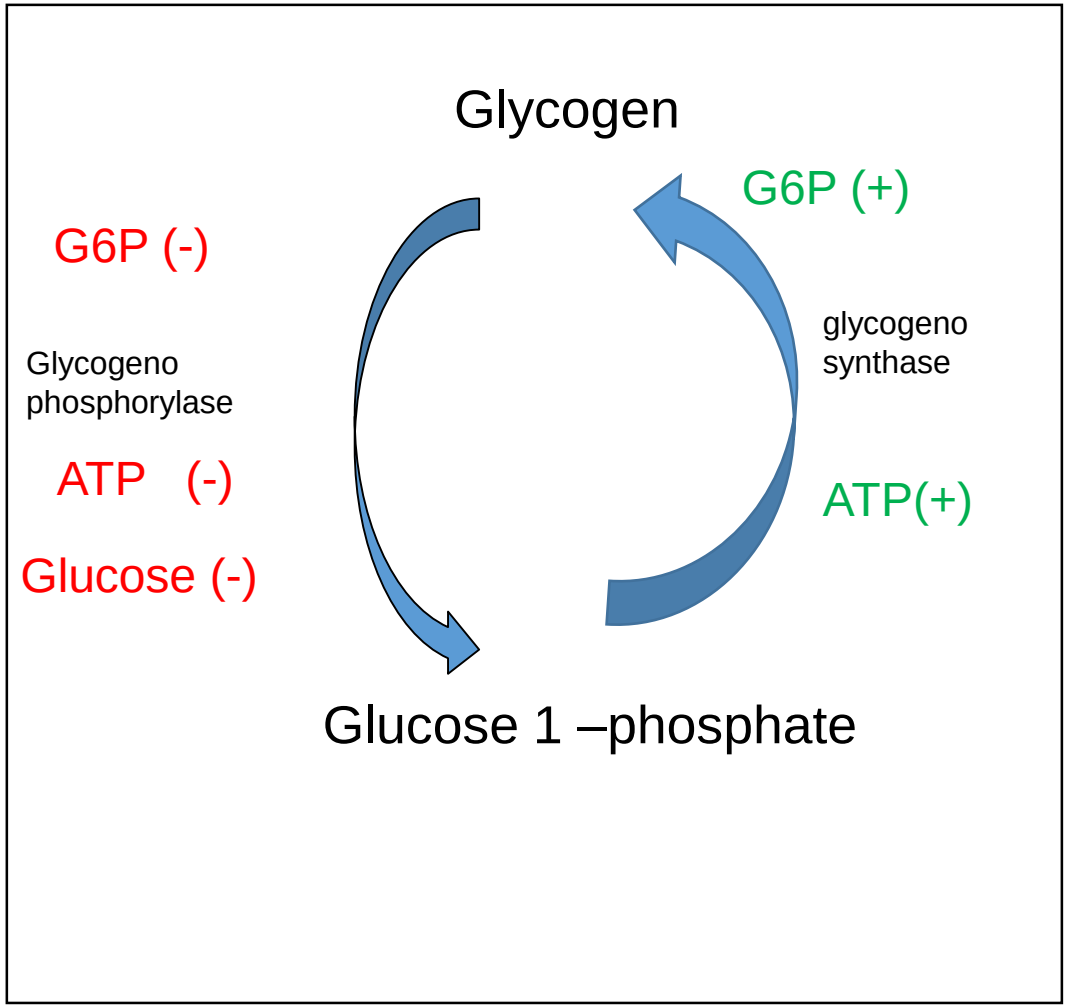
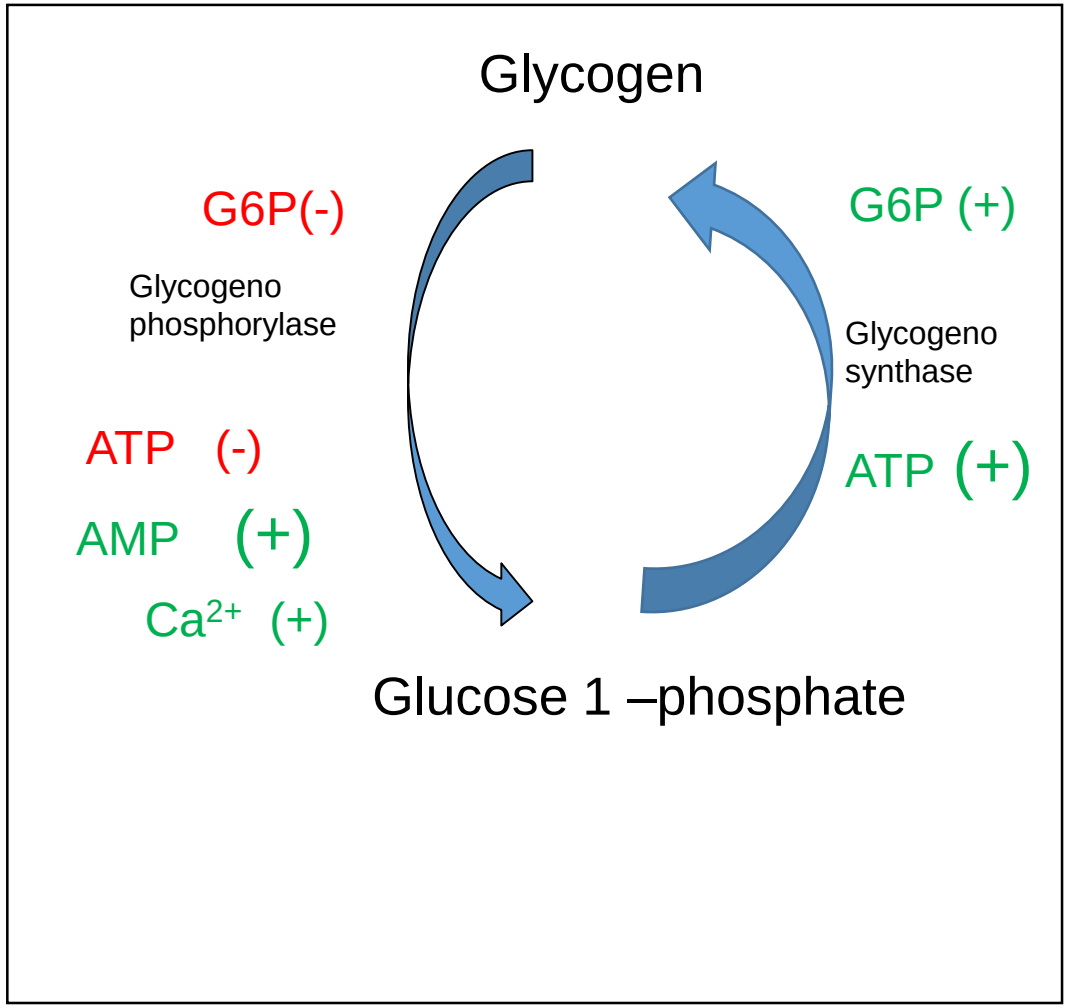


