Biochemistry Team 435

جامعة الملك سعود
King Saud University 1957

GLUCOSE HOMEOSTASIS

* Please check out this link to know if there are any changes or additions.

Revised by
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Color index: Important | Doctors notes | Further explanation.

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.

Introduction

❖ What is "Glucose Homeostasis"?

Is a process that **controls glucose metabolism** and **maintains blood glucose level** in the body.

- **Glucose** is a major source of energy. The body favours to consume glucose first because it's easy to breakdown.
- The **liver** plays a major role in maintaining blood glucose level. normal range of fasting blood glucose is 82-100 mg/dl
- It is **tightly controlled** because the **brain** constantly needs **glucose**. the **brain** uses only glucose for its source of energy! But in extreme situation when the body has been fasting for prolonged period, then the brain can use ketone bodies.

Chronic hyperglycemia

- **Glycation of proteins***
  Ex: HBA1C
- **Endothelial dysfunction**
- **Diabetes**

Severe hypoglycemia

- **can cause coma and death**

*Other proteins can be glycated also, and if they become big they can start blocking small capillaries leading to endothelial dysfunction.
That's why some diabetic patient suffer from diabetic foot due to obstructed blood supply by these glycated proteins leading to destruction of the tissues and formation of gangrene.

Sources of glucose:	
Dietary	**Metabolic**
▪ Dietary CHO is digested in the GI to **mono-saccharides.** ▪ **Starch** provides glucose directly ▪ **Fructose** and **galactose** are converted to **glucose** in the liver.	Via **gluconeogenesis** **Glycerol**, **lactate**, **pyruvate**, **glucogenic amino acids**

Video

Video

Overview

1-

You get CHO from the diet → broken down into: Glucose – fructose – galactose (in the GIT) → blood stream:

2-

- Some of them go to the peripheral tissues.
- Remaining → Liver → convert it into glucose.

