Pharmacology - 2

Dr. Yousef Abusamra. Ph.D.

Assistant professor of pharmacology and pharmacognosy

Faculty of Pharmacy

Philadelphia University – Amman - Jordan

yabusamra@philadelphia.edu.com

Anti-diabetic Agents

Pharmacology-2/ Anti-diabetic agents/ Dr. Y. Abusamra

Faculty of Pharmacy

Philadelphia University

LEARNING OUTCOMES:

After studying this chapter, the student should be able to:

- Classify the antidiabetic agents illustrating their mechanisms of action.
- Numerate the antidiabetic agent clinical indications, side effects, precautions, contraindications and important interactions with concomitantly employed drugs.
- Illustrate the pharmacokinetic parameters of these antidiabetic agents.
- Highlight certain pharmacodynamic considerations related to these agents, such as the benefits of metformin as a medication in polycystic ovary syndrome.

Anti-diabetic drugs

- The endocrine pancreas in the adult human consists of approximately 1 million islets of Langerhans interspersed throughout the pancreatic gland.
- Within the islets, at least five hormone producing cells are present.
- Their hormone products include **insulin**, the storage and anabolic hormone of the body; **islet amyloid polypeptide** (IAPP, or **amylin**), which modulates appetite, gastric emptying, and glucagon and insulin secretion; **glucagon**, the hyperglycemic factor that mobilizes glycogen stores; **somatostatin**, a universal inhibitor of secretory cells; **pancreatic peptide**, a small protein that facilitates digestive processes by a mechanism not yet clarified; and **ghrelin**, a peptide known to increase pituitary growth hormone release.

Anti-diabetic drugs

TABLE 41–1 Pancreatic islet cells and their secretory products.

Cell Types	Approximate Percent of Islet Mass	Secretory Products
Alpha (A) cell	20	Glucagon, proglucagon
Beta (B) cell	75	Insulin, C-peptide, proinsulin, amylin
Delta (D) cell	3–5	Somatostatin
G cell	1	Gastrin
F cell (PP cell)[1]	1	Pancreatic polypeptide (PP)

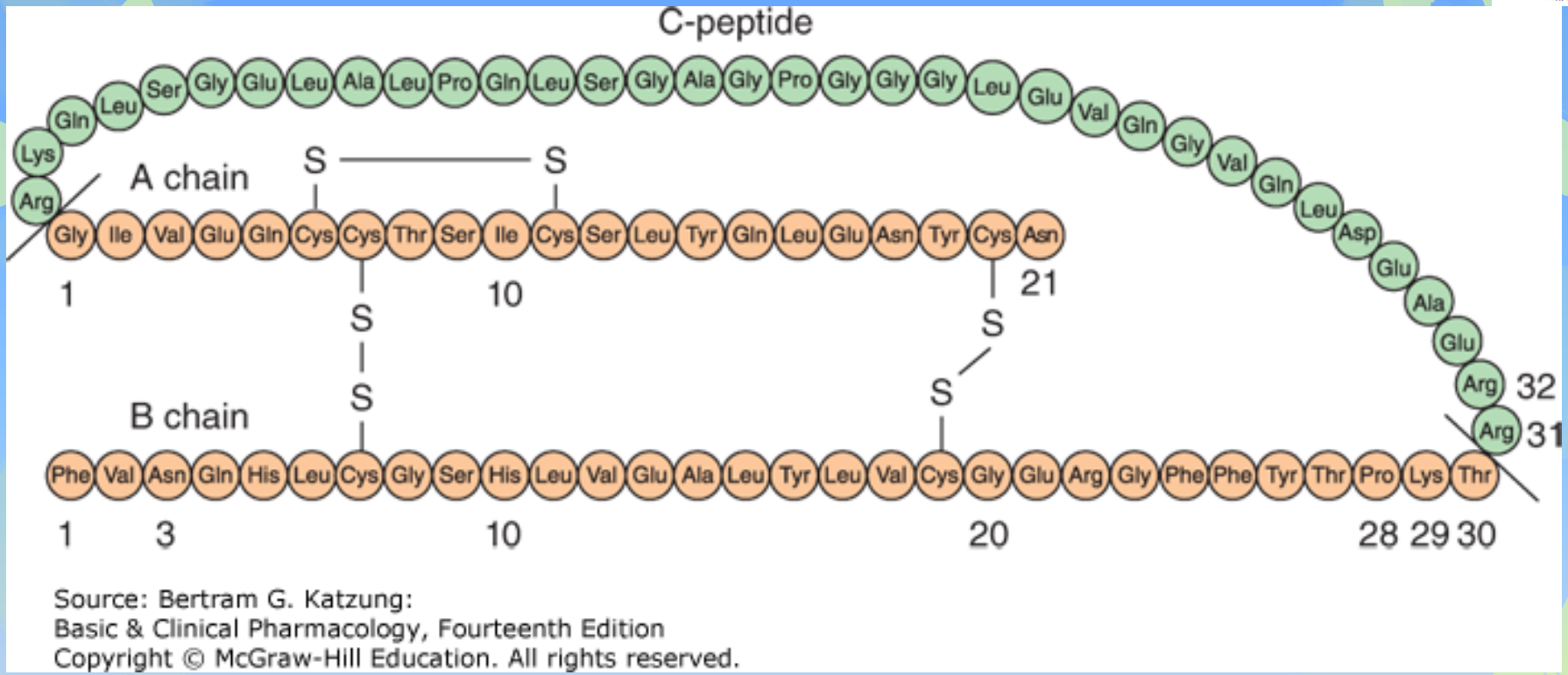
[1]Within pancreatic polypeptide-rich lobules of adult islets, located only in the posterior portion of the head of the human pancreas, glucagon cells are scarce (< 0.5%) and F cells make up as much as 80% of the cells.

- Insulin is a small protein that contains 51 amino acids arranged in two chains (A and B) linked by disulfide bridges; there are species differences in the amino acids of both chains.
- Proinsulin, a long single-chain protein molecule is hydrolyzed into insulin and a residual connecting segment called C-peptide.

Anti-diabetic drugs

- Insulin and C-peptide are secreted in equimolar amounts in response to all insulin secretagogues.
- C-peptide has no physiologic effect, thus, it is a marker for insulin.
- Because insulin undergoes significant hepatic extraction, circulating insulin levels may not reflect insulin production. Thus, measurement of circulating C-peptide provides a better index of insulin levels.

Anti-diabetic drugs



- Structure of human proinsulin (C-peptide plus A and B chains) and insulin. Insulin is shown as the shaded (orange color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for the rapid-acting insulin analogs (aspart, lispro, and glulisine) and long-acting insulin analogs (glargine and detemir).

Anti-diabetic drugs

Insulin secretion:

Insulin secretion is stimulated as a result of a variety of stimuli:

1. Glucose.
2. Other sugars, such as mannose.
3. Amino acids (especially, gluconeogenic ones, leucine and arginine).
4. Hormones, such as glucagon-like polypeptide 1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP) and glucagon.
5. High concentrations of fatty acids.
6. β-adrenergic sympathetic activity.
7. Stimulatory drugs, such as sulfonylureas, meglitinide and nateglinide, isoproterenol, and acetylcholine.

Anti-diabetic drugs

❖ **Inhibitory signals include:**

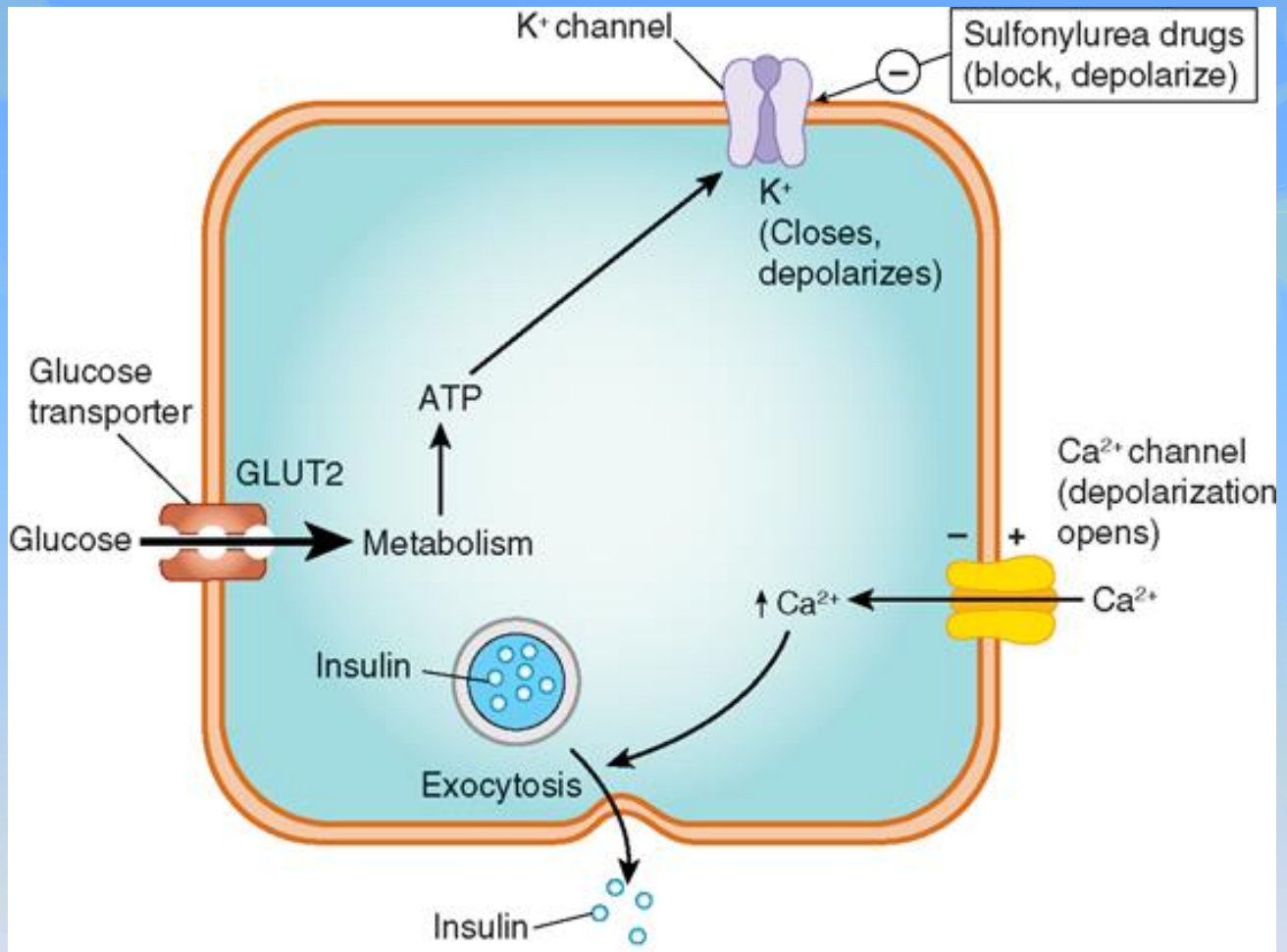
1. Hormones including insulin itself, somatostatin, leptin {a hormone predominantly made by adipose cells and enterocytes in the small intestine that helps to regulate energy balance by inhibiting hunger, which in turn diminishes fat storage in adipocytes}.