ALLOSTERIC INTERACTION

LIVER



MUSCLE

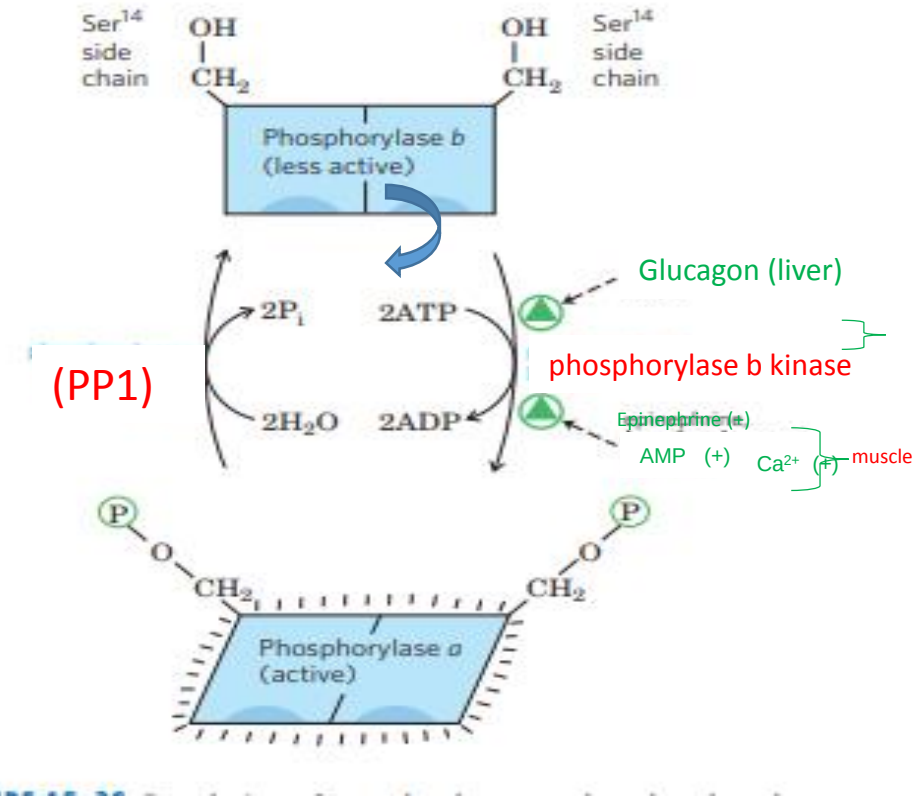


Phosphoprotein Phosphatase 1 (PP1) Is Central to Glycogen Metabolis

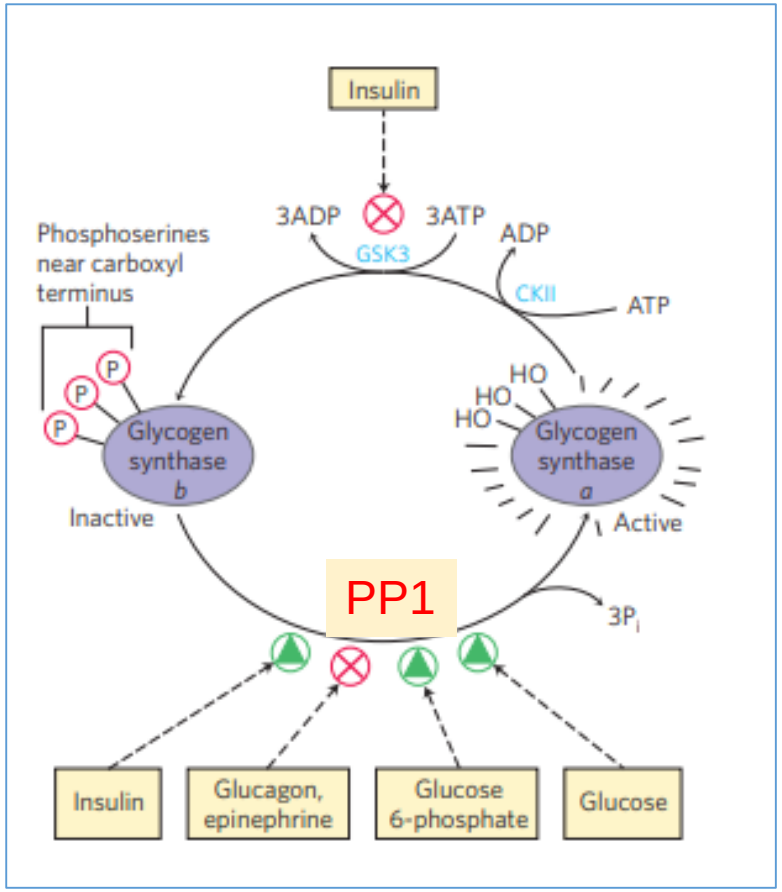
Phosphoprotein Phosphatase 1 (PP1) Is Central to Glycogen Metabolis

