GLUCOSE HOMEOSTASIS: An Overview

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What is Homeostasis?

- Homeostasis(Homeostatic control): A fundamental characteristic of all living organism;
  - Condition in which disturbances to systems by stimuli are minimized, because the stimulus is able to start a series of events that can restore the system to its original state;
- It simply means: maintenance of a relatively constant internal environment within tolerable limits;
- Break down in Homeostatic control leads to disease;
- Example of Homeostatic control:
  - Maintenance of Blood Glucose level, which is under control of numerous exquisitely sensitive Homeostatic mechanisms;

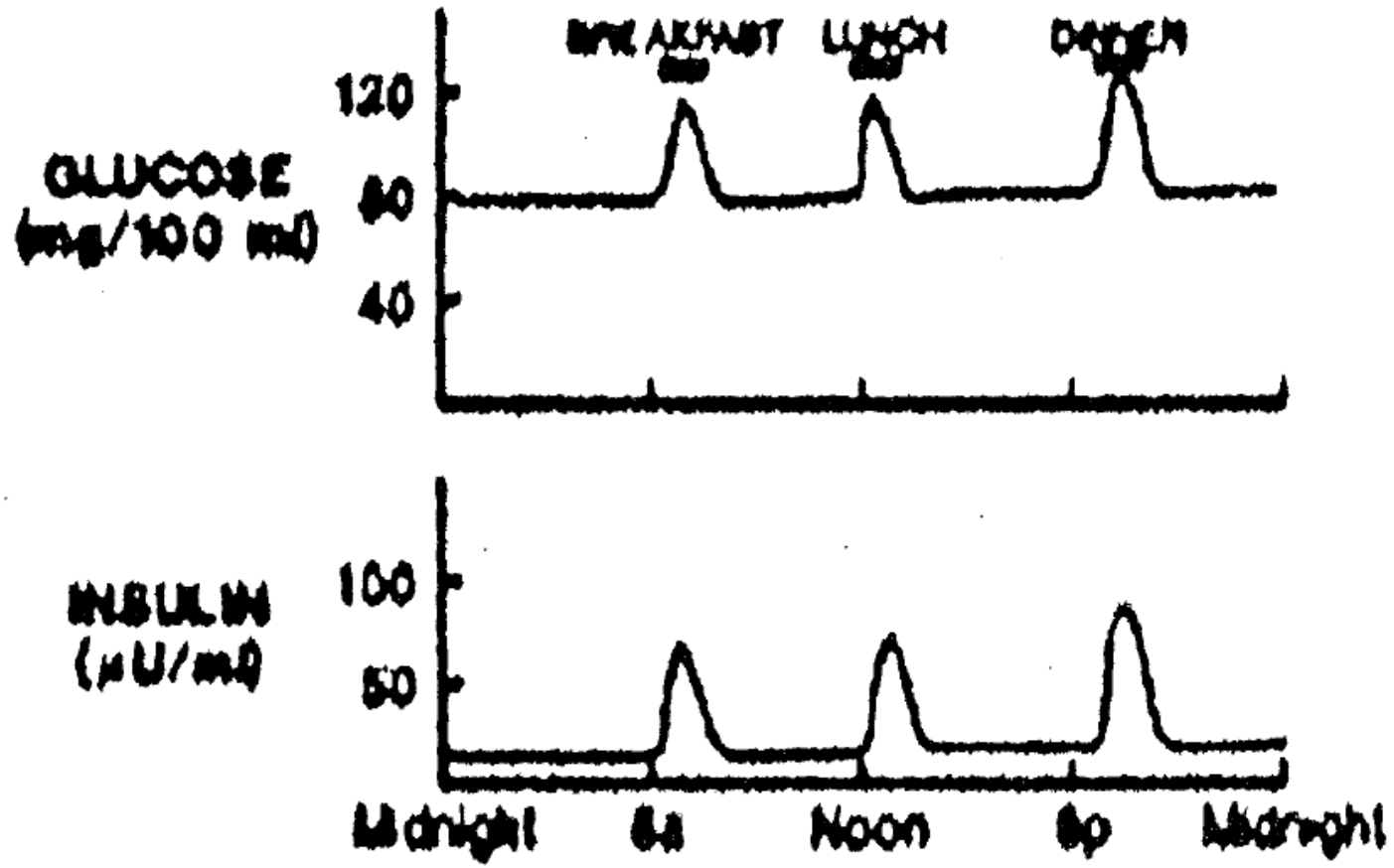
Why the need for Blood Glucose level to be “Normal”?

