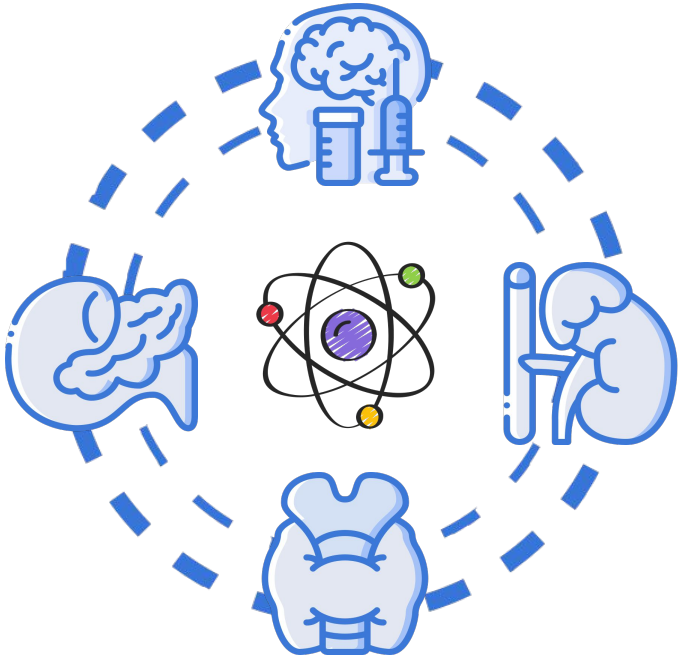
Glucose Homeostasis



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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:
- control glucose metabolism
- Maintains normal blood glucose level in the body

01

Glucose is a major source of body's energy

02

The liver plays a key role in maintaining blood glucose level

03

It is tightly controlled as the brain constantly needs glucose

04

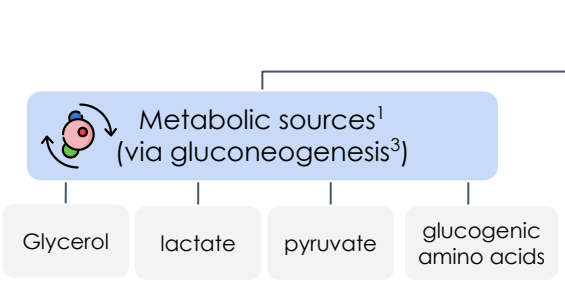
Severe hypoglycemia can cause coma and death

05

Chronic hyperglycemia results in glycation of proteins, endothelial dysfunction and diabetes mellitus

06

Sources of Glucose



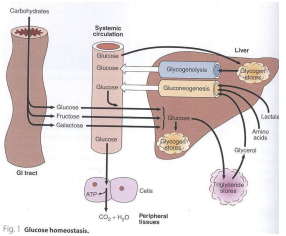


Fig. 1 Glucose homeostasis.

1. Endogenous sources 2. Exogenous sources 3. New glucose formation (from non-carbohydrate substrates)

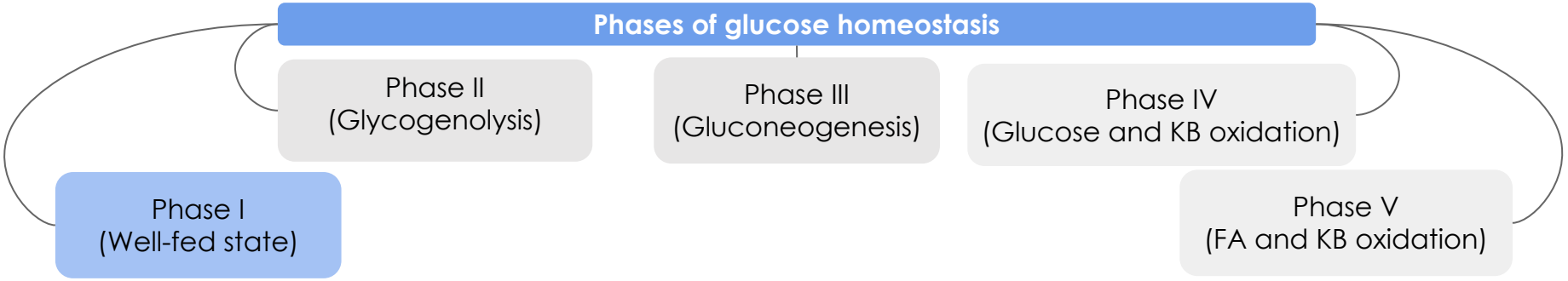
Phases of Glucose Homeostasis

1 Phase I (Well-fed state) 2 Phase II (Glycogenolysis) 3 Phase III (Gluconeogenesis) 4 Phase IV (Glucose, KB[1] oxidation) 5 Phase V (Fatty acid, KB oxidation)