PP1, can remove phosphoryl groups from all three of the enzymes phosphorylated in response to glucagon (liver) and epinephrine (liver and muscle):

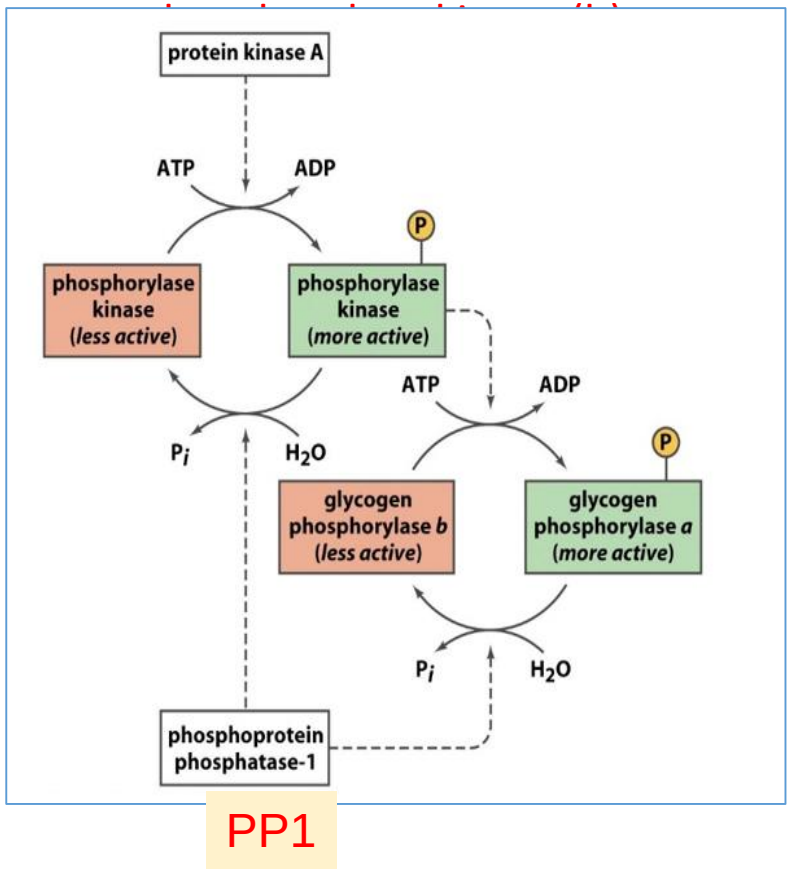
glycogen phosphorylase



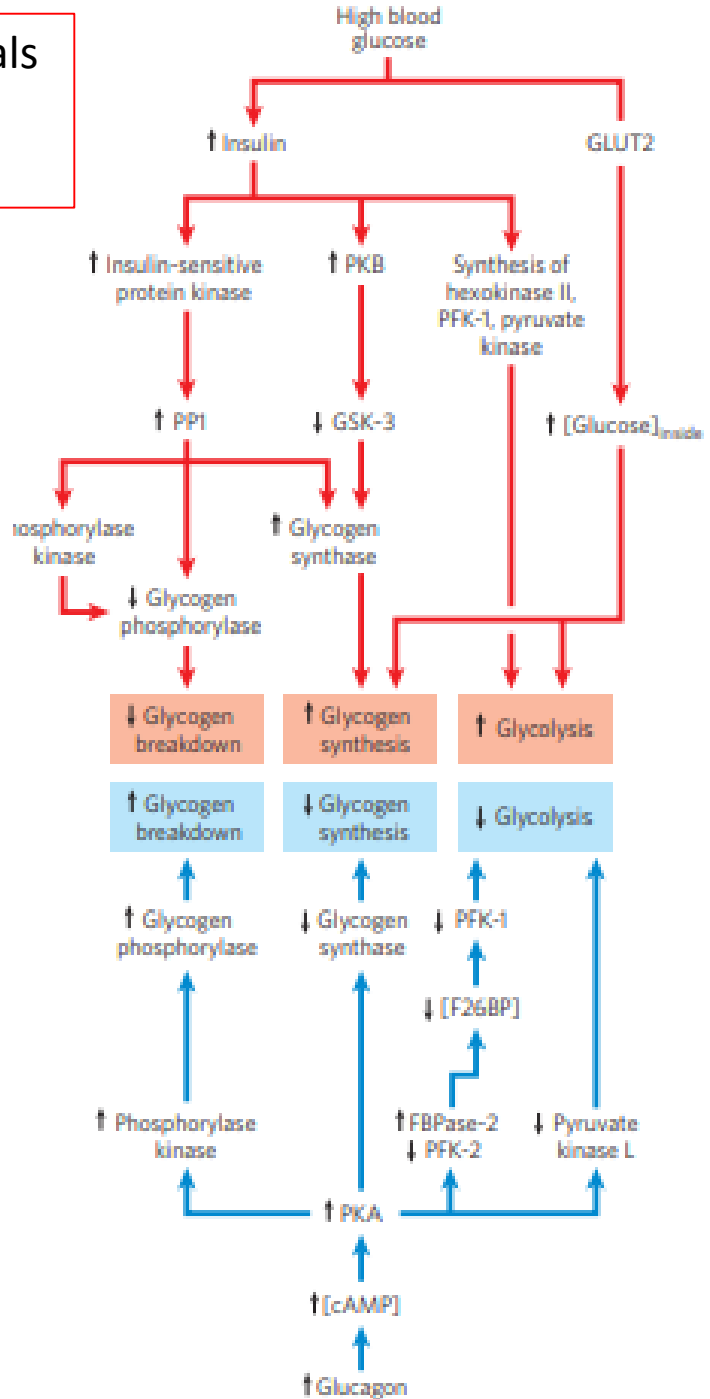
glycogen synthase



phosphorylase kinase



Allosteric and Hormonal Signals Coordinate Carbohydrate Metabolism Globally



Exist two cases in which regulation serves different ends:

(1) the role of hepatocytes in supplying glucose to the blood,

(2) the use of carbohydrate fuels by nonhepatic tissues such as skeletal muscle (myocytes),

Having looked at the mechanisms that regulate individual enzymes,

we can now consider the overall shifts in carbohydrate metabolism that occur:

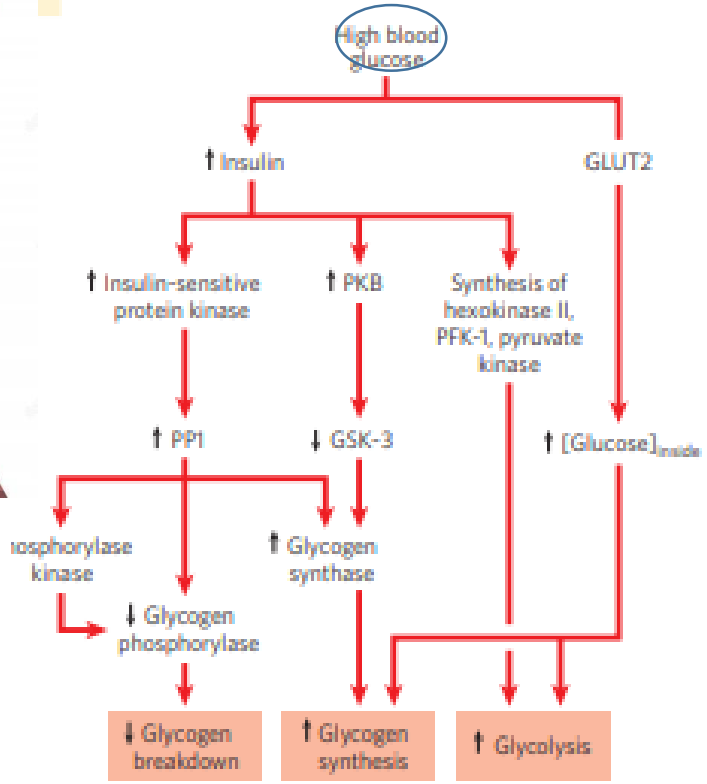
- in well-fed state,
- during fasting,
- in the fight-or-flight response

signaled by insulin, glucagon, and epinephrine

After ingestion of a carbohydrate-rich meal,

the elevation of blood glucose triggers insulin release

Hepatocyte



insulin has two immediate effects:

- inactivates GSK3,
- activates a protein phosphatase PP1.

These two actions fully activate glycogen synthase.

- PP1 also inactivates glycogen phosphorylase a and phosphorylase kinase by dephosphorylating both, effectively stopping glycogen breakdown.

During an extended fast

blood glucose DECREASE

Glucagon RELEASE

ACTIVES cascade that activates PKA

PKA

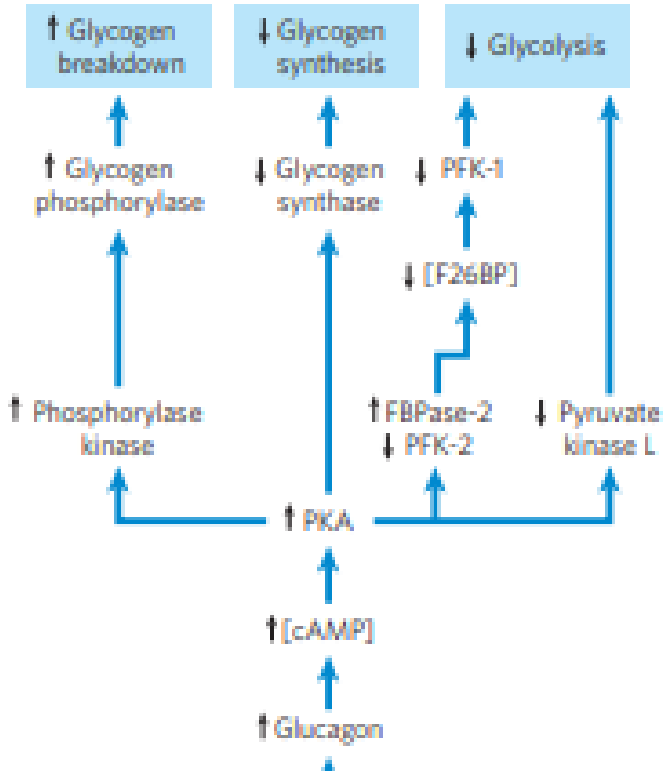
3

1

2

Phosphorylates phosphorylase kinase, activating it and leading to the activation of glycogen phosphorylase.

Phosphorylates glycogen synthase, inactivating it and blocking glycogen synthesis.