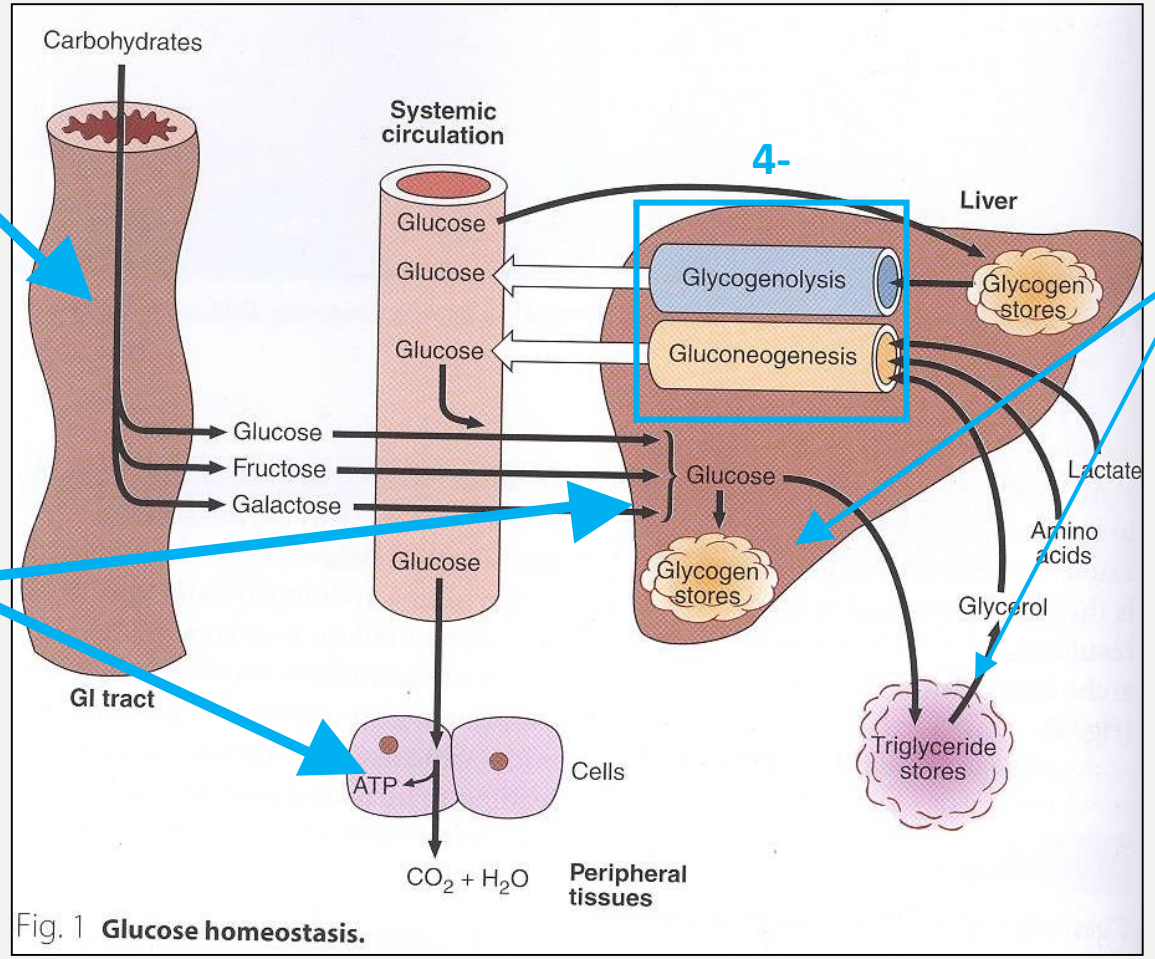


Fig. 1 **Glucose homeostasis.**

3-

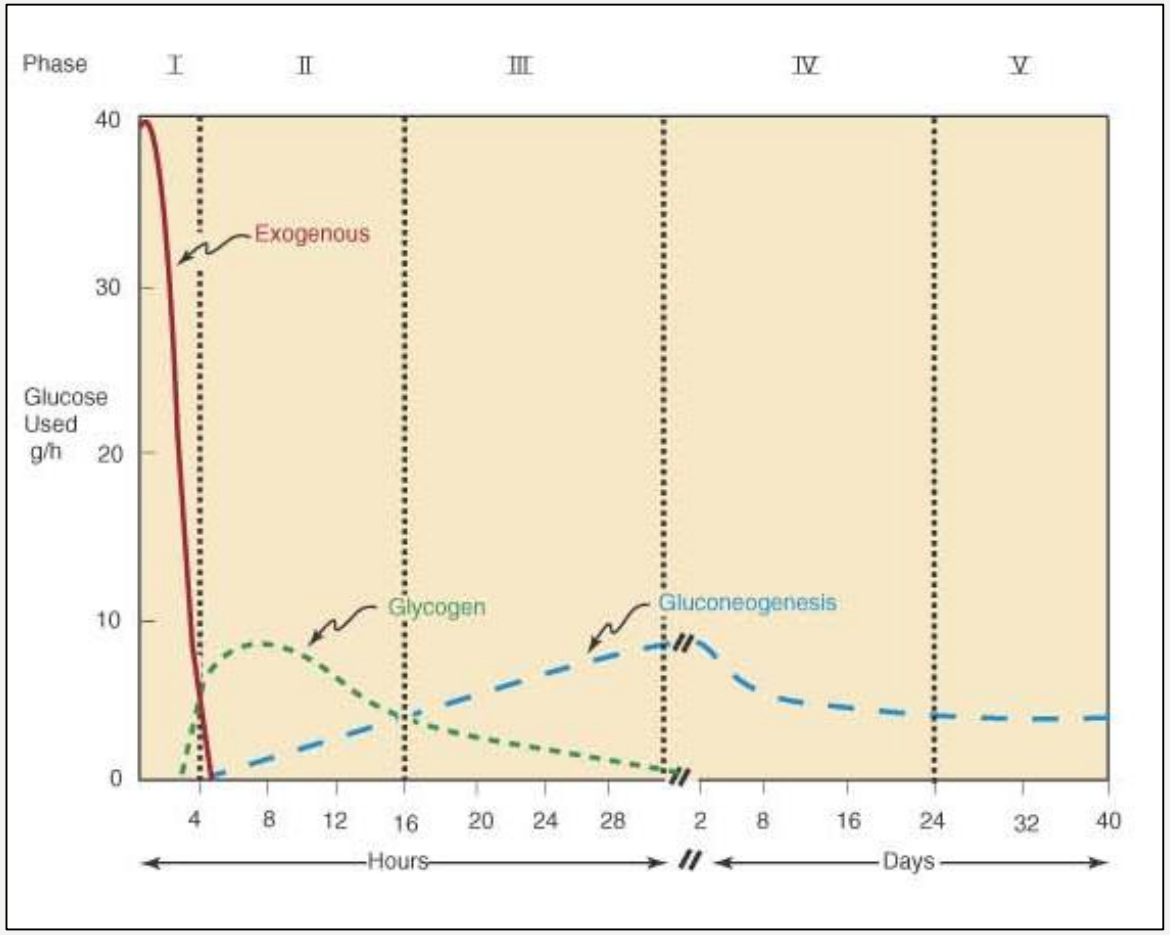
- Some of glucose is used to make glycogen " **glycogenesis**" (for storage).
- Excess glucose is converted to fatty acids and **triglycerides** in the liver These are transported via VLDL (very low density lipoproteins) to adipose tissue for storage.

