Biochemistry lec.
2nd stage

BY

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Regulation of blood glucose (Homeostasis)

- Blood glucose levels is maintained within physiological limits to (65-110 mg/dl) "true glucose" in fasting state, and (100-140 mg/dl) following ingestion of carbohydrate containing meal ,or even under circumstances when a person does not eat for extended periods of time, blood glucose levels decrease only slowly, by a balance between two sets of factors :

A) Rate of glucose entrance into the blood stream

B) B) Rate of its removal from the blood stream.

A) Rate of supply of glucose to blood.

- Blood glucose may be derived directly from the following sources:
- By absorption from the intestine.
- Breakdown of glycogen of liver (Hepatic glycogenolysis).
- By gluconeogenesis in liver; source being glucogenic amino acids, lactate and pyruvate, glycerol and propionly CoA.
- glucose obtained from other carbohydrates, e.g., fructose, galactose, …

B) Rate of removal of glucose from blood.

- Oxidation of glucose by the tissues to supply energy.
- Glycogen formation from glucose in the liver (Hepatic glycogenesis).
- Glycogen formation from glucose in muscles (Muscle glycogenesis).
- Conversion of glucose to fats (lipogenesis) especially in adipose tissue.
- Synthesis of compounds containing carbohydrates-blood glucose is **utilized e.g.:**

- Formation of fructose in seminal fluid, formation of lactose (sugar of milk) in lactating mammary gland, synthesis of glycoproteins and glycolipids.

- Formation of ribose sugars from glucose required for nucleic acid synthesis.

- Excretion of glucose in urine (glycosuria), when blood glucose level exceeds the renal threshold (180 mg/dl).

The major hormones that regulate blood glucose are **insulin** and **glucagon**

Homeostasis of blood glucose

Low blood glucose

High blood glucose



Alpha cells release glucagon

Beta cells release insulin

Glycogenolysis in the liver; Glucose released to blood

Normal blood glucose

Peripheral tissue Cells take glucose From blood

Biologic effects of insulin:

- Insulin is a **polypeptide hormone** produced by **β-cells** of the islets of Langerhans of the pancreas.
- **Insulin** is the most important hormone coordinating the use of fuels by tissues.
- Its metabolic effects are **anabolic**, favoring, for example, synthesis of **glycogen**, **triacyl- glycerol**, **and protein.**

- The effects of **insulin** on **glucose metabolism** are most prominent in **three tissues**: **liver, muscle and adipose tissue.**
- **In the liver:** insulin decreases the production of glucose by inhibiting gluconeogenesis and glycogenolysis.
- **In the muscle and liver**, insulin increases glycogenesis.
- **In the muscle and adipose tissue**, insulin increases glucose uptake.

Biologic effects of insulin

Increases (↑)	Decrease (↓)
• Glucose uptake • Glycogenesis • Protein synthesis • Fat synthesis	• Gluconeogenesis • Glycogenolysis • Lipolysis

Biologic effects of glucagons:

- **Glucagon** is a **polypeptide hormone** secreted by the **a-cells** of the pancreatic islets of Langerhans.
- **Glucagon**, along with **epinephrine**, **cortisol**, and **growth hormone** (The "counter regulatory hormones"), opposes many of the actions of insulin.

