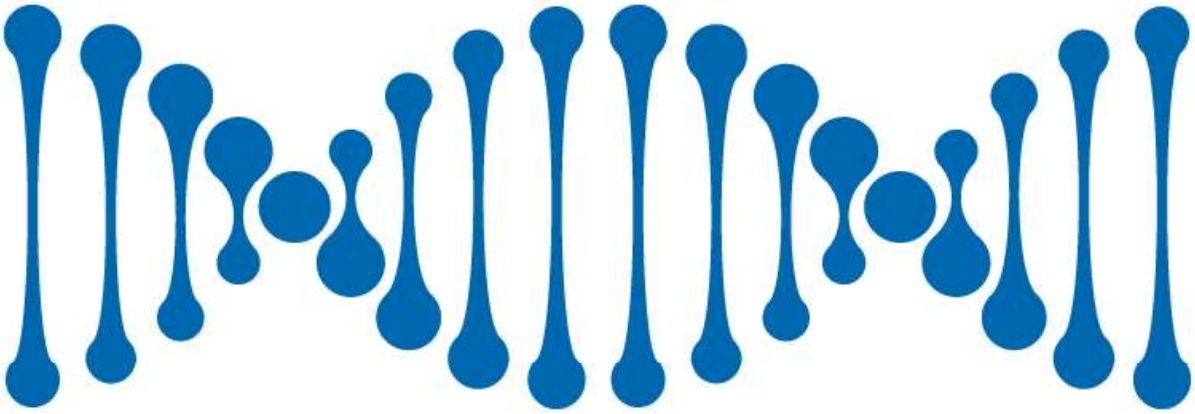

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Biochemistry and Molecular Biology (BCMB2X01)

Course Notes

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University of Sydney
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Contents

an early intermediate in the Krebs cycle, which inhibits it. Therefore, when the Krebs cycle is working too hard, glycolysis is slowed, and as a result, so too is the Krebs cycle.

Hexokinase catalyses the trapping of glucose inside the cell, producing glucose 6-phosphate. Glucose 6-phosphate itself inhibits hexokinase, preventing excessive trapping.

Pyruvate dehydrogenase (PDH) is another rate-limiting step, but is outside of glycolysis. When phosphorylated by PDH kinase, it is inactivated. When dephosphorylated by PDH phosphatase, it is activated. The total amount of enzyme doesn't change, just the ratio of activated to inactivated forms.

Overall, the rate-limiting steps are controlled by several factors, including availability of substrates, oxidative capacity, cofactor availability and AMP level.

Lecture 19: Fuel selection in early starvation: energy stores, glycogenolysis and lipolysis

Early starvation is defined as the start of the post-absorptive period, and is when there are no substrates coming in from the gut. Instead, stored fuel is used to maintain homeostasis.

The brain requires around 120 g of glucose each day to function normally, and no other forms of fuel can be used. Fatty acids cannot be converted into carbohydrates, and breaking down proteins is unfavourable. In addition to the brain, parts of the kidney, skin and red blood cells don't have mitochondria, and consequently rely on glucose to function. Other tissues, such as muscle, can switch to fatty acid oxidation during starvation.

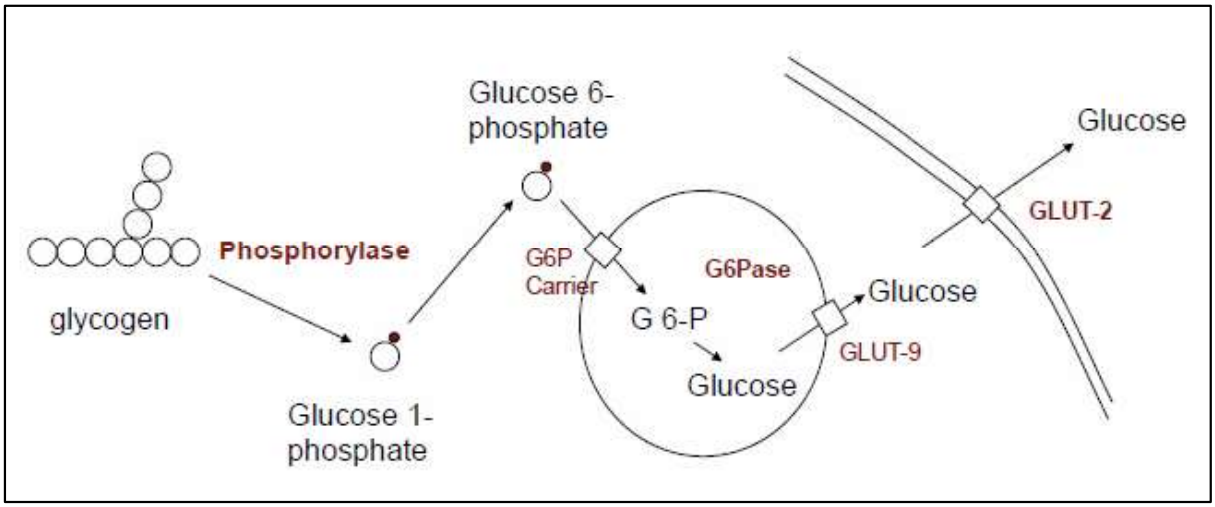
The general strategy during early starvation is:

