Homeostasis

1. Introduction

In multicellular organisms, different parts of the body perform different functions. Communication is of utmost importance to ensure that bodily functions can be coordinated and carried out efficiently.

Communication ensures that there is coordination between organs so that the organisms can function as a whole in responses to changes. In particular, the composition of the internal environment must be maintained at a narrow, optimum range to support the proper functioning of the body cells.

In this segment, we will be learning about the concept of homeostasis to appreciate how such optimum conditions of the internal environment may be maintained, so that cells can function in a state of maximum efficiency. In particular, we will focus on insulin and glucagon regulation of the blood glucose concentration in the body.

2. Learning Outcomes

3 (p) Outline **how insulin and glucagon regulate the concentration of blood glucose** through the respective tyrosine kinase receptor and G-protein linked receptor.

(The outline should be limited to describing how the ligand induces a conformational change in a membrane-bound receptor to trigger downstream signaling pathways that elicit physiological changes in blood glucose concentration. Details of different second messengers and specific kinases activated in the pathway are not required.)

Students should be able to use the knowledge gained in this section in new situations or to solve related problems.

3. References

- Campbell, N.A. and Reece, J.B. (2008). Biology, 8th edition. Pearson.
- Sherwood, Fundamental of Human Physiology, 4th edition
- Brooker *et al.*, Biology, McGraw-Hill
- Ho YK (2003) A-level course in Biology – Core syllabus, Longman

4. Organisation of Lecture Content

5. Overview of Homeostasis

Notes to self

A Definition: What is Homeostasis?

- Homeostasis is the **maintenance** of a **constant internal cellular environment** of an organism, providing it with a **degree of independence from its external environment**.

- It involves **self-regulating** and **negative feedback mechanisms** to control the level of substances that are to be maintained.

Note: *The concept of 'self-regulating and negative feedback' will be detailed later.*

- The **external** environment refers to the environment in which the **organism** lives, whereby the conditions fluctuate beyond the control of the organism.

- In complex multicellular organisms, most living cells of the body are not directly exposed to the external environment. They are bathed in a liquid internal environment known as **interstitial fluid**.

- The **internal** environment refers to the immediate surrounding which the **individual cells** live (e.g. the interstitial fluid, shown in Fig. 1).

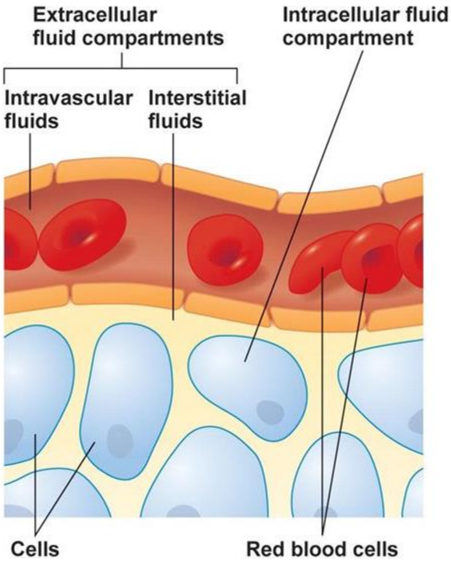

Figure 1: Interstitial Fluid (The fluid between cells, also known as the internal environment of individual cells)

- Components of the internal environment which are homeostatically regulated and kept constant: -

  a) Concentration of chemical constituents in blood, e.g. glucose, ions, nitrogenous waste products
  b) Concentration of respiratory gases e.g. oxygen and carbon dioxide
  c) Body temperature
  d) pH
  e) Osmotic pressure

B The Importance of Homeostasis

Notes to self

- Homeostasis provides optimal conditions for cellular activities. This is crucial to cells because cells can only function within a **narrow range** of conditions, so as to ensure **maximum efficiency**.

- **Homeostatic mechanisms** **buffer** the body against fluctuations from optimal conditions.

- This provides the organisms with a degree of **independence** from the external environment.

- As a result, a **stable internal environment** with minimal disturbances is maintained.

- **What are the consequences if homeostasis is disrupted?**

  - Altered conditions can be detrimental. It can lead to illness and death.

  - E.g. Increased temperature/ acidity may denature enzymes.

C The Principles of Homeostasis

- Organisms are **open** systems; they interact with the external environment and have a **continuous exchange** of matter with it.

- To maintain stability in the internal environment and prevent it from coming to equilibrium with the external environment, **control systems** are required.

