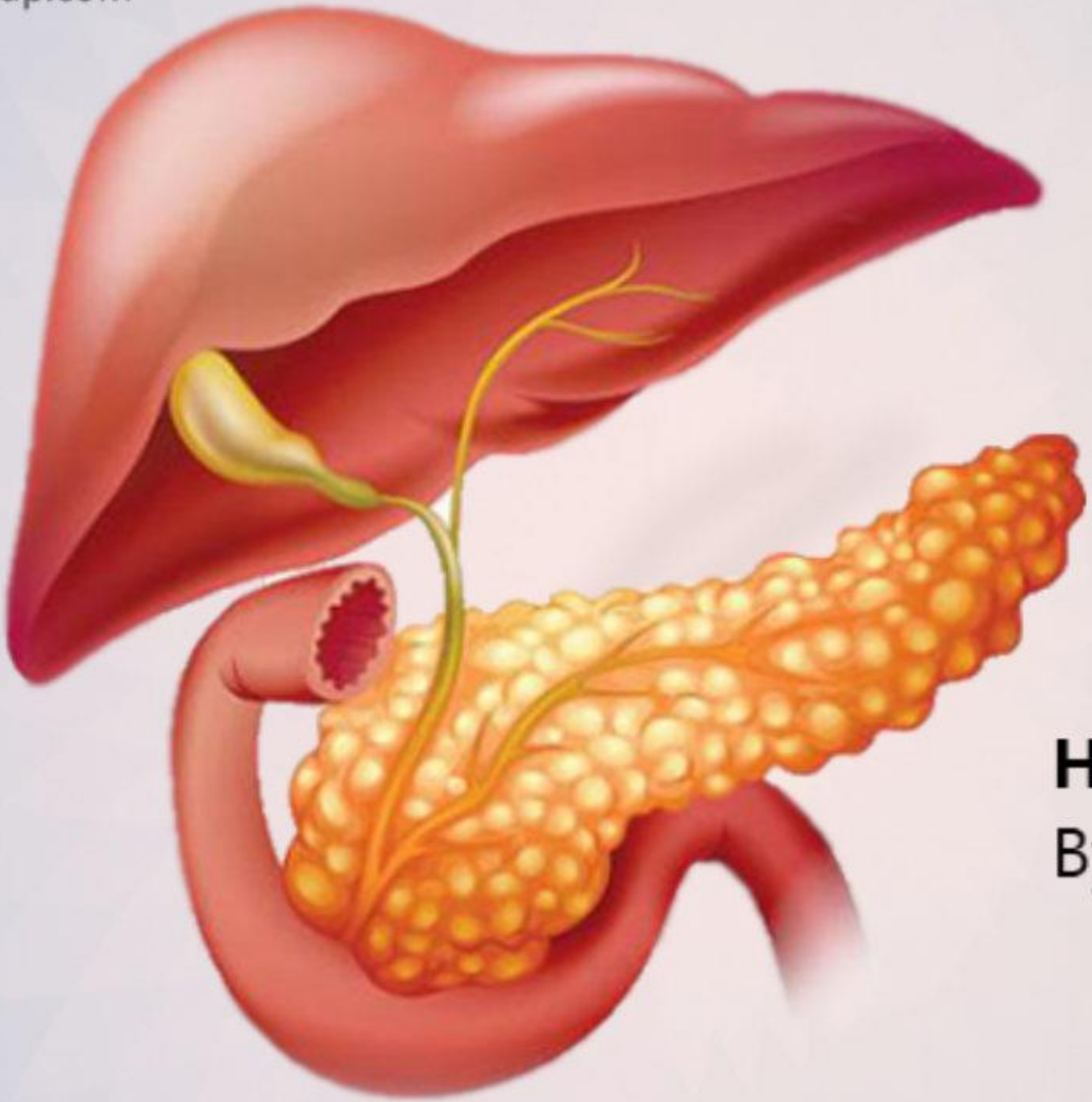
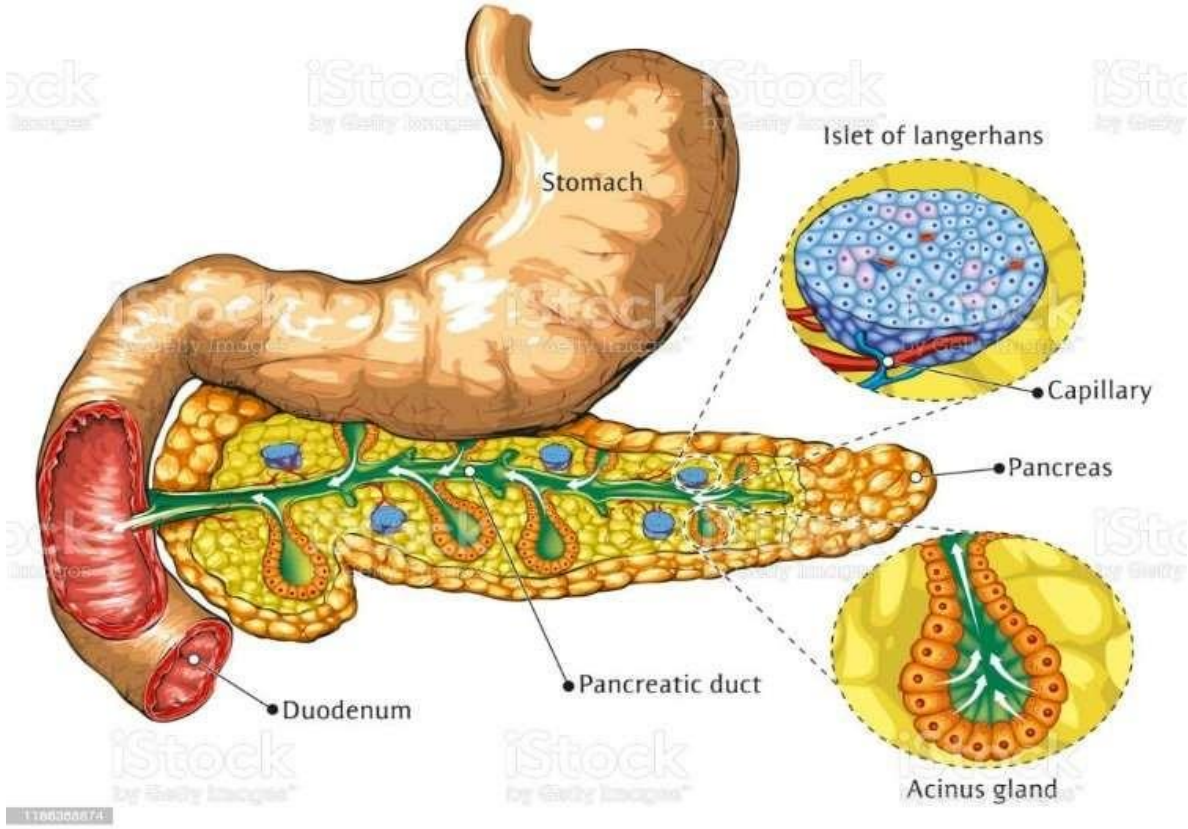


