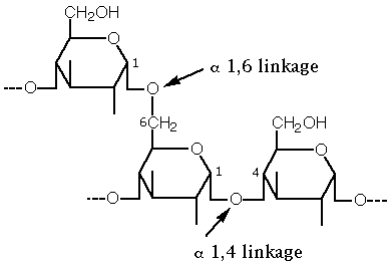
Glycogenesis

Glycogen is the storage form of glucose in animals and humans which is analogous to the starch in plants. Glycogen is synthesized and stored mainly in the liver and the muscles.



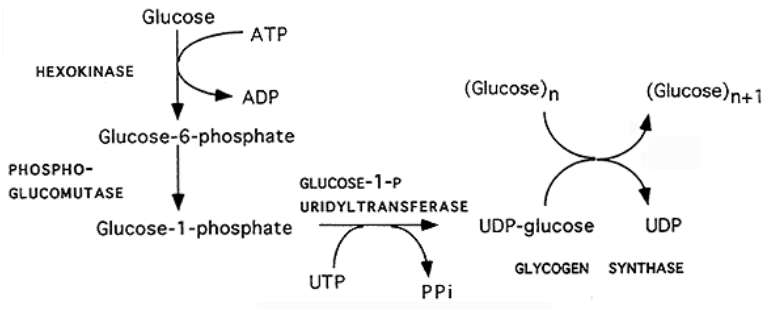
Structurally, glycogen is very similar to amylopectin with alpha acetal linkages, however, it has even more branching and more glucose units are present than in amylopectin. Various samples of glycogen have been measured at 1,700-600,000 units of glucose.
The structure of glycogen consists of long polymer chains of glucose units connected by an **alpha acetal** linkage. All of the monomer units are alpha-D-glucose, and all the alpha acetal links connect C # 1 of one glucose to C # 4 of the next glucose.
The branches are formed by linking C # 1 to a C # 6 through acetal linkages. In glycogen, the branches occur at intervals of 8-10 glucose units (in amylopectin the branches are separated by 12-20 glucose units).
Carbon # 1 is called the anomeric carbon and is the center of an acetal functional group.
The Alpha position is defined as the ether oxygen being on the opposite side of the ring as the C # 6. In the chair structure this results in a downward projection.

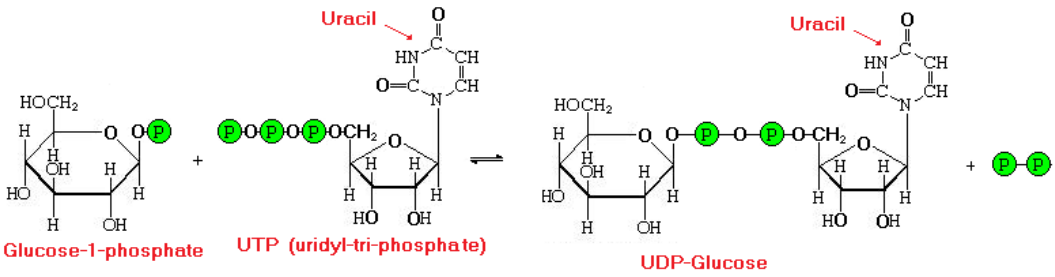
Plants make starch and cellulose through the photosynthesis processes. Animals and human in turn eat plant materials and products. Digestion is a process of hydrolysis where the starch is broken ultimately into the various monosaccharides. A major product is of course glucose which can be used immediately for metabolism to make energy. The glucose that is not used immediately is converted in the liver and muscles into glycogen for storage by the process of glycogenesis. Any glucose in excess of the needs for energy and storage as glycogen is converted to fat.

Glycogenesis is the name of the process of glycogen synthesis, in which glucose molecules are added to chains of glycogen for storage.
This process is activated:

- during rest periods following the Cori cycle, in the liver,
- by insulin in response to high glucose levels, for example after a carbohydrate-containing meal.

As we saw in glycolysis, Glucose is converted into glucose-6-phosphate by the action of glucokinase or hexokinase.
After that, Glucose-6-phosphate is converted into glucose-1-phosphate by the action of phosphoglucomutase. Here glycolysis and glycogenesis diverge.
In the latter, Glucose-1-phosphate is converted into UDP-glucose by the action of UTP through enzyme UDP-glucose phosphorylase.
In this reaction, Pyrophosphate is formed, which is later hydrolysed by pyrophosphatase into two phosphate molecules. This hydrolysis is highly exergonic, which drives the over-all reaction forward.





