Hormones

University Of Fallujah
College Of Medicine

Lecture : (6)

Stage : 2th Stage

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Department: Chemistry and Biochemistry

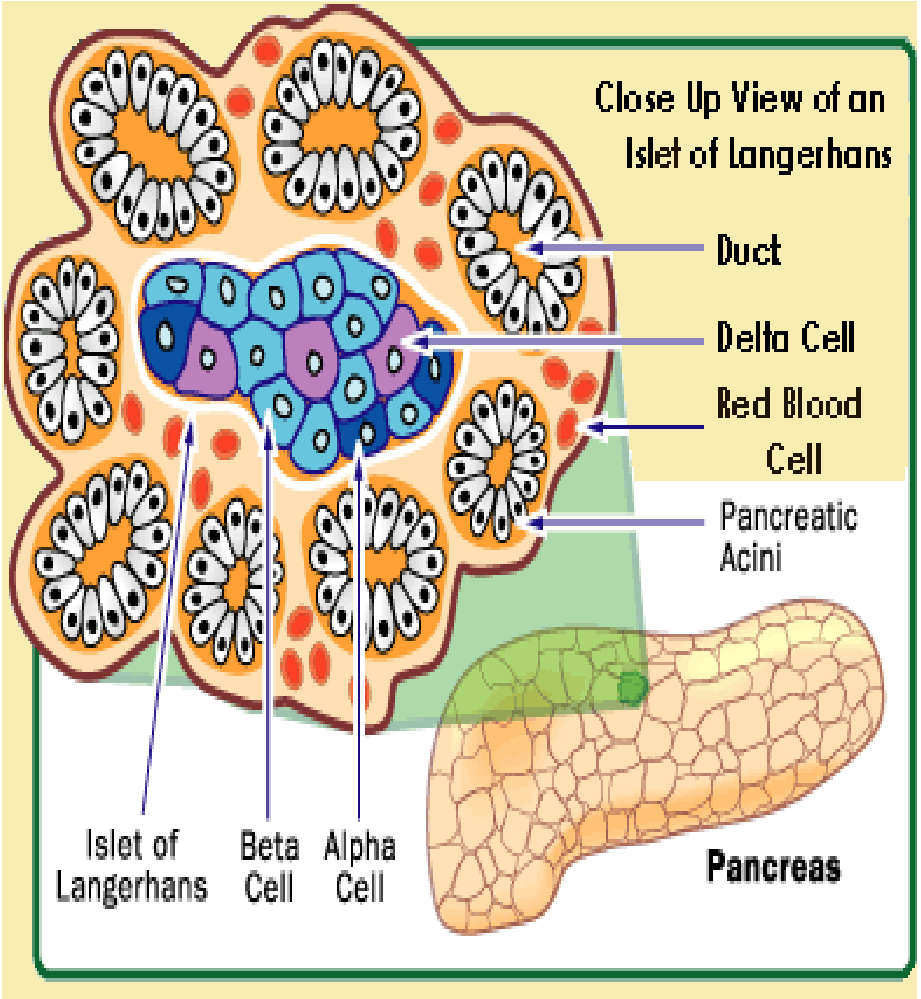
Biochemistry and Disorders of Hormones of the Pancreas

Objectives

- List the hormones synthesized and secreted from the pancreas and state their functions and clinical significance
- Understand the mechanism of synthesis and release of insulin and glucagon
- Understand the mechanism of interaction of insulin with its receptor which is the platform for developing medications for type 1 and type 2 DM
- Understand the mechanism of interaction of glucagon with its receptor
- Define insulinoma and the laboratory results obtained in the assessment of the disease

- The bulk of the pancreas is an exocrine gland secreting jubpancreatic fluid into the duodenum after a meal.

- However, scattered through the pancreas are several hundred thousand clusters of cells called **islets of Langerhans**. The islets are endocrine tissue containing four types of cells



In order of abundance they are the :

1. Beta cell, which secrete (insulin , Amylin and preptin) .
2. **alpha** cells, which secrete **glucagon**.
3. **delta** cells, which secrete. **somatostatin**, and
4. **gamma** cells, which secrete pancreatic polypeptide (PP).

