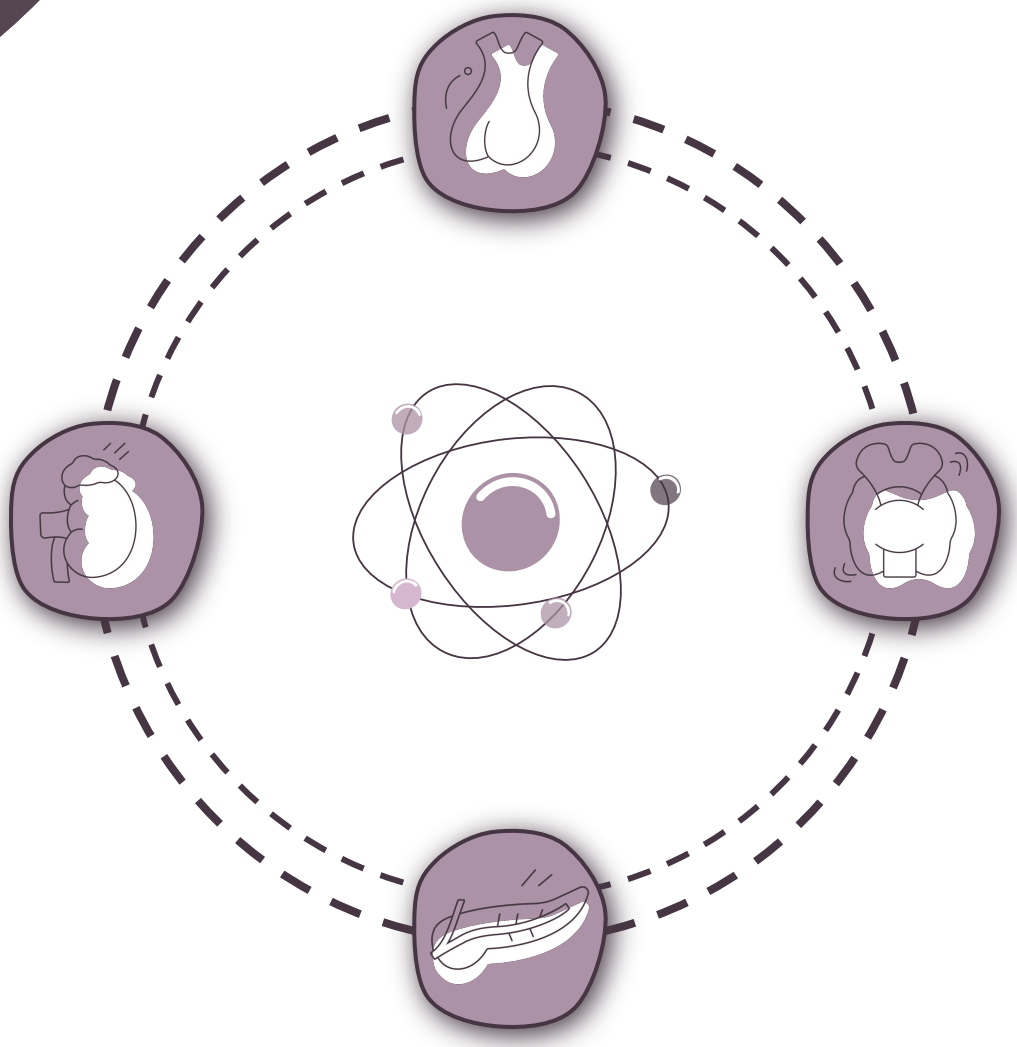

L6: Glucose homeostasis

Color Index:
Main Text
Male's Slides
Female's Slides
Important
Doctor's Notes
Extra Info

Editing File link:

Objectives

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

To be in touch: click on the icons

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1

Glucose homeostasis

Glucose homeostasis

- A process that : Controls glucose metabolism 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.
- 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 mellitus.

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.

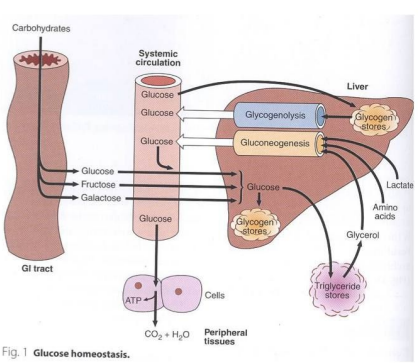


Fig. 1 Glucose homeostasis.