4-

When blood glucose goes down → you start breaking down glycogen "Glycogenolysis" and start forming glucose from AA, lactate,.. .

هذي فكرة المحاضرة بشكل عام، خلال هالمحاضرة بنتناول هالموضوع بشيء من التفصيل!

Overview



- First there is a lot of glucose used from **exogenous** sources.
- Time 0 start after you have had meal , then the starving period start.
- By 4 to 5 hours glucose supply will be limited " fasting phase" at this time you start to break down your glycogen you can survive up to 15 to 16 hours.
- By the time your **glycogen** stores are finishing up " exhausted", your body start **gluconeogenesis** phase
- There is no clear demarcation between phase **3** and **4** the difference is in the gluconeogenesis.
  - ✓ mainly is **hepatic** gluconeogenesis in phase **3** while the **renal** gluconeogenesis will start in phase **4**
- In phase **4** basically start **breaking fat stores**, so ketone bodies are produced and used by cell.
- In phase **5** the fatty acid stores are kind of exhausted and then will go for the last thing " protein"

these phases happens among patients that have fasted for 40 days, only getting water!

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 I (Well-fed state)

Origin of Glucose:	dietary CHOs (Exogenous).
Tissue using glucose:	**All** body tissues
Major fuel for brain:	**Glucose.**
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).

المرحلة الأولى تذكروها بـ **"احفظ قرشك الأبيض ليومك الأسود"**
بهالمرحلة بيكون مصدر الطاقة هو الكربوهيدرات اللي نحصل عليهم من الغذاء "ماصار لنا ماكلين الحمدالله"
فالجسم بيحاول انه يتصرف بهالكربوهيدرات بطريقة ذكية بدون تبذير..
٣٠% من هالكربوهيدرات بتاخذهم البرفرال تشوز "كلهم بيوصلهم" و٧٠% بتروح للكبد "العقل المدبر اللي بيضبط لنا بنك الطاقة"..
بيمسك هالكربوهيدرات وبيحولهم لجلايكوجين "علشان نستخدمه بيومنا الأسود" والكمية الزايدة من الجلوكوز بيحولها الى فاتي اسيدز وتراي اسيل جليسرول اللي بتركب سيارة الفي ال دي ال وبتروح للأنسجة الدهنية..
بكذا خلاص امورنا صارت تمام الأنسجة واصلتها طاقة وفوق كذا موفرين فلوس "طاقة" للزمن!
طبعا عملية الجلوكنيوجنسز مثبطة بهالمرحلة.. وش نبي بالجلوكوز وهو عندنا لا وزيادة على كذا مخزنين منه كميات على شكل جلايكوجين؟!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!!! ☺ ☺

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)

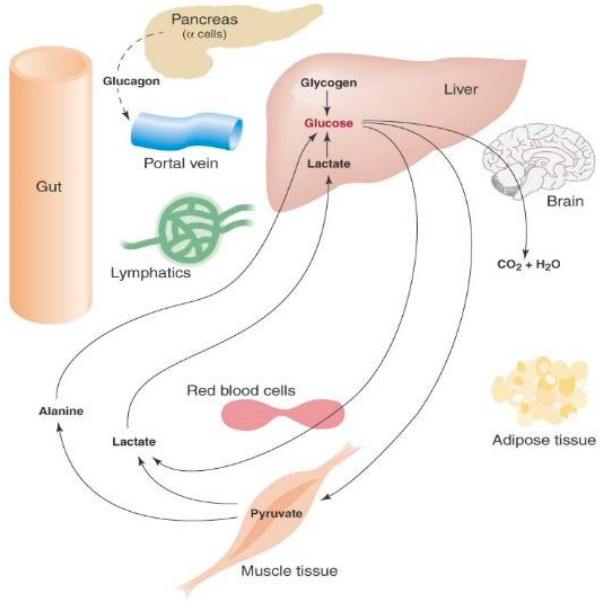
Phase II (Glycogenolysis)

When does it start?	
during **early fasting** when dietary glucose supply is exhausted. Peaks after 8 hours	
Origin of Glucose:	**Hepatic Glycogenolysis** & **gluconeogenesis** are the major sources of blood glucose in this phase maintain blood glucose level in this phase.
Tissue using glucose:	All except liver
Major fuel for brain:	**Glucose.**

- Dr. Uthman said: you'll be fool if you think that fasting burns your fat, it's your glycogen which is gone. Adipose tissue has no role here.
- **in overnight/1day fasting, what is maintaining blood glucose?**

Mainly glycogenolysis and gluconeogenesis!

بالمرحلة الثانية بنبدأ باستخدام الجلايكوجين اللي كوناه بالمرحلة الأولى..
المرحلة هذي تبدأ تقريبا ٤-٥ ساعات بعد تناولنا الوجبة لمن يخلصن الجلوكوزات اللي من الدايت..
الجسم بيحصل فيها على الجلوكوز من خلال مصدرين:
١- من الجلايكوجين (الكبد بيحول الجلايكوجين اللي كونه بفايز ١ الى جلوكوز اللي بيروح للعضلات وكريات الدم البيضاء).
٢- من الجلوكنيوجنسز (مينمال موب مره زي الجلايكوجينولايسز)!
طبعا نلاحظ ان الانسجة الدهنية لسى ماجيناها ولا استخدمناها بشي



Phases of glucose homeostasis

- Phase I (Well-fed state)
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Phase III (Gluconeogenesis)

When does it start?	
Phase III starts **when glycogen stores in liver are exhausted** (within 4-6 hours) BUT picks up (within <20 hours).	
Origin of Glucose:	**Hepatic Gluconeogensis (mainly) & Glycogen** "glycogenolysis". Hepatic gluconeogenesis from **lactate**, **pyruvate**, **glycerol** and **alanine** maintains blood glucose level
Tissue using glucose:	**All** except liver (Muscle and adipose tissue at rate intermediate between II & IV).
Major fuel for brain:	**Glucose.**
Duration of phase III depends on:	✓ Feeding status. ✓ Hepatic glycogen stores. ✓ Physical activity.

*obese people take long time (3 mothns) than normal people to reach this phase **WHY?** Because they have more fat & Carb.

لمن الجلايكوجين يقرب يخلص الجسم لازم يشوف له حل ويدبر نفسه!
فبيتجه للجلوكنيوجنسز "اللي تصير بالكبد" (طبعا مانسى ان الجلايكوجينولايسز مازالت شغالة لكن موب زي كفاءة فايز ون، والاعتماد الأكبر بيكون على الجلوكونيوجنسز) بنهاية هالمره خلاص الجلايكوجين بيخلص..
المدة الزمنية اللي بتستمر عليها هالمرحلة يعتمد على عوامل كثيرة منها كميات الجلايكوجين المخزنة بالكبد (لو عندنا كثير بنطول أكثر) – نشاط الشخص (اكيد لمن يزيد نشاط الشخص بيحتاج كميات طاقة أكبر فبتقل الفايز).. الخ

Phases of glucose homeostasis

- Phase I (Well-fed state)
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Phase IV (Glucose and KB oxidation)

When does it start?	
Several days of fasting leads to phase IV.	
Origin of Glucose:	**Hepatic & renal Gluconeogensis**
Tissue using glucose:	Brain, RBCs, renal medulla and small amount by muscle.
Major fuel for brain:	**Glucose & Ketone bodies** (byproduct of liver metabolism)
What happens in this phase?	▪ **Several days of fasting** leads to phase IV. ▪ Gluconeogenesis starts to decrease. ▪ FA oxidation increases the KB accumulation as the 3rd step before the accumulation. ▪ **KB** enter the brain and muscle for energy production.

This is the phase when **you start to breakdown the fatty acids** and your gluconeogenesis starts to decrease!

بالمرحلة هذي الجسم يبدأ يدور له على مصدر ثاني غير الجلوكوز للطاقة (الجلايكوجين مخلص وكفاءة الجلوكونيوجنسز ميب زي اول)..
فيبدأ الجسم باستخدام الفاتي اسيدز

Phases of glucose homeostasis

- Phase I (Well-fed state)
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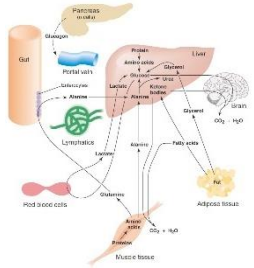
Phase V (FA and KB oxidation)

When does it start?	
Prolonged fasting leads to phase V	
Origin of Glucose:	➢ **Hepatic** & **Renal gluconeogenesis** ✓ Gluconeogenesis somewhat maintains blood glucose level in this phase. ✓ Less dependence on gluconeogenesis
Tissue using glucose:	**All body tissues** use **FA** and **KB** oxidation for energy production.
Major fuel for brain:	**Glucose** & **ketone** bodies.
What happens 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

✓ **Muscles is the last choice to be used for energy, why ?**

لو أنك عالق في صحراء مثلًا والجسم استخدم عضلاتك أول علشان ينتج الطاقة ، ما راح تقدر تتحرك وتبحث عن مخرج للمشكلة اللي أنت فيها

✓ Protein stores breakdown. proteins are spared as much as possible. It can be used up to 30% maximally! After that vital organs will be compromised and it can be fatal.



Hormones and glucose homeostasis

lowers blood glucose level: Insulin.

Antagonize insulin action

Insulin

- ✓ A small **protein** composed of **two** chains.
- ➢ **Synthesized by:** the β-cells of islets of Langerhans of pancreas.
- ➢ **Stimulus:** **Rise** in blood glucose level stimulates insulin secretion.
- ➢ **Plays a major role in:** glucose **homeostasis** by promotes **entry** of glucose into cells.

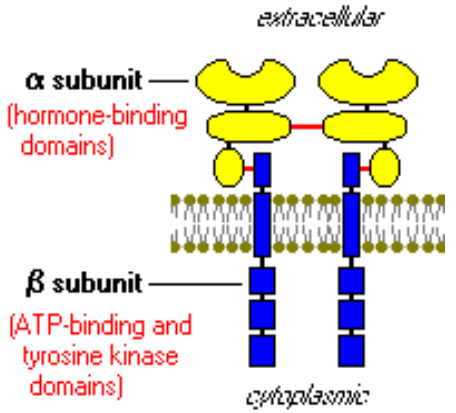
❖ Actions: **Decreases** blood glucose levels

Inhibits:	Stimulates:
Gluconeogensis	Glucose uptake in muscle and adipose
Glycogenolysis	**Glycolysis**
Lipolysis	Glycogen synthesis
Ketogenesis	**Protein synthesis**
Proteolysis	Uptake of Ions (K+ and PO4)

❖ Mechanism of action:

- The insulin receptor is present on **the plasma membrane of cell**.
- Composed of:
  - **α-subunit** (**extra**cellular)
  - **β-subunit** (**cyto**plasmic)
- **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.

إعادة للكلام اللي قلناه بنهاية المحاضرة الأولى وللفزيولوجي.. لا جديد!



Hormones and glucose homeostasis

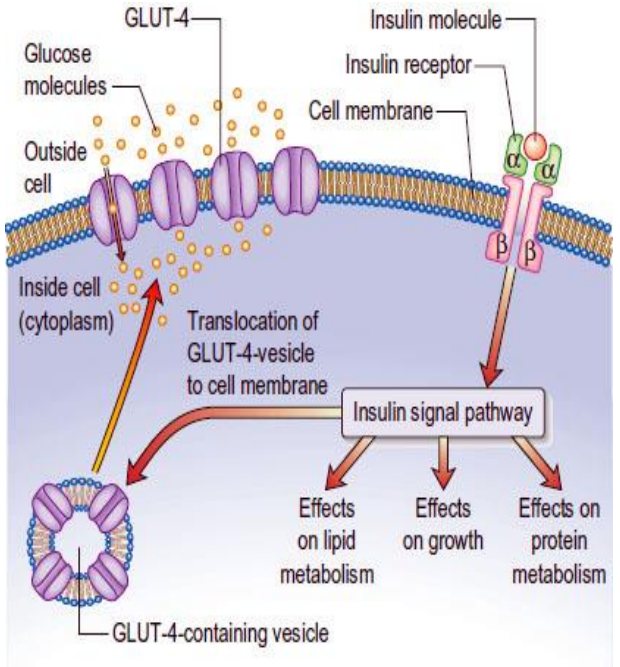
lowers blood glucose level: Insulin.

Antagonize insulin action

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**.
- **Brain** and **liver** have **non-insulin dependent glucose transporter** "Insulin Independent" "Adipose tissues and muscles are insulin dependent"

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



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

when cells are not responding to insulin, could be due to less receptors or dysfunctional receptors, the beta cells thinks there isn't enough insulin! So they keep on secreting more and more insulin to blood causing hyperinsulinemia. Happens in type 2 diabetes

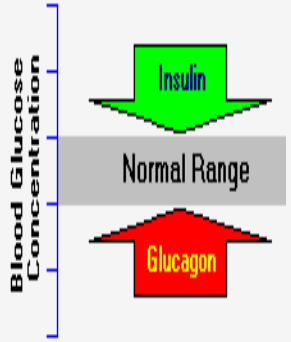
الموضوع جدا بسيط:
الانسولين يقلل نسبة الجلوكوز بالدم عن طريق انه يدخل الجلوكوز للخلية.. لكن كيف؟
بيرتبط بالريسبتور وبتصير الأشياء اللي قلناها بالسلايده الماضية "سالفة الالفا والبيتا سب يونتس" بالنهاية بيصير عندنا سقنلق باثواي اللي وش بيسوي؟ بيروح للقلوت ٤ "الممر\الباب اللي يسمح بدخول الجلوكوز" وبيطلعها من الفزكل لسطح الخلية علشان يقدر الجلوكوز يدخل! السلايده هذي موضع جيد للاسئلة ☺

Hormones and glucose homeostasis

lowers blood glucose level: Insulin.

Antagonize insulin action

Glucagon	Glucocorticoids (Cortisol)	Epinephrine	Growth Hormone
A **peptide** hormone	a **steroid** hormone	A **catecholamine** hormone	A **protein** hormone
Secreted by: **α-cells of pancreatic islets** in response to hypoglycemia	Secreted by: **adrenal gland**	Secreted by: **adrenal gland**	Secreted by: **anterior pituitary gland**

• **Increases glucose levels**
• **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
	  • Inhibits glucose uptake by cells
	• **Stimulates fat breakdown** in adipose tissue
		• **Stimulates lipolysis** in adipose tissue when blood glucose levels fall
		• **Promotes** glycogenolysis in skeletal muscle
		• Kicks in phase 4 and 5
			• **Maintains** blood glucose levels by:
			  i. **Inhibiting** insulin action
			  ii. **Stimulating** gluconeogenesis in the liver

Phases of glucose homeostasis (Summary) *Complete summary is available on the download center					
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 rates intermediate between II and IV	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** ○ Feeding status ○ Hepatic glycogen Stores ○ 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

Check your understanding!

Q1: Which ONE of these mechanisms takes place in phase 2 of glucose homeostasis?

A. Glycogenolysis.
B. Gluconeogenesis.
C. Ketone bodies formation.
D. Glycolysis

Q2: Which of the following phases of glucose homeostasis inhibit gluconeogenesis?

A. Phase I.
B. Phase III.
C. Phase IV.
D. Phase V.

Q3: Phase v in glucose homeostasis depends on what for energy production?

A. glucose intake
B. FA
C. Glycogenolysis.
D. Glycogenolysis.

Q4: Insulin receptor is present in:

A. Cytosol
B. Plasma membrane
C. Nucleus

Q5: In which phase there will use glucose from the hepatic gluconeogenesis MAINLY:

A- phase 2
B- phase 3
C- phase 4
D- phase 5

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

Done by:

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Resources:

- 435's slides and notes.

Focus on your goals.

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