Hormones Secreted
By The Pancreas

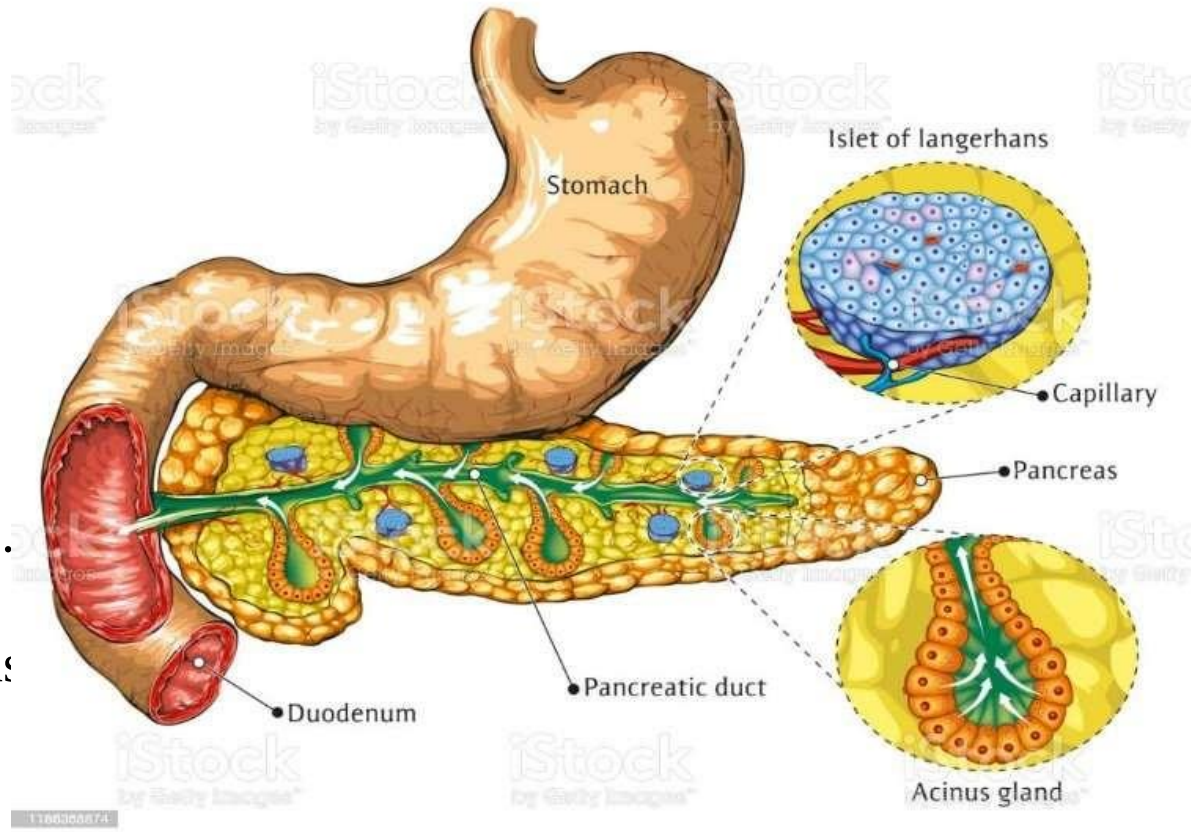
PANCREATIC HORMONE

- Pancreas are the leaf like structure present below stomach.
- 2% of pancreatic tissue are endocrine.
- 98% of pancreatic tissues are exocrine.

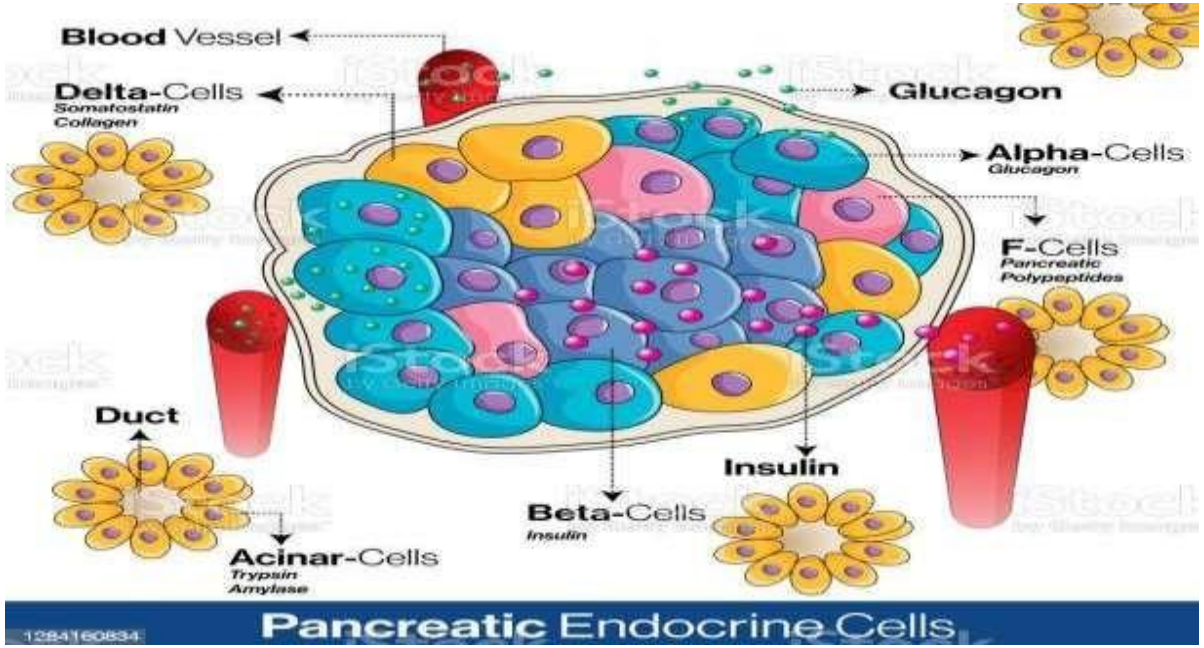


PANCREATIC HORMONE

- Made up of 4 types of cells
  1) Alpha (A) cells secretes glucagon
  2) Beta (B) cells secretes insulin
  3) Delta (D) cells secretes somatostatin
  4) Gamma (F) cells secretes pancreatic polypeptide.
- Group of pancreatic cells called as Islets of Langerhans



- Arrangement of cells

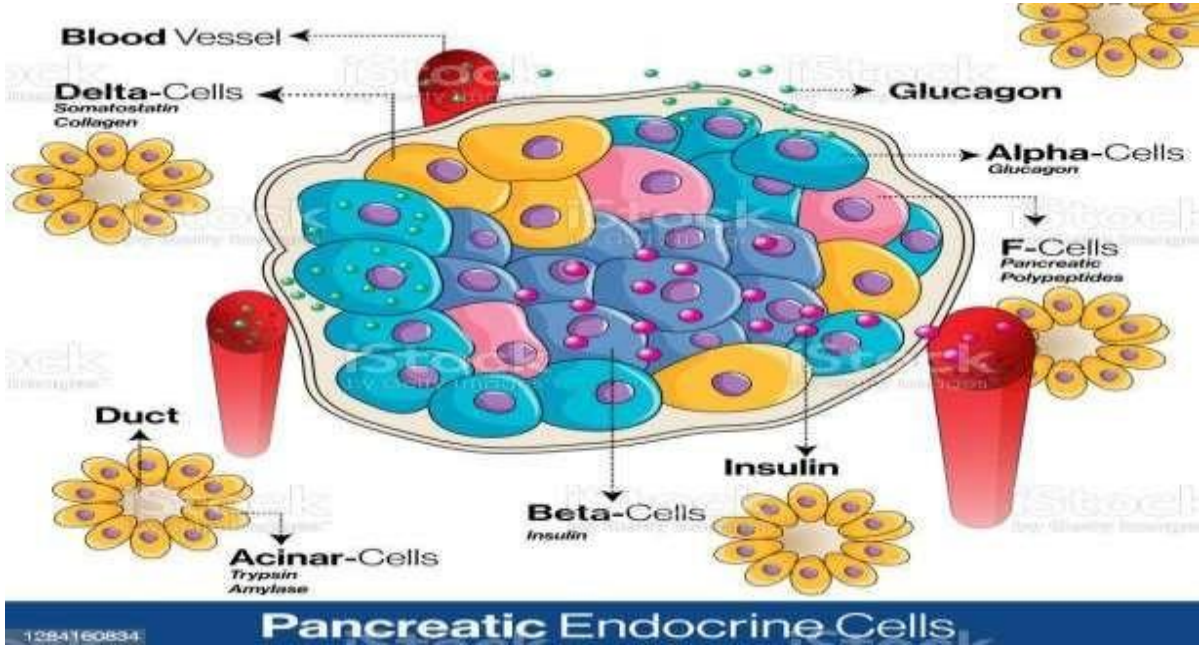


- ✓ Exocrine - Endocrine - Exocrine
- ✓ Beta cells are present at the interior of pancreas
- ✓ Alpha, delta and gamma cells placed at the

periphery and surrounds the centrally placed insulin producing cells.

