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

- **Type I**

  due to autoimmune or viral diseases

- **Type II**

  due to obesity, genetic factors

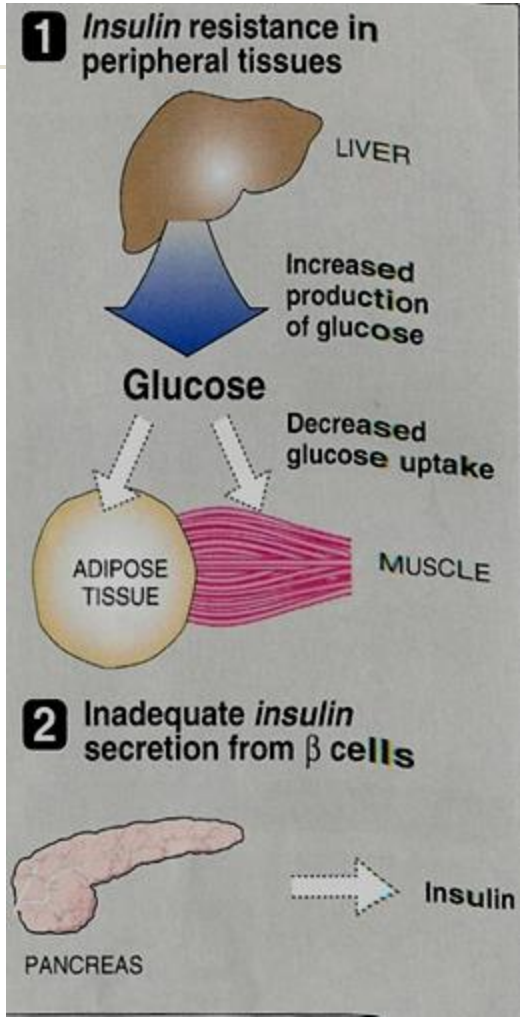
Type II Diabetes

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

Pts with Type II diabetes have two physiological defects

1. **Abnormal insulin secretion.**

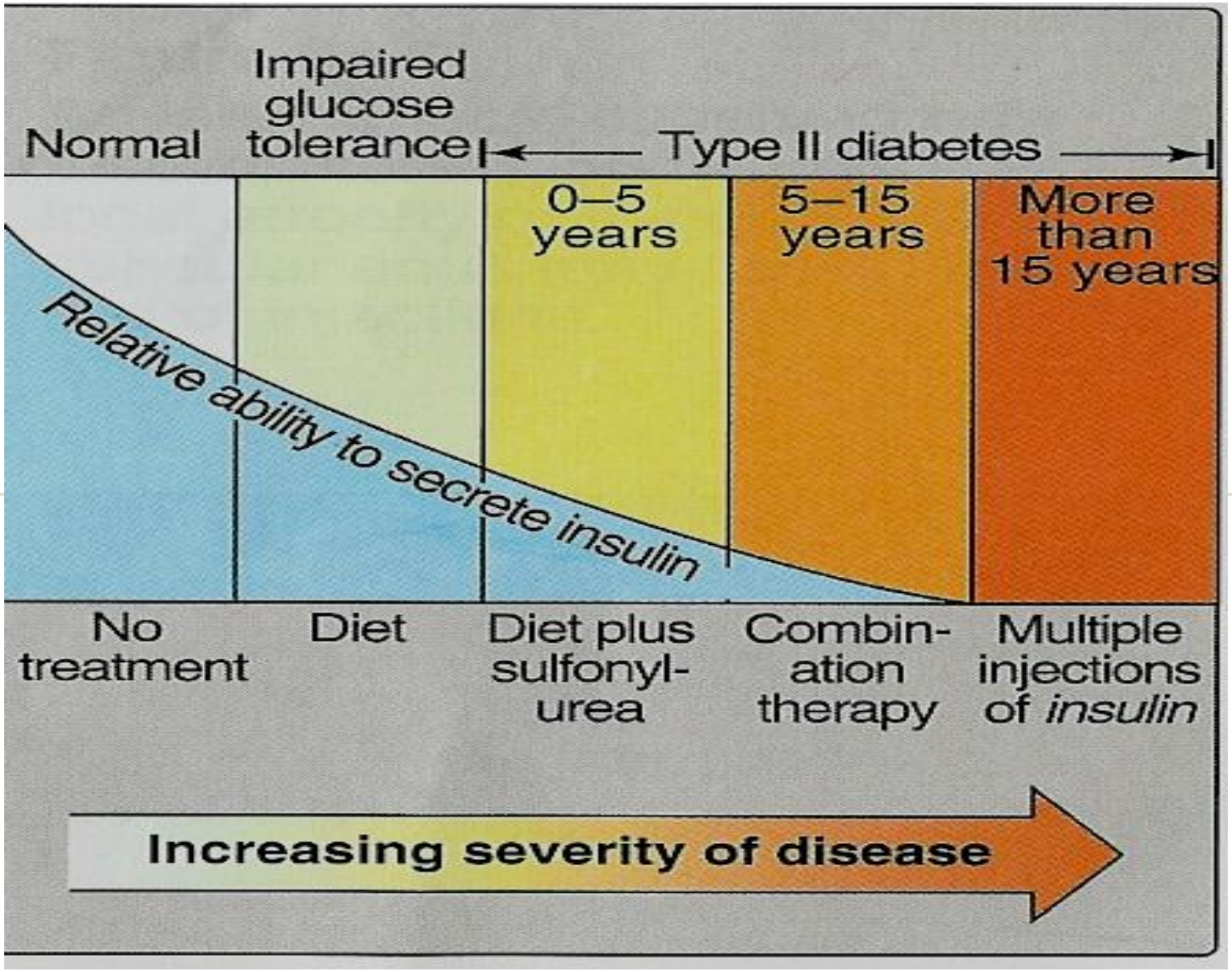
2. **Resistance to insulin action in target tissues associated with decreased number of insulin receptors.**