- Control systems are homeostatic mechanisms that exhibit two principles:

  i. **Self- Regulation**
     - This involves **corrective mechanisms** which are **triggered by the very entity/ parameter that it serves to regulate.**

       E.g. In the control of blood glucose level, the secretion of hormones (glucagon and insulin) to regulate any fluctuation is triggered by changes in blood glucose level.

  ii. **Negative Feedback**
     - Negative feedback is a corrective/ regulatory mechanism in which **a deviation from the set/ reference point** serves as a **stimulus** to **trigger a response** by the control system.
     - The response is in the opposite direction to the stimulus, and it **opposes the initial deviation/ reduces the initial stimulus.**
     - In other words, **a change sets off events that counteract the change.**

- Homeostasis operates primarily via a **negative feedback control loop** (Fig. 2):

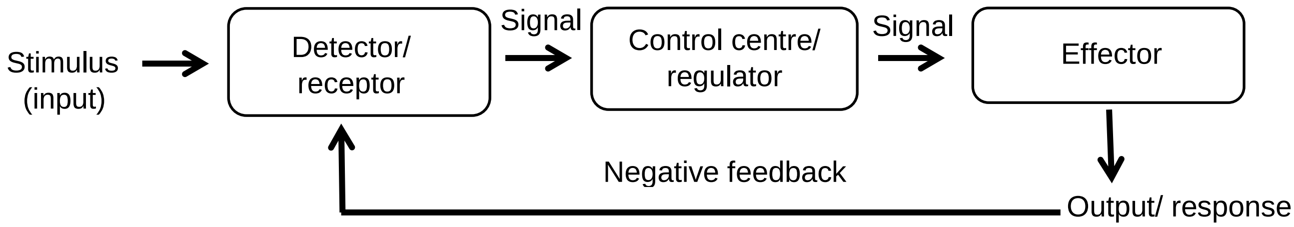

Figure 2: Basic components of a homeostatic control system/ Negative feedback loop

- The table below summarises the various components of the homeostatic control system:

1.	**Reference point**	▪ The set level or optimal level at which the system operates.
2.	**Detector (or receptor)**	▪ Continuously monitors the parameter for deviation from the reference point. ▪ Signals the extent of any deviation from the reference point. ▪ Relays information to regulator or control centre.
3.	**Control Centre/ Regulator**	▪ Coordinates the information from various detectors. ▪ Sends out instructions to correct any deviations by activating the appropriate effectors.
4.	**Effector**	▪ Brings about the necessary change needed to restore system to the reference point.

- The response/output (**changed condition**) serves as a negative feedback to the receptor for monitoring of any **displacement from the set/reference point** that is caused by the stimulus.
- Negative feedback is associated with increasing stability of the system because the disturbance triggers a sequence of events to **restore** the system **back to norm / set point**.
- Homeostasis is a dynamic process: it works by constantly making adjustments to compensate for fluctuations of output. Thus it is more accurate to describe such system as steady state or dynamic equilibrium.
    - E.g. when a parameter (e.g. glucose concentration in blood) increases above the set point, the corrective mechanism will act to cause that parameter to decrease and return to set point.

6 Communication systems

- There are two major internal communications systems, namely the **endocrine** and the **nervous** systems (Fig. 3).
- These systems **detect** any changes known as **stimuli** in the external or internal environment, and **coordinate** an appropriate response.
- Together, they **maintain** a **homeostatic state** within the body.

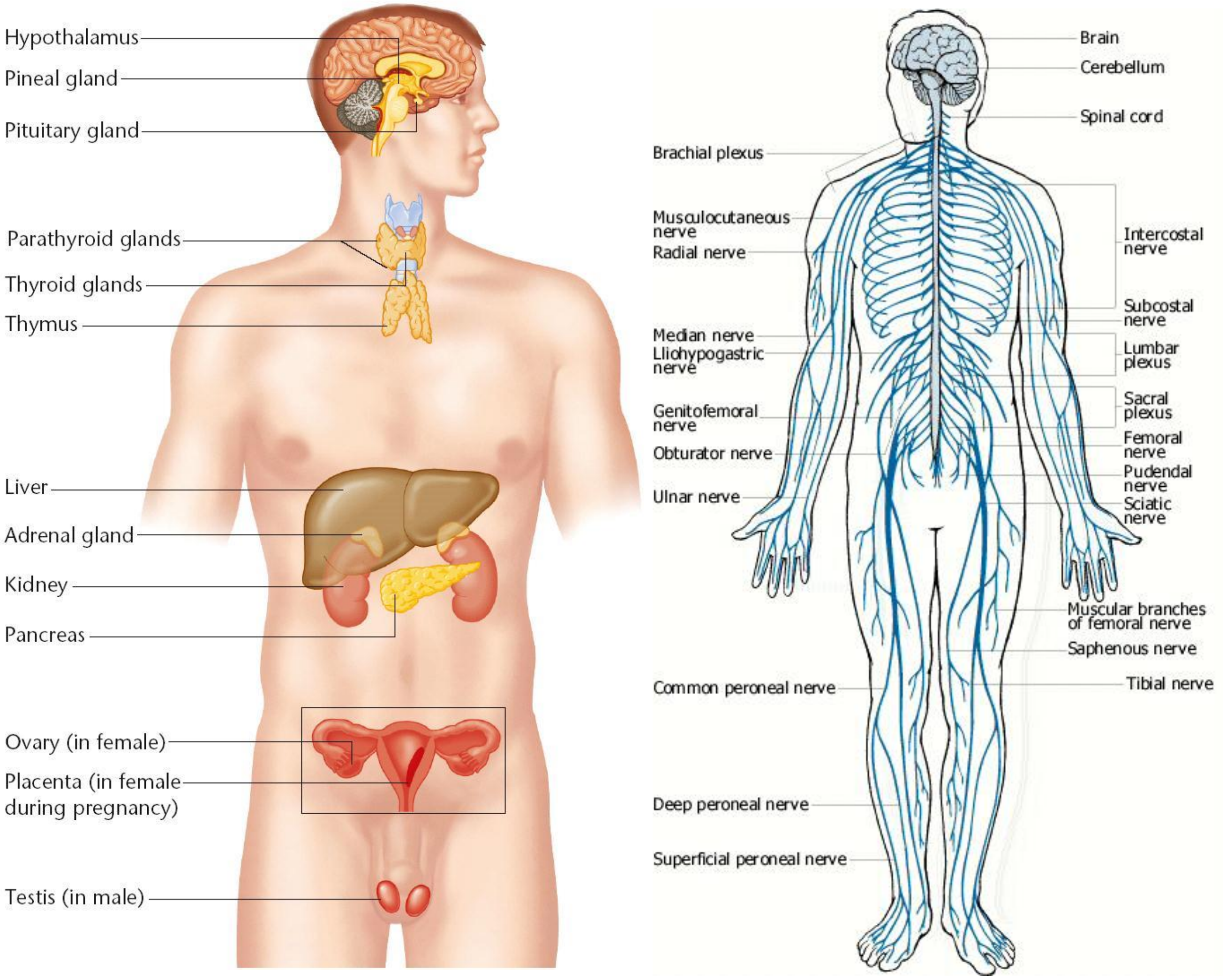

Figure 3: Two major communication systems in humans – the endocrine system (Left) and nervous system (right)

A Hormonal Control: The Endocrine System

- The endocrine system is made up of a number of **endocrine glands** that maintain homeostasis via **long-term control** by secreting chemical signals known as **hormones**.
- A **gland** is an organ that **secretes** **specific chemical substances.**
- **Endocrine glands** have the following characteristics:
  - Secrete chemical substances called **hormones.**

Notes to self

- **Ductless**, hence **secrete hormones directly into the bloodstream** so as to be brought to their **target site.**
- Is richly supplied with **networks of blood capillaries** that facilitate the secretion of hormones into the bloodstream.

  Note: We cannot say that 'endocrine glands excrete hormones' because excrete means to eliminate waste, but secrete means to produce a useful substance.

B Hormones

- Hormones are **small, organic molecules.**
- Hormones can be grouped into three classes:
  - **Proteins/ peptides** e.g. insulin, growth hormone
  - **Amines** (derivatives of a single type of amino acid) e.g. adrenaline
  - **Steroids** e.g. testosterone, oestrogen
- Hormones function as **chemical messengers.**
  - Hormones exert their specific effect at a site different from the site of production, hence are termed as '**messengers**'.
- Hormones have the following characteristics:
  - **Secreted directly into bloodstream** by ductless endocrine glands.
  - **Transported by blood** to exert its effect on **target cells** with **specific receptors** (Fig. 4).
  - Effective in **small quantity**. (KIV **signal amplification,** which will be covered in cell signalling section later)

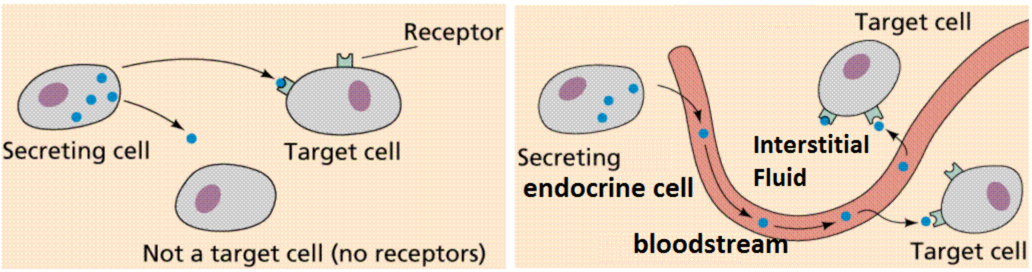

Figure 4: (left) Only target cells with specific receptors can respond to the hormone.

(right) Hormones travel via blood vessels/ in the bloodstream from the cells where it is produced/ secreted to distant target cells

C Mechanisms of Hormone Action

- The effects of hormones on their target cells can be complex.
  - Hormones are **extracellular chemical messengers** that bring about **specific** cell responses through **cell signalling** (will be covered in cell signalling later).
  - Each type of hormone is **specific to its particular target cells**. This is because hormones have **complementary shape** that allows them to fit precisely into their **receptor** molecules found on their target cells.

Notes to self

- **Receptors** for **protein or peptide** hormones are found on the **cell membrane** of target cells.
- **Receptors** for **steroid** hormones are **intracellular**, and thus are found in the **cytoplasm or nucleus** of the target cell.
- Non-target cells lack the specific receptors and thus do not respond to the circulating hormones.

- Hormones **exert their effects** by the following mechanisms:
  - **Change permeability of cell membrane (**e.g. insulin increases the permeability of cell membrane to glucose).
  - Use a **second messenger** (e.g. **cyclic AMP**) to trigger the activation of a series of enzyme controlled reactions.
  - **Activate specific gene transcription**.
- After exerting their effects, hormones are degraded by enzymes and excreted in the urine.

D The Pancreas: Islets of Langerhans

- The pancreas is a unique organ in that it contains **both** endocrine and exocrine functions.
  - The **exocrine** cells secrete pancreatic juice into the duodenum through the pancreatic duct (for information only, not in syllabus).
  - The **endocrine** cells secrete hormones, **insulin** and **glucagon**, which are involved in the **homeostatic regulation of blood glucose levels**.
- The **endocrine** function of the pancreas is carried out by **a group or cluster of cells** called the **islets of Langerhans.**
- Each cluster of islet of Langerhans has a population of
  - **alpha cells** which secrete hormone **glucagon**
  - **beta cells** which secrete hormone **insulin**

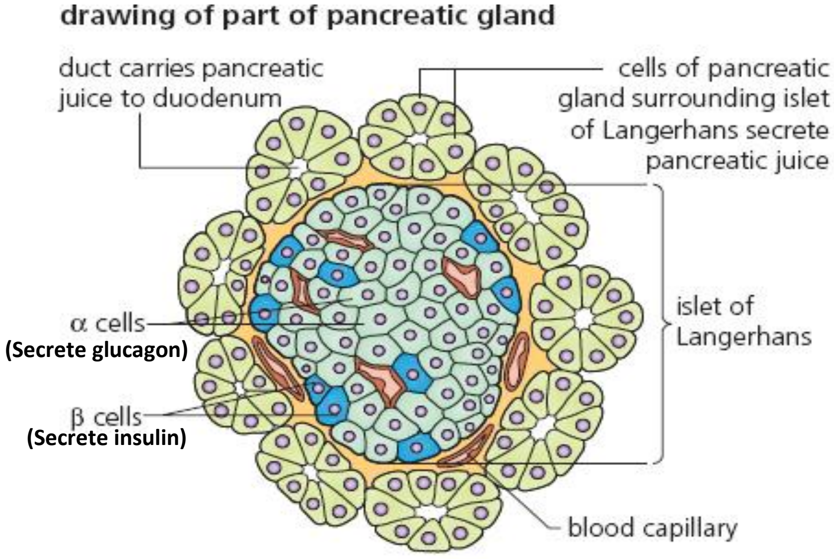

Figure 5: Drawing of a section of the pancreas, showing the islets of Langerhans and the alpha and beta cells.

E Blood Glucose Regulation by Insulin and Glucagon

Notes to self

- The **hormones** secreted by the pancreas are responsible for **regulating blood glucose levels,** thus ensure that blood glucose levels are **kept within normal limits**.

- Importance of regulating human blood glucose levels:

  - Glucose is the **ideal substrate for cellular respiration**. Also, the brain **only** uses glucose for cellular respiration.
  - Cellular respiration yields **energy**. Energy must be **constantly available** for cell metabolism. However, dietary fuel intake is intermittent and not continuous.
  - As a result, excess energy must be stored for use during fasting periods between meals. Stored energy fills in the gap between meals.
  - A drastic decrease in blood glucose level could lead to fainting, convulsion, coma and finally death.

- Human blood glucose level is regulated by 2 hormones secreted from **the islets of Langerhans** of the **pancreas**:
  - **Insulin** from the **beta cells** and
  - **Glucagon** from the **alpha cells**

- Both **insulin** and **glucagon** are **peptide hormones** that have **antagonistic effects** on the control of blood glucose levels.

- Insulin **decreases** blood glucose concentration; Glucagon **increase** blood glucose concentration.

- It is the **ratio of their concentrations** that is critical in the regulation of blood glucose concentration than their actual levels.

$$\text{Glucose} \quad \underset{\textbf{Glucagon}}{\overset{\textbf{Insulin}}{\rightleftharpoons}} \quad \text{Glycogen (storage)}$$

- An **increase** in blood glucose level (**hyperglycemia)** – **stimulates insulin secretion** and **inhubits glucagon secretion.**

- A **decrease** in blood glucose level (**hypoglycemia**) – **inhibits insulin secretion**, and **stimulates glucagon secretion.**

- Secretion of insulin is vital to life as it is the **only** hormone that **lowers** blood glucose level.

- **Deficiency of insulin** leads to **type I diabetes mellitus**, in which there is hyperglycemia and blood glucose levels exceed the level that kidneys can reabsorb, hence the excess glucose is excreted in the urine.

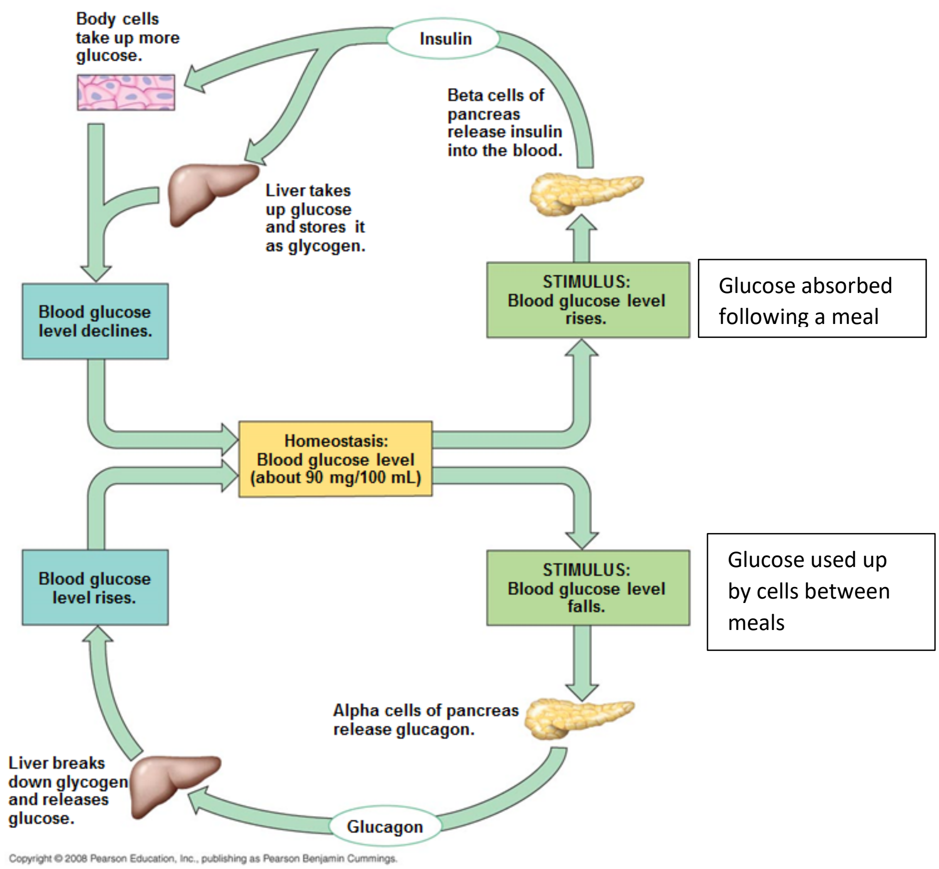

Figure 6: Regulation of blood glucose concentration by insulin and glucagon

I. Role of Insulin – decrease blood glucose concentration

	Insulin decreases blood glucose concentration when blood glucose levels rise above set/ reference point
Occurence	▪ **High** levels of blood glucose concentration (**more than set point 90mg/100ml**) ▪ Occurs after a meal rich in carbohydrates
Stimulus	▪ **Increase** in blood glucose level **above** the **homeostatic reference point** or **set point of 90mg/100ml**
Detector/ Receptor	▪ **Beta cells of the Islet of Langerhans** of the **pancreas**. ▪ **Detects** an increase of blood glucose **above set point of 90mg/100ml**
Regulator	▪ Triggers the **secretion** of hormone **insulin** by the **β-cells of the islets of Langerhans** ▪ Insulin released travel via the **bloodstream** and **binds** to **complementary -shaped insulin receptors** on **cell membrane of target cells** (eg. liver cells) ▪ **Liver, muscle, adipose tissues** are the **effectors**
Effectors and the effects of insulin on target cells	▪ **Increases** the **permeability** of cell membrane to glucose by increasing the number of **glucose carrier proteins** • This increases the **rate of uptake of glucose** by cells, especially the muscle cells. ▪ **Increase rate of glycogenesis** – **conversion of glucose to glycogen**; which takes place mainly in the **liver and muscle**. This stimulates **glycogen storage** in liver and muscle. ▪ **Inhibits glycogenolysis** – the **breakdown of glycogen to glucose** in liver and muscle. ▪ **Inhibits gluconeogenesis (glucose synthesis)** – the breakdown of fats and proteins and the conversion of non-carbohydrate sources to glucose in **liver cells**. ▪ Increases the use of glucose as a **substrate for cellular respiration**, hence increase rate of **glucose oxidation** and **synthesis of ATP** ▪ **Increases rate of protein synthesis** ▪ **Increases rate of conversion of glucose to fats** and the **rate of fat deposition** in adipose tissues.
Response and Negative feedback	▪ Overall response: **lowered blood glucose concentration** which returns back to the normal homeostatic **reference point**. ▪ **Negative feedback inhibits further secretion of insulin**. ▪ **β-cells** of islets of Langerhans in pancreas **detect** normal blood glucose level and **respond** by **stopping insulin secretion**. ▪ Thus, blood insulin level also returns to normal. ▪ Any remaining circulating insulin is eventually destroyed and hydrolysed to amino acids in the liver.

Question: Is it correct to say insulin converts excess glucose to glycogen?

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II. Role of Glucagon - Increase blood glucose concentration

	Glucagon increases blood glucose concentration when blood glucose levels fall below set/ reference point
Occurence	▪ **Low** levels of blood glucose (**less than set point 90mg/100ml**) ▪ Occurs after strenuous physical activity or fasting
Stimulus	▪ **Decrease** in blood glucose level **below** the **homeostatic reference point** or **set point of 90mg/100ml**
Detector	▪ **Alpha cells of the Islet of Langerhans** of the **pancreas**. ▪ Detects a **decrease** of blood glucose **below set point of 90mg/100ml**
Regulator	▪ Triggers the **secretion** of hormone **glucagon** by the **α-cells of the islets of Langerhans** ▪ Glucagon released travel via the **bloodstream** and **binds** to **complementary -shaped glucagon receptors** on **cell membrane of target cells** (eg. liver cells) ▪ **Liver** is the main effector.
Effectors and the effects of insulin on target cells	▪ **Increases rate of glycogenolysis** – the **breakdown of glycogen to glucose in liver.** ➢ Note that glucagon has no effect on **muscle glycogen.** ▪ **Increases rate of gluconeogenesis (glucose synthesis)** – the breakdown of fats and proteins and the conversion of non-carbohydrate sources to glucose in **liver cells**. (e.g. **Increases rate of conversion of lactic acid to glucose**.) ▪ **Increases rate of breakdown of lipids into fatty acids (lipolysis)** ▪ **Inhibits glycogenesis**
Response and Negative feedback	▪ Overall response: **increased blood glucose concentration** which returns back to the normal homeostatic reference point. ▪ **Negative feedback inhibits further secretion of glucagon**. ▪ **α-cells detect** normal blood glucose level and **respond** by **stopping glucagon secretion**. ▪ Thus, blood glucagon level also returns to normal. ▪ Any remaining circulating glucagon is eventually destroyed and hydrolysed to amino acids in the liver.

Question: What is the order of metabolic fuel usage in the body?

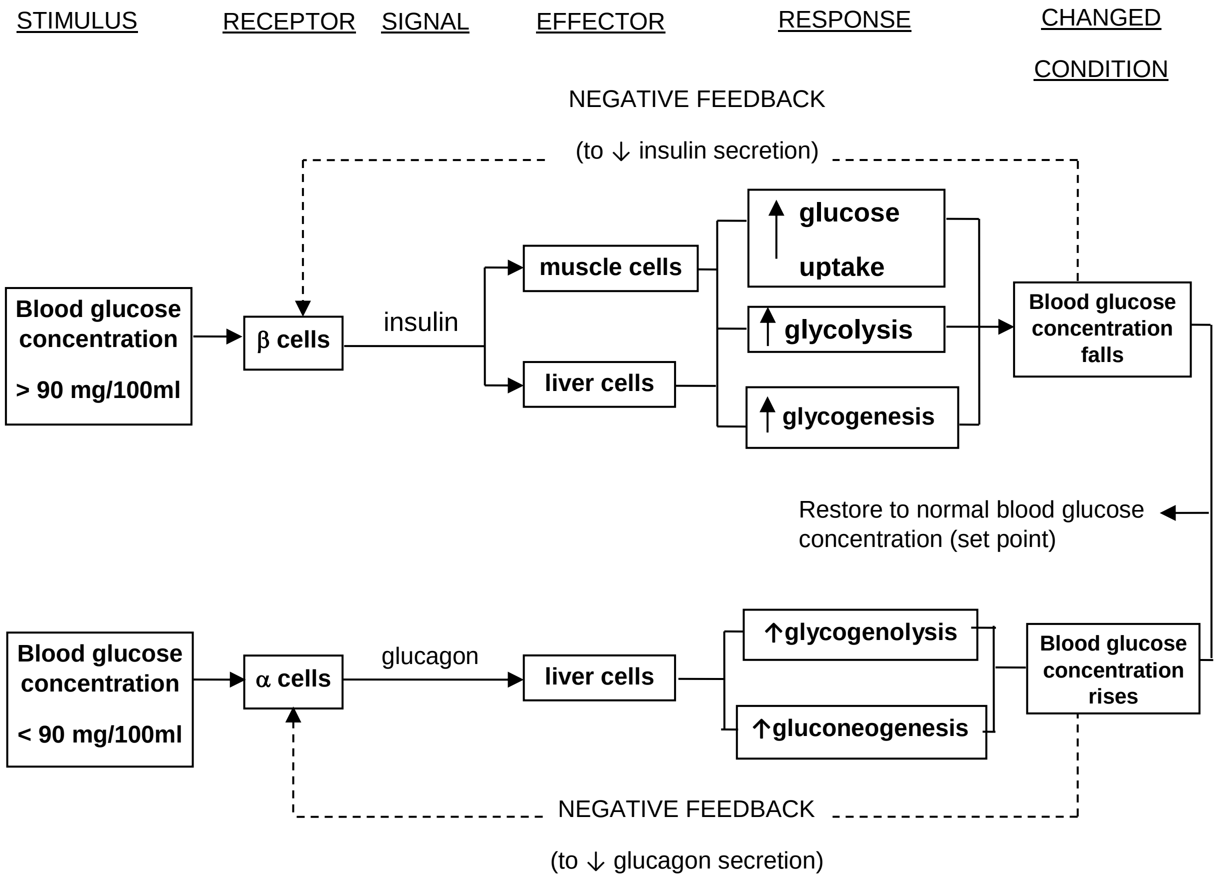

Figure 7. Overview on homeostatic control for blood glucose level using negative feedback mechanism