Biochemistry of the Endocrine Block

Glucose Homeostasis

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A process that

- Controls glucose metabolism and
- Maintains normal blood glucose level in the body

- Glucose is a major source of body's energy, that's why we should maintain its normal level in body.
- The liver plays a key role in maintaining blood glucose level
- Blood glucose level is tightly controlled because the brain constantly needs glucose.
- Brain depends on Glucose as a source of energy and in some cases ketone bodies.
- Brain doesn't have the ability to store fuel.
- Severe hypoglycemia can cause coma and death
- Chronic hyperglycemia results in glycation of proteins, endothelial dysfunction and diabetes mellitus

Glycation of Proteins: Bonding of Proteins to Glucose molecules, without the controlling action of an enzyme.

Sources of Glucose:

1. **Dietary sources:**

- Dietary CHOs are digested to monosaccharides
- **Starch** provides glucose **directly**
- **Fructose and galactose** are converted to glucose in the **liver** "indirectly"

2. **Metabolic sources (via gluconeogenesis):**

- Glycerol by glycogenolysis, lactate, pyruvate, glucogenic amino acids by gluconeogenesis.

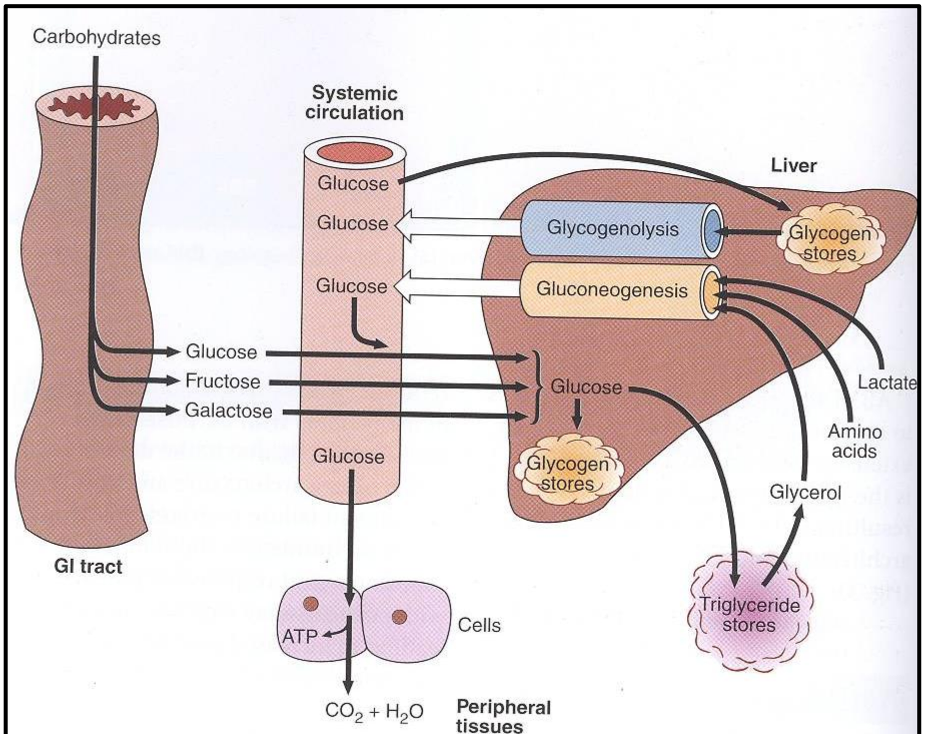


Fig. 1 **Glucose homeostasis.**

- Glucose is stored in the liver in the form of glycogen, when its needed glycogen undergoes glycogenolysis to produce glucose.
- The remaining glucose goes to adipose tissue and stored as triglycerol.

