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GLUCOSE HOMEOSTASIS – An Overview

WHAT IS HOMEOSTASIS?

- Homeostasis is one of the fundamental characteristics of all organisms.
- Homeostasis simply means – maintenance of a relatively constant internal environment within tolerable limits.
- All organisms have mechanisms in place for maintaining Homeostasis.
- These mechanisms also provide for appropriate responses to changes in the external environment and the associated demands those changes place on maintaining Homeostasis – in other words:
    - Changes that potentially produce a stress on the system,
    - A means of sensing the changes,
    - A graded response, and
    - A correction of the stress put on the system,
- Break down in any of the Homeostatic mechanisms may lead to disease.

What systems are responsible for homeostatic control (give an example)?

- Endocrine system, Nervous system, Immune system, etc. are responsible for mediating both detection and response to homeostatic changes from the level of the cell to that of the whole organism.
- Example of Homeostatic control is the maintenance of Glucose level in the blood.
    - Maintenance of blood glucose level is significant to humans and normally this is under control of numerous exquisitely sensitive Homeostatic mechanisms.
    - One of the major mechanisms involves the cells of the Endocrine pancreas, their detection of blood glucose levels, and the hormones that they secrete.
- Defects in this homeostatic mechanism are responsible for one of the major challenges to human health – **Diabetes Mellitus**.

Why the need for adequate amount of Glucose?

- Under normal Physiological conditions the Brain and the rest of the Nervous tissue utilize Glucose as Major Substrate for Energy production.
- Brain still requires significant amount of Glucose during prolonged fasting.
- Mature RBC do not contain Mitochondria, thus energy is obtain via Anaerobic Glycolysis.
- Skeletal muscle at rest uses predominantly Lipid as source of energy, but in heavy exercise draws upon muscle Glycogen and blood glucose for energy production.
- **Thus, is essential that Glucose is always available in adequate amount in the blood, because Brain and Red Blood Cells utilize glucose almost exclusively as major substrate for energy.**

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

- Glucose level increases in the blood shortly after dietary intake (following a meal).
- Within 2 to 3 hours after consumption of the meal, blood glucose level is restored to the Pre-prandial level.
- Increase in blood glucose level after a meal is immediately followed by increase in Blood Insulin level (See **Fig. 1**.)
- **Figure 1** shows schematic representation of the relationship between Plasma Glucose and Plasma Insulin levels during periods of eating and fasting.

<u>TAKE NOTE</u>:

- Insulin secretion is stimulated by several events that are associated with Glucose intake.
- These events include the following:
    - Elevated blood glucose directly stimulates Pancreatic Insulin release from the Beta cells (Islets of Langahan) in the Pancreas.
    - Insulin release is also stimulated by other components of the typical diet, notably **Leucine** and **Arginine** derived from the digestive hydrolysis of protein in the diet.
    - The digestive process also stimulates the release from the GIT of Gastrin, Pancreozymin, Cholecystokinin, and the Glucagon-like Gastrointestinal peptide Glicentin.
    - These hormones appear to feed forward to the Pancreatic β-cell and stimulate insulin release in an anticipatory manner.
    - Insulin release is also under Neural Control, possibly also as an anticipatory event.

How does the composition of the meal affect blood levels of Insulin and Glucagon?

- Blood levels of both Insulin and Glucagon are changed after consumption of a meal.
- The magnitude and direction of the change depends on the composition of the meal consumed.
- If the meal contains only Carbohydrate, then, there will be a Fall in the Blood Level of Glucagon as a result of:
    - Direct Inhibition of the Alpha-cells in the Islets by high glucose level, and
    - Increase in the release of Insulin from the Beta cells in the Islets.
- If the meal contains High Protein and Low Carbohydrate then Glucagon secretion will be stimulated as a consequence of Amino Acid Influx.
- For a Typical meal that contains both Carbohydrate and Protein, plasma Glucagon levels often may not change noticeably, while Insulin level may increase.

How does the body normally dispose of high dietary glucose?
What is the role of the Liver in the disposal of high dietary glucose?