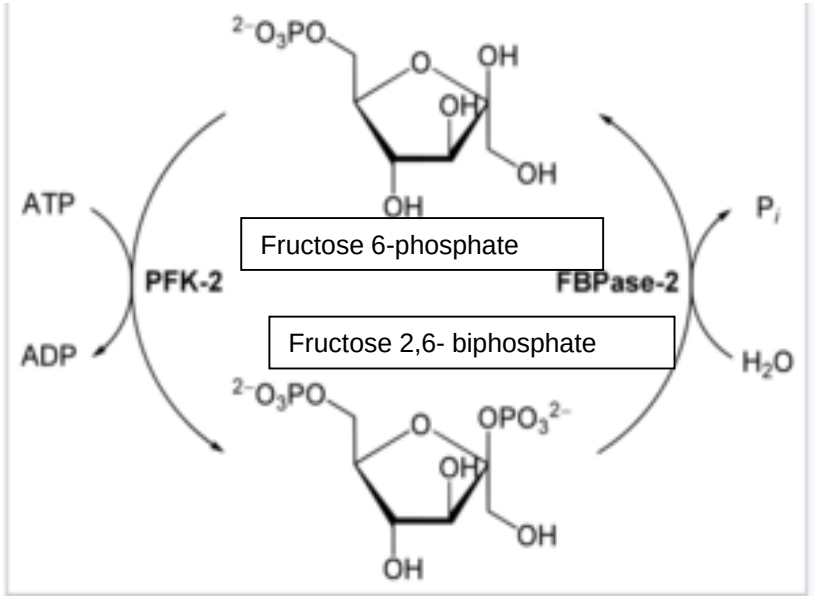
Phosphofructokinase-2(PFK-2).

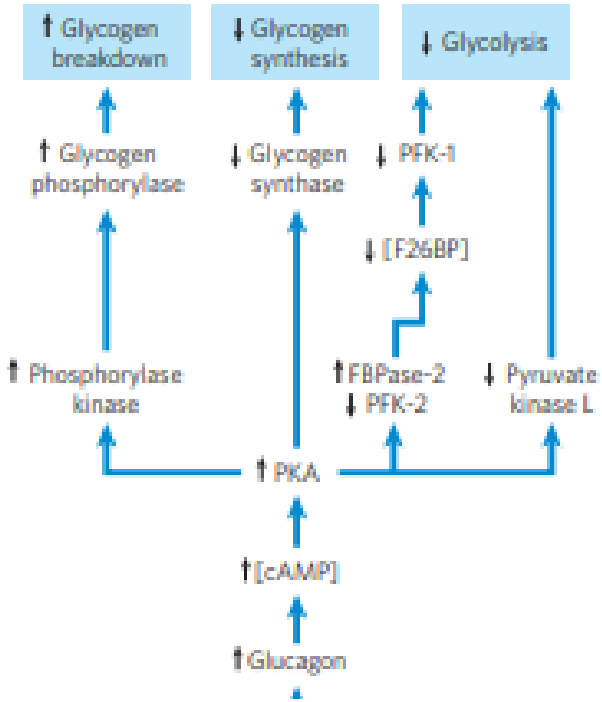
PKA

3

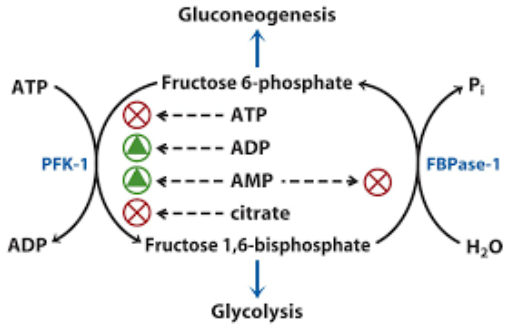
Phosphorylates PFK-2/FBPase-2

DECREASE Fructose 2,6-bisphosphate





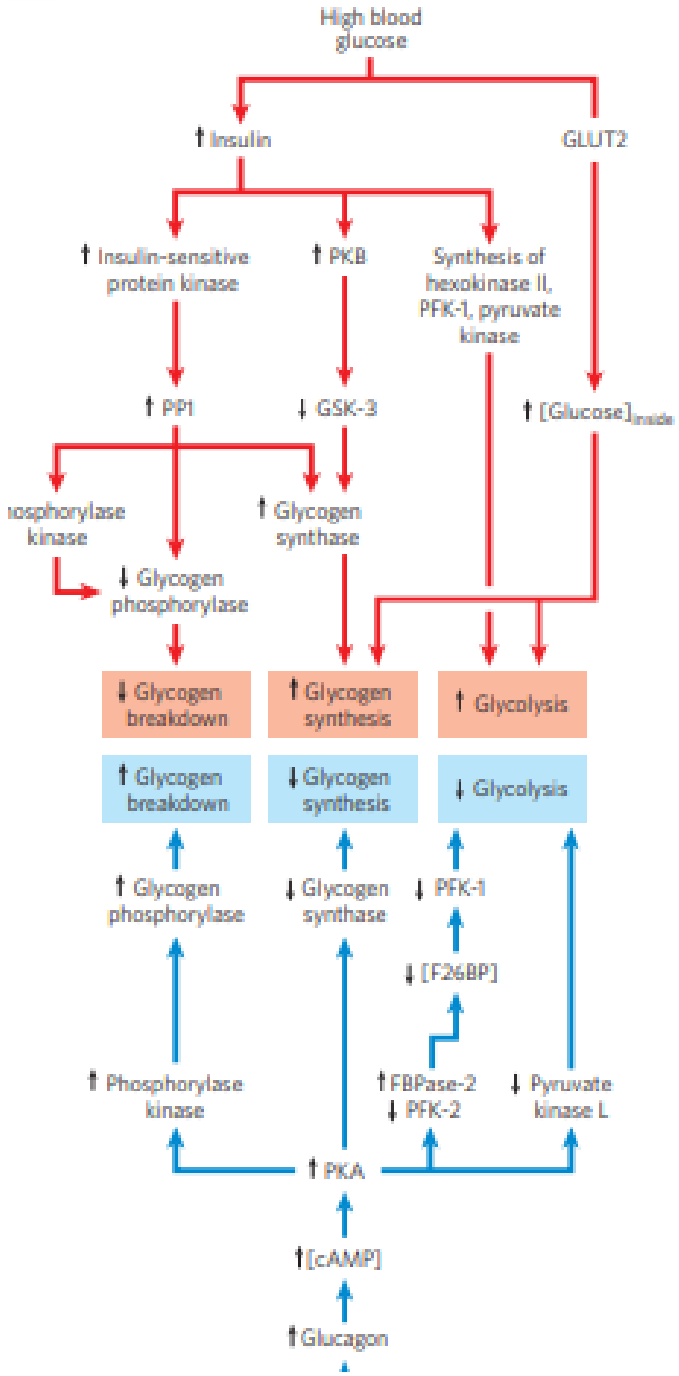
Fructose 2,6-biphosphate is allosteric activator of PFK-1)



