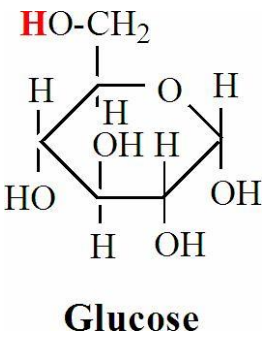
# Glycogen Synthesis

As previously explained, considerable research attention in the exercise and clinical sciences has been devoted to understanding glycogen metabolism. The rationale for this is clear in both disciplines areas, as muscle glycogen is a large determinant of endurance exercise performance and capacity, while muscle and liver glycogen are highly important for understanding metabolic changes causing and in response to type-II diabetes. For the athlete, being able to replenish muscle and liver glycogen is terribly important for performance during the next training bout, or in preparation for a competitive event. For the patient suffering from type-II diabetes, their cells have difficulty getting glucose from the blood and must rely more on fatty acid catabolism for cellular energy. This compromises their capacity to sustain more intense exercise training, which is a large problem given that quality (more intense) exercise is a means to rehabilitate from type-II diabetes.



Glucose

The chemical reactions involved in **glycogen** synthesis are the same in all cells, however, different tissues can have different substrates leading to the glucose used to form glucose-1-phosphate. In this Topic, I will focus on skeletal muscle and liver glycogen synthesis.

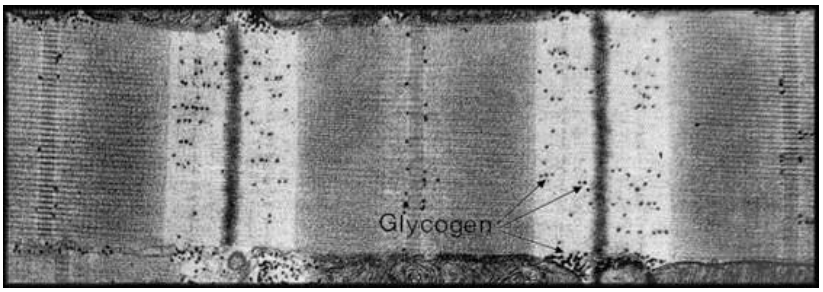


**Figure 1. An electron micrograph of muscle glycogen granules distributed throughout numerous intracellular regions of the muscle fiber.**

***Skeletal Muscle***

Figure 1 provides an electron micrograph of the location of glycogen within the skeletal muscle fiber. Note the widespread distribution of glycogen as dark stained granules, **glycogen granules**, throughout the cytosol, and more specifically, between the contractile proteins of the sarcomere, throughout the myofibrilar spaces and surrounding mitochondria.

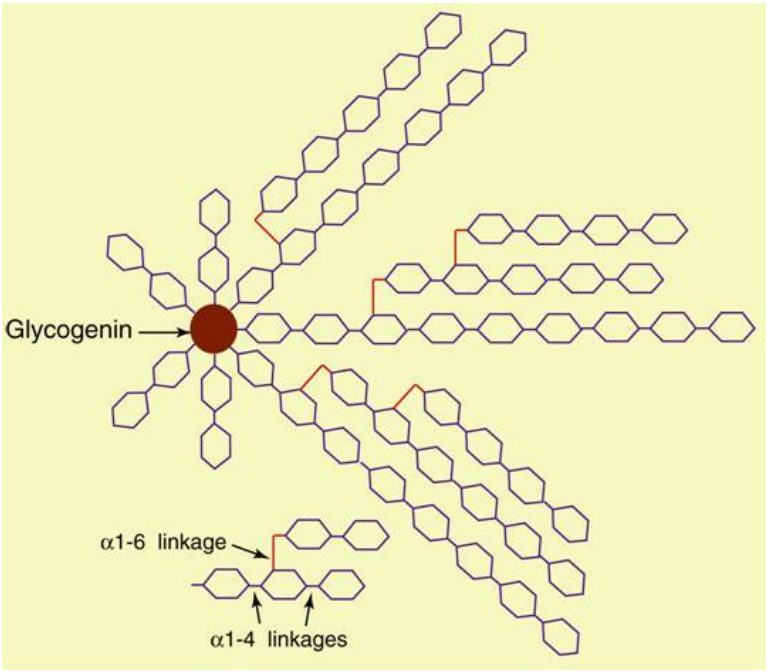


**Figure 2. The structure of glycogen.**

Figure 2 presents a schematic of the glycogen structure. Based on your study of glycogenolysis, you should now be aware that

muscle glycogen is the predominant source of fuel for glycolysis during moderate to high intensity exercise. Clearly, in order to repeat moderate to high intensity exercise again and again, during sports and athletics, as well as train or perform again on a daily basis, muscle must replenish this glycogen store. This is the importance of muscle glycogen synthesis.

