# Lecture NO.-7

## PANCREAS

- The pancreas has both endocrine and exocrine functions.
- In 1869, Langerhans described the islet cells of the pancreas. In 1921, Banting and Best isolated pancreatic extract containing insulin from the islet cells. Sanger and his associates in 1955 elucidated the chemical structure of insulin.
- The endocrine portion of the pancreas consists of **clusters of cells called *islets of Langerhans***. Four kinds of cells are found in these clusters.

**Endocrine Cells and Hormones of Pancreas**

- α(A) Cells (20%) -> Glucagon.
- β(B) Cells (70%) -> Insulin.
- δ (D) Cells (<5%) -> Somatostatin
- F Cells (<5%) ->pancreatic polypeptide (PP)

- Insulin and glucagon are often secreted and act reciprocally. Glucagon and insulin are concerned with regulation of blood sugar level.

## INSULIN

1. **Insulin, a protein hormone with 51 amino acids contains two polypeptide chains (A & B) with 21 and 30 amino acids respectively connected by two disulphide bridges with a third disulphide bridge in the A-chain.**
2. Insulin is synthesised as preproinsulin, processed in the endoplasmic reticulum and released.
3. During processing of proinsulin, along with insulin another polypeptide called *C peptide* is produced which also enters the plasma along with insulin.

4. Levels of C peptide in plasma indicate beta cell function in insulin deficient patients.
5. **Insulin has a half-life of 5 minutes**.
6. Structurally insulin of dogs, cats and pigs is identical.
7. Insulin from cattle, sheep, horse, pig and dog differs only in positions 8th, 9th and 10th in A chain, hence the biological actions of insulin are not highly species specific.
8. Insulin from one species is mildly antigenic when injected into another.

## BIOLOGICAL EFFECTS OF INSULIN

- **Liver, skeletal muscle and adipose tissue are the principal target organs of insulin** where it enhances the entrance of glucose, amino acids, fatty acids, $K^+$ and $Na^+$ ions.
- It stimulates glycogenesis, lipogenesis, glycolysis and protein synthesis, whereas it inhibits gluconeogeneis, lipolysis and ketogenesis.
- It lowers blood glucose, fatty acids and aminoacids levels and promotes intra cellular conversion of these compounds to glycogen, triglycerides and protein respectively

**On Carbohydrate Metabolism**

1. *Glucose does not readily penetrate* the cell membranes except in neurons, liver, intestinal epithelium, RBCand WBC, renal tubular epithelium and retina.
2. Presence of insulin causes more amount of glucose entry (2 to 5 fold more) through the plasma membrane into the muscle and adipose cells.
3. Glucose can be transported down their concentration gradient across the cell membrane by transport proteins called ***glucose transport proteins*** **(GLUTs)** which are present in the cell membrane of all cells. Detection of plasma glucose

by pancreatic islet cells as well as uptake/ release of glucose from cells involve GLUT. GLUT is present in many isoforms

4. When insulin concentration rises in the plasma, number of GLUT-4 molecules increases in the cell membrane and glucose transport into the cell is increased
5. In liver, insulin activates the enzyme *glucokinase* to initiate phosphorylation of glucose, thus the *glucose is trapped* inside the liver cells.
6. Insulin promotes the activities of *glycogen synthase* to *favour glycogenesis*, while it *inhibits phosphorylase* and prevents the split of glycogen into glucose.
7. Liver can store glycogen up to 10 to 15% of its mass.
8. The normal resting muscle membrane is almost impermeable to glucose.
9. In the presence of insulin, glucose permeability is increased and muscle glycogen synthase activity is enhanced.
10. However during heavy exercise the muscle membrane becomes highly permeable to glucose even in the absence of insulin. Much of the glucose in the muscle is stored in the form of muscle glycogen instead of being used for energy. Approximately 75% of the glucose is converted into glycogen and only 20 to 30% undergo glycolysis.
11. In many cells, insulin facilitates glycolysis by activating glycolytic enzymes.
12. Insulin inhibits proteolysis in the peripheral tissues, thereby reducing amino acid availability for *gluconeogenesis*.