- Approximately 60 % of cells are beta cells, 25 % A cells and 10% D cells.

- Specialized arrangement of plasma membrane located at the regions of cell – cell contact are



1. Tight junction –cells are arranged closely, no gap, interstitial fluid.

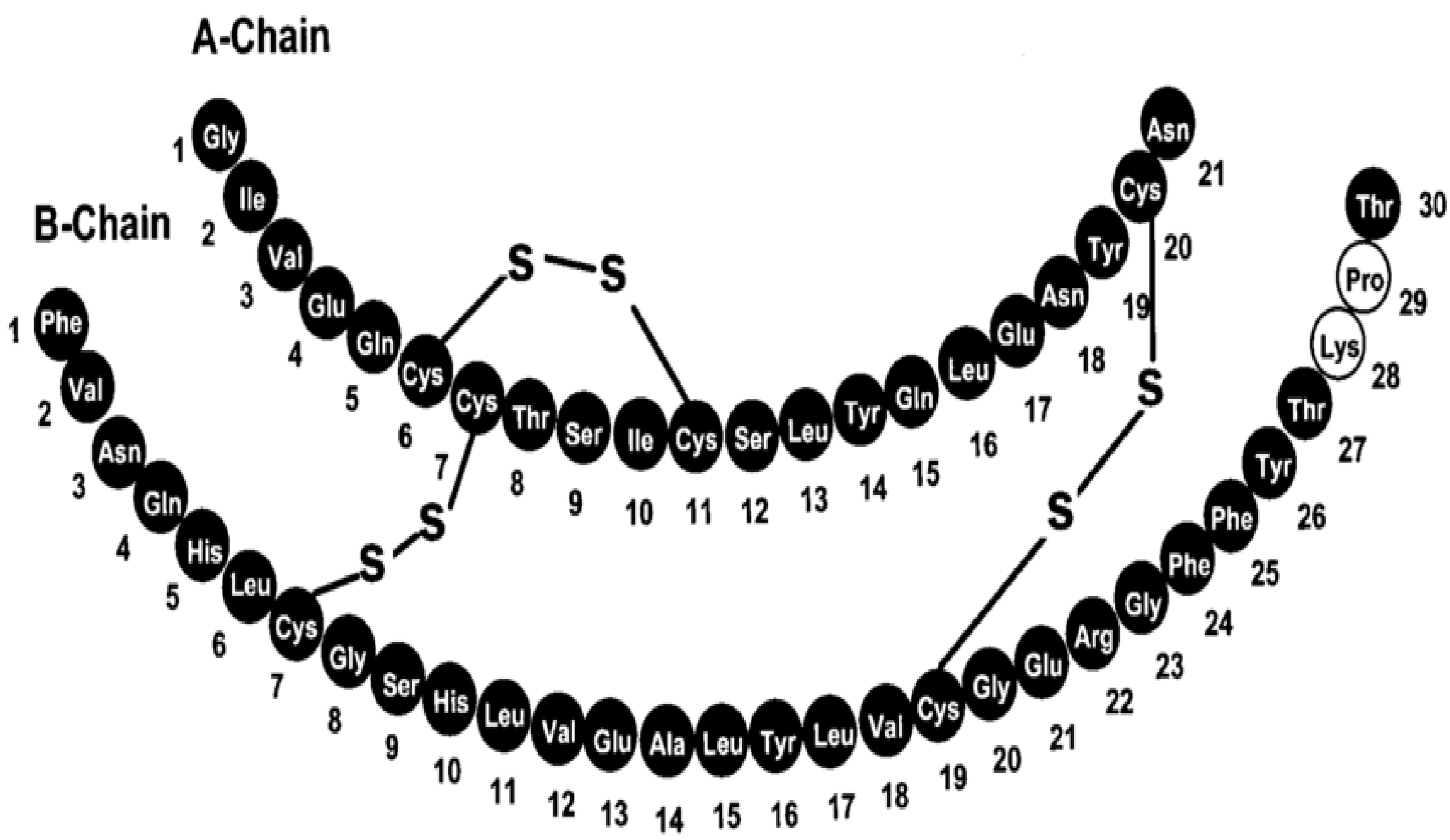
2. Gap junction – a gap, loosely arranged. Transport of ions takes place through the gap.

Structure of insulin

- Small globular protein with MW of 5700.
- Polypeptide hormone
- Human insulin contains 51 amino acids.
- Active insulin contains two polypeptide chains A and B chain linked by disulphide linkage.

Structure of insulin

- A chain contains 21amino acid
- B chain contains 30 amino acid
- A chain contains intra-disulphide linkage at A6-11.
- Two Inter-chain disulphide linkage at A7-B7 & A20-B19.
- COOH terminal end contains hydrophobic region which forms dimerization of insulin.


A-Chain
B-Chain
1 Gly
2 Ile
3 Val
4 Glu
5 Gln
6 Cys
7 Cys
8 Thr
9 Ser
10 Ile
11 Cys
12 Ser
13 Leu
14 Tyr
15 Gln
16 Leu
17 Glu
18 Asn
19 Tyr
20 Cys
21 Asn
1 Phe
2 Val
3 Asn
4 Gln
5 His
6 Leu
7 Cys
8 Gly
9 Ser
10 His
11 Leu
12 Val
13 Glu
14 Ala
15 Leu
16 Tyr
17 Leu
18 Val
19 Cys
20 Gly
21 Glu
22 Arg
23 Gly
24 Phe
25 Phe
26 Tyr
27 Thr
28 Lys
29 Pro
30 Thr
S
S
S
S
S

Insulin biosynthesis and secretion

Preprohormone

Preproinsulin (M.Wt 11.5kd)- 109 AA - RER

↓ 23 aa leader sequence removed

86 aa proinsulin (9kd)

↓

Golgi complex

↓

Proteolytic enzymes – Prohormone convertase I and II (PC1 & PC2) - hydrolysis C terminal end amino acid