It would be very convenient if muscle could reverse glycolysis, and use lactate and glycolytic intermediates to reform glycogen as these accumulate in muscle during intense exercise. However, muscle does not have the needed enzymes to convert the triose-phosphate, pyruvate or lactate intermediates of glycolysis back into glucose. These alternate enzyme catalyzed reactions are needed to divert the reactions of glycolysis that have such a highly negative ΔG that no alteration of substrate and product concentrations can reverse this directionality. Despite there being some research evidence of carbons from lactate appearing in muscle glycogen, the enzymology data for muscle is clear in showing deficient enzymes necessary to reverse phases I and II of glycolysis. These reactions are detailed in the Topic on Gluconeogenesis. However, note that for glycolytic intermediates preceding **fructose-1,6-bisphosphate**, these reactions are readily reversible. The bottom line is that muscle is heavily reliant on blood glucose to support glycogen synthesis. Figure 3 presents the source of substrate and the individual reactions in the formation of UDP-glucose, the final substrate for muscle glycogen synthesis. Figure 4 reveals the glycogen synthase reaction.

As discussed in the Topic on macronutrient structure, glycogen consists of alpha 1-4 and alpha 1-6 carbon linkages between glucose molecules. The regulation of the enzyme **phosphorylase** was discussed in detail in the Topic on **Glycogenolysis**, and revealed that this was a highly exergonic reaction that was allosterically regulated. Clearly, another enzyme is needed to catalyze the addition of glucose residues to glycogen during glycogen synthesis. This enzyme is called **glycogen synthase** (also known as glycogen synthetase) and is also an allosterically regulated enzyme. Figure 5 summarizes this regulation, as well as the opposing regulation of phosphorylase, which of course, must be regulated to be inactive to prevent a futile cycle of opposing glycogen breakdown. Note the role of the hormone **epinephrine** in this regulation. Remember from the content presented in the Section on Neuroendocrinology that epinephrine increases during exercise, and is responsible for the increase in the intracellular second messenger cyclic AMP (cAMP). The cAMP in turn stimulates the activity of certain enzymes that phosphorylate phosphorylase to activate the enzyme, and phosphorylate glycogen synthase to inhibit the enzyme.

