

# Antidiabetic Drugs

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(Slides are adopted and modified from Prof. Hanan Hagar)

# *Objectives*

*By the end of this lecture, students should be able to:*

- 1. Classify different categories of antidiabetic drugs.*
- 2. Identify mechanism of action, pharmacokinetics and pharmacodynamics of each class of antidiabetic drugs.*
- 3. Identify the clinical uses of antidiabetic drugs*
- 4. Know the side effects, contraindications of each class of antidiabetic drugs.*



# Types of diabetes mellitus

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- **Type I**

*due to autoimmune or viral diseases*

- **Type II**

*due to obesity, genetic factors*

# Type II Diabetes

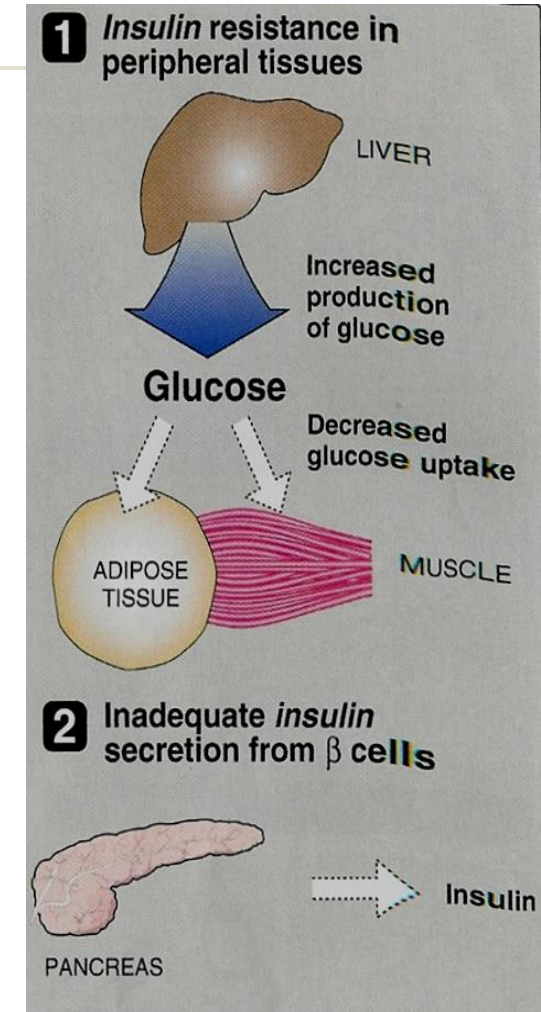
- **80-90% occurrence**
- **Over age 35**
- **Obesity** is an important factor.

# Pts with Type II diabetes have two physiological defects



1. Abnormal insulin secretion.

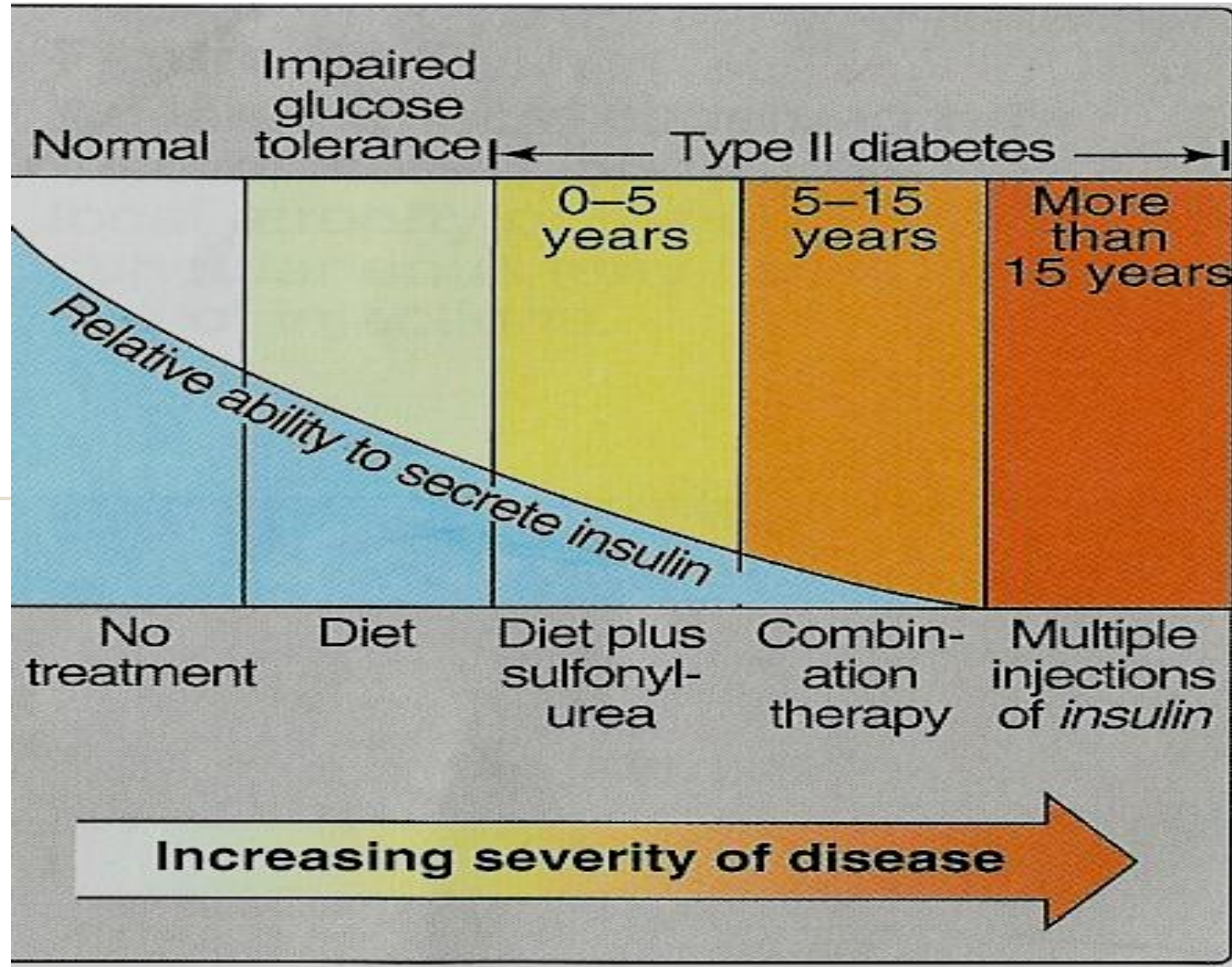
2. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.