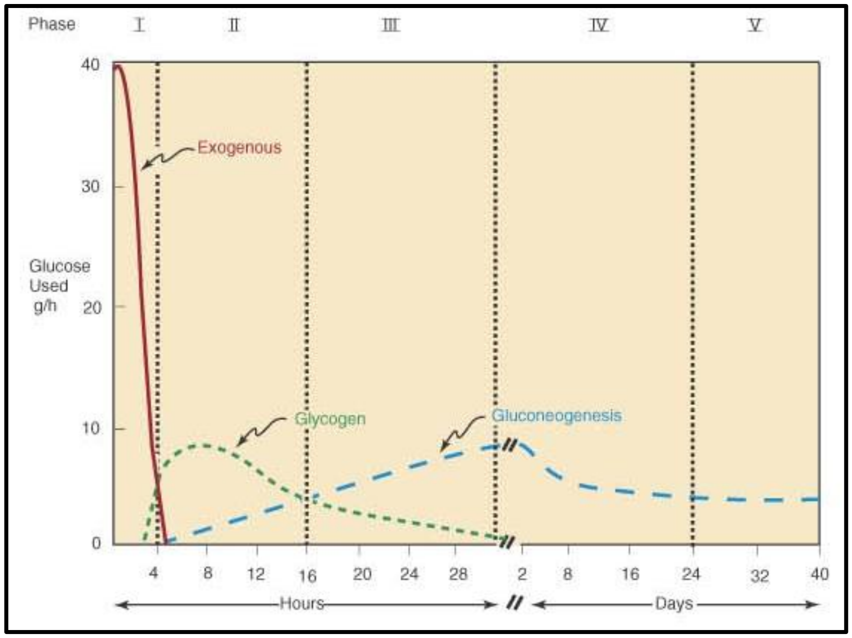
Phases of Glucose Homeostasis:

Five phases:

- Phase I (Well-fed state)
- Phase II (Glycogenolysis)
- Phase III (Gluconeogenesis)
- Phase IV (Glucose, ketone bodies (KB) oxidation)
- Phase V (Fatty acid (FA), KB oxidation)

1 – Overlapped stages.

2- Glucose from diet is converted to glycogen by glyconeogenesis.



Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate between II and IV	Glucose
IV	Gluconeogenesis, hepatic and renal	Brain, RBCs, renal medulla. Small amount by muscle	Glucose, ketone bodies
V	Gluconeogenesis, hepatic and renal	Brain at a diminished rate, RBCs, renal medulla	Ketone bodies, glucose

16-40 hours

Main Source

Glucose is a main source in the 2nd phase and almost is finished in the 3rd phase.

Phase 4: break down of fatty acids by FA oxidation → brain starts using ketone bodies (KB) such as Acetone because KB cross the BBB, while Fatty Acids doesn't. So Ketone Bodies are an alternative source of energy.

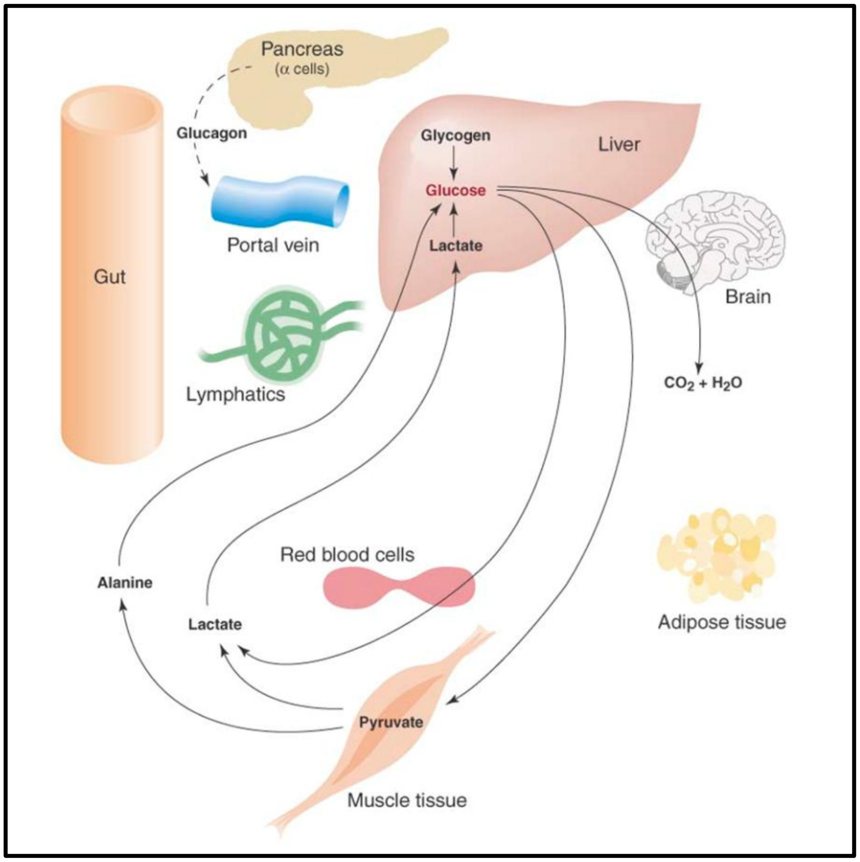
Phase 5: Glucose level is going down and now Ketone Bodies are the main source of energy not glucose.

