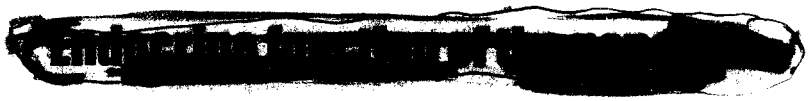

The islets of langerhan's contain 4 types of cells:

1- **Alpha (A) cells:** (25% of cells) produce a hyperglycemic hormone Glucagon.
2- **Beta (B) cells:** (60%) produce a hypoglycemic hormone Insulin.
3- **Delta (D) cells:** (10%) produce somatostatin → Pan inhibitory hormone
4- **F cells (PP cells):** (5%) secrete pancreatic polypeptide hormone.

Insulin

Formation: Insulin is formed in the ribosomes as proinsulin from which the C peptide is removed in the Golgi apparatus to produce insulin. Both insulin and the C peptide are stored in cytoplasmic granules to be secreted by exocytosis. Insulin, proinsulin and C peptide are all present in plasma and can be determined by radioimmuno-assay.

Transport and metabolism:

- Insulin circulates in the blood in almost entirely free form.
- Insulin is metabolized by:
  a. Insulin – glutathione trans-hydrogenase in the liver.
  b. Proteolytic enzyme (insulinase) in the tissues and liver.

Action of Insulin:

I- Metabolic effect:-

1. **On CHO:** (Hypoglycemic)
   a. Increased entry and oxidation of glucose (increased glucose utilization) in most tissues (skin, skeletal muscle, heart and adipose tissues) but does not affect glucose transport in some tissues (brain, liver, renal tubules, RBCs and intestine).
   b. Increased glycogenesis in the muscles (mainly) and liver.
   c. Decrease glucose production by the liver by inhibiting glycogenolysis and gluconeogenesis.
2. **On Ptn:** (Anabolic)
   Insulin increases protein synthesis by:
   a. Increased amino acid transport into cells.
   b. Increased mRNA and protein synthesis in the ribosomes.
   c. Inhibition of protein breakdown, glucose is used as a fuel instead of amino acids (Protein sparing effect of insulin).
3. **On Fat:** (Lipogenic)
   It increases lipogenesis and inhibits lipolysis.

4. **On potassium:-** Insulin helps K^+ entry into the cell by increasing the activity of Na^+ - K^+ Atpase in the cell membrane.

II- **Growth promoting effect:-** Act synergistically with growth H to promote growth. Thus ↓ insulin → retarded growth.

Regulation of insulin secretion:

- Insulin secretion is increased by:
  1. Hyperglycemia: Glucose is the most powerful stimulus for insulin secretion followed by maltose, fructose.
  2. Amino acids:- Especially arginine and lysine.
  3. G.I.T hormones: Gastrin, secretin, CCK and G.I.P. stimulate insulin secretion. Thus, oral glucose is more effective than I.V. glucose in stimulating insulin secretion.
  4. glucagon, growth hormone and Cortisol:- stimulate insulin secretion directly and by their hyperglycemic effect.
  5. Parasympathetic stimulation:
  6. Decreased plasma Na^+.
  7. Sulphonyl urea e.g., tolbutamide.
- Insulin secretion is inhibited by:
  1. Fasting.
  2. Somatostatin.
  3. Sympathetic stimulation and catecholamine (Via alpha receptors)
  4. Decreased plasma K^+.

Disorders of insulin secretion:-

I- **Diabetes Mellitus:** (decreased insulin secretion):-

- It is due to absolute or relative lack of insulin.
- **It is characterized by:**

A- Hyperglycemia:- Which result from decreased glucose utilization and leads to:

1. polyuria (↑urine volume):- results from glucosuria→ osmotic diuresis.
2. Polydypsia (↑ water intake):- increased H_2O loss stimulates thirst sensation.
3. Dehydration (↓ ECF) → decreased VR, COP and ABP decreased renal and cerebral blood flow and tissue hypoxia.

B- Increased protien catabolism which leads to:-

1. Amino acidemia (↑ amino acids in blood).
2. Increased gluconeogenesis (from amino acids resulting from protein breakdown).
3. Increased urinary excretion of nitrogen.
4. weight loss.

5. Growth retardation in diabetic children.

C- Increased lipolysis:- which leads to:-

1. lipaemia and increased FFA in blood.
2. Increased ketogenesis, ketonemia and ketonuria.
3. Metabolic acidosis from ketonemia (from breakdown of FFA), lactacidemia (from tissue hypoxia).
4. Rapid development of atherosclerosis and fatty liver.
5. Ketonemia leads to coma and death.

- **Types:-**

1) Insulin dependant diabetes mellitus (IDD) (type I diabetes):-
   - Occurs in children.
   - Results from destruction of Beta cells (e.g. by virus or autoimmune diseases), thus insulin secretion is nearly absent.
2) Non insulin dependant diabetes (NIDD) (type II diabetes):-
   - Occurs after age of 40 y.
   - Results from:-
     a. ↓ sensitivity of beta cells →↓insulin secretion.
     b. ↓insulin receptors →ineffective insulin.