Insulin (A & B chain) + C-peptide – Golgi complex

↓

Secretory vesicle released

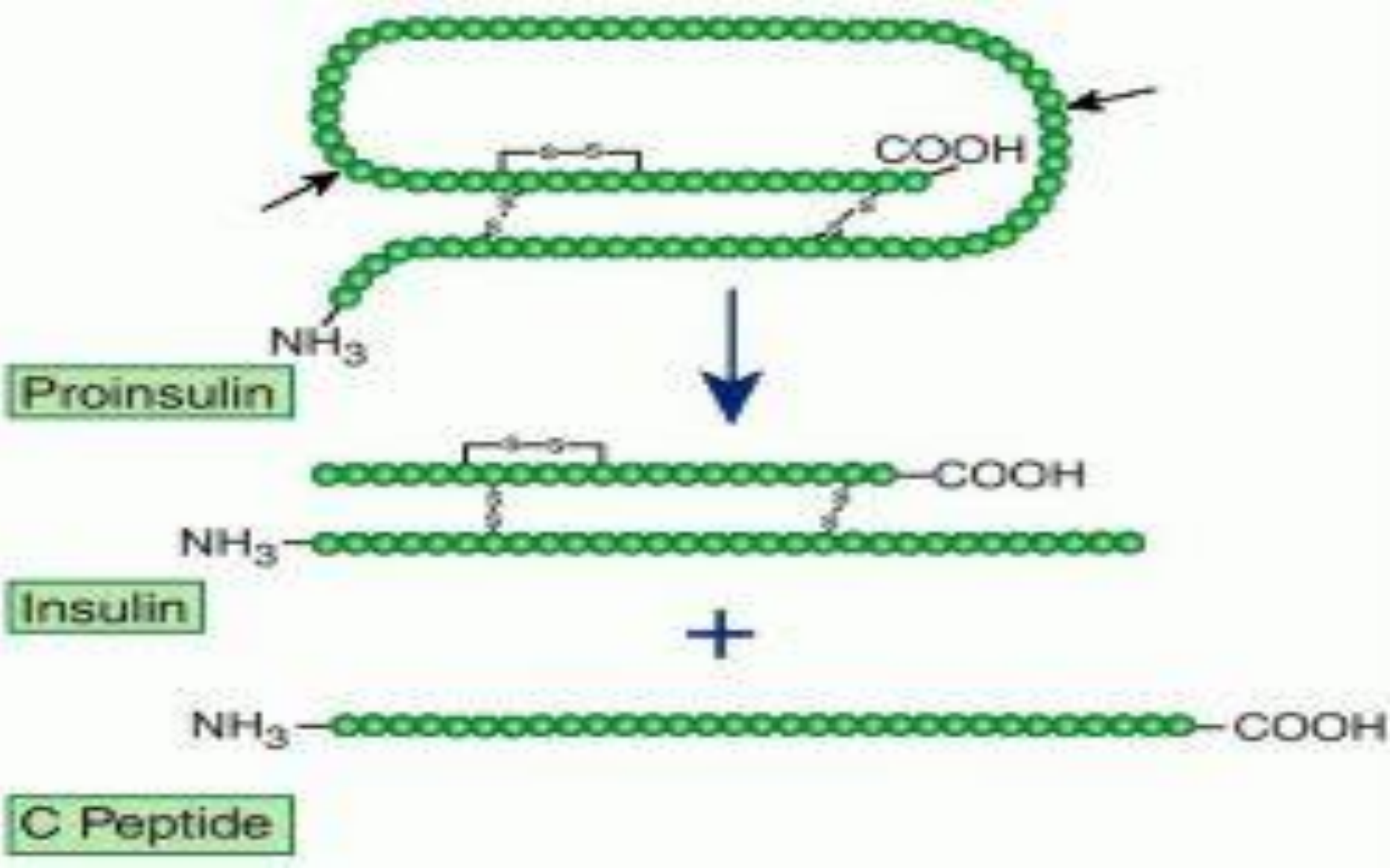
↓

Fuses with plasma membrane

↓

Releases insulin onto blood stream (exocytosis)

↓


COOH
NH3
Proinsulin
COOH
NH3
Insulin
NH3
COOH
C Peptide

Biosynthesis of Insulin

- Gene responsible for synthesis is located at Chr 11.
- Insulin synthesis occurs in rough endoplasmic reticulum of beta cells in islets of Langerhans.
- Synthesis of insulin involves two precursor molecules

    a) Preproinsulin (109 Amino acids)

    b) Proinsulin (86 Amino acids)

- Preprohormone is cleaved into proinsulin in ER.
- Proinsulin is cleaved into active insulin and a peptide fragment called C-peptide (connecting peptide) in GC.

- Synthesized C-peptide has no biological activity. However, its estimation in plasma serves as the useful index for endogenous production of insulin.
- Thus on sequential degradation precursor molecules are converted into active insulin molecule.
- After synthesis insulin binds with zinc, forms a complex and gets stored in granules.
- When stimuli arrives insulin are released into the blood stream.

Insulin destruction

- In human beings, injected insulin has a half life of about 5 to 10 mins
- Insulin gets cleared from the circulation within 10-15 mins.
- Major pathway for insulin destruction are Receptor mediated uptake followed by proteolysis in the organelle lysosomes
- Glutathione – insulin transhydrogenase found in liver and a lesser extent in other tissues capable of inactivating insulin by cleaving disulfide bonds, resulting in the scission of insulin into A and B chains.
- Insulinase (protease enzyme) degrades insulin in liver and kidney.

Biological actions of insulin

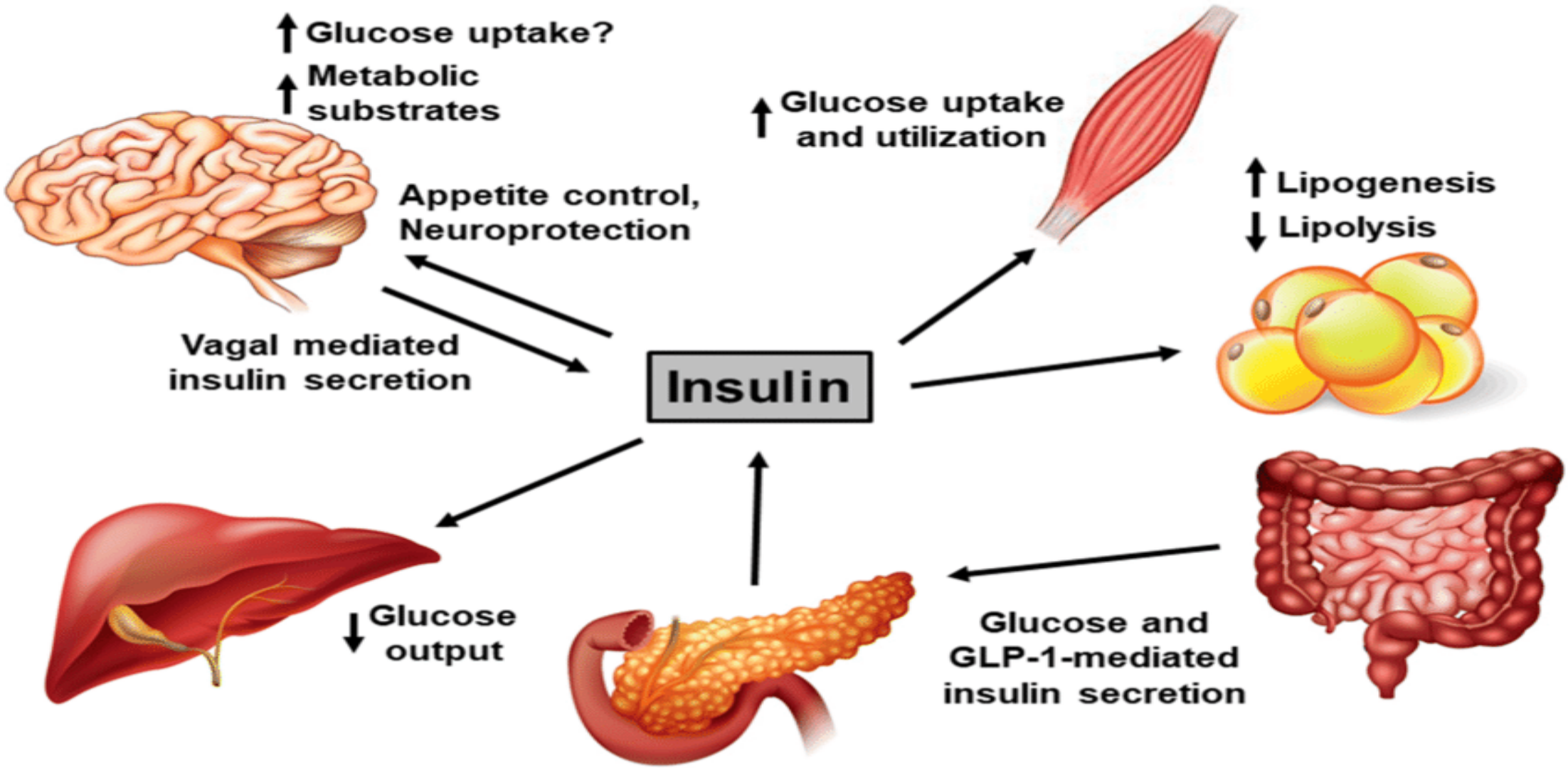
i) Role of insulin in membrane transport of glucose

ii) Role of insulin on carbohydrate metabolism.

iii) Role of insulin on lipid metabolism.

iv) Role of insulin on protein metabolism.

