Revised & Approved

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BIOCHEMISTRY TEAM
439

MED439
KING SAUD UNIVERSITY

Glucose Homeostasis

Editing File

Color Index

- Main Text
- Important
- Extra
- Dr.'s Notes
- Girls slides
- Boys slides

Objectives

- 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 **and** □ Maintains 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
- Blood glucose level is tightly controlled because the brain constantly needs glucose
- Severe hypoglycemia can cause coma and death
- Chronic hyperglycemia results in glycation of proteins, endothelial dysfunction and diabetes.

Sources of glucose

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

→ **Dietary sources**

→ **Metabolic sources**

(via gluconeogenesis **):**

□ Glycerol, lactate, pyruvate, glucogenic amino acids

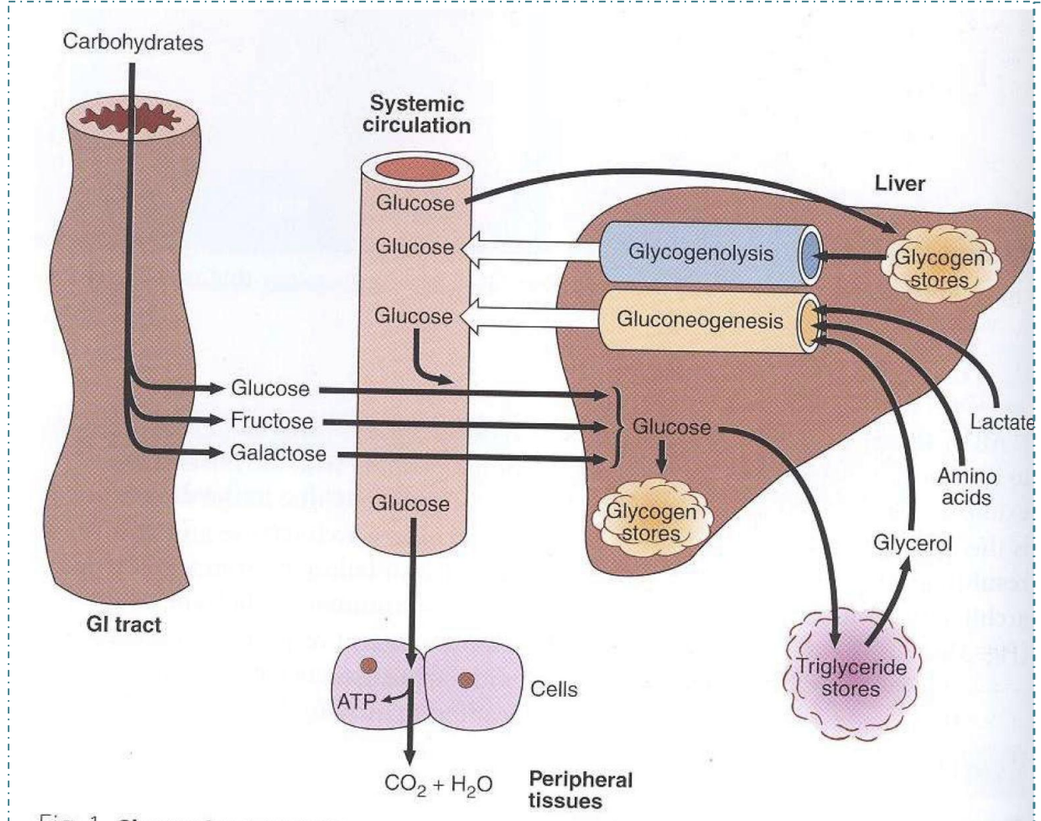


Fig. 1 **Glucose homeostasis.**

Dr's explanation :

1- Lactate (not hypoxia) (comes from the body tissue because of the absence of (pyruvate dehydrogenase) this enzyme is inhibited in the **fasting state**.

2- Glycerol comes from fatty acid oxidation.