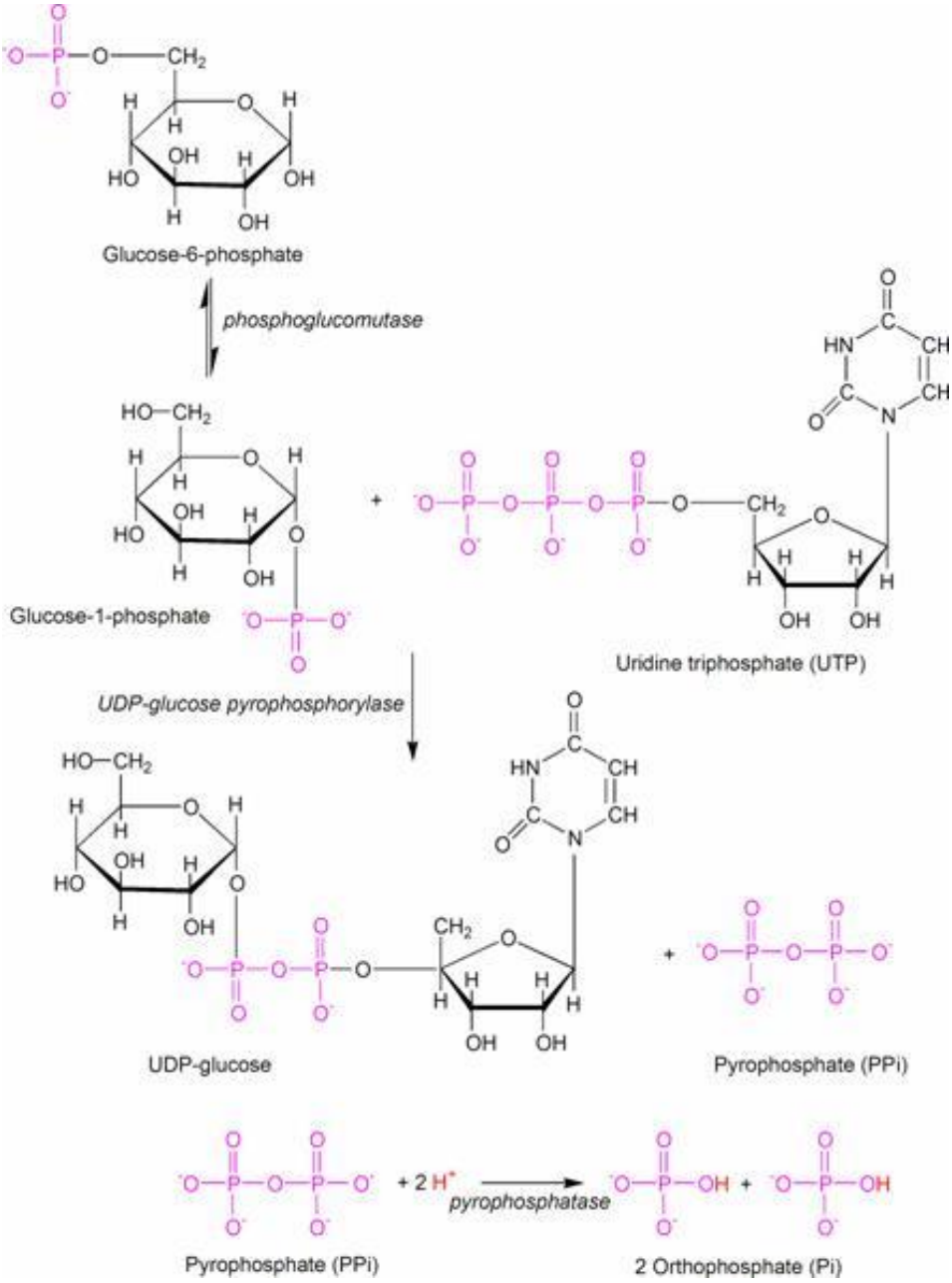



**Figure 3. A schematic of the reactions involved in the production of UDP-glucose.**

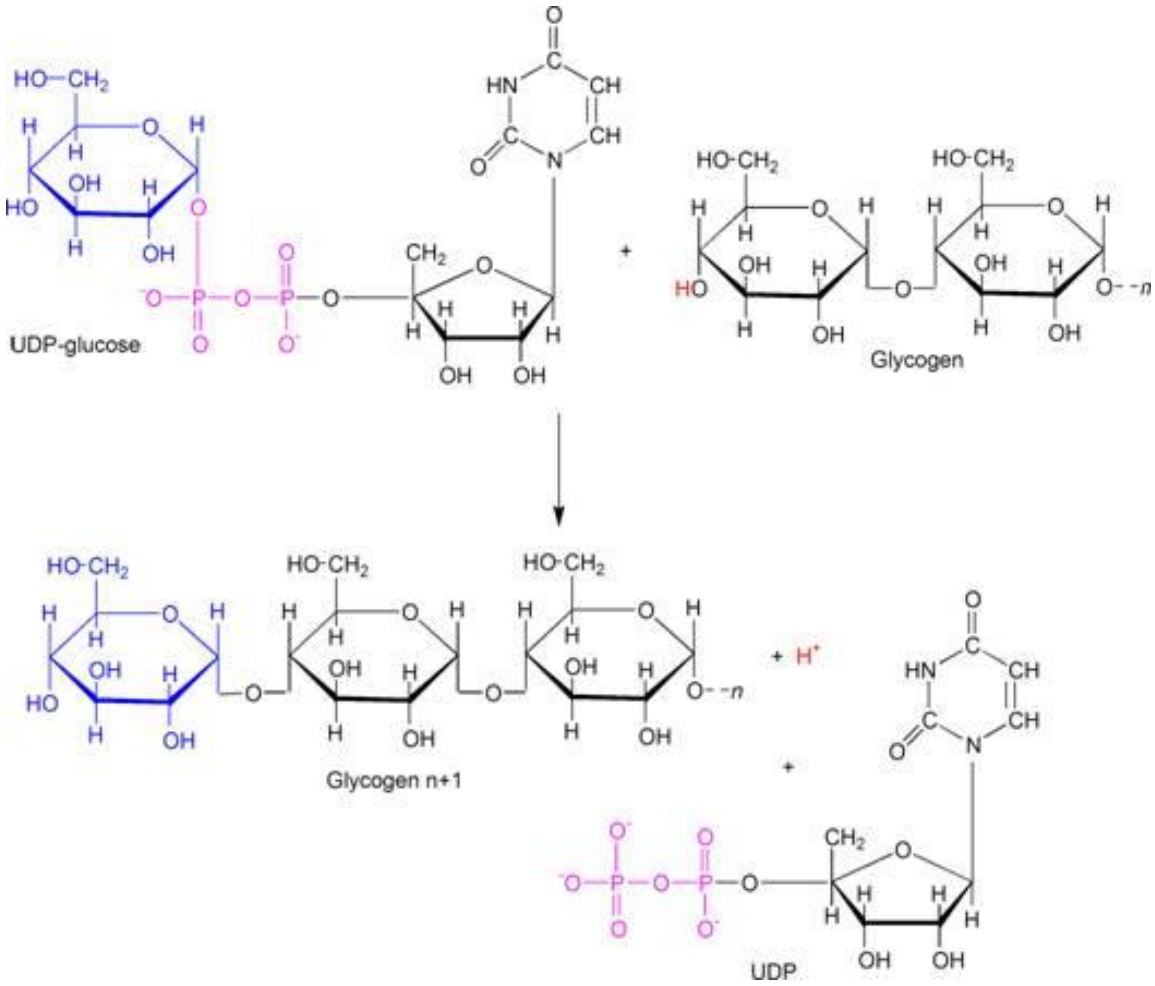



**Figure 4. The glycogen synthase reaction.**

During post-exercise or pre-exercise conditions, as well as during and after feeding, epinephrine concentrations in blood are low, and conversely, insulin concentrations are higher after a meal that contains carbohydrate due to increases in blood glucose. The increases in blood glucose and insulin stimulate activity of glycogen synthase by causing the removal of the phosphate group on enzyme. The same phosphate removal also occurs with phosphorylase, which decreases its activity (Figure 5). The ample supply of blood glucose and the now active enzyme support glycogen synthesis.

Another activator of glycogen synthase is glucose-6-phosphate (G6P). The muscle concentration of G6P increases when muscle is inactive and when there is increased muscle glucose uptake via the **GLUT4 glucose transporters** (Figure 6). Of course, insulin increases muscle glucose uptake, but is not necessary to cause glucose uptake, as the GLUT4 transporters are also responsive to prior exercise, with a response that can last for as long as 12 hours. Nevertheless, the post-exercise uptake of glucose into muscle is highest immediately post exercise due to a combination of higher muscle

blood flow and therefore higher glucose supply so long as simple carbohydrate is ingested during or immediately after exercise.