Decrease fructose 2,6-bisphosphate , (inactives the glycolytic enzyme PFK-1 and activates the gluconeogenic enzyme FBPase-1.)

Glycolysis is Inhibited

Gluconeogenesis is favored


High blood glucose
↑ Insulin
GLUT2
↑ Insulin-sensitive protein kinase
↑ PKB
Synthesis of hexokinase II, PFK-1, pyruvate kinase
↑ PP1
↓ GSK-3
↑ [Glucose]inside
↑ Glycogen synthase
↓ Glycogen phosphorylase
↓ Glycogen breakdown
↑ Glycogen synthesis
↑ Glycolysis
↑ Glycogen breakdown
↓ Glycogen synthesis
↓ Glycolysis
↑ Glycogen phosphorylase
↓ Glycogen synthase
↓ PFK-1
↓ [F26BP]
↑ Phosphorylase kinase
↑ FBPase-2
↓ PFK-2
↓ Pyruvate kinase L
↑ PKA
↑ [cAMP]
↑ Glucagon

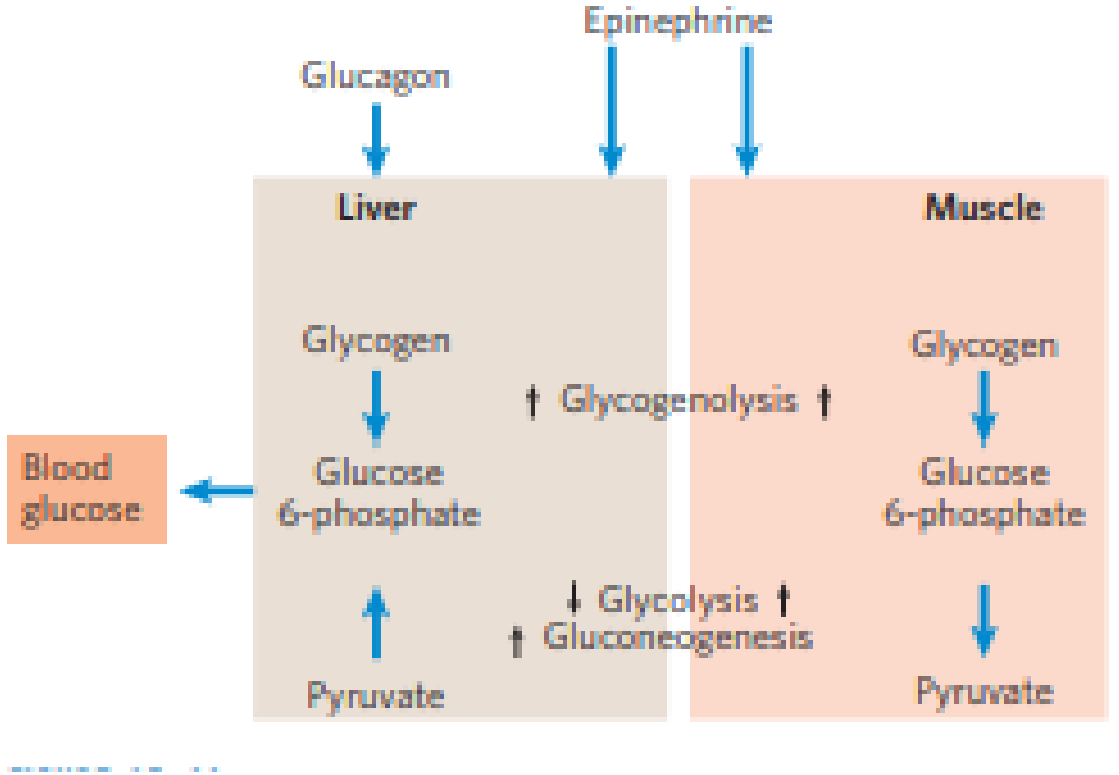
Liver

1) produces glucose 6-phosphate by glycogen breakdown and by gluconeogenesis,

2) stops using glucose to fuel glycolysis or make glycogen

3) INCREASES the amount of glucose it can release to the blood.

