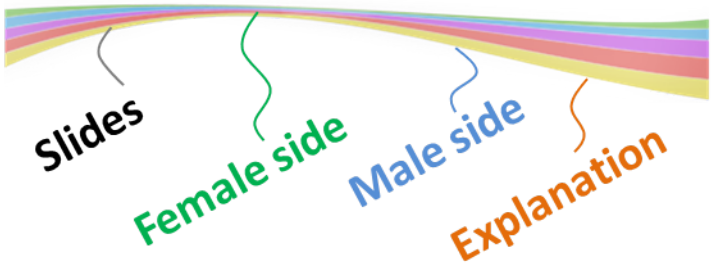
Endocrine System

PHARMACOLOGY 432 TEAM

This lecture was done by:
Ibrahim Alqasir
Hossam alshehri

And reviewed by:
Najoud Alotaibi,
Shatha al-shanqeti



ORAL HYPOGLYCEMICS

Learning Objectives:

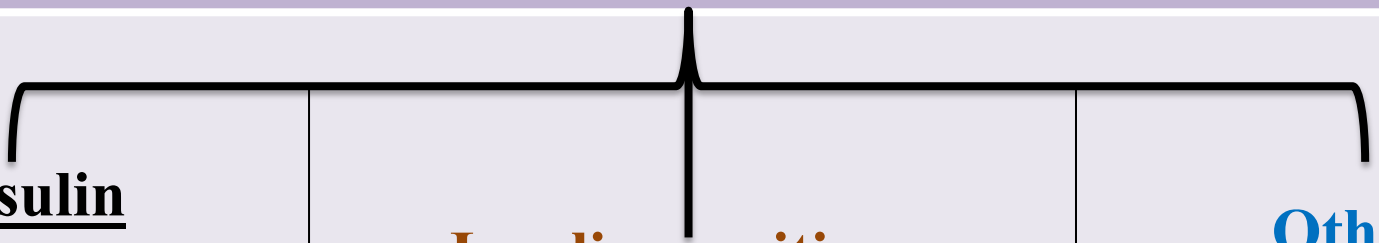
- Classify different categories of oral hypoglycemic drugs.

- Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class oral hypoglycemic drugs.

- Identify the clinical uses of hypoglycemic drugs

- Know the side effects, contraindications of each class of oral hypoglycemic drugs

Oral hypoglycemic drugs



Insulin secretagogues	Insulin sensitizers	Others
Sulfonylurea drugs	Biguanides	Alpha glucosidase inhibitors
Meglitinide analogues	Thiazolidinediones	Incretin mimetics
		Dipeptidyl peptidase 4 (DPP-4) inhibitors

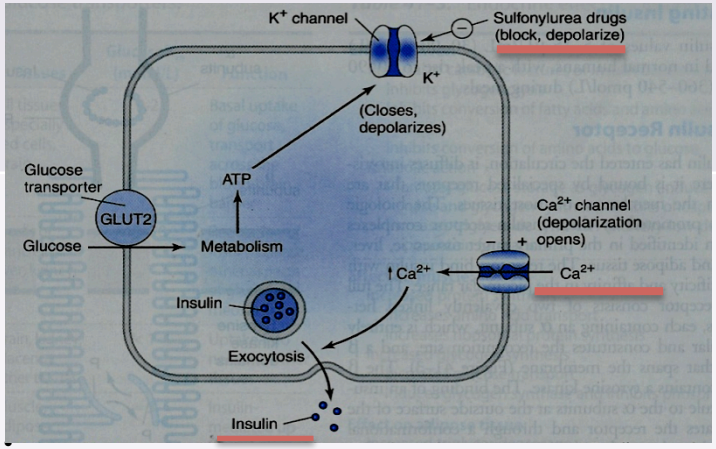
Insulin secretagogues

sulfonylureas

Mechanism: **Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels resulting in depolarization and calcium influx(Hence, not effective in totally insulin-deficient pts" type-1).**

-Potentiation of insulin action on target tissues.

-Reduction of serum glucagon concentration.



Kinetics of sulfonylureas:

Orally, well absorbed.

Reach peak concentration after 2-4 hr.

