STUDY MATERIALS

On

GLUCOSE HOMEOSTASIS

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Glucose Homeostasis

Homeostasis is the maintenance of the stable internal environment within the organism. Glucose is a simple sugar with the molecular formula $C_6H_{12}O_6$. Glucose is the most abundant monosaccharide, a subcategory of carbohydrates. Carbohydrates are most commonly consumed as polysaccharides (e.g. starch, fibre or cellulose) or disaccharides (e.g. lactose, sucrose, galactose) and therefore need to be broken down into their simpler monosaccharide forms which the body can utilise. The digestion process of polysaccharides such as starch will begin in the mouth where it is hydrolysed by salivary amylase. In human body glucose homeostasis implies the careful regulation of glucose levels in the blood. Normally in a healthy man plasma glucose concentration is maintained at 110mg/dl, in the fasting state which is called as normal blood sugar level. However this level of blood sugar may alter during long term fasting as well as after taking meal. The low blood concentrations of glucose can causes seizures, loss of consciousness, and death. On the other hand, long lasting elevation of blood glucose concentrations, can result in blindness, renal failure, vascular disease, and neuropathy. Therefore, blood glucose concentrations need to be maintained within narrow limits. The process of maintaining blood glucose at a steady-state level is called glucose homeostasis. This is accomplished by the finely hormone regulation of peripheral glucose uptake, hepatic glucose production and glucose uptake during carbohydrate ingestion. This maintenance is achieved through a balance of several factors, including the rate of consumption and intestinal absorption of dietary carbohydrate, the rate of utilization of glucose by peripheral tissues and the loss of glucose through the kidney tubule, and the rate of removal or release of glucose by the liver and kidney.

Major tissues that are involved in the Glucose homeostasis mechanism are basically –

1) Liver
2) Muscle
3) Brain
4) Adipose tissue

Phase of Glucose Homeostasis-

The homeostasis mechanism can be discussed under four phases-

Phase 1- Normal intake of food.

Phase 2- Post –absorptive stage of food.

Phase 3- Early fasting

Phase 4- Prolonged fasting.

The maintenance of homeostasis state during all these stages can be shown as follows-

	Phase 1	**Phase 2**	**Phase 3**	**Phase 4**
Nutritional status	Well feel	Postprandial	Early gluconeogenic	Prolonged Gluconeogenic
Origin of blood glucose	Exogenous	Hepatic glycogen gluconeogenesis	Hepatic and renal gluconeogenesis	Hepatic and renal gluconeogenesis
Tissue using glucose	All	All tissue except liver, muscle, and adipose tissue in diminished state	Brain, RBC and small amount of muscles	Brain at a diminished rate
Major fuel of the brain	All	Glucose	Glucose and ketone bodies	Glucose and ketone bodies