Alpha Cells

- The alpha cells of the islets secrete **glucagon**, a polypeptide of 29 amino acids.
- Glucagon acts principally on the **liver** where it stimulates the conversion of
  - ✓ glycogen into glucose ("glycogenolysis")
  - ✓ fat and protein into intermediate metabolites that are ultimately converted into glucose ("gluconeogenesis).
  - ➢ In both cases, the glucose is deposited in the blood. Glucagon secretion is
    - ✓ stimulated by low levels of glucose in the blood;
    - ✓ inhibited by high levels of glucose in the blood, and
    - ✓ inhibited by amylin.

❑Beta Cells

- **Insulin** is a small protein consisting of
  - ✓an alpha chain of 21 amino acids linked by two disulfide (S—S) bridges to a
  - ✓beta chain of 30 amino acids.
- Beta cells have channels in their plasma membrane that serve as glucose detectors.
- Beta cells secrete insulin in response to a rising level of circulating glucose **("blood sugar").**

Insulin affects many organs.

1. **It stimulates skeletal muscle fibers to**
   - ✓take up glucose and convert it into glycogen;
   - ✓Take up amino acids from the blood and convert them into protein.
2. **acts on liver cells.**

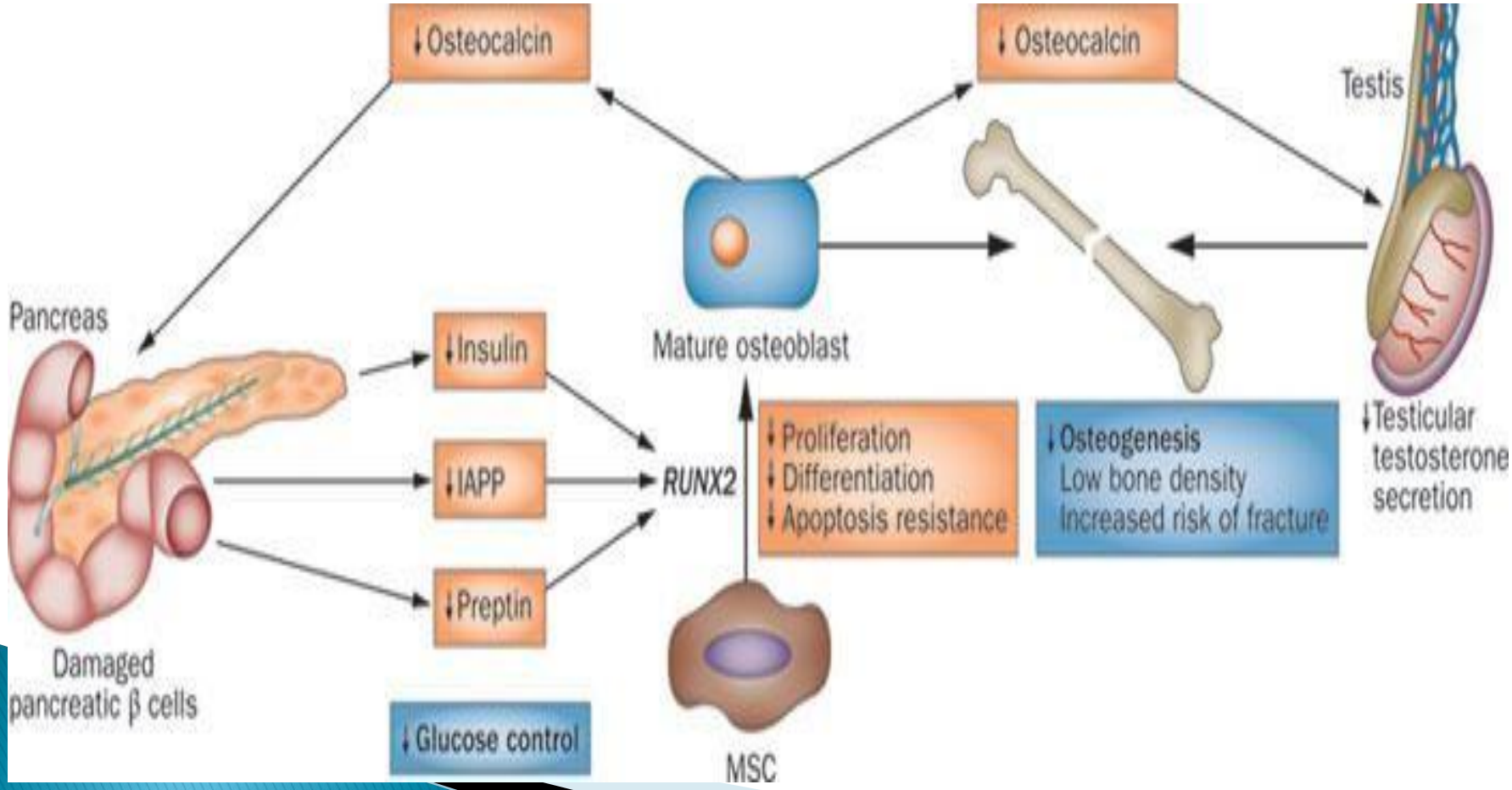
- ✓ stimulating them to take up glucose from the blood and convert it into glycogen
  - ✓inhibiting production of the enzymes involved in breaking glycogen back down ("glycogenolysis") and
  - ✓inhibiting "gluconeogenesis"; that is, the conversion of fats and proteins into glucose.