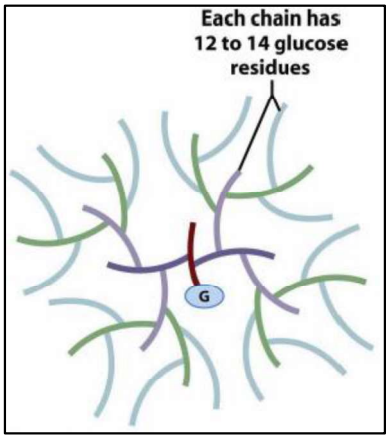
1. Glucose conservation – don't use it unless you need to.
2. Glucose recycling – don't fully oxidise it – regenerate it from lactate.
3. *De novo* glucose formation – make it from amino acids and glycerol.

During the first few hours of starvation, blood glucose concentration will fall rapidly. The liver will release glucose into the bloodstream to maintain euglycemia (around 4 Mm, equivalent to around 90 mg/dL). This process is referred to as glycogen mobilisation, or glycogenolysis.

Glycogenolysis is a multi-step procedure:

- Glycogen chains are converted to glucose 1-phosphate by phosphorylase.
- This cannot leave the liver cell, so it is converted to glucose 6-phosphate inside a vesicle.
- Glucose 6-phosphate is converted to glucose by glucose 6-phosphatase.
- GLUT-9 and GLUT-2 transporters rapidly equalise the concentration of glucose in the liver cell and the bloodstream.

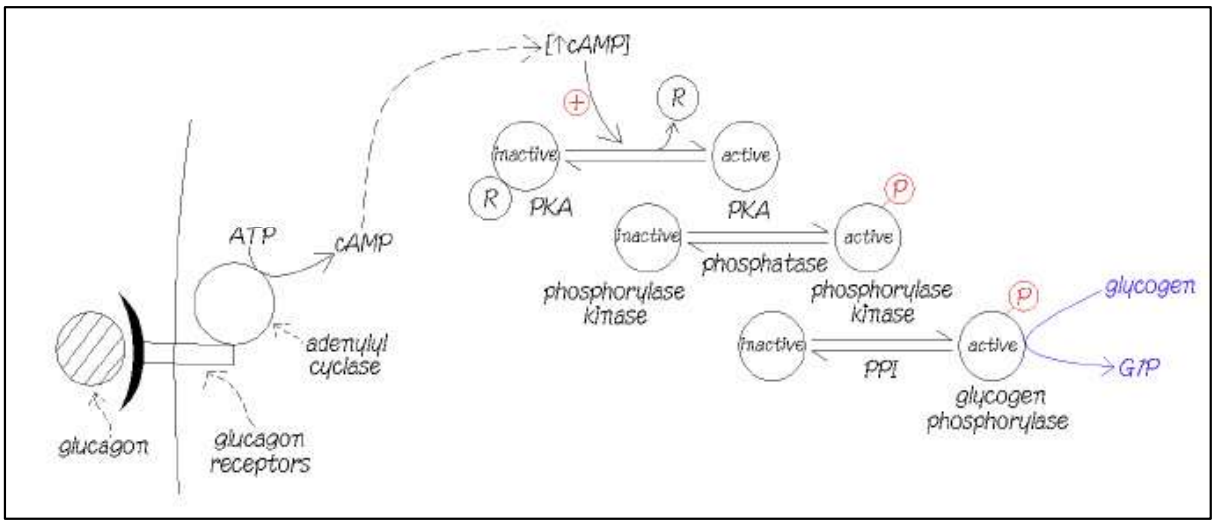




The conversion of glycogen to glucose 1-phosphate is the rate-limiting step of this reaction.

The structure of glycogen is pictured left. Note that since many side chains exist, phosphorylase can act on many parts of the glycogen molecule at once.