Mechanism of Glucose Homeostasis-

To avoid postprandial hypoglycemia and fasting hypoglycemia, the body can adjust glucose levels by secreting two hormones, insulin and glucagon that work in opposition to each other. During periods of hyperglycemia, the β-cells of the pancreatic islets of Langerhans secrete more insulin. Insulin is synthesized in β-cells of pancreas in response to an elevation in blood glucose and amino acid after a meal. The major function of insulin is to counter the concerned action of a number of hyperglycemia-generating hormones to maintain low blood glucose levels. It also plays an important role in the regulation of glucose metabolism. This hormone regulates glucose metabolism at many sites reducing hepatic glucose output, via decreased gluconeogenesis and glycogenolysis, facilitates the transport of glucose into striated muscle and adipose tissue, and inhibits glucagon secretion. Insulin is not secreted if the blood concentration is ≤ 3 mmol/L, but is secreted in increasing amounts as glucose concentrations increase beyond this threshold [Gerich, 1993]. When blood glucose levels increase over about 5 mmol/L the β-cells increase their output of insulin. The glucagon producing α-cells of the pancreatic islets of Langerhans remain quiet, and hold on their hormone. It is to note, that postprandially, the secretion of insulin occurs in two phases. An initial rapid release of preformed insulin, followed by increased insulin synthesis and release in response to blood glucose. Long-term release of insulin occurs if glucose concentrations remain high [Aronoff et al., 2004; Cryer, 1992]. On the other hand, during periods of hypoglycemia, the α-cells of the pancreatic islets of Langerhans secrete more glucagon. It is the principal hormone responsible for maintaining plasma glucose at appropriate levels during periods of increased functional demand [Cryer, 2002]. This hormone counteracts hypoglycemia and opposes insulin actions by stimulating hepatic glucose production. It induces a catabolic effect, mainly by activating liver glycogenolysis and gluconeogenesis, which results in the release of glucose to the bloodstream, thereby increasing blood glucose levels. The digestion and absorption of nutrients are associated also with increased secretion of multiple gut hormones that act on distal targets. There are more than 50 gut hormones and peptides synthesized and released from the gastrointestinal tract. These hormones are synthesized by specialized enteroendocrine cells located in the epithelium of the stomach, small bowel, and large bowel. It was demonstrated that ingest food caused a more potent release of insulin than glucose infused intravenously [Perley & Kipnis, 1967]. This effect, termed the "incretin effect" suggests that signals from the gut are important in the hormonal regulation of glucose disappearance. Incretin hormones are peptide hormones secreted from the gut and specific criteria have to be fulfilled for an agent to be called an incretin. They have a number of important biological effects, as for example, release of insulin, inhibition of glucagon, maintenance of β-cells mass, and inhibition of feeding. Several incretin hormones have been characterized, but currently, GLP-1 (Glucagon-Like Peptide-1) and GIP (Glucose-Dependent Insulinotropic Polypeptide) are the only known incretins. Both GLP-1 and GIP are secreted in a nutrient-dependent manner and stimulate glucose-dependent insulin secretion. Gut hormones are secreted at low basal levels in the fasting state. The secretion of gut hormones is regulated, at least in part, by nutrients. Plasma levels of most gut hormones rise quickly within minutes of nutrient uptake and fall rapidly thereafter mainly because they are cleared by the kidney and are enzymatically inactivated [Drucker, 2007].

Role of Hormones in Glucose Homeostasis

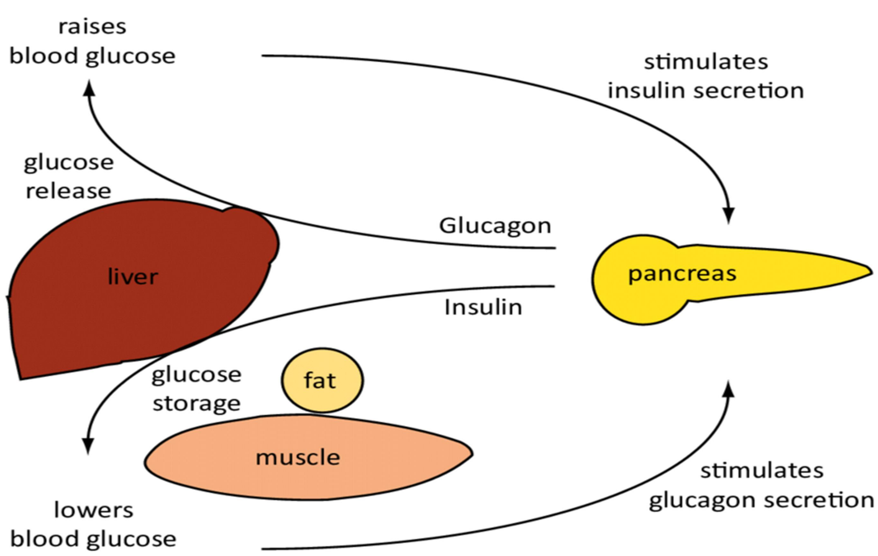
1) Role of Insulin-

This hormone helps in decreasing the blood glucose level by the following ways-

- Enhances Glycogenesis by the liver.
- Prevents glycogenolysis in liver.
- Decreases gluconeogenesis in liver, muscles and adipose tissues.
- Activates glucose transport-4 (GLUT-4) of the cells to enhance the entry of glucose into the cells.