3. acts on fat (adipose) cells to stimulate the uptake of glucose and the synthesis of fat.
4. acts on cells in the hypothalamus to reduce appetite.

❑Amylin

- Amylin is a peptide of 37 amino acids, which is also secreted by the beta cells of the pancreas.
- Some of its actions:
  - ✓inhibits the secretion of glucagon;
  - ✓slows the emptying of the stomach;
  - ✓sends a satiety signal to the brain.
- Amylin, also known as Islet Amyloid Polypeptide (IAPP), was independently identified by two research groups in 1987 as the principal component of islet amyloid deposits associated with diabetes.

- **Preptin** is a peptide of 34 amino acids co-secreted with insulin and amylin. Some of its actions:
  - Stimulates proliferation of primary fetal osteoblast
  - Reduces osteoblsat apoptosis



Delta Cells

- The delta cells secrete **somatostatin**. This consists of two polypeptides, one of 14 amino acids and one of 28.
- Somatostatin has a variety of functions. Taken together, they work to reduce the rate at which food is absorbed from the contents of the intestine.

Gamma Cells

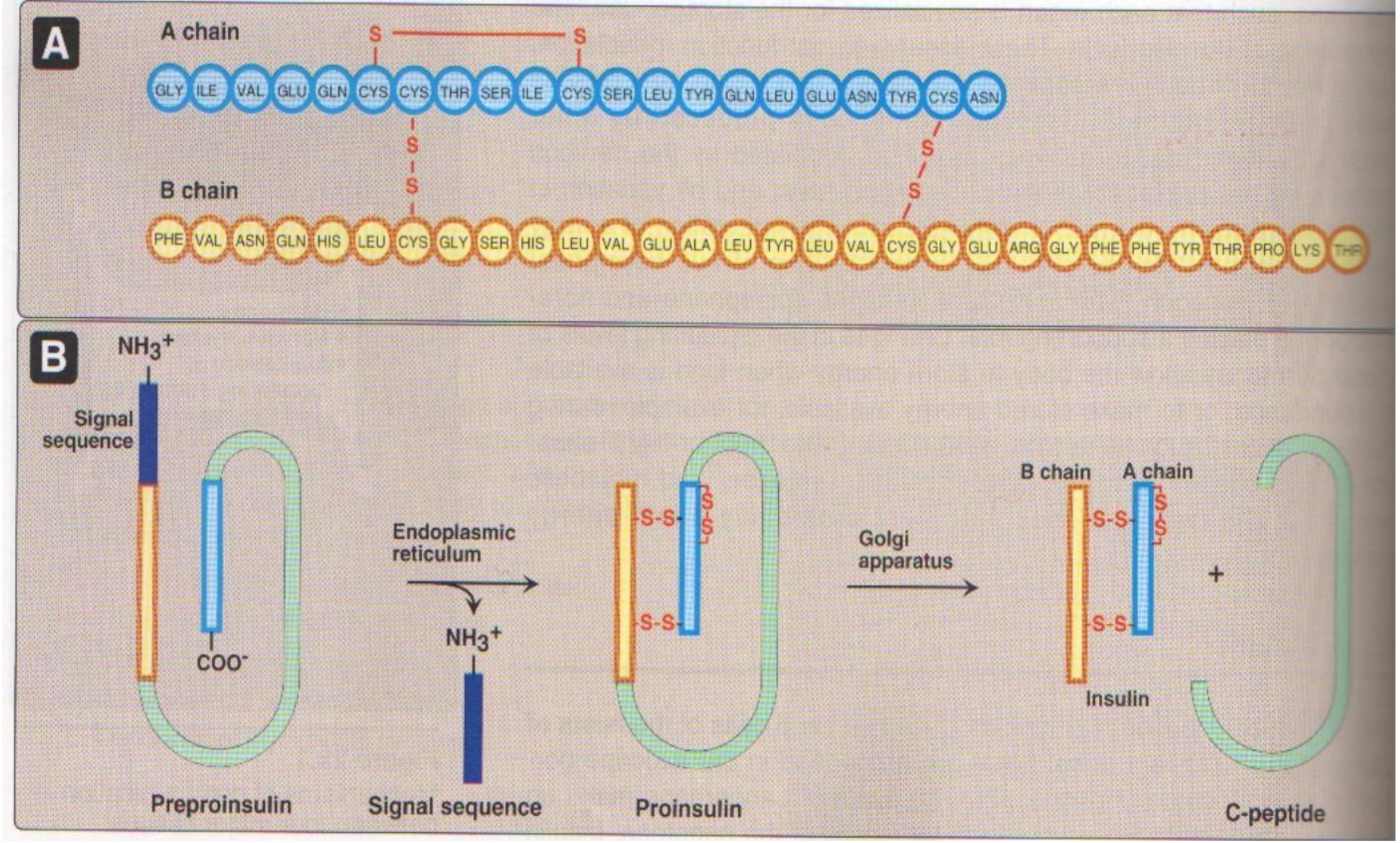
- The gamma cells of the islets secrete a 36-amino-acid **pancreatic polypeptide**.
- Its function is to self regulate the pancreas secretion activities.
- It also has effects on hepatic glycogen levels and gastrointestinal secretions.
- Its secretion human is increased after a protein meal, fasting, exercise and acute hypoglycemia and is decreased by somatostatin.,.

Synthesis and release of insulin and glucagon

- Insulin and glucagon are synthesized in different cell types of the endocrine pancreas, which consists of microscopic clusters of small glands (the islets of Langerhans) .
- The α cells secrete glucagon, and the β cells secrete insulin into the hepatic portal vein via the pancreatic veins.

Synthesis and secretion of Insulin

- Insulin is a polypeptide hormone. The active form of insulin is composed of two polypeptide chains (the A-chain and the B-chain) linked by two inter chain disulfide bonds. The A-chain has an additional intra chain disulfide bond



Insulin Structure and Its Biosynthetic Pathway

- **Zinc ions** are transported into the storage vesicles as well. After C-peptide is cleaved, the solubility of insulin decreases, allowing the hormone to coprecipitate with zinc.

- Exocytosis of the insulin storage vesicles from the cytosol of the β cell into the blood is stimulated by rising levels of glucose in the blood bathing the β cells.

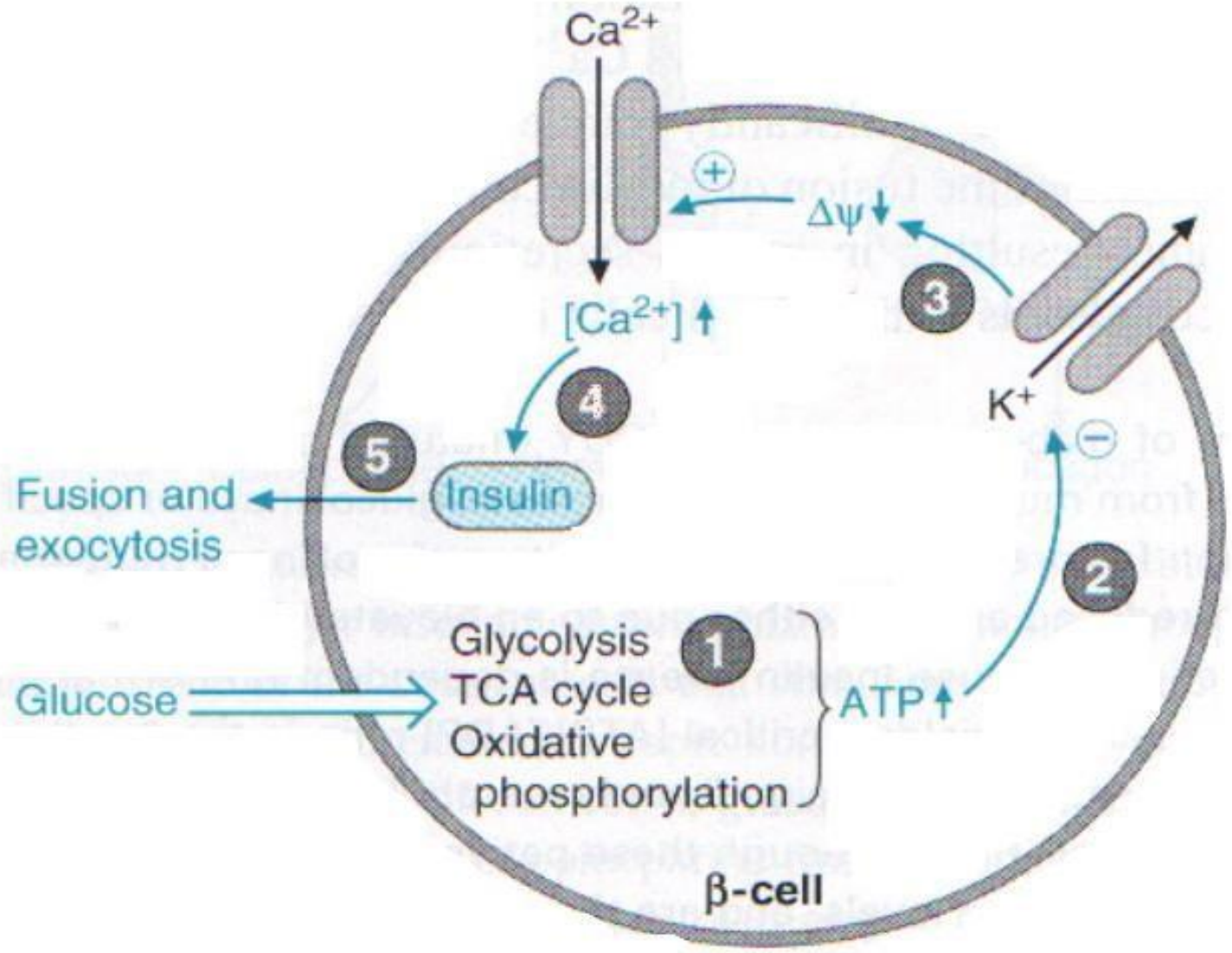
- Glucose enters the β cell via specific glucose transporter proteins known as **GLUT2**.

- Glucose is phosphorylated through the action of glucokinase to form glucose 6- phosphate, which is metabolized through glycolysis, the TCA cycle, and oxidative phosphorylation.

- These reactions result in an increase in ATP levels within the β cell. As the β cell [ATP|/ [ADP] ratio increases, the activity of a membrane-bound, ATP- dependent K^+ channel is inhibited (i.e.,the channel is closed).

- The closing of this channel leads to a membrane depolarization, which activates a voltage-gated Ca^{2+} channel that allows Ca^{+} to enter the β cell such that intracellular Ca^{2+} levels increase significantly.

- The increase in intra-cellular Ca^{2+} stimulates the fusion of insulin containing exocytotic vesicles with the plasma membrane, resulting in insulin secretion. Thus, an increase in glucose levels within the β cells initiates insulin release.



Release of insulin by the β-cells.

Stimulation and inhibition of insulin release

- The release of insulin occurs within minutes after the pancreas is exposed to a high glucose concentration.
- The threshold for insulin release is approximately 80 mg/glucose /dL. Above 80 mg/dL, the rate of insulin release is not an all-or-nothing -response but is proportional to the glucose concentration up to approximately 300 mg/dL glucose.

- As insulin is secreted, the synthesis of new insulin molecules is stimulated, so that secretion is maintained until blood glucose level fall.

- Insulin is rapidly removed from the circulation and degraded by the liver and to a lesser extent by kidney and skeletal muscle) so that blood insulin levels decrease rapidly

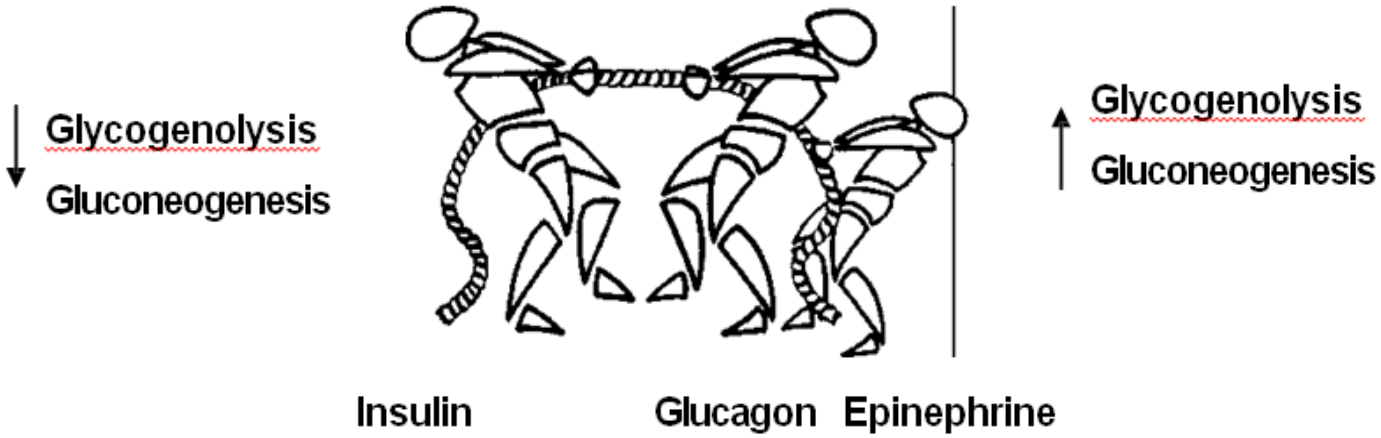
- **A number of factors other than the blood glucose concentration can modulate insulin such as:**

A. Neural signals
B. Certain amino acids
C. Gastric inhibitory polypeptide (GIP, a gut hormone released after the ingestion of food)
D. Epinephrine secreted in response to fasting, stress, trauma and vigorous exercise decrease the release of insulin

❑Synthesis and secretion of Glucagon

- Glucagon a polypeptide hormone, is synthesized in the α cells of the pancreas by cleavage of the much larger preproglucagon, a 160-amino acid peptide.
- Like insulin preproglucagon is produced on the rough endoplasmic reticulum and is converted to proglucagon as it enters the ER lumen.
- Proteolytic cleavage at various sites produce the mature 29-amino acid glucagon and larger glucagon-containing fragments (named glucagon-like peptides I and 2).

- Glucagon is rapidly metabolized, primarily in the liver and kidneys. Its plasma half-life is only about 3 to 5 minutes.



- **Glucagon secretion is regulated principally by circulating levels of glucose and insulin. Increasing levels of each inhibit glucagon release**

- The suppression of glucagon secretion from α cells by glucose is likely mediated by both direct actions on the α cell and indirect paracrine effects, the latter of which are facilitated by insulin release.
- **Certain hormones stimulate glucagon secretion. :**

1. **catecholamines (epinephrine)**
2. **cortisol**
3. **gut hormones**
4. **Many amino acids also stimulate glucagon release.**

Metabolic effects of glucagon

Effects on carbohydrate metabolism:

The intravenous administration of glucagon leads to an immediate rise in blood glucose.

Effects on lipid metabolism:

Glucagon favors hepatic oxidation OF fatty acids and the subsequent formation of ketone bodies acetyl CoA.

Effects on protein metabolism:

Glucagon increases uptake of amino acids by the liver, resulting in increased availability of carbon skeletons for gluconeogenesis.

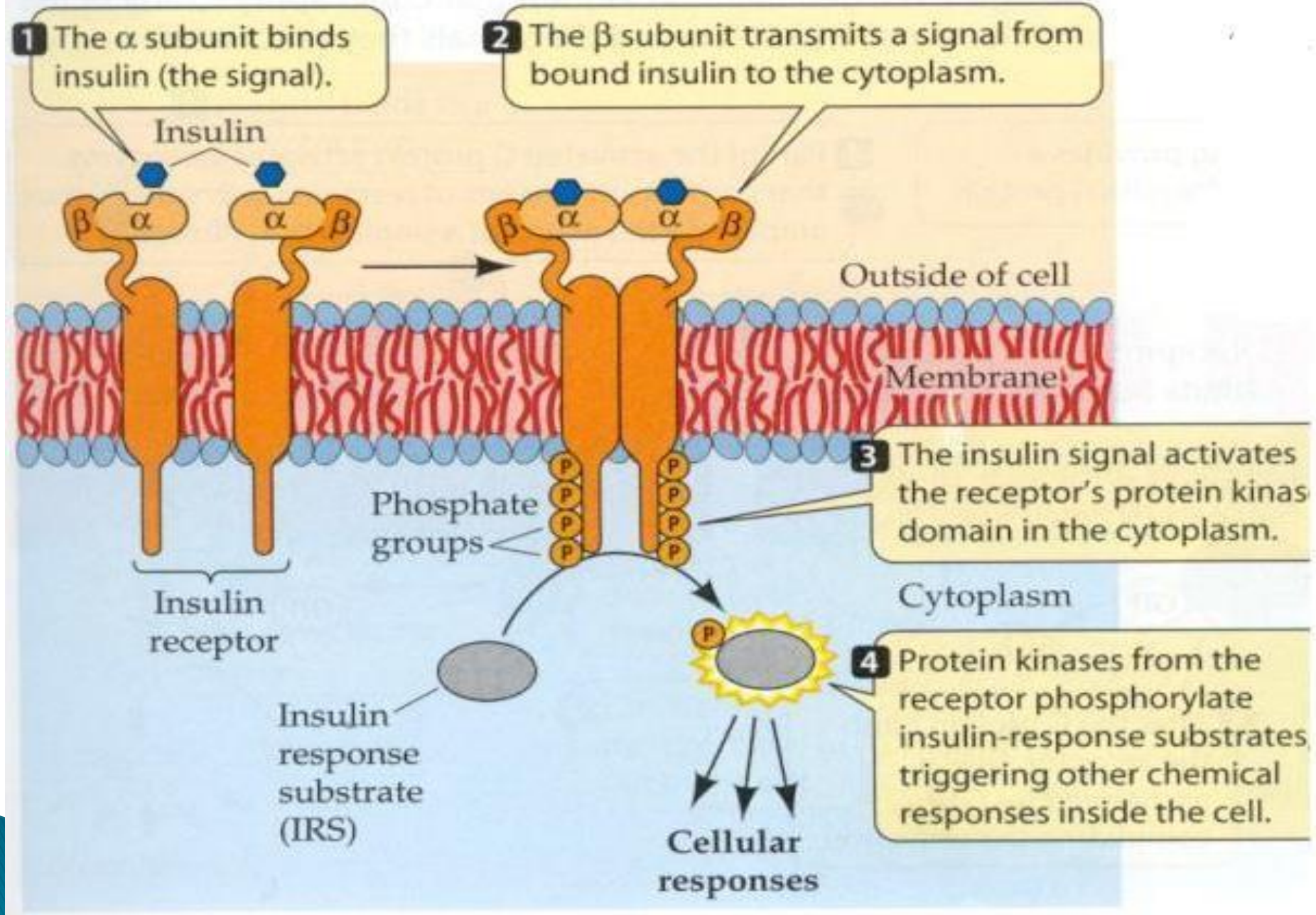
Insulin and Glucagon receptors

1. **Insulin Receptor**

- Insulin Binding to it's Receptor Followed by Activation of the Receptor:

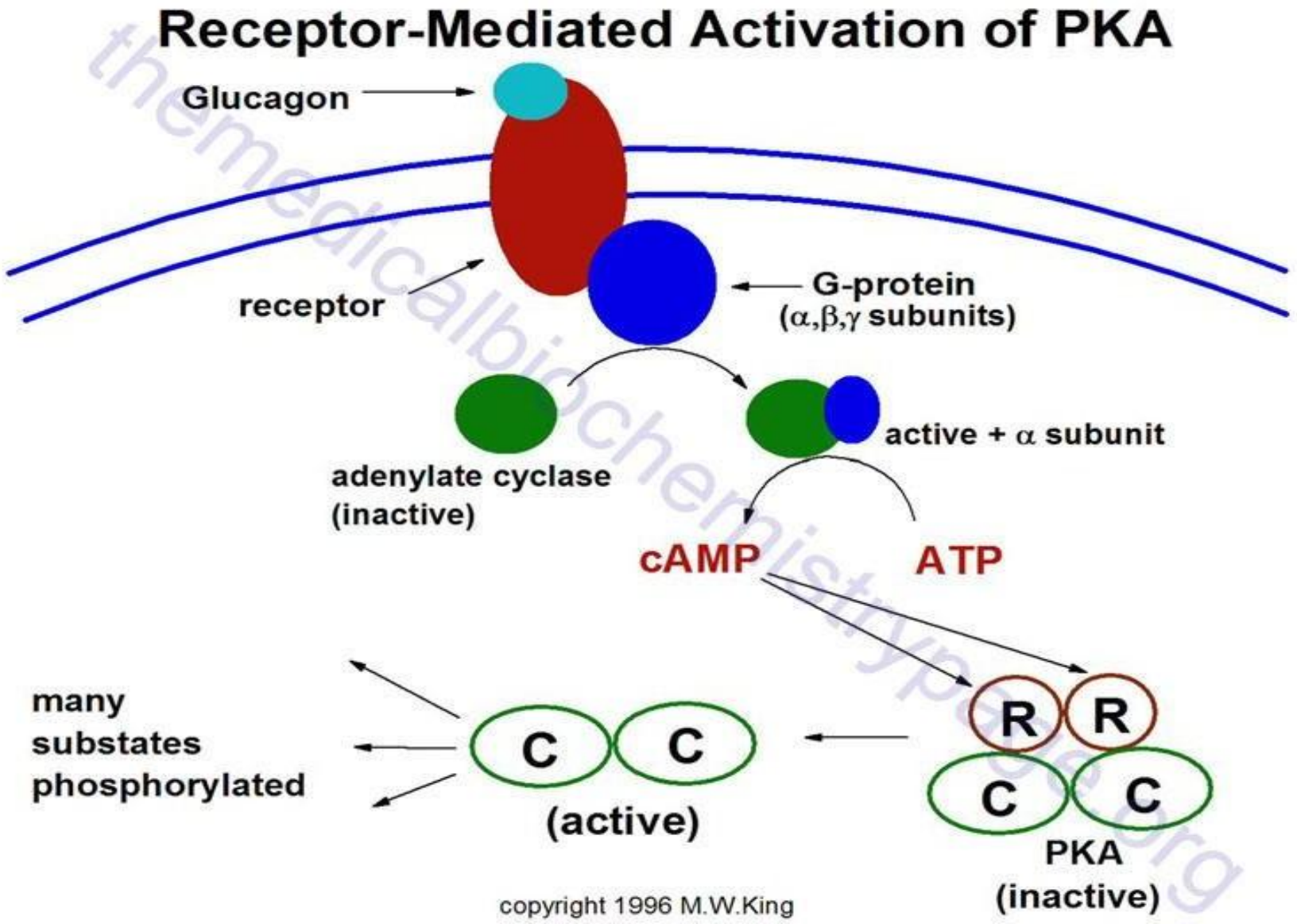
1. Insulin binds switching ON the receptor. Once the receptor is ON (catalytically active) insulin may disaccociate and be degraded.

2. The Tyr Kinase domain is phosphorylated.
3. A "cascade" of events takes place (see below).
4. Biochemical / Physiological Responses:


1 The α subunit binds insulin (the signal).
2 The β subunit transmits a signal from bound insulin to the cytoplasm.
Insulin
β α α β
Outside of cell
Membrane
3 The insulin signal activates the receptor's protein kinas domain in the cytoplasm.
Phosphate groups
P
Insulin receptor
Cytoplasm
4 Protein kinases from the receptor phosphorylate insulin-response substrates triggering other chemical responses inside the cell.
Insulin response substrate (IRS)
Cellular responses

- **The importance of this finding is that:**
- insulin is a key therapy for type 1 and type 2dm diabetes mellitus and pharmaceutical industries are interested in making insulin that have varying properties so that:
  - ✓people might not have to **inject** insulin quite often or
  - ✓might **ingest** insulin in different ways or
  - ✓might be **interested** in making insulin that can be stored in normal temps.

2. Glucagon Receptor



Insulinoma

- The insulinoma was producing insulin. Because of the excessive amount of insulin- secreting tissue, too much insulin was released after dietary carbohydrate intake.
- This caused hypoglycemia during the 5-hr glucose tolerance test and after meals, producing the spells of weakness and dizziness.

- In addition, to this normal insulin release when carbohydrate was ingested, the tumor also was secreting some insulin continuously. This inappropriate insulin release caused the low blood glucose concentration during prolonged fasting.

- Note :
- The initial precursor, preproinsulin, is produced on ribosomes and enters the lumen of the endoplasmic reticulum, where its signal (leader) peptide is removed, forming proinsulin.
- Proinsulin is then transported to the Golgi apparatus, packaged into secretory granules, and stored.
- Inside these granules, proinsulin undergoes proteolytic cleavage to form insulin; however, this conversion is not completely efficient, so some proinsulin remains.
- During insulin secretion, both insulin and the residual proinsulin are released from the β-cell.
- C-peptide, which is cleaved from proinsulin during its conversion to insulin, is also released but has no insulin-like biological activity.

The End