

# Highlights of Glycogen Metabolism II

In the notes below, I refer to Glycogen Phosphorylase a as GP<sub>a</sub> and Glycogen Phosphorylase b as GP<sub>b</sub>. I also refer to Glycogen Synthase a as GS<sub>a</sub> and Glycogen Synthase b as GS<sub>b</sub>. You are welcome to do the same.

1. Glycogen phosphorylase is present in two covalently different forms, GP<sub>a</sub> and GP<sub>b</sub>. They differ in phosphorylation. GP<sub>a</sub> is phosphorylated and GP<sub>b</sub> is not. GP<sub>b</sub> is converted into GP<sub>a</sub> by phosphorylation at two sites. Covalent modifications are DIFFERENT from allosteric controls, which interconvert the R and T states of BOTH GP<sub>a</sub> and GP<sub>b</sub>.

2. The different glycogen phosphorylase forms have different allosteric regulation, as well. GP<sub>b</sub> is converted to the R state by AMP and converted to the T state by ATP and G6P. The latter two are more commonly abundant in the cell than AMP, so we think of GP<sub>b</sub> as less active. GP<sub>a</sub> is converted to the T state by glucose (rarely present much). When glucose is absent, GP<sub>a</sub> is automatically in the R state. Thus, we think of GP<sub>a</sub> as the more active form.

3. Phosphorylation of GP<sub>b</sub> to make GP<sub>a</sub> is catalyzed by an enzyme known as phosphorylase kinase. Full activation of phosphorylase kinase requires both calcium ions and phosphorylation by protein kinase A

4. Thus, the binding of epinephrine to the cell surface stimulates the following events in muscle relating to glycogen breakdown

- A. Epinephrine binds receptor
- B. Receptor activates a G protein to bind GTP
- C. Alpha subunit of G protein activates adenylate cyclase
- D. Adenylate cyclase catalyzes formation of cAMP
- E. cAMP activates protein kinase A
- F. Protein kinase A phosphorylates phosphorylase kinase, activating it.
- G. Phosphorylase kinase phosphorylates GP<sub>b</sub>, converting it to GP<sub>a</sub>
- H. GP<sub>a</sub> breaks down glycogen to yield G1P

5. Glycogen synthase (catalyzes formation of glycogen) exists in two different covalent forms - GS<sub>a</sub> (has no phosphate and is the most active) and GS<sub>b</sub> (has phosphate and is the least active).

6. Thus, binding of epinephrine or glucagon to a cell surface receptor ultimately results in the phosphorylation of GP<sub>b</sub> and GS<sub>a</sub> to make GP<sub>a</sub> and GS<sub>b</sub>, respectively. The products of these phosphorylations - GP<sub>a</sub> and GS<sub>b</sub> have opposite activities. GP<sub>a</sub> is MORE ACTIVE and GS<sub>b</sub> is LESS ACTIVE. Thus, reciprocal regulation of glycogen metabolism is mediated through phosphorylation and dephosphorylation. The conversion of R and T states occurs allosterically.

7. Reversal of the process (removal of the phosphates of all of the phosphorylated enzymes) occurs as the result of catalysis by phosphoprotein phosphatase (PP-1). PP-1 is stimulated to be

active by insulin. Thus, increasing glucose concentration in the bloodstream causes insulin to be released, which causes cells to take up glucose and also (inside the cell) to cause the glucose to be made into glycogen. I'll talk more next time about how PP-1 is regulated.