Phase	Origin of blood glucose	Tissue using glucose	Major fuel of brain
I	Exogenous	All	Glucose
II	Glycogen, Hepatic gluconeogenesis	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 All body tissues mainly use FA and KB	Ketone bodies, glucose

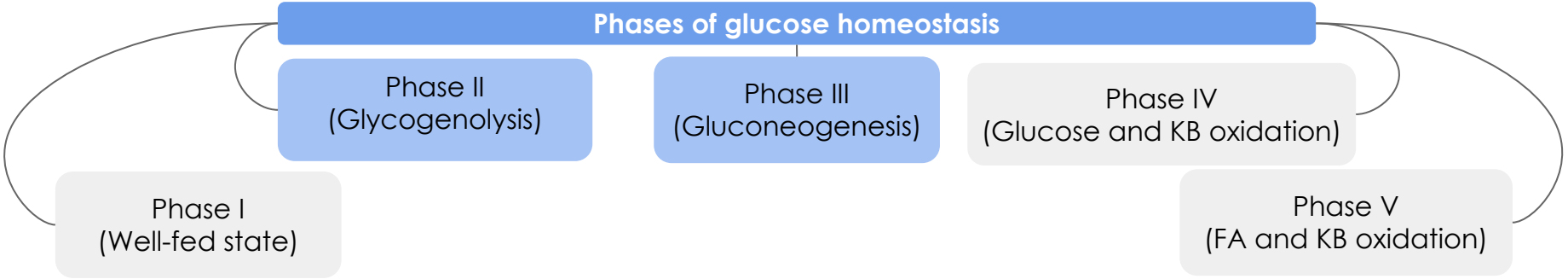
1. Ketone bodies

Phases of Glucose Homeostasis



	Phase I (Well-fed state)
Origin of glucose	Dietary CHOs (Exogenous)
What happens in this phase	• Liver removes about 70% of glucose load after a CHO meal • 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 and glucose-alanine cycles are inhibited)

Phases of Glucose Homeostasis



	Phase II (Glycogenolysis)	Phase III (Gluconeogenesis)
When does it start	during early fasting when dietary glucose supply is exhausted	starts when glycogen stores in liver are exhausted (< 20 hours)
Origin of Glucose	Hepatic glycogenolysis and gluconeogenesis maintain blood glucose level in this phase	Hepatic gluconeogenesis from: lactate, pyruvate, glycerol and alanine maintains blood glucose level
Major source of blood glucose	Glycogenolysis[1] and gluconeogenesis	Gluconeogenesis
Duration	-	Feeding status, Hepatic glycogen stores and Physical activity

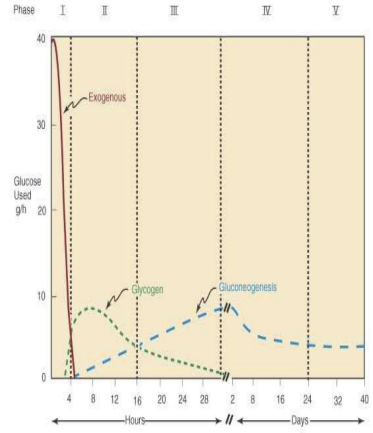
1. Note that while both of them occur in this phase, Glycogenolysis is the main one

Phases of Glucose Homeostasis

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)

	Phase IV (Glucose and KB oxidation)	Phase V (FA and KB oxidation)
When does it start	Several days of fasting	Prolonged fasting
Origin of glucose	Hepatic & Renal gluconeogenesis	Hepatic & Renal gluconeogenesis • Less dependence on gluconeogenesis • Gluconeogenesis somewhat maintains blood glucose level in this phase
What happens in this phase	• 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	• 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)



Hormones and Glucose Homeostasis

Hormones that regulate glucose metabolism:

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

Antagonizing the insulin effect

Insulin

- Play a major role in glucose homeostasis
- Synthesized by the Beta-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

