Activity 3 – Understanding insulin resistance

Defining insulin sensitivity

Receptors for insulin are present on target cells where insulin normally acts. Insulin secreted by the pancreas is transported by the bloodstream to target organs, where it binds to insulin receptors. The ligand-receptor interaction triggers downstream signaling cascades, leading to effects summarized on the following site:
http://www.vivo.colostate.edu/hbooks/pathphys/endocrine/pancreas/insulin_phys.html
Recall that feeding stimulates insulin secretion – why are these processes important after feeding?
When 'normal' concentrations of insulin produce quantitatively-normal biological responses in the body, we say the patient is *insulin sensitive.*

Defining insulin resistance

When 'normal' concentrations of insulin produce 'smaller than normal' biological responses in the body (i.e. is not able to correct an elevated blood glucose adequately), the patient is said to be *insulin resistant*. Greater than normal amounts of insulin are then required to elicit a 'normal' response in the body. The concept of insulin resistance is important clinically, as it is also seen in patients with other hormonal and congenital disorders, not just in diabetes mellitus.
Insulin resistance can be estimated from levels of blood insulin (low) and corresponding blood glucose (high), which are usually measured when the patient is fasting. Alternatively, endocrinologists sometimes perform an "oral glucose tolerance test". Check out this link for more details:
http://www.diabetes.co.uk/oral-glucose-tolerance-test.html

Mechanisms of insulin resistance

How might someone develop insulin resistance? No one is quite sure of the answer yet, although a vast amount of research has been devoted to addressing this question. Some possible mechanisms are listed below. Many scientists agree that at least the first mechanism is important in the development of T2DM.

1. Interference with downstream signaling events: Interactions between insulin and its receptors on target cells should activate downstream signaling events in the cell. However, signaling molecules involved in these could be modified (e.g. by phosphorylation or dephosphorylation) or whole signaling pathways inhibited by the energy status of the target cell, presence of other metabolites or the activation of pathways with the opposing effects ('antagonistic' pathways). The following could potentially interfere with downstream signaling of insulin, leading to insulin resistance:

    - Fat stores, fat metabolites and fat hormones (adipokines) –

    - Over-activity or over-production of certain hormones whose actions oppose the functions of insulin, e.g. cortisol or testosterone

- Inherent problems with the ways target cells handle energy supply and demand, e.g. cells with deficiencies in certain mitochondrial functions may not be able to metabolise glucose in an appropriate way, even if an insulin signal is received at the cell surface.

2. Mutations in the insulin receptor itself, resulting in an inability to initiate downstream signaling events even after insulin binds to the receptor.

3. Side effects of medications:
    - Medications commonly prescribed for mental illness (schizophrenia, bipolar illness) and steroid medicines prescribed for asthma and other inflammatory conditions, can oppose the effects of insulin

4. Inflammation in the body: rare infections (congenital rubella and cytomegalovirus), rare immune-mediated disorders (autoimmune diseases of the central nervous system) are known to lead to insulin resistance, but operate through unknown mechanisms