GLUCOSE HOMEOSTASIS PART-I

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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;

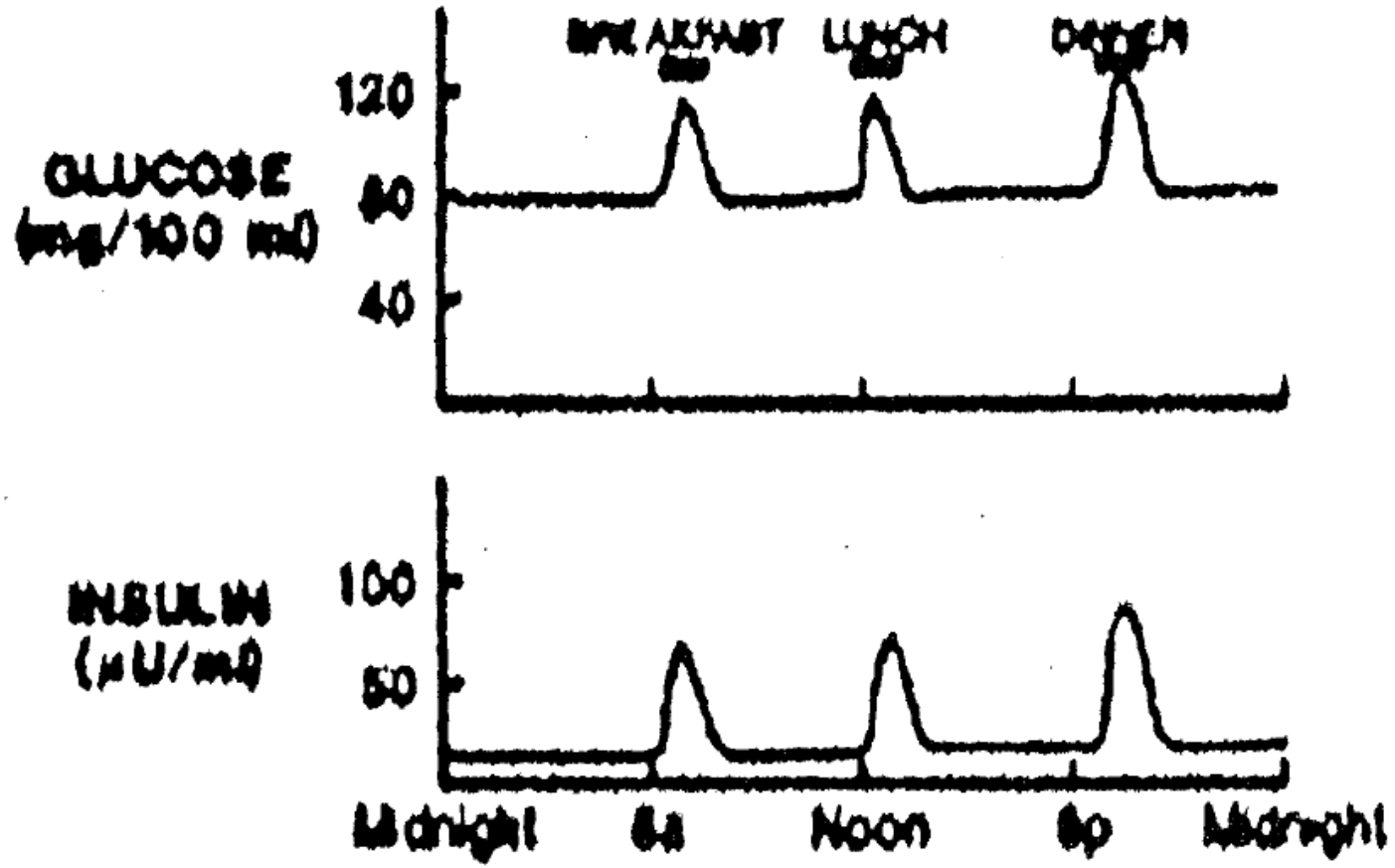
Why the need for Blood Glucose level to be "Normal"?

- **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 (2,3-BPG)** 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 energy production;**

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 Insulin level;
- **Fig 1:** Schematic representation of relationship between Glucose and Insulin levels 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; (Davidson et al 1994)



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?