This release of glucose is possible only in liver and kidney, because other tissues lack glucose 6-phosphatase



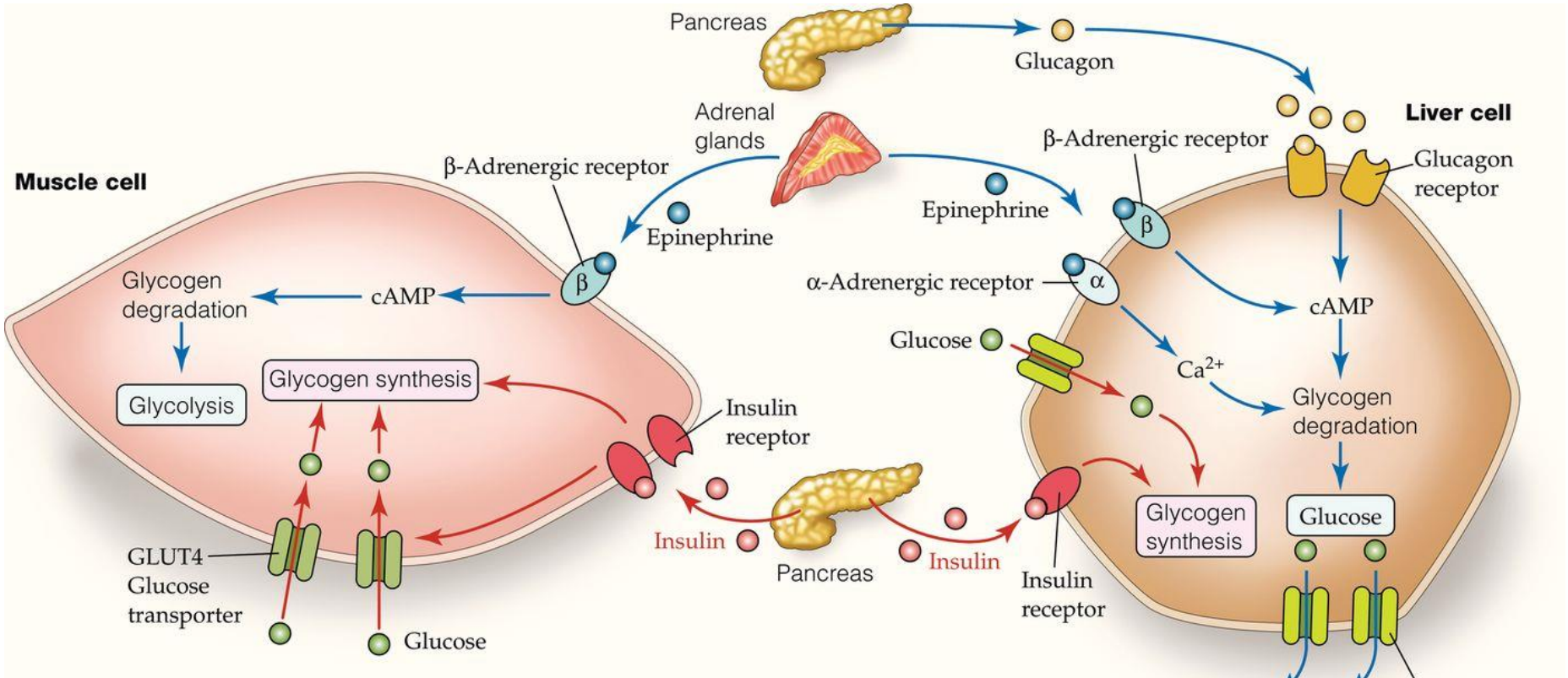
Skeletal muscle differs from that of liver in three ways :

(1) muscle uses its stored glycogen only for its own needs;

(2) as it goes from rest to vigorous contraction, muscle undergoes very large changes in its demand for ATP, which is supported by glycolysis;

(3) muscle lacks the enzymatic machinery for gluconeogenesis.