3- Amino acids come from muscles

N.B : gluconeogenesis can occur in the kidney but only in starvation

Phases of glucose homeostasis

(Not separated phases they are overlapped)

Phase I — Well-fed state (Postprandial state) — 1

Phase II — Glycogenolysis — 2

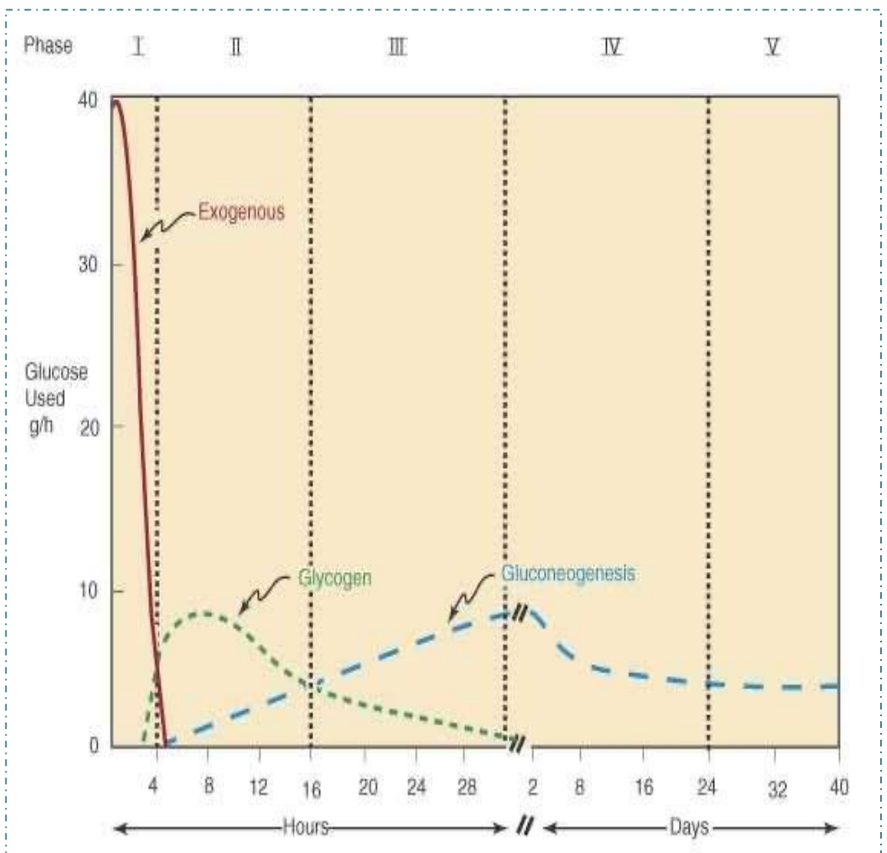
Phase III — Gluconeogenesis — 3

Phase IV — Glucose, ketone bodies (KB) oxidation — 4

Phase V — Fatty acid (FA), KB oxidation — 5

Before you start keep that in your mind :
1- What is providing glucose in the blood?
2- What are the different organs that used as a fuel?

Phase	Origin of blood glucose	Tissue using glucose	Major fuel of brain
I	Exogenous	All	Glucose
II	Glycogen(major source) , Hepatic gluconeogenesis	All except liver(Liver is the first organ that switch to fatty acid) , Muscle and adipose tissue at diminished rates	Glucose
III	Hepatic gluconeogenesis(major source) , 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 RBC and renal medulla cannot take ketone bodies	Ketone bodies(mainly), glucose



- Exogenous glucose comes from diet .
- (As we see the phases are overlapped, as glycogen decreases the gluconeogenesis increases).

Phases of glucose homeostasis

Well-fed state

Origin of glucose — Glucose is mainly supplied by dietary CHOs

Actions

- 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

Inhibited

- Gluconeogenesis
- Cori and glucose-alanine

Gluconeogenesis

Origin of glucose — Hepatic gluconeogenesis from lactate, pyruvate, glycerol and alanine maintains blood glucose level

Start — when glycogen stores in liver are exhausted (within < 20 hours)

Major source of glucose — Gluconeogenesis

Duration — **depends on :** Feeding status , Hepatic glycogen stores and Physical activity.