- **Under normal Physiological conditions:**
  - Nervous tissue uses Glucose as major substrate for energy,
  - Brain requires Glucose during prolonged fasting,
  - Mature RBC do not contain Mitochondria, thus energy is via Anaerobic Glycolysis,
  - In RBC 2,3-Bis-Phosphoglycerate is required for effective transport of Oxygen,
  - During heavy exercise skeletal muscle utilizes Glycogen and blood glucose for energy production;
- **It is essential that blood contains adequate amount of Glucose, because Brain and RBC utilize glucose almost exclusively as major substrate for their functions;**

How does dietary intake of Glucose relate to Insulin level in blood?

- Glucose level in blood increases shortly after dietary intake,
- Within 2 to 3 hours after consumption of a meal, blood glucose level should be restored to the Pre-prandial level,
- Increase in blood glucose level after a meal is immediately followed by increase in Blood Insulin level;
- **Fig 1:** Schematic representation of relationship between Blood Glucose and Insulin level in blood during periods of eating and fasting;

Fig. 1: Variations in blood glucose and blood insulin levels correlated with periods of eating and fasting;



HOW DOES THE BODY NORMALLY DISPOSES OF HIGH LEVEL OF GLUCOSE IN BLOOD AFTER A MEAL?

What is the role of Liver in disposal of high blood glucose after a meal?

- After a period of fasting (overnight fasting), large amount of Carbohydrate consumed in the diet is converted to Hepatic Glycogen,
- Liver is the first site for metabolism of Ingested Glucose,
- Liver is freely permeable to glucose, it extracts about 50% of digested Carbohydrate from Portal Blood;
- Glucose transporter in Liver is **GLUT 2**, which is not sensitive to Insulin;
- **Insulin does not mediate uptake of glucose into the hepatocytes;**

- In Hepatocytes Glucose is converted to **G-6-P** (Glucokinase reaction) and then via **G-1-P** to **Glycogen**,

- Insulin promotes synthesis of Glycogen in Hepatocytes via activation of Glycogen Synthase;

- Glycogen Synthase promotes storage of Glucose as Hepatic Glycogen until the Hepatocytes have restored their optimal level of Glycogen;

- After filling up of Hepatic Glycogen store, Glucose remaining in blood is distributed to other tissues;

What is the role of Muscle in disposal of blood glucose after the action of the liver?

- Insulin mediates uptake of blood glucose into muscle;
- Glucose transporter in muscle is **GLUT 4**, which is sensitive to Insulin,
- Glucose taken into muscle is used to replenish Glycogen store in muscle;
- Extra Glucose in muscle is used for Protein Synthesis, so as to replenish those proteins that might have been degraded for Gluconeogenesis during the period of fasting;
  - {**NB**: Carbon skeletons in non-essential amino acids are formed from intermediates in glucose metabolism}

What happens to glucose remaining in blood after Liver and Muscle have stored enough glucose as Glycogen?

- With the exception of the **Brain, Liver and Blood cells**, Insulin mediates uptake and use of Glucose by tissues,
- Liver plays major role in converting excess glucose into Triacylglycerols (Fat) packaging them into VLDL for storage in Adipose tissue;
  - Most of glucose in excess of that needed to restore Glycogen levels in the Liver and Muscle are stored as fat in Adipocytes;
- Insulin mediates the conversion of excess glucose to Triacylglycerols for storage in Adipocytes;

REGULATION OF BLOOD GLUCOSE DURING FASTING

How is Blood Glucose level regulated during fasting?

- Blood glucose level should normally remains constant, even if no food is consumed within 24-hour period;
- During prolonged fasting:
  - Blood glucose level usually decreases only slightly, but remains within normal range,
  - Brain and RBC are still actively metabolizing glucose, thus the blood glucose utilized must be replenished;

- Liver is the major source for Glucose that keeps blood glucose level within normal range during period of fasting;
- This is done:
  - Initially by bread down of Glycogen stored in the Liver (Hepatic Glycogenolysis),
  - Later by contribution from Gluconeogenesis (synthesis of Glucose from Non-carbohydrate sources) in the liver;

What is the role of the Liver in regulating blood glucose during fasting?

