GLUCOSE HOMEOSTASIS-II: An Overview

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What is 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;

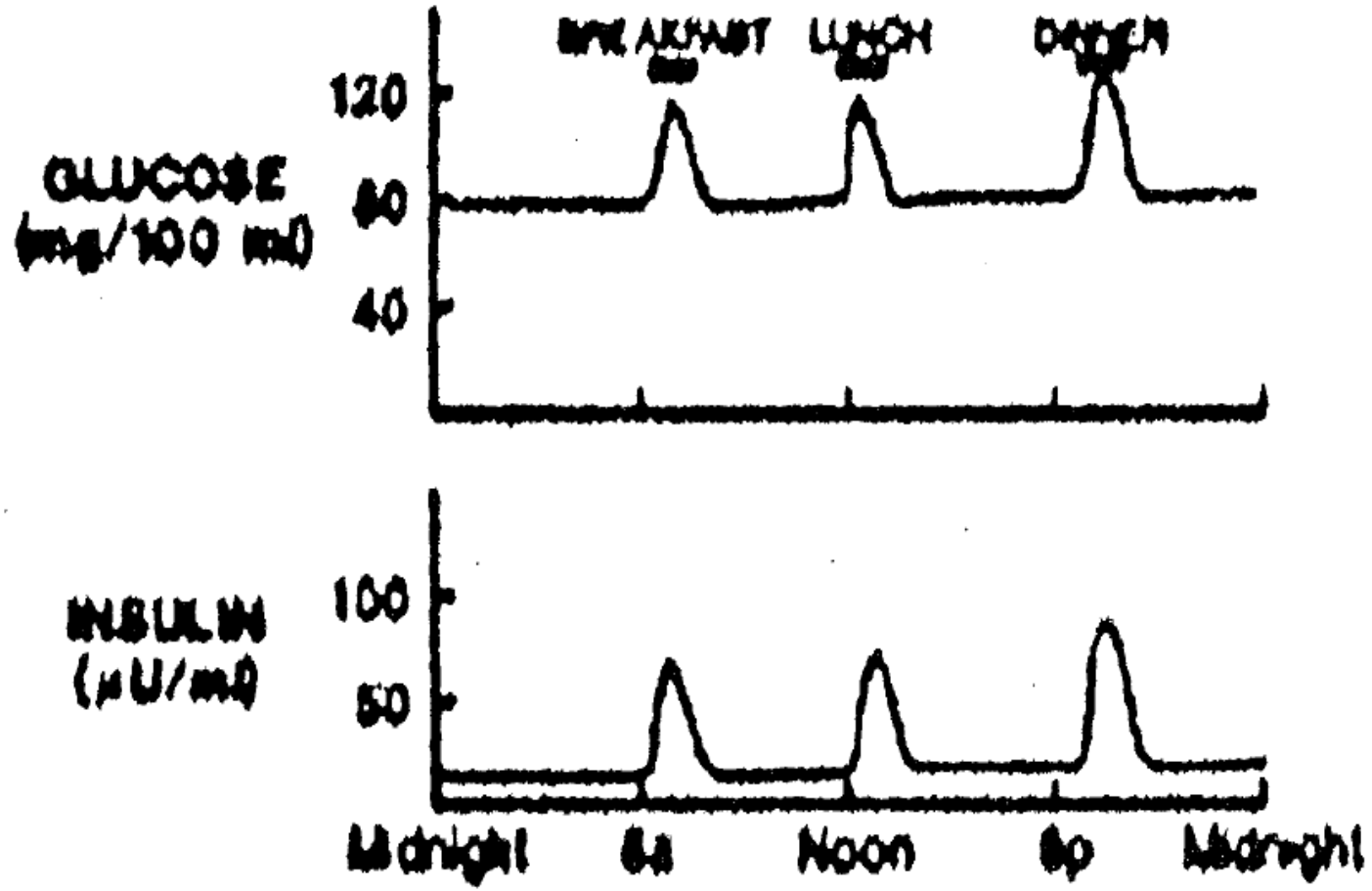
Why the need for Blood Glucose level to be “Normal”?

- **Under normal Physiological conditions:**
  - Nervous tissue uses Glucose as major energy substrate
  - 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 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 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 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 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 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 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 RBC**, Insulin mediates uptake and use of Glucose by tissues with GLUT-4 transporter,
- Liver plays major role in converting excess glucose into Triacylglycerols (Fat) packaging them into VLDL for storage in Adipose tissue;
  - Most of the 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?