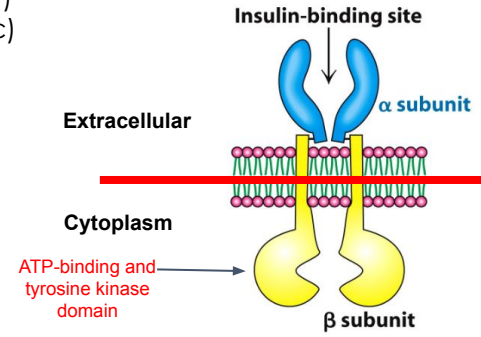
Insulin Actions

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

Insulin Mechanism of action

Recall from the 1st lecture (General mechanism of hormone regulation)

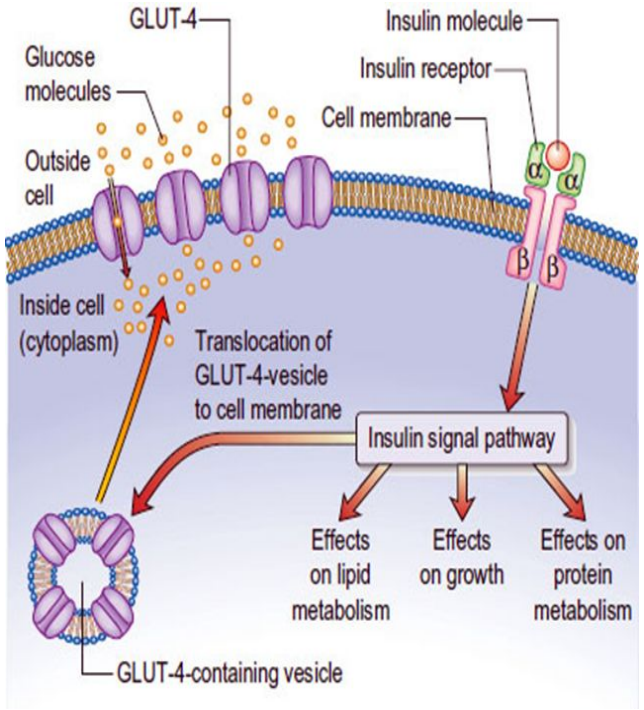
1. The insulin receptor is present on the plasma membrane of cell
2. Composed of:
   - Alpha subunits (Extracellular)
   - Beta subunits (Cytoplasmic)
3. Binding of insulin to alpha subunit causes phosphorylation of Beta subunit
4. This activates the receptor
5. The activated receptor then phosphorylates 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
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



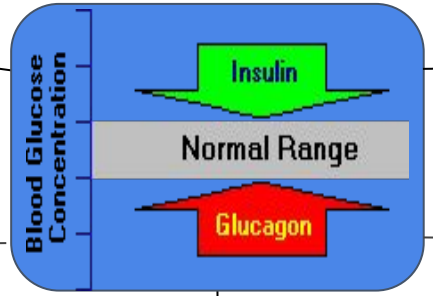
Insulin's MOA in decreasing blood glucose levels

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 or Metabolic syndrome)

Glucagon

A peptide hormone secreted by *α*-cells of pancreatic islets

Secreted in response to hypoglycemia



Activates hepatic gluconeogenesis

Increases glucose levels

Stimulates glycogenolysis

Glucocorticoids (Cortisol)

01

- Cortisol is a steroid hormone secreted by adrenal gland

02

- Contributes to glucose homeostasis

03

- Maintains normal glucose levels in fasting

04

- Stimulates gluconeogenesis in the liver

05

- Mobilizes amino acids for gluconeogenesis

06

- Stimulates fat breakdown in adipose tissue

Growth hormone

1

A protein hormone secreted by anterior pituitary gland

2

Maintains blood glucose levels by:

