Glucose Homeostasis

Biochemistry Team

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GLUCOSE HOMEOSTASIS:

A process that

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

click here for graph explanations

- Glucose is a major source of body's energy
- The liver plays a key role in maintaining blood glucose level
- Blood glucose level is tightly controlled because the brain constantly needs glucose
- Severe hypoglycemia can cause coma and death
- Chronic hyperglycemia results in [1]glycation of proteins, [2]endothelial dysfunction and [3]diabetes

**Glycation of proteins: is a non-enzymatic attachment of glucose to a class of proteins, producing AGE molecules (Advanced Glycation End-products) in diabetics. Can cause complications as: diabetic cataract.

SOURCES OF GLUCOSE:

Dietary sources:

- Dietary CHO is digested in the GI to monosaccharides
- Starch provides glucose directly
- Fructose and galactose are converted to glucose in the liver

Metabolic sources (via gluconeogenesis):

Glycerol, lactate, pyruvate, glucogenic amino acids (none carbohydrate molecules)

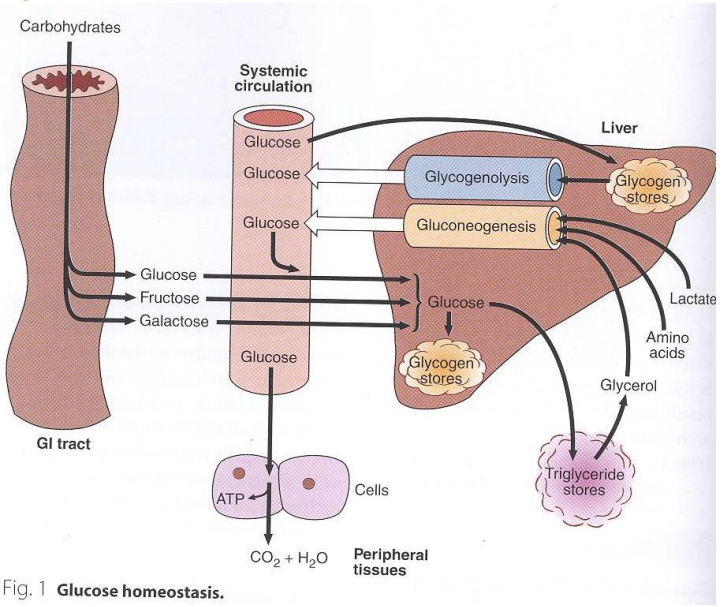


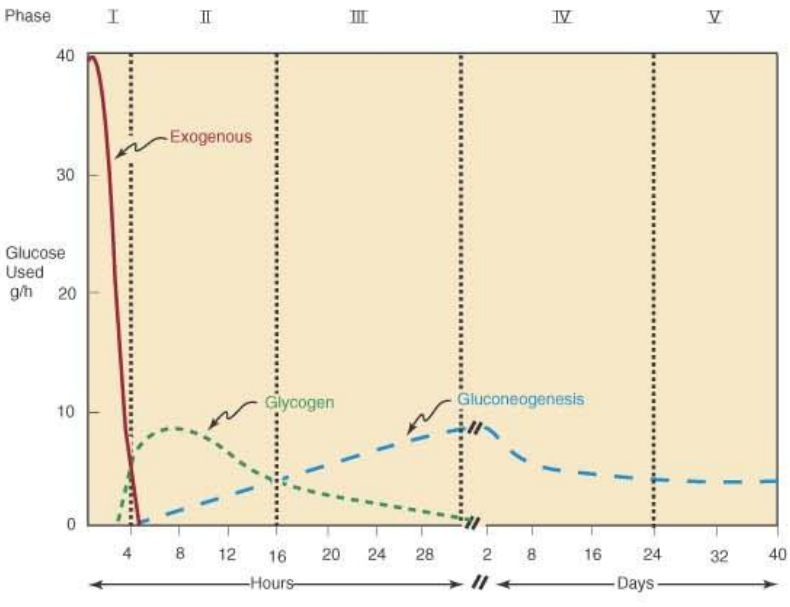
Fig. 1 **Glucose homeostasis.**

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

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



PHASES OF GLUCOSE HOMEOSTASIS

PHASE I (WELL-FED) STATE:

- Glucose is mainly supplied by dietary CHOs
- Liver removes about 70% of glucose load after a CHO meal
- 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
- Cori (lactate produced from muscles gets converted in the liver to glucose) and glucose-alanine cycles are inhibited

PHASE II (GLYCOGENOLYSIS):

- Phase II starts during early fasting when dietary glucose supply is being exhausted
- Hepatic glycogenolysis maintains blood glucose level in this phase
- Glycogenolysis is the major source of blood glucose in this phase

PHASE III (GLUCONEOGENESIS):

- Phase III starts when glycogen stores in liver are exhausted (within 16-20 hours)
- Duration of phase III depends on
    - Feeding status ➔ how much food did you eat last night
    - Hepatic glycogen stores
    - Physical activity ➔ how active you were before this phase
- Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level
- Gluconeogenesis is the major source of blood glucose in this phase

PHASE IV (GLUCOSE AND KB OXIDATION):

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

PHASE V (FA AND KB OXIDATION):

- Prolonged fasting leads to phase V
- Less dependence on gluconeogenesis
- All body tissues 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) (protein sparring effect)
- When all fat and KBs are used up
- Body uses muscle protein to maintain blood glucose level (at late stage = starvation)

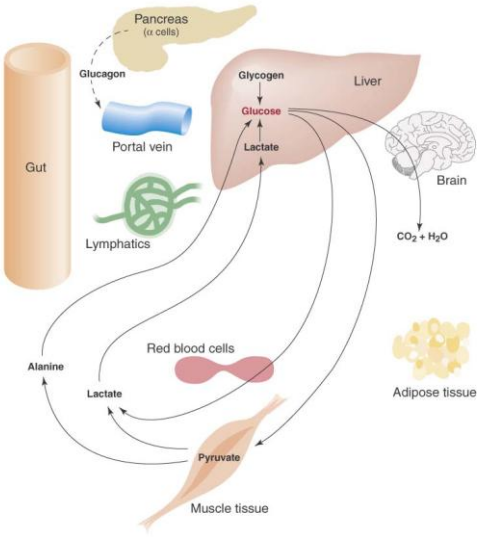


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

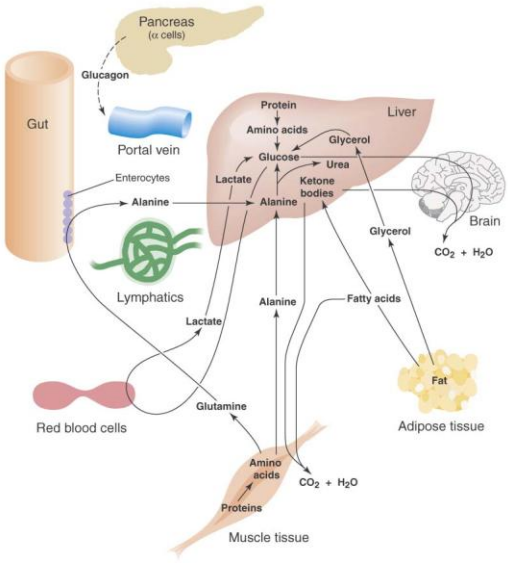


Figure 22.4. Metabolic interrelationships of major tissues in fasting state.

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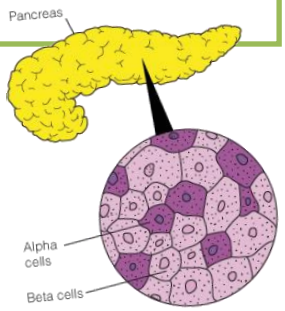
HORMONES AND GLUCOSE HOMEOSTASIS:

Hormones that regulate glucose metabolism:

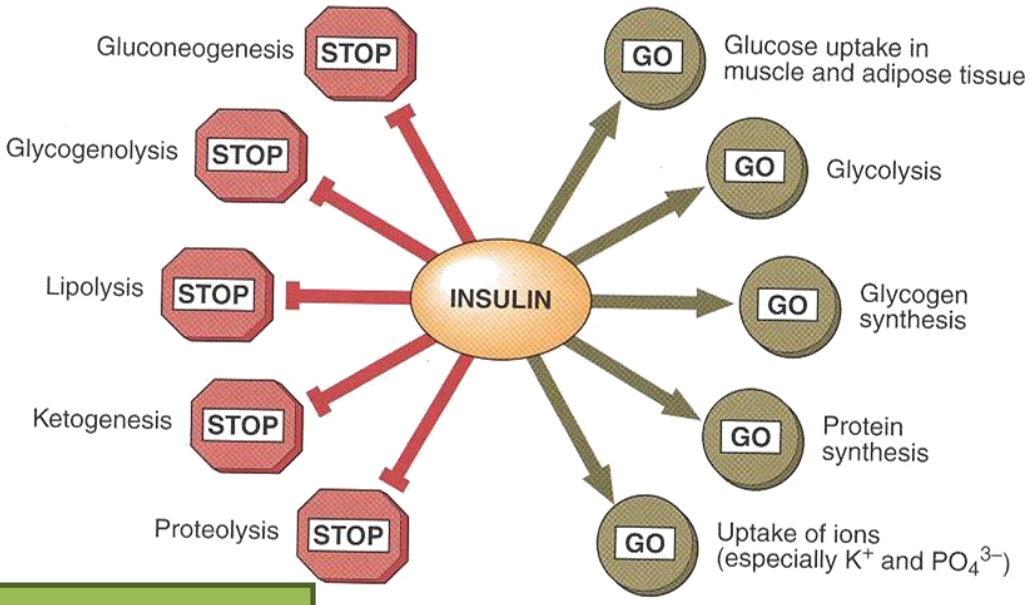
- **Insulin** (lowers blood glucose level)
- **Glucagon**
- Somatostatin
- Cortisol
- Growth hormone
- Adrenaline

} Antagonize insulin action.



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
- Formed as prepro-insulin and converted to pro-insulin upon secretion
- Rise in blood glucose level stimulates insulin secretion
- Promotes entry of glucose into cells



Actions of Insulin

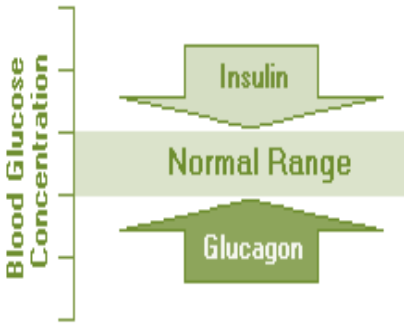
MECHANISM OF ACTION:

- The insulin receptor is present on the plasma membrane of cell (tyrosine kinase cascade)
- Composed of
  - 2α-subunit (extracellular)
  - 2β-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
- 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 (they need glucose all the time)
- Stimulates glycogen synthesis (glycogenesis)
- Decreases blood glucose levels
- Increases glycolysis
- Stimulates protein synthesis
- Insulin deficiency causes diabetes mellitus (type 1)
- Hyperinsulinemia is due to insulin resistance in:
  - Diabetes mellitus (type 2)
  - Or Metabolic syndrome



GLUCAGON:

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

SOMATOSTATIN:

- A peptide hormone secreted by δ-cells of pancreatic islets, stomach, hypothalamus 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
- Inhibits glucose uptake by cells
- Stimulates fat breakdown in adipose tissue

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

Questions:

Q1: Glucose uptake by liver cells is:
A. Energy-consuming
B. A saturable process
C. Insulin-dependent
D. Insulin-independent

Q2: The conversion of alanine to glucose is termed:
A. Glycolysis
B. Oxidative decarboxylation
C. Specific dynamic action
D. Gluconeogenesis

Q3: Which of following sources is used in phase III of glucose homeostasis:
A. Glycogenolysis
B. Fatty acid oxidation
C. Gluconeogenesis
D. Diet

Q4. Which of the following is an action of insulin:
A. Simulate ketogenesis
B. inhibit glucose up take in muscle
C. stimulate glycogenolysis
D. Lipogenesis

Q5. Regarding the action of glucagon:
A. It stimulates glycogenolysis
B. It stimulates glycolysis
C. It inhibits glycogenolysis
D. It stimulates insulin activity

Answers:

- D
- D
- C
- D
- A

BEST OF LUCK!!