Glycogenin is the first enzyme involved in converting UDP-glucose to glycogen. It acts as a primer, by polymerizing the first few glucose molecules.
Glycogenin has a tyrosine residue on each subunit that serves as the anchor for the reducing end of glycogen. Initially, about eight UDP-glucose molecules are added to each tyrosine residue by glycogenin, forming α(1→4) bonds.

Once a chain of eight glucose monomers is formed, glycogen synthase binds to the growing glycogen chain and adds UDP-glucose to the 4-hydroxyl group of the glucosyl residue on the non-reducing end of the glycogen chain, forming more α(1→4) bonds in the process.

Branches are made by glycogen branching enzyme (also known as amylo-α(1:4)→α(1:6)transglycosylase), which transfers the end of the chain onto an earlier part via α-1:6 glycosidic bond, forming branches, which further grow by addition of more α-1:4 glycosidic units.
Branching is very important for glycogenolysys rate. Glucose can be removed from non-reducing ends only. On a linear chain, we have only one non-reducing ends, but on a branched chain we have a lot - one on every branch. Branching allows simultaneous release of glucose, increasing glycogenolysis rate.

Glycogenolysis

Glycogenolysis is the breakdown of glycogen (n) to glucose-1-phosphate and glycogen (n-1).
Glycogen branches are catabolized by the sequential removal of glucose monomers via phosphorolysis, by the enzyme glycogen phosphorylase.

The overall reaction for the breakdown of glycogen to glucose-1-phosphate is:

$$\text{Glycogen}_{\text{(n residues)}} + P_i \rightleftharpoons \text{Glycogen}_{\text{(n-1 residues)}} + \text{Glucose-1-phosphate}$$

Here, glycogen phosphorylase cleaves the bond linking a terminal glucose residue to a glycogen branch by substitution of a phosphoryl group for the α[1→4] linkage.
Glucose-1-phosphate is converted to glucose-6-phosphate by the enzyme phosphoglucomutase.

Glucose residues are phosphorolysed from branches of glycogen until four residues before a glucose that is branched with a α[1→6] linkage. Glycogen debranching enzyme then transfers three of the remaining four glucose units to the end of another glycogen branch.
This exposes the α[1→6] branching point, which is hydrolysed by α[1→6] glucosidase, removing the final glucose residue of the branch as a molecule of glucose and eliminating the branch. This is the only case in which a glycogen metabolite is not glucose-1-phosphate. The glucose is subsequently phosphorylated to glucose-6-phosphate by hexokinase.

Glycogenolysis takes place in the cells of the muscle and liver tissues in response to hormonal and neural signals. In particular, glycogenolysis plays an important role in the fight-or-flight response and the regulation of glucose levels in the blood.

In myocytes (muscle cells), glycogen degradation serves to provide an immediate source of glucose-6-phosphate for glycolysis, to provide energy for muscle contraction.
In hepatocytes (liver cells), the main purpose of the breakdown of glycogen is for the release of glucose into the bloodstream for uptake by other cells.

Hormonal Control

Adrenaline

Glycogenesis and glycogenolysis respond to hormonal control.
One of the main forms of control is the varied phosphorylation of the two dedicated enzymes, glycogen synthase and glycogen phosphorylase.
Glycogen phosphorylase is activated by phosphorylation, whereas glycogen synthase is inhibited.
The hormone adrenaline (or Epinephrine) acts heavily on this mechanism during the fight-or-flight response.
Glycogen phosphorylase is converted from a less active "b" form to an active "a" form by the enzyme phosphorylase kinase.
This latter enzyme is itself activated by protein kinase A and deactivated by phosphoprotein phosphatase-1.
Protein kinase A itself is activated by adrenaline.
It binds to a receptor protein that activates adenylate cyclase.
The latter enzyme causes the formation of cyclic AMP from ATP; two molecules of cyclic AMP bind to the regulatory subunit of protein kinase A, which activates it allowing the catalytic subunit of protein kinase A to dissociate from the assembly and to phosphorylate other proteins.