- Inhibiting insulin action
- Stimulating gluconeogenesis in the liver

Epinephrine

1

A catecholamine hormone secreted by adrenal gland

2

Stimulates lipolysis in adipose tissue when blood glucose levels fall

3

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

Summary

Phases	Phase I	Phase II	Phase III	Phase IV	Phase V
Origin of blood glucose	**Dietary CHOs (Exogenous)**	**Hepatic glycogenolysis and gluconeogenesis**	**Hepatic gluconeogenesis**	**Hepatic & Renal gluconeogenesis**	**Hepatic & Renal gluconeogenesis** Less dependence on gluconeogenesis
Tissue using glucose	All body tissue	All except liver, Muscle and adipose tissue.	All except liver, Muscle and adipose tissue.	Brain , RBCS , renal medulla . Small amount by muscle	**All body tissues use FA and KB oxidation** brain, RBC, Adrenal medulla
Major fuel for brain	Glucose	Glucose	Glucose	glucose and KB	glucose and KB
Notes	• Liver removes about 70% of glucose • Glycogenesis • Gluconeogenesis is inhibited (Cori and glucose-alanine cycles are inhibited)	Start during early fasting when dietary glucose supply is exhausted	starts when glycogen stores in liver are exhausted (< 20 hours)	• Gluconeogenesis starts to decrease • FA oxidation increases KB accumulation • KBs enter the brain and muscle for energy production	High KB conc. and glucose levels inhibit proteolysis in muscle (conservation of muscle)

Summary

Insulin	Glucagon	Cortisol	Growth hormone	Epinephrine
A protein hormone	**A peptide** hormone	**A steroid** hormone	**A protein** hormone	**A catecholamine** hormone
secreted by **β-cells of pancreatic islets**	secreted by **a-cells of pancreatic islets**	secreted by **adrenal gland**	secreted by **anterior pituitary gland.**	secreted by **adrenal gland**
Stimulates: 1- Glycolysis 2-Glucose uptake 3-Glycogen and protein synthesis Inhibits: 1-Glucogenogenesis 2-Glycogenolysis 3-Ketogenesis	Increases glucose levels by: • Stimulates glycogenolysis. • Activates hepatic gluconeogenesis.	• Stimulates gluconeogenesis in the liver. • Mobilizes amino acids for gluconeogenesis. • Stimulates fat breakdown in adipose tissue.	• Inhibiting insulin action. • Stimulating gluconeogenesis in the liver.	1- Stimulates lipolysis in adipose tissue when blood glucose levels fall. 2- Promotes glycogenolysis in skeletal muscle.

Quiz

MCQs :

Q1: Which of the following phases is transported via VLDL?

a) Phase I **b)** Phase II **c)** Phase III **d)** Phase IV

Q2: Insulin stimulate the uptake of which ions?

a) K **b)** PO4 **c)** Na **d)** Both a&b

Q3: Where does the ATP-binding receptor located?

a) Cytoplasm **b)** Extracellular
c) Nucleus **d)** Nucleolus

Q4: Which one of the following does the insulin stimulates?

a) Lipolysis **b)** Gluconeogenesis
c) Glycolysis **d)** Glycogenolysis

Q5: Which of the following phases of glucose homeostasis inhibit gluconeogenesis?

a) Phase I **b)** Phase II **c)** Phase III **d)** Phase IV

Q6: Which ONE of these mechanisms takes place in phase 2 of glucose homeostasis?

a) Ketone bodies formation **b)** Glycogenolysis
c) Gluconeogenesis **d)** Glycolysis

SAQs :

Q1: How does growth hormone contribute in maintaining blood glucose?

Q2: What are the sources of glucose?

Q3: Name 4 hormones antagonize insulin action

Q4: What does chronic hyperglycemia result in?

★ **MCQs Answer key:**

1) a 2) d 3) a 4) c 5) a 6) b

★ **SAQs Answer key:**

1) Inhibit insulin action, stimulating gluconeogenesis in the liver
2) Dietary sources and metabolic sources
3) Glucagon, cortisol, growth hormone, epinephrine
4) Glycation of proteins, endothelial dysfunction and diabetes mellitus

Team members

Girls Team:

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- Deema Almaziad
- Ghaliah Alnufaei
- Haifa Alwaily
- Leena Alnassar
- Lama Aldakhil
- Lamiss Alzahrani
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- Noura Alturki
- Sarah Alkhalife
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- Taif Alotaibi

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- Fares Aldokhayel
- **Fahad Alsultan**
- Khayyal Alderaan
- Mashal Abaalkhail
- Naif Alsolais
- Omar Alyabis
- **Omar Saeed**
- Rayyan Almousa
- Yazen Bajeaifer

Team Leaders

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Mohannad Alqarni

★ **"No matter how great the talent or efforts, some things just take time. You can't produce a baby in 1 month by getting 9 women pregnant" - Warren Buffet**

438 BIOCHEMISTRY TEAM

We hear you