MUSCLE

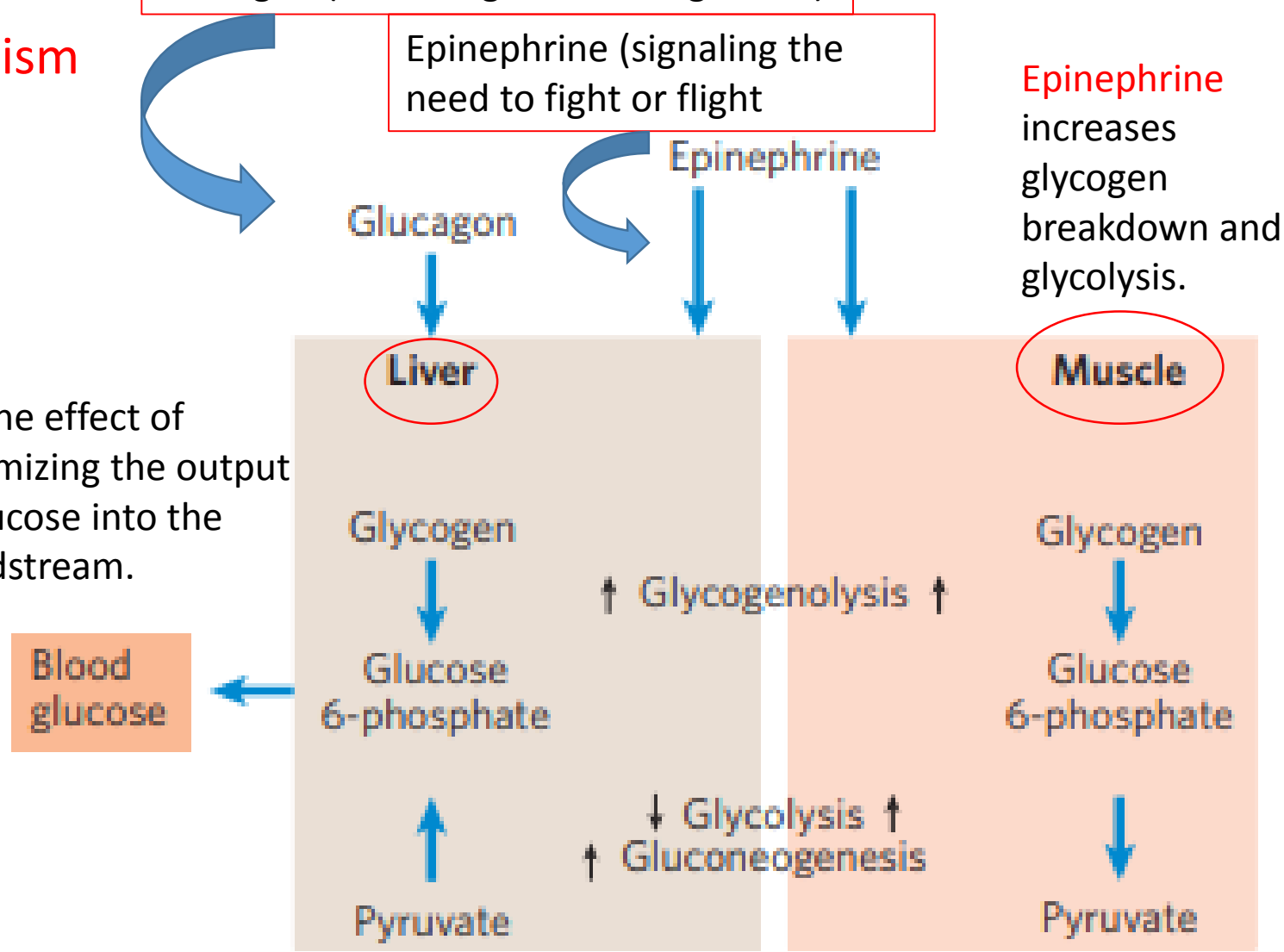


Regulation of carbohydrate metabolism in liver and muscle

Glucagon (indicating low blood glucose)

Epinephrine (signaling the need to fight or flight

Epinephrine increases glycogen breakdown and glycolysis.

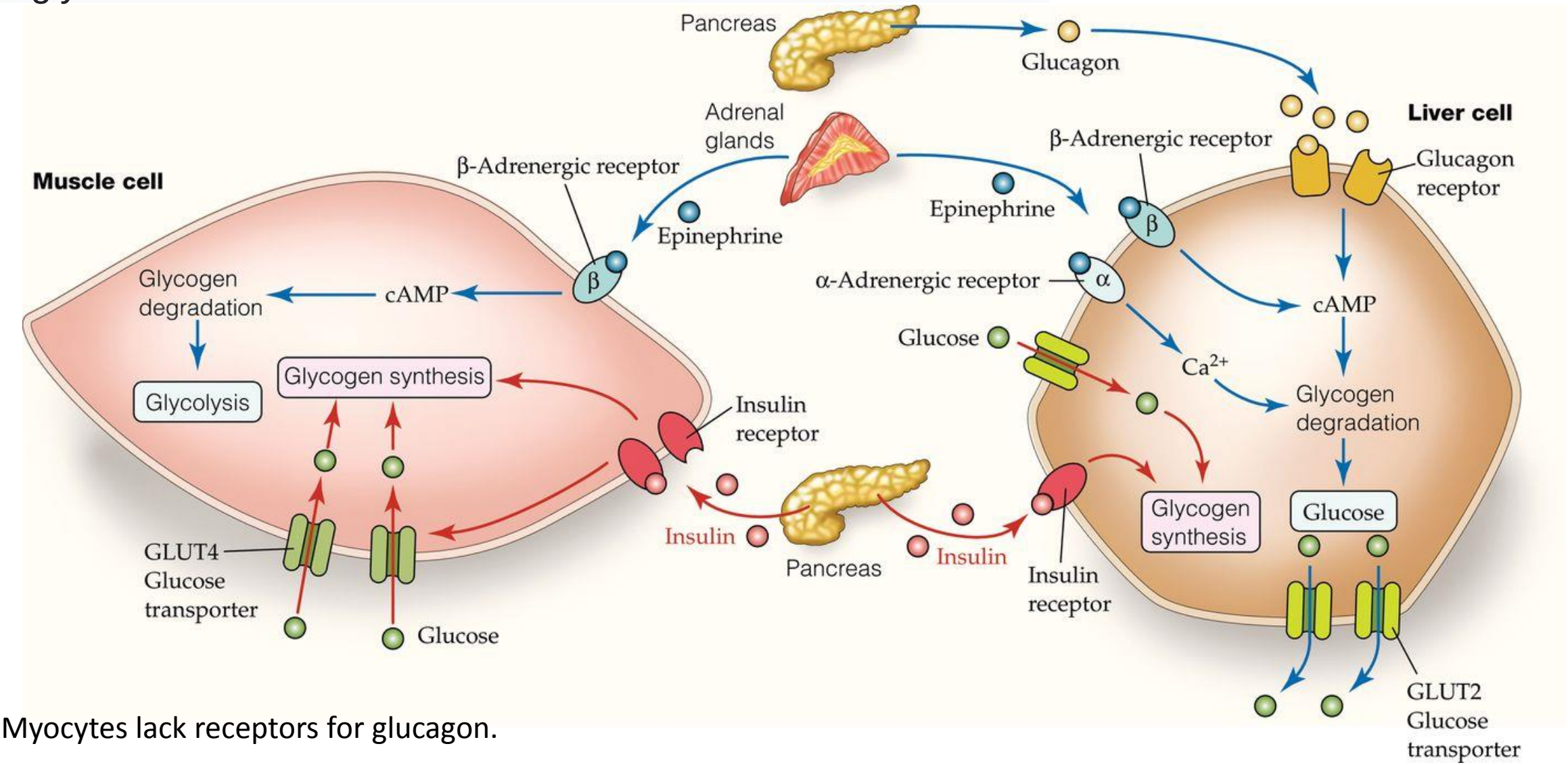


has the effect of maximizing the output of glucose into the bloodstream.

which together provide fuel to produce the ATP needed for muscle contraction

Hormonal Control of Glycogen Metabolism

Hyperglycemic hormon: GLUCAGON and Ephinephrine
Hypoglycemics: INSULIN



Myocytes lack receptors for glucagon.