Insulin action on multiple tissues



i) Role of insulin in membrane transport of glucose

- Blood glucose concentration is high compared with inside of the cell after the meal hence, glucose is transported inside the cell across the plasma membrane.
- Transport carried out in the presence of a carrier protein.
- Transport mechanism with a carrier protein termed as facilitated diffusion.

i) Role of insulin in membrane transport of glucose

- Diffusion is a process in which movement of ions from a higher concentration to lower concentration without any energy.
- The carrier protein involved in the mechanism is glucose transporter (GLUT).
- GLUT is present on plasma membrane of liver, adipose tissue and muscles.

- Types of Glucose transporters

GLUT1, GLUT2,GLUT3, GLUT4.

- ✓ GLUT1 - Transports glucose in blood brain barrier.
- ✓ GLUT2 - Transports glucose in liver catalyzed by enzyme Glucokinase
- ✓ GLUT3 – Adipose tissue
- ✓ GLUT4 - Adipose tissue and muscles catalyzed by enzyme hexokinase.

Mechanism of Glucose transport into the cell by insulin molecule

Insulin

↓

Binds with insulin receptor on plasma membrane.

↓

Glucose transport present in the cytosol

↓

Insulin + receptor – HR complex – cAMP

↓

Signal to bind glucose transporter to the plasma membrane and forms a glucose canal

↓

Through which glucose enters into the cell

↓

Immediately the GLUT gets detaches from the PM

↓

Closing of the channel

- Glucose transported along with Na^+ ions.
- Transporter binding site for glucose faces outside of the PM – Conformation I
- Transporter binds with Glucose
- Now the transporter with glucose molecule faces inside of the cell – Conformation II

The actions can't be displayed.

- Glucose level low inside the cell
- Transporter releases the Glucose into the cell
- Glucose is immediately phosphorylated to glucose – 6 –phosphate which cannot leave the cell.
- Transporter comes to original position.
- Subsequent transport will takes place.

ii) Role of insulin on carbohydrate metabolism.

❑ Role of insulin on liver cells

- Insulin by its direct action it increases the activity of enzymes such as glucokinase, phosphofructokinase and pyruvate kinase involved in glycolysis.

- Insulin activates the enzyme glucokinase which catalysis the conversion of Glucose into Glucose 6 phosphate in Liver cells.

ii) Role of insulin on carbohydrate metabolism.

❑ Role of insulin on liver cells

- By indirect action, insulin decreases the activity of enzymes such as glucose – 6-phosphatase, fructose 1,6 bisphosphatase, phosphoenol pyruvate carboxykinase and pyruvate carboxylase involved in **gluconeogenesis**, in liver.

- Insulin promotes the activation of enzyme glycogen synthase by stimulating glycogen synthase D phosphatase and inhibits cAMP dependent protein kinase.

- Insulin inhibits Glycogenolysis by inhibiting the enzyme liver phosphorylase. Thus inhibits the conversion of glycogen into glucose.

- Increased glycogen synthase and decreased phosphorylase activity in liver promotes glycogen formation. Net effect is increased storage of glycogen in liver. Thus maintains glucose level.

❑ Role of insulin on skeletal muscle

- Insulin promotes Glucose transporter, thus allows glucose into the cells.
- Activates the enzyme hexokinase, involved in glycolysis
- Stimulates lipogenesis in adipose tissue by activating the enzyme acetyl COA carboxylase.

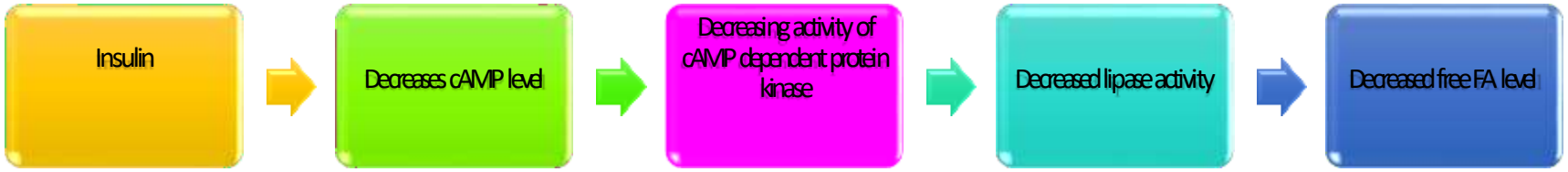
❑ Role of insulin in liver and muscles cells

- Stimulates Glycogenesis by activating the enzyme Glycogen synthase which promotes the synthesis of glycogen from glucose.

iii) Role of insulin on lipid metabolism

- Dephosphorylation of acetyl coA carboxylase (Active) promotes fatty acid synthesis (lipogenesis)
- Inhibits lipolysis in liver and adipose tissue.

Dephosphorylation of triacylglycerol lipase (inactive) inhibits lipolysis (anti-lipolytic action) in liver and adipose cells.



- **iii) Role of insulin on lipid metabolism**

In addition, insulin increases the activity of membrane bound lipoprotein lipase and fatty acid synthase thus increases the availability of fatty acids to cells.

iv) Role of insulin on protein metabolism.

- Insulin inhibits protein degradation (catabolism) and thus, decreases the rate of amino acids release from the cells.
- Insulin decreases the rate of gluconeogenesis in liver and thus conserves amino acids for protein synthesis.
- Insulin promotes protein synthesis.

Over all actions of insulin

- Stimulates glycolysis, glycogenesis, lipogenesis and protein synthesis (Hypoglycemic effect)
- Inhibits glycogenolysis, gluconeogenesis, lipolysis and breakdown of proteins.

Insulin Receptors

- Glycoprotein in nature situated on the plasma membrane of respective cells.
- Tetramer formed by 4 subunits.
- 2 Alpha subunits and 2 Beta subunits.
- 2 Alpha subunits present outside the cell membrane and two beta subunits present inside the cell cytoplasm.

