GLUCOSE HOMEOSTASIS-II: An Overview

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What is Homeostasis?

- Homeostasis(Homeostatic control):
  - A fundamental characteristic of living organism;
  - **A self-regulating process by which biological systems tend to maintain stability while adjusting to conditions that are optimal for survival;**
  - If homeostasis is successful, life continues;
  - If it is unsuccessful, illness or death may occur;
- The stability attained is a steady state condition in which continuous change occurs yet relatively uniform conditions prevail.

- Break down in Homeostatic control may lead to disease;
- Homeostasis simply means: **maintenance of a relatively constant internal environment within tolerable limits;**
- **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”?

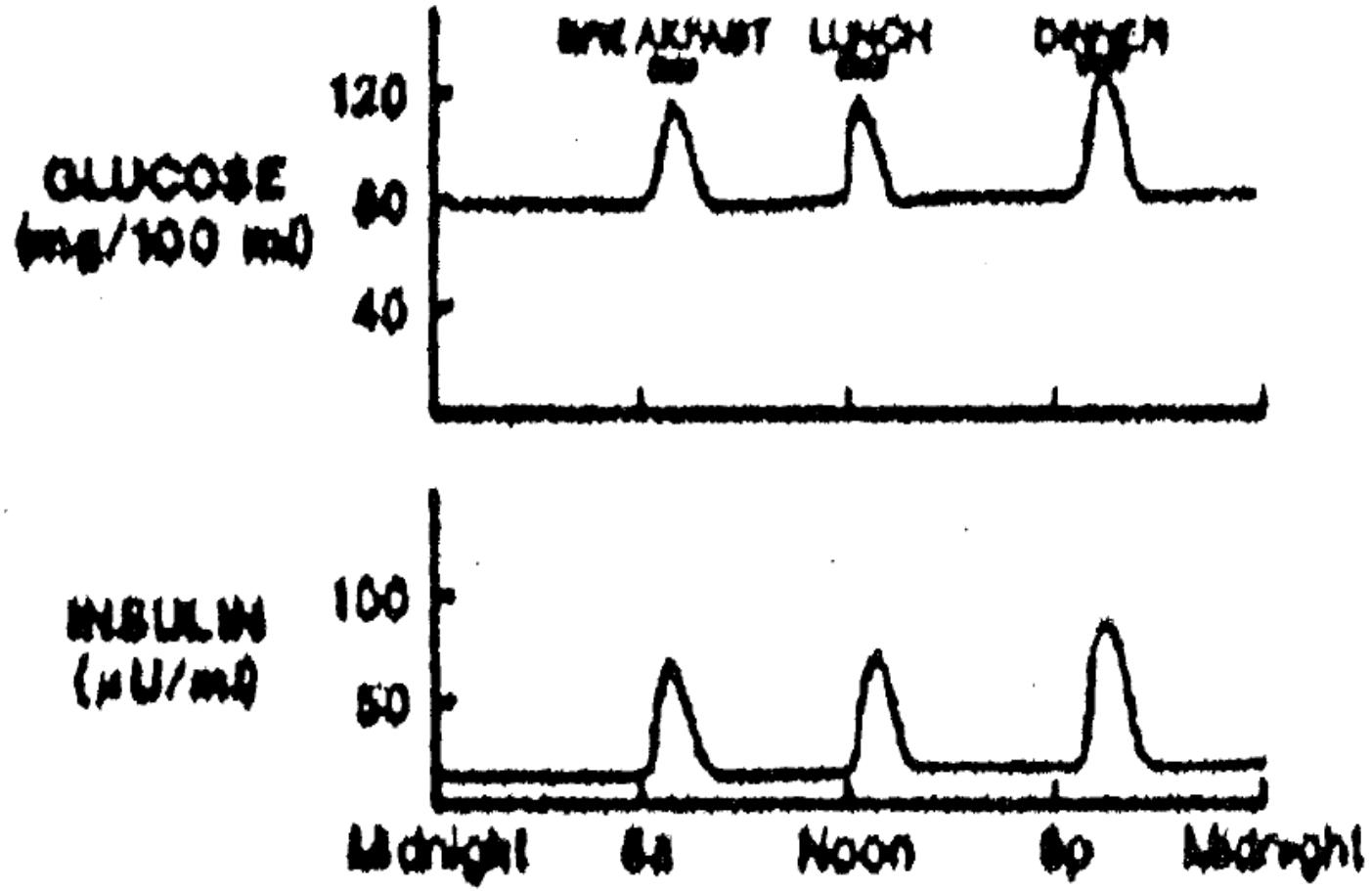
- **Under normal Physiological conditions:**
  - CNS uses Glucose as major substrate for energy
  - Brain requires Glucose during prolonged fasting
  - Mature RBC do not contain Mitochondria, thus energy is obtained via Anaerobic Glycolysis,
  - In RBC 2,3-Bis-Phosphoglycerate (2,3-BPG) is required for effective transport of Oxygen,