# **Treatment of Type II Diabetes (NIDDM)**

- **Proper dietary management.**
- **Caloric restriction and weight loss are important in obese diabetic patients.**
- **Increase physical activity.**
- **Antidiabetic drugs.**

# Types II diabetes



# Antidiabetic drugs

## Insulin secretagogues

- **Sulfonylurea drugs**
- **Meglitinides**
- **Incretin mimetics**

## Insulin sensitizers

- **Biguanides**
- **Thiazolidinediones**

Note: Antidiabetic drugs = oral hypoglycemic and others



## Others

- Agents that reduce carbohydrate absorption  
(Alpha glucosidase inhibitors).
- **Agents that reduce glucose renal reabsorption**  
(SGLT-2, Sodium/glucose cotransporter 2 inhibitors)

# Insulin secretagogues

- **Are drugs which increase the amount of insulin secreted by the pancreas.**
- **Their action depends upon functioning pancreatic  $\beta$ -cells**

## **Include:**

- **Sulfonylureas**
- **Meglitinides**
- **Incretin mimetics**

## **Mechanism of action of sulfonylureas:**

- **Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels which causes depolarization and opening of voltage- dependent calcium channels, which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release.**

# Insulin secretagogues (sulfonylureas)

↑ Hyperglycemia



Blockade of ATP dependent  $K^+$  channels



Opening of voltage-dependent  $Ca^{++}$  channels

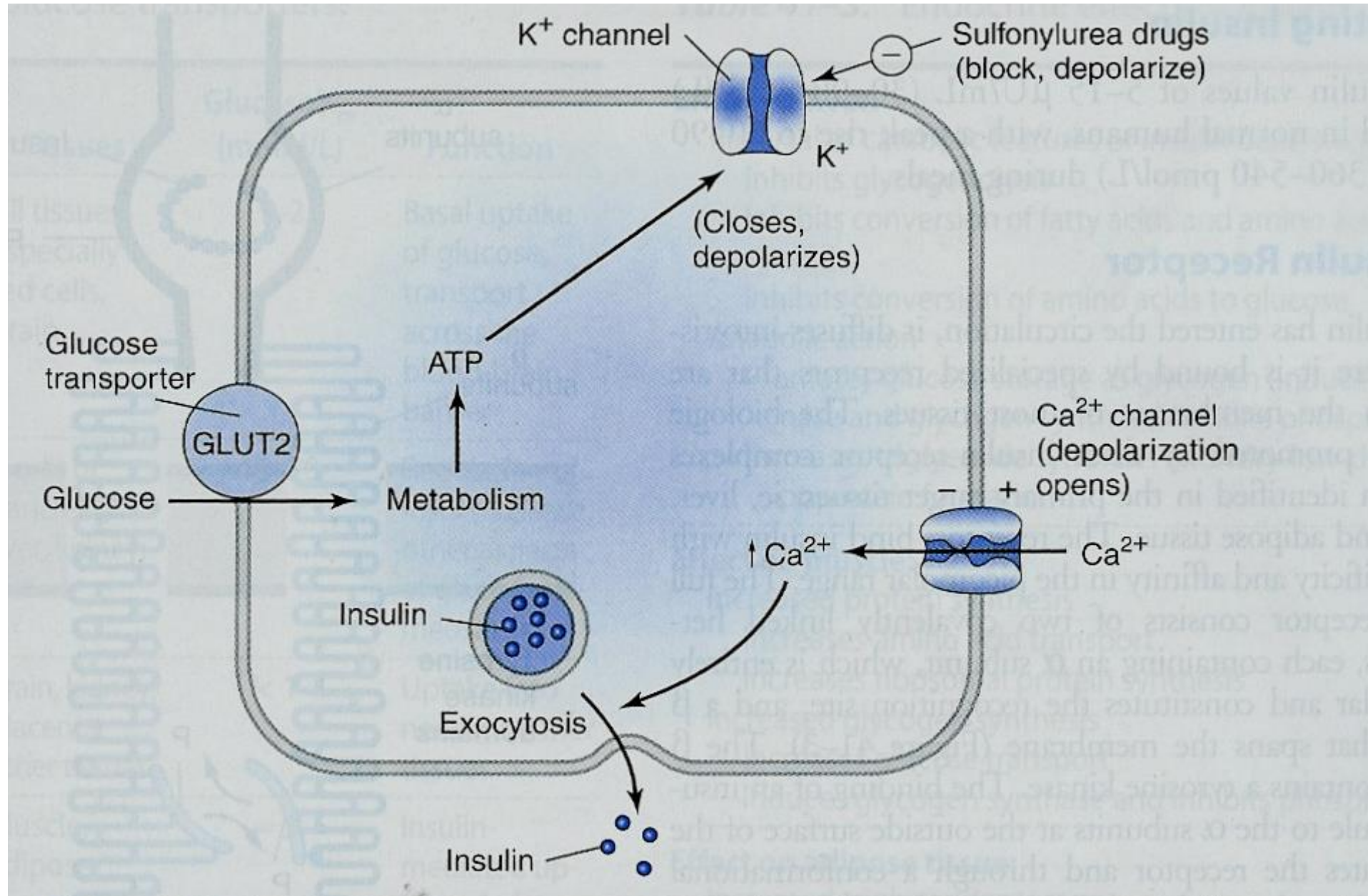


↑ intracellular calcium in the beta cells



↑ Insulin release

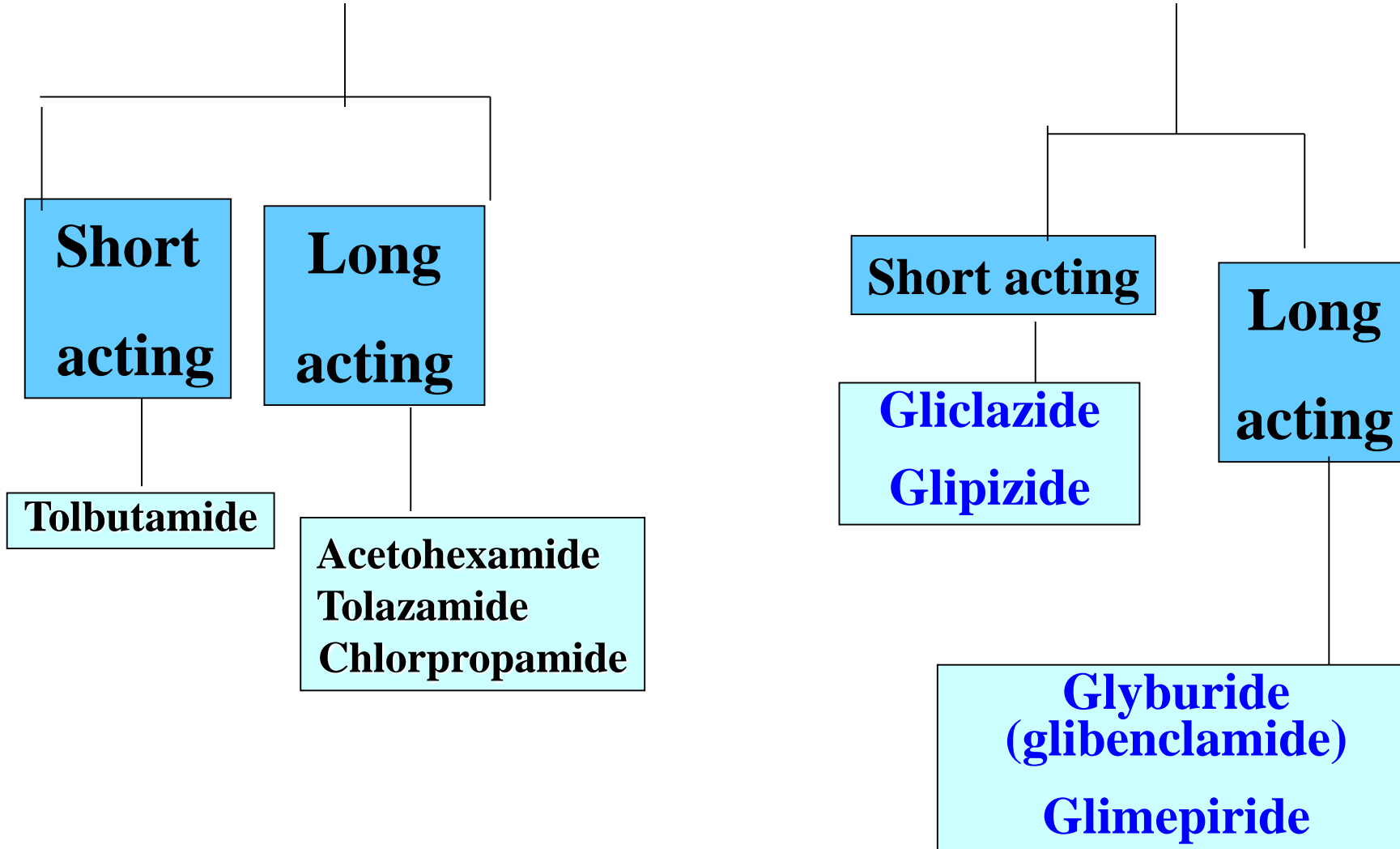
# Mechanisms of Insulin Release



# Classification of sulfonylureas

**First generation**

**second generation**



## Pharmacokinetics 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.**

## Pharmacokinetics of sulfonylureas:

- **Metabolized in liver**