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.

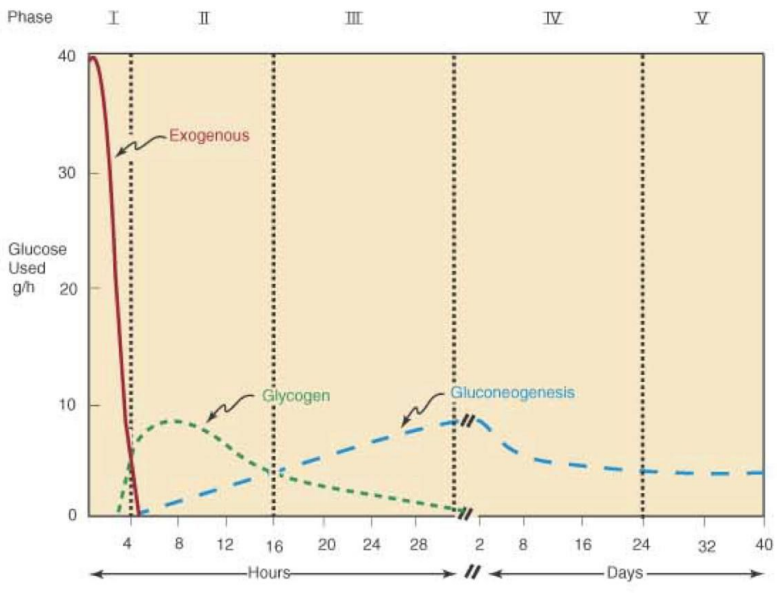
2 Phases of Glucose Homeostasis

KB : Ketone Bodies

Phases of Glucose Homeostasis

- **Phase I** Well-fed state
- **Phase II** Glycogenolysis
- **Phase III** Gluconeogenesis
- **Phase IV** Glucose, KB oxidation
- **Phase V** Fatty acid, KB oxidation

	Origin of Blood Glucose	Tissue Using Glucose	Major Fuel of Brain
Phase I	**Exogenous**	**All**	**Glucose**
Phase II	**Glycogen** (major) **Hepatic gluconeogenesis** (minor)	**All except Liver, Muscle and adipose tissue at diminished rates.**	**Glucose**
Phase III	**Hepatic gluconeogenesis** (major) **Glycogen** (minor)	**All except liver, Muscle and adipose tissue at rates intermediate between II and IV.**	**Glucose**
Phase IV	**Gluconeogenesis both Hepatic and Renal** (only start in 4th)	**Brain, RBCs, renal medulla. small amount by muscle.** *Note that it's not deliver to adipose, because it starts using ketone bodies as brain fuel.	**Glucose** **ketone bodies**
Phase V	**Gluconeogenesis both Hepatic and Renal**	**Brain at diminished rate, RBCs,renal medulla.** RBC and renal medulla Cannot take ketone bodies as fuel	**Ketone bodies** **Glucose**



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

3

Phases of Glucose Homeostasis

Phase I | Phase II | Phase III | Phase IV | Phase V

Origin of glucose	Glucose is mainly supplied by **dietary CHOs.**
Action	- 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** and lipolysis **is inhibited.** - **Cori cycle.** (Lactate from muscle, and it convert to glucose in liver) - **glucose-alanine cycles.** Alanine from muscle→ glucose (in liver) *No need for gluconeogenesis in phase 1 and it is inhibited by insulin.

Phase I | **Phase II** | Phase III | Phase IV | Phase V

Origin of glucose	**Hepatic glycogenolysis and gluconeogenesis** maintain blood glucose level in this phase.
Start	during early fasting when dietary glucose supply is exhausted.
Major source of blood glucose	Glycogenolysis and **gluconeogenesis.**

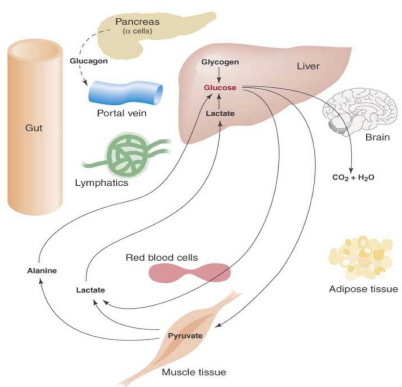


Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

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.