All are highly bound to plasma proteins.

Duration of action is variable.

Second generation has longer duration than first generation.

Metabolized in liver

excreted in urine

Cross placenta, stimulate fetal B cells to release insulin → hypoglycemia at birth.

Uses of sulfonylureas

Type II diabetes: monotherapy or in combination with other antidiabetic drugs

Unwanted effects :

Hyperinsulinemia & Hypoglycemia

Weight gain due to increase in appetite

Allergic reactions of sulfa drugs

Contraindications:

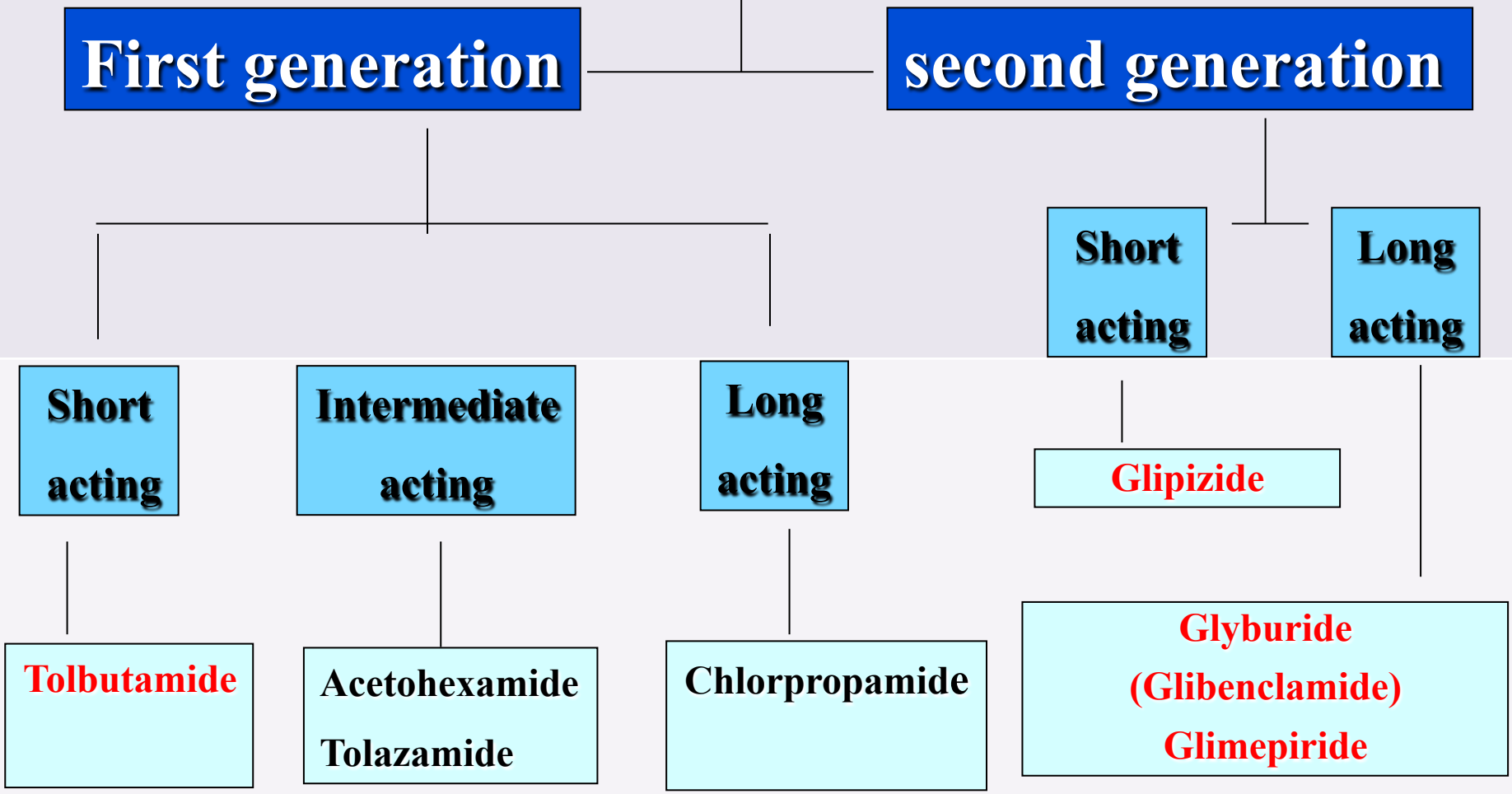
Hepatic impairment

renal insufficiency

Pregnancy & lactation

Insulin secretagogues

Classification of sulfonylureas



Insulin secretagogues

First generation sulfonylurea

	Tolbutamid short-acting	Acetohexamide intermediate-acting	Tolazamide intermediate-acting	Chlorpropamide long- acting
Absorption	Well	Well	Slow	Well
Metabolism	Yes	Yes	Yes	Yes
Metabolites	Inactive**	Active***	Active***	Inactive***
Half-life	4 - 5 hrs	6 – 8 hrs	7 hrs	24 – 40 hrs
Duration of action	Short (6 – 8 hrs)	Intermediate (12 – 20 hrs)	Intermediate (12 – 18 hrs)	Long (20 – 60hrs)
Excretion	Urine	Urine	Urine	Urine

**safe for old diabetic patients or pts with renal impairment.

***Pts with renal impairement can expect long $t_{1/2}$.

SECOND GENERATION SULPHONYLUREA

	Glipizide	Glibenclamide (Glyburide)	Glimepiride
Absorption	Well	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Moderate activity	Moderate activity
Half-life	2 – 4 hrs	Less than 3 hrs	5 - 9 hrs
Duration of action	short (10 – 16 hrs)	long (12 – 24 hrs)	long (12 – 24 hrs)
Excretion	Urine	Urine	Urine

Insulin secretagogues

Meglitinide analogues

e.g. Repaglinide
Rapidly acting insulin secretagogues
Mechanism of Action:Insulin secretagogue as sulfonylureas (same MOA)

Kinetics of Meglitinides :
Orally, well absorbed.
Very fast onset of action, peak 1 h.
