Endocrine

PHARMACOLOGY

Title: Sheet 5 – Diabetes Mellitus

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Insulin & Oral Antidiabetic Drugs

Diabetes mellitus

- Definition: a syndrome of **disordered metabolism** due to a combination of **hereditary or environmental causes**.
- Classification: **Type 1: Lack of insulin**. **Type 2: Cells resistance to insulin**
- Signs and symptoms:
  - ✓ Feeling very **thirsty**
  - ✓ Feeling **tired**
  - ✓ **Using the toilet often to urinate**
  - ✓ **Constant hunger**
  - ✓ **High levels of glucose in urine & in fasting blood** **(The table is required)**

TABLE 67.1 Features of Type I and Type II Diabetes Mellitus

Characteristic	Type I	Type II
Onset (age)	Usually <30	Usually >40
Type of onset	Abrupt	Gradual
Nutritional status	Often thin	Often obese
Clinical symptoms	Polydipsia, polyuria, polyphagia	Often asymptomatic
Ketosis	Present	Usually absent
Endogenous insulin	Absent	Variable
Insulin therapy	Required	Sometimes
Oral hypoglycemics	Usually not effective	Often effective
Diet	Mandatory with insulin	Mandatory with or without drugs

- **Harms (complications)**
  - ✓ **Acute**: Diabetic ketoacidosis (DKA) & Nonketotic hyperosmolar coma
  - ✓ **Chronic:**
    - Microvascular disease→ such as impotence and poor wound healing
    - Atherosclerosis→ associated with strokes and coronary heart disease
    - Renal failure, retinal damage, nerve damage
    - Infective disease→ increases the risk of Tuberculosis due to the decrease in the body immune system function as a whole

- Diabetic ketoacidosis (DKA) is **a potentially life-threatening complication** in people with diabetes mellitus. It happens predominantly in those **with type 1 diabetes** but it can occur in those with type 2 diabetes under certain circumstances. DKA **results from a shortage of insulin**; in response the body switches to burning fatty acids and **producing acidic ketone bodies** that cause most of the symptoms and complications.

- Hyperosmolar hyperglycemic state (HHS) is a complication of diabetes mellitus (**predominantly type 2**) in which the **high blood sugar causes severe dehydration**, **increases in osmolarity** (relative concentration of solute) and a high risk of complications, coma and death.

❖ **Treatment**

- Type 1: **Insulin must be injected or inhaled**
- Type 2: **Food control, exercise and medicines** with different mechanisms**:**
  1. Agents which **increase insulin secretion**
  2. Agents which **increase the sensitivity of target organs to insulin**
  3. Agents which **decrease glucose absorption**
  4. Insulin is needed for patients with serious complications or an emergency

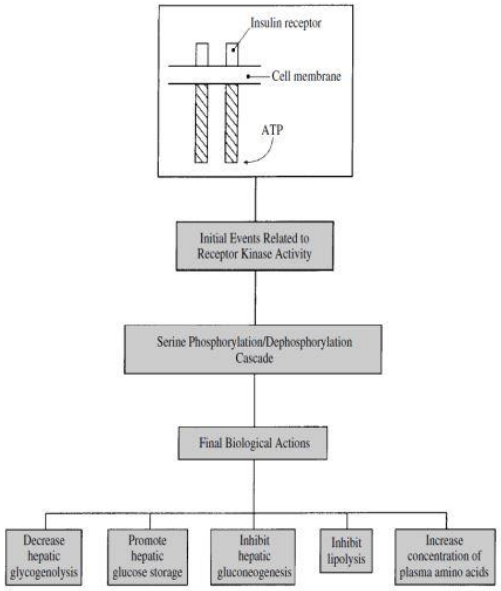
TABLE 67.2 Antidiabetic Drugs

Augment Insulin Supply	Enhance Insulin Action	Delay Carbohydrate Absorption
Sulfonylureas Meglitinides Insulins	Biguanides Thiazolidine-diones	α-Glucosidase inhibitors

(The table is required)

Insulin

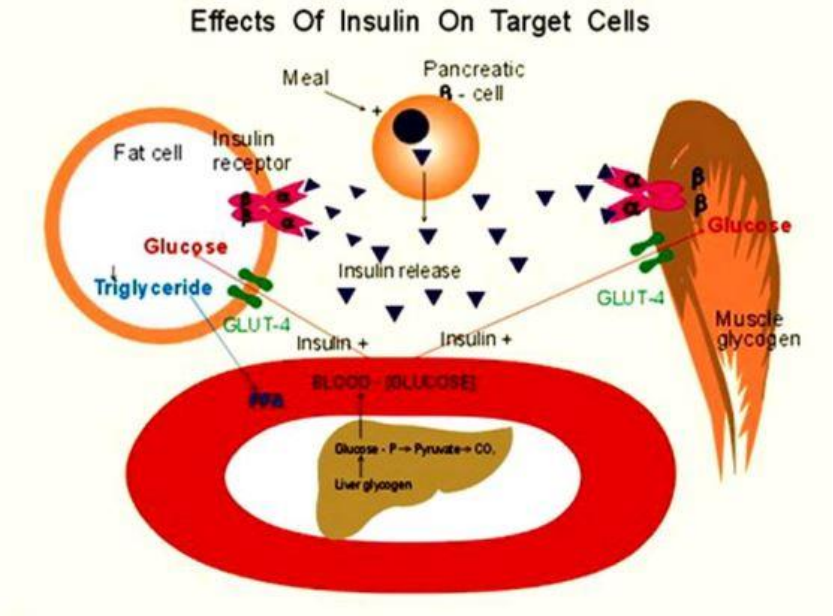
- Chemistry: 51 AA arranged in two chains (A & B) linked by disulfide bridges.
- Secretion: By β cells in pancreatic islet.
- Degradation: Liver & kidney
  - ✓ Endogenous: Liver (60%) & kidney (35%-40%)
  - ✓ Exogenous: Liver (35%-40%) & kidney (60%), and that is why patients who use insulin as a therapy for a long time have complications in the kidneys
- $T_{1/2}$ in plasma: 3-5 mins



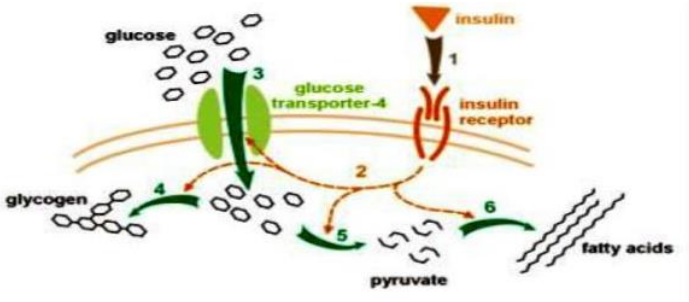
❖ **Biochemical and Pharmacological Actions of Insulin**

- In addition to its effects in stimulating glucose uptake by tissues, insulin has five major physiological effects on fuel homeostasis. It can:

1. Diminish hepatic glycogenolysis by inhibiting glycogen phosphorylase.
2. Promote hepatic glucose storage into glycogen by stimulating glycogen synthetase.
3. Inhibit hepatic gluconeogenesis (converting noncarbohydrate substrates like amino acids into glucose).
4. Inhibit lipolysis by inhibiting hormone-sensitive lipase activity, thereby decreasing the plasma free fatty acids and glycerol levels.
5. Promote the active transport of amino acids into cells for incorporation into proteins, thereby producing a net positive nitrogen balance.



- The insulin receptor is a heterotetrameric tyrosine kinase receptor composed of two α and two β subunits.
- Insulin binds to the α subunit on the extracellular surface of the cell and activates tyrosine kinase activity in the intracellular portion of the β subunit.
- The effect of insulin on glucose uptake and metabolism:
  1. Insulin binds to its receptor
  2. Which in turn starts many protein activation cascades
  3. These include: translocation of the GLUT4 transporter to the plasma membrane and influx of glucose
  4. Glycogen synthesis
  5. Glycolysis
  6. Fatty acid synthesis



❖ **Sources of exogenous insulin**

- Bovine & porcine insulin
- Human insulin: through the replacement of porcine insulin 30-alanine in the β chain by threonine
- Recombinant human insulin by *Escherichia coli*

❖ **Clinical use**

- Diabetes mellitus
  - ✓ The **only effective** drug for **type 1 diabetes**
  - ✓ The following situations of type 2 diabetes:
    1. Not effectively controlled by **food limitation and oral antidiabetic drugs**
    2. Nonketotic hyperosmolar **hyperglycemia coma**
    3. Accompanying a **serious infection**

- Others:
  - **Hyperkalemia**
  - A component of **GIK solution** (for limiting myocardial infarction and arrhythmias)
- Note: Context Glucose-insulin-potassium (GIK) infusion is a widely applicable, low-cost therapy that has been postulated to improve mortality in patients with acute myocardial infarction
- Note: the distribution of potassium between the intracellular and the extracellular fluid compartments is regulated by physiologic factors such as insulin and catecholamines which stimulate the activity of the Na+-K+ ATPase.

❖ **Adverse reactions**

- **Insulin allergy**: itching, redness, swelling, anaphylaxis shock
- **Insulin resistance** (especially in high dose)
- **Hypoglycemia**: nausea, hungry, tachycardia, sweating, and tremulousness. (First aid is needed when convulsions and coma happens)
- Lipodystrophy at injection sites: **atrophy** (we can change the place of injection)

❖ **Insulin Preparations**

- Commercially available insulins differ in their onset of action, maximal activity, and duration of action (rapid onset of action→ short duration of action).
- They can be classified as:
  - ✓ **Rapid acting** (0–5 hours) & **Short acting** (0–8 hours)
  - ✓ **Intermediate acting** "most common" (2 to 16 hours) & **long acting** (4 to 36 hours)

Oral Antidiabetic Drug Classification

I. Sulfonylureas

❖ **Representative Drugs**

- 1st generation: **Tolbutamide**, **Chlorpropamide** and **Tolazamide**
- 2nd generation: **Glybenclamide**, **Glyburide**, **Glipizide** and **Glymepride**
- 3rd generation: **Glyclazide**

❖ **Pharmacological effects**

1. **Hypoglycemic effect** (most important)
2. Antidiuretic effect (chlorpropamide & glybenclamide)
3. Antiplatelet-aggregation effect (**gliclazide**)

- Hypoglycemic mechanism

1. **Rapid** mechanism: stimulation of insulin secretion

The primary mechanism of action of the sulfonylureas is the direct stimulation of insulin release from the pancreatic β-cells.

- Sulfonylurea receptor in β-cell membrane is activated → ATP-sensitive K+-channel is inhibited → Cellular membrane is depolarized → Ca^{+2} entry via voltage-dependent Ca2+ channel → Insulin release

2. **Long** term profit involved mechanism
    - Inhibition of glucagon secretion by pancreas α cells
    - Ameliorating (improving) insulin resistance *[decreasing insulin resistance]*
    - Increasing insulin receptors number & the affinity to insulin

❖ **Clinical use**

- **Type 2 diabetes mellitus**
- **Diabetes insipidus**: chlorpropamide
- Note: Diabetes insipidus (DI) is a condition characterized by excessive thirst and excretion of large amounts of severely dilute urine, with reduction of fluid intake having no effect on the concentration of the urine.

❖ **Adverse reactions**

- Gastrointestinal disorders & Allergy
- Hypoglycemia (Chlorpropamide forbidden for ages and patients with functional disorder in liver or kidney).
- Hepatic injury

Ⅱ. Thiazolidinediones (Tzds)

- Thiazolidinediones (sometimes termed **glitazones**) are a novel class of drugs that were initially identified for their insulin-sensitizing properties.
- They all act to **decrease insulin resistance and enhance insulin action in target tissues so they increase the sensitivity of insulin.**

❖ **Representative Drugs**

Rosiglitazone, **Troglitazone**, **Pioglitazone** and **Ciglitazone**

❖ **Pharmacological effects**

- Improving the function of pancreas β cells
- Ameliorating insulin resistance
- Ameliorating fat metabolic disorder
- Preventing and treating type 2 diabetes mellitus and their cardiovascular complications

❖ **Mechanism (possible)**

- Activating peroxisome proliferator-activated receptor-γ**(PPAR-γ)** → Activates nuclear genes involved in glucose & lipid metabolism and adipocyte differentiation

❖ **Clinical use:** Insulin resistance & type 2 diabetes mellitus
❖ **Adverse reactions: Troglitazone** occasionally induces hepatic injury

Ⅲ. Biguanides

❖ **Representative Drugs**
- **Phenformin** and **Metformin**

❖ **Key points**
- **Insulin secretion and appetite are unchanged**
- Hypoglycemic mechanism remains unclear
- Used for obese diabetes and type 2 diabetes
- **Alone** or **co-administered with insulin or Sulfonylureas**
- **Metformin** is also used to treat **atherosclerosis** for down-regulation of LDL & VLDL
- **Lactic acidosis is a major adverse reaction**
- Note: Arteriosclerosis occurs when the blood vessels that carry oxygen and nutrients from your heart to the rest of body (arteries) become thick and stiff

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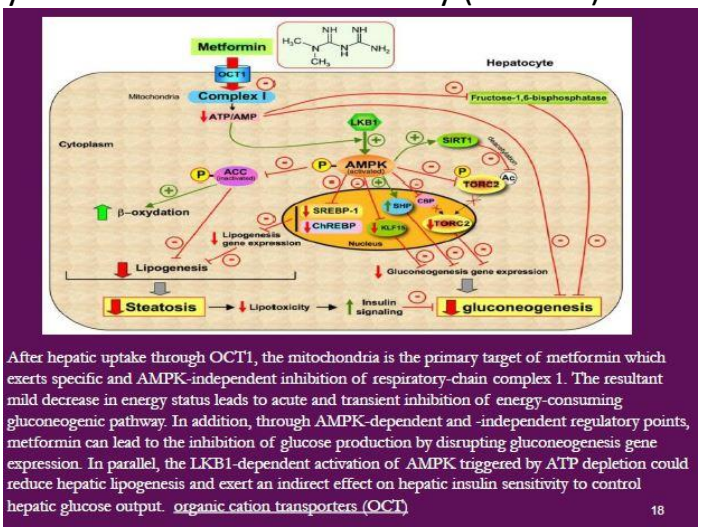

Ⅳ. α-glucosidase inhibitors

❖ **Representative Drugs**
- **Acarbose**, **Voglibose** and **Miglitol**

❖ **Key points**
- To **inhibit the digestion of starch &** disaccharides via competitively inhibiting intestinal α-glucosidase (sucrase, maltase, glycoamylase, dextranase)
- Used **alone** or **together with sulfonylureas** to treat type 2 diabetes
- Main adverse reactions: flatulence, diarrhea, bellyache. (because they inhibit the
- absorption process)
- Patients with inflammatory bowel disease & kidney-impaired are forbidden from taking such drugs.

Ⅴ. Meglitinides

❖ **Representative Drugs**

- **Repaglinide**

❖ **Key point**

- To **increase insulin release by inhibiting ATP-sensitive K+-channel**
- Unlike sulfonylureas, they have **no direct effect on insulin release**
- Used **alone or together with biguanides** to treat type 2 diabetes
- **Carefully** used for **kidney or liver-impaired patients.**