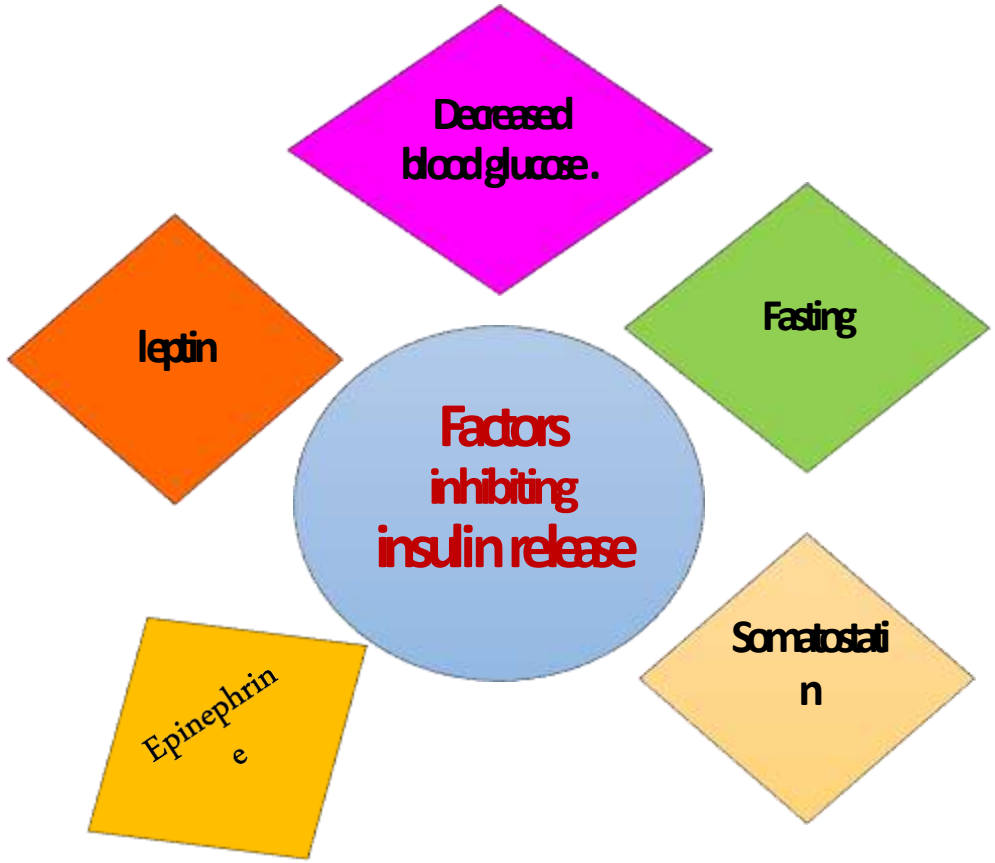
Insulin Receptors

- Alpha and beta subunits are linked by disulphide bonds.
- It is an enzyme – linked receptor.
- Made up of multiple enzyme groups called as insulin receptor substrates (IRS).
- Each cell has 10^3 to 10^5 receptors.
- Multi-subunit composed of non identical subunits MW = 130,000 and 90,000.

Regulation of insulin secretion

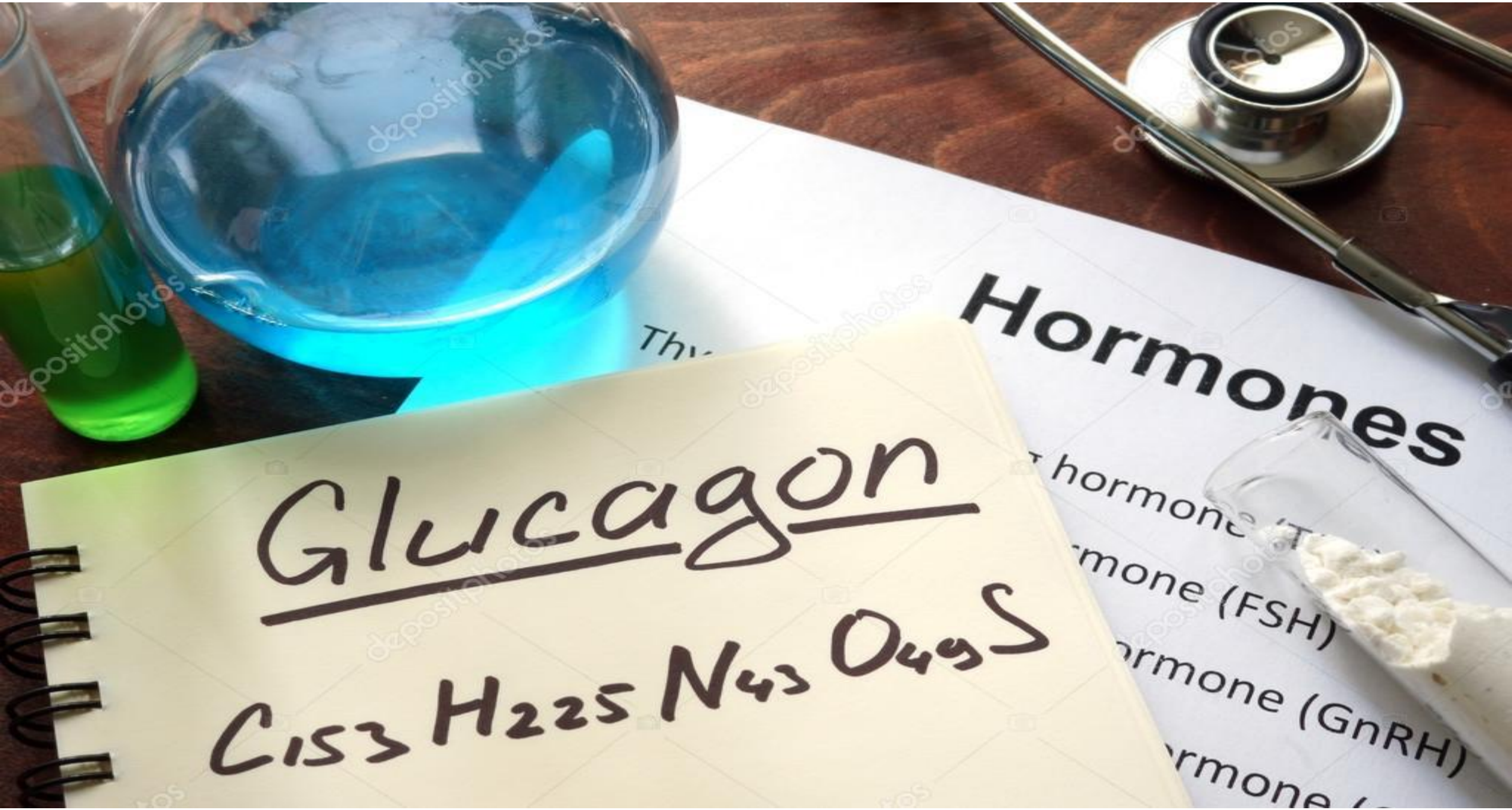
- About 40 -50 units secreted daily by human pancreas.
- Normal value =20 – 30 µU/mL.
- Following mechanism regulate insulin secretion
- Chemical – mainly by glucose uptake by the cells.
- Hormonal – paracrine interactions between the hormones produced by islet of Langerhans
- Neural mechanism – Adrenergic and cholinergic nerves

FACTORS AFFECTING INSULIN SECRETION



Effects of insulin deficiency

- Hyperglycemia
- Glycosuria
- Polyuria
- Polydipsia and polyphagia
- Weight loss
- Increase in plasma cholesterol and phospholipid concentration.
- Hyperlipidemia
- Diabetes mellitus


Glucagon
C153H225N43O49S
Hormones
hormone (FSH)
rmone (GnRH)

GLUCAGON

- Opposite action to insulin
- Secreted by pancreatic alpha cells or A cells in islets of pancreas.
- Also synthesized by A cells of stomach and L cells of intestine.
- Single chain polypeptide containing 29 amino acid residues.