short duration of action (4 h).
Metabolized in the liver & excreted in bile.

Uses of Meglitinides

-Type II diabetes(monotherapy or combined with other antidiabetics).

-Patients allergic to sulfonylurea.

Adverse effects of Meglitinides

-Hypoglycemia

-Weight gain.

Insulin sensitizers

Biguanides, e.g. Metformin

Mechanism of action of metformin

Does not stimulate insulin release.
Increases liver,muscle&adipose tissues sensitivity to insulin & increase peripheral glucose utilization.
Inhibits gluconeogenesis.
Impairs glucose absorption from GIT.

Kinetics of metformin:

orally.
Not bound to serum protein.
Not metabolized.
t ½ 3 hours.
Excreted unchanged in urine.

Uses of metformin

-Obese patients with type II diabetes
Monotherapy or in combination.

Advantages:

No risk of hyperinsulinemia or hypoglycemia or weight gain (anorexia).

Adverse effects of metformin

Metallic taste in the mouth
GIT disturbances: nausea, vomiting, diarrhea
Lactic acidosis(rare 1:30,000)
Long term use interferes with vitamin B_{12} absorption.

Contraindications of metformin

Renal impairement.
Liver impairement.
Lung disease
Alcoholism.
Heart failure

Insulin sensitizers

Thiazolidinediones E.g Pioglitazone

Mechanism of action

Increase sensitivity of target tissues to insulin.

Increase glucose uptake and utilization in muscle and adipose tissue.

Kinetics of Pioglitazone:

Orally (once daily dose).
Highly bound to plasma albumins (99%)
Slow onset of activity
Half life 3-4 h
Metabolized in the liver
Excreted in urine 64% & bile

Uses of Pioglitazone

-Type II diabetes with insulin resistance.
-Used either alone or combined with sulfonylurea, biguanides or insulin.
-No risk of hypoglycemia when used alone

Adverse effects of Pioglitazone

Hepatotoxicity ?? (liver function tests for 1st year of therapy).

Fluid retention (Edema).