- **Excreted in urine (elderly and renal disease)**
- **Cross placenta, stimulate fetal  $\beta$ -cells to release insulin  $\rightarrow$  fetal hypoglycemia at birth.**



## **Second generation sulfonylureas**

**Short acting: Gliclazide, Glipizide**

**Long acting: Glyburide, Glimepiride**

- **More potent than first generation**
- **Have longer duration of action.**
- **Less frequency of administration**
- **Have fewer adverse effects & drug interactions.**

# SECOND GENERATION SULPHONYLUREAS

	<b>Glipizide</b>	<b>Glyburide (Glibenclamide)</b>	<b>Glimepiride</b>
<b>Absorption</b>	<b>Well reduced by food</b>	<b>Well</b>	<b>Well</b>
<b>Metabolism</b>	<b>Yes</b>	<b>Yes</b>	<b>Yes</b>
<b>Duration of action</b>	<b>10 – 16 hrs short</b>	<b>12 – 24 hrs long</b>	<b>12 – 24 hrs long</b>
<b>Doses</b>	<b>Divided doses 30 min before meals</b>	<b>Single dose</b>	<b>Single dose</b>
<b>Excretion</b>	<b>Urine</b>	<b>Urine</b>	<b>Urine</b>

# Uses of sulfonylureas

**Treatment of Type II diabetes monotherapy or  
in combination with other antidiabetic drugs.**

## Unwanted Effects:

### **1. Hyperinsulinemia & Hypoglycemia:**

- **More common in long acting sulfonylureas. particularly (glyburide, and glimepiride)**
- **More in old age, hepatic or renal diseases.**

**2. Weight gain due to increase in appetite** unless the diabetic diet and exercise program are followed.



# Meglitinides

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## Drugs

- **Repaglinide**

## Mechanism of Action:

- **Rapidly acting insulin secretagogues**
- **Mechanism of action is identical to sulfonylureas.**

## Pharmacokinetics of meglitinides

- **Orally, well absorbed.**
- **Very fast onset of action, peak 1 h.**
- **Short duration of action (4 h).**
- **Metabolized in liver and excreted in bile.**
- **Taken just before each meal (3 times/day) the dose should be skipped if the meal is missed.**

## Uses of Meglitinides

- **Type II diabetes:**
  - monotherapy or in combination with other oral hypoglycemic drugs
- **As alternative to sulfonylureas (SU) in patients allergic to SU.**



# **Adverse effects of Meglitinides**

## **Less incidence than sulfonylureas**

- **Hypoglycemia.**
- **Weight gain.**

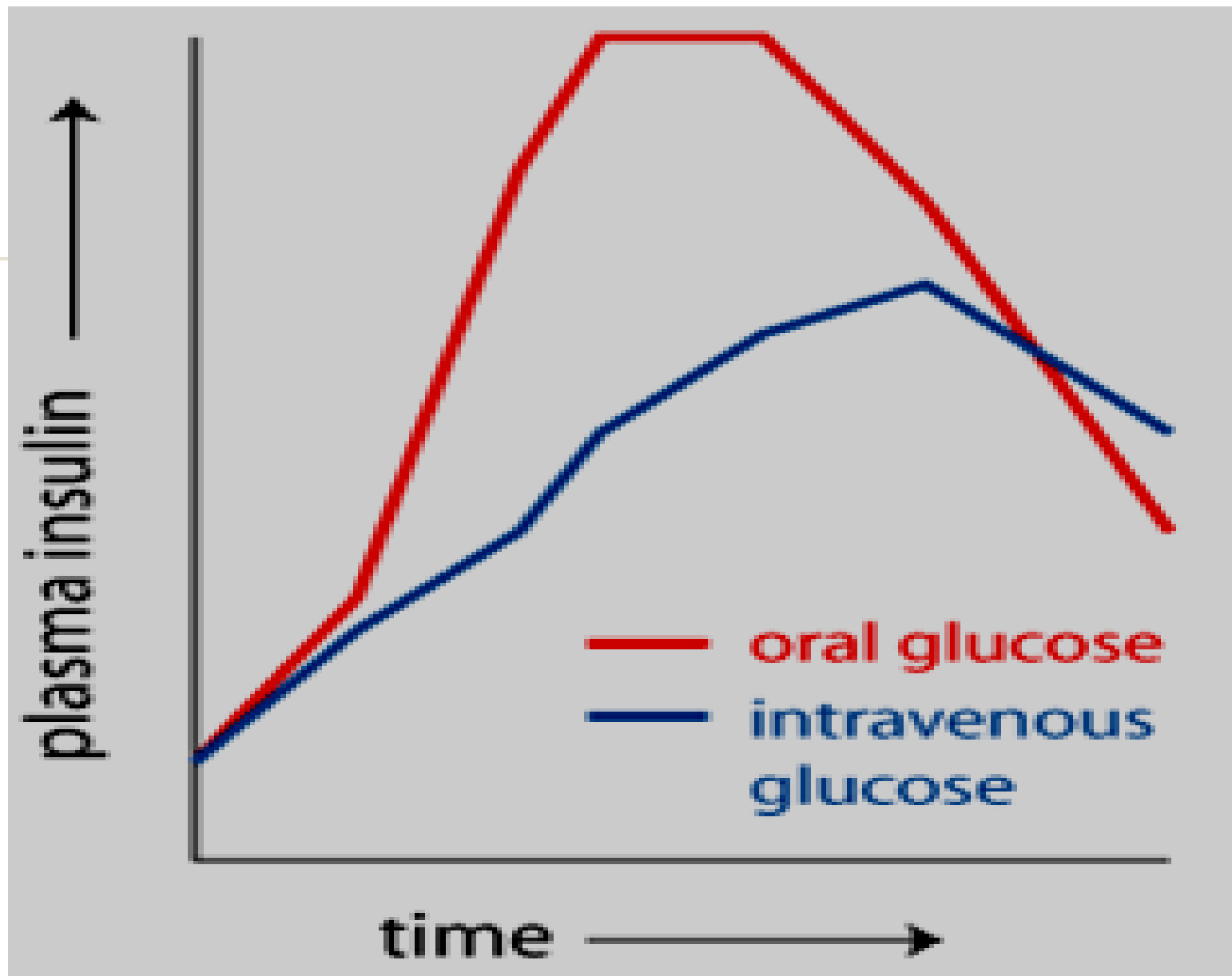