GLUCAGON

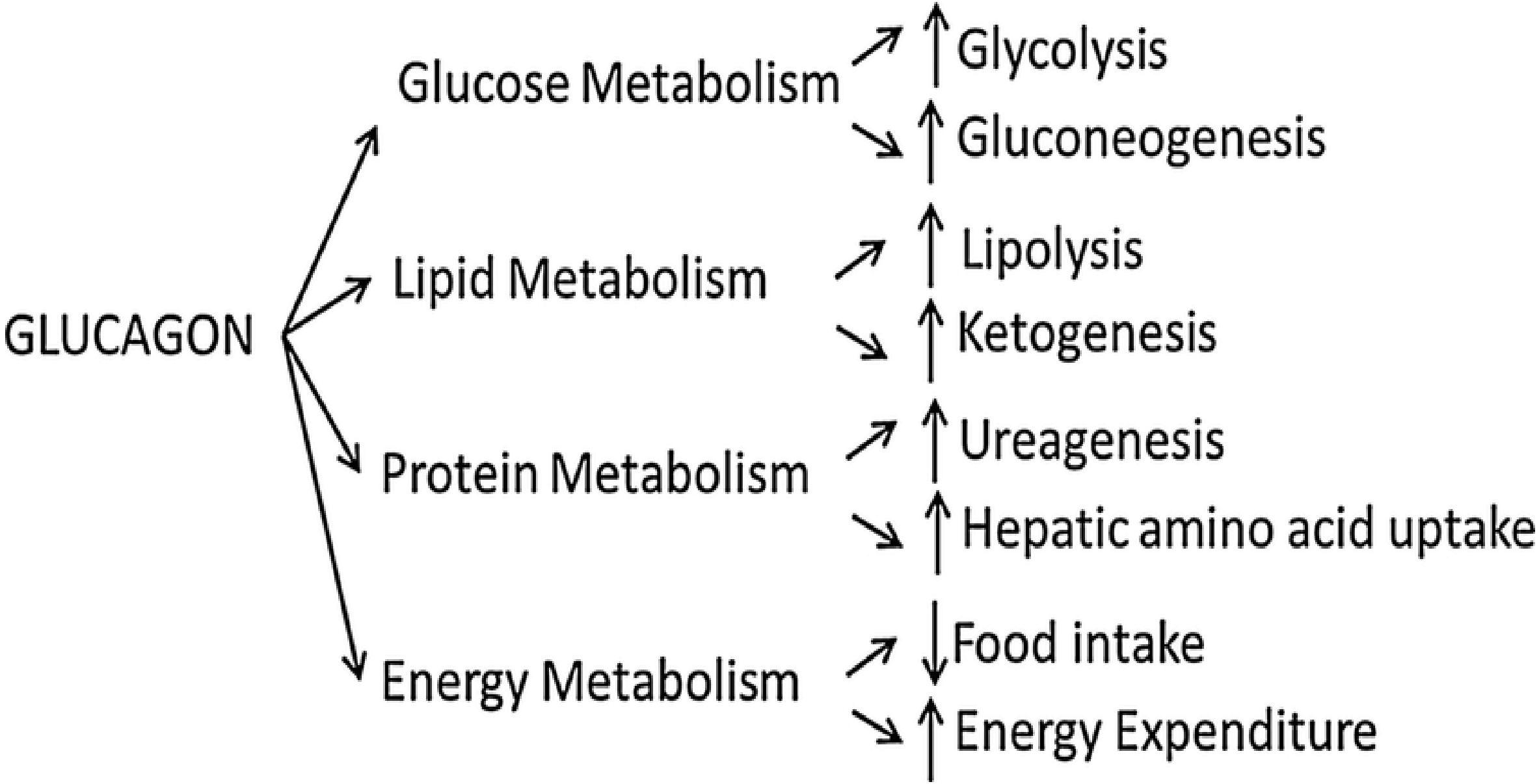
- Circulated in plasma in free form
- Does not bind with transport protein.
- Plasma half life of 5 minutes.
- Glucose, insulin, insulin like growth factor (IGF-1), amino acids, ketones, neurotransmitter inhibits glucagon release.

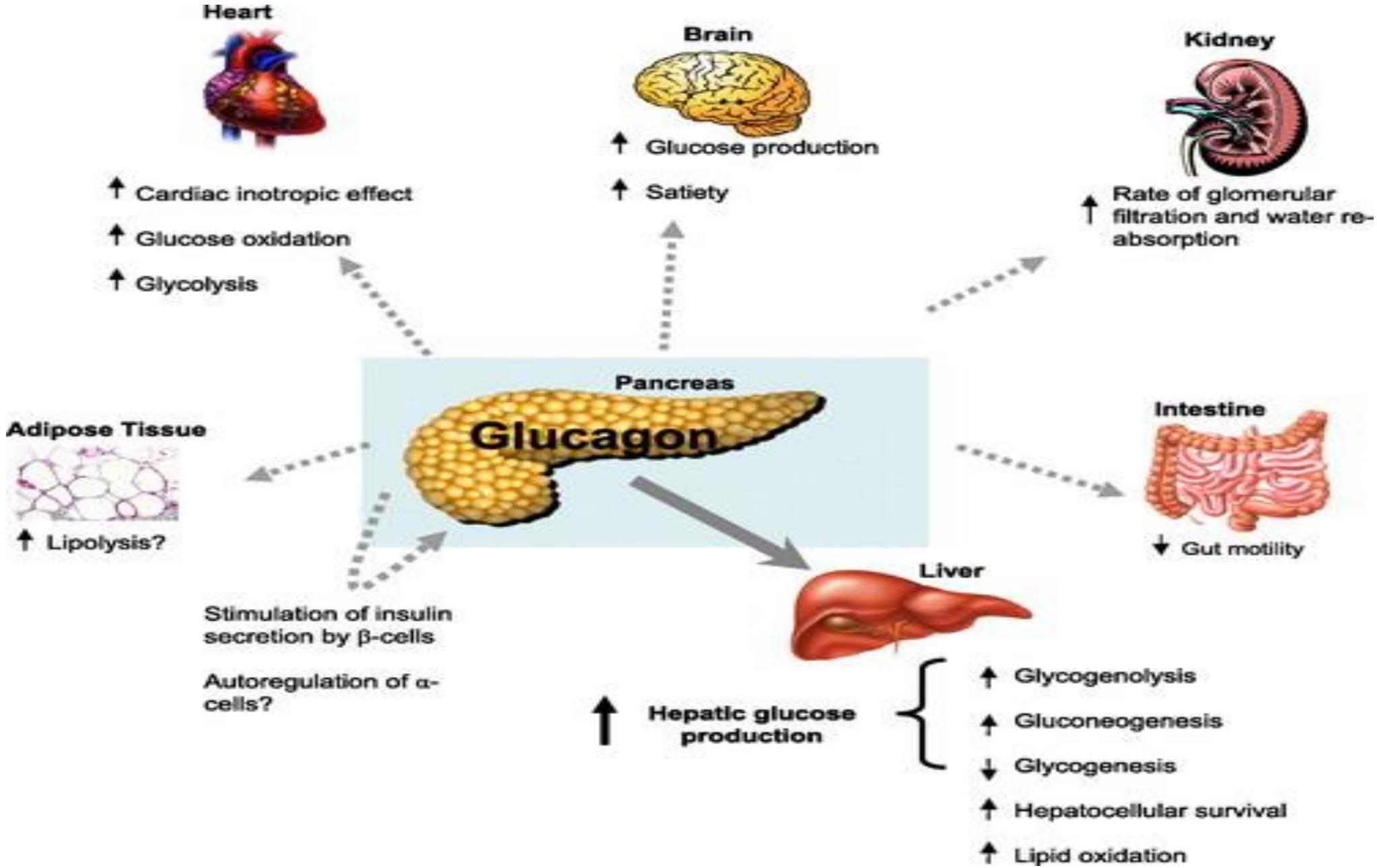
Synthesis and secretion of Glucagon

- Synthesized from preprohormone precursor called proglucagon (MW = 18,000) in the alpha cells of islets of Langerhans.
- Proglucagon is converted into active glucagon with 29 amino acid (3.48Kd).
- Trypsin – like and carboxypeptidase B- like enzyme activities are required during the process.
- After synthesis they are stored in a dense granules.
- Released by exocytosis process.
- Ca required for exocytosis process.

