Glucose Homeostasis

Glucose homeostasis

- **A process that**
  - Controls glucose metabolism
  - 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

1-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

2-Metabolic sources (via gluconeogenesis):

- Glycerol, lactate, pyruvate, glucogenic amino acids

1- Glucose, fractose and glactose "monosaccharides" going into blood stream

2- From blood to periphral tissue to provide energy and it goes to liver "Liver removes about 70% of glucose load after a CHO meal"

3- When it goes to liver some of glucose used to make glycogen " glycogenesis" (for storage)

4-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

*All these happen when you have enough glucose

5- when you are starving the gluconeogenesis will start .

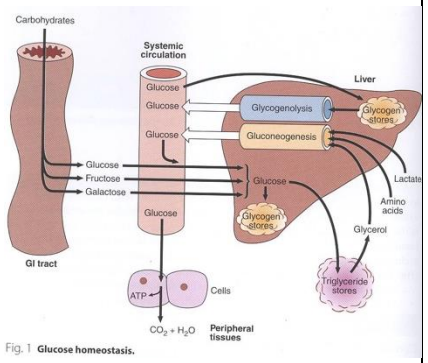

Fig. 1 **Glucose homeostasis.**

1- First there is a lot of glucose used from exogenous sources

2- Time 0 start after you have had meal , then the starving period start

3- 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.

4- By the time your glycogen stores are finishing up " exhausted" , your body start gluconeogenesis phase

5- There is no clear demarcation between phase 3 and 4 the difference is in the gluconeogenesis

6- mainly is hepatic gluconeogenesis in phase 3 while the renal gluconeogenesis will start in phase 4

7- In phase 4 basically start breaking fat stores , so ketone bodies are produced and used by cells

8- In phase 5 the fatty acid stores are kind of exhausted and then will go for the last thing " protein" .

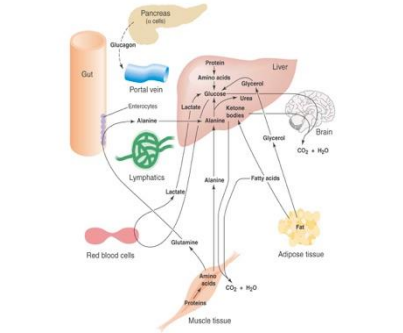

Figure 22.4. Metabolic interrelationships of major tissues in fasting state.

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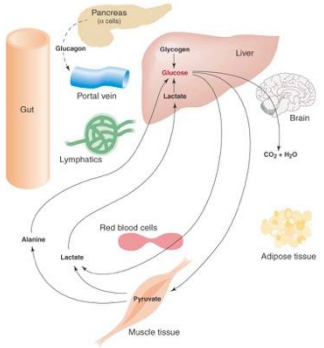

Figure 22.3. Metabolic interrelationships of major tissues in early fasting state.

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	Phases of glucose homeostasis				
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 , renal 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 glucose level

Hormones and glucose homeostasis

Hormones that regulate glucose metabolism:

Insulin (lowers blood glucose level)

- 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

Stimulate	Inhibit
1- Glucose uptake in muscle and adipose tissue 2- Glycolysis 3- Glycogen synthesis 4- Protein synthesis 5- Uptake of ions (especially K^+ and PO_4^{-3})	1- Gluconeogenesis 2- Glycogenolysis 3- Lipolysis 4- Ketogenesis 5- Proteolysis

Mechanism of action

- 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 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**
- 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
- 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**

Antagonize insulin 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**

Cortisol

- Cortisol is a steroid hormone secreted by **adrenal gland**
- 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

Growth hormone

- A protein hormone secreted by **anterior pituitary gland**
- Maintains blood glucose levels by:
  - **Inhibiting insulin action**
  - Stimulating **gluconeogenesis** in the liver

Adrenaline

- A **catecholamine** hormone secreted by **adrenal gland**
- Stimulates **lipolysis** in adipose tissue when glucose blood levels fall
- Promotes **glycogenolysis** in skeletal muscle

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