**On Fat Metabolism**

- Insulin by increasing rate of utilization of glucose in many body tissues functions as *fat sparer*.
- In the liver when the liver glycogen level goes above 15%, insulin promotes the conversion of glucose to fatty acid and their transport to the adipose cells for triglyceride synthesis and storage.

- Insulin increases acetyl-CoA formation from pyruvate, the substrate for fattyacids synthesis. Glycolytic break down of glucose by insulin supplies large quantities of a -glycerophosphate which is the source of glycerol. Binding of glycerol with fatty acids forms triglycerides; the triglycerides are transported to adipose tissue and stored as fat.
- Insulin also promotes glucose transport into adipose cells, where they are converted to a- glycerophosphate and to glycerol for triglyceride synthesis.
- Insulin inhibits the action of *hormone-sensitive lipase* and prevents hydrolysis of the triglycerides in adipose tissue and release of fatty acids into the circulating blood.
- Insulin diminishes beta oxidation of fat, thus inhibits ketone body production. In adipose tissue, insulin induces the synthesis of lipoprotein lipase, (promotes movement of fatty acids into adipose tissue) inhibits intracellular lipase and enhances fatty acid esterification. Cholesterol synthesis is also enhanced by insulin.

**Ketogenic and Acidotic Effects of INSULIN LACK**

- Lack of insulin promotes the activation of *hormone -sensitive lipase* and rapid breakdown of fatty acids from the liver and adipose cells and excessive production of acetyl - CoA.
- Portion of acetyl-CoA utilized for energy in the liver; excess is condensed to form acetoacetic acid, beta hydroxy butyric acid and acetone, which are the *ketone bodies* and their presence in large quantities in the body fluids is called as *ketosis*.

**On Protein Metabolism**

- Insulin acts along with growth hormone and cause active transport of amino acids into the cells and increases the rate of transcription of DNA in the cell

uncles, thus affects the ribosomes to increase the translation of messenger RNA forming new proteins.

- Insulin greatly enhances the rate of protein synthesis and prevents the degradation of proteins for gluconeogenesis and promotes positive nitrogen balance.
- Due to its effects on protein metabolism,insulin is required for growth of the animal; GH and insulin act synergistically to promote growth.

## REGULATION OF INSULIN SECRETION

- The most important factor in the control of insulin secretion is the *concentration of blood glucose*.
- Increased concentration of blood glucose initiates the synthesis and release of insulin by positive feedback mechanism.
- Gastrin, secretin, CCK, gastric inhibitory peptides, ACTH, cortisol, estrodiol, GH, glucagon, progesterone, thyroxine and acetylcholine, amino acids (arginine and lysine are the most potent) and fatty acids in plasma stimulate insulin secretion.
- In sheep the short chain fatty acid butyrate and propionate stimulates the release of insulin, whereas in dog the long chain fatty acids stimulate insulin release.
- Glucagon has direct stimulatory effect on beta cells and insulin secretion, whereas somatostatin and adrenergics inhibit the secretion of insulin.
- Calcium is the final triggering step in the release of insulin from the islet cells; hence hypocalcemic condition in cows and pigs depresses insulin secretion.

## DIABETES MELLITUS

- *Diabetes mellitus* is a metabolic disorder of carbohydrates, proteins and fats due to deficiency of insulin and with insulin resistance. It is observed in dogs, humans and cats.
- Diabetes mellitus can be classified into three types – *Type I, Insulin-dependent diabetes mellitus* – (IDDM); *Type II – noninsulin-dependent diabetes mellitus* – (NIDDM) and *impaired glucose tolerance* (IGT).
- Type I diabetes mellitus is characterized by loss of beta cells leading to insulin deficiency.
- Type II diabetes is characterized by insulin resistance which may occur along with reduced insulin secretion. Type 2 diabetes is the most common type.
- Diabetes mellitus is characterized by persistent hyperglycemia
- A fasting blood glucose level of 125mg/dl or more is suggestive of diabetes mellitus.
- Insulin deficiency affects entire metabolism of the organism: fat, protein, carbohydrate, electrolyte and water. It leads to the inability of peripheral tissues to use glucose for energy or for glycogen synthesis, whereas it *stimulates glycogenolysis* and gluconeogenesis which results in hyperglycemia.
- Glucose appears in urine (*glucosuria*) and causes osmodiuresis leading to water and electrolyte loss, polyuria, dehydration and hemoconcentration. Other signs include polyphagia, polydipsia, and hypercholestrolemia.
- Insulin deficiency activates hormone-sensitive lipase activity leading to increased fatty acid mobilization for oxidation and energy, increased acetyl-CoA formation which on conversion to ketone bodies causes ketonemia and ketonuria.