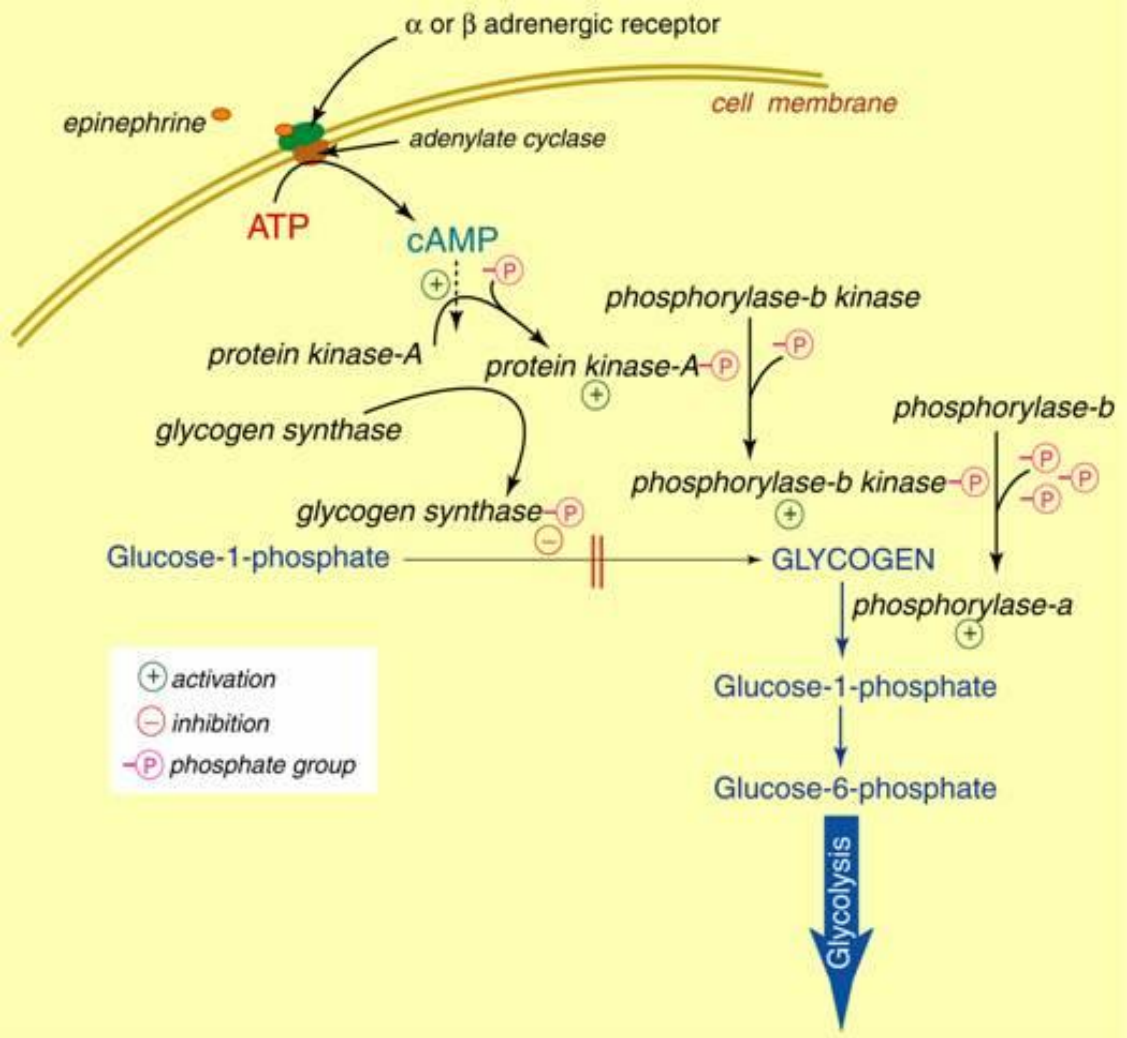



**Figure 5. Summary of the phosphorylation/dephosphorylation regulation of both phosphorylase and glycogen synthase.**

The activators and inhibitors of the substrates and products of the reactions of glycogen synthase are presented in Table 1. The inhibitors of glycogen synthetase comprise ATP, AMP, ADP, **UDP** and Pi. The inactive, phosphorylated structure of glycogen synthase is termed **glycogen synthase-D**. The unphosphorylated structure is termed **glycogen synthase-I**. The "D" and "I" abbreviations are based on a dependence (D) and independence (I) of activity to the muscle **G6P** concentration. Higher concentrations of G6P (> 0.1 mmol/kg) stimulate activity of the D-form, with greater G6P concentrations causing greater activity. Furthermore, due to multiple phosphorylation sites on glycogen synthase, the more phosphorylated the D-structure, the less the activity for a given G6P concentration. The I-form, which is completely dephosphorylated, is independent of G6P for activity. The **adenylate** molecules (ATP,

ADP, AMP) are not that influential as inhibitors as their absolute concentrations are well regulated to be nearly constant in muscle during rest conditions. Thus, the most important regulators of glycogen synthase are phosphorylation/dephosphorylation and the muscle G6P concentration.