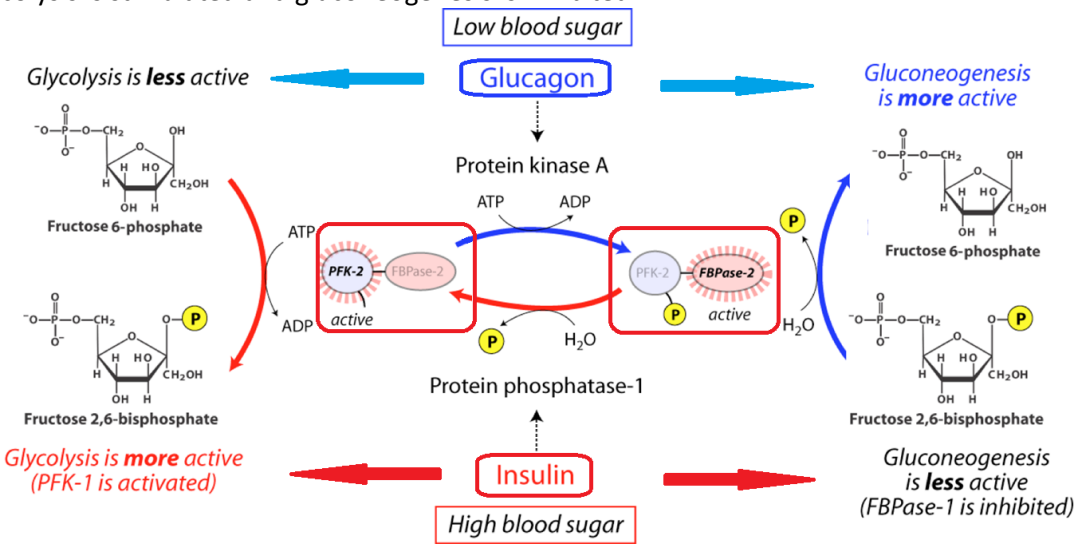
Returning to glycogen phosphorylase, the less active "b" form can itself be activated without the conformational change. 5'AMP acts as an allosteric activator, whereas ATP is an inhibitor, as already seen with phosphofructokinase control, helping to change the rate of flux in response to energy demand.
Epinephrine not only activates glycogen phosphorylase but also inhibits glycogen synthase. This amplifies the effect of activating glycogen phosphorylase. This inhibition is achieved by a similar mechanism. This is known as co-ordinate reciprocal control.

Glucagon and insulin

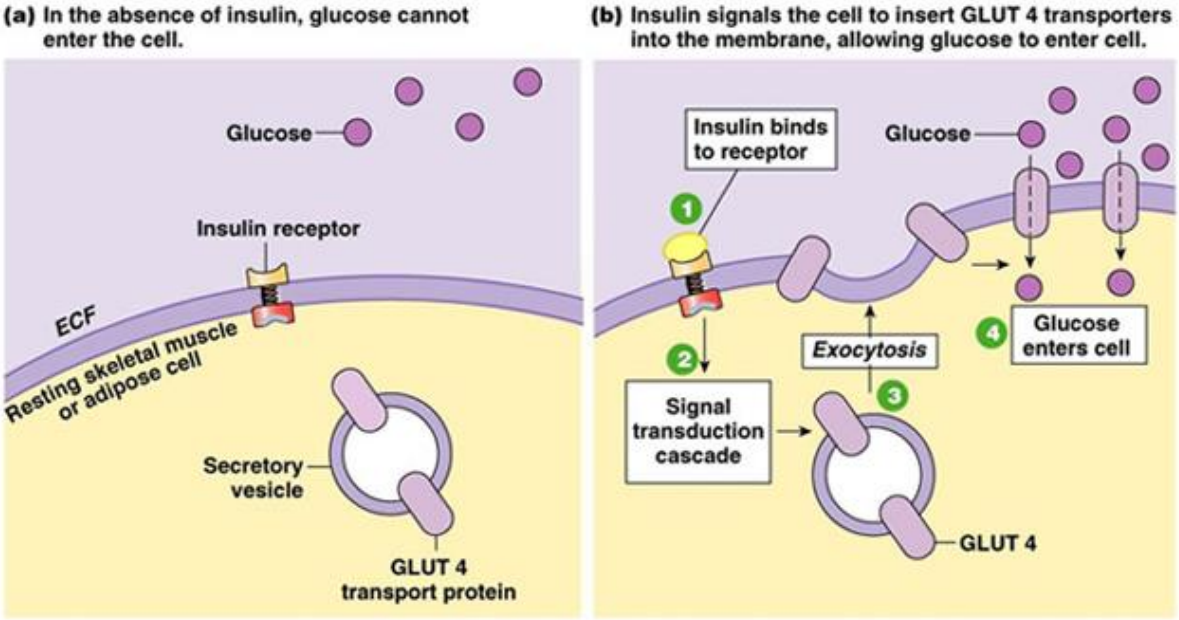
Glycogenolysis and glycogenesis are regulated hormonally in response to blood sugar levels too. The regulation is performed by glucagon and insulin.
Phosphofructokinase 2 (**PFK2**) and **fructose bisphosphatase 2** (**FBPase2**) are the enzymes responsible for regulating the rates of glycolysis and gluconeogenesis in the human body.
They are indeed a single enzyme, a homodimer of 55 kDa with each polypeptide chain consisting of independent kinase and phosphatase domain. When Ser-32 of the bifunctional protein is phosphorylated, the negative charge causes the conformation change of the enzyme to favor the FBPase2 activity; otherwise, PFK2 activity is favoured.