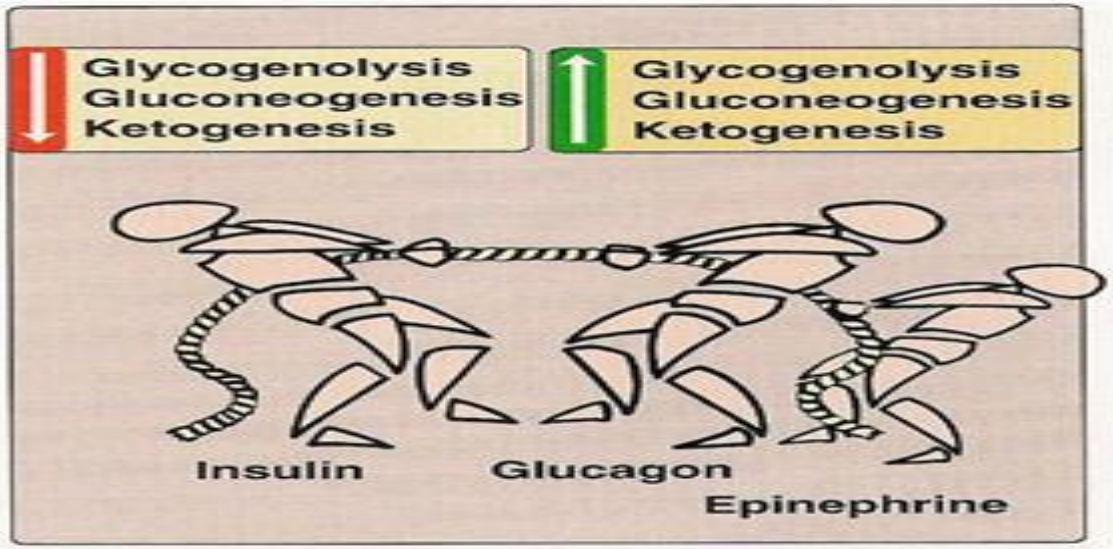


Figure 2.
Opposing actions of insulin and glucagon plus epinephrine.

- Stimulation of glucagons secretion by:
- Low blood glucose: A decrease in plasma glucose concentration stimulates glucagon release.
- During an **overnight** or **prolonged fast**, **elevated** glucagon levels prevents **hypoglycemia.**
- Amino acids: stimulate the release of both glucagon and insulin.
- Elevated levels of Epinephrine.

Biologic effects of glucagon

Increases (↑)	Decrease (↓)
• Glycogenolysis • Gluconeogenesis • Ketogenesis • Uptake of amino acid	• Glycogenesis

Blood glucose levels in the fed state:
1- Changes in insulin and glucagon levels:

- a- **Blood insulin** levels **increases** as a meal is digested, following the **rise** in blood glucose.
- b- Blood glucagon levels change depending on the content of the meal. **A high carbohydrate** meal cause **decreases in glucagon** levels, while **high protein meal causes glucagon to increase.**

On a normal mixed diet, glucagon will remain relatively constant after a meal while insulin increases.

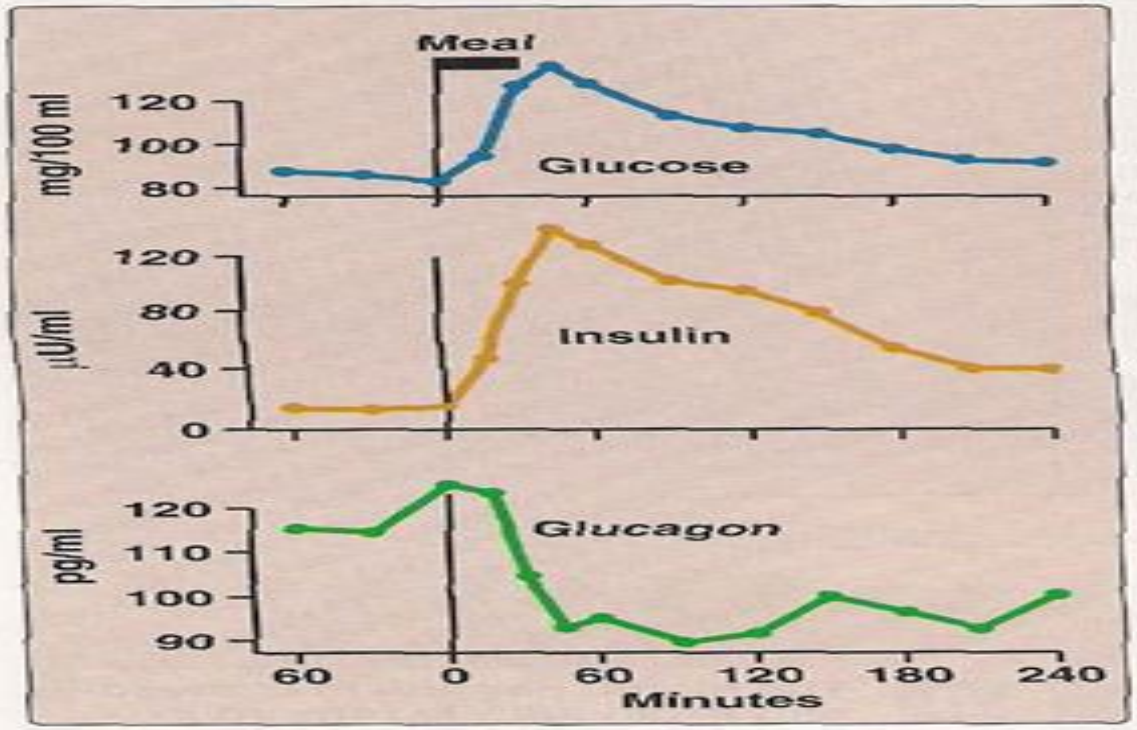


Figure 4.
Changes in blood levels of glucose, insulin, and glucagon after ingestion of a carbohydrate-rich meal.