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, **S**odium/**gl**ucose co**t**ransporter 2 inhibitors**)**

Insulin secretagogues

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

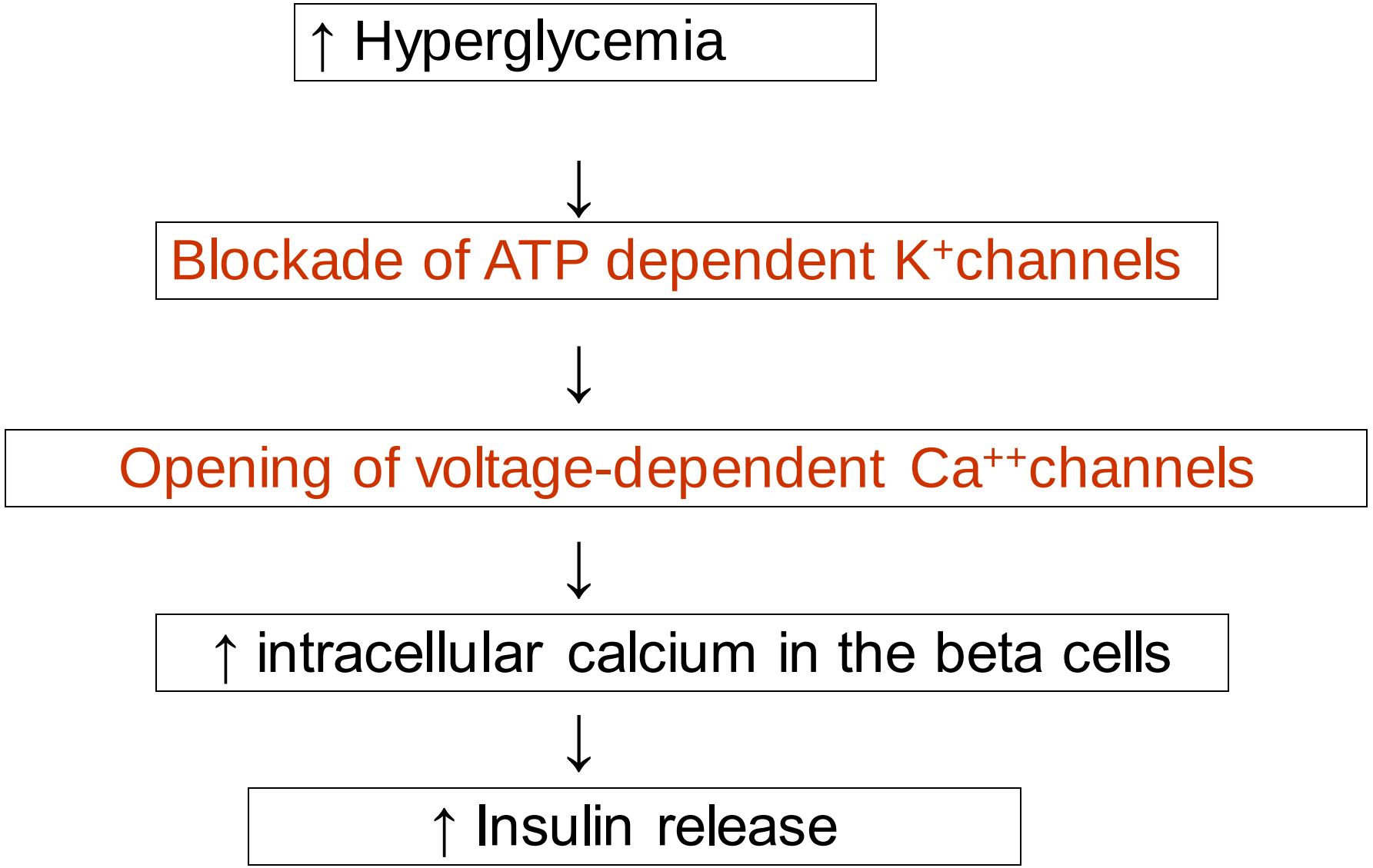
Include:

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

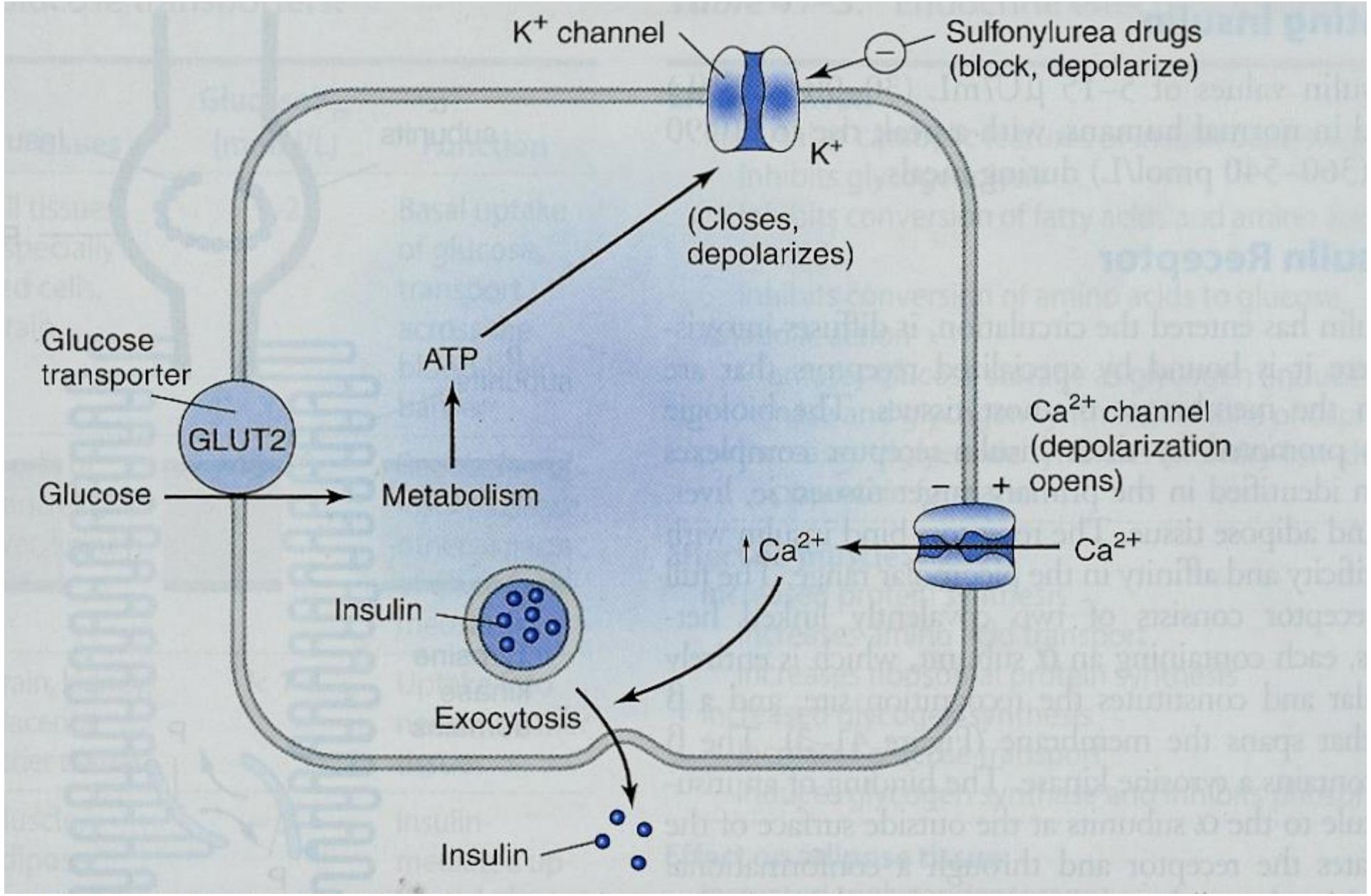
Mechanism of action of sulfonylureas:

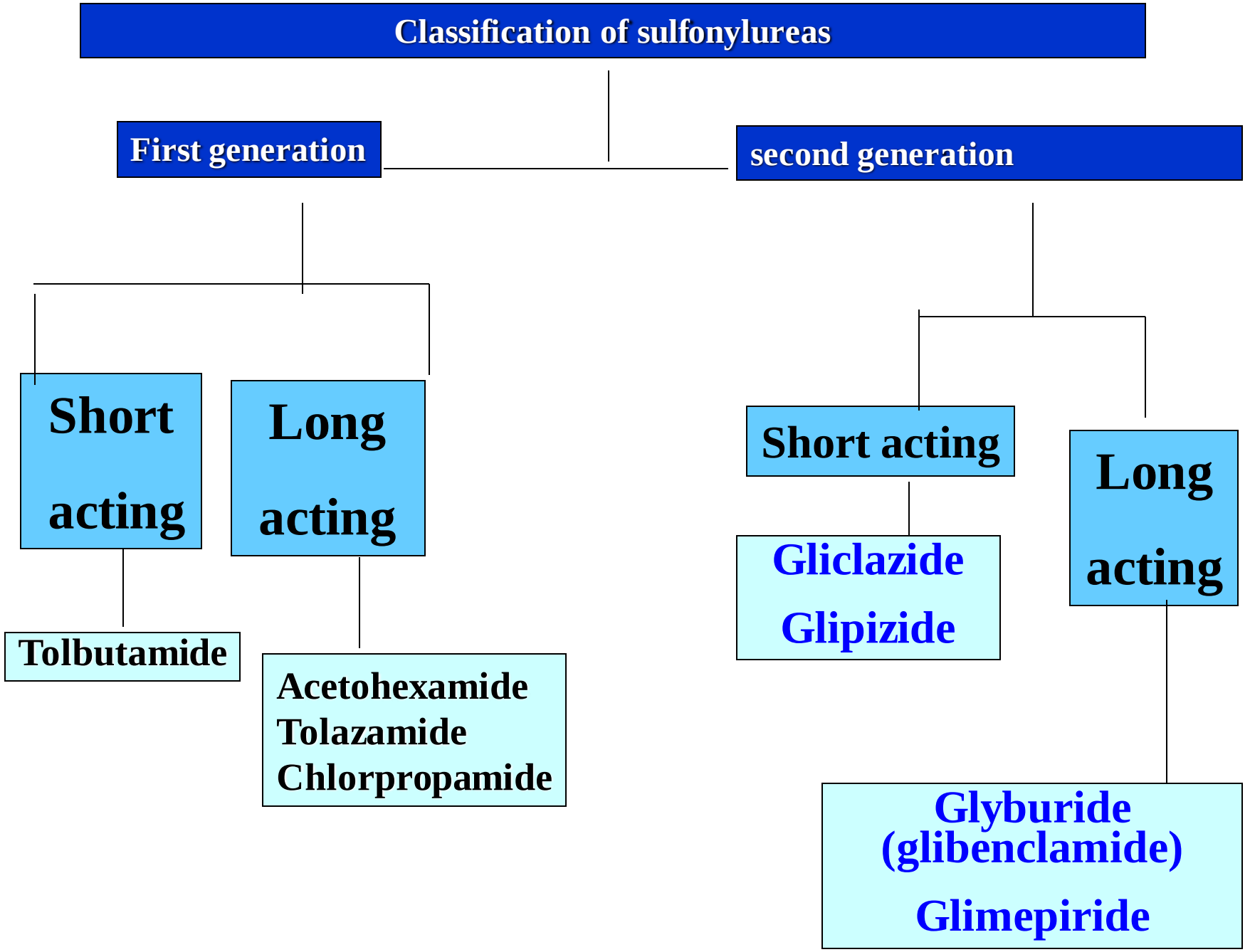
- **Stimulate insulin release from functioning B cells by blocking of ATP-sensitive K channels which causes depolarization and opening of voltage- dependent calcium channels, which causes an increase in intracellular calcium in the beta cells, which stimulates insulin release.**

