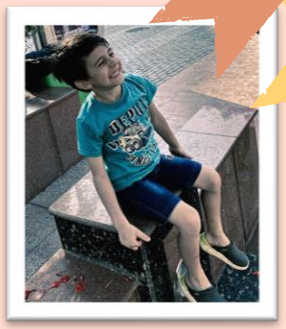

Hello Everyone

Hope You Are Having
A Wonderful Physiological Day
☺☺☺


ARE YOU
READY ?
LET'S GET STARTED!

Glucose Hemostasis

Sem 4

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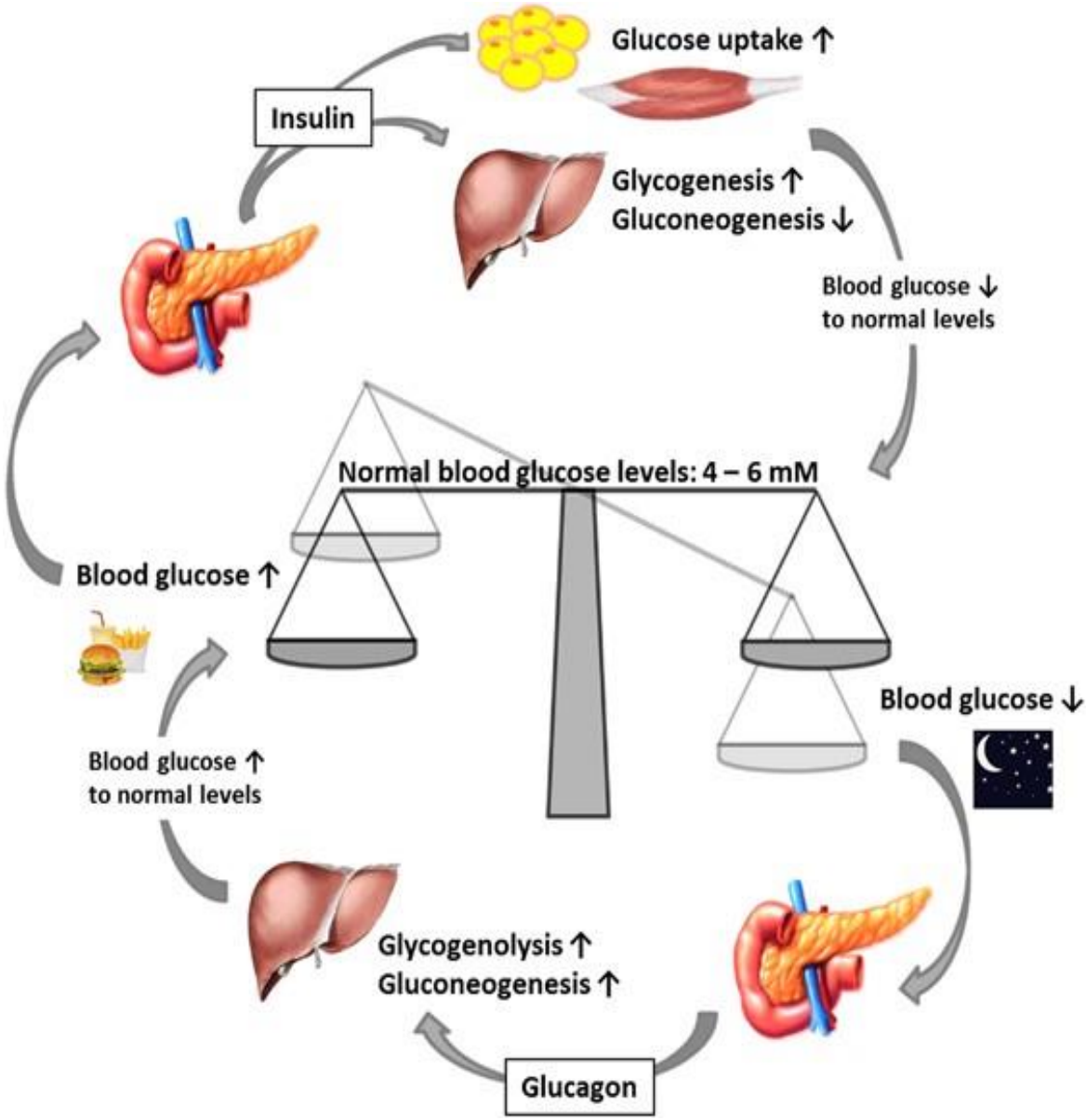
Glucose Homeostasis

Def:

Maintain the blood glucose at a nearly constant level.

Why ???

- Glucose is the primary source energy for the human body, and it is the **only energy source** for the **brain** in normal conditions.
- It is achieved by a balance between rate of **addition** and rate of **withdrawal** of glucose from blood to avoid hypo or hyperglycemia

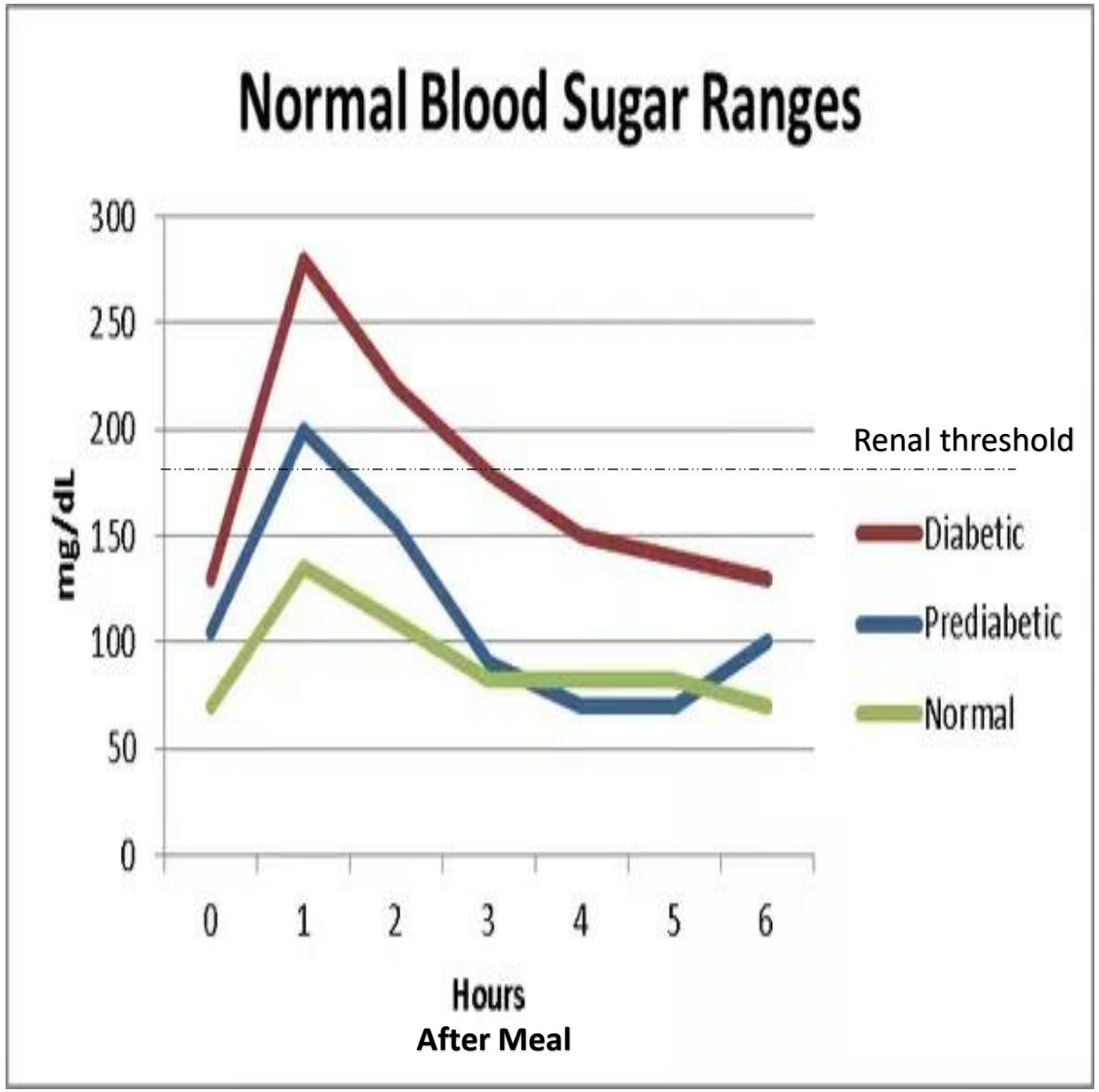


Normal Blood Glucose

- Normal **fasting** blood glucose level is about **70-100 mg %.**
- Reaches **140 mg %** during the **first hour** after meal, then returns to **fasting level within 2** hours after.