2- Fate of dietary glucose in the liver.

- Glucose is oxidized for energy. Excess glucose is converted to glycogen and to the triacylglycerols of very low density lipoprotein VLDL, by the following mechanisms :
- **A-Increased phosphorylation of glucose:** the enzyme **glucokinase** has a high Km for glucose, thus its velocity increases after a meal when glucose levels are elevated.
- **B- Increased glycogen synthesis:** is promoted by **insulin** which activates glycogen synthase.
- **C- Increased glycolysis:**

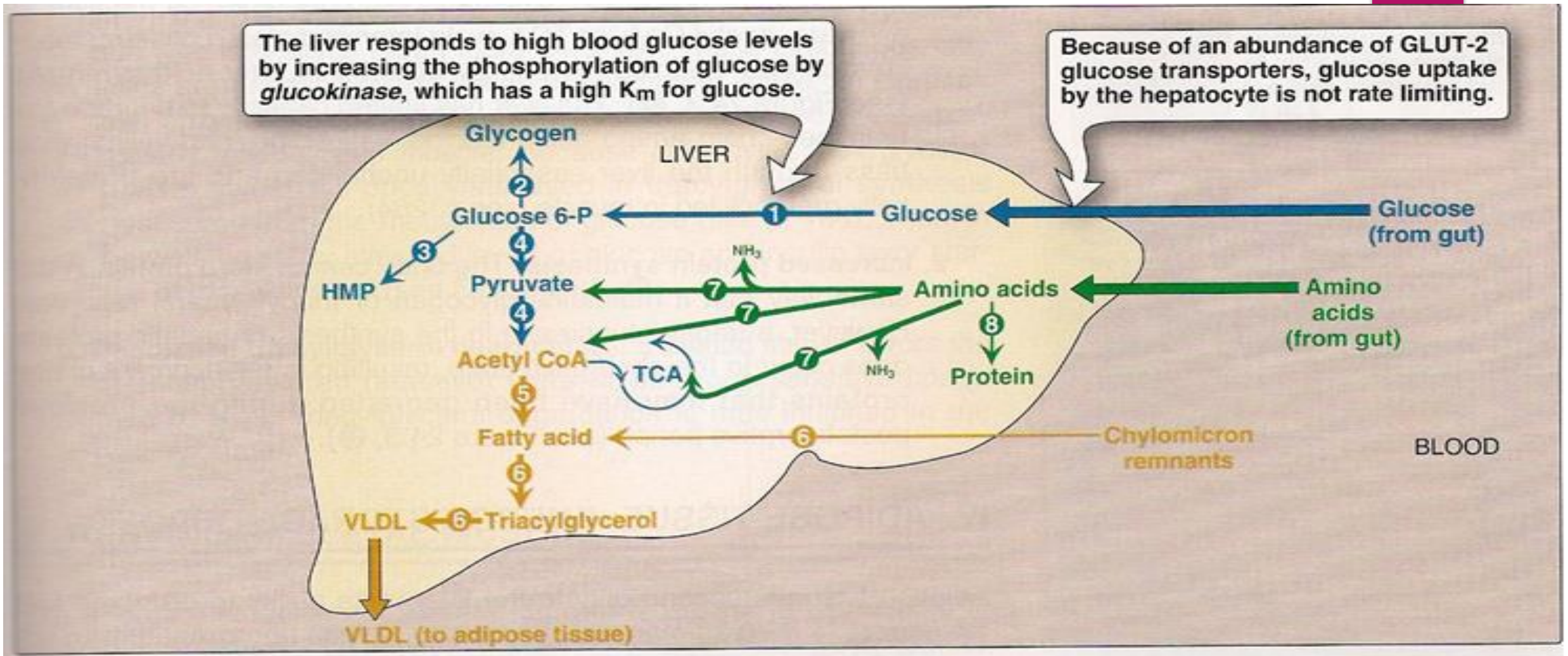


Figure 5.
Major metabolic pathways in liver in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate, fat, or protein metabolism.]
Key: **Blue text** = intermediates of carbohydrate metabolism; **Brown text** = intermediates of lipid metabolism; **Green text** = intermediates of protein metabolism.

3- Fate of dietary glucose in Adipose tissue:

- **A- Increased glucose transport:** circulating insulin levels are elevated in the fed – state resulting in an influx of glucose into adipocytes.
- **B- Increased glycolysis:** increased intracellular availability of glucose results in an enhanced rate for glycolysis which serves a synthetic function by supplying glycerol phosphate for triacylglycerol synthesis.