FA and KB oxidation

(Maximum fat burning takes place in this phase)

Origin of glucose — Hepatic & Renal gluconeogenesis

Start — Prolonged fasting leads to phase V

Actions

- 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) **because** :
  - Muscles contain amino acids that can be used in gluconeogenesis
  - Muscles are the last source of energy, to give you a chance to escape the situation

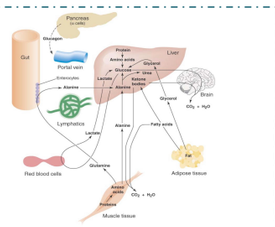


Figure 22.4. Metabolic interrelationships of major tissues in fasting state.
Textbook of Biochemistry With Clinical Correlations, Sixth Edition. Edited by: Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

The picture : Fatty acid mobilized out of adipose tissue and used by muscles to produce energy and their byproduct which is ketone bodies they are synthesized again in the liver through fatty acid oxidation and these ketone bodies are used by the brain and some of them are used by the muscle as well .

Phase I → **Phase II** → **Phase III** → **Phase IV** → **Phase V**

Glycogenolysis

Origin of glucose — Hepatic glycogenolysis(major source) and gluconeogenesis maintain blood glucose level in this phase

Start — During early fasting when dietary glucose supply is exhausted

Major source of glucose — Glycogenolysis and gluconeogenesis

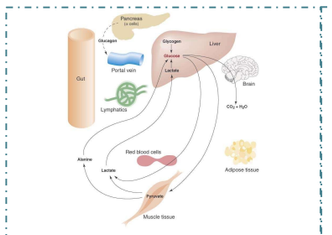


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.
Textbook of Biochemistry With Clinical Correlations, Sixth Edition. Edited by: Thomas M. Devlin. Copyright © 2006 John Wiley & Sons, Inc.

1- **In this phase,** the adipose tissue does not start breaking down its fat.

2- **Cori cycle :** When amino acids go back to the liver to get converted into glucose

Glucose and KB oxidation

Origin of glucose — Hepatic & Renal gluconeogenesis

Start — Several days of fasting

Actions

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

Hormones and glucose homeostasis

(Major hormones in glucose homeostasis are insulin and glucagon the remaining are minor)

Hormones that regulate glucose metabolism:

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

Antagonize insulin action

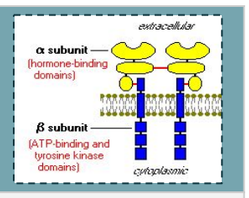
Insulin

- 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

Insulin Actions

Inhibits	Stimulate
Gluconeogenesis	Glucose uptake in muscles and adipose
Glycogenolysis	Glycolysis
Lipolysis	Glycogen synthesis
Ketogenesis	Protein synthesis
Proteolysis	Uptake of ion (K^+ and PO_4^{3-})