Normal Urinary Glucose

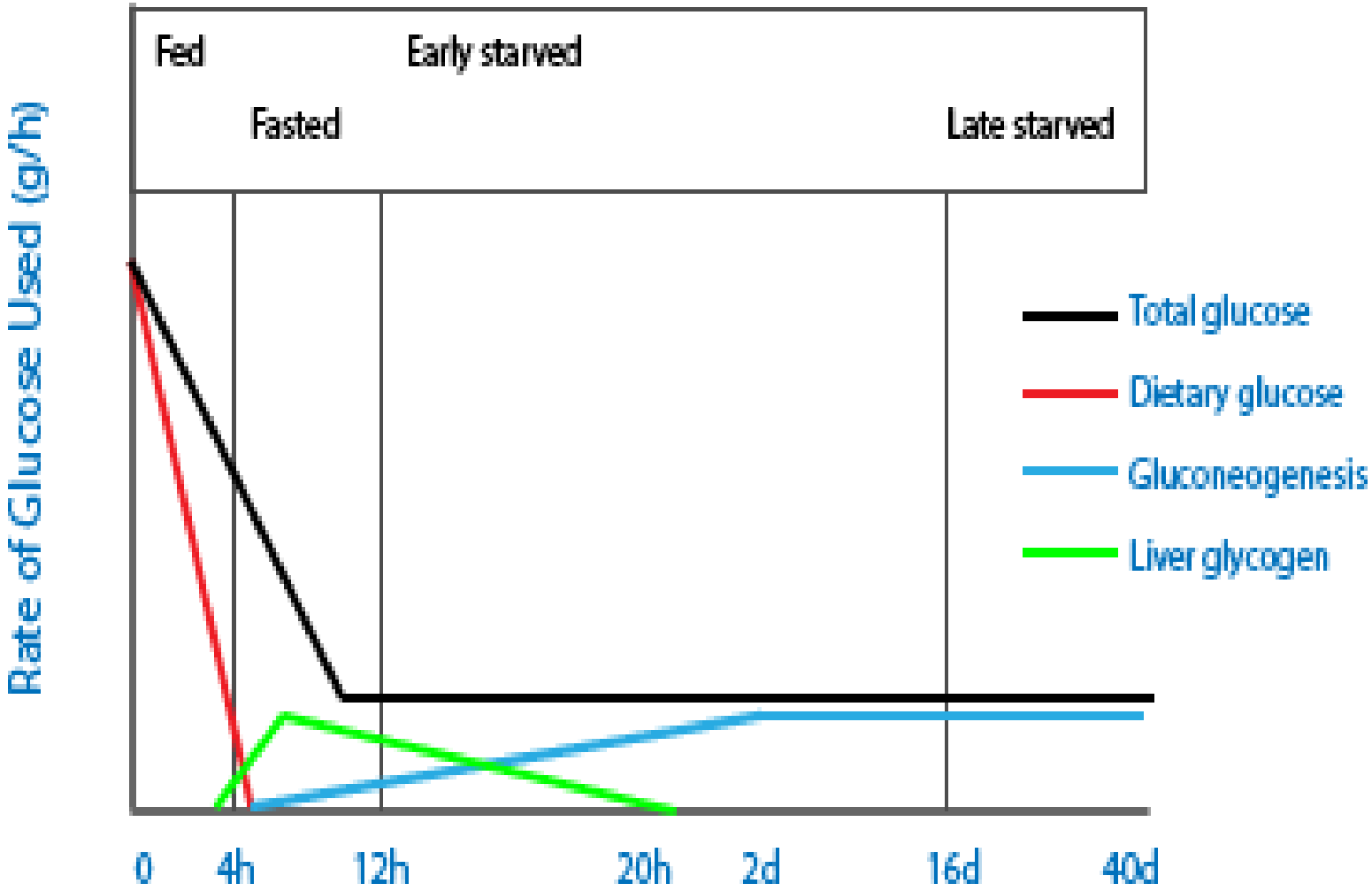
- Normally the **urine doesn't contain** any glucose due to its **complete reabsorption** from the renal tubules.
- when blood glucose concentrations exceed **180 mg/dL (Renal threshold)** , urinary glucose excretion occurs.



Main Sources of Blood Glucose

Blood glucose increases by 3 mechanisms:

- Dietary Intake
- Glycogenolysis
- Gluconeogenesis



Mechanisms of Glucose Homeostasis

Normal Blood glucose is regulated by 2 main factors

Tissues

- **The liver** (Glucostat)
- **Other tissues** involved in gluconeogenesis e.g. the kidney

Hormones

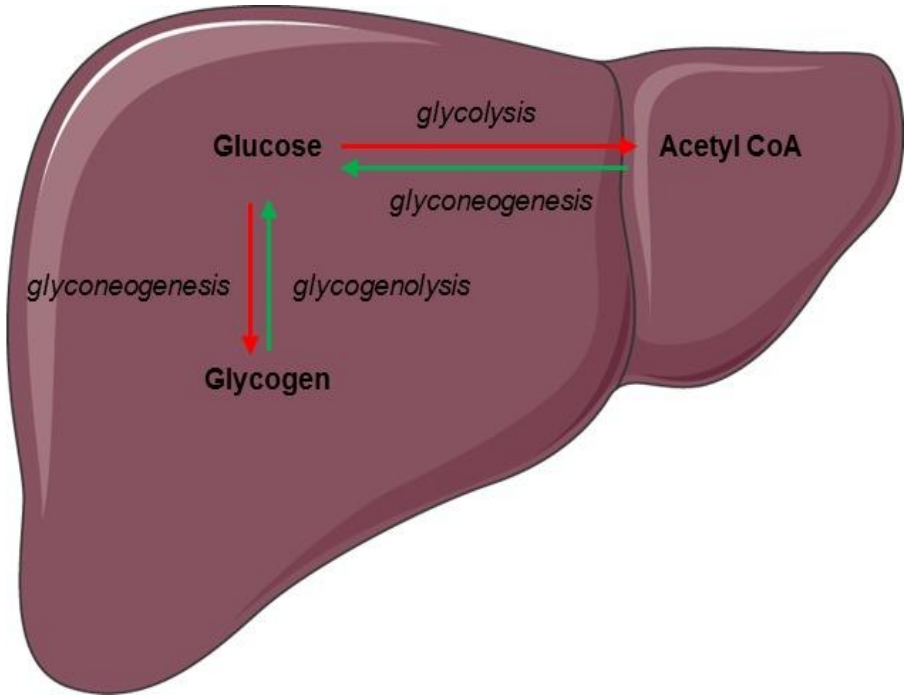
- **Pancreatic hormones :**
  Insulin & Glucagon
- **Other hormones:**
  Growth hormone, Cortisol , Thyroxin & Epinephrin.

Role of the liver in Glucose Hemostasis

The liver functions as an important blood glucose buffer system **(Glucostat)**.

After Meals:

- About two-thirds of the glucose absorbed from the small intestine is rapidly stored as glycogen in the liver **(glycogenesis)** .



During the following fating state:

- The liver releases the glucose back into the blood through **glycogenolysis and gluconeogenesis**.