Precipitate congestive heart failure

Mild weight gain.

others : α-Glucosidase inhibitors

Acarbose, Meglitol

Mechanism: **Reversible inhibitors of intestinal α-glucosidases in intestinal brush border responsible for degradation of oligosaccharides to monosaccharides**
(competitively inhibit carbohydrates digestion)

Kinetics of Acarbose:
Given orally, poorly absorbed.
Metabolized by intestinal bacteria.
Excreted in stool and urine.

Side effects:
1-GIT: Flatulence, diarrhea, abdominal pain.
2- No hypoglycemia if used alone.

Actions:
1-decrease carbohydrate digestion and absorption in small intestine.

2-Decrease postprandial hyperglycemia.

3-Taken just before meals.

others : Incretin mimetics

Exenatide(GLP-1)

Kinetics:

1- is glucagon-like peptide-1 (GLP-1) agonist.

2- given s.c. once or twice daily.

Mechanism Of Action:

Stimulation of GLP-1 secretion from intestine which in turn stimulate insulin secretion from β cells.

Indications:

Therapy of patients with type 2 diabetes. who are not controlled with oral medicine

Side Effects:

Nausea & vomiting

Others :Dipeptidyl peptidase-4 (DPP- 4) inhibitors

Sitagliptin, Vildaglibtin

Kinetics:

Orally

Given once daily

half life 8-14 h

Dose is reduced in pts with renal impairment

Mechanism Of Action:

Inhibit DPP-4 enzyme and leads to an increase in incretin hormones level. (leads to more insulin and less glucagon)

Indications:

1-Type 2 DM as an adjunct to diet & exercise

2- as a monotherapy or in combination with other antidiabetic drugs.

Side Effects:

1-Nausea, abdominal pain, diarrhea

2- Nasopharyngitis

Summary

	Drugs	MOA	Kinetics	uses	Advers Effects	Contraindic.
Insulin secretagogues	Sulfonylurea There are further classifications (1^{st},2^{nd}). Site of action : Pancreatic B cells	Stimulate insulin release from functioning B cells by blocking ATP-sensitive K^+ channels which causes depolarization and opening of voltage-dependent Ca^{2+} channels, which causes an increase in intracellular calcium in the beta cells and stimulates insulin release.	-Orally, well absorbed. -Reach peak conc. after 2-4 hr. - bound to plasma proteins. -Duration of action is variable. -Second generation has longer duration than first generation. -Metabolized in liver -excreted in urine (elderly and renal disease) -Cross placenta, stimulate fetal β-cells to release insulin →fetal hypoglycemia	1^{st} gen. Tolbutamide (short) safe for old diabetic patients or patients with renal impairment. 2^{nd} gen. Glipizide (short) - glyburide (Glibenclamide) (long) Better then 1^{st} gen.	Hyperinsulinemia & Hypoglycemia: --Less in tolbutamide. --More in old age, hepatic or renal diseases. Weight gain due GIT upset. Allergic reactions in pts sensitive to sulfa drugs	Hepatic impairment Or renal insufficiency Pregnancy & lactation
	Meglitinides e.g. Repaglinide rapidly acting insulin secretagogue Site of action : Pancreatic B cells	Stimulate insulin release from functioning β cells via blocking ATP-sensitive K-channels resulting in calcium influx and insulin exocytosis. Same as Sulfonylurea!	-Orally, well absorbed. -Very fast onset of action, peak 1 h. -short duration of action (4 h). -Metabolized in liver -excreted in bile. -Taken just before each meal (3 times/day).	-Type II diabetes - patients allergic to sulfa drugs e.g. sulfonylureas. - used as monotherapy or combined with metformin	Hypoglycemia. Weight gain.	

