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;
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

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