- Protein catabolism is enhanced in insulin deficiency and amino acids are used for gluconeogenesis. There is a negative nitrogen balance with weight loss. BUN is elevated in dogs.
- *Pituitary diabetes* is weakly sensitive to insulin whereas *adrenal diabetes* is moderately insulin sensitive and *pancreatic diabetes* is highly sensitive to insulin.
- When plasma glucose is elevated for a long time, small amounts of Hb are non-enzymatically glycosylated to form HbA1c. Controlling the diabetes with insulin reduces this level; HbA1c concentration is measured clinically as an index of diabetic control for the 4-6 week period before the measurement. Higher level will be observed in poorly controlled diabetes.

## GLUCAGON

- **Glucagon is the *hyperglycemic factor***
- **secreted by the alpha cells of the pancreas and**
- **L cells of GI tract.**
- **It has 29 amino acids in straight chain and synthesized as preproglucagon.**
- There is a considerable homology in the amino acid composition of glucagons of different species. Glucagon is also produced from other sites– from stomach *gut glucagons* (identical to pancreatic glucagons), and from small intestine *glycentin* (immunologically similar to pancreatic glucagons) are produced. This catabolic peptide hormone raise plasma sugar levels. Its secretion from the alpha cells of the pancreatic islets is directly stimulated by:
    - low plasma glucose concentrations: glucagon levels rise in the postabsorptive state some hours after a meal.

- high levels of circulating amino acids. This may be important in the maintenance of normal plasma glucose levels during absorption of a protein meal, since amino acids also stimulate insulin secretion and this might cause hypoglycaemia in the absence of any opposing action on carbohydrate metabolism.

**Regulation of Secretion**

- Low blood glucose level stimulates glucagon synthesis and release.
- Glucogenic amino acids–serine, glycine, alanine are powerful activators of glucagon output
- Both insulin and glucagon work *in-tantum* to regulate blood glucose.
- Both sympathetic and parasympathetic systems of ANS, hypoglycemia, gastrin, CCK, gastric inhibitory polypeptide, glucogenic amino acids, protein ingestion and exercise or stress stimulate glucagon release while increased levels of glucose and fatty acids and secretin are inhibitory to glucagon release.
- Somatostatin is more inhibitory to glucagon than to insulin.

## BIOLOGICAL EFFECTS OF GLUCAGON

- **Glucagon has glycogenolytic, gluconeogenic, lipolytic and ketogenic effects**
- Glucagon blocks the synthesis of glycogen by inhibiting the enzyme **glycogen synthase**. By activating phosphorelase, glucagon stimulates *glycogenolysis* and *gluconeogenesis*.
- It stimulates adenylcyclase activity in the liver cells and formation of cyclic AMP to activate protein kinase, a regulator protein.
- Protein kinase activates phosphorylase-b kinase that converts phosphorylase-b to phosphorylase-a and promotes the degradation of glycogen into

glucose-1-$PO_4$ which on dephosphorylation yields glucose in liver cells. It also promotes lipolysis.