Phase I (Well-fed state):

- Glucose is mainly supplied by dietary CHOs
- Liver removes about 70% of glucose load after a CHO meal, 30% stays in the systemic circulation.
- All body tissues use dietary glucose for energy in this phase
- Some glucose is converted to glycogen for storage in the liver (glycogenesis)
- Excess glucose is converted to fatty acids and triglycerides in the liver
- These are transported via VLDL (very low density lipoproteins) to adipose tissue for storage
- Gluconeogenesis is inhibited in this phase because the body doesn't need any extra source.
  - Cori and glucose-alanine cycles are inhibited

Phase II (Glycogenolysis):

- Phase II starts during early fasting when dietary glucose supply is exhausted
- Hepatic glycogenolysis maintain blood glucose level in this phase
- Major sources of blood glucose in this phase:
  - Glycogenolysis



Phase III (Gluconeogenesis):

- Phase III starts when glycogen stores in liver are exhausted (within 20 hours)
- Duration of phase III depends on
  - Feeding status
  - Hepatic glycogen stores
  - Physical activity
- Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level
- Major source of blood glucose in this phase:
  - Gluconeogenesis

Phase IV (Glucose and KB oxidation):

- Several days of fasting leads to phase IV
- Gluconeogenesis starts to decrease
- FA oxidation increases KB accumulation
- KBs enter the brain and muscle for energy production
- Brain uses both glucose and KB for energy

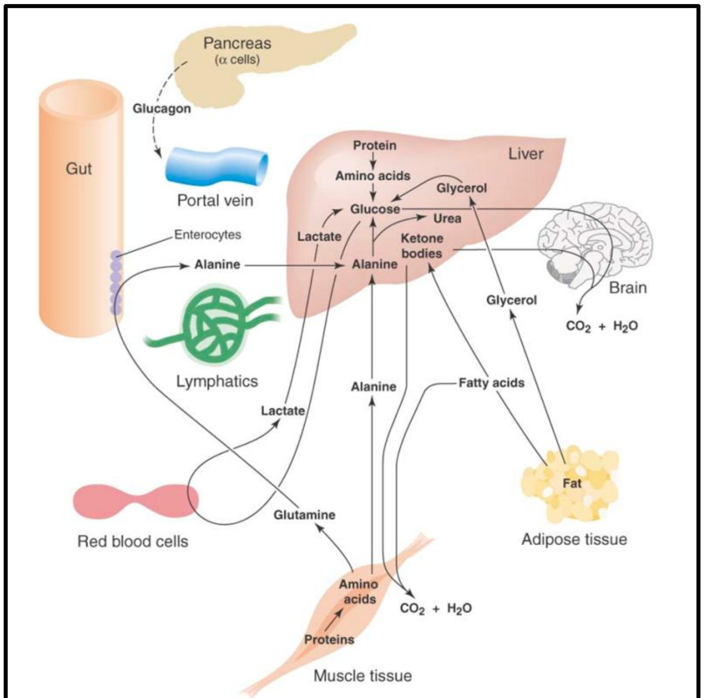
Phase V (FA "fatty acids" and KB "keton bodies" oxidation):

- Prolonged fasting leads to phase V
- Less dependence on gluconeogenesis
- All body tissues mainly use FA and KB oxidation for energy production
- Gluconeogenesis somewhat maintains blood glucose level in this phase
- High KB conc. and glucose levels inhibit proteolysis in muscle (conservation of muscle)
- When all fat and KBs are used up
  - Body uses muscle protein to maintain blood glucose level

Fatty Acids → glycerol → glucose and thus energy.