4

Phases of Glucose Homeostasis

Phase I | Phase II | **Phase III** | Phase IV | Phase V

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 blood glucose	**Gluconeogenesis.**
Duration	**depends on: 1- Feeding status. 2- Hepatic glycogen stores. 3- Physical activity.**

Phase I | Phase II | Phase III | **Phase IV** | Phase V

Origin of glucose	**Hepatic & Renal gluconeogenesis.**
Start	Several days of fasting leads to phase IV.
Action	- 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 I | Phase II | Phase III | Phase IV | **Phase V**

Origin of glucose	**Hepatic & Renal gluconeogenesis.** Click here for an explanation
Start	Prolonged fasting leads to phase V.
Action	- **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 concentration. 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.**

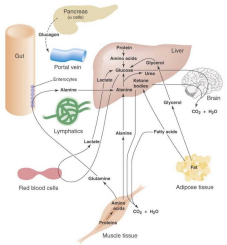
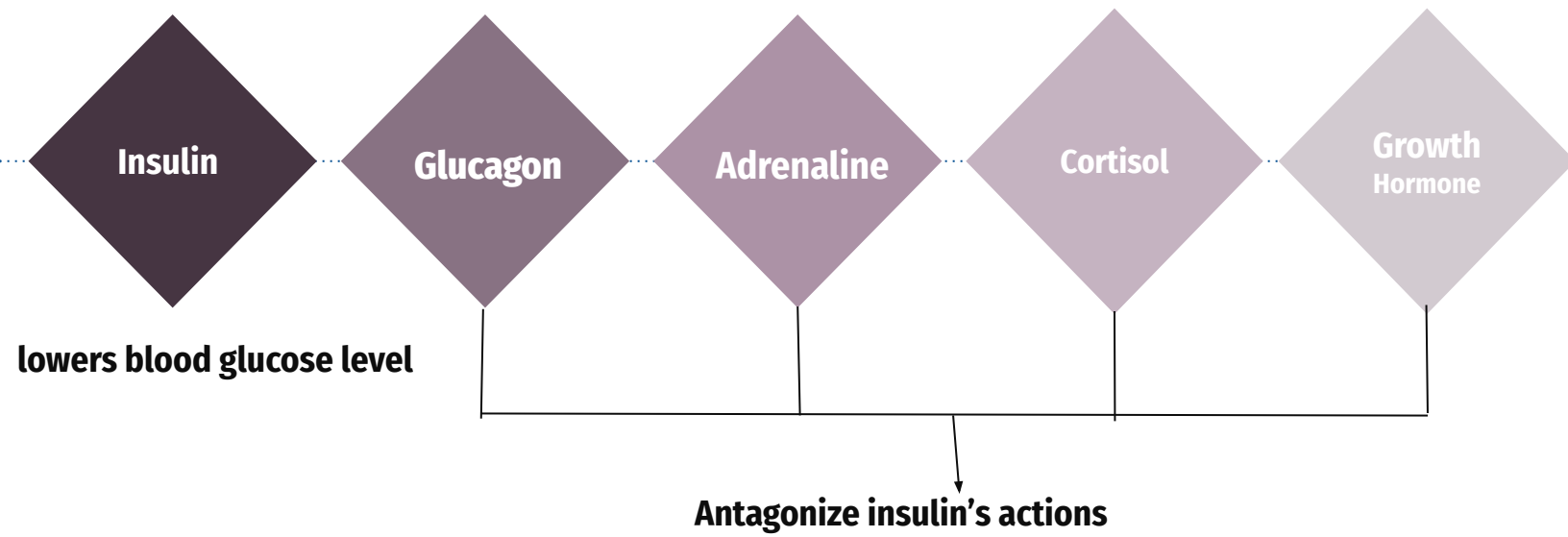


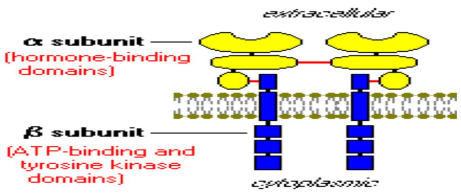
Figure 22.4. Metabolic interrelationships of major tissues in fasting state.

