**Q8 Outline the physiological consequences of an inability to produce insulin (Sept 2010)**

Insulin is a 51 amino acid hormone (MW 5734 D) consisting of two chains ($\alpha$ and $\beta$) made in the pancreatic beta cells as a folded protein. It is released in response to blood glucose levels > 5mmol/L.

Actions:

- Acts by binding to the insulin receptors ($\alpha$ and $\beta$ subunits) on the surface of target cells, causing a shape change which results in the phosphorylation of several proteins within the cell, which modulate the activity of several processes. Insulin is anabolic, increasing the storage of glucose, fatty acids, and amino acids.

Roles:

CHO →

- Stimulates GLUT 4 receptors to move to the surface of muscle and adipose tissue cells to increase glucose uptake (this does not happen in RBC, brain tissue, intestinal mucosal cells or renal tubule cells).
- Upregulates Glycogen Synthase to increase glycogen production
- Upregulates glucokinase in hepatocytes to trap glucose in cells by phosphorylating it
- Decreases gluconeogenesis and glycogenolysis (by inhibiting glucose-6-phosphatase)

Proteins →

- Upregulates amino acid uptake, enhances protein synthesis, and inhibits protein degradation in muscle and other tissues, thereby decreasing the plasma concentrations of most amino acids

Lipids →

- Upregulates Pyruvate Dehydrogenase, Lipoprotein Lipase and Fatty Acid Synthase to facilitate the breakdown of TAGs to fatty acids for uptake by adipose tissue cells
- Inhibits Hormone Sensitive lipase to decrease the hydrolysis of triglycerides stored in the adipocyte

Inability to produce insulin will therefore result in:

- Hyperglycaemia (but relative intracellular hypoglycaemia, as glucose is unable to enter cells)
- Loss of inhibition of gluconeogenesis from proteins and adipose tissue
- Reduction in protein synthesis and TAG synthesis
- Utilisation of fatty acids as an alternative fuel source →
    - Adipose tissue is broken down to FFA via Hormone Sensitive lipase (which is no longer inhibited by insulin), and Acetyl CoA produced from the FFA.
    - Acetyl CoA can enter the Krebs cycle or be transported to the liver for ketone body production via beta oxidation (acetoacetate, beta-hydroxybutyrate and acetone)
    - Ketone bodies are distributed to the tissues, converted back to Acetyl CoA and used as fuel
    - The presence of high levels of ketone bodies results in a metabolic acidosis → produces 'air hunger' and Kussmaul breathing in an attempt to compensate for this acidosis
- Acidosis produces hyperkalaemia (the lack of insulin-induced K entry to cells also contributes)
- Increase in plasma free fatty acids and amino acids
- Hyperglycaemia exceeds the renal tract's ability to reabsorb glucose and a glycosuria occurs along with an osmotic diuresis of the large, osmotically active glucose molecule
- Patient becomes hypovolaemic and hyponatremic due to loss of Na through the renal tract