- After periods of fasting, such as overnight fasting, a substantial amount of Carbohydrate consumed in the diet is converted to Hepatic Glycogen.
- The first important site of ingested Glucose metabolism is the Liver.
- The liver, which is freely permeable to glucose, quite typically extracts about 50% of the digested Carbohydrate.
- In the liver glucose is first converted to G-6-P (by either Gluco-kinase or Hexokinase) and then to Glycogen.

- The major signals for this include:
  - Insulin, which promotes the activation of Glycogen Synthase.
  - Low level of plasma Glucagon that causes reduction in the level of Hepatic Cyclic-AMP; thus blocking the Cyclic-AMP-dependent Protein Kinase-catalyzed inactivation of Glycogen Synthase.
  - High levels of plasma glucose that promote high levels of G-6-P, which serves as a feed-forward mechanism to allosterically stimulate the Glycogen Synthase.
- These signals promote storage of Glucose as Hepatic Glycogen until the liver has restored its optimal level of Glycogen.
- The signal that terminates the synthesis of Glycogen is the level of Glycogen itself, which acts by inhibiting Glycogen Synthase Phosphatase.
- Remaining Glucose that is not taken up by the liver is distributed to other tissues, for metabolism in those tissues.

What is the role of the Muscle tissue in disposal of high dietary glucose after the action of the liver?

- Insulin directly stimulates the uptake of glucose into muscle.
- Glucose taken up by the muscle is normally used to replenish the muscle stores of Glycogen.
- Excess glucose can also be used for Protein Synthesis, so as to replenish those proteins that might have been degraded for Gluconeogenesis during the period of fasting.
- The signal for elevated protein synthesis from glucose is Insulin.

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

- With the exception of the **Brain, Liver, and Blood cells**, insulin directly stimulates both the entrance of glucose into most cells of the body and its use as substrate for Anabolic processes.
- Liver plays a major role in converting excess glucose into Triacylglycerols (Triglycerides), packaging them into VLDL and exporting the VLDL to Adipose tissue.
- As a consequence, much of the glucose in excess of that needed to restore Glycogen levels in the Liver and Muscle ends up as Triacylglycerols stored in Adipocytes.
- Insulin is the Primary signal for conversion of excess glucose to Triacylglycerols for storage in Adipocytes.

<u>TAKE NOTE</u>:

A summary of the disposition of high dietary glucose is as follows:

- Optimal amount of glucose is stored as glycogen in Liver and Muscle.
- The remaining glucose is used for other biosynthetic purposes and any excess is then converted into Fatty acids and stored as Triacylglycerols.
- Although the glucose levels in systemic blood are elevated, they do not exceed the Renal Threshold (about 200mg/dl or 11mmol/L) therefore, glucose does not spill into the urine.
- In the disposal of high blood glucose, Insulin plays a pivotal role in stimulating a range of Anabolic processes in addition to those of Glycogen, Protein and Triacylglycerol synthesis.
- Insulin does so by a variety of Regulatory mechanisms, which may involve either the modification of key regulatory enzymes and/or regulation of their synthesis.
- **In addition to the role of Insulin is the absence of the Insulin "Counter-Regulatory" Hormones – Glucagon, Glucocorticoids and Catecholamines**.

How is Blood Glucose level regulated during fasting?

- In a 'healthy" individual, the blood glucose level usually remains constant, even if no food is consumed within a 24-hour period.
- During prolonged fasting:
  - Blood glucose level usually decreases only slightly, but is within normal range.
  - The Brain and the RBC are still actively metabolizing glucose, thus the blood glucose that is utilized must be replenished.
- The primary source of the glucose that keeps the blood glucose level within the normal range during the period of fasting is the Liver.
- 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 level during fasting?
Glycogenolysis (Glycogen breakdown):

- Glycogen stored in the liver (about 5 to 10% wet weight of liver) is usually mobilized and used up within the first 24 to 36 hours of fasting.
- The First positive signal for stimulation of Glycogenolysis in the liver is increase plasma level of Glucagon, which is secreted in response to Hypoglycemia.
- The second positive signal is the absence of insulin (hypoglycemia)
- During hepatic Glycogenolysis:
  - Glucose-1-Phosphate (G-1-P) is produced from Glycogen
  - G-1-P is then converted to Glucose-6-Phosphate (G-6-P)
  - G-6-P is then converted to Glucose by **Glucose-6-Phosphatase**, which is an enzyme that is very active in the Liver.
  - Glucose formed in the liver is then released into the blood to keep the blood glucose level normal.
- **Thus, through the hormones Glucagon and Insulin there is a tight regulation of Glycogen breakdown to Glucose that directly maintains the level of Glucose in the blood**.
- **In the initial phases of starvation/fasting this is the major Glucose-producing mechanism.**
- Hepatic Glycogenolysis is also regulated by Catecholamines (Adrenaline and Noradrenaline).
- Catecholamine release is a less sensitive hypoglycemic signal compared to Glucagon, but it does play a significant role in stimulating hepatic Glycogenolysis in circumstances of additional stress and marked Hypoglycemia.