Metabolism

- Half life is 6 mins
- About 30% of glucagon is degraded in liver and 20% of glucagon is degraded in kidney.
- Cleaved glucagon fragments gets excreted in urine.
- 50% of circulating glucagon is degraded in blood itself by enzymes such as serine and cysteine proteases.


GLUCAGON
Glucose Metabolism
Glycolysis
Gluconeogenesis
Lipid Metabolism
Lipolysis
Ketogenesis
Protein Metabolism
Ureagenesis
Hepatic amino acid uptake
Energy Metabolism
Food intake
Energy Expenditure


Heart
↑ Cardiac inotropic effect
↑ Glucose oxidation
↑ Glycolysis
Brain
↑ Glucose production
↑ Satiety
Kidney
↑ Rate of glomerular filtration and water re-absorption
Pancreas
Glucagon
Adipose Tissue
↑ Lipolysis?
Stimulation of insulin secretion by β-cells
Autoregulation of α-cells?
Intestine
↓ Gut motility
Liver
↑ Hepatic glucose production
↑ Glycogenolysis
↑ Gluconeogenesis
↓ Glycogenesis
↑ Hepatocellular survival
↑ Lipid oxidation

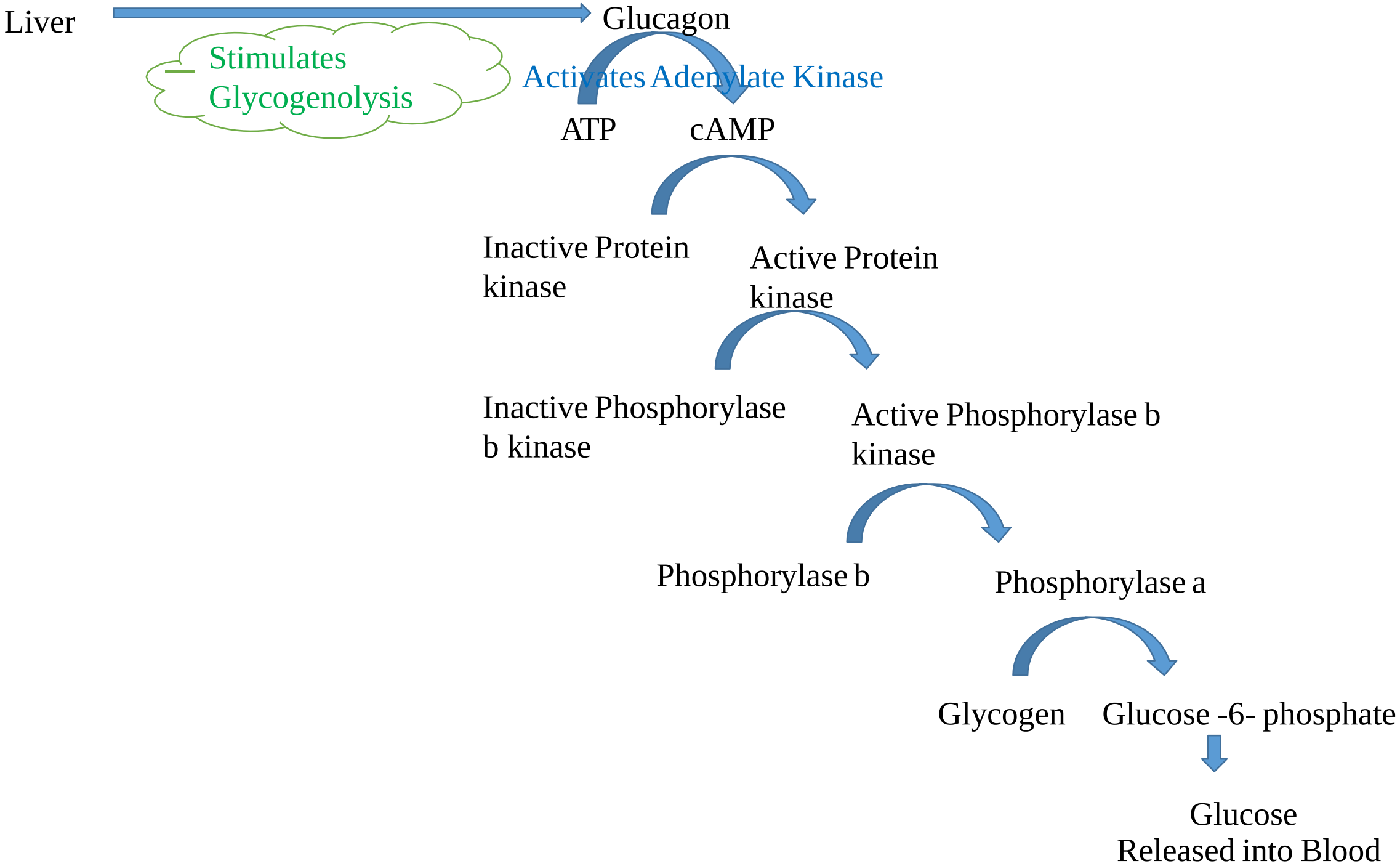
Actions of Glucagon

- Effect of glucagon on carbohydrate metabolism.
- Effect of Glucagon on protein metabolism.
- Lipolytic and ketogenic effect.
- Other actions of Glucagon.

i) Effect on carbohydrate metabolism

❑ Glucagon increases blood sugar level by

- Increases glycogenolysis in liver and releases glucose from the liver cells into the blood.
- Glucagon does not induce glycogenolysis in muscle.
- Increases gluconeogenesis in liver by activating the enzyme Phophoenol pyruvate kinase which convert pyruvate into phosphoenol pyruvate. It also increases the transport of amino acids into the liver cells.
- Inhibits glycogenesis by inhibiting the enzyme glycogen synthase.
- Thus Glucagon has hyperglycemic effect.


Liver
Glucagon
Stimulates Glycogenolysis
Activates Adenylate Kinase
ATP
cAMP
Inactive Protein kinase
Active Protein kinase
Inactive Phosphorylase b kinase
Active Phosphorylase b kinase
Phosphorylase b
Phosphorylase a
Glycogen
Glucose -6- phosphate
Glucose Released into Blood

ii) Effect on protein metabolism

- Glucagon increases the transport of amino acids into liver cells by increasing gluconeogenesis by activating the key enzymes.
- The amino acids are utilized for formation of glucose in cells.
- This lowers plasma amino acids level.

iii) Lipolytic and ketogenic Effect

Glucagon

↓

Adipose tissue

↓

cAMP

↓

Activates enzyme hormone sensitive lipase

↓

Triglycerides converted into diacyl glycerol and free fatty acid in plasma

↓

Free fatty acids undergoes β –oxidation

↓

Increased ketone bodies – Keto acidosis in liver

- **High insulin Glucagon ratio**:

  Induced glucokinase, acetyl coA carboxylase, pyruvate kinase, 6-phosphofructokinase, citrate synthase.

- **Low insulin glucagon ratio:**

  Induced glucose-6-phosphatase, phosphoenol pyruvate carboxykinase, fructose 1,6 disphosphatase.

iv) Other Actions of Glucagon

- Stimulates insulin secretion by the islet B cells.
- Increases glomerular filtration rate and renal plasma flow.
- High concentration of glucagon stimulates cardiac contractility, stimulates growth hormone secretion, inhibits motility of GI tract and stimulates catecholamines release by adrenal medulla.

Mode of action of glucagon

- Specific receptors binds with Glucagon in target cells.
- In liver cells glucagon binds with the receptor and activates membrane adenylate cyclase via G protein.
- Adenylate cyclase synthesis cAMP.
- Increase in cAMP activates protein kinases and phosphorylation of specific enzymes in mitochondria and lysosomal membranes of respective tissues.
- Glucagon receptor is a peptide with a molecular weight of 62,000.

Regulation of Glucagon