When degradation of fats is finished proteins starts to break down → into amino acids → glucose by gluconeogenesis (Muscles).

Proteins breaking down are the latest stage.



Hormones and Glucose Homeostasis:

Hormones that regulate glucose metabolism:

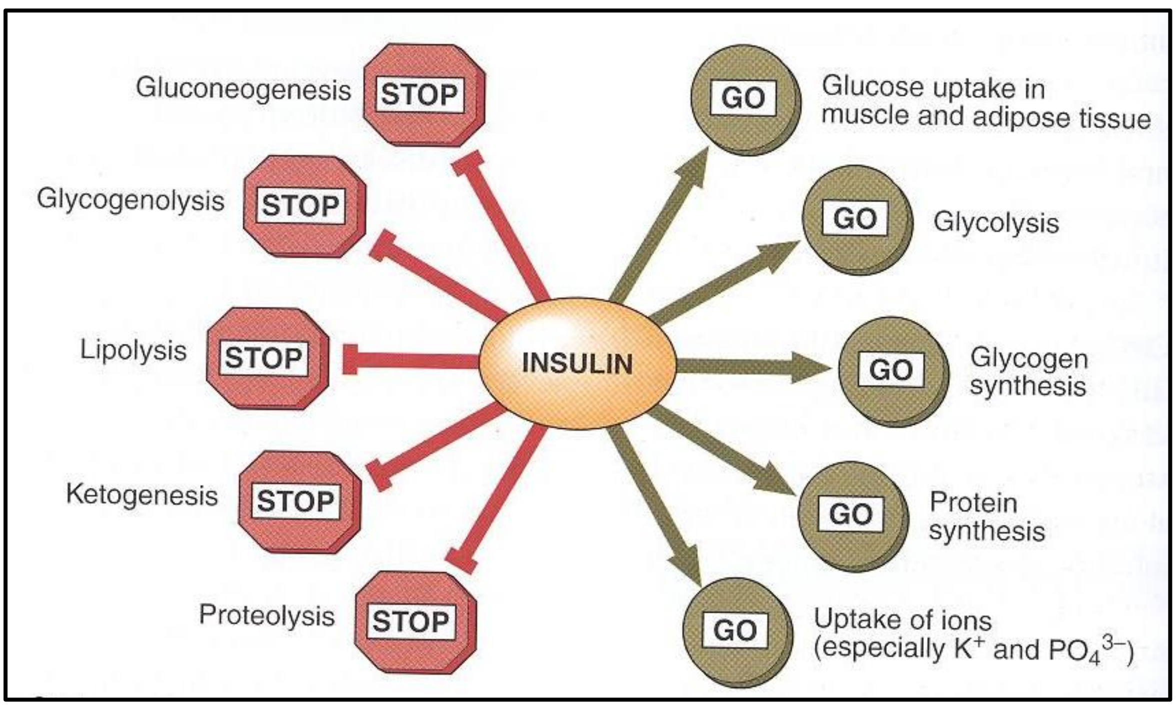
- **Insulin (lowers blood glucose level)**
- **Glucagon**
- Somatostatin
- Cortisol
- Growth hormone
- Epinephrine

(Glucagon, Somatostatin, Cortisol, Growth hormone, Epinephrine:) **Antagonize insulin action;** do not necessarily increase blood glucose level

Insulin:

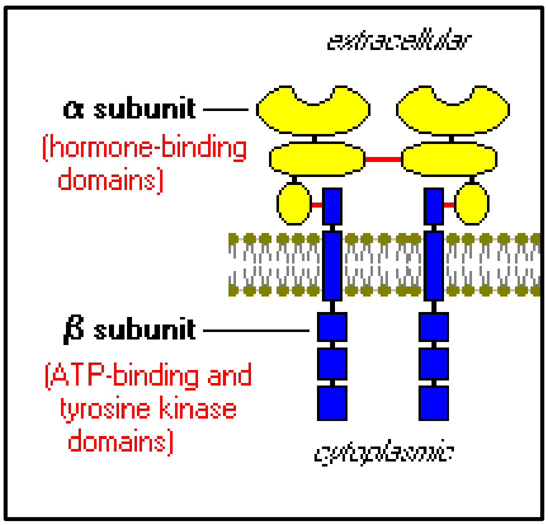
- Plays a major role in glucose homeostasis
- Synthesized by the β-cells of islets of Langerhans of pancreas
- A small protein composed of two chains
- Rise in blood glucose level stimulates insulin secretion
- Promotes entry of glucose into cells

