Biochemistry 401 Lecture 24
Today we're going to talk about the regulation of glycogen metabolism. We're going to discuss both local signals and global signals that affect glycogen metabolism.

Now if you'll recall, glycogen catabolism is catalyzed by the enzyme glycogen phosphorylase, and this is one of the primary sites of regulation for this pathway.

The glycogen phosphorylase enzyme is shown here. It is a homodimer that is allosterically regulated. One of the subunits of this dimer is shown in yellow and the other one is shown in white. Now this enzyme is generally found attached right to glycogen. But its activity is dictated by its phosphorylation state and also by the presence or the absence of noncovalent allosteric regulators.

Now glycogen phosphorylase enzyme exists in two different states, a tense state and a relaxed state. The tense state is less active and the relaxed state is more active. Now the thing is the enzyme shifts back and forth between the tense state and the relaxed state, but different factors can shift the equilibrium between the tense and the relaxed state to favor either one or the other conformation. Now in the tense state, the active site for the enzyme is partially blocked by an alpha helix that extends into the active site. When the enzyme is phosphorylated, this helix is kept out of the way, and so the enzyme is more apt to be relaxed When phosphorylated, glycogen phosphorylase is known as *phosphorylase a* and in this phosphorylation state, the enzyme is more apt to be in the relaxed state, whereas when glycogen is not phosphorylated it's known as *phosphorylase b,* and in this state, the enzyme is more apt to be in the tense state and we can see this in the figure. Now this figure is little complex but let me walk you through it. In the upper panel, we see *phosphorylase b* and *phosphorylase a*, both of which are in the relaxed state and in the bottom of the diagram we see glycogen *phosphorylase b* and *a* when they're in the tense state. Now if you look at the length of the arrows that lie between *phosphorylase b* in the relaxed state and in the tense state, you can see that arrows indicate that *phosphorylase b* is most often in the tense state, and in this state the alpha-helices extend into the active site, and so *phosphorylase b* is more often tense and more often inactive. In *phosphorylase a* on the other hand, the arrows are shown to favor the relaxed state. And so when glycogen phosphorylase is phosphorylated, the conformation exists such that it favors the relaxed state, and in the relaxed state, glycogen

phosphorylase is more active. As we shall see in a minute, the phosphorylation of glycogen phosphorylase occurs in response to global signals. And so to recap, when glycogen *phosphorylase b* becomes phosphorylated, it is known as glycogen *phosphorylase a*. Glycogen *phosphorylase a* is more apt to be in the relaxed conformation, in which the active site is open and accessible. When glycogen *phosphorylase a* becomes dephosphorylated, it is known as *phosphorylase b*, and again, in this conformation, glycogen phosphorylase is more apt to be in the tense state, in which an alpha helix extends partially into the active site and so glycogen phosphorylase will be less active.

Now the phosphorylation of glycogen phosphorylase happens by way of glycogen phosphorylase kinase.

So far we know that glycogen phosphorylase is regulated by phosphorylation such that when phosphorylated, *phosphorylase b* is turned into *phosphorylase a,* which is the more active confirmation. But what phosphorylates this enzyme?

Well, that is phosphorylase kinase that is shown here. This is a homo-tetramer consisting of alpha, beta, gamma and delta subunits, four of each, and it's arranged in a molecule that looks like a butterfly. Now in this homo-tetramer the subunits have different functions. Gamma is catalytic, the alpha, beta, delta subunits are regulatory. The beta subunit is a phosphorylation site, and the delta subunit is a calmodulin homolog. It binds calcium. Both phosphorylation and calcium binding partially activate the kinase. However, when calcium is bound, and when the beta subunit is phosphorylated, phosphorylase kinase is maximally active. And so now we have two pieces of the puzzle. We know that glycogen *phosphorylase b* is activated when it's phosphorylated to become *phosphorylase a*, and we also know that this happens through phosphorylation through the action of phosphorylase kinase. We also know the phosphorylase kinase is activated by both phosphorylation and by calcium. So now what we need to know is what phosphorylates phosphorylase kinase, and also how is it that there's an increase in calcium in the cell?

This happens by two different methods, through global regulation and local regulation. In the global regulation in muscles, this phosphorylation occurs through the action of Protein Kinase A, PKA, and the local regulation occurs

through an increase in intracellular calcium, and this happens in response to nerve impulse and muscle contraction. When muscles contract, one of the things that happens is calcium is released from intracellular stores to allow this contraction to actually occur, and so muscles will have an increase in intracellular calcium when they're contracting, and let's face it, if your muscles are contracting, that means you're going to be burning energy and you're going to need glucose, and so this is a really good signal. In the liver, the global regulation is by phosphorylation through Protein Kinase A also, and also through an increase in intracellular calcium. So now we have another piece of the puzzle, but how is it that PKA becomes activated?

What about those global regulators?

Global regulation occurs through two different signals, epinephrine, which is also known as adrenaline and glucagon. Now, epinephrine is released from the adrenal glands that are shown here, in yellow. These glands sit on top of the kidneys and are about the size of a walnut. Epinephrine is released from cells that are found in the adrenal medulla. This is the central portion of the adrenal glands in response to a fight or flight mechanism that's initiated.

And so when do you release epinephrine? Well, you release epinephrine during the fight or flight response. This can be activated when you're really hungry or when you're really upset and afraid of something. So I don't know if you've experienced this, but sometimes when you have gone without food for a while, you can become agitated. You can see this in children quite often, because they become especially cranky when they're hungry, and this actually is the body's response to hunger. Your system is trying to get you moving so that you'll go and find food, and also when your glucose levels are low

glucagon will be released from the alpha islet cells in the pancreas and then glucagon can bind to its receptors and activate mobilization of glycogen stores.

So how is it that glucagon in the liver and epinephrine in the muscle and liver have an effect on glycogen breakdown? When these global signals bind to their receptors, they cause a conformational change to occur in the receptor such that the alpha subunit is released from the beta and gamma subunits, and the alpha