Phosphorylase is activated via a secondary messenger cascade pathway. When blood glucose concentration falls, alpha cells of the pancreas secrete glucagon hormone. This binds to receptors of the liver cell membrane. Adenyl cyclase then converts ATP into cAMP. cAMP preferentially binds to the inhibitory subunits on protein kinase A (PKA), therefore activating it. PKA phosphorylates phosphorylase kinase (PK), activating it. PK phosphorylates glycogen phosphorylase, activating it and the breakdown of glycogen. This is summarised in the diagram below.



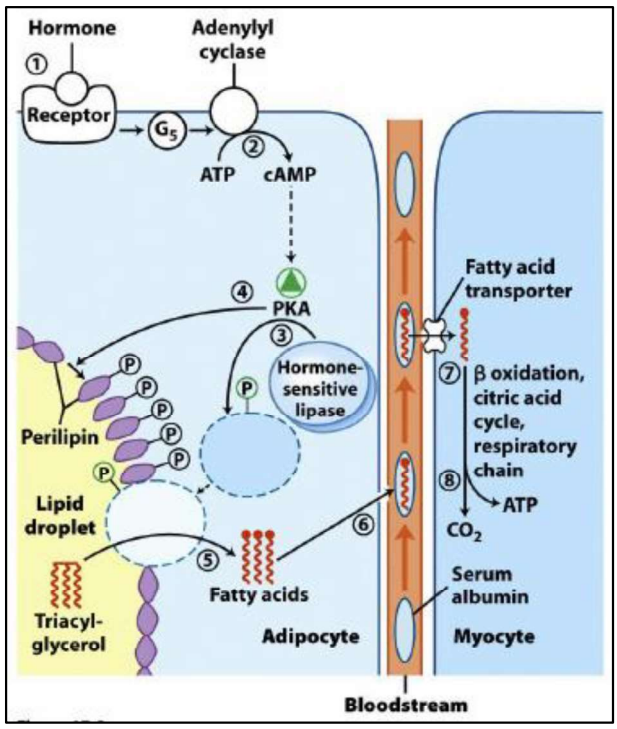
This activation pathway is very complicated to allow for a massive response from a small signal. This is because the concentrations of cAMP are in the pico- and nano-molar ranges. Additionally, each of the enzymes can be controlled by other factors, such as calcium and AMP.

This pathway also occurs in myocytes (muscle cells). However, the hormone stimulant is adrenaline instead of glucagon. The glycogen released goes into glycolysis instead of being released into the bloodstream.

As mentioned earlier, glycogen has many branch points. To get around this, phosphorylase requires a debranching enzyme. Around 1 in 10 glucose residues in glycogen have a branch point, and are released as neat glucose instead of glucose 1-phosphate.

The body has two major pools of glycogen. Around 100 g in the liver, and 150 g in the muscles. However, the muscles don't break down much glycogen during starvation, as they don't have glucagon receptors. Additionally, glucose 6-phosphatase is only found in the liver, and so glucose cannot be formed and released into the bloodstream. (Although, the 10% neat glucose residues from glycogenolysis may be transported into the bloodstream by GLUT-1 transporters.) Instead, glucose 6-phosphate must undergo glycolysis, be converted to lactate, and be recycled into glucose by the liver.

The 100 g of glucose stored in the liver will last less than 24 hours! The body must persuade other tissues to start using fat rather than glucose well before liver glycogen is depleted.



Glucagon also binds to receptors on the cell membrane of white adipose tissue. Like glycogenolysis, this stimulates an increase in cAMP concentration, activating protein kinase A. PKA then phosphorylates hormone-sensitive lipase, which breaks down fat, and perilipin, which allows lipase to interact with the fat. A lack of insulin also slows the degradation of cAMP, hence contributing to the pathway.

This is summarised in the diagram pictured left. Note that glycerol is also released into the bloodstream, but isn't pictured.

Now that fatty acids are present in the bloodstream, β-oxidation will occur, and the rise in acetyl-CoA will inhibit pyruvate dehydrogenase (PDH), hence preventing wasteful oxidation of glucose. GLUT-1 will continue to take up glucose, but it won't be oxidised past lactate. This is called the Cori-cycle: muscle glucose → pyruvate → lactate → (move to liver) → glucose (via gluconeogenesis). Gluconeogenesis can also use the glycerol released from white adipose tissue as a substrate.

Lecture 20: Fuel selection in later starvation: gluconeogenesis, proteolysis and ketone bodies