- Gluconeogenesis is enhanced. It decreases the activities of glycolytic enzymes. The ratio between phosphofructokinase and fructose 1-6-diphosphatase determines the relative rate of glycolysis and gluconeogenesis.
- It also promotes lipolysis by stimulating hormone-sensitive lipase activity in the adipose tissue.
- Glucagon secretion begins with ingestion of food and increases with the interval from food ingestion and declining blood glucose level. This helps the animal to mobilize energy stores for maintaining glucose homeostasis i.e., prevent postprandial hypoglycemia.
- **In birds, glucagon has a predominant role than insulin on carbohydrate metabolism.**
- **Glucagon is a ketogenic hormone, activates the hormone-sensitive adipose tissue lipase in adipose tissues to cause lipolysis.**
- It inhibits $Na^+$ resorption from the renal tubules causing natriuresis

## SOMATOSTATIN

- It is available in two molecular forms **-14 and 28 amino acid peptides**.
- It acts as a **humoral regulatory agent and found in CNS, pancreas and cells lining the GI tract**.
- Released from hypothalamus it inhibits the secretions of GH and TSH,
- It may also acts as a neurotransmitter in retina and spinal cord.
- It inhibits variety of metabolic and digestive functions.
- Pancreatic somatostatin is the secretion from δ cells of the islets of Langerhans

- It inhibits α, β and F cells thereby the secretion of insulin, glucagon and pancreatic polypeptide are inhibited.
- Gastric somatostatin inhibits the secretion of gastrin, secretin, CCK and pancreatic exocrine secretions, HCl and pepsin secretions, GI motility and gall bladder activity, thereby the absorption of nutrients.
- Somatostatin secretion is stimulated by increased level of glucose, amino acids, catecholamines, acetylcholine and glucagon.

## PANCREATIC POLYPEPTIDE

- Pancreatic polypeptide is a peptide hormone, containing 36 amino acids and secreted by the stimulation of F (PP) cells in the islets of pancreas.
- It is related to two other 36 amino acid polypeptides – *polypeptide YY (*PYY) of intestine and *neuropeptide Y* (NPY)of brain and ANS.
- It increases gut motility and gastric emptying, stimulates the secretions of the intestinal hormones- gastrin, secretin and CCK.
- It inhibits pancreatic enzyme secretion and gall bladder contraction.
- Protein has stimulatory effect on its secretion, somatostatin inhibits its release.

## BLOOD GLUCOSE

- The normal blood glucose concentration varies from 62 to 120 mg/dl in dogs, cats,horses and pigs; in cows, sheep and goats it varies from 42 to 80 mg/dl;
- Adult ruminants have lower level than newborn ruminants.
- The normal blood level is termed *euglycaemia;*
- when the blood glucose level is increased it is *hyperglycemia* and a decreased level is *hypoglycaemia.*

**Control of blood glucose**

- There are two major sources of blood glucose
    - Dietarycarbohydrates – absorbed from intestine
    - Synthesisof glucose in liver – from glucogenic substances – glycogen, glucogenic aminoacids, glycerol and propionate in ruminants,

**Role of Liver**

- Liver is the major organ involved in regulating blood glucose. After a carbohydrate meal, the increase in blood glucose is prevented by liver by converting glucose to glycogen and fatty acids. **Liver can store glycogen up to 10 to 15% of its weight**.
- During decrease in blood glucose level, liver glycogen is broken down to glucose and released into circulation.

**Role of Hormones**

- The only hormone that produces **hypoglycaemia is insulin**
- All other hormones – **glucagon, growth hormone, cortisol and epinephrine have hyperglycaemic effect.**
- When insulin effect is removed by pancreatectomy, IGF-I sustains weak insulin activity (but not sufficient to maintain life).
- Glucagon and epinephrine promotes glycogenolysis while insulin has antagonistic effect of glycogenesis. Molar ratio of insulin: glucagon rather than the absolute concentration is the determining factor of glycogen breakdown or synthesis.
- Glucagon stimulates gluconeogenesis from amino acids.

**Glucose tolerance test**

- The capacity of the body's control mechanisms to regulate blood glucose level canbe evaluated by ***oral glucose tolerance test*.**
- About1 to 2 g of glucose / kg weight is given orally and blood samples are collected 30 min intervals for 120 or 240 min.

- In normal dogs, blood glucose level should reach close to **160 mg/dl in 30 to 60min** and the level should reach the baseline normal values by **120 to 180 min**.
- In horses, by 120 min, the glucose level should reach 175 mg/dl which should return to normal by 360 min.