- During heavy exercise skeletal muscle utilizes glucose for energy production;
- **Adequate Glucose in blood is essential because Brain and RBC utilize glucose almost exclusively as major substrate for their functions;**
- Thus the need for blood glucose to be kept within normal range;

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

- 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 followed by increase in blood Insulin level;
- **Fig 1:** Relationship between Glucose and Insulin level in blood during eating and fasting;

Fig. 1: Variations in glucose and insulin levels in blood 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 role of Liver in disposal of high blood glucose after a meal?

- After fasting (e.g. overnight), large amount of Carbohydrate consumed in diet is converted to Hepatic Glycogen,
- Liver is first major site for uptake of Ingested Glucose,
- Hepatocytes are permeable to glucose; liver may extract up to 70% 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 Hepatocytes have optimal level of Glycogen;

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

What is 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 is used to replenish Glycogen store in muscle;
- Extra Glucose in muscle is used for Protein Synthesis, to replenish proteins degraded for Gluconeogenesis during 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 exception of **Brain, Liver and RBC**, Insulin mediates uptake of Glucose by tissues with **GLUT-4 transporter**,
- Liver plays major role in converting excess glucose into fat packaging them in VLDL for storage in Adipocytes;
  - Glucose in excess of that needed to restore Glycogen levels in Liver and Muscle are converted to fat and stored in Adipocytes;
- **Insulin mediates conversion of excess glucose to Triacylglycerols for storage in Adipocytes;**

REGULATION OF BLOOD GLUCOSE DURING FASTING

How is Blood Glucose level regulated during fasting?

- In “apparently” healthy person [glucose] in blood should be within normal range, even if no food is consumed within 24-hour period;
- During prolonged fasting:
  - [Glucose] in blood decreases only slightly, but remains within normal range,
  - Brain and RBC are actively metabolizing glucose, thus blood glucose utilized must be replenished;

- **Liver is major source** for Glucose that keeps [glucose] in blood within normal range during period of fasting;
- This is done:
  - Initially: By Hepatic **Glycogenolysis** (breakdown of Glycogen),
  - Later: by **Gluconeogenesis** in liver (synthesis of Glucose from Non-carbohydrate sources);

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

Glycogenolysis (Glycogen breakdown):

- Glycogen in Hepatocytes is mobilized and used up within 24 to 36 hours of fasting,
  - **1st positive signal** for start of Glycogenolysis in liver is increase plasma level of **Glucagon** secreted in response to Hypoglycemia,
  - **2nd positive signal** is **absence of Insulin;**

- **During Hepatic Glycogenolysis**:
  - G-1-P is produced from Glycogen,
  - G-1-P is then converted to G-6-P,
  - G-6-P to Glucose by **G-6-Phosphatase;**

- **Glucose formed in Hepatocytes are released in blood to maintain [Glucose] in blood;**

- **Glucagon** and **Insulin** tightly regulates [Glucose] in blood via Glycogen metabolism;
  - **They directly maintains [Glucose]** in Blood;

- **In the initial phases of starvation/fasting Glycogenolysis is the major Glucose-producing mechanism**;

- Hepatic Glycogenolysis is also regulated by the **Catecholamines**:
  - **Epinephrine (Adrenaline) ,**
  - **Norepinephrine (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 get depleted during fasting (starvation) Gluconeogenesis becomes major Glucose source;