Summary

	Drugs	MOA	Kinetics	uses	Advers Effects	Contraindic.
Insulin sensitizers	Biguanides e.g. Metformin Does not require functioning B cells. Does not stimulate insulin release. Site of action : Liver	-Decrease insulin resistance. -Increases peripheral glucose utilization (tissue glycolysis). -Inhibits hepatic gluconeogenesis. -Impairs glucose absorption from GIT. ↓LDL , ↓ VLDL & ↑ HDL	-orally. -Not bound to serum protein. -Not metabolized. -t ½ 3 hours. -Excreted unchanged in urine No risk of hypoglycemia!!! Mild weight loss (anorexia).	Type II diabetes particularly in overweight and obese people (with insulin resistance).	-GIT disturbances -Long term use interferes with vitamin B12 absorption. -Lactic acidosis: in patients with renal, liver, pulmonary or cardiac diseases. -Metallic taste.	-Pregnancy. -Renal disease. -Liver disease. -Alcoholism. Conditions predisposing to hypoxia as cardiopulmonary dysfunction
	Thiazolidinediones (glitazones) Pioglitazone (Actos) Site of action : Fat and Muscles	-Activate PPAR-γ (peroxisome proliferator-activated receptor - γ). -Decrease insulin resistance. -Increase sensitivity of target tissues to insulin. -Increase glucose uptake and utilization in muscle and adipose tissue.	-Orally (once daily dose) -Highly bound to plasma albumins (99%) -Slow onset of activity -Half life 3-4 h -Metabolized in liver -Excreted in urine 64% & bile -No risk of hypoglycemia when used alone.	-Type II diabetes with insulin resistance. -Used either alone or combined with sulfonylureas, bigunides.	-Hepatotoxicity ? ? (LFT for 1st year of therapy). -Fluid retention (Edema). -**Precipitate congestive heart failure** -Mild weight gain.	-Congestive heart failure. -Pregnancy. -Lactating women -Significant liver disease.

	Drugs	MOA	Kinetics	uses	Advers Effects	Contraindic.
Others	Alpha glucosidase inhibitors Acarbose Site of action : GIT	-Reversible inhibitors of intestinal α-glucosidases in intestinal brush border that are responsible for carbohydrate digestion. -Decrease carbohydrate digestion and glucose absorption in small intestine.	-Given orally, poorly absorbed. -Metabolized by intestinal bacteria. -Excreted in stool and urine. Decrease postprandial hyperglycemia. Taken just before meals. No hypoglycemia if used alone.	-Decrease postprandial hyperglycemia. -earliest stages of impaired glucose tolerance -combined with sulfonylurea in the treatment of Type 2 diabetes to improve blood glucose control.	GIT: Flatulence, diarrhea, abdominal pain	
	Dipeptidyl peptidase-4 (DPP-4) inhibitors e.g. Sitagliptin Site of action : GIT	-itagliptin inhibits DPP-4 enzyme, which metabolizes the naturally occurring incretin hormones thus increase incretin secretion (gastrointestinal hormones secreted in response to food). - Incretin hormones	-Orally -Given once daily -half life 8-14 h -Dose is reduced in pts with renal impairment -decreases blood glucose level by : ---Increasing insulin secretion ---Decreasing glucagon secretion.	Type II diabetes mellitus as a monotherapy or in combination with other oral antidiabetic drugs when diet and exercise are not enough.	GIT: Nausea, abdominal pain, diarrhea.	

Q1: A patient with T2D was given a certain drug to control his glucose levels, the patient has been vomiting since then, which drug is responsible?

A) Exenatide
B) Sitagliptin
C) Acarbose
D) Miglitol

Q2: Nasopharyngitis is a SE of :

A) Exenatide
B) Sitagliptin
C) Acarbose
D) Miglitol

Q3: Which drug dose you should adjust when prescribing to your T2D patient who's kidneys are insufficient ?

A) Exenatide
B) Sitagliptin
C) Acarbose
D) Miglitol

Answers: 1- A 2-B 3-B

Q4: patient with t2dm on oral hypoglycemics was admitted to the clinic with megaloblastic anemia, which one of the following oral hypoglycemics was he taking ?

A) Exenatide
B) metformin
C) Acarbose
D) Tolbutamide

Q5: which of the following is the MOA for Pioglitazone

A) is glucagon-like peptide-1 (GLP-1) agonist
B) blocking of ATP-sensitive K channels
C) Increase sensitivity of target tissues to insulin
D) competitively inhibit carbohydrates digestion

Answers: 4- B 5-C

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PHARMACOLOGY 432 TEAM

Pharmacology Leaders

Tuqa Al-Kaff & Abdullah Al-Anzi

Pharmacologyteam1@gmail.com