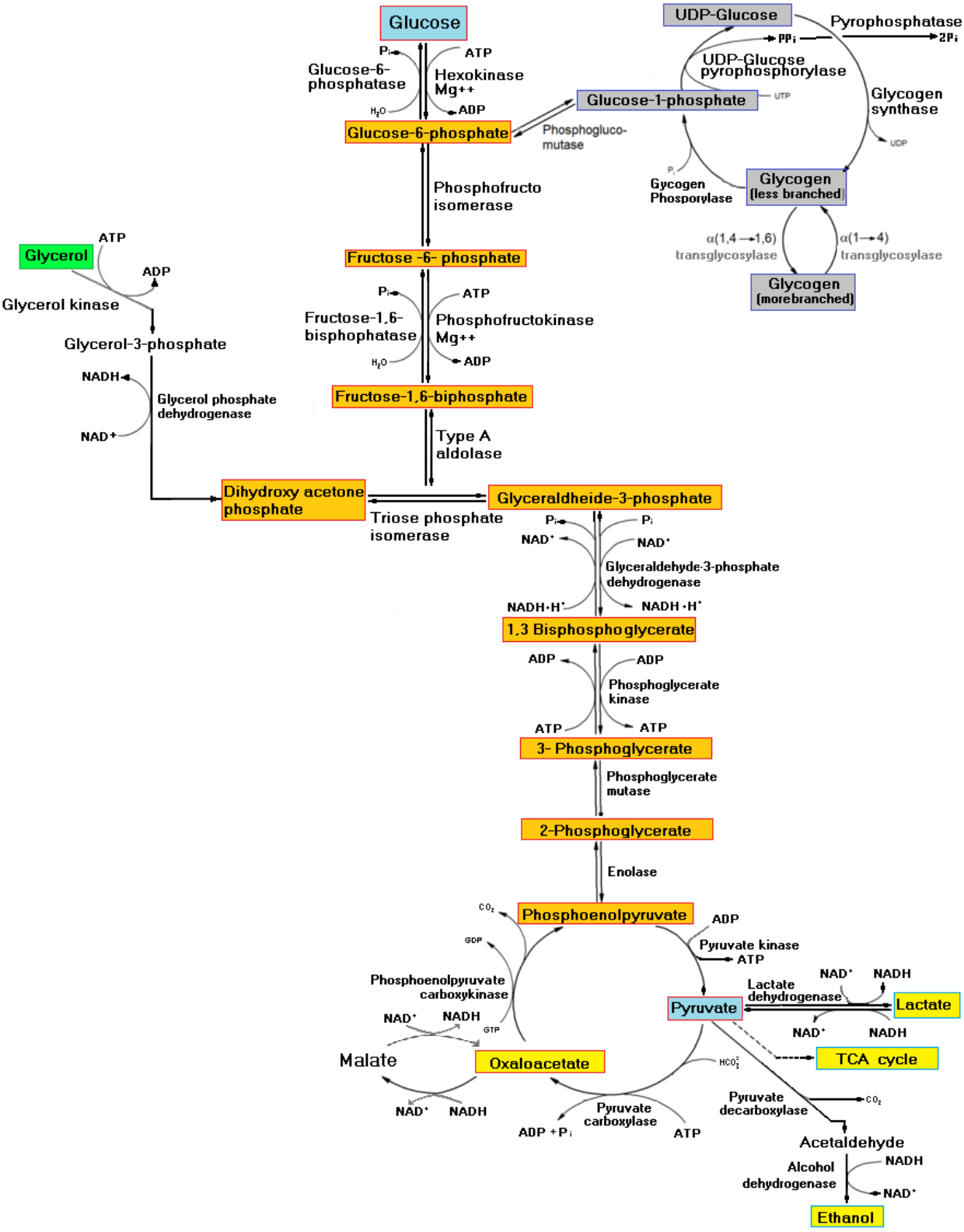
When glucose level is low, glucagon is released into the bloodstream, triggering a cAMP signal cascade. The PFK-2 domain of the bifunctional enzyme is inactivated via phosphorylation (however this does not occur in skeletal muscle).
The F-2,6-BPase domain is then activated which lowers fructose 2,6-bisphosphate (F-2,6-BP) levels. Because F-2,6-BP normally stimulates phosphofructokinase-1(PFK1), the decrease in its concentration leads to the inhibition of glycolysis and the stimulation of gluconeogenesis.
On the other hand, when the glucose level increases, the level of fructose 6-phosphate (F6P) subsequently rises and the molecule stimulates phosphoprotein phosphatase-1, which removes phosphoryl group from