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

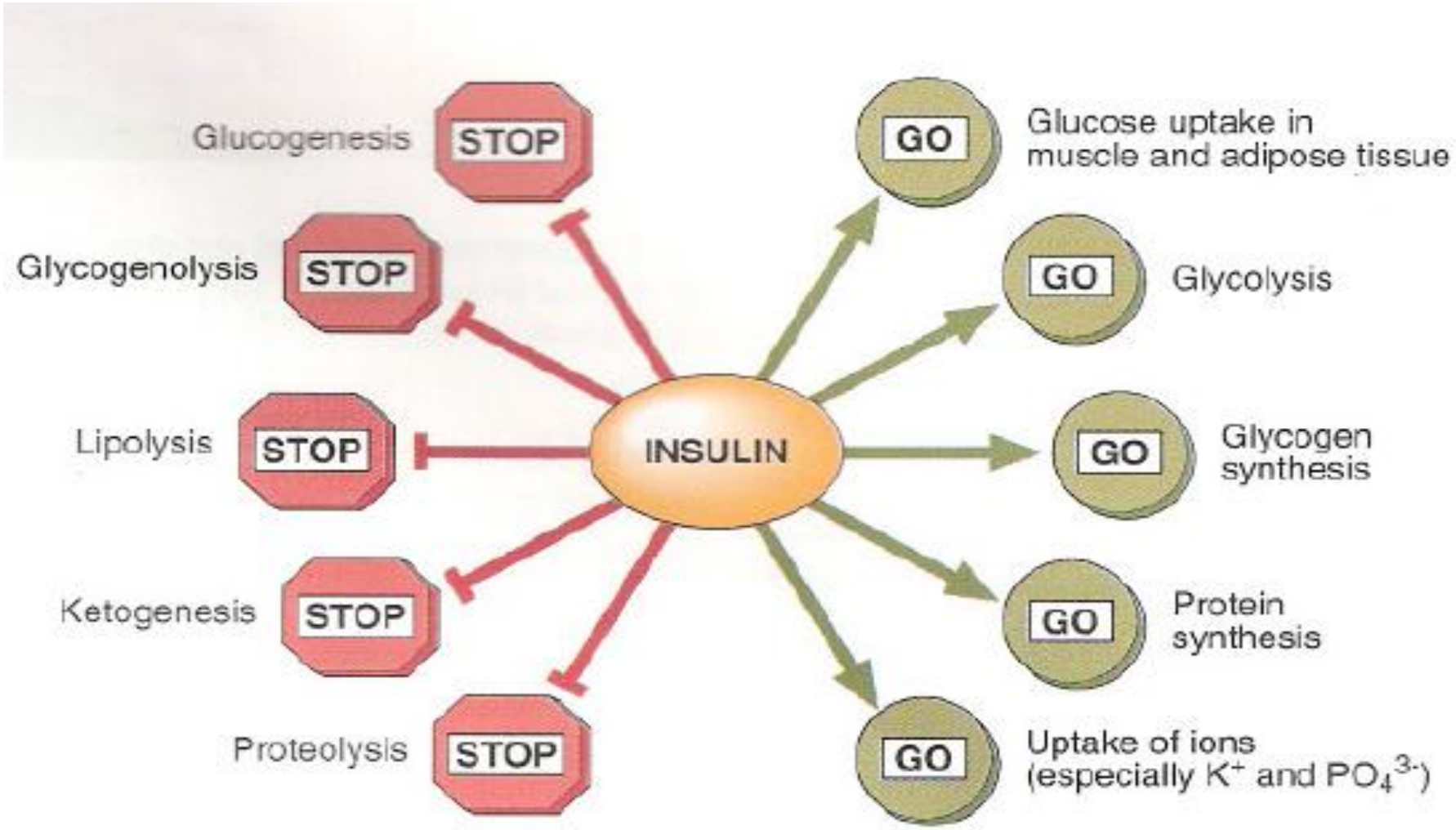
- Although Kidneys assume importance as a source of new glucose during protracted starvation, during brief fasting, over 90% of total Gluconeogenesis occurs in Liver;

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

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

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

Stop – Go actions of Insulin



The actions of insulin.

SUMMARISE THE ACTIONS OF INSULIN & GLUCAGON

- **Actions of Insulin are directly opposite to Glucagon**:
- **Insulin stimulates**:
  - Glycogen synthesis,
  - Glycolysis,
  - Biosynthesis of Fatty Acids;
- **Glucagon stimulates**:
  - Gluconeogenesis,
  - Glycogenolysis,
  - Lipolysis,
  - Ketogenesis,
  - Proteolysis

Outline the actions of Glucocorticoids

Glucocorticoids are chronic modulators of glucose;

- 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;

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 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 into 3 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:
  - **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;

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