Insulin's MOA



The insulin receptor is present on the plasma membrane of cell

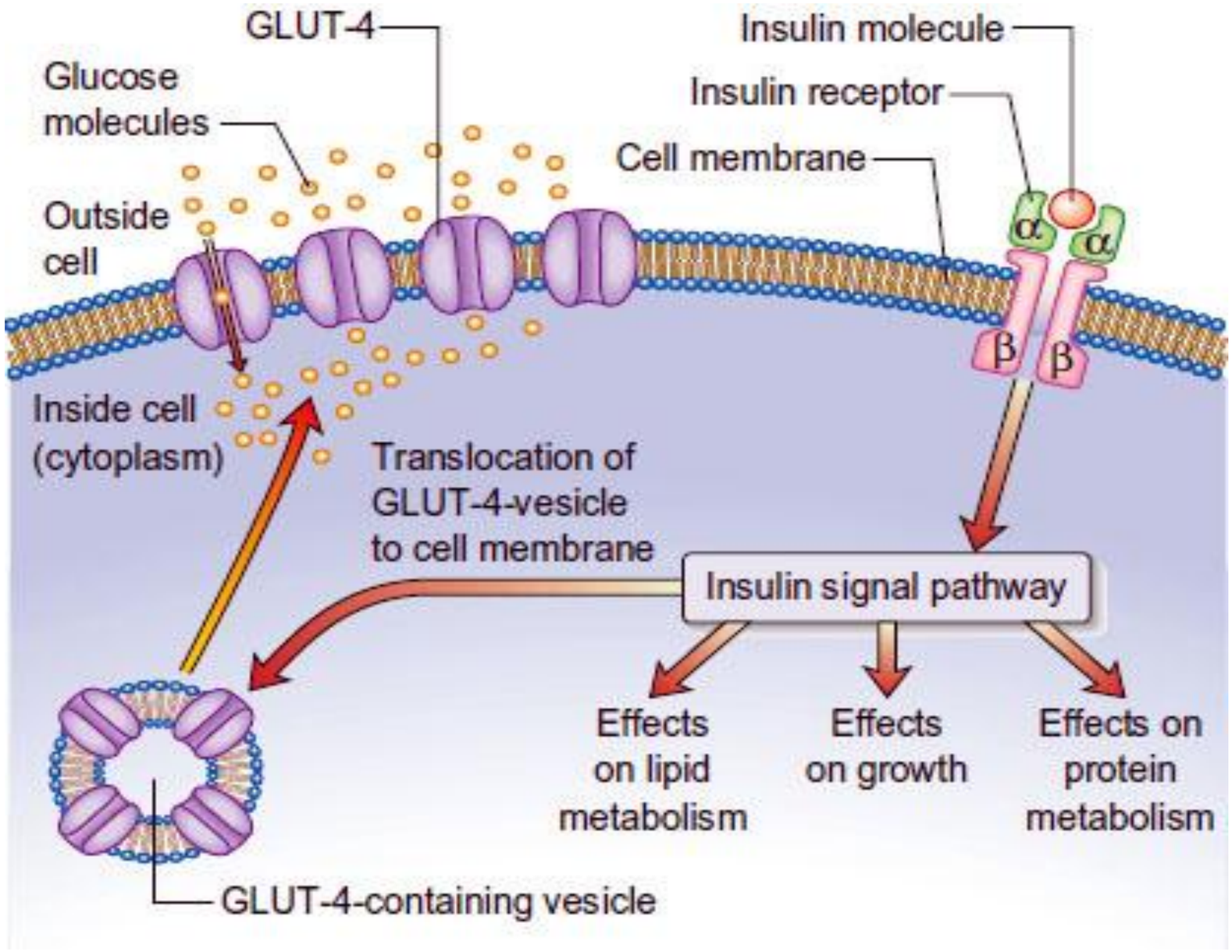
Composed of:
- 2α-subunit (extracellular)
- 2β-subunit (cytoplasmic) (transmembrane)

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:

1. Glucose is diffused into cells through hexose transporters such as GLUT4
2. GLUT4 is present in cytoplasmic vesicles
   GLUT4 vesicles are channels which present inside the cell that promote entry of glucose into the Cell
3. Insulin binding to its receptor causes vesicles to diffuse into plasma membrane
4. GLUT4 is inserted into the membrane
5. Allowing glucose transport into the cell
6. Brain and liver have non insulin dependent glucose transporter

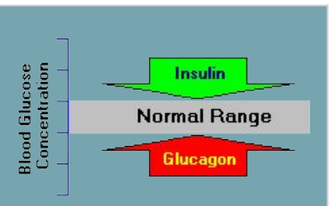
Insulin's MOA in decreasing blood glucose levels:

1. Stimulates glycogen synthesis
2. Decreases blood glucose levels
3. Increases glycolysis
4. Stimulates protein synthesis
5. Insulin deficiency causes diabetes mellitus
6. Hyperinsulinemia is due to insulin resistance in:
   - Diabetes mellitus
   - Metabolic syndrome

   Insulin resistance= receptor defect or action defect

Hormones that antagonize insulin actions

Glucagon



A peptide hormone secreted by α-cells of pancreatic islets

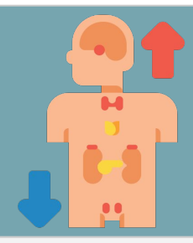
Secreted in response to hypoglycemia

Increases glucose levels

Stimulates glycogenolysis

Activates hepatic gluconeogenesis

Glucocorticoids (Cortisol)



Cortisol is a steroid hormone secreted by adrenal gland

Contributes to glucose homeostasis

Maintains normal glucose levels in fasting by:

- 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

Extra **Summary**

Glucose	Sources of glucose	• Dietary sources : CHO (starch , fructose and galactose) • Metabolic sources : Glycerol, lactate, pyruvate, glucogenic amino acids (**via** gluconeogenesis)	
	Glucose homeostasis	• **A process that :** Controls glucose metabolism **and** □ Maintains blood glucose level in the body • 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 glycation of proteins, endothelial dysfunction and diabetes.	
	Phases of glucose homeostasis	**Phase I** (Well-fed state) **Phase II** (Glycogenolysis) **Phase III** (Gluconeogenesis) **Phase IV** (Glucose and KB oxidation) **Phase V** (FA and KB oxidation)	
	Hormones that regulate glucose homeostasis	• Insulin • Glucagon • Cortisol • Growth hormone • Epinephrine	
Insulin	Overview	• Plays a major role in glucose homeostasis • Synthesized by the β-cells of islets of Langerhans of pancreas	
	Actions	**Stimulate** ON	Glucose uptake in muscle and adipose tissue, glycolysis, glycogen synthesis, protein synthesis and uptake of ions
		Inhibit OFF	Gluconeogenesis, glycogenolysis, lipolysis, ketogenesis, proteolysis
	MOA	Binding of insulin to α-subunit causes phosphorylation of β-subunit → activates the receptor → the activated receptor then phosphorylates intracellular proteins generating a biological response	
Glucagon	Overview	A peptide hormone secreted by α-cells of pancreatic islets	
	Secretion	Secreted in response to hypoglycemia	
	Actions	Increases glucose levels Activates glycogenolysis Activates hepatic gluconeogenesis	
Cortisol	Overview	Cortisol is a steroid hormone secreted by adrenal gland contributes to glucose homeostasis	
	Actions	- Maintains normal glucose levels in fasting by: • Stimulates gluconeogenesis in the liver • Mobilizes amino acids for gluconeogenesis • Inhibits glucose uptake by cells* - Stimulates fat breakdown in adipose tissue	
Growth hormone	Overview	A protein hormone secreted by anterior pituitary gland	
	Actions	Maintains blood glucose levels by: • Inhibiting insulin action • Stimulating gluconeogenesis in the liver	
Epinephrine	Overview	A catecholamine secreted by adrenal glands	
	Actions	• Stimulates lipolysis in adipose tissue when glucose blood levels fall • Promotes glycogenolysis in skeletal muscle	

Take Home Messages

- Glucose homeostasis is a process that controls glucose metabolism and maintains blood glucose level in the body

- There are five phases of glucose homeostasis - 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)

- Hormones that regulate glucose metabolism include insulin (lowers glucose level) and glucagon (increases glucose level

- Other hormones such as cortisol ,growth hormone and adrenaline are known to antagonize the actions of insulin thus increases the blood glucose level

MCQs

1- Which structure plays a key role in maintaining blood glucose level?			
A-Kidney	B-Intestines	C-Liver	D-Brain
2- Which process is inhibited during Phase I ?			
A-Glycogenolysis	B-Gluconeogenesis	C- KB oxidation	D-proteolysis
3-When Does Phase III takes place?			
A-glycogen stores in liver are exhausted	B- Dietary glucose supply is exhausted	C-Prolonged fasting	D-Early Fasting
4- Which one of the following does the insulin Inhibits?			
A- Glycolysis	B- Glycogenolysis	C- Glycogen synthesis	D- Protein synthesis
5- A peptide hormone secreted by α-cells of pancreatic islets:			
A- Cortisol	B- Epinephrine	C- Glucagon	D- Growth hormone
6- What is the organ that has non insulin dependent glucose transporter?			
A- Brain	B- Liver	C- Kidney	D- A&B

Answers key

1-C 2-B 3-A 4-B 5-C 6-D

SAQs

1- What are the complications of chronic hyperglycemia ?

glycation of proteins, endothelial dysfunction and diabetes

2- What are the 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

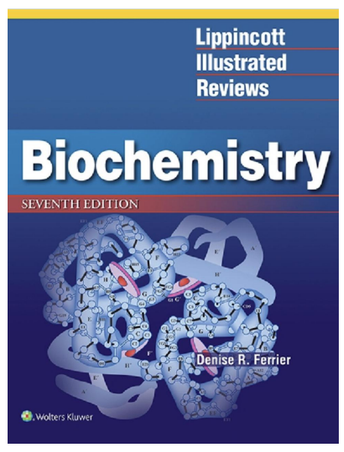
-Metabolic sources: (via gluconeogenesis): Glycerol, lactate, pyruvate, glucogenic amino acids

3- How does Glucagon contribute in maintaining blood glucose?

Stimulates glycogenolysis, Activates hepatic gluconeogenesis.

Resources

Click on the book to download the resource



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