- Glucose level in blood should normally remains constant, even if no food is consumed within 24-hrs;
- During prolonged fasting:
  - Blood glucose level usually decrease 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,
  - 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 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 the Liver;

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

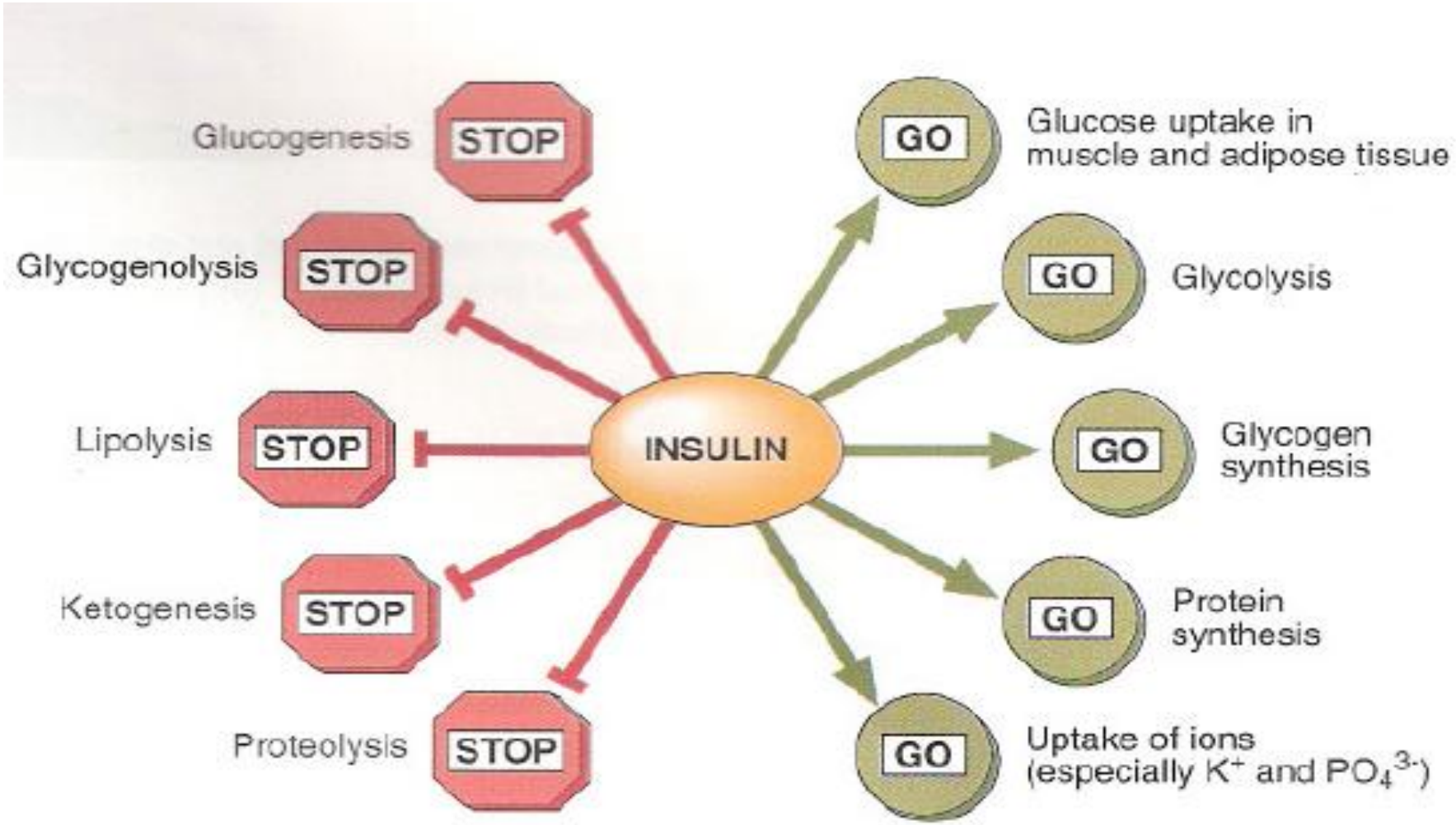
- Glycogen in skeletal muscle is not readily available to maintain blood glucose concentration;
- Muscle tissue does not contain **Glucose-6-Phosphatase**,
- Thus, Glucose-6-Phosphose **cannot** be converted to Glucose in muscle tissue;
- **Muscle does not play any significant role in maintaining blood 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.

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

What are some of 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,

What are the Insulin Counter-Regulating Hormones?

- **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 restricted to the Liver and Adipose tissue **WHY??**
  - Glucagon stimulates Gluconeogenesis and breakdown Glycogen in Hepatocytes,
  - Glucagon stimulates breakdown of Triglycerides in Adipose tissues to give substrates for Gluconeogenesis in Hepatocytes,

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

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