Actions of Insulin:



Mechanism of Action:

- The insulin receptor is present on the plasma membrane of cell
- Composed of
  - α-subunit (extracellular)
  - β-subunit (cytoplasmic)
- Binding of insulin to α-subunit causes phosphorylation of β-subunit
- This activates the receptor
- The activated receptor then phosphorylates intracellular proteins generating a biological response

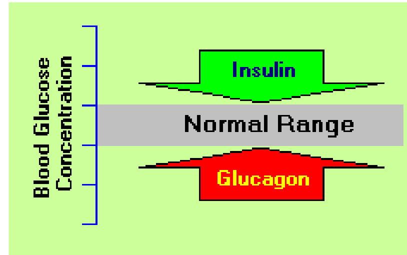


Insulin and CHO metabolism:

Promotes glucose uptake into cell:

- Glucose is diffused into cells through hexose transporters such as GLUT4
- GLUT4 is present in cytoplasmic vesicles
- Brain has no GLUT4
- Insulin binding to its receptor causes vesicles to diffuse into plasma membrane
- GLUT4 is inserted into the membrane
- Allowing glucose transport into the cell
- Brain and liver have non-insulin dependent glucose transporter
- Stimulates glycogen synthesis
- Decreases blood glucose levels
- Increases glycolysis
- Stimulates protein synthesis
- Insulin deficiency causes diabetes mellitus
- Hyperinsulinemia is due to insulin resistance in:
  - Diabetes mellitus or
  - Metabolic syndrome

Glucagon:



- A peptide hormone secreted by a-cells of pancreatic islets
- Secreted in response to hypoglycemia
- Increases glucose levels
- Stimulates glycogenolysis
- Activates hepatic gluconeogenesis

Somatostatin

- A peptide hormone secreted by d-cells of pancreatic islets, stomach and intestine
- An inhibitory hormone
- Inhibits secretion of both insulin and glucagon
- Affects glucose homeostasis **indirectly**

Glucocorticoids (Cortisol)

- Cortisol is a steroid hormone secreted by adrenal gland
- Contributes to glucose homeostasis
- **Maintains normal glucose levels in fasting**
  - Stimulates gluconeogenesis in the liver
  - Mobilizes amino acids for gluconeogenesis
  - Stimulates fat breakdown in adipose tissue

Stressed ladies are prone to gain weight, because of the high cortisol level

Growth hormone

- A protein hormone secreted by anterior pituitary gland
- Maintains blood glucose levels by:
  - Inhibiting insulin action
  - Stimulating gluconeogenesis in the liver

Epinephrine

- A catecholamine hormone secreted by adrenal gland
- Stimulates lipolysis in adipose tissue when glucose blood levels fall
- Promotes glycogenolysis in skeletal muscle

Summary

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Insulin and CHO metabolism:

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Hormone	Effect on blood glucose levels
Ensulin	↓by: hepatic gluconeogenesis + glycogenolysis
Glucagon	↑by: • Stimulation of glycogenolysis • Activation of hepatic gluconeogenesis
Somatostatin	• Inhibits secretion of both insulin and glucagon • Affects glucose homeostasis **indirectly**
Glucocorticoids (cortisol)	↑ by: – Stimulates gluconeogenesis in the liver – Mobilizes amino acids for gluconeogenesis – Stimulates fat breakdown in adipose tissue
Growth hormone	↑by: – Inhibiting insulin action – Stimulating gluconeogenesis in the liver
epinephrine	↑by: – lipolysis in adipose tissue – glycogenolysis in muscles

Mechanism of action of insulin: