Hypoglycemic agents

Diabetes Mellitus

- Also known as Diabetes, diabetes mellitus is a group of metabolic diseases characterized by chronically high blood sugar levels.
- In this condition, the body cannot effectively regulate blood sugar levels.

Symptoms

- Excessive urination
- Glucose present in urine
- Increased thirst
- Increased appetite
- Feeling weak and tired

Causes

- Defects in insulin formation, secretion, or action
- Obesity and inactive lifestyle
- Family history and genetic factors
- High carbohydrate (glucose) diet
- Heart and blood vessel diseases

Types of Diabetes Mellitus



A. Type I Diabetes Mellitus

- Known as insulin-dependent diabetes mellitus.
- Pancreatic beta-cells are destroyed, leading to little or no insulin production.
- It is a chronic condition typically found in children.
- Insulin injections are required as treatment.

B. Type II Diabetes Mellitus

- Known as non-insulin dependent diabetes mellitus.
- A chronic condition in which the body's cells in the liver, muscle, and fat become resistant to insulin.
- Glucose uptake by the cells is reduced.

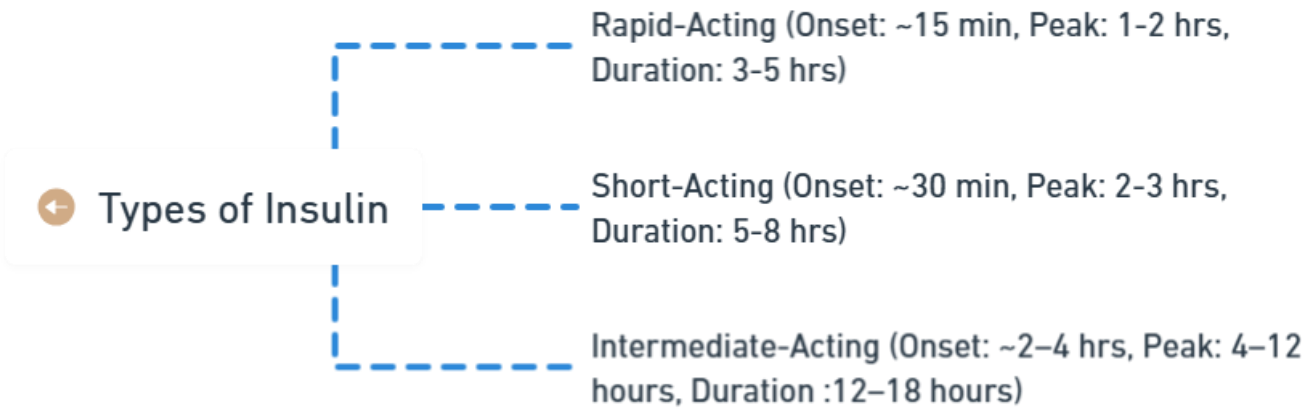
- Oral hypoglycemic agents are used as treatment.

Insulin

Introduction:

- Insulin is a peptide hormone produced by beta cells in the pancreas.
- It regulates blood glucose levels by facilitating glucose uptake into cells (liver, fat, and muscle tissues) and aids in the metabolism of carbohydrates, fats, and proteins.
- In diabetes, impaired insulin production or function necessitates external administration.

Types of Insulin



1. **Rapid-Acting** (Onset: ~15 min, Peak: 1-2 hrs, Duration: 3-5 hrs)
    - **Examples**: Lispro, Aspart, Glulisine
    - **Uses**: Mealtime glucose control.
2. **Short-Acting** (Onset: ~30 min, Peak: 2-3 hrs, Duration: 5-8 hrs)
    - **Examples**: Regular Insulin (Humulin R, Novolin R)
    - **Uses**: Pre-meal and basal needs.
3. **Intermediate-Acting** (Onset: ~2-4 hrs, Peak: 4-12 hrs, Duration: 12-18 hrs)
    - **Examples**: NPH Insulin (Humulin N, Novolin N)
    - **Uses**: Basal coverage.
4. **Long-Acting** (Onset: ~1-2 hrs, Peak: Minimal, Duration: ~24 hrs)
    - **Examples**: Glargine, Detemir, Degludec
    - **Uses**: Basal insulin, once/twice daily.
5. **Ultra-Long-Acting** (Onset: ~30-90 min, Peak: None, Duration: >24 hrs)
    - **Examples**: Degludec
    - **Uses**: Extended basal needs.

Mechanism of Action

Insulin lowers blood glucose by:

- **Facilitating Glucose Uptake:** Promotes entry of glucose into muscle and fat cells.
- **Inhibiting Gluconeogenesis:** Reduces glucose production in the liver.
- **Promoting Glycogen Synthesis:** Enhances storage of glucose as glycogen in the liver and muscles.
- **Stimulating Lipogenesis:** Encourages fat storage and inhibits lipolysis.

Uses

- **Type I Diabetes Mellitus:** Essential for survival due to absolute insulin deficiency.
- **Type II Diabetes Mellitus:** Used when oral antidiabetics are insufficient to control blood glucose levels.
- **Gestational Diabetes:** Manages elevated blood sugar levels during pregnancy.
- **Hyperkalemia:** Insulin shifts potassium into cells, lowering blood potassium levels.

Side Effects

- **Hypoglycemia:** Low blood sugar levels, presenting as dizziness, sweating, confusion, and in severe cases, loss of consciousness.
- **Weight Gain:** Increased fat storage due to insulin's anabolic effects.
- **Injection Site Reactions:** Redness, swelling, or itching at the injection site.
- **Allergic Reactions:** Rare but may include rash or anaphylaxis.
- **Lipodystrophy:** Changes in fat tissue at injection sites from repeated use.

Preparation of Insulin

1. Formation of Preproinsulin:

➢ Insulin synthesis begins with **preproinsulin** (110 amino acids), synthesized in the rough endoplasmic reticulum.

2. Conversion to Proinsulin:

➢ Preproinsulin is processed in the Golgi apparatus to form **proinsulin**, an inactive precursor.

3. Folding and Bond Formation:

➢ Proinsulin folds to form three **disulfide bonds**, linking the **A-chain** and **B-chain**.

4. Packaging into Vesicles:

➢ Folded proinsulin is packaged into secretory vesicles for further processing.

5. Cleavage by Enzymes:

- Enzymes (**Proprotein Convertase 1/3** and **Proprotein Convertase 2**) cleave the **C-peptide** from proinsulin.

6. Final Processing:

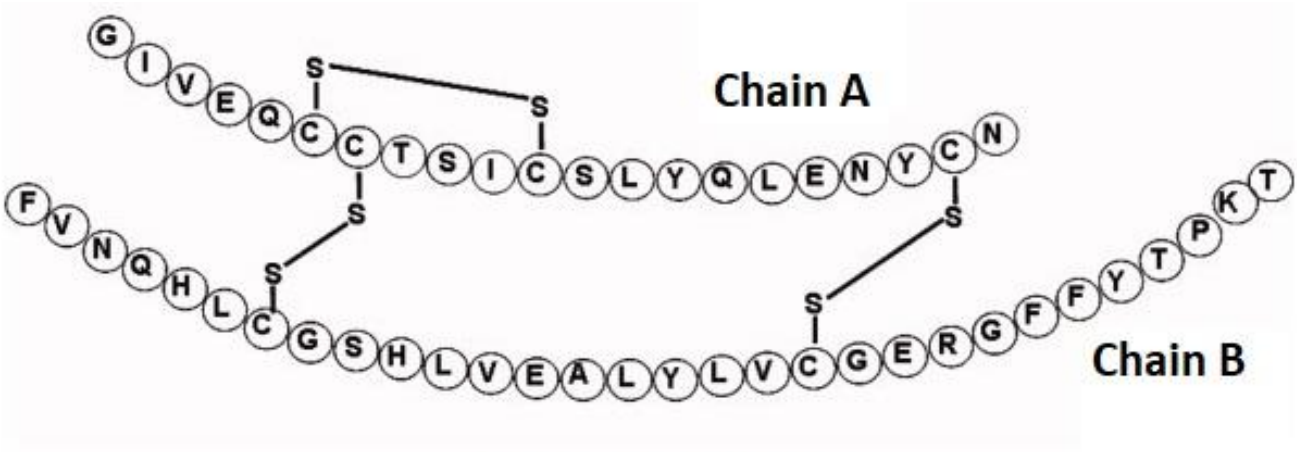
- **Carboxypeptidase E** removes terminal amino acids, yielding **active insulin**.

7. Active Insulin:

- Active insulin consists of:
  - **Chain A**: 21 amino acids.
  - **Chain B**: 30 amino acids.
- Chains are connected by two disulfide bonds.

8. Secretion:

- Active insulin is secreted into the bloodstream to regulate blood sugar and metabolic processes.



Structure of Insulin

Antidiabetic agents

- Antidiabetic agents are medications used to manage blood glucose levels in individuals with diabetes mellitus.
- These agents work through various mechanisms to enhance insulin action, increase insulin secretion, reduce hepatic glucose production, or decrease glucose absorption from the gastrointestinal tract.
- Proper classification of antidiabetic agents is essential for selecting appropriate therapy based on the patient's specific needs, type of diabetes, and potential side effects.

Classification of antidiabetic agents



A. Sulfonylureas

- **Mechanism:** Stimulate insulin secretion from pancreatic β-cells by closing ATP-sensitive potassium channels, leading to cell depolarization and calcium influx.
  - **Tolbutamide**
  - **Chlorpropamide**
  - **Glipizide**
  - **Glimepiride**

B. Biguanides

- **Mechanism:** Decrease hepatic glucose production (gluconeogenesis) and increase insulin sensitivity, particularly in muscle tissues.
  - **Metformin**

C. Thiazolidinediones (TZDs)

- **Mechanism:** Activate peroxisome proliferator-activated receptor-gamma (PPAR-γ), enhancing insulin sensitivity in adipose tissue, muscle, and the liver.
  - **Pioglitazone**
  - **Rosiglitazone**
  - **Repaglinide**
  - **Nateglinide**

D. α-Glucosidase Inhibitors

- **Mechanism:** Delay the absorption of carbohydrates from the small intestine by inhibiting α-glucosidase enzymes, thereby reducing postprandial blood glucose spikes.
  - **Acarbose**
  - **Voglibose**

Summary of Proper Classification

Class	Agents

First Hope

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