II- Hyperinsulinism (↑ insulin secretion):-

- Cause:- Adenoma of B cells of islets of langrhan's.
- Characterized by:-
  1. Hypoglycemia. 2. Exessive sweating. 3. irritability.
  4. May lead to permenant brain damage.

Glucagon

- Secreted from alpha cells of islets of langrhan's.
- Acts through cAMP.
- **Actions.**

1. **On carbohydrate metabolism:-** Hyperglycemic.
   leads to hyperglycemia through stimulation of:-
   a. Glygogenolysis. b. Gluconeogenesis.
2. **On lipid metabolism:-** Lipolytic
   leads to lipolysis which results in:-
   a. ↑ plasma FFA. b. ↑Ketone body formation.
3. **Other effect:-**
   a. ↑ myocardial contractility.
   b. ↑ bile secretion.
   c. ↑ Secretion of growth H., insulin and pancreatic somatostatin.
   d. ↓ gastric acid secretion.

- **Regulation of glucagon secretion:-**
  - **Glucagon secretion is increased by:-**
    1) Hypoglycemia.
    2) ↑ plasma amino acids (e.g. after protein meal)
    3) GIT hormones:- Gastrin and CCK
    4) Muscular exercise.
    5) Sympathetic stimulation.
  - **Glucagon secretion is decreased by:-**
    1) Hyperglycemia 2) ↓ amino acids. 3) GIT hormone:- Secretin.

Somatostatin hormones

- Secreted by delta cells of islets of Langerhan's.
- It is polypeptide that has the same chemical structure as GHIH (somatostatin secreted by hypothalamus).
- **Action:-** Multiple inhibitory effects.
  1- Inhibits secretion of both glucagons and insulin.
  2- Decreases motility of stomach, duodenum and gall bladder.
  3- Decreases secretion and absorption in GIT.
- **Control of secretion of somatostatin:-** Its secretion is increased by:-
  1. ↑ blood glucose.
  2. ↑ amino acids.
  3. ↑ FFA.
  4. ↑ secretion of GIT hormones.

Blood glucose regulation
(Blood glucose homeostasis)

Normal blood level:-

- Normal fasting (post absorptive) blood glucose level is about 80-120 mg %.
- It normally fluctuates between 70 – 150 mg%. Reaches 150 mg % during the first hour after meal, then returns to fasting level within 2 hours after meal.
- It is kept within this relatively narrow range by balance between the rate of addition and rate of withdrawal of glucose from blood.

Mechanisms of glucose addition to blood:-

1) **Small intestine:-**
   - Glucose is absorbed in duodenum and jejunum.
   - Rate of glucose absorption reaches peak within 1-2 hours and is complete in 3-4 hours after meal.
   - The absorption capacity of small intestine is 120 gm / hours.
2) **Liver:-**

- In between meals, liver adds glucose to blood by two mechanisms, glycogenolysis and gluconeogenesis.
- After carbohydrate rich meal, liver contains about 100 gm of glycogen which is totally exhausted 24-48 hours of fasting.

3) **Kidney:-**
   - Adds glucose to blood by gluconeogenesis.
   - It is only of value in prolonged starvation.

Mechanisms of glucose withdrawal from blood:-

1) **liver:-** 10% of ingested glucose is taken by the liver for glycogenesis.
2) **Muscles:-** about 40% of ingested glucose is taken by the muscles for:-
   - Energy production.
   - Storage as glycogen (glycogenesis).
3) **Adipose tissue:-** About 40% of ingested glucose is taken by adipose tissue for lipogenesis.
4) **Other tissues:-** consumes about 10% of ingested glucose for energy production.

Mechanism of regulation:-

1) **Hormonal regulation:-**

I- Hypoglycemic hormone: Insulin, it:
   a. Stimulates glucose utilization by tissues and glycogenesis by liver.
   b. Inhibits glycogenolysis and gluconeogenesis in liver.

II- Hyperglycemic hormones:-

1- Glucagon:- Stimulates glycogenolysis and gluconeogenesis.

2- Growth hormones:-
   a. Inhibits glucose utilization by tissues (anti- insulin effect).
   b. Stimulates gluconeogenesis.

3- Cortisol:-
   a. Inhibits glucose utilization by tissues (anti insulin effect).
   b. Stimulates gluconeogenesis.

4- Thyroxine:-
   a. Stimulates glucose absorption from GIT.
   b. Stimulates glycogenolysis and gluconeogenesis.

5- Adrenaline:-
   a. Stimulates glycogenolysis.
   b. Inhibits insulin secretion

2) **Neural regulation:-** In addition to their effect on insulin and glucagon, autonomic nerves directly affect glucose in liver:-
   a) Sympathetic stimulation → glycogenolysis.
   b) Parasympathetic stimulation → glycogenesis.
3) **Autoregulation by blood glucose level:-** ↑ blood glucose directly stimulate glycogenesis and inhibit glycogenolysis independent on insulin.