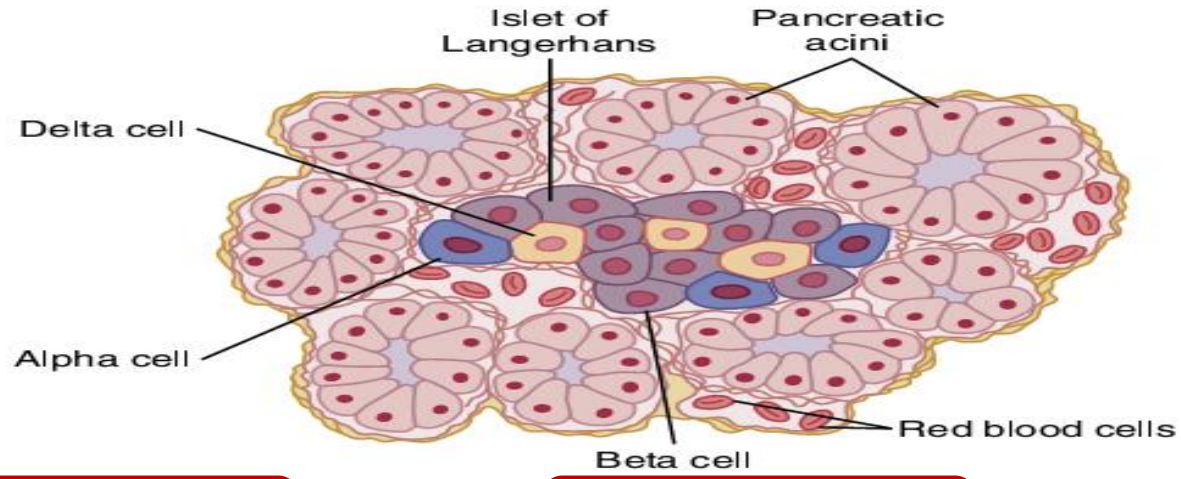
- The liver decreases fluctuations in blood glucose concentration so blood glucose concentration after a meal rich in carbohydrates may rise two to three times as much as in a person with normal liver function.

Hormonal Regulation of Blood Glucose

Hyperglycemia	**Insulin** secretion from the pancreas
Hypoglycemia	**Glucagon** secretion from the pancreas
Prolonged Hypoglycemia	**Growth hormone** and **cortisol** decrease glucose utilization & increase fat utilization by most cells of the body. **Thyroxin** increase glucose absorption from the intestine
Sever Hypoglycemia	**Epinephrin** from the adrenal medulla stimulate glucagon and inhibit insulin secretion and stimulate gluconeogenesis and glycogenolysis

Pancreatic Hormones

The human pancreas has 1 to 2 million **islets of Langerhans**.



Alpha cells

- 25 %
- Secretes **Glucagon**

Beta cells

- 60 %
- Secretes **Insulin**

Delta cells

- 10 %
- Secretes **Somatostatin**

F cells

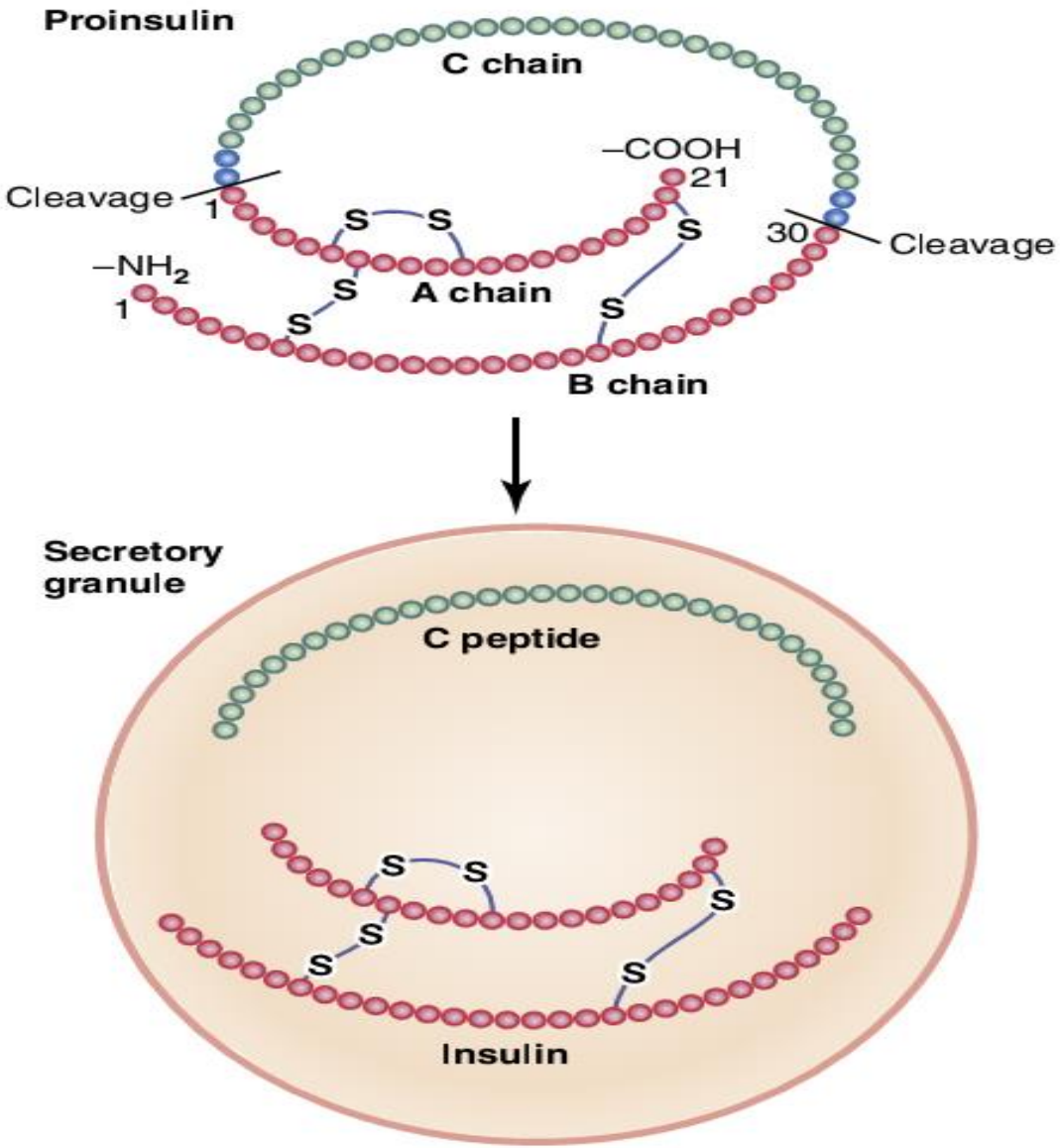
- 5 %
- Secretes **Pancreatic polypeptide**

Insulin

- polypeptide hormones.
- It consists of 2 straight chains linked by 2 disulfide bridges.
  1. A chain → contains 21 amino acids and an intra-chain disulfide ring.
  2. B chain → contains 30 amino acids.

Synthesis and Release :

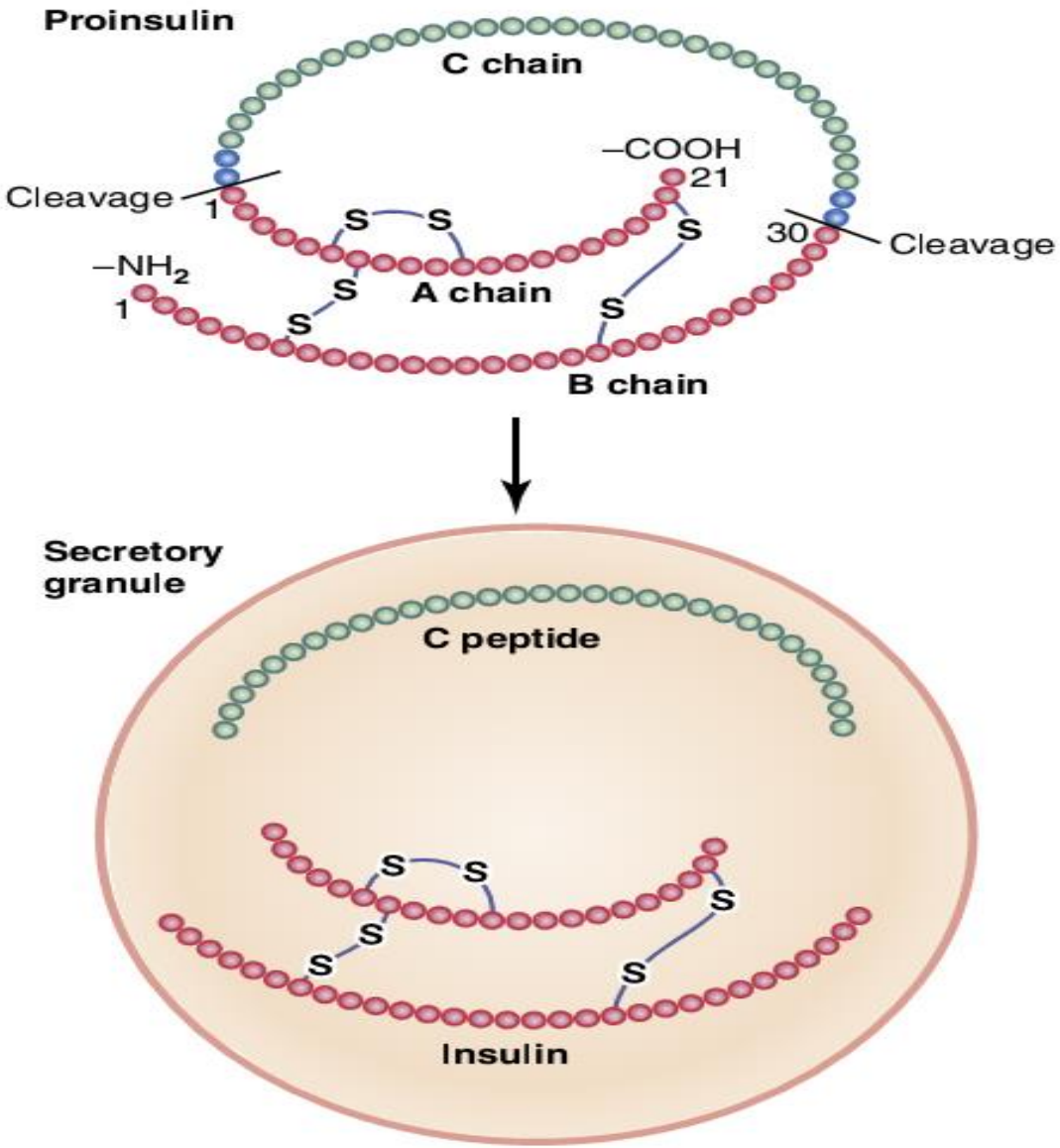
- A **preproinsulin** is first synthesized on the ribosomes as directed by a specific mRNA.
- 23 amino acid residue is rapidly cleared at the site of synthesis to yield a **proinsulin** chain.



Insulin

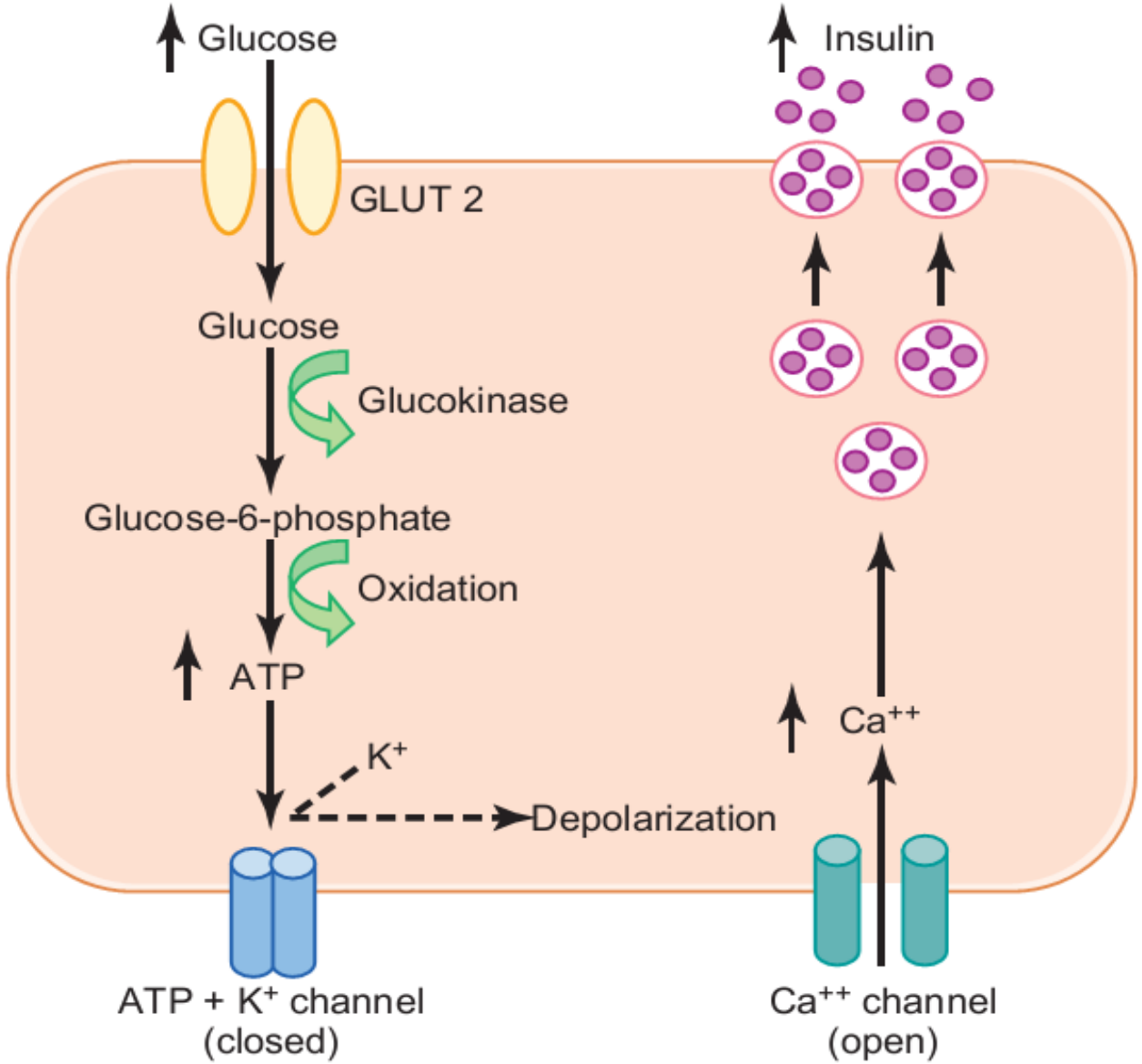
Synthesis and Release :

- proinsulin is slowly cleaved by trypsin-like and carboxypeptidase-like enzyme
- The generated **insulin and C-peptide** molecules are retained in the granules and released during secretion in equimolar amounts.
- **C-peptide** has no known function, but it serves as a **marker of endogenous insulin secretion**.



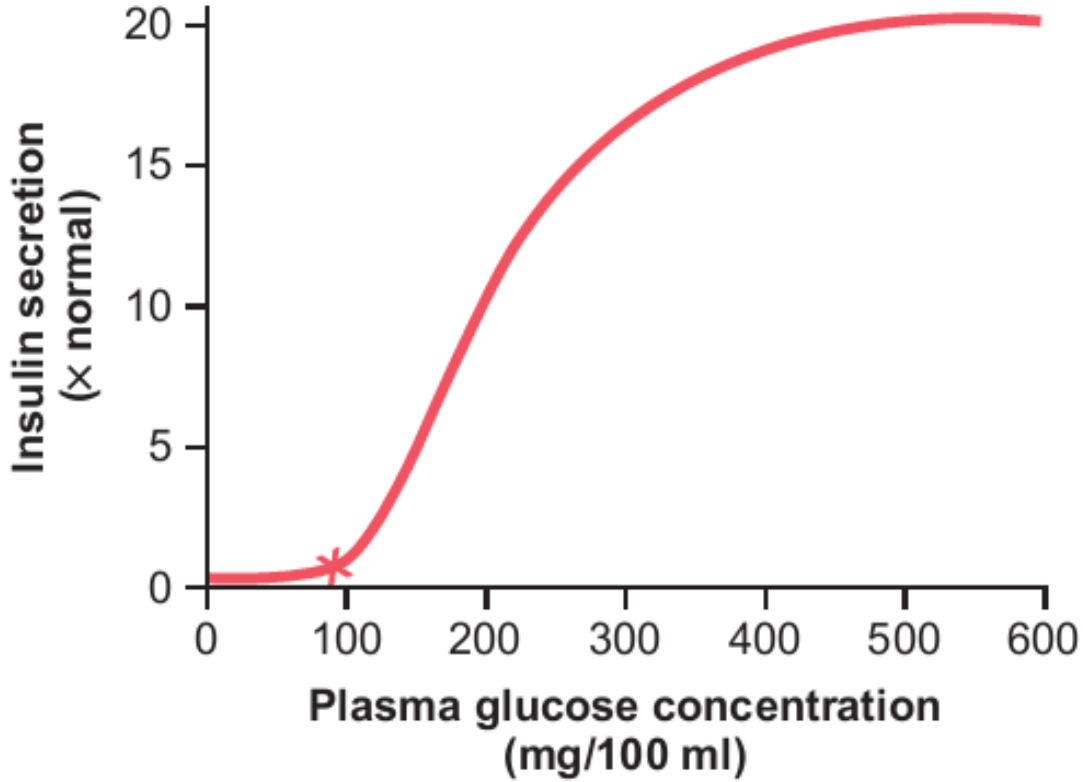
Mechanism of Insulin secretion

↑blood glucose → ↑glucose influx to Beta cells through **GLUT2** → **↑ATP** production → closure of ATP sensitive K^+ channels → **↓ K^+ efflux** → Depolarization → opening of voltage gated Ca^{++} channels → **↑ Ca^{++} influx** → release of insulin by **exocytosis**.



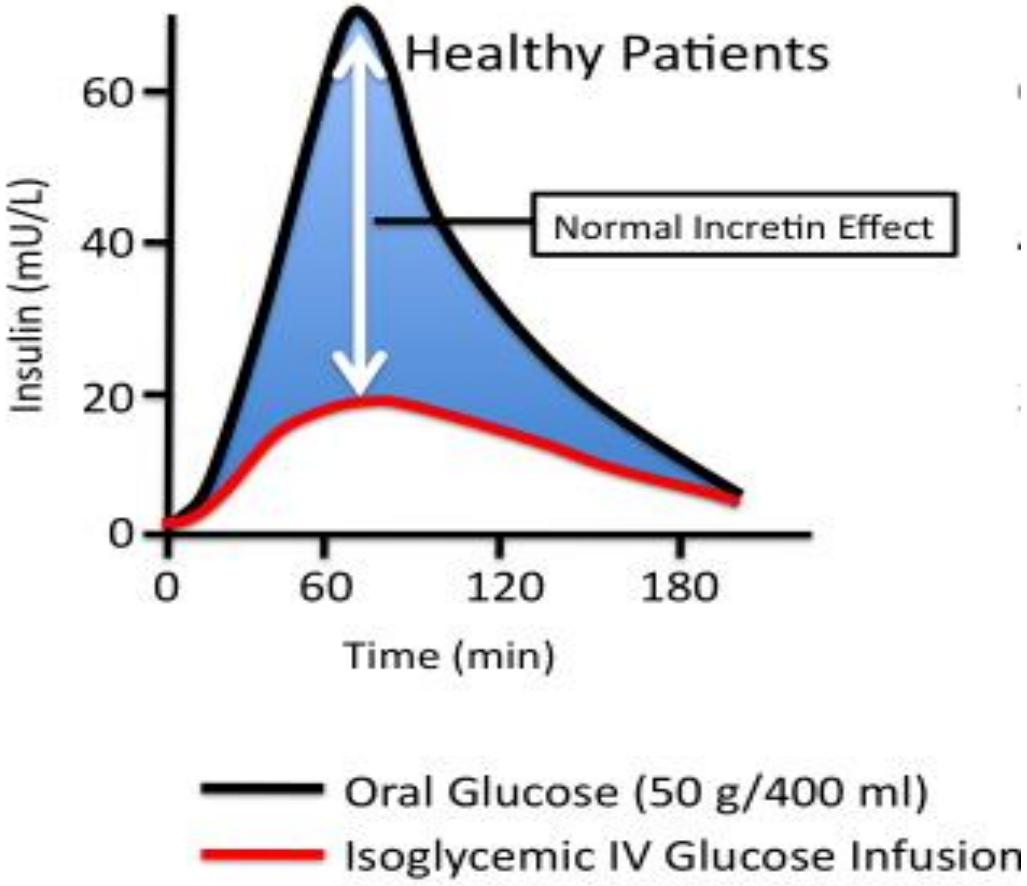
Control of Insulin secretion

- The major regulation is the plasma glucose level.
- No insulin is secreted below a plasma glucose level of 50 mg%.
- A half maximum insulin secretory response occurs at a plasma glucose level of about 150 mg% and a maximum response at 300 to 500 mg%.



Control of Insulin secretion

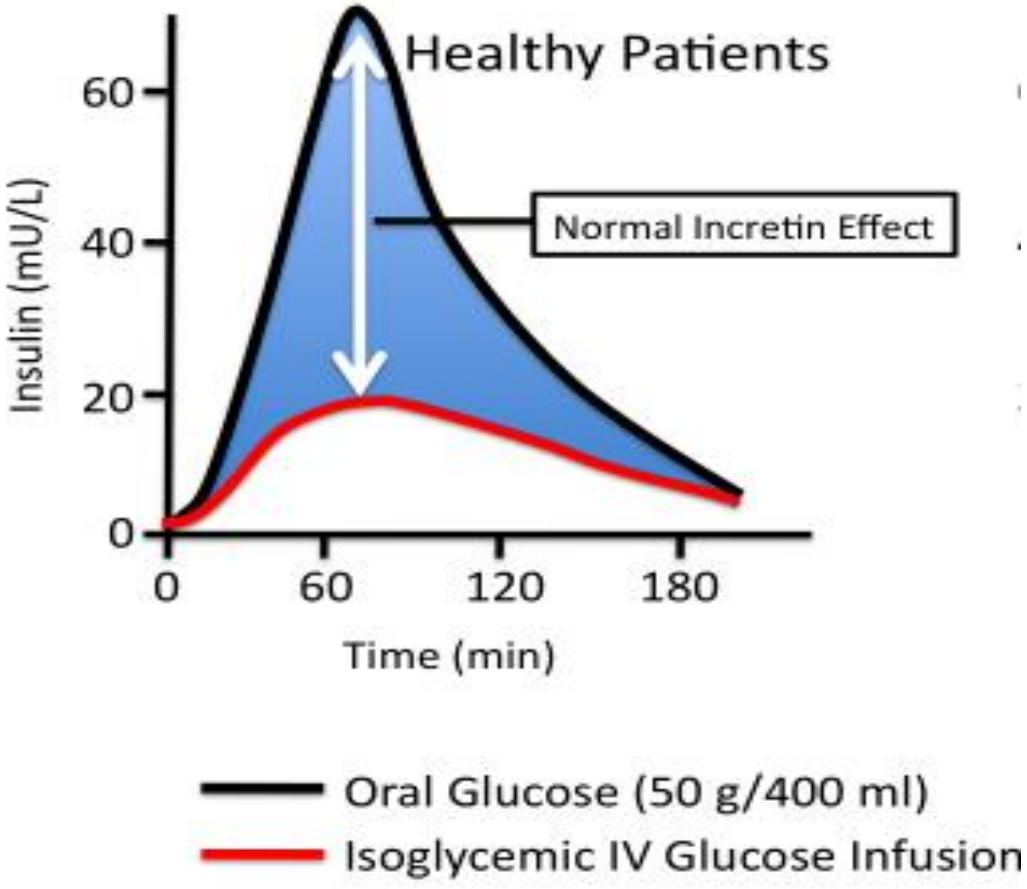
- Oral glucose produce a greater insulin than intravenous glucose.
- This is accounted for by the release of a number of gastro-intestinal hormones **(Incretins)** which are capable of potentiating glucose-stimulated insulin secretion.



Control of Insulin secretion

Incretins include the following hormones:

- **Gastric inhibitory polypeptide (GIP)** also called glucose dependent insulinotropic peptide is probably the most important of these Hormones.
- High concentrations of **gastrin, secretin, cholecystokinin** .



This GIT mechanism of insulinogenesis **reduces** the early rise of **glucose** that follows the ingestion and absorption of a carbohydrate **meal**.

Increase Insulin Secretion

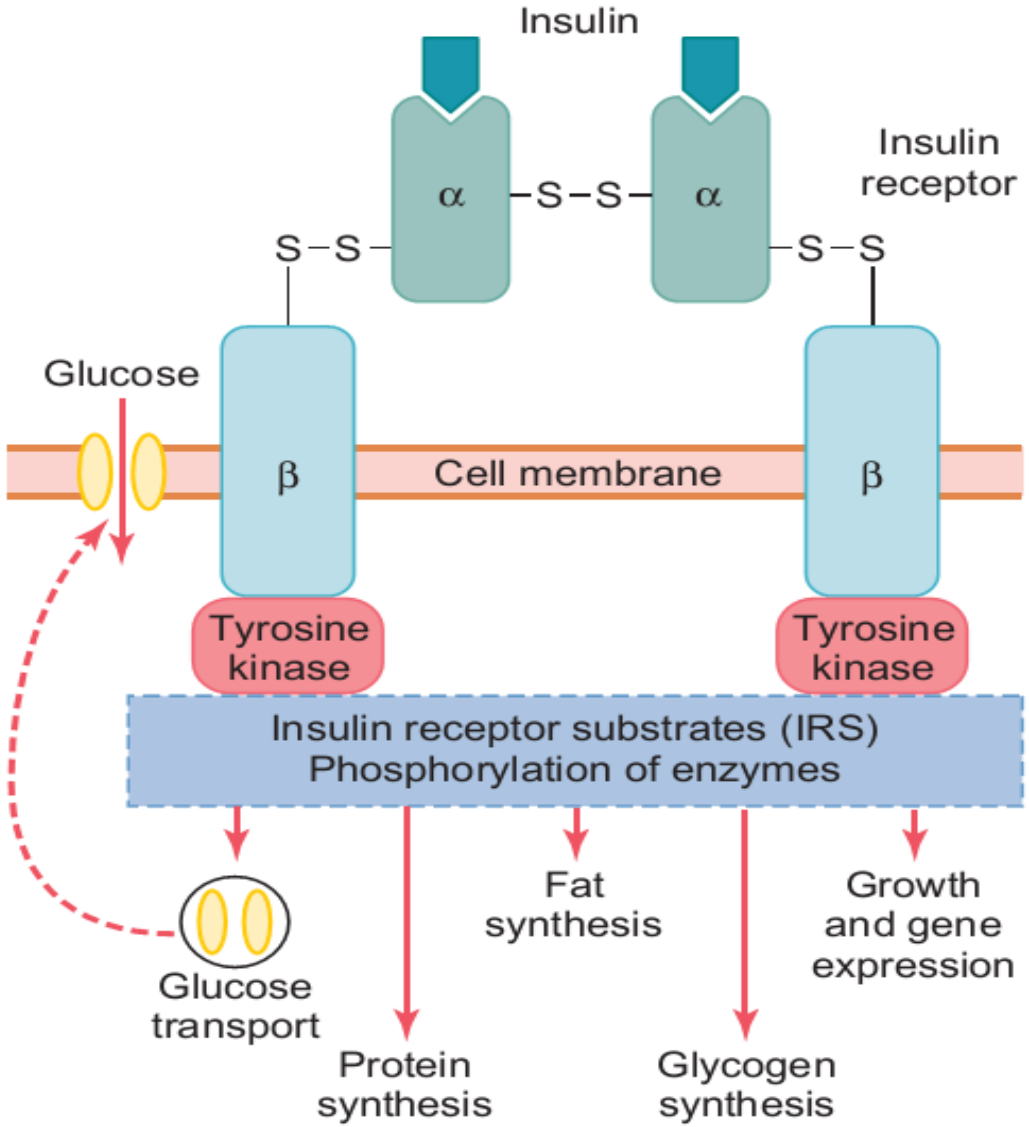
- Increased blood glucose, fatty acids & amino acids
- Incretins
- Glucagon (Directly through paracrine action & indirectly through ↑ Blood glucose)
- Growth hormone, Cortisol
- Parasympathetic stimulation; acetylcholine
- β-Adrenergic stimulation

Decrease Insulin Secretion

- Decreased blood glucose
- Fasting
- Somatostatin
- α-Adrenergic stimulation
- Leptin (hormone secreted from the adipose tissue)

Mechanism of Insulin Action

Insulin binds to the α subunit of its receptor, which causes autophosphorylation of the β-subunit receptor, which in turn induces tyrosine kinase activity.
The receptor tyrosine kinase activity begins a cascade of cell phosphorylation that increases or decreases the activity of enzymes, including insulin receptor substrates (IRS) → biological response



Function of Insulin

- Insulin's overall function is the storage of ingested nutrients.
- The main insulin targets are **liver, skeletal muscle, and adipose tissue.**

Liver

1. Stimulate glycogenesis
2. Inhibition of glycogenolysis
3. Inhibition of gluconeogenesis
4. ↑ activity of glucokinase → ↑glucose entry into the liver

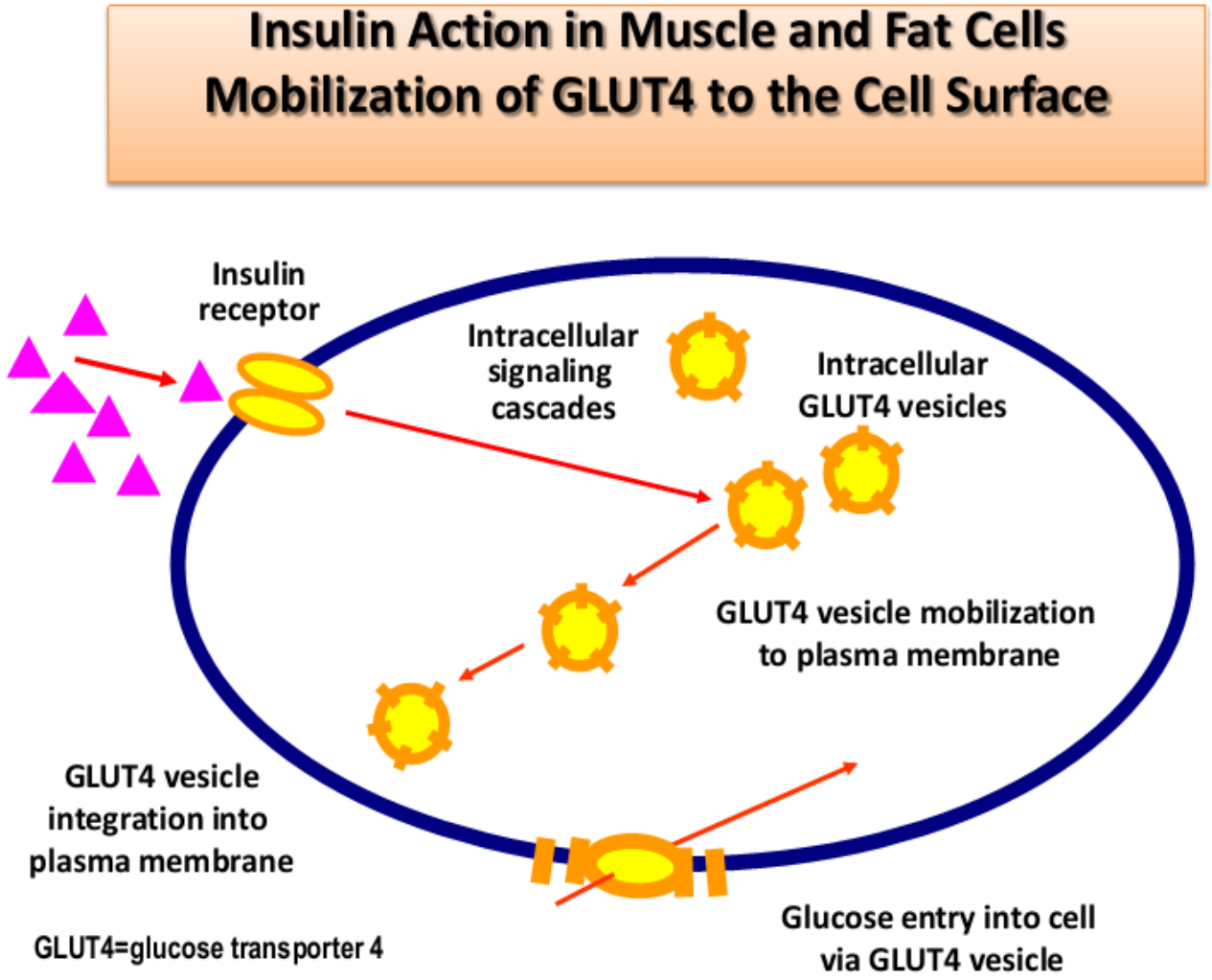
Adipose tissue

1. Increase GLUT4 availability → Increase glucose entry.
2. Glucose is converted to glycerol → ↑ (stored triglycerides)

Function of Insulin

Muscle

1. Increase GLUT4 availability
   → Increase glucose uptake
2. Stimulate glycogenesis through glycogen synthetase enzyme



Function of Insulin

Protein metabolism

1. Stimulates the uptake of certain amino acids by Sk. Ms.
2. Stimulates the rate of protein synthesis (enhance activity of ribosomes)
3. Anticatabolic effects i.e. inhibits proteolysis.

Fat metabolism

1. ↓Fat utilization (Fat Sparer), excess hepatic glucose uptake → Fat formation (T.G) in liver which are transported by VLDL to adipose tissue
2. ↓ the activity of hormone sensitive lipase in adipose tissue → inhibits lipolysis

Electrolyte

1. Insulin increases cellular uptake of potassium, phosphate and magnesium.
2. It increases the reabsorption of potassium, phosphate and sodium by renal tubules.

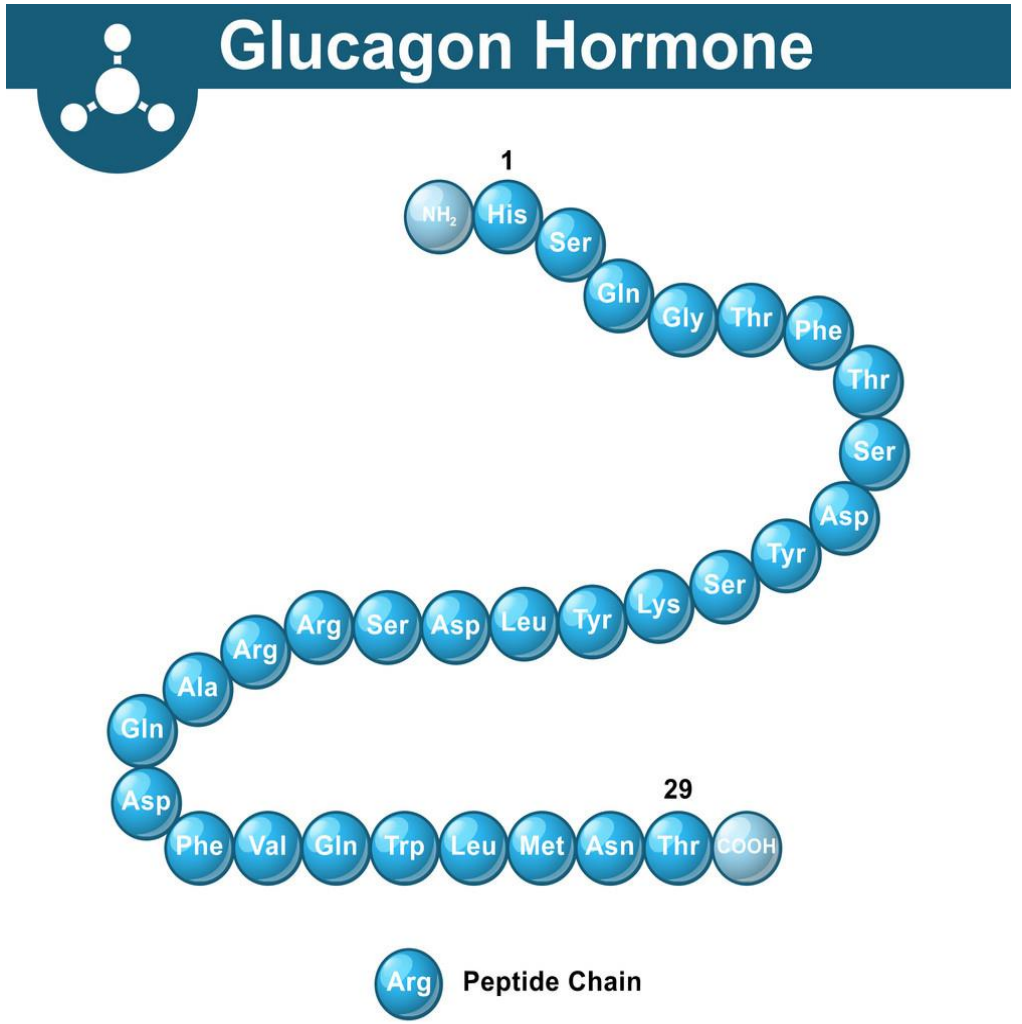
Clinical Note

- Insulin activate Na-K pump → ↓ Extracellular K^+ level , So it can be used for the treatment of Hyperkalaemia.

Why and when Give KCl to a diabetic patient??

Glucagon

- Glucagon is a polypeptide of 29 amino acid residues, synthesized from a precursor called proglucagon.
- glucagon is formed exclusively by the alpha cells of the pancreatic islets. In addition, glucagon-like peptides, including glycentin, are synthesized and secreted by the small intestinal cells.

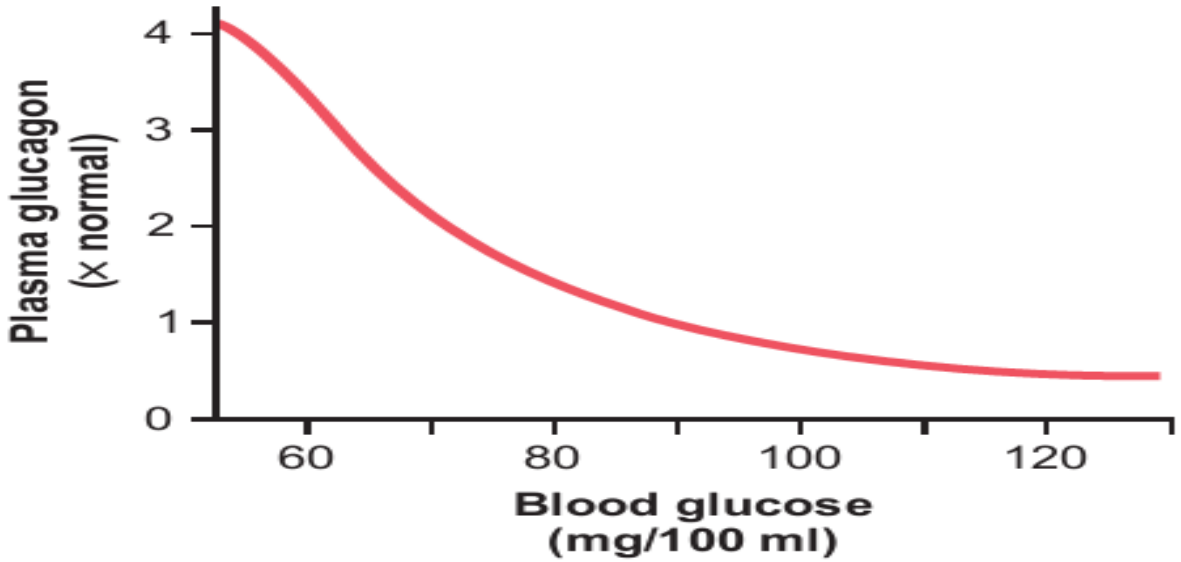


Increase glucagon Secretion

- Hypoglycemia
- Exercise of sufficient intensity and duration.
- Vagal stimulation
- Stress, including infection, toxemia, burns and major surgery.
- Growth hormone.