2) Role of glucagon-

- Increases glycogenolysis in liver and muscle.
- Increases gluconeogenesis in liver, muscle and adipose tissue.
- Decreases rate of glycolysis.
- Decreases rate of glycogenesis in liver and muscles.



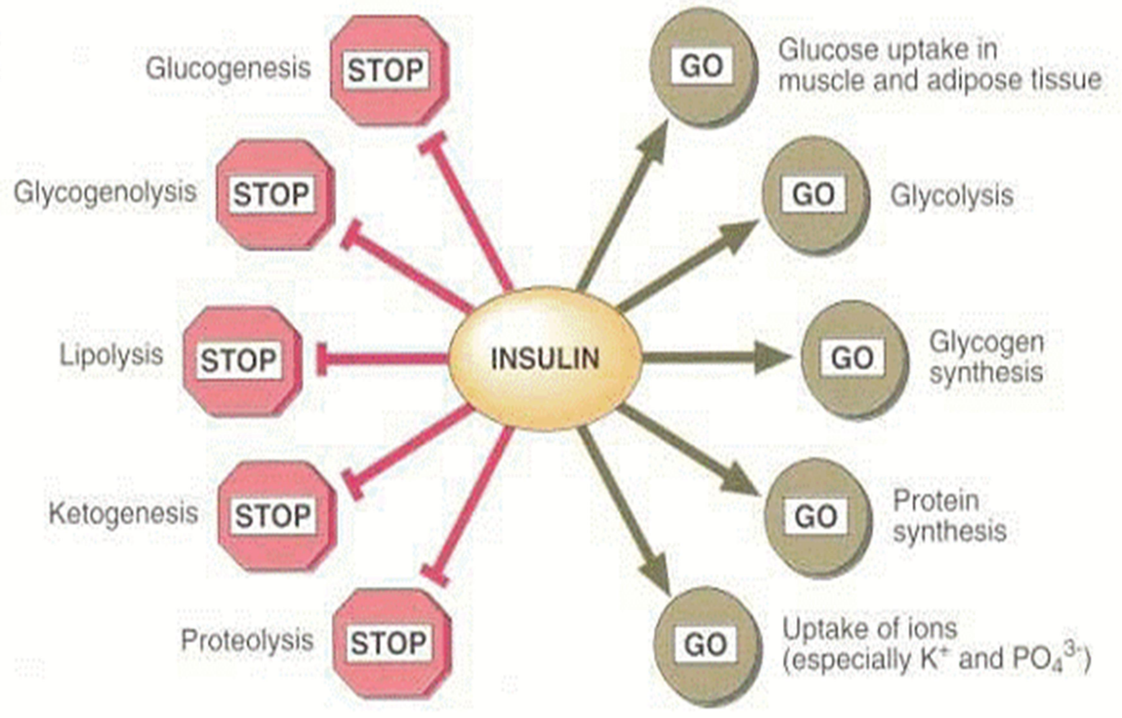


Fig. 2 **The actions of insulin.**

3) Role of other hormones-

Apart from the Insulin and glucagon there are also other hormones which have a certain role in glucose homeostasis in the human body to maintain a hypoglycemic or hyperglycemic free condition.