# Incretins

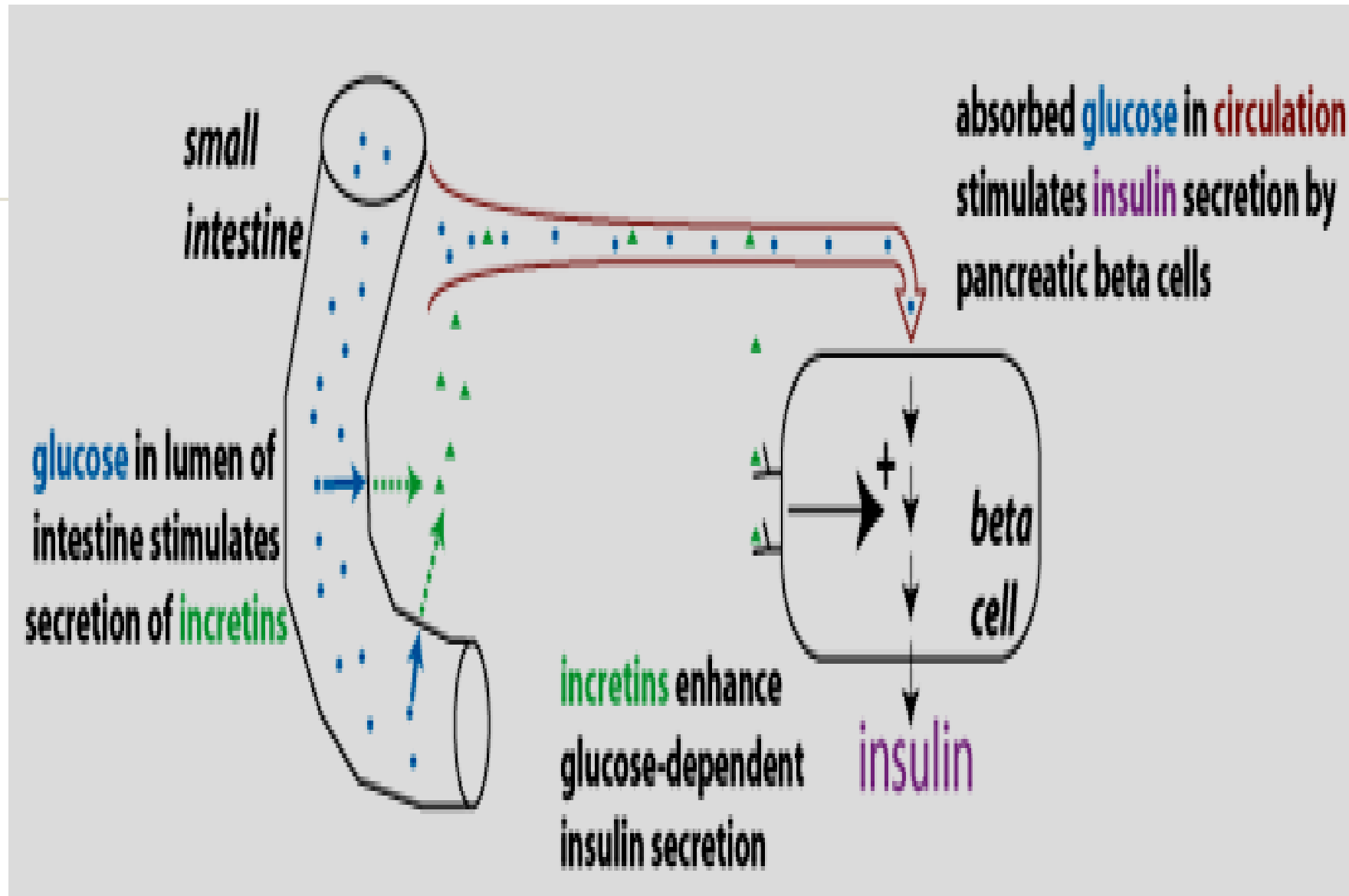
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- **Incretins** are GI hormones secreted from intestine in response to food even before blood glucose level becomes elevated. They are carried through circulation to pancreatic beta cells.
- **Incretins regulate blood glucose by:**
  - Increase insulin secretion
  - Decrease glucagon secretion

# Incretins



# Incretins



# Incretins

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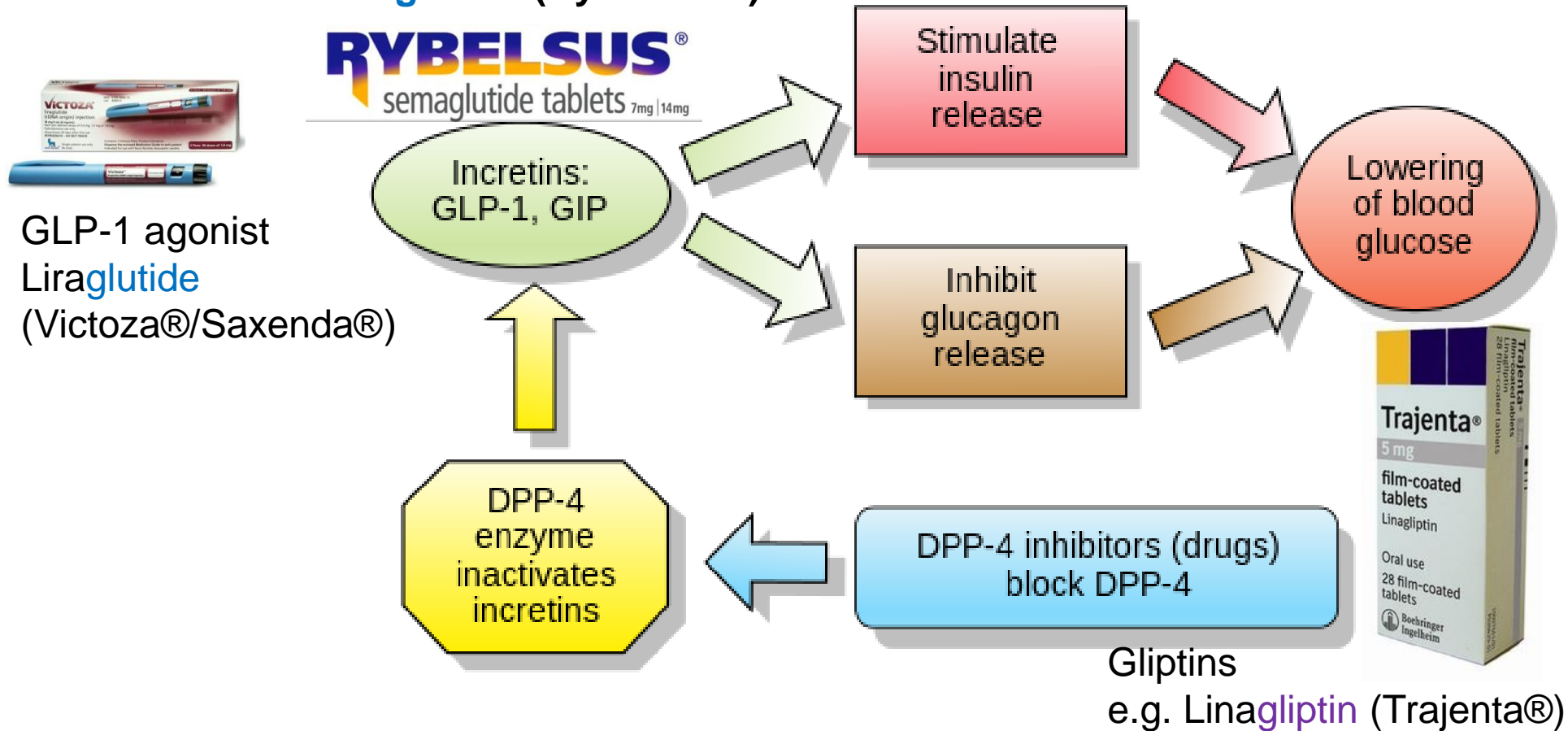
- **Incretins include:**
  - **GLP-1** (glucagon-like peptide-1)
  - **GIP** (gastric inhibitory peptide)

