جامعة الملك سعود
King Saud University

"اللَّهُمَّ لا سَهْلَ إلاَّ ما جَعَلْتَهُ سَهْلاً، وأنْتَ تَجْعَلُ الحَزْنَ إذَا شِئْتَ سَهْلاً "

Biochemistry437

Glucose Homeostasis

Biochemistry Team 437

Color index:
Doctors slides
Doctor's notes
Extra information
Highlights

Endocrine block

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Objectives:

By the end of this lecture, students should be able to:

- Define glucose homeostasis and the metabolic processes involved
- Differentiate between different phases of glucose homeostasis
- Discuss the primary sources of energy and major organs utilizing glucose during the five phases of homeostasis
- Understand the role of hormones in maintaining glucose homeostasis

Overview:

- Introduction
- Sources of glucose
- Phases of glucose homeostasis
- Hormones in glucose homeostasis (actions, role in CHO metabolism)
    - Insulin
    - Glucagon
    - Cortisol
    - Growth hormone
    - Epinephrine

Glucose Homeostasis

- A process that
  - Controls glucose metabolism[1] and
  - Maintains normal blood glucose level in the body
- Glucose is a major source of body's energy
- The liver plays a key role in maintaining blood glucose level[2]
- It is tightly controlled as the brain constantly needs glucose[3]
- Severe hypoglycemia can cause coma and death
- Chronic hyperglycemia results in glycation[4] of proteins, endothelial dysfunction and diabetes mellitus

1- Main pathways: glycolysis+gluconeogenesis+glycogenolysis+glycogenesis
2- The kidney has a role as well, but muscles do not play a role in glucose homeostasis
3- a process of adding sugar to a protein or a lipid in a haphazard manner
4- to provide energy for all body tissues, especially brain and RBCs, and to prevent the adverse effects of hyperglycemia

Sources of Glucose

Dietary Sources

- Dietary CHOs are digested 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

*But not not glycogenolysis, because glycogen is already derived from glucose (stored form of glucose) whereas gluconeogenesis is generation of glucose from certain non-carbohydrate carbon substrates.

Sources of Glucose

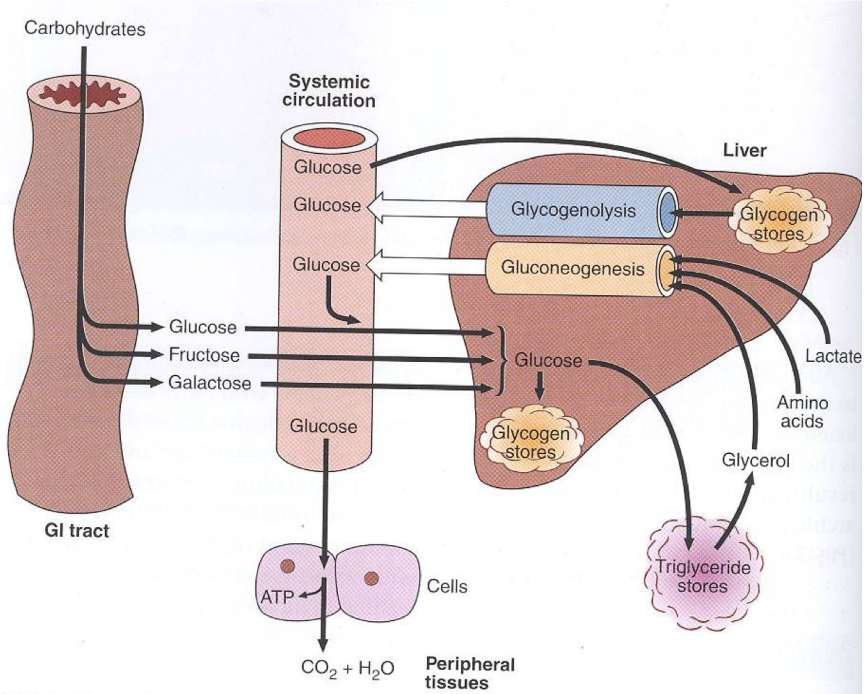

Fig. 1 **Glucose homeostasis.**

1- Dietary glucose, fructose and galactose are absorbed to the bloodstream.

2- Some of it goes to the peripheral tissue to be used as energy, and the remaining goes to the liver where:

- Fructose and galactose are converted into glucose
- Some of the glucose is used to make glycogen
- The extra glucose "amount above glycogen formation limit" will be converted into fatty acids and triglycerides then sent to adipose tissue for storage

3- When blood glucose levels go down:

- The adipose tissue break down fat and produces glycerol which goes back to the liver and forms glucose (gluconeogenesis)
- Glycogen is broken down (glycogenolysis)
- We start forming glucose from amino acids and lactate from muscles(by cori cycle). (gluconeogenesis).

Phases of Glucose Homeostasis

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Five Phases:

(within parentheses) the the source of energy is shown

Glucose homeostasis is approximately divided into 5 phases, these 5 phases can overlap

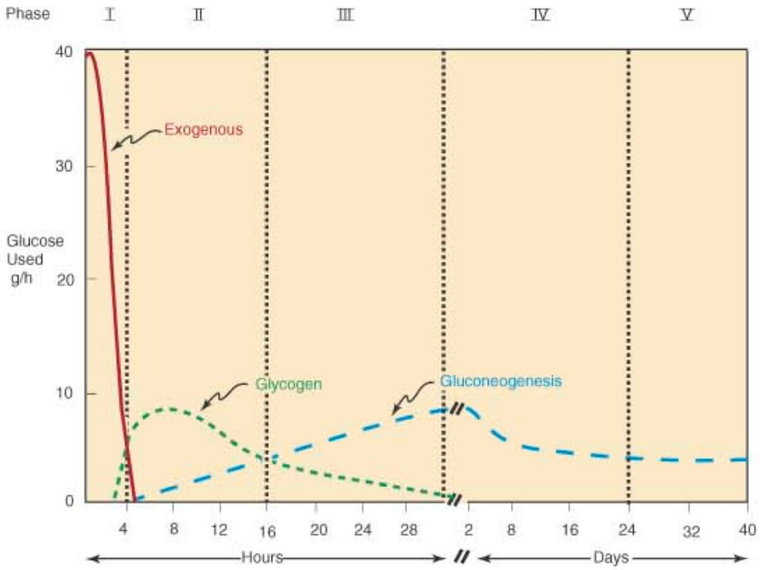
Phase I *	Phase II	Phase III	Phase IV	Phase V
(Well-fed state) (Git phase)	(Glycogenolysis)	(Gluconeogenesis)	(Glucose, ketone bodies (KB) oxidation)	(Fatty acid (FA), KB oxidation)

Phase 1: initial increase in blood glucose after a meal, followed by lowered glucose due to utilization. ***Its also called postprandial phase.**

Phases 2-5: during starvation, as the blood level of sugar goes down below normal, the body will start the glucose providing mechanisms

Don’t skip the picture!

A study done for Treatment of obesity by complete starvation

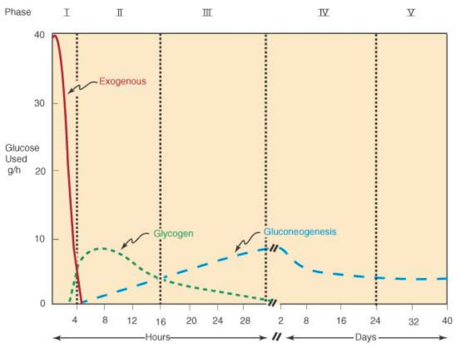


Phase	ORIGIN OF BLOOD GLUCOSE	TISSUES USING GLUCOSE	MAJOR FUEL OF BRAIN
I	Exogenous	All	Glucose
II	Glycogen Hepatic gluco–neogenesis	All except liver. Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis Glycogen	All except liver. Muscle and adipose tissue at rates intermediate 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

This was a study done where obese patients were made to undergo starvation as a treatment for their obesity, the graph shows the response of the body to starvation and low blood glucose including the 5 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[1] and glucose-alanine[2] cycles are inhibited



- This phase Starts right after eating where Blood Glucose levels are initially increased.

- It slowly starts decreasing back to normal due to utilization by various body tissues.

- Depending on how much the meal was this phase can go up to 6-8 or 4-6 hours .

- If starvation continuous blood glucose levels will decrease below normal and glycogen will start to breakdown “phase 2”.

- **Note that the phases overlap**.

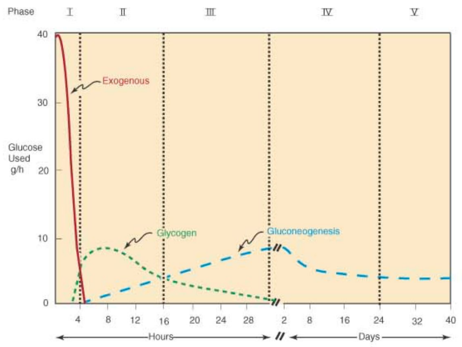
- In this phase, all tissues including the brain use glucose.

[1]Cori cycle: lactate produced by the muscles ,goes to the liver and get converted into glucose.
[2]Glucose-alanine cycle: alanine produced from the muscles,converted to glucose,comes back and get converted to alanine.

Phase II (Glycogenolysis)

- Phase II starts during early fasting when dietary glucose supply is exhausted
- Hepatic glycogenolysis and gluconeogenesis* maintain blood glucose level in this phase
- Major sources of blood glucose in this phase:
  - Glycogenolysis(major) and gluconeogenesis(minor)

- Glycogen is the first molecule that comes to rescue the blood glucose level.
- Depending on how much glycogen was present in the liver (glycogen stores) it can go up to 16-20 hours , and gluconeogenesis is started before the glycogen stores in the body are exhausted.
- Gluconeogenesis is continuously happening all the time except in Phase 1(postprandial phase) due to insulin action.



Phase II (Glycogenolysis)

What happens during early fasting stage?

- When fasting glucagon is released, but it doesn't do anything because all stores are finished.
- Glycogen starts to breakdown to provide glucose which goes to the brain,RBCs and muscles.
- Muscles produce alanine and lactate which goes to the liver to get converted into glucose.
- Adipose tissue is still not involved.

Why people don't lose weight during fasting in ramadan ?

- Because the body uses glycogen stores while fasting. After eating they remake the glycogen stores (fat stores are not even touched)

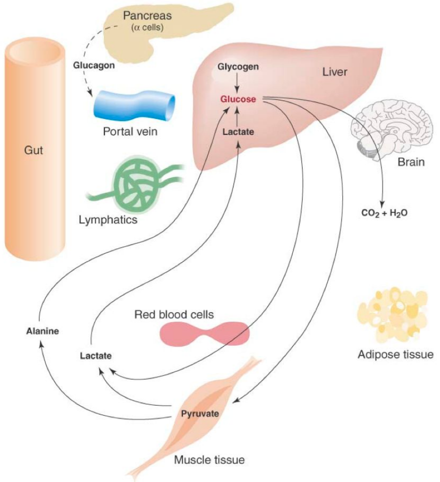


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

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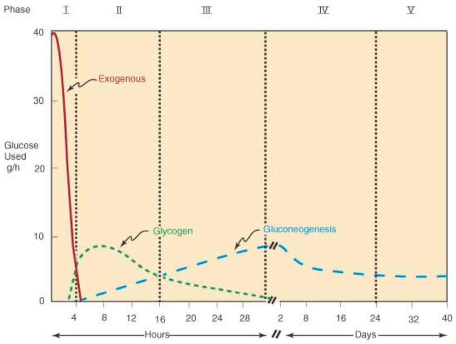
Phase III (Gluconeogenesis)

- 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[1]
- Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level
- Gluconeogenesis Is the major source of blood glucose in this phase

-After glycogen the other molecules that are involved in gluconeogenesis rescue the blood levels.
[1] Inactive — prolonged
Active — short phase



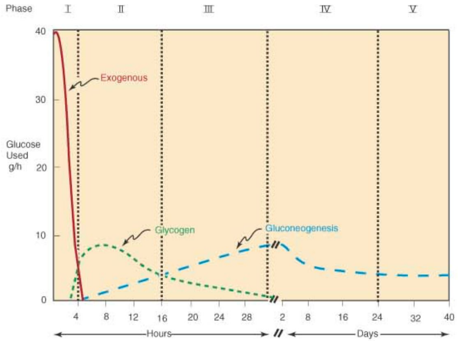
Phase IV (Glucose and KB oxidation)

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

- In both phases 3 and 4 there is gluconeogenesis but in phase 3 mainly hepatic while in phase 4 both hepatic and renal gluconeogenesis.

- In phase 4 only the tissue that critically need glucose like the brain , RBCs uses it , the rest of the tissue uses ketone bodies for energy.

- Ketone body : byproduct of fatty acids oxidation
(acetone , acetoacetate and beta-hydroxybutyrate)
During starvation they are used by the tissue “including the brain” for energy.



Phase V (FA and KB 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

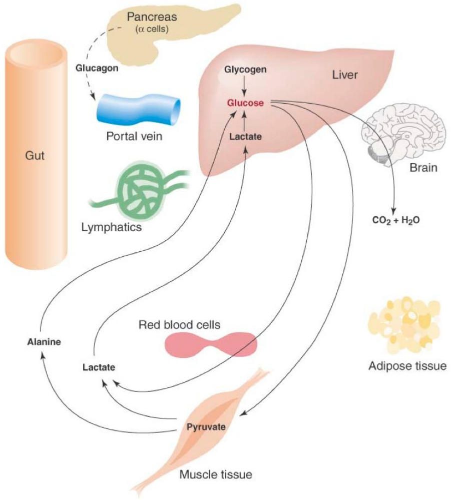


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

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If this phase continues, ketone bodies and fatty acid (fat stores) will end up, protein will start breaking down — severe protein loss, and before the protein finish the person will die.

Hormones and Glucose Homeostasis

Hormones that regulate glucose metabolism:

Mainly insulin and glucagon

- Insulin
- Glucagon
- Cortisol
- Growth Hormone
- Adrenaline

Insulin: (Lowers blood glucose level)

Glucagon, Cortisol, Growth Hormone, Adrenaline: Antagonize insulin action (Increase blood glucose level)

Insulin

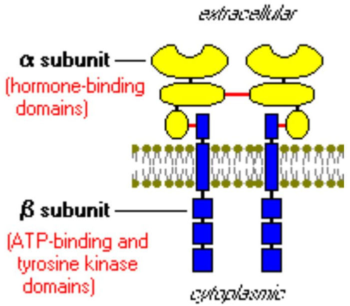
- Plays a major role in glucose homeostasis.
- Synthesized by the b-cells of islets of Langerhans of pancreas.
- A small protein composed of two chains.
- Rise in blood glucose level stimulates insulin secretion.
- Promotes entry of glucose into cells.

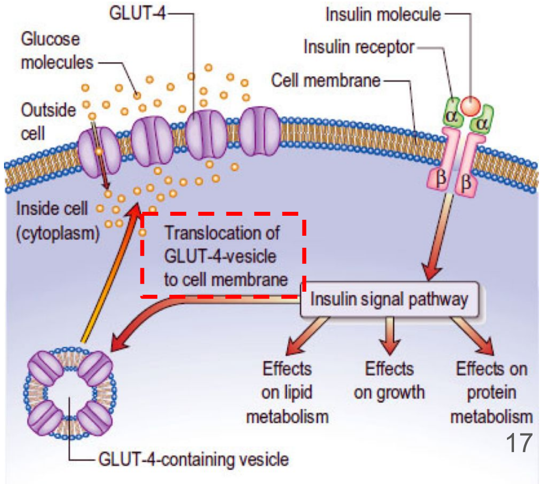
- **Muscle & adipose** tissue have **GLUT4** which is insulin **dependant** transporter.
- **Hepatocytes & intestine** have **GLUT-2** which is insulin **independent** transporter.
- GLUT-5 is for fructose transport not glucose

Insulin actions	
Stimulates	**Inhibits**
Glucose uptake in muscle and adipose	Gluconeogenesis
Glycolysis	Glycogenolysis
Glycogen synthesis	Lipolysis
Protein synthesis	ketogenesis
Uptake of Ion (K+ and PO4)	proteolysis

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. (glucose homeostasis)





- Glut4 containing vesicles are present in the cytoplasm
- Insulin causes translocation of Glut4 to the cell membrane to facilitate glucose uptake

Insulin and CHO Metabolism

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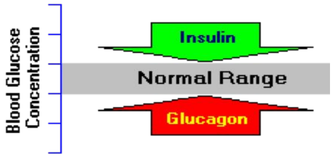
Promotes glucose uptake into cell:

- 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

- 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
  - Metabolic syndrome

Sometimes insulin is present, but the receptors are defected, so glucose can’t enter inside the cells

Hormones and Glucose Homeostasis

Glucagon	Glucocorticoids (Cortisol)	Growth hormone	Epinephrine
A **peptide** hormone	**A steroid** hormone	**A protein** hormone	**A catecholamine** hormone
secreted by **α-cells of pancreatic islets** in response to hypoglycemia.	secreted by **adrenal gland.** In response to stress or hypoglycemia	secreted by **anterior pituitary gland.**	**adrenal gland** In response to sympathetic stimulation
Increases glucose levels by: ● Stimulates glycogenolysis. ● Activates hepatic gluconeogenesis.  	-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.	-Maintains blood glucose levels by: ● Inhibiting insulin action. ● Stimulating gluconeogenesis in the liver.	-Stimulates lipolysis in adipose tissue when blood glucose levels fall. -Promotes glycogenolysis in skeletal muscle. (but REMEMBER: that DOES NOT contribute to the homeostasis of glucose in blood, it's a fight or flight hormone, not for maintaining the blood glucose level)

Summary

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)
Origin of blood glucose	• Glucose is mainly supplied by **dietary CHOs** • Liver removes about 70% of glucose load after a CHO meal	• Hepatic glycogenolysis maintains blood glucose level in this phase • **Glycogenolysis** is the major source of blood glucose in this phase	• **Gluconeogenesis** is the major source of blood glucose in this phase • Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level • Glycogen	Hepatic & Renal gluconeogenesis	• Hepatic & Renal gluconeogenesis • Gluconeogenesis somewhat maintains blood glucose level in this phase
Tissue using glucose	All body tissues use dietary glucose for energy in this phase	All except liver . Muscle and adipose tissue. At diminished rate	All except liver . Muscle and adipose tissue. At diminished rate	Brain , RBCS , renal medulla . Small amount by muscle	• **All body tissues use FA and KB oxidation for energy production** • brain at a diminished rate , RBC , Adrenal medulla
Major fuel for brain	Glucose	Glucose	Glucose	**Brain uses both glucose and KB for energy**	glucose and KB
Notes	• 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 and glucose-alanine cycles are inhibited** • **Some glucose is converted to glycogen for storage in the liver (glycogenesis)**	• Phase II starts during early fasting when dietary glucose supply is exhausted	• Phase III starts when glycogen stores in liver are exhausted (within 20 hours) • Duration of phase III depends on o Feeding status o Hepatic glycogen Stores o Physical activity	• Several days of fasting leads to phase IV • Gluconeogenesis starts to decrease • KB accumulation increases which enter the brain for energy production	• Prolonged fasting leads to phase V • Less dependence on gluconeogenesis • 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

MCQs:

1.Chronic hyperglycemia results in
A) Protein oxidation
B) endothelial dysfunction
C) hepatocyte destruction
D) glycation of fat

2.Which of the following converted to glucose in the liver
A) Fructose
B) Maltose
C) Sucrose
D) Starch

3.Which one of the following is the third phase of glucose homeostasis
A) Glycogenolysis
B) Gluconeogenesis
C) Glucose oxidation
D) Glycogen oxidation

4.Which one of the following does the insulin stimulates
A) Glycogenolysis
B) Gluconeogenesis
C) Glycolysis
D) Lipolysis

5.which one of the following Antagonize insulin action
A) Thyroxine
B) LH
C) GH
D) MSH

1- B
2- A
3- B
4- C
5- C

Team leaders

- رهام الحلبي
- معاذ الحمود

Boys team

Girls team

- ريناد الغريبي
- رهف الشنيبر
- نورة بن حسن
- اروى الجهني
- شهد الجبرين

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