- In “apparently” healthy person, blood glucose level should be within normal range, 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 Hepatic Glycogenolysis (Degradation of Glycogen),
  - Later by Gluconeogenesis (synthesis of Glucose from Non-carbohydrate sources) in the liver;

What is the role of Liver in maintaining blood glucose level 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;**

- **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 Glucose level in blood via Glycogen metabolism; thus directly maintains the level of Glucose in Blood;
- **In the initial phases of starvation/fasting Glycogenolysis 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 get depleted during fasting (or starvation) the other major Glucose source becomes Gluconeogenesis:

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

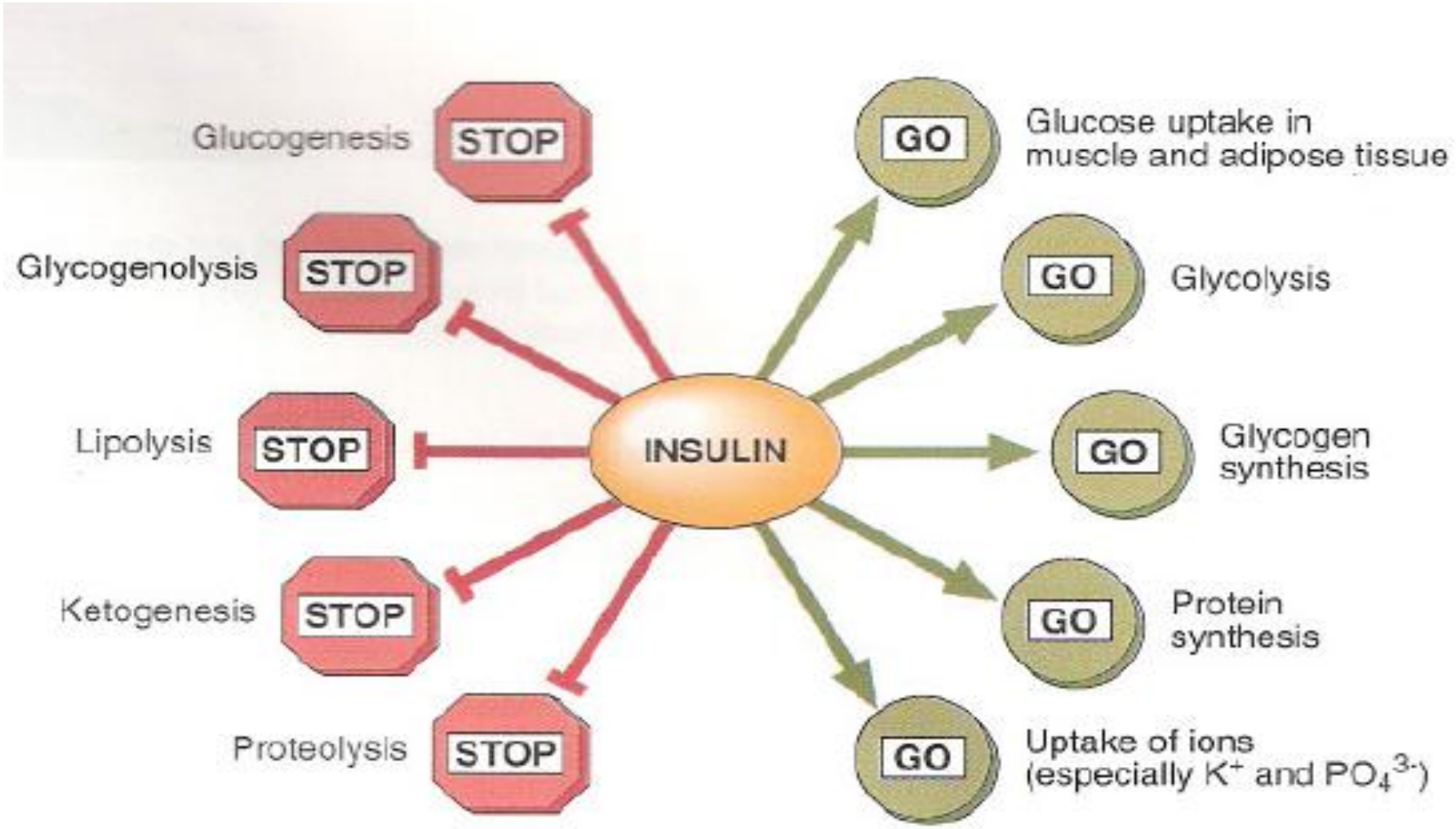
- Although Kidneys assume importance as a source of new glucose during protracted starvation, during brief fasting, over 90% of total Gluconeogenesis occurs in the Liver;

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

- Glycogen in skeletal muscle is not readily available for 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);

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;

- 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;

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;

REFERENCES

- Textbook of Biochemistry, with clinical correlations, Ed. By T. M. Devlin, 4th Edition. Pages: 62, 287, 390, 537, 548 – 551; 536 – 540
- Harper's Biochemistry 24th Edition. Ed. By R. K. Murray et. al. Page: 203, 204, 586, 587, and 826, 827.
- Biochemistry, By V. L. Davidson & D. B. Sittman. 3rd Edition. Pages: 517 – 519.
- WWW.zonehome.com/met/metglucose.html
- WWW.niko.unl.edu/bs101/notes/lecture12.html
- WWW.mun.ca/biochem/courses/1430/diabetes.html
- VJ Temple Biochemistry 1001: Review and Viva Voce Questions and Answers Approach:; Sterling Publishers Private Limited, 2012, New Delhi-110 – 020.