- **C- Increases activity in HMP pathway:** which provide NADPH for fat synthesis.

4- Fate of dietary glucose in resting skeletal muscle:

- A- Increased glucose transport.
- B- Increased glycogen synthesis.

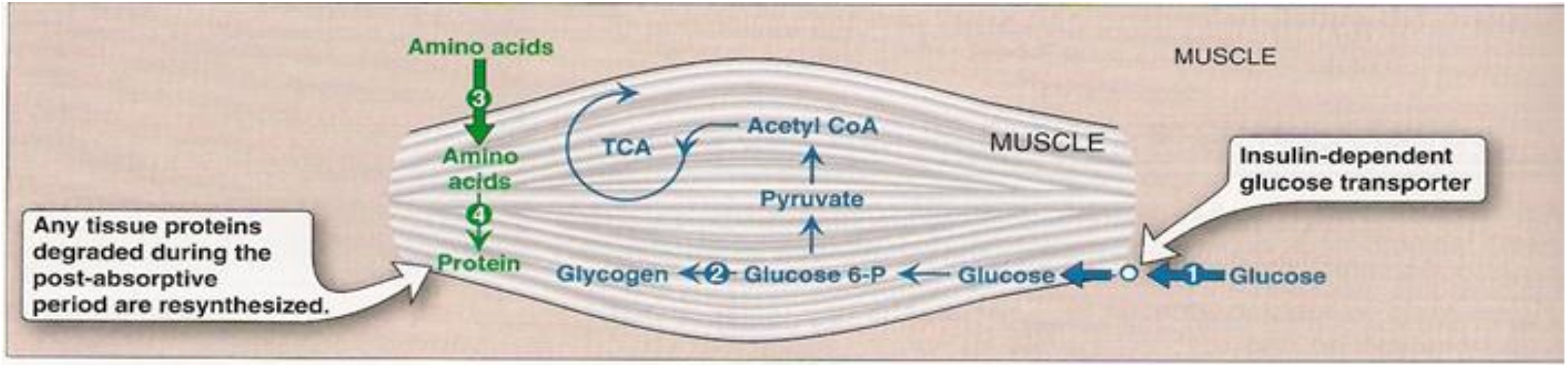


Figure 7.
Major metabolic pathways in skeletal muscle in the absorptive state. [Note: The numbers in circles, which appear both on the figure and in the text, indicate important pathways for carbohydrate or protein metabolism.]

Blood glucose levels in the fasting state:

1- Changes in insulin and glucagon levels:

- During fasting, insulin levels decrease and glucagon levels increase.

2- Liver in fasting:

- a- Stimulation of glycogenolysis: the increased levels of glucagon stimulate glycogenolysis and begin to supply glucose to the blood. Liver glycogen is nearly exhausted after (10-18) hours of fasting; therefore, hepatic glycogenolysis is a transient response to early fasting.

- **b- Stimulation of gluconeogenesis:** Gluconeogenesis begins (4-6) hours after the last meal and becomes fully active as stores of liver glycogen are depleted. Gluconeogenesis plays an essential role in maintaining blood glucose during both overnight and prolonged fasting.

3- Adipose tissue in fasting: Low levels of insulin leads to a **decrease** in **fatty acid** and **triacylglycerol** synthesis, **fasting stimulate lipolysis.**

- a- During fasting, the breakdown of adipose triacylglycerol, is stimulated, and **F.A** and **glycerol** are released into the blood.
- b- Glycerol is a **source of carbon** for **gluconeogenesis** in the liver.

4- Resting skeletal muscle in fasting.

- Low levels of insulin caused a depressed in glucose metabolism. Resting muscle uses F.A as its major fuel source, while exercising muscle uses glycogen stores as a source of energy.

