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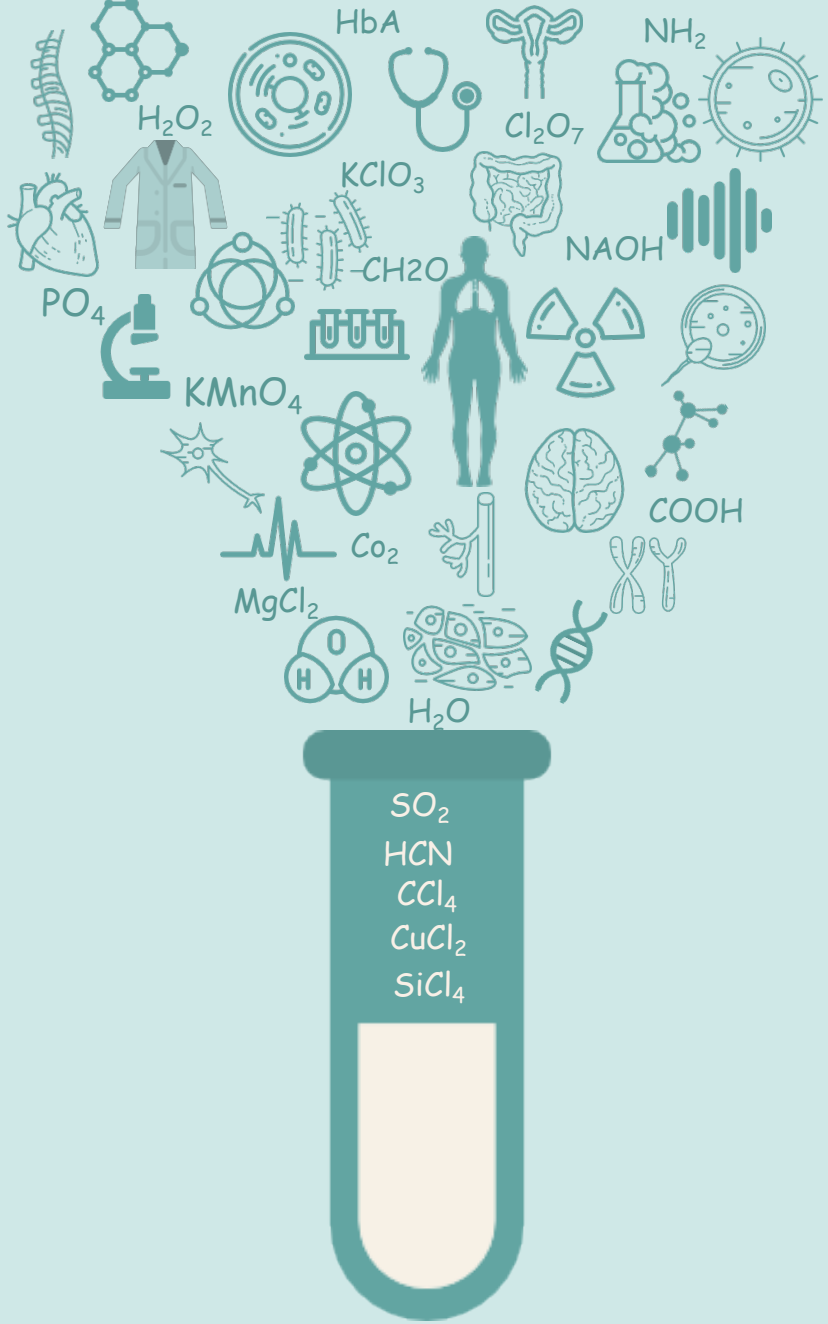
King Saud University
1957