2. Alpha-adrenergic sympathetic activity.
3. Low concentrations of fatty acids.
4. Inhibitory drugs such diazoxide {a medication used to treat low blood sugar}, vinblastine and colchicine.

Anti-diabetic drugs

- **Mechanism of secretion of insulin:**
  - Hyperglycemia results in increased intracellular ATP levels, which close ATP-dependent potassium channels.
  - Decreased outward potassium efflux results in depolarization of the beta cell and opening of voltage-gated calcium channels.
  - The resulting increased intracellular calcium triggers secretion of the hormone.
- The insulin secretagogue drug group (sulfonylureas, meglitinides, and d-phenylalanine) exploits parts of this mechanism.

Anti-diabetic drugs



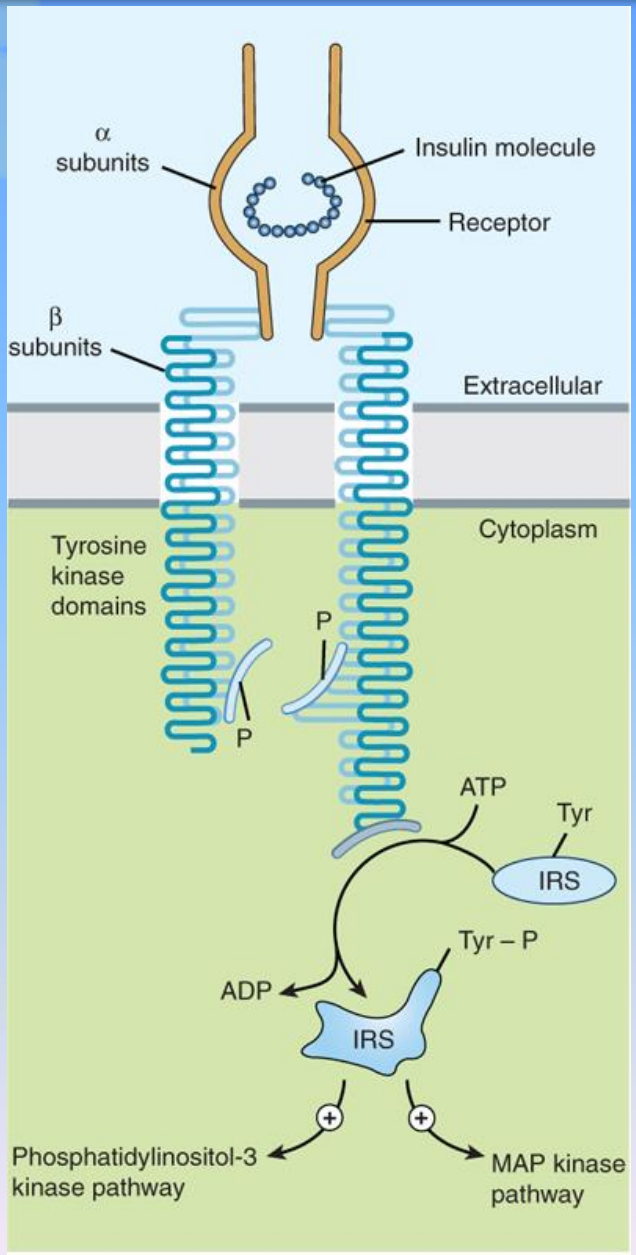
Source: Trevor AJ, Katzung BG, Kruidering-Hall M, Masters SB: *Katzung & Trevor's Pharmacology: Examination & Board Review*, 10th Edition: www.accesspharmacy.com

Copyright © The McGraw-Hill Companies, Inc. All rights reserved.

Anti-diabetic drugs

- The full insulin receptor consists of two covalently linked heterodimers, each containing an α subunit, which is entirely **extracellular** and constitutes the recognition site, and a β subunit that spans the membrane.
- The binding of an insulin molecule to the α subunits at the outside surface of the cell activates the receptor and through a conformational change brings the catalytic loops of the opposing cytoplasmic β subunits into closer proximity. This facilitates mutual phosphorylation of tyrosine residues on the β subunits and tyrosine kinase activity directed at cytoplasmic proteins.
- Further phosphorylations occur followed by several events resulting in the translocation of glucose transporters that carry out glucose uptake into the cells.

Anti-diabetic drugs



Source: Bertram G. Katzung:
Basic & Clinical Pharmacology, Fourteenth Edition
Copyright © McGraw-Hill Education. All rights reserved.

Major target organs of insulin action:

- Liver.
- Skeletal muscles.
- Adipose tissues.

Anti-diabetic drugs

Endocrine effects of insulin.

Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very-low-density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

Anti-diabetic drugs

	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5 to 10 percent of diagnosed diabetics	90 to 95 percent of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	β cells are destroyed, eliminating the production of insulin	Inability of β cells to produce appropriate quantities of insulin; insulin resistance; other defects

Anti-diabetic drugs

- Various hormonal agents (e.g. glucocorticoids) lower the affinity of insulin receptors for insulin.
- Growth hormone in excess increases this affinity slightly.
- Aberrant (irregular) serine and threonine phosphorylation of the insulin receptor β subunits may result in insulin resistance and functional receptor down-regulation {including decrease in receptor number}.

Pharmacological effects of glucagon:

- The first six amino acids at the amino terminal of the glucagon molecule bind to specific Gs protein–coupled receptors on liver cells. This leads to an increase in cAMP, which facilitates catabolism of stored glycogen and increases gluconeogenesis and ketogenesis. The result ,thus, is rise in blood glucose.

Anti-diabetic drugs

- There is no effect on the skeletal muscle glycogen, presumably, due to the lack of the receptors there.
- Glycogen has positive inotropic and chronotropic effects on the cardiac muscles.

Clinical uses:

1. Severe hypoglycemia: for emergency treatment of severe hypoglycemic reactions in patients with type 1 diabetes when unconsciousness precludes oral feedings and intravenous glucose treatment is not possible.
2. Endocrine diagnosis: In patients with type 1 diabetes mellitus.
3. Beta-Adrenoceptor Blocker Overdose: Glucagon is sometimes useful for reversing the cardiac effects of an overdose of β-blocking agents. However, it is not clinically useful in the treatment of heart failure.

Anti-diabetic drugs

4. Radiology of the bowel: as it relaxes the intestine.

- It should not be used in patients with pheochromocytoma.

Gestational Diabetes Mellitus:

- Gestational diabetes (GDM) is defined as any abnormality in glucose levels noted for the first time during pregnancy.
- During pregnancy, the placenta and placental hormones create an insulin resistance that is most pronounced in the last trimester.

Hemoglobin A1c (HbA1c):

- Hemoglobin linked to glucose.(normal: 4-6 %).
- The HbA1c fraction is abnormally elevated in people with diabetes with chronic hyperglycemia. Since red cells have a lifespan of up to 120 days, the HbA1c value reflects plasma glucose levels over the preceding 8–12 weeks.

Anti-diabetic drugs

Medications for hyperglycemia:

Insulin preparations:

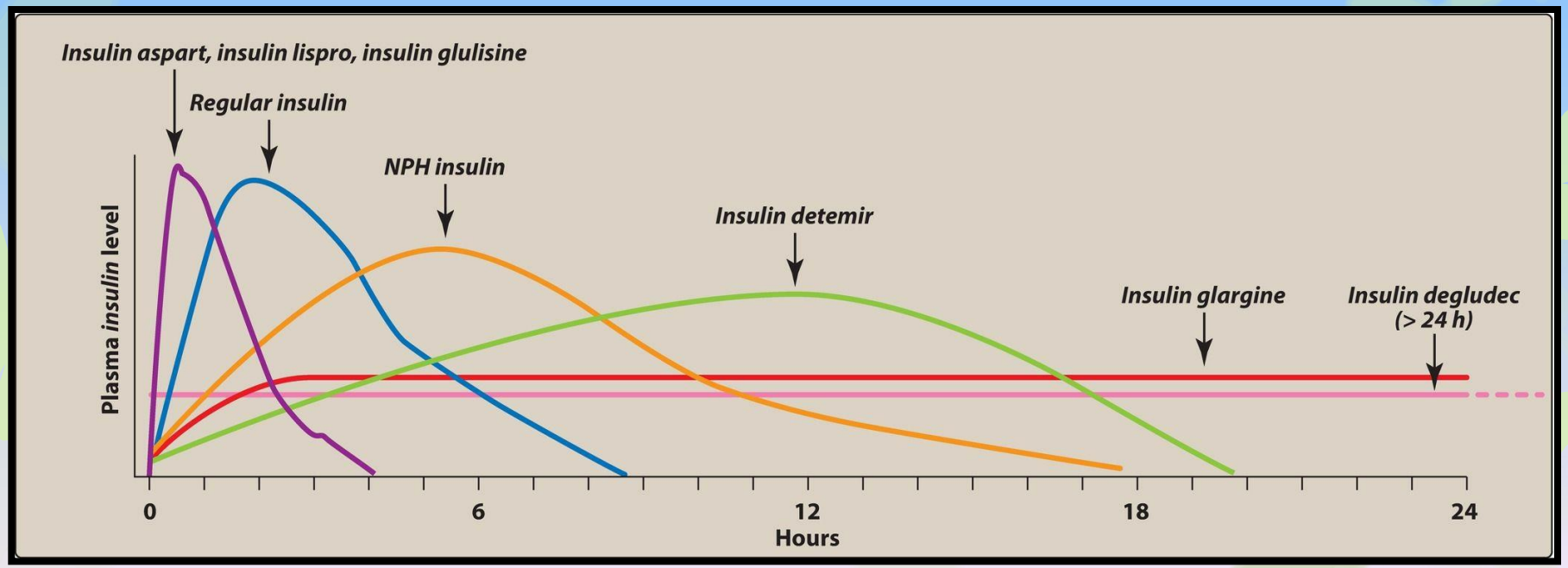
A. Short-acting (rapidly-acting):

- The short-acting preparations include **regular human insulin** and the **three rapidly acting insulin analogs**.
- All are clear solutions at neutral pH.
- The insulin molecules exist as dimers that assemble into hexamers in the presence of two zinc ions.
- The hexamers are further stabilized by phenolic compounds such as phenol and meta-Cresol (3-methylphenol).
- The mutations engineered into the rapidly acting insulin analogs are designed to disrupt the stabilizing intermolecular interactions of the dimers and hexamers, leading to more rapid absorption into the circulation after subcutaneous injection.

Anti-diabetic drugs

1) Regular insulin:

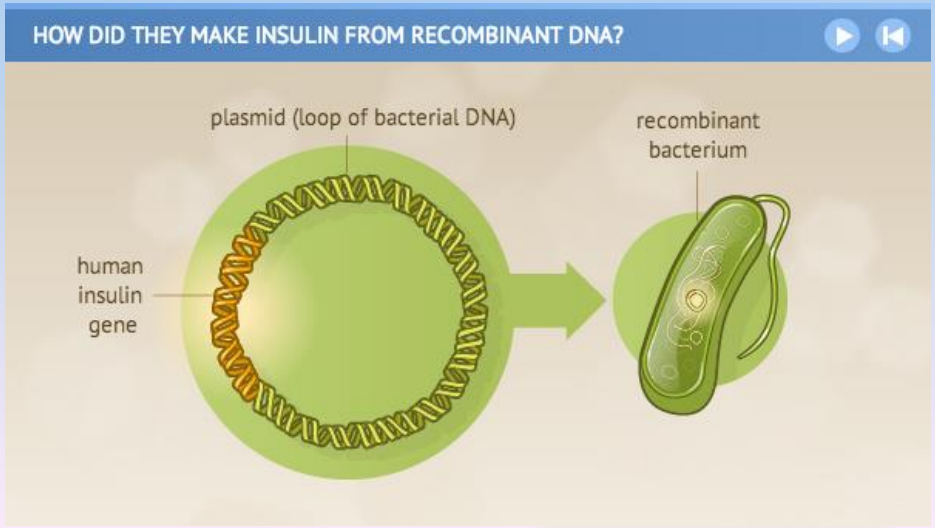
- A short-acting, soluble, crystalline zinc insulin whose hypoglycemic effect appears within 30 minutes after s.c. injection, peaks at about 2 hours.
- Intravenous infusions of regular insulin are particularly useful in the treatment of diabetic ketoacidosis.



Anti-diabetic drugs

2. Rapidly acting insulin analogs:

- Lispro, aspart and glulisine.
- Through genetic engineering of DNA, the amino acid sequence of insulin can be changed to alter its ADME (absorption, distribution, metabolism, and excretion) characteristics.
- When injected subcutaneously, these three analogs quickly dissociate into monomers and are absorbed very rapidly, reaching peak serum values in as little as 1 hour.
- Recombinant DNA: is a technology where a human gene is inserted into a the genetic material of a common bacterium.



Anti-diabetic drugs

- The amino acid changes in these analogs do not interfere with their binding to the insulin receptor, with the circulating half-life, or with their immunogenicity, which are all identical to those of human regular insulin.
- Clinical trials have demonstrated that the optimal times of preprandial subcutaneous injection of comparable doses of the rapid-acting insulin analogs and of regular human insulin are 15 minutes and 45 minutes before the meal, respectively.
- The patients must be taught to ingest adequate absorbable carbohydrate early in the meal to avoid hypoglycemia during the meal.
- The analogs also have lowest variability of absorption: approximately 5%. This compares with 25% for regular insulin.

Anti-diabetic drugs

- Analogs have also another advantage; they have a duration of action of about 4 hours for most commonly used dosages, where, regular insulin duration of action is only prolonged with larger doses.

- The rapidly acting analogs are commonly used in insulin pumps.
- In a double-blind crossover study comparing insulin lispro with regular insulin in insulin pumps, persons using insulin lispro had lower HbA1c values and improved postprandial glucose control with the same frequency of hypoglycemia.

- While insulin aspart has been approved for intravenous use (e.g. in hyperglycemic emergencies), there is no advantage in using insulin aspart over regular insulin by this route.

B. Long-acting insulin preparations:

1. NPH (neutral protamine Hagendorn, or Isophane):

- An intermediate-acting insulin whose absorption and onset of action are delayed by combining appropriate amounts of insulin and **protamine** {an antidote for heparin overdose}.
- It is a suspension of crystalline zinc insulin combined at neutral pH with the positively polypeptide protamine.
- After subcutaneous injection, proteolytic tissue enzymes degrade the protamine to permit absorption of insulin.
- NPH insulin has an onset of approximately 2–5 hours and duration of 4–12 hours.
- it is usually mixed with regular, lispro, aspart, or glulisine insulin and given two to four times daily for insulin replacement.
- This has an advantage accelerating onset of action with prolongation of the duration.

Anti-diabetic drugs

2. Insulin glargine:

- Is a soluble, “peakless” (having a broad plasma concentration plateau), long-acting insulin analog.
- Amino acid modification resulted in an analog that is soluble in an acidic solution but precipitates in the more neutral body pH after subcutaneous injection.
- Individual insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin.
- Slow onset of action; 1-1.5 hr./ max. effect after 4-6 hours that lasts for 11-24 hours.
- It is given once daily. Some patients with insulin resistance may need the administration twice.
- It should not be mixed with other insulin (use separate syringes).

3. Insulin detemir:

- Amino acid modifications prolong the availability of the injected analog by increasing both self-aggregation in subcutaneous tissue and reversible albumin binding.
- The duration of action for insulin detemir is about 17 hours at therapeutically relevant doses.
- It is recommended that the insulin be injected once or twice a day to achieve a stable basal coverage.
- This insulin has been reported to have lower within-subject pharmacodynamic variability compared with NPH insulin and insulin glargine {reproducibility}.

4. Insulin degludec:

- It is an **ultralong-acting basal** insulin analogue recently developed.
- In the vial, in the presence of **phenol** and **zinc**, the insulin is in the form of **dihexamers** but, when injected subcutaneously, it self-associates into large **multihexameric chains** consisting of thousands of dihexamers.
- The chains slowly dissolve in the subcutaneous tissue, and insulin **monomers** are steadily released into the systemic circulation.
- The half-life of the insulin is 25 hours.
- Its onset of action is in 30–90 minutes, and its duration of action is more than 42 hours.
- Adminstered1-2 times to achieve a stable basal coverage.

Advantages and properties of basal insulin therapy:

- Mimics normal pancreatic basal insulin secretion.
- Long duration of action.
- Smooth peakless profile ----- flexibility in meal time.
- Flexible dosing.
- Reproducible and predictable effect.
- Reduction in the risk of nocturnal hypoglycemia.

Anti-diabetic drugs

Mixtures of insulins: (rapid and longer action)

- Because intermediate-acting NPH insulins require several hours to reach adequate therapeutic levels, their use in patients with diabetes usually requires supplements of rapid- or short-acting insulin before meals.
- For convenience, these are often mixed together in the same syringe before injection.
- The regular insulin or rapidly acting insulin analog is withdrawn first, then the NPH insulin and then injected immediately.
- Stable premixed preparations are available (70% NPH-30% regular).
- Premixed preparations of rapidly acting insulin analogs (lispro, aspart) and NPH are not stable (This problem was solved)

Anti-diabetic drugs

- The main advantages of these new mixtures are:

1. They can be given within 15 minutes of starting a meal.
2. They are superior in controlling the postprandial glucose rise after a carbohydrate-rich meal.

- Insulin glargine or insulin detemir cannot be acutely mixed with either regular insulin or the rapid-acting insulin analogs.
- Insulin degludec, however, can be mixed and is available as 70% insulin degludec/ 30% insulin aspart.
- It is injected once or twice a day.

Insulin Delivery Systems:

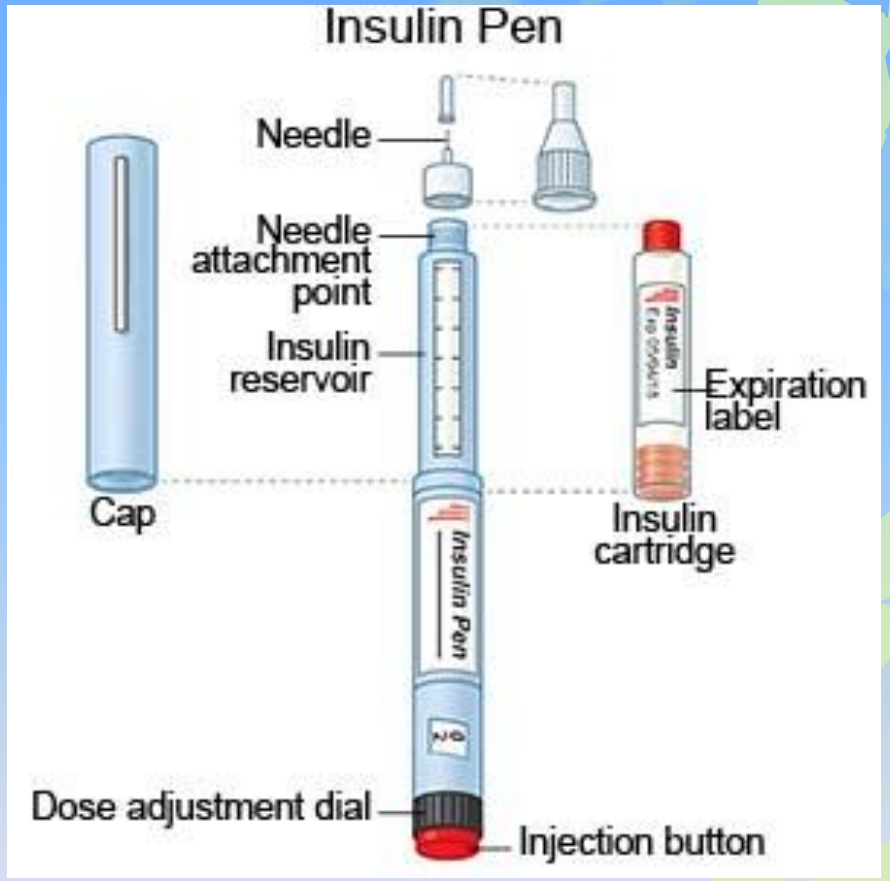
A. Insulin Syringes and Needles:

- Disposable plastic syringes with needles attached.
- The "low-dose" 0.3-mL syringes are popular because many patients with diabetes do not take more than 30 units of insulin in a single injection except in rare instances of extreme insulin resistance.
- Three lengths of needles are available; longer needles are preferable in obese patients to reduce variability of insulin absorption.
- If the skin is clean it is not necessary to use alcohol.
- Rotation of sites is recommended to avoid problems with absorption due to lipohypertrophy from overuse of injection sites.

B. Insulin Pens:

- The pens eliminate the need for carrying insulin vials and syringes.

- Cartridges of insulin lispro, insulin aspart, and insulin glargine are available for reusable pens.



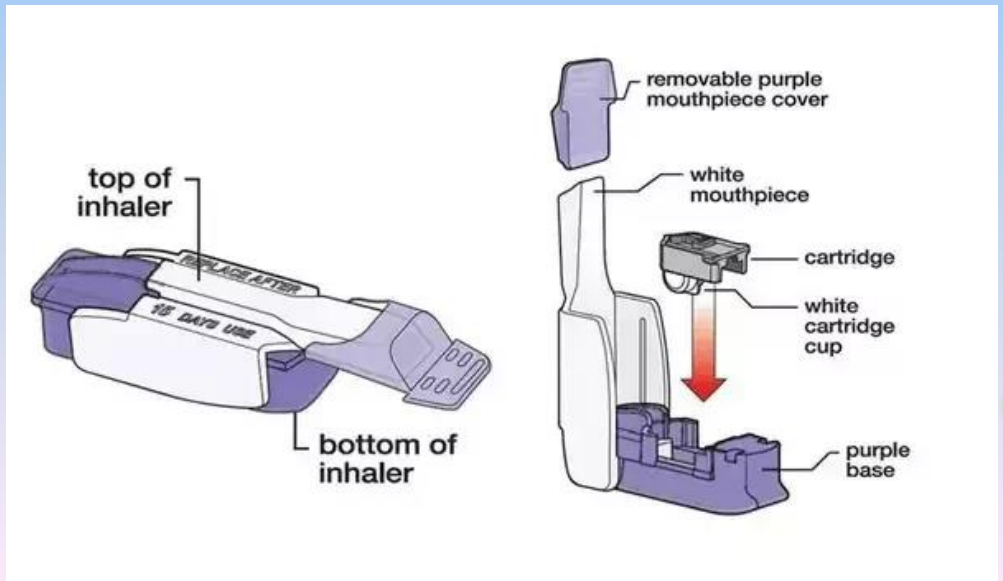
Anti-diabetic drugs

Inhaled insulin:

- A dry powder formulation of recombinant regular insulin is now approved for use in adults with diabetes.
- It consists of 2- to 2.5-µm crystals of the excipient, fumaryl diketopiperazine, that provide a large surface area for adsorption of proteins like insulin.
- After inhalation, peak levels are reached in 12–15 minutes and decline to baseline in 3 hours, significantly faster in onset and shorter in duration than subcutaneous insulin.
- The inhaler is about the size of a referee's whistle.
- The most common adverse effect of inhaled insulin was **cough**, affecting 27% of trial patients.
- Inhaled insulin is contraindicated in smokers and patients with chronic lung disease, such as asthma and chronic obstructive pulmonary disease.

Anti-diabetic drugs

- Spirometry should be performed to identify potential lung disease prior to initiating therapy.
- Spirometry is a common test used to assess how well lungs work by measuring how much air is inhaled, how much is exhaled and how quickly exhaling is.
- Spirometry is used to diagnose asthma, chronic obstructive pulmonary disease (COPD) and other conditions that affect breathing.



Anti-diabetic drugs

Immunopathology of Insulin Therapy:

At least five molecular classes of insulin antibodies may be produced in diabetics during the course of insulin therapy: IgA, IgD, IgE, IgG, and IgM. There are two major types of immune disorders in these patients:

1. **Insulin allergy:** an immediate type hypersensitivity, is a rare condition in which local or systemic urticarial results from histamine release from tissue mast cells sensitized by anti-insulin **IgE** antibodies.

- In severe cases, anaphylaxis results.
- Because sensitivity is often to non-insulin protein contaminants, the human and analog insulins have markedly reduced the incidence of insulin allergy, especially local reactions.

2. Immune insulin resistance:

- Low titer of circulating IgG anti-insulin antibodies that neutralize the action of insulin to a negligible extent develops in most insulin-treated patients.
- Rarely, the titer of insulin antibodies leads to insulin resistance and may be associated with other systemic autoimmune processes such as lupus erythematosus.
- Lupus erythematosus; the body's immune system mistakenly attacks healthy tissue in many parts of the body.

Lipodystrophy at Injection Sites:

- Injection of animal insulin preparations sometimes led to atrophy of subcutaneous fatty tissue at the site of injection.
- Since the development of human and analog insulin preparations of neutral pH, this type of immune complication is almost never seen.
- Hypertrophy of subcutaneous fatty tissue remains a problem if injected repeatedly at the same site.
- However, this may be corrected by avoiding the specific injection site.

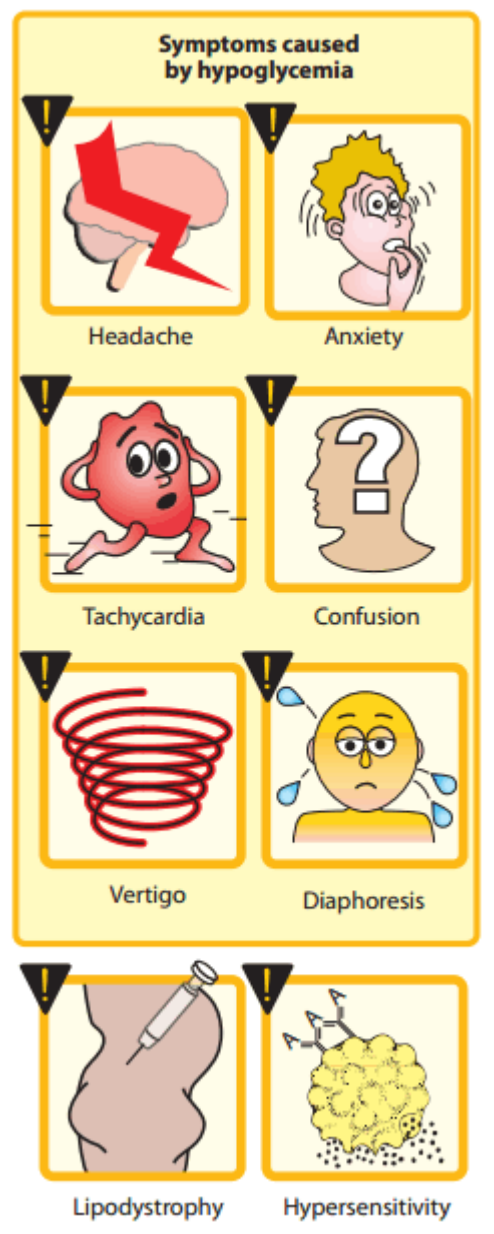
ADVERSE RACTIONS TO INSULINS:

1. Symptoms of hypoglycemia are the most serious and common adverse reactions to an excessive dose of insulin.
2. Weight gain.
3. Lipodystrophy (less common with human insulin; abnormal or degenerative conditions of the body's adipose tissue = atrophy or dystrophy of subcutaneous fatty tissues at the site of injection).
4. Allergic reactions.

- Diabetics with renal insufficiency may require insulin dose adjustment.

Anti-diabetic drugs

SYMPTOMS SEEN WITH HYPOGLYCEMIA; Ignition of the sympathetic pathway.



MEDICATIONS OF TYPE 2 DIABETES

S/N	Drug class	Example of drugs	Adverse effects
1	Insulin and analogues	Regular Insulin	Hypoglycemia, Weight gain, Insulin allergy, Lipodystrophy at injection sites
2	Sulphonylureas	Glibenclamide	Hypoglycaemia, Weight gain, Cardiovascular risk, rash, Cholestatic jaundice, Bone marrow damage, Photosensitivity
3	Meglitinides	Repaglinide	Hypoglycemia, Sensitivity reactions
4	Biguanides	Metformin	Gastrointestinal effects, Lactic acidosis
5	GLP-1 agonists	Exenatide	Gastrointestinal effects, Pancreatitis, risks for cancer and cardiovascular events
6	DPP-4 inhibitors	Saxagliptin	Pancreatitis, risk for cancer, acute hepatitis and kidney impairment
7	Thiazolidinedions	Pioglitazone	Hepatitis, Cardiovascular risk, Bladder cancer, Water retention and weight gain
8	Dual PPAR agonists **peroxisome proliferator-activated receptors**	Saroglitazar	Gastritis, asthenia and pyrexia
9	Alpha-glucosidase inhibitors	Acarbose	Gastrointestinal effects, Hepatitis,
10	Amylin analogues	Pramlintide	Hypoglycemia, Allergy
11	SGLT 2 inhibitors	Canagliflozin	Glycosuria, Cardiovascular concern

DRUGS THAT PRIMARILY STIMULATE INSULIN RELEASE BY BINDING TO THE SULFONYLUREA RECEPTOR

Sulfonylureas:

Mechanism of action: {Figure on slide 11}

- They bind to a high-affinity sulfonylurea receptor that is associated with a beta-cell-ATP-sensitive potassium channel.
- Binding of a sulfonylurea inhibits the efflux of potassium ions through the channel and results in depolarization.
- Depolarization opens a voltage-gated calcium channel and results in calcium influx and the release of insulin.

Anti-diabetic drugs

Pharmacokinetics:

- Sulfonylureas are metabolized by the liver and, with the exception of acetohexamide, the metabolites are either weakly active or inactive.
- Acetohexamide (1st G agent) is thus metabolized to its active metabolite hydroxyhexamide.
- Acetohexamide is the only sulfonylurea possessing uricosuric activity and therefore it has particular value in diabetics with gout.
- The metabolites are excreted by the kidney and, in the case of the second-generation sulfonylureas, partly excreted in the bile.
- Used with caution in patients with hepatic or renal insufficiency, accumulation.

Anti-diabetic drugs

- Glyburide (glibenclamide; 2nd G); minimal transfer across the placenta- a reasonable safe alternative to insulin for diabetes in pregnancy.
- 2nd G agents have higher affinity to the receptor compared to the 1st G-ones. Thus, 2nd G agents are more potent – lower risk of drug-drug interactions.

Adverse effects:

- Weight gain, hyperinsulinemia, hypoglycemia.
- Idiosyncratic reactions are rare; skin rashes – hematologic (leukopnea, thrombocytopnea, 0.1%).

Anti-diabetic drugs

First-generation sulfonylureas:

- Tolbutamide, chlorpropamide, tolazamide and acetohexamide.
- Tolbutamide is with a short $t_{1/2}$ and is inactivated by the liver, thus, it is safe in elderly and patients with renal impairment.
- Tolbutamide: Prolonged hypoglycemia has been reported rarely, mostly in patients receiving certain antibacterial sulfonamides (sulfisoxazole), phenylbutazone for arthralgias, or the oral azole antifungal medications to treat candidiasis – these agents inhibit tolbutamide hepatic metabolism.
- Chlorpropamide: longer $t_{1/2}$, prolonged hypoglycemia, so it is contraindicated in elderly.
- Chlorpropamide: an additional side effect is hyponatremia due to its effect on vasopressin (ADH).

Anti-diabetic drugs

- **Tolazamide:** is comparable to chlorpropamide but with shorter half-life.
- **Tolazamide** is no longer available in the United States.
- **Acetohexamide:** its half-life is only about 1 hour but its **more active** metabolite, hydroxyhexamide, has a half-life of 4–6 hours; thus the drug duration of action is 8–24 hours.
- Chlorpropamide, tolazamide, and acetohexamide are now rarely used in clinical practice.

Anti-diabetic drugs

- Glyburide, glipizide, gliclazide, and glimepiride are 100–200 times more potent than tolbutamide.
- They should be used with caution in patients with cardiovascular disease or in elderly patients, in whom hypoglycemia would be especially dangerous.
- Glyburide (glibenclamide) other adverse effects other than its potential for causing hypoglycemia: flushing has rarely been reported after ethanol ingestion, and the compound slightly enhances free water clearance {rendering urine less concentrated, more dilute, than plasma}.
- Glyburide is contraindicated in the presence of hepatic impairment and in patients with renal insufficiency.

Anti-diabetic drugs

- Glipizide has the shortest half-life (2–4 hours) of the more potent agents.
- For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 minutes before breakfast because absorption is delayed when the drug is taken with food.
- At least 90% of glipizide is metabolized in the liver to inactive products, and the remainder is excreted unchanged in the urine.
- Glipizide therapy is therefore contraindicated in patients with significant hepatic impairment.
- Glipizide: preferred in elderly – renal impairment (short t1/2).

Anti-diabetic drugs

Drugs that may reduce the effects of sulfonylureas, leading to loss of glucose control:

- Atypical antipsychotics
- Corticosteroids
- Diuretics
- *Niacin*
- Phenothiazines
- Sympathomimetics

Drugs that may potentiate the effects of sulfonylureas, leading to hypoglycemia:

- Azole antifungals
- Beta-blockers
- *Chloramphenicol*
- *Clarithromycin*
- Monoamine oxidase inhibitors
- *Probenecid*
- Salicylates
- Sulfonamides

Drugs interacting with sulfonylureas.

Source : Lippincott Illustrated Reviews, Pharmacology - Whalen, Karen

Drug Interactions with Sulphonylureas

Hypoglycemic action is increased by:	Hypoglycemic action is decreased by:
Insulin*	Corticosteroids$^{\Omega}$
Alcohol*	Hormonal contraceptives$^{\Omega}$
Sulfonamides◆	Loop and thiazide diuretics$^{\Omega}$
Probenecid	Rifampin❖
Chloramphenicol◆	

* Intricsic hypoglycemic action
◆ Inhibition of hepatic metabolism of sulfonylureas
Inhibition of urinary secretion of sulfonylureas
Ω Intrinsic hyperglycemic action
❖ Stimulation of hepatic metabolism of sulfonylureas

- **Niacin**: opposes their action (?); increases insulin resistance (hyperglycemia).
- **Phenothiazines**: not known (?).
- **Sympathomimetics**: via the adrenergic effect.
- **Atypical antipsychotics**: 2nd G antipsychotics; that are less likely to cause the known side effects such as extrapyramidal reflexes: via intrinsic effect.
- **MAO inhibitors**: displacement from b.s.

Anti-diabetic drugs

- Glimepiride (Amaryl®) is approved for once-daily use as monotherapy or in combination with insulin.
- Glimepiride achieves blood glucose lowering with the lowest dosage of any sulfonylurea compound.

++

Meglitinide analogs:

1. Repaglinide:

Mechanism of action:

- These drugs modulate beta-cell insulin release by regulating potassium efflux through the potassium channels previously discussed.
- There is overlap with the sulfonylureas in their molecular sites of action because the meglitinides have two binding sites in common with the sulfonylureas and one unique binding site.

Anti-diabetic drugs

Pharmacokinetics:

- Repaglinide has a fast onset of action, with a peak concentration and peak effect within approximately 1 hour after ingestion.
- It is cleared by hepatic CYP3A4 with a plasma half-life of 1 hour.
- Because of its rapid onset, repaglinide is indicated for use in controlling postprandial glucose excursions.
- It can be used in patients with renal impairment or in elderly.
- Repaglinide is approved as monotherapy or in combination with biguanides.
- There is no sulfur in its structure, so repaglinide may be used in type 2 diabetics with sulfur or sulfonylurea allergy.

2. Nateglinide:

- It is absorbed within 20 minutes after oral administration with a time to peak concentration of less than 1 hour.
- It is metabolized in the liver by CYP2C9 and CYP3A4.
- The overall duration of action is about 4 hours.
- It is taken before the meal and reduces the postprandial rise in blood glucose levels.
- The lower dose is used in patients with mild elevations in HbA1c.
- Nateglinide is efficacious when given alone or in combination with non-secretagogue oral agents (such as metformin).
- It can be used in patients with renal impairment and in the elderly.

Anti-diabetic drugs

Adverse effects:

- Hypoglycemia: incidence is lower than that with sulfonylureas.
- Weight gain: incidence is lower than that with sulfonylureas.

Drug interactions:

- Nateglinide and repaglinide X CYT3A4 inhibitors = its effect is increased; e.g. {azoles (antifungal) – erythromycin and clarithromycin.
- Nateglinide and repaglinide X CYT3A4 inducers = its effect is decreased; e.g. {carbamazepine – barbiturates – rifampin}.
- Repaglinide X gemfibrozil (lipid-lowering) = severe hypoglycemia; slowing its hepatic metabolism by CYT2C8.

DRUGS THAT PRIMARILY LOWER GLUCOSE LEVELS BY THEIR ACTIONS ON THE LIVER, MUSCLE, & ADIPOSE TISSUE:

Biguinides:

- Phenformin (an older biguanide) was discontinued in the US because of its association with lactic acidosis.
- Metformin is the only biguanide currently available in the United States.
- It is an insulin sensitizer.
- It does not promote insulin secretion, so hyperinsulinemia is not a problem.
- Hyperglycemia is less than with sulfonylureas, and can occur in case of inadequate caloric intake or over-exercising or efforts that are not calorically compensated.

Anti-diabetic drugs

Mechanism of action:

- Inhibition of hepatic gluconeogenesis, thus, reduction in hepatic glucose output {excess glucose produced by the liver is a major source of high blood glucose in DM-T2}.
- Slows intestinal absorption of sugars.
- Improves peripheral glucose uptake and utilization.
- An important merit of the drug; it modestly reduces hyperlipidemia {LDL and VLDL cholesterol, meanwhile, HDL rises}. These effects may not be seen before 4 to 6 weeks of use pass.

❑ The patient commonly loses weight because of loss of appetite; metformin has been shown to induce weight loss in obese non-diabetic populations; therefore, can help in this respect.

Anti-diabetic drugs

- It is recommended to use metformin as the drug of choice in the newly diagnosed DM-T2.
- Maybe used **alone** or in **combination** with insulin, {insulin dose may require adjustment}.

Pharmacokinetics:

- It is not bound to plasma proteins, is not metabolized, and is excreted by the kidneys as the active compound.
- As a consequence of metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of **lactic acid**.
- In patients with renal insufficiency, the biguanide accumulates and thereby increases the risk of lactic acidosis, which appears to be a dose-related complication.
- It is contraindicated if the eGFR (estimated) is less than **30** mL/min per 1.73 m^2.

Anti-diabetic drugs

- Biguanides are recommended as first-line therapy for type 2 diabetes.
- Because metformin is an insulin-sparing agent and does not increase body weight or provoke hypoglycemia, it offers obvious advantages over insulin or sulfonylureas in treating hyperglycemia in such persons.
- Some reports consider that metformin therapy decreases the risk of macrovascular {damage to large blood vessels} as well as microvascular disease {damage to smaller blood vessels}; this is in contrast to the other therapies, which only modified microvascular morbidity.
- Biguanides are also indicated for use in combination with insulin secretagogues or thiazolidinediones in type 2 diabetics in whom oral monotherapy is inadequate.

Anti-diabetic drugs

- Metformin is useful in the prevention of type 2 diabetes.
- Reports: metformin is efficacious in preventing the new onset of type 2 diabetes in middle-aged, obese persons with impaired glucose tolerance and fasting hyperglycemia.
- It is interesting that metformin did not prevent diabetes in older, leaner (slimmer) prediabetics.
- Epidemiologic studies suggest that metformin use may reduce the risk of some cancers.
- Other studies suggest a reduction in cardiovascular deaths in humans and an increase in longevity (length of life) in mice.

Toxicity:

- The most common toxic effects of metformin are GIT-related. They are dose related, tend to occur at the onset of therapy, and are often transient.
- Metformin interferes with the calcium-dependent absorption of vitamin B12 in the terminal ileum, and vitamin B12 deficiency can occur after many years of metformin use.
- Periodic screening for vitamin B12 deficiency should be considered, especially in patients with peripheral neuropathy or macrocytic anemia (large with low Hb).
- Increased intake of calcium may prevent the metformin-induced B12 malabsorption.

Anti-diabetic drugs

- Lactic acidosis can sometimes occur with metformin therapy.
- It is more likely to occur in conditions of tissue hypoxia when there is increased production of lactic acid and in renal failure when there is decreased clearance of metformin.

Contraindications:

- Kidney, liver, or cardiorespiratory insufficiency.
- **It should be discontinued in:**
- Acute myocardial infarction.
- Exacerbation of CHF.
- Severe infection.
- It should be, temporarily discontinued on the day of radiocontrast administration and restarted a day or two later after confirmation that renal function has not deteriorated (acute kidney failure).

Anti-diabetic drugs

Metformin should be used with caution patients in:

- Patients older than 80 years of age.
- Patients with a history of CHF.
- Patients with alcohol abuse.

❑ Renal function should be checked at least annually in patients on metformin therapy.

❖ Lower doses should be used in the:

- Elderly .
- Those with eGFR between 30 and 45 mL/min per 1.73 m2

Anti-diabetic drugs

THIAZOLIDINEDIONES:

- Thiazolidinediones act to decrease insulin resistance.
- They are ligands of peroxisome proliferator-activated receptor gamma (PPAR-γ), part of the steroid and thyroid superfamily of nuclear receptors.
- These PPAR receptors are found in muscle, fat, and liver.
- PPAR-γ receptors modulate (decrease)the expression of the genes involved in lipid and glucose metabolism, insulin signal transduction, and adipocyte and other tissue differentiation.
- Observed effects of the thiazolidinediones include = mechanisms how these agents decrease resistance to insulin:

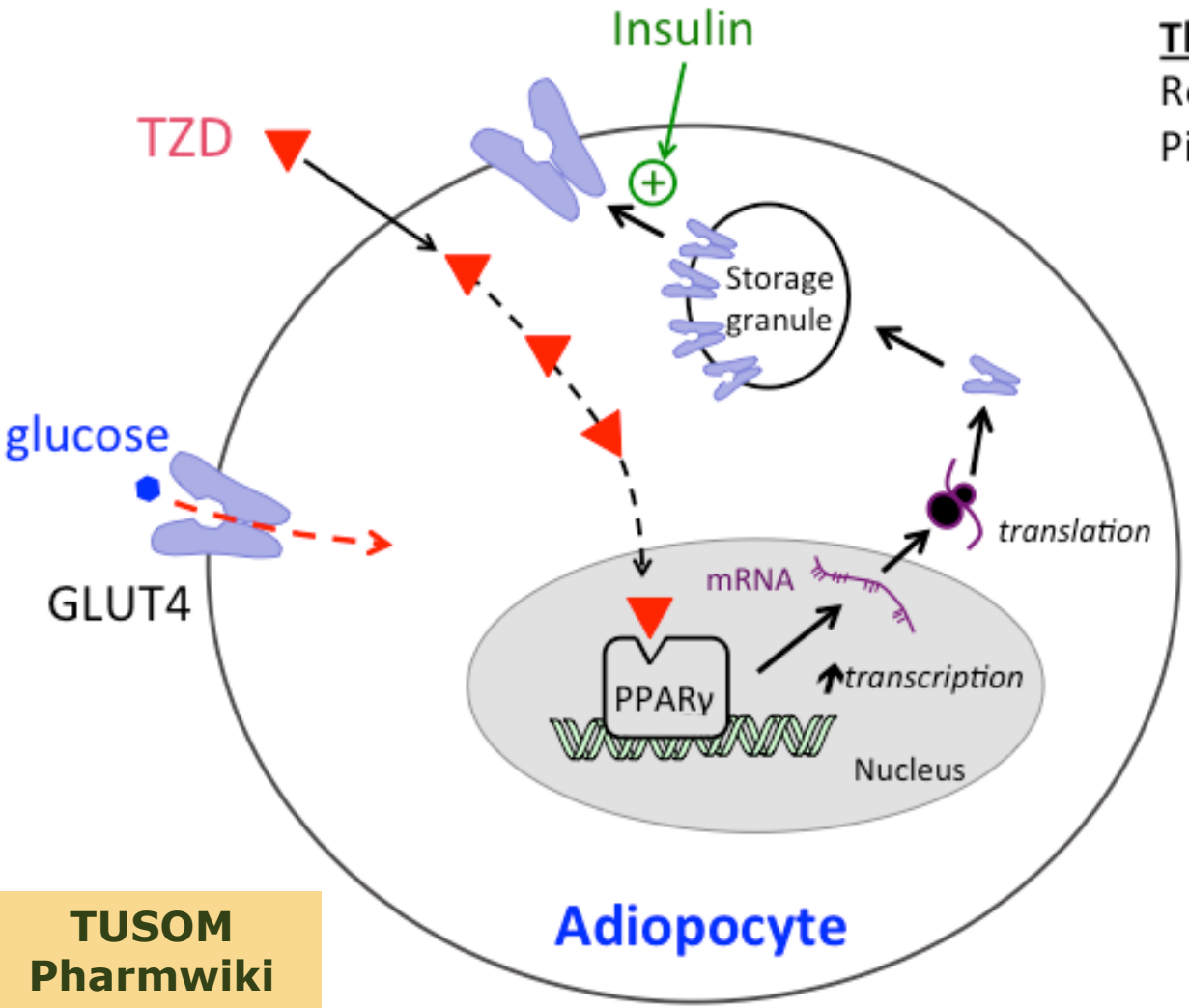
1. Increased glucose transporter expression (GLUT 1 and GLUT 4).{See the coming fig. – increase glucose uptake by the cells}
2. Decreased free fatty acid levels.
3. Decreased hepatic glucose output.

Anti-diabetic drugs

4) Increased adiponectin {a protein hormone which is involved in regulating glucose levels as well as fatty acid breakdown}.
5) Decreased release of resistin from adipocytes {an adipocyte-released peptide. It is a unique signaling molecule, is being proposed as a significant factor in the pathogenesis of obesity-related insulin resistance}.
6) Decrease levels of plasminogen activator inhibitor type 1 {promotes fibrinolysis by inhibiting enzymes {tPA} that catalyze conversion of plasminogen to plasmin}, matrix metalloproteinase 9 {degradation of the extracellular matrix}, C-reactive protein {A high level of CRP in the blood is a marker of inflammation}, and interleukin 6 {a pro-inflammatory cytokine}.

❖ Two thiazolidinediones are currently available: pioglitazone and rosiglitazone. Troglitazone was withdrawn (hepatotoxic)

Anti-diabetic drugs



Thiazolidinediones (TZDs):

Rosiglitazone - PPARγ

Pioglitazone - PPARγ > PPARα

PPARγ expression:

Adipose tissue

Skeletal muscle (↑in obesity)

Pancreatic β cells

Vascular endothelium

Macrophages

CNS

PPARα expression:

Liver

Heart

Skeletal muscle

Vascular wall

TUSOM Pharmwiki

Anti-diabetic drugs

Pioglitazone:

- Has some PPAR-α as well as PPAR-γ activity.
- Complete bioavailability although food can delay absorption.
- Absorption is decreased with concomitant use of bile acid sequestrants {resins such as cholestyramine colestipol, and colesevelam are medications for lowering LDL cholesterol in conjunction with diet modification; by combining with bile constituents and preventing their reabsorption from the gut}.
- Pioglitazone is metabolized by CYP2C8 and CYP3A4 to active metabolites.
- The bioavailability of numerous other drugs also degraded by these enzymes may be affected by pioglitazone therapy, including **estrogen-containing oral contraceptives**; additional methods of contraception are advised.
- Thus estrogen may interfere with the levels of glucose by decreasing the activity of these drugs.

Anti-diabetic drugs

Rosiglitazone:

- Rapidly absorbed and highly protein bound.
- It is metabolized in the liver to minimally active metabolites.
- Rosiglitazone is approved for use in type 2 diabetes as monotherapy, in double combination therapy with a biguanide or sulfonylurea, or in quadruple combination with a biguanide, sulfonylurea, and insulin.
- Rosiglitazone when combined with metformin, both have the advantage of not causing hypoglycemia.

- Pioglitazone lowers triglycerides and increases high-density lipoprotein (HDL) cholesterol without affecting total cholesterol and low-density lipoprotein (LDL) cholesterol.

Anti-diabetic drugs

- Rosiglitazone increases total cholesterol, HDL cholesterol, and LDL cholesterol, but does not have significant effect on triglycerides.
- Safety concerns and troublesome side effects have significantly reduced the use of this class of drugs;
- A meta-analysis of 42 randomized clinical trials with rosiglitazone suggested that this drug increased the risk of angina pectoris or myocardial infarction.
- As a result, its use was suspended in Europe and severely restricted in the United States.
- A subsequent large prospective clinical trial failed to confirm the meta-analysis finding and so the United States restrictions have been lifted. The drug remains unavailable in Europe.

Anti-diabetic drugs

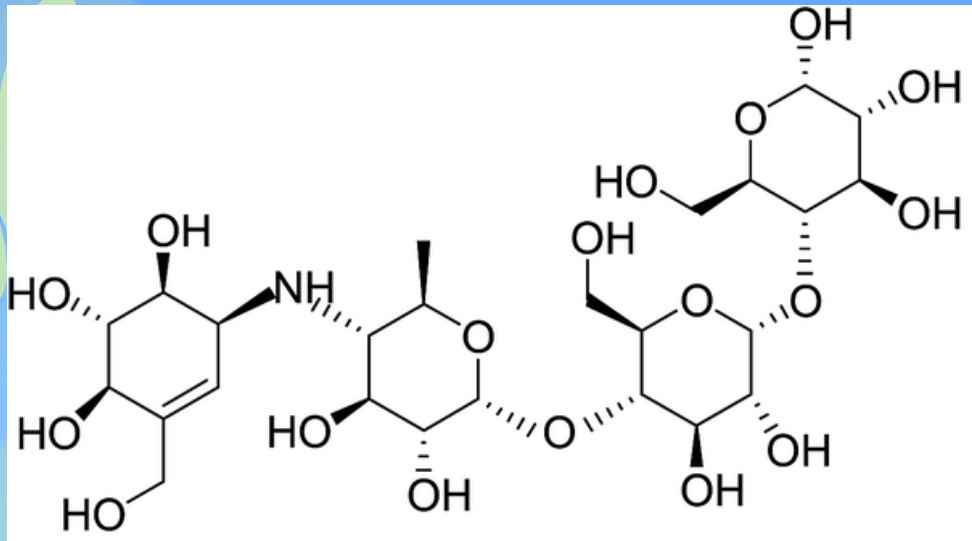
Adverse effects:

- Hepatoxicity (routine liver enzyme level measurement – contraindication in acute liver injury, elevated liver enzyme levels).
- Weight gain (due to increase of subcutaneous fat or fluid retention).
- Fluid retention and edema (HF can occur; a contraindication).
- Loss of bone mineral density and increased atypical extremity bone fractures in women.
- Anemia (decrease in RBC mass).
- Bladder tumors were observed in male rats on pioglitazone, huge studies failed to relate these drugs use with this cancer. However, a study related pioglitazone with increased incidence of bladder cancer.

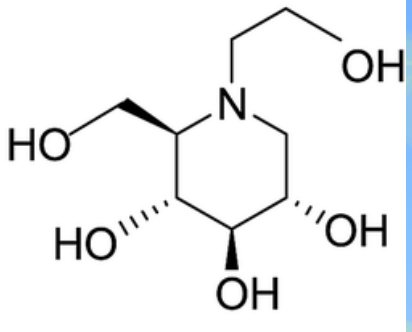
DRUGS THAT AFFECT ABSORPTION OF GLUCOSE:

- The α-glucosidase inhibitors competitively inhibit the intestinal α-glucosidase enzymes and reduce post-meal glucose by delaying the digestion and absorption of starch and disaccharides.
- **Acarbose** and **miglitol** are available in the United States. **Voglibose** is available in Japan, Korea, and India.
- Acarbose and miglitol are potent inhibitors of glucoamylase, α-amylase, and sucrose.
- **Acarbose**: structural features of a tetrasaccharide -- and very little is absorbed.
- **Miglitol** has structural similarity to glucose and is absorbed.

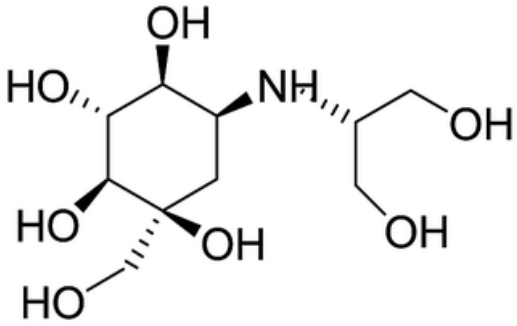
Anti-diabetic drugs



Acarbose (1)



Miglitol (2)



Voglibose (3)

Anti-diabetic drugs

- Miglitol is not metabolized and is cleared by the kidney. It should not be used in renal failure.
- Adverse effects of α-glucosidase inhibitors include flatulence, diarrhea, and abdominal pain and result from the appearance of undigested carbohydrate in the colon that is then fermented into short-chain fatty acids, releasing gas.
- Although not a problem with monotherapy or combination therapy with a biguanide, hypoglycemia may occur with concurrent sulfonylurea treatment.
- Hypoglycemia should be treated with glucose (dextrose) and not sucrose, whose breakdown may be blocked (by the enzyme α-glucosidase inhibitor).
- These drugs are infrequently prescribed in US because of their {1} prominent GIT adverse effects and {2} relatively modest glucose-lowering benefit.

DRUGS THAT MIMIC INCRETIN EFFECT OR PROLONG INCRETIN ACTION:

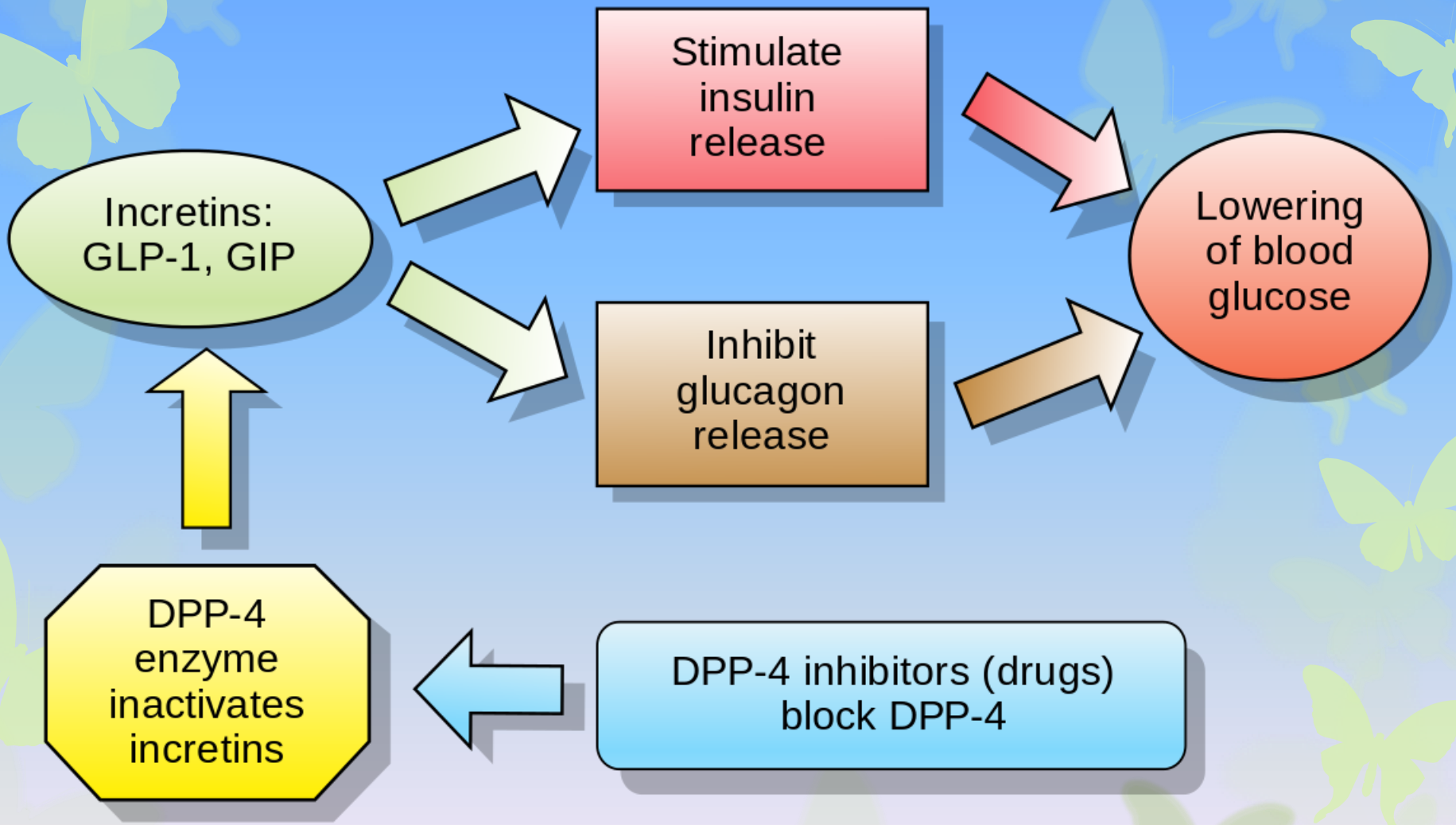
- Oral glucose causes a release of gut hormones ("incretins"), principally GLP-1(Glucagon-like peptide-1) and glucose-dependent insulinotropic peptide (GIP), that amplify the glucose-induced insulin secretion.
- When GLP-1 is infused in patients with type 2 diabetes, it stimulates insulin release and lowers glucose levels.
- The GLP-1 effect is glucose dependent in that the insulin release is more pronounced when glucose levels are elevated, or this reason, GLP-1 has a lower risk for hypoglycemia than the sulfonylureas.
- In addition to its {1} insulin stimulatory effect, GLP-1 {2} suppresses glucagon secretion, {3} delays gastric emptying, {4} reduces apoptosis of human islets in culture and {5} anorectic effect {causes anorexia}.