5 Hormones and Glucose Homeostasis

Hormones that regulate glucose metabolism :



Insulin



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

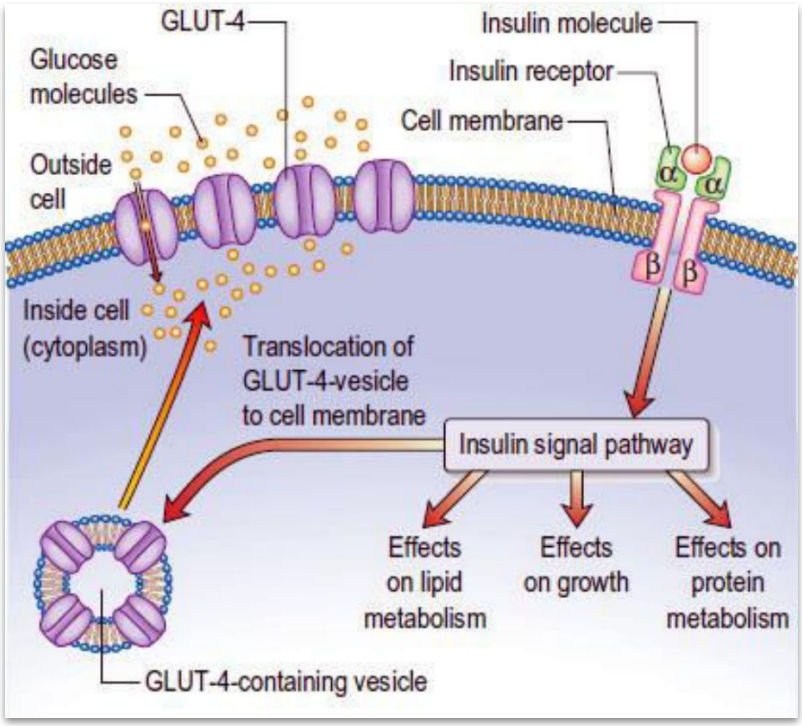
Insulin's MOA

- The insulin receptor is present on the plasma membrane of cell
- 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 actions

Stimulate	Inhibit
Glucose uptake in muscles and adipose	Gluconeogenesis
Glycolysis	Glycogenolysis
Glycogen synthesis	Lipolysis
Protein synthesis	Ketogenesis
Uptake of ions (K+ and PO43-)	Proteolysis

6 Insulin and CHO metabolism



Linda (Extra)

Insulin MOA (linda):

1. Insulin binds to the α subunits of the tetrameric insulin receptor, producing a conformational change in the receptor. The conformational change activates tyrosine kinase in the β subunits, which phosphorylate themselves in the presence of ATP. In other words, the β subunits autophosphorylate.

2. Activated tyrosine kinase phosphorylates several other proteins or enzymes that are involved in the physiologic actions of insulin, Phosphorylation either activates or inhibits these proteins to produce the various metabolic actions of insulin (eventually GLUT-4 translocate to the cell membrane).

Promotes glucose uptake into cell:

1- Glucose is diffused into cells through hexose transporters such as GLUT4.

2- GLUT4 is present in cytoplasmic vesicles.

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:

Stimulates glycogen synthesis.

Decreases blood glucose levels.

Increases glycolysis.

Stimulates protein synthesis.

Insulin deficiency causes diabetes mellitus.

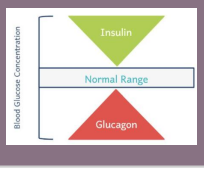
Hyperinsulinemia is due to insulin resistance in:

- Diabetes mellitus
- Metabolic syndrome

(Insulin resistance = receptor defect or action defect)

7 Hormones that Antagonize Insulin's Action

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

Cortisol is a stress hormone, so in stressful conditions cortisol levels are high and this may impair glucose homeostasis -> DM

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

Take home message Male slides

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

All thanks to team442	Summary	
Glucose Homeostasis	A process that controls glucose metabolism and maintains blood glucose level in the body.	
Sources of Glucose	**Dietary sources**	Dietary CHOs are digested in the GI to monosaccharides.
	Metabolic sources	Gluconeogenesis: Glycerol, Lactate, Pyruvate, Glucogenic amino acids.

Phases of Glucose Homeostasis (Very Important !)