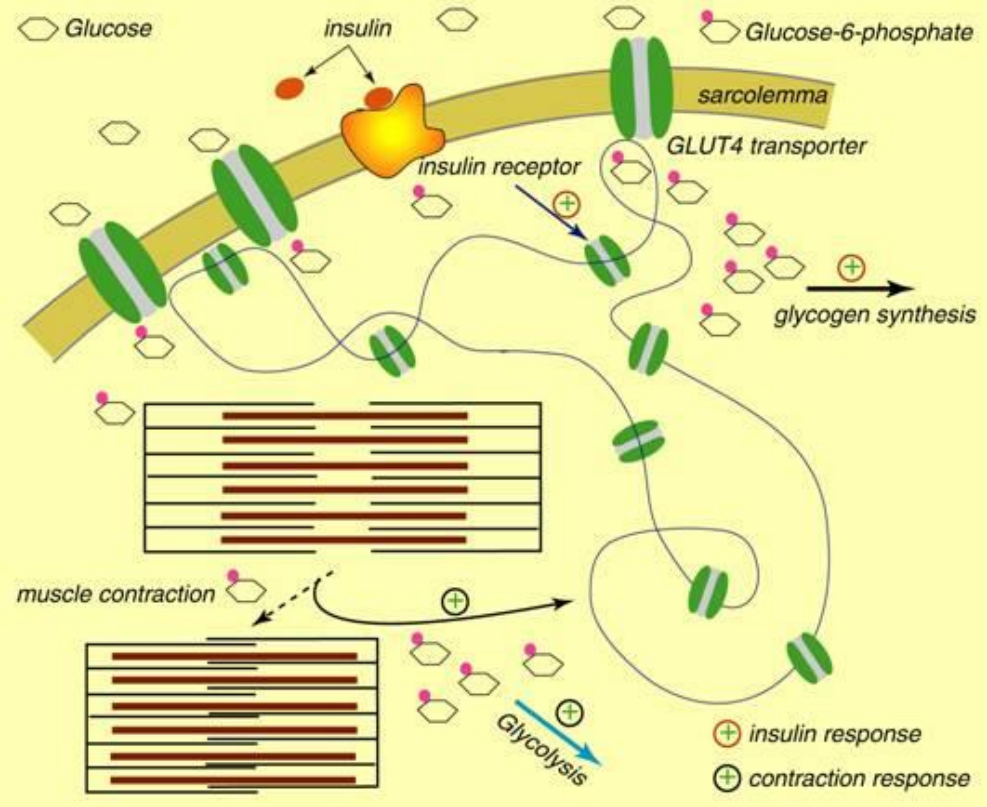



**Figure 6. Schematic showing the roles of insulin and muscle contraction in increasing the density of GLUT4 glucose transporters on the sarcolemma of skeletal muscle, thereby increasing glucose uptake.**

**Table 1. The enzyme activators and inhibitors of the reactions of glycogen synthesis.**

| Reaction | Enzyme | Inhibitors | Activators |
|---|---|---|---|
| Glucose + ATP → G6P + ADP<br>G6P → G1P<br>G1P + UTP → UDP-glucose + PPi<br>UDP-glucose + $Glycogen_n$ → $Glycogen^{n+1}$ | **Hexokinase**<br>**Phosphoglucomutase**<br>**Glycogen synthase** | **G6P**<br><br>**Phosphorylation**<br>**ATP**<br><br>**AMP**<br>**ADP**<br>**UDP**<br>Pi | <br><br>Dephosphorylation<br>G6P |

### *The Importance of Glycogenin*

**Glycogenin** is the protein core, or **primer**, of glycogen that also has enzymatic activity through a **glucosyltransferase** component enzyme (Figure 7). Glycogenin also contains glycogen synthase, but this connection is non-covalent. You can interpret glycogenin as the starting point for a glycogen granule. As such, each separate

glycogen granule exists due to the presence of a separate glycogenin complex that initiated the synthesis of the granule. The glucosyltransferase component enzyme is extremely important to initiate glycogen synthesis, as glycogen synthase cannot add glucose residues to glycogenin until there are at least 8 glucose residues connected via $\alpha$1-4 linkages. Hence, this is the role of the glucosyltransferase activity. This enzyme attaches glucose residues to glycogenin until this 8 residue chain is achieved, after which glycogen synthase takes over in glycogen synthesis, as described in the next sub-section.

