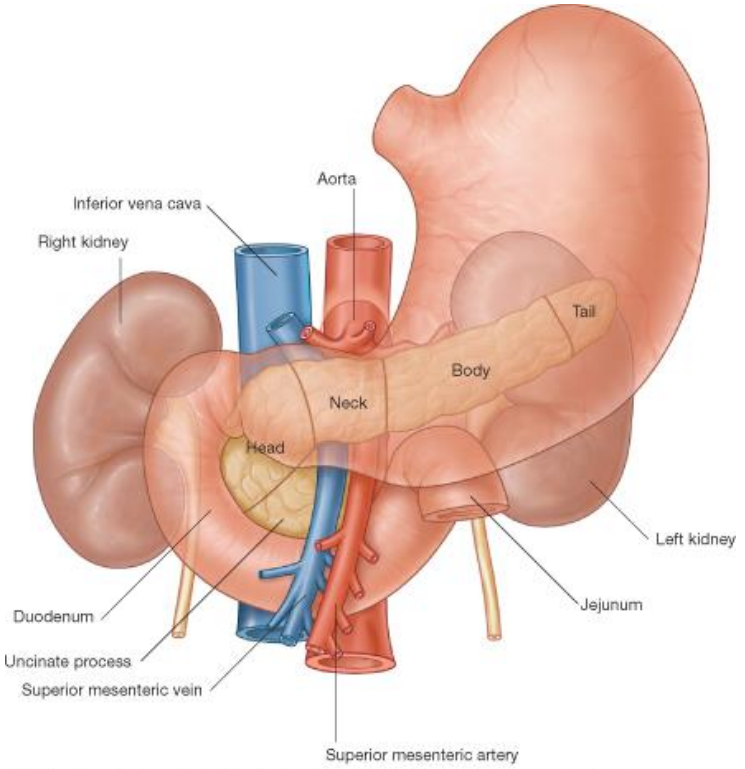
Metabolism module

The endocrine pancreas

Pancreas

- Large organ
- Inferior and anterior to stomach
- Mostly an exocrine gland
  - Digestive secretions
- But also contains Islets of Langerhans
- Which are endocrine glands
  - About 1million in the pancreas



Hormones of the endocrine pancreas

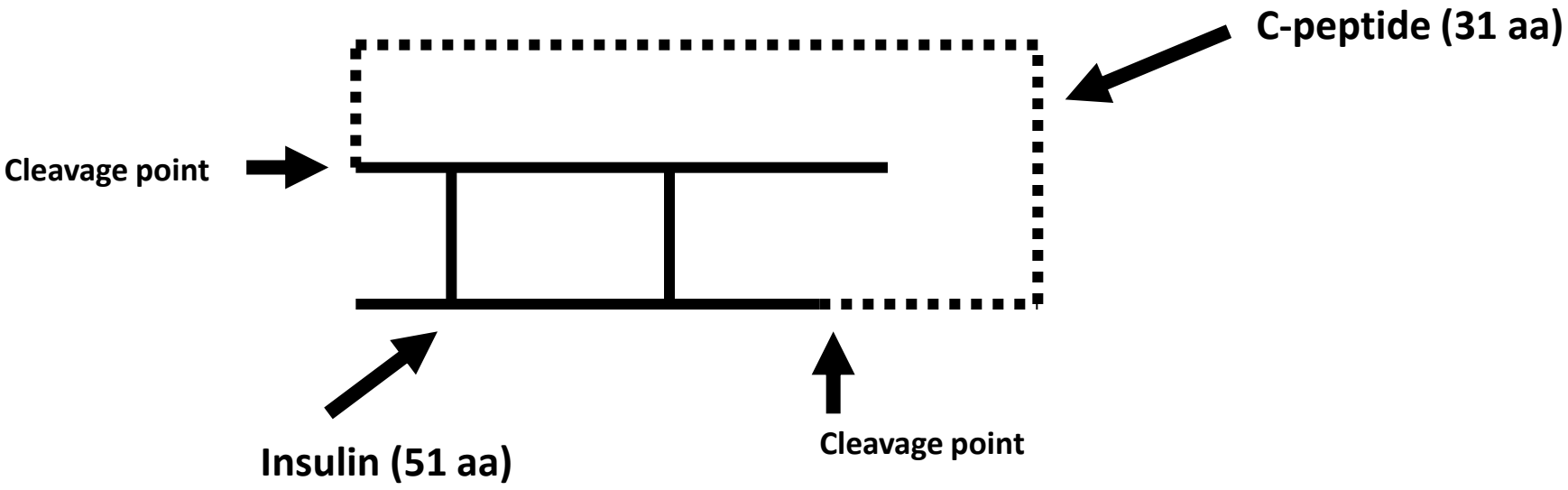
- **Insulin**
  - **Secreted by β-cells**
- **Glucagon**
  - **Secreted by α-cells**
- **Both critical to the control of blood glucose concentration**