**Both are inactivated by dipeptidyl peptidase-4 (DPP-4).**

# Mechanism of Action of Incretin Mimetics



New FDA approved and  
1<sup>st</sup> oral GLP-1 ago  
**Semaglutide (Rybelsus®)**



**GLP**, glucagon-like peptide; **DDP**, dipeptidyl peptidase  
**GIP**, gastric inhibitory peptide (also called **g**lucose-dependent insulinotropic peptide)

# Incretins mimetics

## Glucagon-like peptide-1 (GLP-1) agonists

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### Include:

- **Dulaglutide (Trulicity®)**
- **Liraglutide**
  - **Victoza®**, is the lower dose for diabetes
  - **Saxenda®**, is the higher dose for obesity
- **Exenatide**
  - **Byetta®**, immediate-release given S.C. twice daily
  - **Bydureon®**, extended-release given once weekly



# Incretins mimetics

## Glucagon-like peptide-1 agonists

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### GLP-1 agonists

**Liraglutide (Victoza, Saxenda)<sup>R</sup>**

### **Mechanism of action**

- Binds to GLP-1 receptors & stimulates insulin secretion from  $\beta$  cells.
- It also reduces glucagon secretion by inhibiting alpha cells of the pancreas.
- It decreases appetite and inhibits body weight gain.



# GLP-1 agonists (Incretin mimetics)

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- **e.g. Liraglutide**
- **Given s.c. once/day (single- dose pre-filled disposable pens)**
- **Used together with diet and exercise to treat type 2 diabetes and in patients who are not controlled with other oral antidiabetics.**
- **Not used in type I diabetes.**

# GLP-1 agonists (Incretin mimetics)

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- e.g. **Liraglutide**

**As a treatment for adults who are obese or overweight with at least one weight-related comorbid condition (e.g. hypertension, type 2 diabetes mellitus, or dyslipidemia).**

# GLP-1 agonists (Incretin mimetics)

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## **Adverse effects**

- **Nausea, vomiting and diarrhea (most common)**
- **Hypoglycemia when combined with sulfonylureas or insulin.**
- **Pancreatitis (rare)**

# First Oral GLP-1



**RYBELSUS**<sup>®</sup>  
semaglutide tablets 7mg | 14mg

- **Rybelsus<sup>®</sup> (Semaglutide)** was the first oral GLP-1 approved by US FDA to for type 2 diabetes treatment (Sep. 2019)

<https://www.fda.gov/news-events/press-announcements/fda-approves-first-oral-glp-1-treatment-type-2-diabetes>

Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors)

e.g. **Sitagliptin**, **vildagliptin**

**Sitagliptin (Januvia)<sup>R</sup>**

- **Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).**
- **Is given orally.**
- **Is given once daily.**

## Mechanism of action

- **Inhibit DPP-4 enzyme and leads to an increase in incretin hormones level.**
- **This results in an increase in insulin secretion & decrease in glucagon secretion.**

# Clinical uses

**Type II DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetic drugs.**

## **Adverse effects**

- **Nausea, abdominal pain, diarrhea.**
- **Nasopharyngitis and headache.**

## Insulin sensitizers

- **Are drugs which increase the sensitivity of peripheral target organs to insulin.**

### **Include**

- **Biguanides e.g. metformin**
- **Thiazolidinediones e.g. pioglitazone**



# Biguanides

**e.g. Metformin**

## Mechanism of action of metformin

- **Reduces insulin resistance.**
- **Increases sensitivity of liver, muscle & adipose tissues to insulin & increase peripheral glucose utilization (tissue glycolysis).**
- **Inhibits hepatic glucose production (gluconeogenesis).**
- **Impairs glucose absorption from GIT.**
- **Improve lipid profile ↓LDL, ↓ VLDL ,↑ HDL**

## Pharmacokinetics of metformin

- **Orally.**
- **NOT bound to serum protein.**
- **NOT metabolized.**
- **$t_{1/2} = 3$  hours.**
- **Excreted unchanged in urine**

## Uses of metformin

- **In patients with type 2 diabetes who are obese** because it promotes modest weight reduction (**first-line therapy**).
- **Type II diabetes as monotherapy or in combination.**

## **Advantages of metformin**

- **No risk of hypoglycemia**
- **No weight gain**
- **Has prominent lipid-lowering activity**
- **Inexpensive**

# Adverse effects of metformin

- **GIT disturbances:**
- **Metallic taste in the mouth, nausea, vomiting, diarrhea.**
- **Metformin should be taken with meals and should be started at a low dose to avoid intestinal side effects then increase gradually.**

# Adverse effects of metformin

- **Lactic acidosis (very rare)**

**Serious lactic acid accumulation usually occurs only in the presence of a predisposing conditions**

- **Renal insufficiency**
- **Severe liver disease**
- **Alcohol abuse.**
- **Heart failure**
- **Pulmonary insufficiency**
- **Cardiogenic or septic shock**

## Adverse effects of metformin

- Interference with **vitamin B<sub>12</sub> absorption** (long term use).