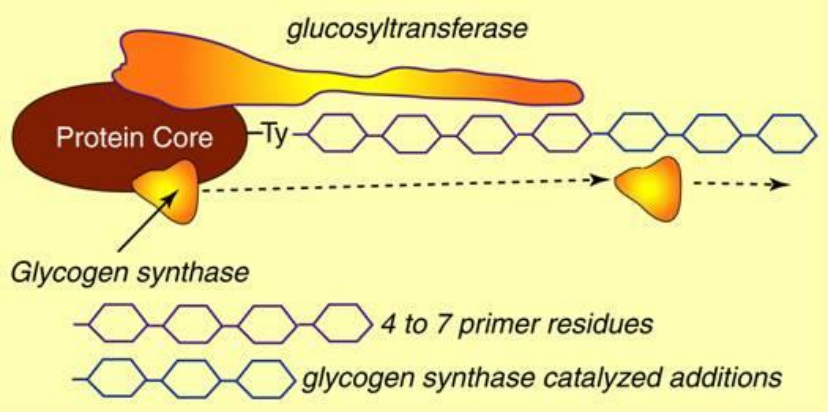



**Figure 7. Schematic of the glycogenin complex, consisting of the protein core, glucosyltransferase component enzyme, glycogen synthase, and the initiation glucose residues needed to commence glycogen synthesis from the glycogen synthase and glycogen-branching enzyme reactions.**

Recent research on the molecular biology of glycogenin genetic expression and related protein synthesis has shown that it is highly influential in determining the muscle capacity for glycogen storage. For example, during post-exercise conditions that favor glycogen synthesis, there is increased glycogenin **mRNA** and it is believed that muscle contraction stimulates this genetic regulation. There is also an as yet undiscovered regulation between the muscle store of glycogen and this glycogenin mRNA expression, as muscle glycogenin activity (proportional to glycogenin content) increases after exercise and lowered muscle glycogen stores (Figure 8) until a set-point of maximal glycogenin content and activity is reached. This sets the maximal density of glycogenin in muscle, which then in combination with the maximal size of each glycogen granule, determines the maximal capacity of muscle glycogen, or the glycogen content of any tissue. Research is

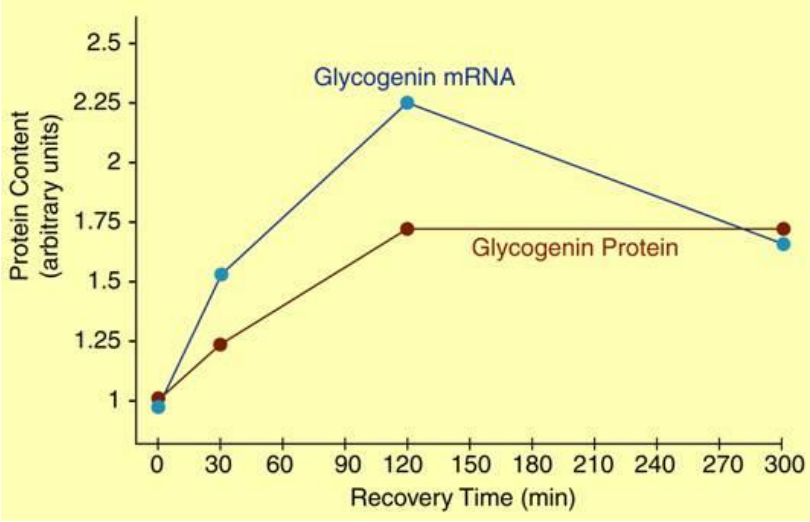



**Figure 8. The increased activity of glycogenin and muscle content of glycogenin mRNA after exercise at 75% $VO_2$max to exhaustion, followed by 5 x 30s sprints at Watts at $VO_2$max. Carbohydrate ingestion occurred at 75 g/hr immediately post-exercise. *Adapted from Shearer J et al. Am J Physiol Endocrinol Metab. 2005;289:E508-E514.***

ongoing to determine what signals such maximal capacities for a given tissue. It is interesting in this regard to note that exercise training increases the maximal capacity of muscle glycogen (Figure 9), so whatever the mechanism(s), they are responsive to exercise training.