Insulin

- Polypeptide
- 51 amino acids in two chains
  - A chain 21 amino acids
  - B chain 30 amino acids
- Held together by disulphide bridges (cysteine)
- Synthesised as pro-insulin

Pro insulin

- Pro insulin is a single chain of 86 amino acids
- Cleaved at two points
  - Loses 2 amino acids at each



Glucagon

- Single chain polypeptide
- 29 amino acids
- No bridges
  - Flexible molecule
- Synthesised as it is secreted

Synthesis of pancreatic hormones

- Made like any other proteins on ribosomes
- But are then packaged for secretion
  - Storage vesicles
- Released by exocytosis

Control of insulin secretion

- **Insulin is secreted when:**
  - **Blood glucose levels rise above 5 mmol.l^{-1}**
  - **Blood amino acid levels rise**
  - **The vagus nerve is activated**
- **Blood glucose changes by far the most important**

Effects of blood glucose rises on the β-cell

- Glucose enters β cells readily
- Stimulates glycolysis
- Extra ATP formed
- Rise in intra-cellular [ATP] acts on ion channels in cell membrane
  - K^+ channels
- Cause Ca^{2+} ions to move in
- Which stimulates exocytosis

Control of glucagon secretion

- **Glucagon is secreted when**
  - **Blood glucose levels fall below 5 mmol.l^{-1}**
  - **Amino acids rise**
  - **Adrenaline secretion is stimulated**

Transport of pancreatic hormones

- Both Insulin & Glucagon are hydrophilic
- Travel in simple solution
- But cannot cross cell membranes
- So must act on cell surface receptors

Actions of Insulin

- Insulin acts upon most tissues
  - Not nervous tissue
  - Especially liver, adipose tissue and muscle
  - Stimulates uptake of glucose
    - Promotes glycolysis
    - And, especially in liver, formation of glycogen
  - Stimulates growth
    - Uptake of amino acids
    - Anabolic

Insulin receptors

- **Membrane bound proteins**
  - **Outer part – α subunit binds insulin**
  - **Membrane spanning part – β subunit**
    - **Protrudes into cytosol of cell**
    - **Has tyrosine kinase, which when activated phosphorylates enzymes to activate them**
- **Binding of Insulin to outside activates enzymes on inside**

Insulin stimulated cells

- Increased production of GLUT-4 transporter proteins
- Incorporated into membrane
- Glucose enters cells more readily
- And is metabolised

Inactivation

- **Insulin/ receptor complex internalised**
- **Broken down to amino acids**

Actions of Glucagon

- Acts mainly on liver and adipose tissue
  - Glucose release from liver
    - From glycogen
  - Fatty acid release from adipose tissue
- In absence of Insulin, muscle etc use fatty acids for fuel
- Leaving glucose for brain
- Also stimulates gluconeogenesis

Glucagon receptors

- Glucagon binds to cell surface receptor
- Linked to G-proteins
- Triggers action of adenylate cyclase
- Produces 3’-5’cyclic-amp (c-amp)
  - Second messenger
- C-amp interacts with protein kinase
- Phosphorylates key enzymes

In the fed state

- **Blood glucose rises**
- **Insulin secreted**
  - **Liver takes up glucose – glycogen production**
  - **Adipose tissue takes up glucose – lipid storage**
  - **Muscle etc take up glucose – support metabolism & a little stored**

In the fasting state

- **Blood glucose falls**
  - **Insulin secretion reduced**
  - **Glucagon increased**
  - **Liver gives up glucose – glycogen breakdown**
  - **Adipose tissue gives up fatty acids**
  - **Glucose cannot easily enter muscle etc, so they use fatty acids for fuel**
    - **Once local glycogen stores depleted**
  - **Blood glucose preserved for brain**

Disorders of the endocrine pancreas

- Diabetes mellitus
- Group of metabolic diseases
  - Affect 120m people worldwide
  - Increasing all the time
- Characterised by hyperglycaemia
- Caused by
  - Insulin deficiency
  - And/or insulin resistance of target cells

Lack of insulin

- Tissues cannot utilise glucose
  - Blood glucose levels high
  - But energy supply to tissues low
    - tiredness
  - Tissues utilise fatty acids
    - Produce ketone bodies
  - High blood glucose leads to glucose in urine
    - Osmotic diuresis
    - Water deprivation and thirst