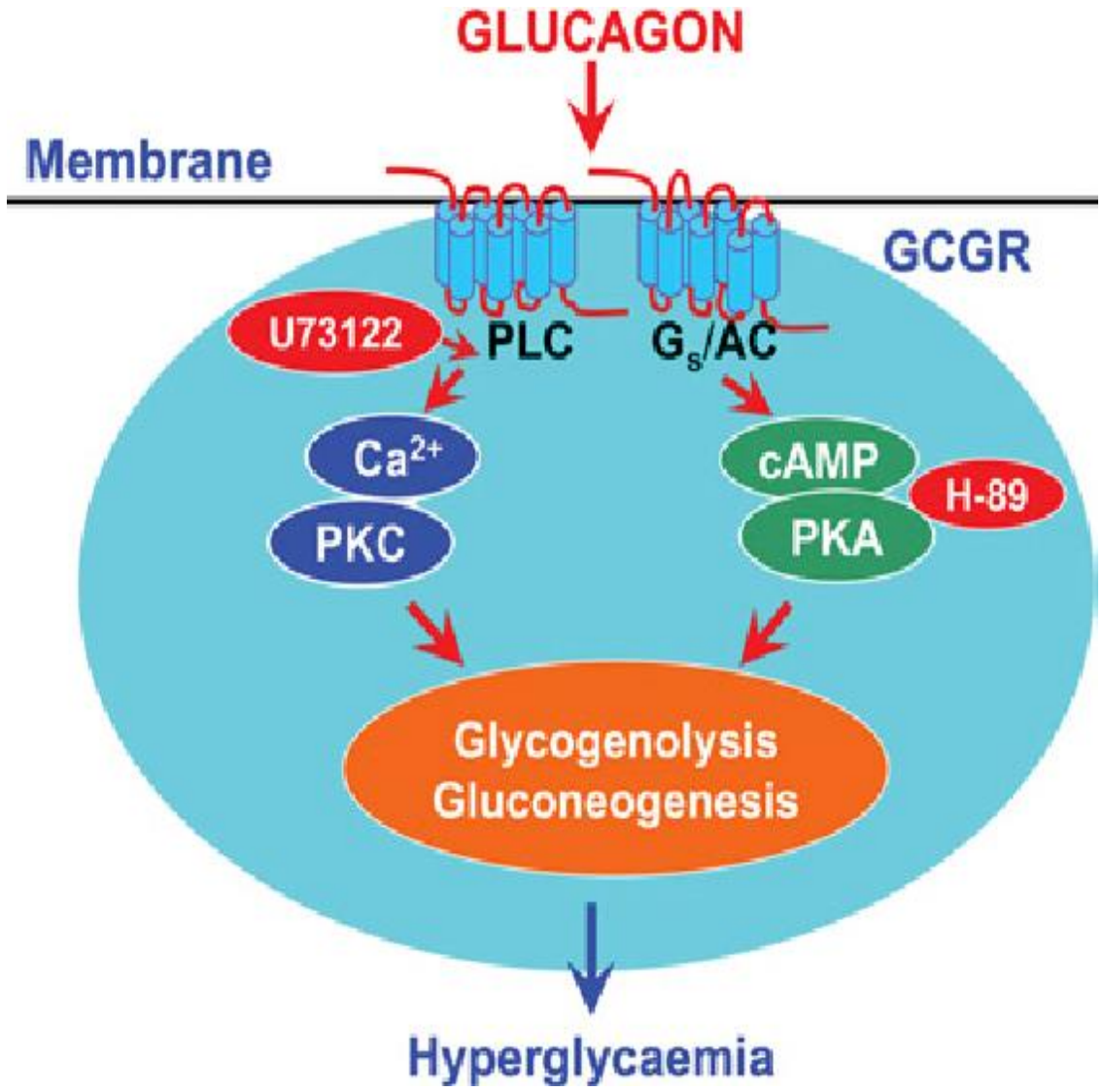
Decrease glucagon Secretion

- Hyperglycemia
- ↑plasma free fatty acids.
- Somatostatin



Mechanism of Glucagon Action

- Glucagon binds to specific plasma membrane receptors (GPCR).
- The glucagon-receptor complex causes a rapid increase in intracellular cAMP, with consequent stimulation of specific enzymatic cascade.



Function of Glucagon

1. It increases blood glucose level (↑hepatic glucose output) by:

a). It exerts **powerful glycogenolytic effect** through activation of glycogen phosphorylase and inhibition of glycogen synthetase.

b)It **stimulates gluconeogenesis** by Increasing hepatic uptake of amino acids.

N.B. Glucagon has little or no influence on glucose utilization by peripheral tissues.

Function of Glucagon

2. Glucagon activates adipose tissue lipase

thereby increasing lipolysis, the delivery of free fatty acids from adipose tissue to the liver and ketogenesis.

3. It decreases hepatic cholesterol synthesis.

4. Natriuresis, by inhibition of renal tubular Na reabsorption.

5. Activation of myocardial adenyl cyclase, causing a moderate increase of cardiac output.

6. May act as a **local CNS hormone** for the regulation of **appetite**.

Somatostatin

Source:

1-Delta cells of islets of Langerhans of pancreas (10% of islet mass)

2-GIT

3-Hypothalamus

Nature: Polypeptide

Functions:

a-Effects on pancreas: inhibit secretion of insulin, glucagon & Panc polypeptide.

b-Effects on the GIT:

1-It **inhibits** the secretion of GIT hormones as gastrin, secretin, VIP, CCK

2-It **inhibits** the motility of the stomach, duodenum, &gall bladder

3-It **inhibits** both secretion & absorption in the GIT

c-Effects on the anterior pituitary: inhibits secretion of GH & TSH

Pancreatic polypeptide

Source:

F cells of islets of Langerhans of pancreas (5% of islet mass)

Functions:

1-Inhibits insulin & somatostatin secretion by direct pancreatic effect

2-Slows the absorption of food in humans

Diabetes mellitus

Feature	Type 1 Diabetes	Type 2 Diabetes
Incidence	8% of diabetes diagnoses	>90% of diabetes diagnoses
Pathology	Insulin deficiency due to autoimmune destruction of beta cells	Cells become resistant to insulin; Inadequate insulin secretion by the pancreas
Risk Factors	Family history, other autoimmune diseases (celiac, hypothyroidism, etc.)	Family history, high BMI, low physical activity, ethnicity - South Asian, African, Caribbean
Onset	Sudden onset in younger patients	Gradual onset in older patients
Symptoms	Polyuria, polydipsia, polyphagia, fatigue, unexpected weight loss, blurred vision	Polyuria, polydipsia, polyphagia, fatigue, unexpected weight loss, blurred vision
Treatment	Insulin	Lifestyle changes, oral hypoglycemics, insulin
Ketoacidosis	Common complication	Rare Complication
Endogenous Insulin	Absent or very low	Low, normal, or high
Prevention	Cannot be prevented	Can be prevented through lifestyle changes
Reversibility	Cannot be reversed	Can be reversed with early diagnosis and lifestyle changes

Diabetes mellitus

Manifestations:

1) **Hyperglycemia**: due to decreased glucose uptake by tissues, & increased hepatic glycogenolysis & gluconeogenesis

2)**Glucosuria**: occur when the plasma glucose concentration exceeds the renal threshold (180mg %)

3)**Polyuria** due to:

a-Glucosuria → omotic diuresis

b-↑ osmotic pressure of blood → drag water out of cells towards the blood→ dehydration of tissue cells

Diabetes mellitus

Manifestations:

4) **Polydipsia**: Excessive drinking of water due to intense thirst resulting from dehydration

5) **Acidosis**: Due to inhibition of carbohydrate metabolism → body depends on fat metabolism to supply energy needs→ accumulation of ketone bodies

6) **Loss of weight & asthenia**: Due to mobilization of fat & proteins for the supply of energy

7)**↑ cholesterol, triglycerides, FFA & lipoproteins**→ atherosclerosis

Any Questions

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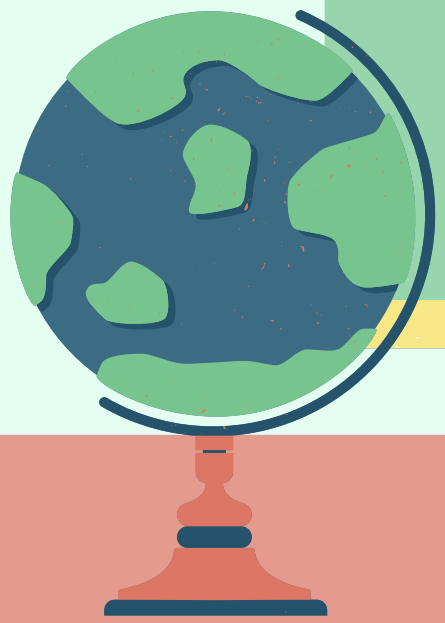


Thank
You