Gluconeogenesis (synthesis of glucose from non-carbohydrate sources):

- As hepatic Glycogen stores become depleted during fasting (or starvation) the only other significant source of Glucose is Gluconeogenesis.
- Sites of Gluconeogenesis and sources of precursors depend upon the duration of Caloric deprivation.
- Although the Kidney assumes importance as a source of new glucose during protracted starvation, during brief fasting at least 90% of total Gluconeogenesis occurs in the Liver.

What is the role of skeletal muscle in regulating blood glucose level during fasting?

- Glycogen content in Skeletal muscle (about 1% wet weight) is lower that in the liver, however because the total mass of skeletal muscle is much higher than that of liver, the total Glycogen content in skeletal muscle is much higher than the total Glycogen content in the Liver.
- Glycogen in skeletal muscle is not readily available to maintain blood glucose concentration.
- Muscle tissue does not contain **Glucose-6-Phosphatase**, and thus cannot convert Glucose-6-Phosphose to Glucose.
- 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 the blood picked up by the Liver and converted to glucose (Cori Cycle).

What primary signals attune the body to the status of Gluconeogenesis?

- The primary signals that attune the body to the status of Gluconeogenesis are as follows:

Glucagon – as an Acute Modulator:

- Actions of Glucagon are directed towards increasing blood glucose from low to normal: Thus
    - In the Hepatocytes:
        - Glucagon stimulates Glycogen breakdown to glucose to maintain blood glucose level.
        - Glucagon stimulates the formation of Glucose from Gluconeogenic intermediates, and
    - In the Adipocytes:
        - Glucagon stimulates Triacylglycerol and Fatty acid breakdown and their Oxidation.

Absence of Insulin:

Actions of Insulin are directly opposite to those of Glucagon.

(See Fig 2: STOP – GO ACTION OF INSULIN)

- Insulin stimulates:
    - Glycogen synthesis,
    - Glycolysis, and
    - Biosynthesis of fatty acids.

Glucocorticoids (e.g. Cortisol) – as Chronic Modulators:

Glucocorticoid actions are more complex than either Insulin or Glucagon.

- In simple terms:
    - 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 the amino acids serving as precursors for Gluconeogenesis.

<u>TAKE NOTE</u>:

- Primary tissues involved in Glucose conservation are: **Liver, Skeletal Muscle and Adipose Tissue**.
- Glucagon actions are essentially restricted to the Liver and Adipose tissue. **WHY??**
- Glucagon stimulates Glycogen breakdown and also stimulates Gluconeogenesis in the Hepatocytes.
- Glucocorticoids activate hepatic Gluconeogenesis synergistically with Glucagon.
- A major site of Glucocorticoids actions is on Skeletal Muscle;
- Presence of Glucocorticoids and the Absence of Insulin are the Primary signals for enhanced Protein degradation.
- Effects of Glucocorticoids are long term,
- Effects of Glucagon are moments to moment.

<u>Five Phases of Glucose Homeostasis</u>:

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

SUMMARY:
Understanding Glucose Homeostasis:
The 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 or high blood glucose concentrations, respectively.
- The circumstances that give rise to Hypoglycemia or Hyperglycemia can generally be divided in three categories, namely:
    - Factors related to effective Insulin concentration,
    - Insulin Counter-Regulatory Hormones
    - Sources of Fuel for the tissues.

Insulin Counter-Regulatory Hormones:

- Insulin Counter-Regulatory Hormones, (Glucagon, Catecholamines, Glucocorticoids and Growth hormones) antagonizes the actions of Insulin.
- Each is elevated in plasma in response to Hypoglycemia.