3. Regulation of metabolism by cell signalling in health and disease

Metabolism is a set of chemical processes that occur in living organisms in order to convert food to energy and biological building blocks (macromolecules), as well as to eliminate waste. In your studies, you might have learnt how adenosine triphosphate (ATP), cellular energetic currency, is produced during processes such as glycolysis and TCA cycle, and then used for synthesis of, for example, proteins. These all are complex, multi-step reactions that need to be tightly regulated in accordance with food availability and projected energy expenditure. The regulation is achieved via cell signalling, by relaying information from external and internal environment into the cells – this is mostly done by proteins.

Insulin signalling and diabetes

Insulin is a peptide (i.e. protein) hormone that affects metabolism in multiple ways across all tissues. Its main purpose is to decrease levels of glucose in the blood and promote its utilisation. It does so by signalling the cells to translocate the glucose transporter GLUT4 from intracellular vesicles onto plasma membrane, thereby increasing the permeability of the cell plasma membrane to glucose, so the sugar can be taken up from the bloodstream. Insulin also signals to cells to activate glycolysis, stimulate the production of glycogen in the liver and muscle, and enhance protein and lipid synthesis.

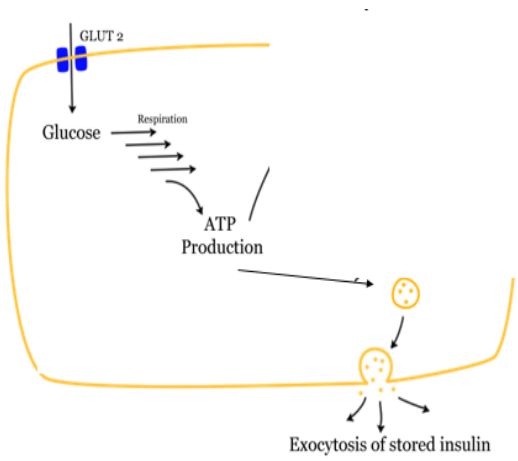

Figure 1. Glucose uptake by beta cells in the pancreas and release of insulin

Insulin is produced and released by beta-cells in the pancreas. These cells are very sensitive to blood glucose levels: glucose can be transported freely into beta cells by a dedicated transporter protein GLUT2. Inside the cell, glucose undergoes oxidation, producing ATP as a result of glycolysis and the TCA cycle. The increased levels of ATP act as a signal for the beta cell to fuse secretory vesicles with stored pro-insulin granules with the plasma membrane, releasing insulin into the bloodstream (Fig.1). In type 1 diabetes, beta-cells are destroyed, and the absence of insulin prevents glucose being taken up from the bloodstream into tissues. This results in sustained high levels of glucose in the blood, leading to complications in many organs – *see the "Type 1 Diabetes" resource for more details on symptoms and treatments*.

Once in circulation in the blood, insulin is recognised by insulin receptors on cell surfaces, e.g. on the cells of muscle and liver tissue, and the binding of an insulin molecule to its receptor on the plasma membrane triggers a signalling cascade

inside the cell. This intracellular signal transduction pathway is extremely complex, with a lot of crosstalk and feedback; scientists are still investigating components of this pathway, and what effect each of them have on different aspects of metabolism. It is particularly important for research into type 2 diabetes, one of the main features of which is insulin resistance. When this occurs, insulin still binds to its receptor. However, cells do not respond properly to the signal, and ultimately GLUT4 transporters do not reach the cell surface. Thus glucose cannot get into cells, leading to its prolonged accumulation in the bloodstream, as in the case of type 1 diabetes.

Further resources:

https://www.youtube.com/watch?v=W0KPwTy0W9k - A video illustration of the role of insulin in the context of different organs in the body, and how it is linked to type II diabetes and its symptoms

To learn more about what happens inside the cell when insulin binds to its receptor and how it results in more glucose uptake, take a look at this general video explanation of insulin signalling cascade: https://youtu.be/FkkK5lTmBYQ?t=86 (from 1:25)

AMP-activated kinase – cellular energy sensor

AMP activated kinase (AMPK) is one of the proteins that plays a central role in controlling the energetic balance of the cell. Its activity is regulated by the ratio of AMP (adenosine monophosphate) to ATP (adenosine triphosphate). The higher this ratio, the more active AMPK is. AMP is formed when ATP gets broken down to release energy, thus high levels of AMP indicate that the cell has used up a lot of ATP, i.e. a lot of energy (Fig. 2). Activated AMPK stimulates fatty acid oxidation as well as uptake of glucose from the blood by promoting GLUT4 translocation to the cell membrane, allowing the cell to get energy from these substrates and thus restore the ATP levels. AMPK can also switch the cell to “energy-saving mode” by inhibiting major biosynthetic pathways that would consume ATP.

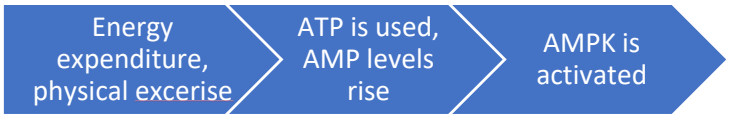

Figure 2. Link between energy consumption and AMPK activation

In skeletal muscle, AMPK is also activated by muscle fibre contraction. This is very likely to be the process that mediates the positive effect of physical exercise on decreasing blood glucose levels. Importantly, AMPK could also be activated pharmacologically. It is thought that the current first-line type 2 diabetes medication drug metformin (marketed under trade name Glucophage) acts by stimulating AMPK, which ultimately will promote glucose uptake from the blood independently of insulin (Fig. 3).

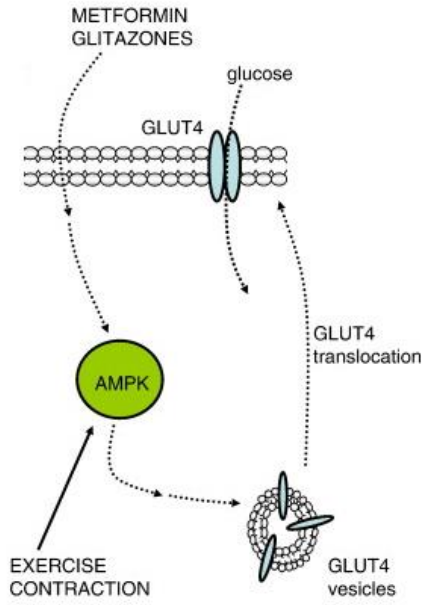

Figure 3. Both exercise and metformin stimulate glucose uptake from the blood via AMPK and GLUT4

Insulin vs AMPK

Complete the table below, indicating whether AMPK/Insulin activate (+) or inhibit (-) the following metabolic processes. Write out the main similarities and differences in terms of the overall metabolic goal(s) that these signalling molecules are "trying to achieve".

	AMPK	**Insulin**
Glucose uptake into the cells		
Glycolysis		
Glycogen synthesis		
Glycogen breakdown		
Lipid synthesis		
Lipid breakdown		
Protein synthesis		
Protein breakdown		
Mitochondrial biogenesis (production)		