## **Contraindications of metformin**

- **Renal disease.**
- **Liver disease.**
- **Alcoholism.**
- **Cardiopulmonary dysfunction.**
- **Pregnancy.**

Insulin sensitizers  
Thiazolidinediones (glitazones)

- **Pioglitazone**
- **Rosiglitazone**

# Mechanism of action

- **Activate peroxisome proliferator-activated receptor  $\gamma$  (PPAR- $\gamma$ ).**
- **Increase sensitivity of target tissues to insulin.**
- **Increase glucose uptake and utilization in muscle and adipose tissue.**

# Pharmacokinetics of glitazones

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

## **Uses of glitazones**

- **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 glitazones**

- **Hepatotoxicity (liver function tests for 1st year of therapy).**
- **Fluid retention (Edema).**
- **Congestive heart failure**
- **Mild weight gain.**
- **Failure of estrogen-containing oral contraceptives**

## $\alpha$ -Glucosidase inhibitors

- **Acarbose**
- **Miglitol**

## $\alpha$ -Glucosidase inhibitors

- Reversible inhibitors of **intestinal  $\alpha$ -glucosidases** in intestinal brush border cells that are responsible for carbohydrate digestion.
- Decrease carbohydrate digestion and glucose absorption in small intestine (**lower postprandial glucose level**).



# $\alpha$ -Glucosidase inhibitors

## **Acarbose**

- **Given orally**
- **Is not absorbed.**
- **Excreted in feces**
- **Taken just before meals.**
- **No hypoglycemia if used alone.**

## Uses of $\alpha$ -glucosidase inhibitors

- **Effective alone in the earliest stages of **impaired glucose tolerance****
- **Not recommended alone as therapy for moderate to severe hyperglycemia**
- **Most useful in combination with other oral hypoglycemic drugs or with insulin.**

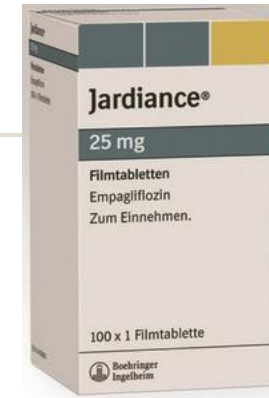
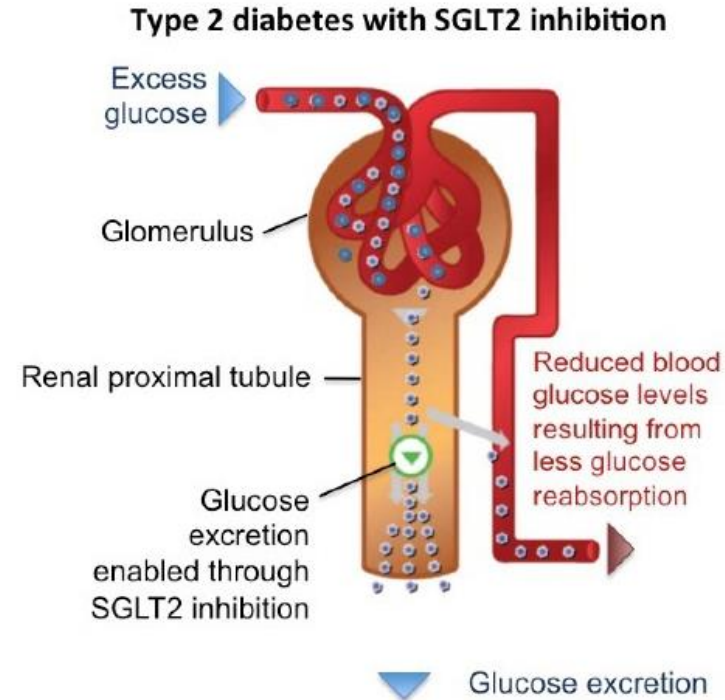
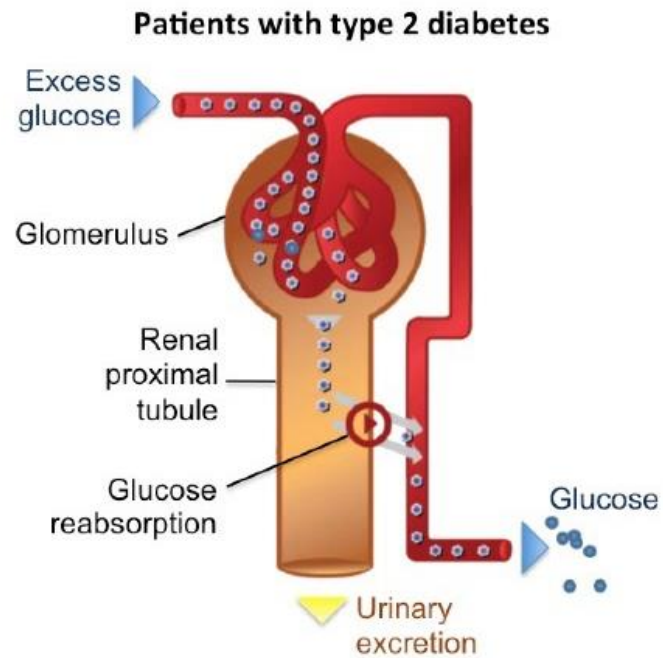
## Adverse effects

- **GIT side effects: Flatulence, bloating, diarrhea, abdominal pain.**

# **Contraindications of $\alpha$ -glucosidase inhibitors**

- **Irritable bowel syndrome**
- **Inflammatory bowel disorders**
- **Intestinal obstruction.**