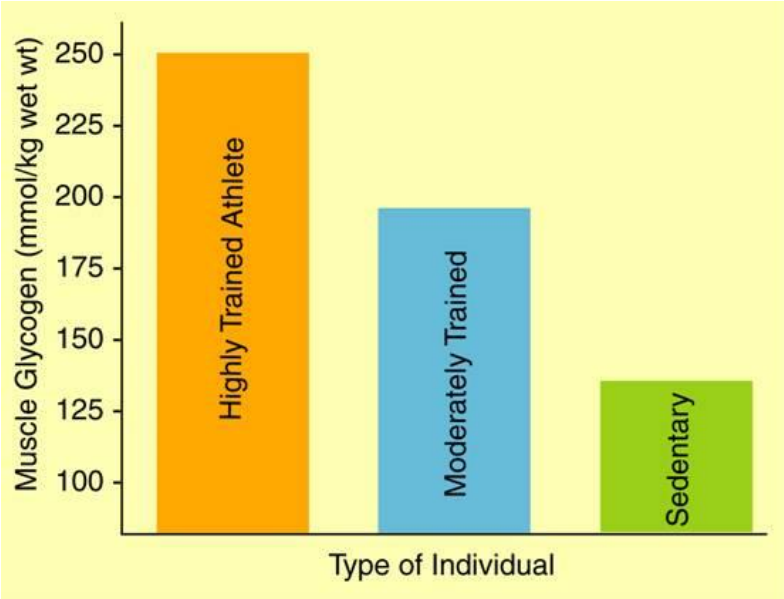



**Figure 9. Differences between muscle glycogen concentrations for subjects of different fitness. Muscle glycogen stores are equally high for trained endurance and strength/power athletes.**

***Reactions of Glycogen Synthesis***

Given that we now understand the cellular conditions necessary to support glycogen synthesis, what are the reactions that form this pathway? The total reactions and chemical structures involved in muscle glycogen synthesis are presented in Figures 3, 4.

For glycogen synthase to add new glucose residues to an alpha-1-4 chain, there must be at least 4 residues present. As synthase cannot add residues to an alpha-1-6 linkage, this is accomplished by the **glycogen-branching enzyme**, which transfers 6 or 7 residues from a chain of at least 11 to a C-6 hydroxyl group, forming the alpha-1-6 linkage. The branched structure of glycogen allows for increased glucose residue binding to the growing glycogen particle. However, there are limits to the size of the glycogen particle, but as yet there is no clear biochemical explanation for such a size restriction. As previously explained, current research evidence indicates that the muscle glycogen store is determined by the expression of glycogenin.

***Liver***

The synthesis of glycogen in the liver occurs from a different source of glucose substrate. As previously stated, muscle glycogen synthesis is heavily reliant on blood glucose and hence a dietary supply of glucose. In contrast, the liver only absorbs glucose from the blood in the post-absorptive state, when blood glucose concentrations are increased. During normal blood glucose conditions (normoglycemic), liver glycogen synthesis is fueled by gluconeogenic precursors such as lactate, amino acid carbon skeletons, and glycerol. These aspects of metabolism will be addressed in the Topic on gluconeogenesis.

# Glycogen Synthesis

## Glossary Words

**glycogen** is the storage form of glucose in cells.

**glycogen granules** are dark stained circular structures of glycogen as seen through electron microscopy.

**fructose-1,6-bisphosphate** is the six carbon product of the phopshofructokinase reaction.

**phosphorylase** is the allosterically regulated enzyme responsible for the catabolism of glycogen.

**glycogenolysis** is the term given for the breakdown/catabolism of glycogen to glucose-1-phosphate (G1P).

**glycogen synthase** is the allosterically regulated enzyme that catalyzes the synthesis of glycogen from UDP-glucose.

**epinephrine** is a catecholamine hormone secreted from the adrenal medulla.

**GLUT4 glucose transporters** are the transport protein sub-class that is responsible for glucose uptake into numerous tissues such as skeletal muscle and the liver.

**UDP** is the abbreviation for uridine diphosphate.

**glycogen synthase-D** is the dependent form of glycogen synthase, which requires G6P for increased activity.
**glycogen synthase-I** is the independent form of glycogen synthase, resulting from the multiple phosphorylation of synthetase-D.

**G6P** is the abbreviation for glucose-6-ohosphate.

**adenylate** pertains to the adenylate base, often used to reference the adenylate phosphates of the phosphagen system, such as ATP, ADP, and AMP.

**glycogenin** is the protein structural core of each glycogen molecule.

**primer** is a chemical compound that provides the structural base or framework for additional synthesis reactions.

**glucosyltransferase** is the enzyme responsible for the addition of glucose residues on a growing chain until 8 residues are located, after which glycogen synthase can exert its function.

# Glycogen Synthesis

**mRNA** is the abbreviation for ribonucleic acid, produced from the process of transcription within the cell nucleus.

**glycogen-branching enzyme** is the enzyme necessary to add the alpha-1-6 linkages necessary to induce the branched structure of glycogen.