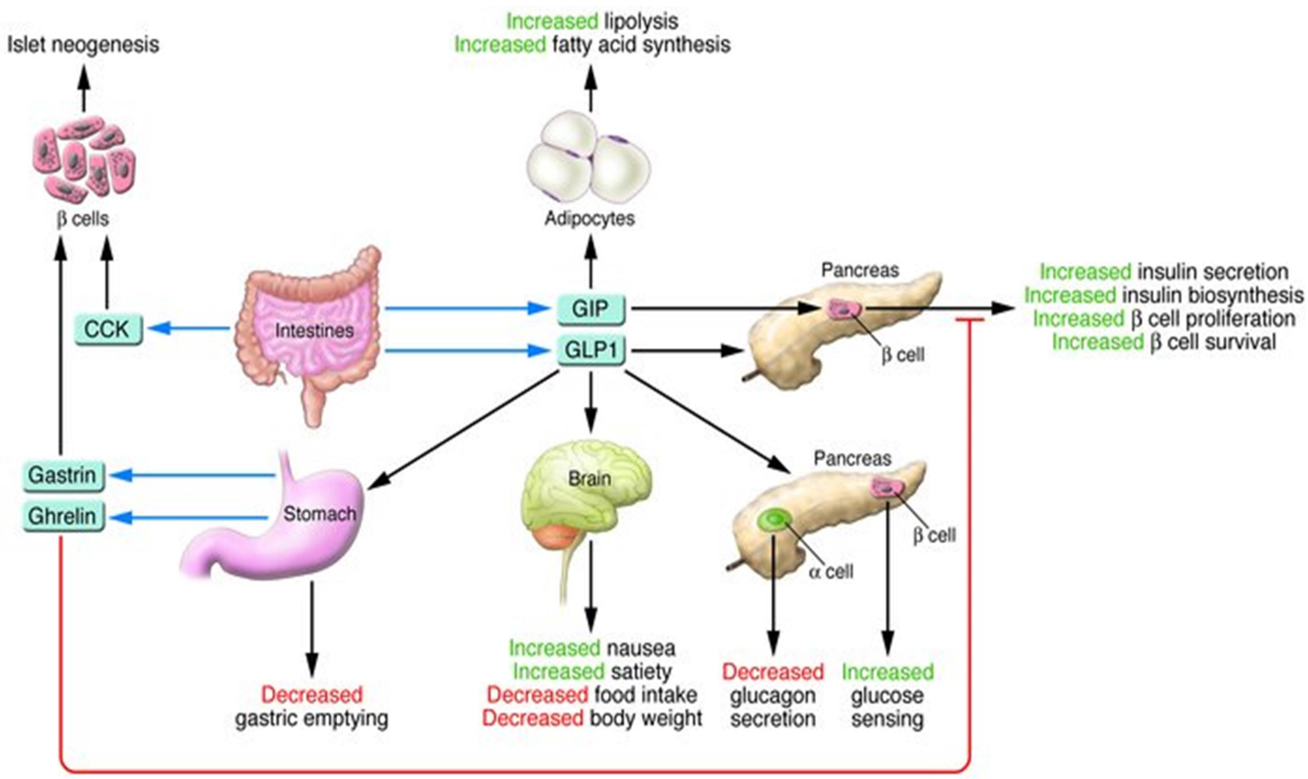


Table:- Showing role of metabolic hormones in regulating blood sugar level (Glucose homeostasis).

	Insulin	**Glucagon**	**Catecholamines**	**Glucocorticoids**	**Growth Hormone**	**TSH**
Glucose absorption	**No effect**	**No effect**	**No effect**	**No effect**	**No effect**	↑
Peripheral glucose uptake	↑	↓	↓	↓	↓	↓
Glycolysis	↑	↓	↓	↓	↓	↓
Glycogenesis	↑	↓	↓	↑	↓	↓
Glycogenolysis	↓	↑	↑	↓	↓	↑
Gluconeogenesis	↓	↑	↑	↑	↑	↑
Lipolysis	↓	↑	↑	↑	↑	↑
Protein catabolism	↓	↑	↓	↑	↓	↓
Net effect	**Hypo-glycemic**	**Hyper-glycemic**	**Hyper-glycemic**	**Hyper-glycemic**	**Hypo-glycemic**	**Hyper-glycemic**

All these hormones exhibit their action in coordinate manner to maintain glucose homeostasis. Secretion of these hormones are under the feedback loop mechanism where neural system is involved. Therefore , neural, hormonal and dietary role are noteworthy for to maintain glucose homeostasis.

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