# Gliflozins are SGLT-2 inhibitors (Dapagliflozin, Canagliflozin, Empagliflozin)

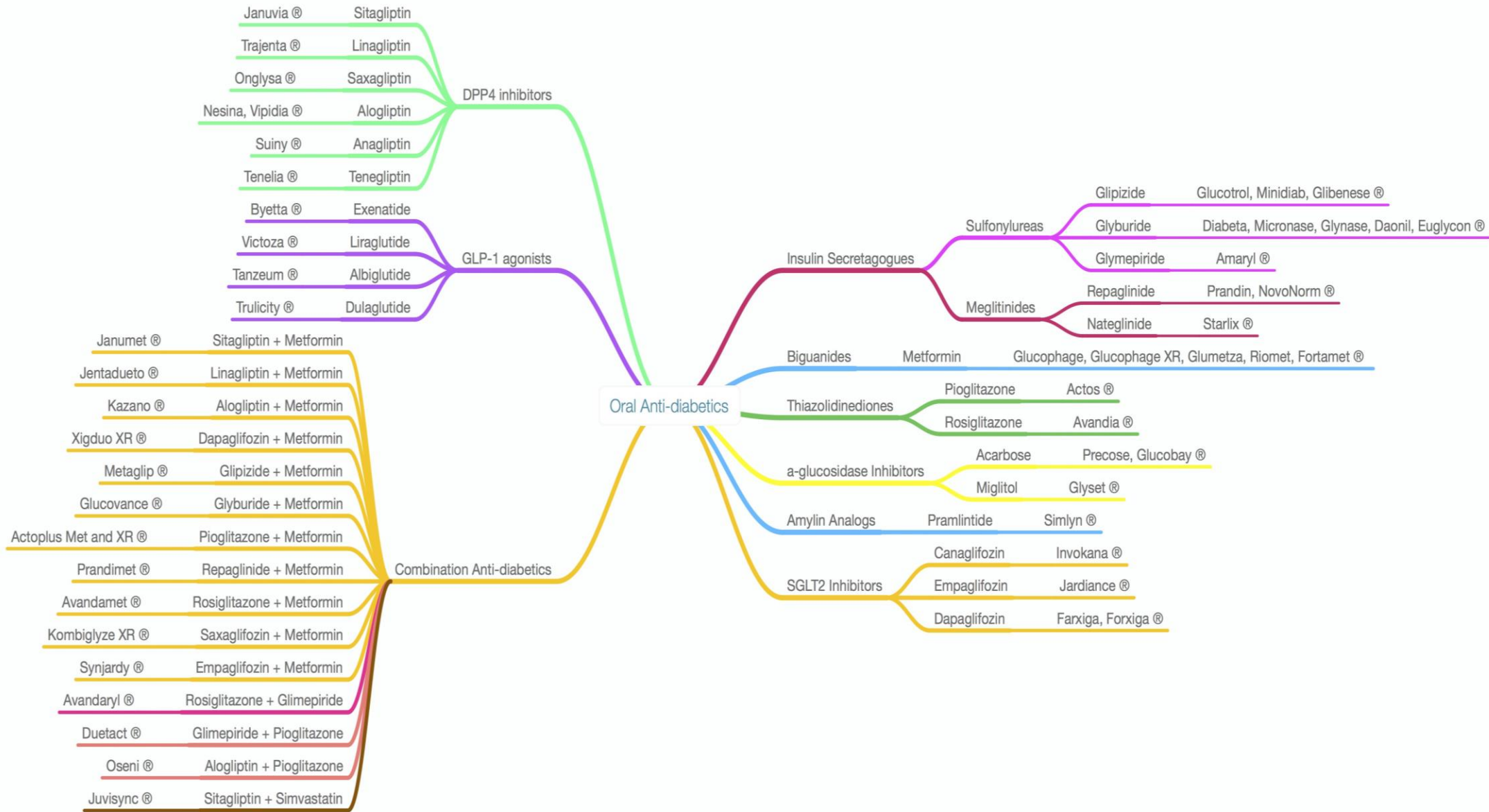


- Adapted from:
1. Chao EC & Henry RR. Nature Reviews Drug Discovery 2010;9:551-559.
  2. DeFronzo RA, et al. Diab Obes Metab 2012;14:5-14.
  3. Washburn WN. J Med Chem 2009;52:1785-1794.

**SGLT-2, Sodium/glucose cotransporter 2**

# SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
<b>Sulfonylureas</b> <b>Gliczide</b>	<u>Stimulates insulin secretion</u>	<b>Pancreatic beta cells</b>	<ul style="list-style-type: none"> <li>• Effective</li> <li>• Inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoglycemia</li> <li>• Weight (Wt) gain</li> </ul>
<b>Meglitinides</b> <b>Repaglinide</b>		<b>Pancreatic beta cells</b>	<b>Sulfa free</b>	<ul style="list-style-type: none"> <li>•Hypoglycemia</li> <li>•Wt gain</li> </ul>
<b>Biguanides</b> <b>Metformin</b>	Decreases <u>insulin resistance</u>	<b>Liver</b>	<ul style="list-style-type: none"> <li>• mild weight loss</li> <li>• No hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>• GIT symptoms,</li> <li>• Lactic acidosis</li> <li>• Metallic taste</li> </ul>
<b>Thiazolidinediones</b> <b>pioglitazone</b>		<b>Fat, muscle</b>	<b>No hypoglycemia</b>	<b>Hepatotoxicity</b> <b>Edema, mild wt gain</b>
<b>Incretins mimetics</b> <b>Dulaglutide</b>	<b>Increase incretin</b>	<b>GI tract</b>	<b>Once/week, s.c.</b>	<b>Nausea &amp; vomiting</b>
<b>DPP-4 inhibitors</b> <b>Sitagliptin</b>	<b>Inhibit incretin breakdown</b>	<b>GI tract</b>	<b>orally</b>	<b>Nausea &amp; abdominal pain</b>
<b><math>\alpha</math>-Glucosidase inhibitors</b> <b>Acarbose</b>	<b>Inhibits <u><math>\alpha</math>-glucosidase</u></b>	<b>GI tract</b>	<b>Low risk</b>	<ul style="list-style-type: none"> <li>•GI symptoms, flatulence</li> </ul>
<b>SGLT-2 inhibitors</b> <b>Dapagliflozin</b>	<b>Inhibit renal SGLT-2</b>	<b>Kidney</b>	<b>Orally</b> <b>Reduced Na (CV benefits)</b>	<b>Genital yeast/UTI</b> <b>Increased urination</b>



# Supplementary Slide



HbA1c test score	MEAN BLOOD GLUCOSE mg/dL	mmol/L
14.0	380	21.1
13.0	350	19.3
12.0	315	17.4
11.0	280	15.6
10.0	250	13.7
9.0	215	11.9
8.0	180	10.0
7.0	150	8.2
6.0	115	6.3
5.0	80	4.7
4.0	50	2.6

The hemoglobin A1c test represents the average level of blood sugar over the past 2-3 months.