Glycogenolysis (Glycogen breakdown):

- Glycogen stored in Hepatocytes (5 to 10% wet weight of liver) is mobilized and used up within the first 24 to 36 hours of fasting,
  - **First positive signal** for stimulation of Glycogenolysis in Hepatocytes is increase plasma level of **Glucagon**, which is secreted in response to Hypoglycemia,
  - **Second positive signal** is **absence of Insulin** resulting from Hypoglycemia,

- **During Hepatic Glycogenolysis**:
  - G-1-P is produced from Glycogen,
  - G-1-P is then converted to G-6-P,
  - G-6-P is converted to Glucose by **G-6-Phosphatase;**
- Glucose formed in Hepatocytes are released in blood to maintain normal blood Glucose level;
- Glucagon and Insulin tightly regulates Glycogen breakdown to Glucose that directly maintains the level of Glucose in Blood;
- **In the initial phases of starvation/fasting this is the major Glucose-producing mechanism**;

- Hepatic Glycogenolysis is also regulated by Catecholamines:
  - Adrenaline, and
  - Noradrenalin
- Catecholamine release is a less sensitive hypoglycemic signal compared to Glucagon,

- Catecholamines play significant role in stimulating Hepatic Glycogenolysis during severe stress and marked Hypoglycemia;

Gluconeogenesis: synthesis of glucose from non-carbohydrate sources

- As hepatic Glycogen stores become depleted during fasting (or starvation) the other significant source of Glucose is Gluconeogenesis :

- Sites of Gluconeogenesis and sources of precursors depend upon the duration of Caloric deprivation,

- Although Kidneys assume importance as a source of new glucose during protracted starvation, during brief fasting over 90% of total Gluconeogenesis occurs in the Liver

What is the role of Skeletal Muscle in regulating blood glucose during fasting?

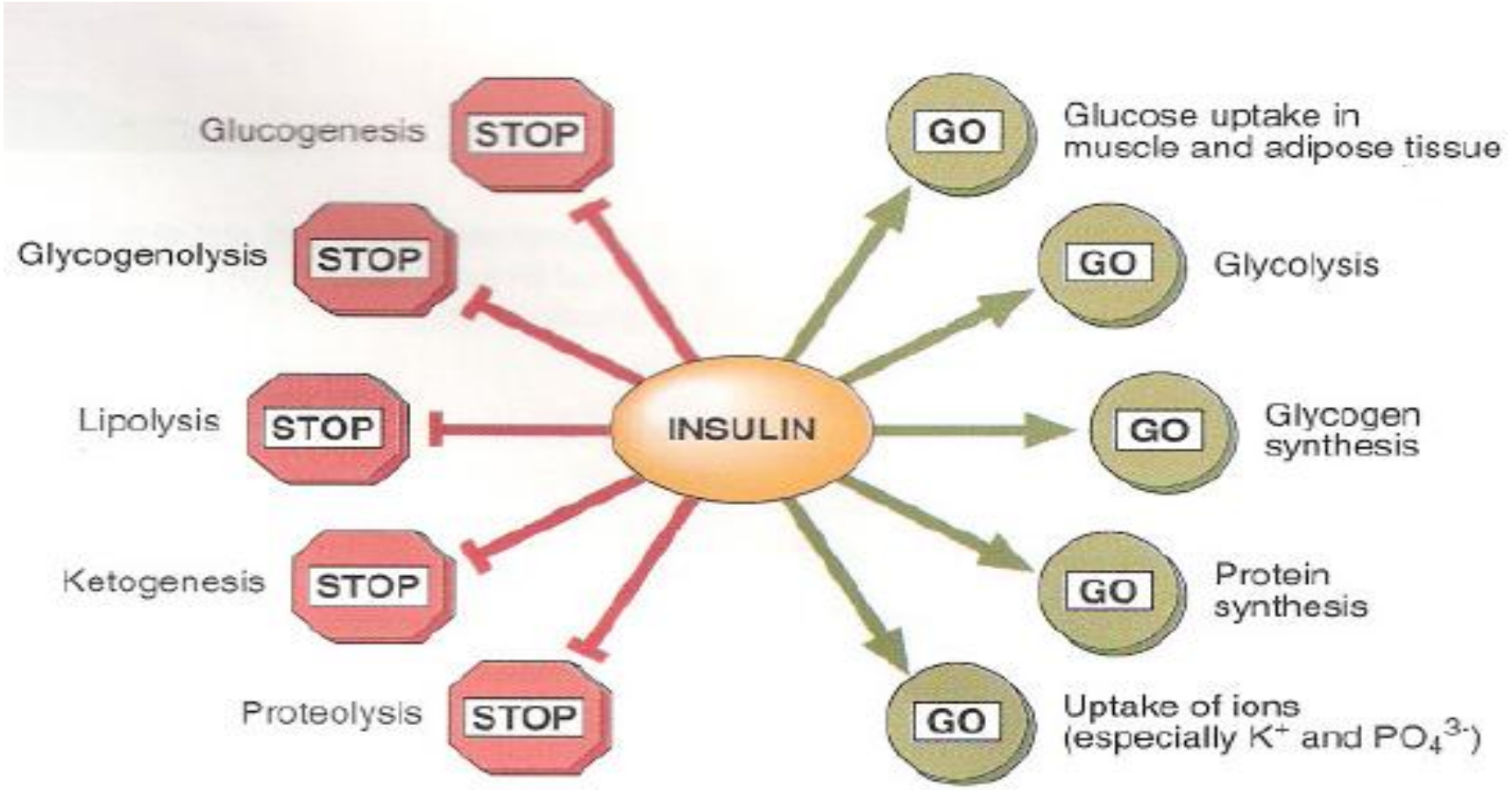
- Glycogen in skeletal muscle is not readily available to maintain blood glucose concentration;
- Muscle tissue does not contain **Glucose-6-Phosphatase**,
- Thus, Glucose-6-Phosphose **cannot** be converted to Glucose in muscle tissue;
- **Muscle does not play any significant role in maintaining blood glucose level;**
- Under Anaerobic conditions the muscle converts Glucose to Lactate, which is released in blood picked up by the Liver and converted to Glucose (Cori Cycle);