436
MEDICINE
KING SAUD UNIVERSITY

BIOCHEMISTRY TEAM 436

Important
Extra Information
Doctors slides
Doctors notes



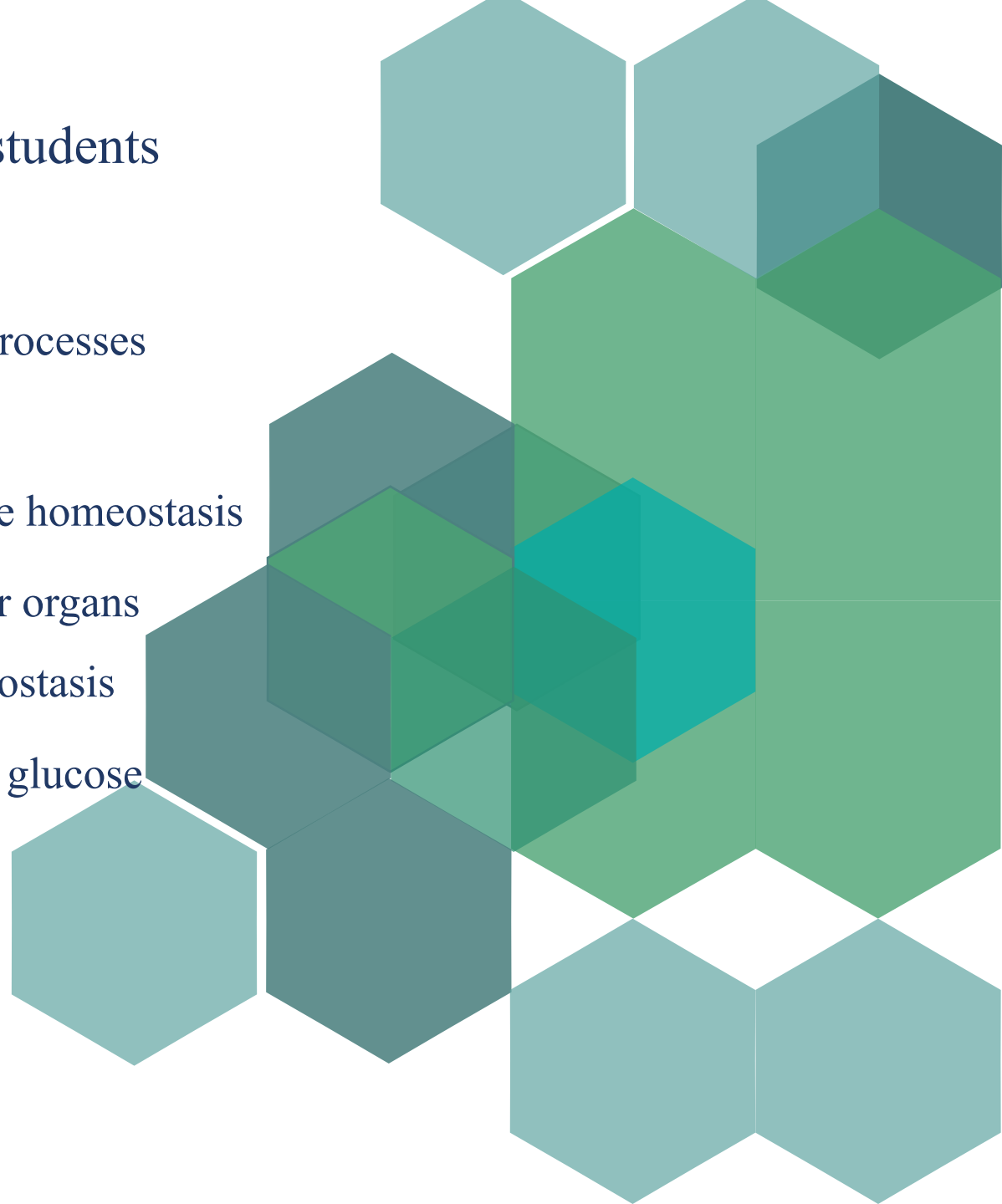
Biochemistry

Thyroid Hormones and Thermogenesis

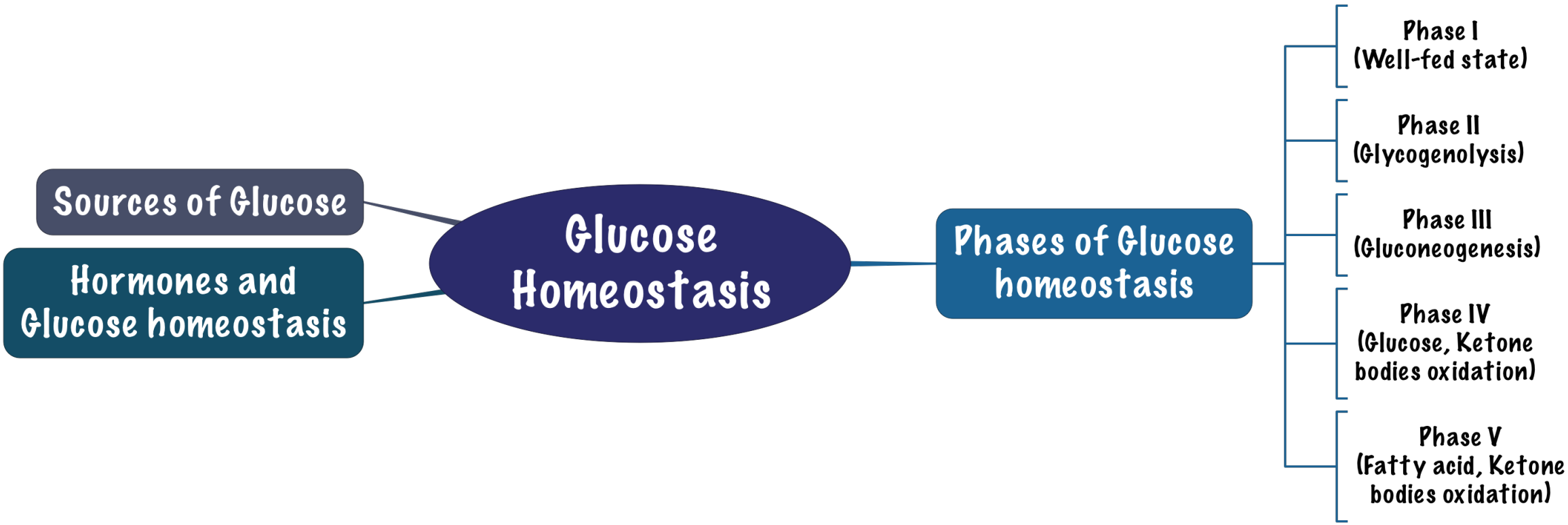
OBJECTIVES

By the end of this lecture, the Second Year students will 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


Sources of Glucose
Hormones and Glucose homeostasis
Glucose Homeostasis
Phases of Glucose homeostasis
Phase I (Well-fed state)
Phase II (Glycogenolysis)
Phase III (Gluconeogenesis)
Phase IV (Glucose, Ketone bodies oxidation)
Phase V (Fatty acid, Ketone bodies oxidation)

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
- It is **tightly controlled** as 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:	Metabolic sources (via gluconeogenesis):
• Dietary CHOs are digested to monosaccharides • Starch provides glucose directly • Fructose and galactose are converted to glucose in the liver	**Glycerol, lactate, pyruvate, glucogenic amino acids** why not glycogenolysis? Because glycogen is a polymer of glucose only, you're not making new glucose you're only bringing your own storage of glucose

Glucose homeostasis

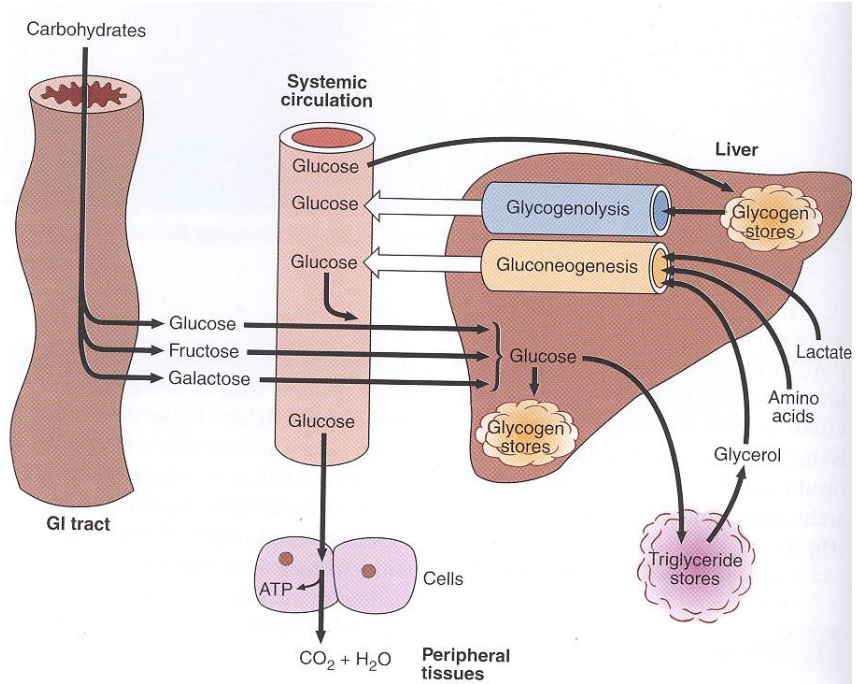


Fig. 1 **Glucose homeostasis.**

1: glucose, fructose and galactose are absorbed to the blood stream
2: Some of it goes to the peripheral tissue to be used as energy, and the remaining goes to the liver to convert fructose and galactose into glucose
3: Some of the glucose is used to make glycogen but as we said before it has a limit for glycogen formation, so excess amounts of glucose will be converted into fatty acids and triglycerides then sent to adipose tissue for storage, then when the adipose tissue breaks down fat it produces glycerol which goes back to the liver and forms glucose again (gluconeogenesis)
4: When blood glucose levels go down > glycogen is broken down (glycogenolysis) and we start forming glucose from amino acids and lactate from muscles

All the carbohydrate that comes from food (glucose-fructose-galactose) are stored in the liver as glycogen(glycogen stores).
-When the body needs glucose it converts glycogen stores back to glucose via Glycogenolysis + also via gluconeogenesis
*Cori cycle is the one that convert lactate into glucose

Phases of glucose homeostasis

Phase I (Well-fed state)

- Glucose is mainly supplied by **dietary CHOs** (Exogenous)
- **All** body tissues use dietary glucose for energy 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

    (both lactate and alanine are coming from the muscles)

These phases are not separate from each other! It doesn't mean that one stops then the other starts.

So when we're fasting during Ramadhan, what are we using for energy? We are NOT breaking down fat for energy, it's only glycogen that is broken down because it's used up to 24 hours, unless we reduce the intake of glucose so the storage will be less but still it needs more time to finish, or if we're exercising so we're consuming more energy, so it's a wrong belief that we break down fat ☺

Phases of glucose homeostasis

Phase II (Glycogenolysis)

pre-fasting state.

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

Phase III (Gluconeogenesis)

- Phase III starts **when glycogen stores in liver are exhausted** (< 20 hours)
- Duration of phase III depends on
  - Feeding status
  - Hepatic glycogen stores
  - Physical activity
- Hepatic gluconeogenesis from **lactate, pyruvate, glycerol and alanine** maintains blood glucose level
- Major source of blood glucose in this phase:
  - **Gluconeogenesis**

Phases of glucose homeostasis

Phase IV (Glucose and KB oxidation)

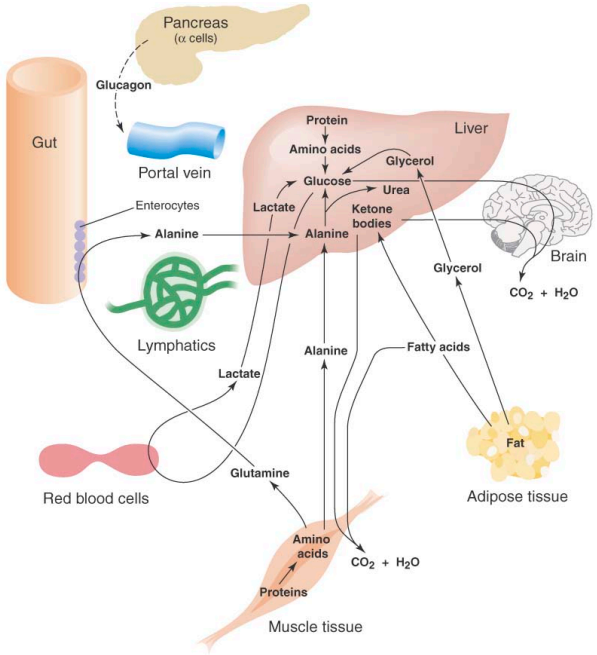
- **Several days of fasting** leads to phase IV
- **Gluconeogenesis** starts to **decrease**
- FA oxidation increases KB accumulation
- **KBs enter the brain** and muscle for energy production
- **Brain** uses **both glucose** and **KB** for energy

is a combination of glucose and fat
Phase II: major source of glucose is glycogen(liver stops using glucose at this phase because it can survive on fatty acids)
Phase III: major source of glucose is from Gluconeogenesis
phase IV: Gluconeogenesis at its maximum level so there is no glycogen here + at this phase the brain starts to use ketone bodies
Phase IV: the major source for brain is ketone bodies (glucose in minor)

Phases of glucose homeostasis

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



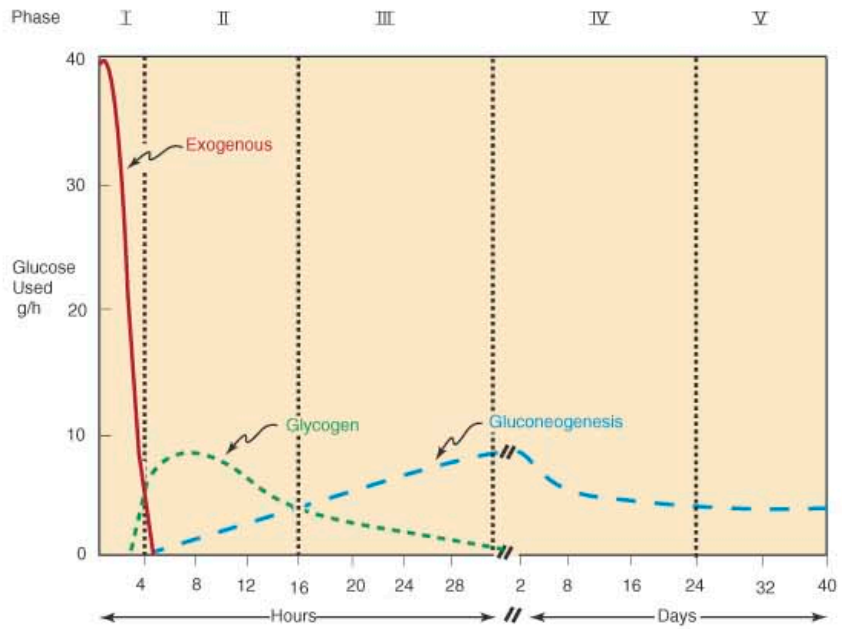
Phases of glucose homeostasis

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 table shows you all the 5 phases and what is the origin of glucose in each one and the tissues that are using it as well as the major fuel for the brain

Ketone bodies are a byproduct of liver oxidation of fat, and these are :(acetone, acetoacetate and beta-hydroxybutarate) and they can be used as a source of energy

Phases of glucose homeostasis



During this study, they were seeing how the glucose is being maintained by the body and divided it into 5 phases (but these phases are not very well-demarcated even though they mention the beginning and the end of each phase it could be different from person to another but the pattern is the same):

Phase 1: starts from 0 after you get a meal and start starvation, the body will use glucose from the exogenous source

Phase 2: starts from 4-6 hours at the max, in this stage you start breaking down your glycogen storage to provide glucose

Phase 3: once you finish your glycogen storage you start gluconeogenesis by triglycerides to glycerol and some of the amino acids, the gluconeogenesis here is happening mainly by the LIVER.

Phase 4: you still make glucose by gluconeogenesis but in this stage your forming it by both the liver AND the kidney but the MAIN ORGAN IS THE KIDNEY, then when you're breaking a lot of fatty acids they're converted to ketone bodies. So in this phase you use limited amounts of glucose because you need it more in RBCs and brain, so majority of tissues will be using ketone bodies for their energy and the brain uses them as well after glucose finishes.

Phase 5: The person continues to use ketone bodies and by the end of this phase fatty acid stores are exhausted so we start breaking down proteins (so the function of your vital organs will be compromised) and if you continue starvation you die ☹☹

Hormones and glucose homeostasis

1- INSULIN (lowers blood glucose level)

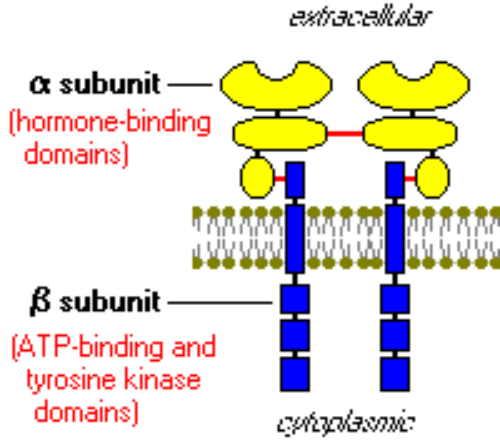
- Plays a major role in glucose homeostasis
- Synthesized by the b-cells of islets of Langerhans of pancreas
- A small protein composed of two chains
- Rise in blood glucose level stimulates insulin secretion "Hyperglycemia"
- Promotes entry of glucose into cells

❖ Action :

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

❖ Mechanism of action :

- The insulin receptor is present **on the plasma membrane of cell**
- Insulin is used for storage and usage of all body energy sources as well as preventing their break down
- 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 generati response

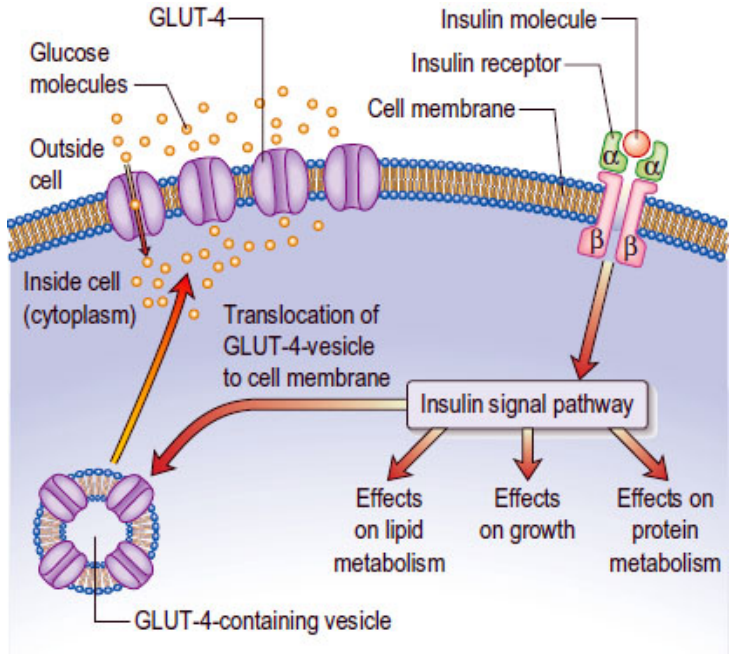


Hormones and glucose homeostasis

1- INSULIN (lowers blood glucose level)

❖ 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**
- (they don't go to the surface of the cell unless insulin is bound to its receptor and signals are sent to these vesicles)



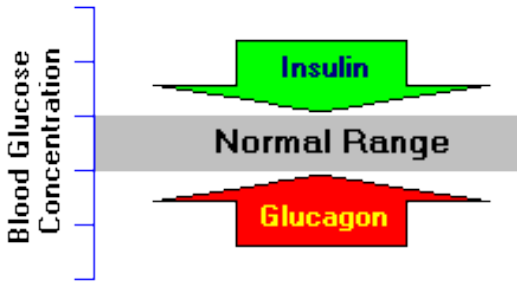
Insulin **binding** to its receptor causes **vesicles** to **diffuse** into **plasma membrane** → **GLUT4** is **inserted** into the membrane → **Allowing** glucose transport into the cell

- **Brain** and **liver** have **non-insulin dependent glucose transporter**

➢ Insulin deficiency causes diabetes mellitus
➢ **Hyper**insulinemia is due to insulin resistance in:
  - Diabetes mellitus or
  - Metabolic syndrome

Hormones and glucose homeostasis

2-ANTAGONIZE insulin action

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**	secreted by **anterior pituitary gland**	**adrenal gland**
• **Increases glucose levels** • Stimulates glycogenolysis • Activates hepatic gluconeogenesis • It is inhibited by insulin 	• **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 • (by increasing the expression of enzymes that break it down, but REMEMBER: that DOES NOT contribute to the homeostasis of glucose in blood)

QUIZ

Q1 : Which one of the following is a complication of chronic hyperglycemia?

A. Liver failure
B. Kidney failure
C. Endothelial dysfunction
D. Nephropathy

Q2 : Excess glucose is converted in the liver during phase 1 into which of the following?

A. LDL
B. HDL
C. Glycogen
D. Fatty acids

Q3 : In which one of the following phases of glucose homeostasis is gluconeogenesis is inhibited?

A. I
B. II
C. III
D. IV

Q4 : Which one of the following is an action of insulin?

A. Increased Gluconeogenesis
B. Increased Glycogenolysis
C. Increased Lipolysis
D. Increased Glycogenesis

Q5 : Which one of the following is correct about ***GLUT 4***?

A. It's present in Golgi apparatus
B. It allows glucose transport into the cell
C. It's insulin dependent in the liver and brain
D. Insulin causes inhibition of GLUT4

Q6 : Which one of the following cells secret Glucagon?

A. Alpha
B. Beta
C. Gamma
D. Delta

QUIZ

Q7 : The previous medical student girl came to your office, to make sure of the SAQ questions she answered in her endocrine block.
And because you are erudite (ضليع) in endocrinology you will answer all of them.

A) Name 4 hormones that antagonize insulin action?

1. Glucagon
2. Cortisol
3. Growth hormone
4. Epinephrine

B) How does the growth hormone contribute in maintaining blood glucose?

1. Inhibiting insulin action
2. Stimulating gluconeogenesis in the liver

C) Name the 5 phases of glucose homeostasis and their main physiological event/function.

1. Phase I: Glycogenesis , inhibition of gluconeogenesis, Cori & glucose-alanine cycles
2. Phase II: Glycogenolysis and Gluconeogenesis.
3. Phase III: Gluconeogenesis from lactate, pyruvate, glycerol& alanine
4. Phase IV: Fatty acid oxidation leads to increased ketone body accumulation
5. Phase V: All body tissues use Fatty acids and ketone bodies oxidation for energy production. When FA and KBs are used up, proteolysis starts.

D) What does the duration of phase III depend on?

1. Feeding status
2. Hepatic glycogen stores
3. Physical activity

Suggestions and recommendations

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

Biochemistry Team 436

THANK YOU

FOR CHECKING OUR WORK

PLEASE CONTACT US IF YOU HAVE ANY ISSUE

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