	Start	Origin of glucose	Tissue Using Glucose	Major Fuel of Brain	Note
Phase I	–	Dietary CHOs (Exogenous)	All	Glucose	- Some glucose is converted to glycogen for storage in the liver (glycogenesis). - Excess glucose is converted to fatty acids and triglycerides in the liver, and these are transported via VLDL to adipose tissue for storage. - Gluconeogenesis is inhibited: Cori and glucose-alanine cycles are inhibited. - Insulin is active in this phase.
Phase II	Starts during early fasting when dietary glucose supply is exhausted.	- Glycogen (major) "Hepatic glycogenolysis" - Hepatic gluconeogenesis (minor)	All except Liver. Muscle, and adipose tissue at diminished rates.	Glucose	–
Phase III	when glycogen stores in liver are exhausted (within 20 hours).	- Hepatic gluconeogenesis (major) - Glycogen (minor)	All except liver. Muscle and adipose tissue at rates intermediate between II and IV.	Glucose	**depends on:** - Feeding status. - Hepatic glycogen stores. - Physical activity.
Phase IV	Several days of fasting	Gluconeogenesis both Hepatic + Renal (only start in 4th)	Brain, RBCs, renal medulla. small amount by muscle.	Glucose, ketone bodies	KB accumulation increase which enter brain for energy production. *Brain uses both glucose and KB for energy.
Phase V	Prolonged fasting	Gluconeogenesis both Hepatic + Renal	Brain at diminished rate, RBCs, renal medulla.	Ketone bodies (mainly), Glucose	- 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. - When all fat and KBs are used up → body uses muscle protein to maintain blood glucose.

Hormones and glucose homeostasis

Lowers Blood Glucose Level	**Insulin**	Overview	Synthesized by	The β-cells of islets of Langerhans of pancreas.
			Type	Peptide hormone.
			Receptor	Tyrosine kinase. (Composed of: 2α-subunit (extracellular) and 2β-subunit (cytoplasmic))
		Stimuli	↑ Blood glucose level (hyperglycemia)	
		MOA	Binding of insulin to α-subunit causes phosphorylation of β-subunit (autophosphorylated) → activates the receptor → phosphorylates intracellular proteins generating a biological response.	
		Actions	Stimulate	- Glucose uptake in muscles and adipose tissue. (GLUT4) - Glycolysis. - Glycogen synthesis. - Protein synthesis. - Uptake of ions (especially K+ and PO4 3-)
			Inhibits	- Gluconeogenesis. - Glycogenolysis. - Lipolysis. - Ketogenesis. - Proteolysis
		Note	Brain and liver have non-insulin dependent glucose transporter.	
		Disorder	Insulin deficiency	Diabetes mellitus (type 1)
			Hyperinsulinemia	Due to insulin resistance in: diabetes mellitus (type 2) or Metabolic syndrome.
Increase Blood Glucose Level (Antagonize insulin action)	**Glucagon**	Overview	Synthesized by	The α-cells of islets of Langerhans of pancreas.
			Type	Peptide hormone.
			Receptor	Adenylate cyclase- cAMP
		Stimuli	↓ Blood glucose level (hyperglycemia)	
		Actions	- Stimulates glycogenolysis. - Activates hepatic gluconeogenesis.	
	Cortisol	Overview	Synthesized in	Zona fasciculata of adrenal cortex.
			Type	steroid hormone.
			Receptor	Intracellular receptor.
		Action	- Stimulates gluconeogenesis in the liver, mobilizes amino acids for gluconeogenesis, and Inhibits glucose uptake by cells. - Stimulates fat breakdown in adipose tissue.	
	Growth hormone	Overview	Synthesized by	Somatotrops in anterior pituitary gland.
			Type	Peptide hormone.
			Receptor	Tyrosine kinase.
		Action	Inhibiting insulin action and stimulating gluconeogenesis in the liver.	
	Epinephrine	Overview	Synthesized in	Adrenal medulla glands.
			Type	Amine Hormone.
			Receptor	Adenylate cyclase- cAMP and Calcium or phosphatidylinositol.
		Action	- Stimulates lipolysis in adipose tissue when glucose blood levels fall. - Promotes glycogenolysis in skeletal muscle.	

Test Yourself!

MCQs

Answers: C-A-C-D

Q1: 1- Which structure plays a key role in maintaining blood glucose level?
A.Intestines
B. Kidney
C. Liver
D. Brain

Q2: 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

Q3: Which one of the following does the insulin Inhibits?
A. Glycolysis
B. Glycogen synthesis
C. Glycogenolysis
D. Protein synthesis

Q4: What is the organ that has non insulin dependent glucose transporter?
A. Brain
B. Liver
C. Kidney
D. A&B

SAQs

Q1: What are the complications of chronic hyperglycemia ?
glycation of proteins, endothelial dysfunction and diabetes

Q2: 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.

Q3: How does Glucagon contribute in maintaining blood glucose?
Stimulates glycogenolysis, Activates hepatic gluconeogenesis.

Meet The Team!

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