DIPEPTIDYL PEPTIDASE 4 (DPP-4) INHIBITORS:

Sitagliptin is given orally once daily.

- It is primarily excreted in the urine.
- Hepatic metabolism is limited and mediated largely by the cytochrome CYP3A4 isoform and, to a lesser degree, by CYP2C8.
- The metabolites have insignificant activity.
- Dosage should be reduced in patients with impaired renal function (50 mg if estimated **GFR** is **30–50** mL/min and 25 mg if **<30** mL/min).
- Sitagliptin has been studied as monotherapy and in combination with metformin, sulfonylureas, and thiazolidinediones.

Anti-diabetic drugs



ADVERSE EFFECTS:

- Nasopharyngitis, upper respiratory infections, and headaches.
- Hypoglycemia when combined with insulin secretagogues or insulin.
- Acute pancreatitis (fatal and nonfatal).
- Severe allergic and hypersensitivity reactions.

❑ Sitagliptin should be immediately discontinued if pancreatitis or allergic and hypersensitivity reactions occur.

Saxagliptin:

Adverse effects:

- An increased rate of infections (upper respiratory tract and urinary tract).
- Headaches.
- Hypersensitivity reactions (urticaria, facial edema).
- May increase risk of heart failure.

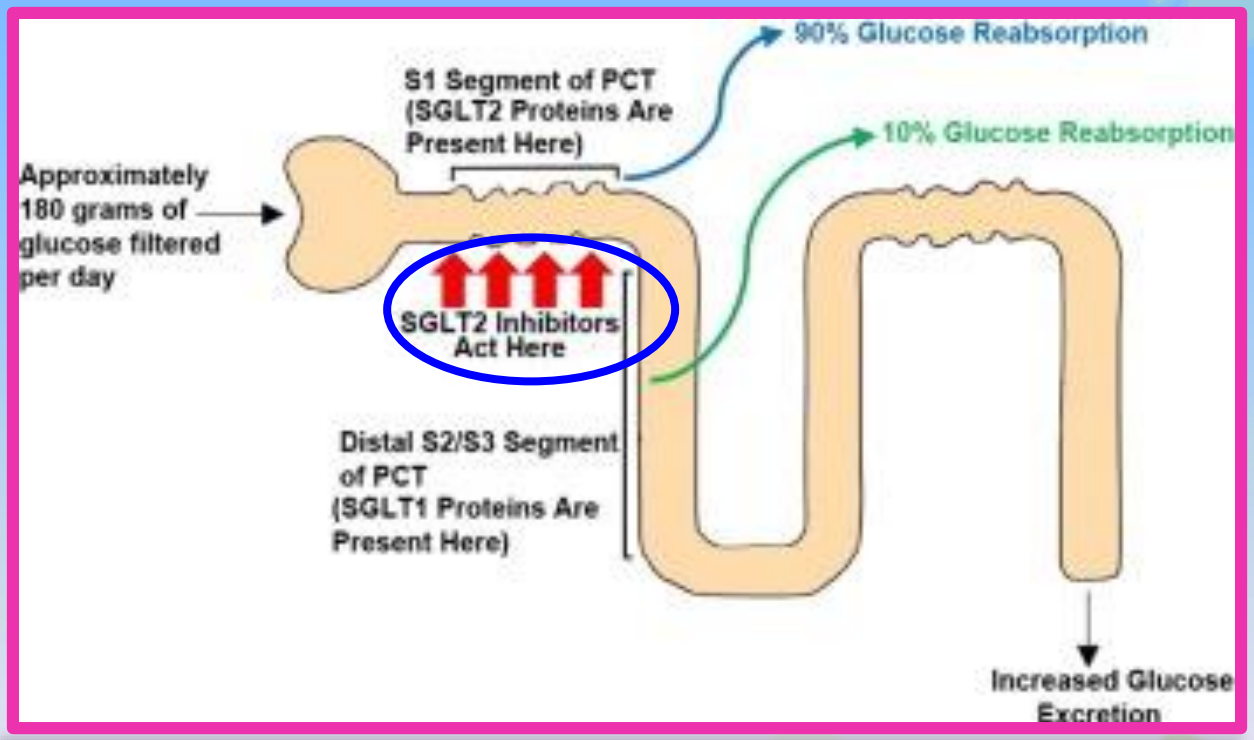
- **Linagliptin – alogliptin – vildagliptin.**

- DDP-4 inhibitors are generally well tolerated.

SODIUM-GLUCOSE CO-TRANSPORTER 2 (SGLT2) INHIBITORS:

- Glucose is freely filtered by the renal glomeruli and is **reabsorbed** in the proximal tubules by the action of sodium glucose transporters (SGLTs).
- SGLT**2** accounts for **90%** of glucose reabsorption, and its inhibition causes glycosuria and lowers glucose levels in patients with type 2 diabetes.
- SGLT2 inhibitors lower glucose levels by changing the renal threshold and not by insulin action.
- The SGLT2 inhibitors canagliflozin, dapagliflozin, and empagliflozin, all oral medications, are approved for clinical use.

Mechanism of action of GSLT2 inhibitors



Anti-diabetic drugs

- In a postmarketing multinational study of 7020 type 2 patients with known cardiovascular disease, the addition of empagliflozin was associated with a **lower** outcome of death from **cardiovascular** causes.
- The mechanisms regarding this **benefit** remain unclear.
- **Weight loss**, **lower blood pressure,** and **diuresis** may have played a role since there were **fewer deaths from heart failure** in the treated group whereas the **rates of myocardial infarction were unaltered.**
- The efficacy of the SGLT2 inhibitors is **reduced** in **chronic kidney disease.**
- **Canagliflozin** and **empagliflozin** are **contraindicated** in patients with estimated GFR **less than 45** mL/min per 1.73 m^2.
- **Dapagliflozin** is **not recommended** for use in patients with estimated GFR **less than 60** mL/min per 1.73 m^2.

Anti-diabetic drugs

Adverse effects:

- Increased incidence of **genital and urinary tract infections** affecting about 8–9% of patients.
- **Hypotension** due to osmotic diuresis (glycosuria).
- A modest **increase in LDL cholesterol** levels (Canagliflozin and empagliflozin, 4–8%).
- Dapagliflozin may increase the rates of **breast and bladder cancers.**
- GSLT2 inhibitors may increase the incidence of **fracture** as it decreases bone mineral density at the lumbar spine and the hip.

- SGLT2 inhibitors should ***not*** be used in patients with type 1 diabetes and in those patients labelled as having type 2 diabetes but who are very insulin deficient and prone to ketosis.

Anti-diabetic drugs

Pramlintide:

- An amylin analog.
- Amylin has the following effects:
  - Reduces glucagon secretion.
  - Slows gastric emptying.
  - Centrally decreases appetite.
- Pramlintide is approved for use in insulin-treated type 1 and type 2 patients who are unable to achieve their target postprandial blood glucose levels.
- It is rapidly absorbed after subcutaneous administration; levels peak within 20 minutes, and the duration of action is not more than 150 minutes.
- Injected with a separate syringe.

Adverse effects:

- Hypoglycemia. Since the drug slows gastric emptying, recovery from hypoglycemia can be problematic because of the delay in absorption of fast-acting carbohydrates.
- Gastrointestinal symptoms.

++

Colesevelam hydrochloride:

- It is a bile acid sequestrant and cholesterol-lowering drug.
- It is approved as an antihyperglycemic therapy for persons with type 2 diabetes who are taking other medications or have not achieved adequate control with diet and exercise.

Anti-diabetic drugs

Mechanism of action:

- It is presumed to involve an interruption of the enterohepatic circulation and a decrease in farnesoid X receptor (FXR) activation.
- FXR is a nuclear receptor with multiple effects on cholesterol, glucose, and bile acid metabolism.

Adverse effects:

- Gastrointestinal; constipation, indigestion, flatulence.
- It can exacerbate triglyceridemia that commonly occurs in people with DM-T2.

THE END

Anti-diabetic drugs

REFERENCES:

- Basic and clinical pharmacology textbook 14th edition, 2018. Katzung.
- Lippincott's Illustrated Reviews, Pharmacology textbooks,7th editions, R. Harvey.
- Medscape (https://www.medscape.com/).
- DrugBank (https://www.drugbank.ca/).
- WebMD (https://www.webmd.com/).
- Drugs.com (https://www.drugs.com/).
- Healthline (https://www.healthline.com/).
- RxList (https://www.rxlist.com/script/main/hp.asp).
- NHS (https://www.nhs.uk/).