What are the actions of Insulin and Glucagon

INSULIN		GLUCAGON	
GO	**STOP**	**GO**	**STOP**
Muscle & Adipose Tissue uptake of Glucose	Gluconeogenesis	Gluconeogenesis	Muscle & Adipose Tissue uptake of Glucose
Glycolysis	Glycogenolysis	Glycogenolysis	Glycolysis
Glycogen synthesis	Lipolysis	Lipolysis	Glycogen synthesis
Protein synthesis	Ketogenesis	Ketogenesis	Protein synthesis
Uptake of K^+ ions & Phosphate ions	Proteolysis	Proteolysis	Uptake of K^+ ions & Phosphate ions

Fig. 2: Actions of Insulin (Gaw et al, Clinical Biochem, 2nd Ed 1999)

Stop – Go actions of Insulin



The actions of insulin.

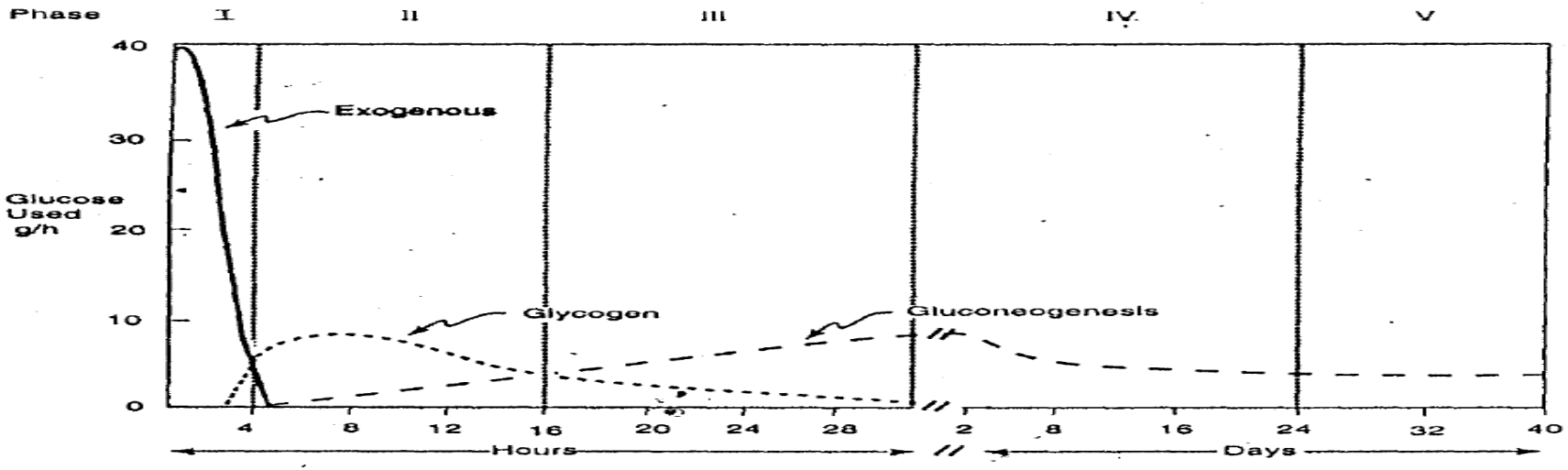
- Actions of Insulin are directly opposite to those of Glucagon;
- Insulin stimulates:
  - Glycogen synthesis,
  - Glycolysis,
  - Biosynthesis of fatty acids and proteins;
- Glucagon stimulates:
  - Gluconeogenesis,
  - Glycogenolysis,
  - Lipolysis,
  - Ketogenesis,
  - Proteolysis

Outline the actions of Glucocorticoids

Glucocorticoids are chronic modulators of glucose;

- Glucocorticoid (Cortisol) actions are more complex than either Insulin or Glucagon,
- Glucocorticoids stimulate:
  - Fatty acid breakdown,
  - Gluconeogenesis,
  - Rate of Hepatic Glycogen synthesis,
- Glucocorticoids are one of the major signals for the degradation of muscle proteins, with amino acids serving as precursors for Gluconeogenesis;

Five Phases of Glucose Homeostasis: For convenience Glucose Homeostasis can be divided into Five Phases as shown in **Fig. 3**.



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

GENERAL CONCEPTS: Understanding Glucose Homeostasis

- **Balancing Act: Hypoglycemia and Hyperglycemia**:
- Glucose Homeostasis involves extensive contributions from various metabolic tissues (Liver, Skeletal muscle, Adipose tissue, etc.) tightly regulated and balanced by the Metabolic Endocrines;