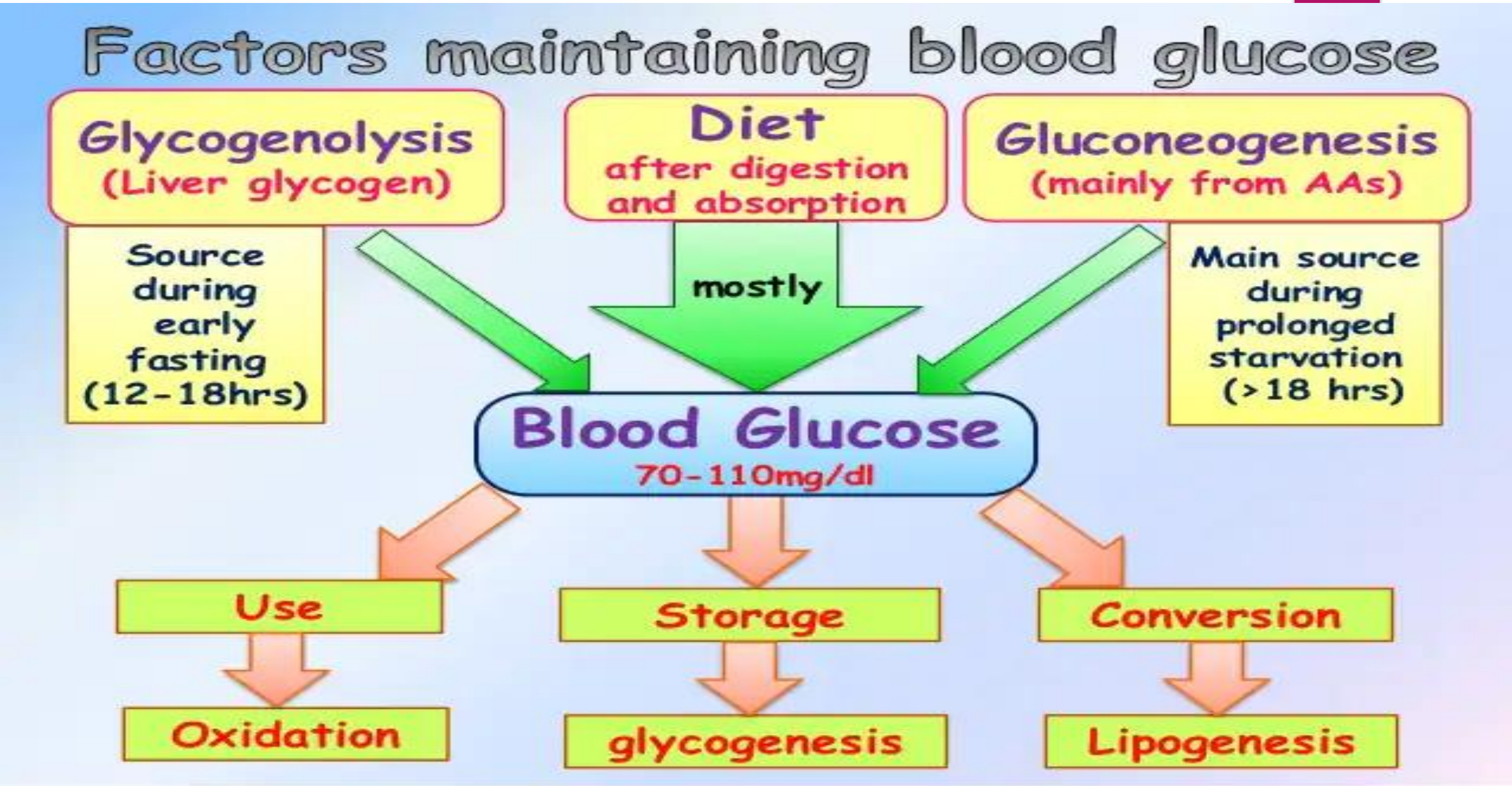
5- Brain in fasting: During the first days of fasting, the brain continues to use glucose exclusively as a fuel.

- In prolonged fasting (greater than 2-3 weeks), plasma ketone bodies, reach significantly elevated levels, are used in addition to glucose as a fuel by the brain.

Blood glucose levels during prolonged fasting (starvation).

- Even after (5-6) weeks of **starvation**, blood glucose levels are still in the range of (65mg/dL).
- **Changes in fuel utilization** by various tissues **prevent** blood glucose levels from **decreasing** during prolonged fasting.

- 1- The levels of **ketone bodies rise** in the blood, and the **brain uses ketone bodies** for energy, **decreasing** its **utilization** of **blood glucose.**
- 2- The rate of **gluconeogenesis** and, therefore, **urea production by the liver decreases.**
- 3- Muscle protein is spared: less muscle protein is used to provide amino acids for gluconeogenesis.


Factors maintaining blood glucose
Glycogenolysis
(Liver glycogen)
Diet
after digestion
and absorption
Gluconeogenesis
(mainly from AAs)
Source
during
early
fasting
(12-18hrs)
mostly
Main source
during
prolonged
starvation
(>18 hrs)
Blood Glucose
70-110mg/dl
Use
Storage
Conversion
Oxidation
glycogenesis
Lipogenesis