the bifunctional protein. So PFK2 domain is activated and the kinase catalyzes the formation of F-2,6-BP. Thus, glycolysis is stimulated and gluconeogenesis is inhibited.



Il **fruttosio 2,6-bisfosfato** è una molecola zuccherina che pur non essendo un composto intermedio del metabolismo di carboidrati ne regola finemente le dinamiche. Il glucagone che segnala bassi livelli di glucosio nel sangue abbassa i livelli di concentrazione di fruttosio 2,6-bisfosfato nel fegato rallentando il consumo di glucosio e stimolando la gluconeogenesi.
Il fruttosio 2,6-bisfosfato si forma da una piccola parte di fruttosio 6-fosfato prodotto nella glicolisi e sottratto grazie all'azione di un enzima bifunzionale ad attività chinasica, *fosfofruttochinasi 2*, PFK 2, e ad attività fosfatasica, *fruttosio 2,6-bisfosfatasi*, FBPasi 2, che hanno ciascuno effetto inverso all'altro.
In condizioni d'ipoglicemia viene prodotto il glucagone che, interagendo con un recettore transmembrana, induce l'attivazione dell'enzima adenilato ciclasi che catalizza la formazione del cAMP. Il cAMP attiva la protein-chinasi A che trasferisce il gruppo fosfato dall'ATP al gruppo –OH della Ser-32 del PFK 2/FBPasi 2. Fosforilando l'enzima se ne blocca l'attività fosfofruttochinasica e attiva l'azione fruttobifosfatasica.
In questo modo il glucagone abbassa la concentrazione cellulare di fruttosio 2,6-bisfosfato e inibisce la glicolisi favorendo la gluconeogenesi, poiché oltre ad essere un inibitore della fosfofruttochinasi è un potente attivatore della fruttosio-1,6-bisfosfatasi, un enzima coinvolto in una delle tre reazioni che distinguono la via della gluconeogenesi, appunto, dalla via glicolitica.




Glucose
Glucose-6-phosphatase
Hexokinase Mg++
ATP
ADP
Glucose-6-phosphate
Phosphogluco-mutase
Glucose-1-phosphate
UDP-Glucose
Pyrophosphatase
UDP-Glucose pyrophosphorylase
Glycogen synthase
Glycogen Phosporylase
Glycogen (less branched
α(1,4→1,6) transglycosylase
α(1→4) transglycosylase
Glycogen (morebranched)
Phosphofructo isomerase
Fructose -6- phosphate
Fructose-1,6-bisphophatase
Phosphofructokinase Mg++
Fructose-1,6-biphosphate
Type A aldolase
Glycerol
Glycerol kinase
Glycerol-3-phosphate
Glycerol phosphate dehydrogenase
NADH
NAD+
Dihydroxy acetone phosphate
Triose phosphate isomerase
Glyceraldheide-3-phosphate
Glyceraldehyde-3-phosphate dehydrogenase
1,3 Bisphosphoglycerate
Phosphoglycerate kinase
3- Phosphoglycerate
Phosphoglycerate mutase
2-Phosphoglycerate
Enolase
Phosphoenolpyruvate
Pyruvate kinase
Phosphoenolpyruvate carboxykinase
GDP
GTP
Pyruvate
Lactate dehydrogenase
Lactate
TCA cycle
Malate
Oxaloacetate
Pyruvate carboxylase
Pyruvate decarboxylase
Acetaldehyde
Alcohol dehydrogenase
Ethanol