- Hypoglycemia and Hyperglycemia refers to circumstances when this balance is disturbed, giving uncharacteristically Low and High Blood Glucose concentrations, respectively

- Conditions resulting in Hypoglycemia or Hyperglycemia can be divided in three categories:
  - Factors related to effective Insulin levels
  - Insulin Counter-Regulatory Hormones,
  - Sources of Fuel for the tissues,

- **Insulin Counter-Regulatory Hormones:** Hormones that counter the actions of Insulin (examples):
  - Glucagon,
  - Catecholamines,
  - Glucocorticoids,
  - Growth hormones,
- They are elevated in blood during Hypoglycemia;

SUMMARY

- Major tissues involved in Glucose conservation are:
  - Liver,
  - Skeletal Muscle,
  - Adipose Tissue;
- Glucagon actions are essentially restricted to Liver and Adipose tissue **WHY??**
  - Glucagon stimulates Glycogen breakdown and Gluconeogenesis in Hepatocytes,
  - Glucagon stimulates breakdown of Triglycerides in Adipose tissues producing substrate for Gluconeogenesis in Hepatocytes

- Glucocorticoids activate hepatic Gluconeogenesis synergistically with Glucagon;
- Skeletal Muscle is major site of Glucocorticoids actions;
- Presence of Glucocorticoids and Absence of Insulin are Primary signals for enhanced Protein degradation;
- Effects of Glucocorticoids are long term,
- Effects of Glucagon are moments to moment;

Study Questions for Glucose Homeostasis

- Why does the body need adequate amount of glucose?
- How is the body able to dispose of high glucose level in the blood after a meal?
- How is the blood glucose level regulated during period of fasting?
- What is the role of the liver in the regulation of blood glucose during fasting?
- What is the role of the muscle in the regulation of blood glucose during fasting?

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