Insulin secretagogues (sulfonylureas)



Mechanisms of Insulin Release




Classification of sulfonylureas
First generation
second generation
Short acting
Long acting
Tolbutamide
Acetohexamide
Tolazamide
Chlorpropamide
Short acting
Long acting
Gliclazide
Glipizide
Glyburide (glibenclamide)
Glimepiride

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 β-cells to release insulin → 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

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

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

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

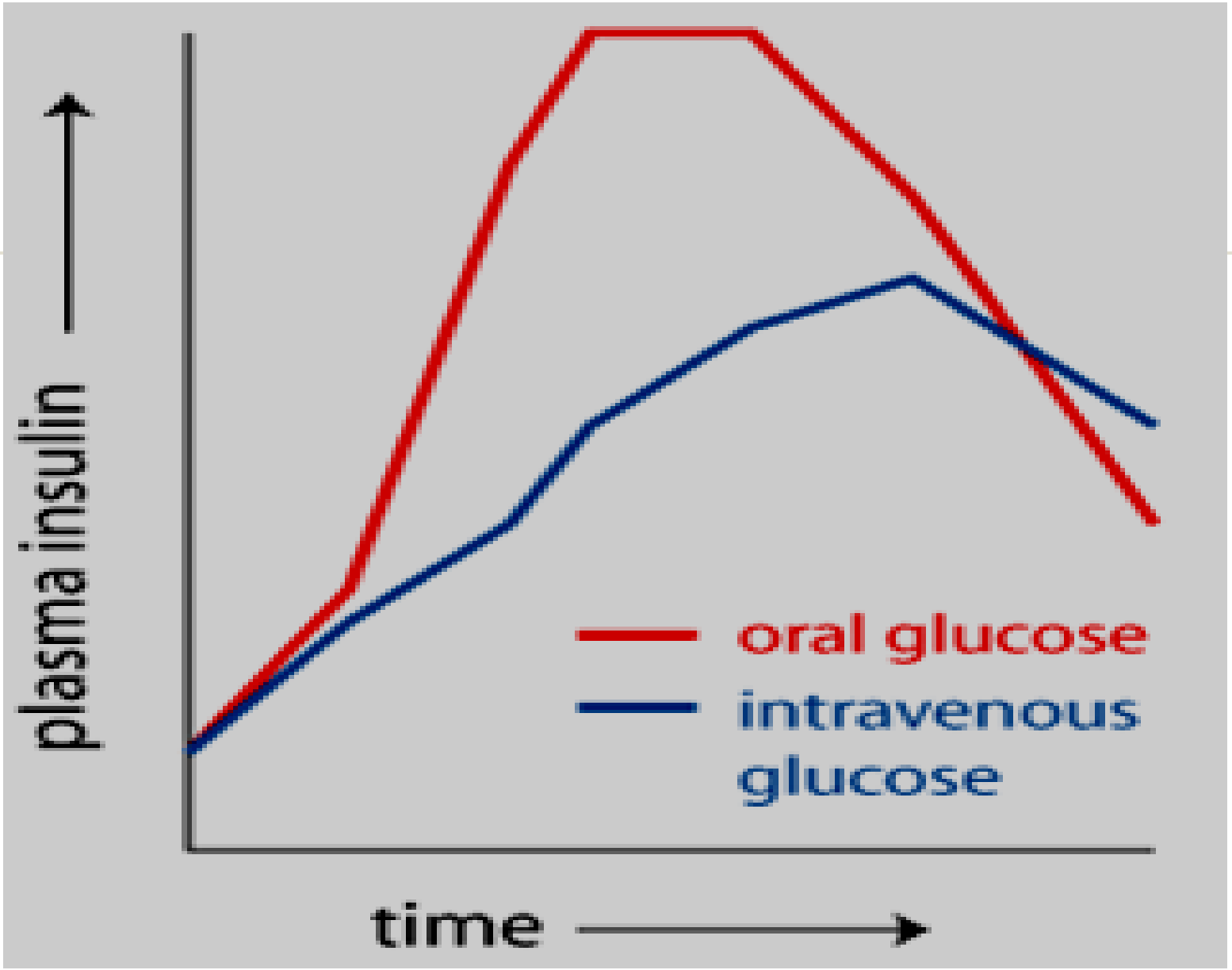
- **Hypoglycemia.**
- **Weight gain.**

Incretins

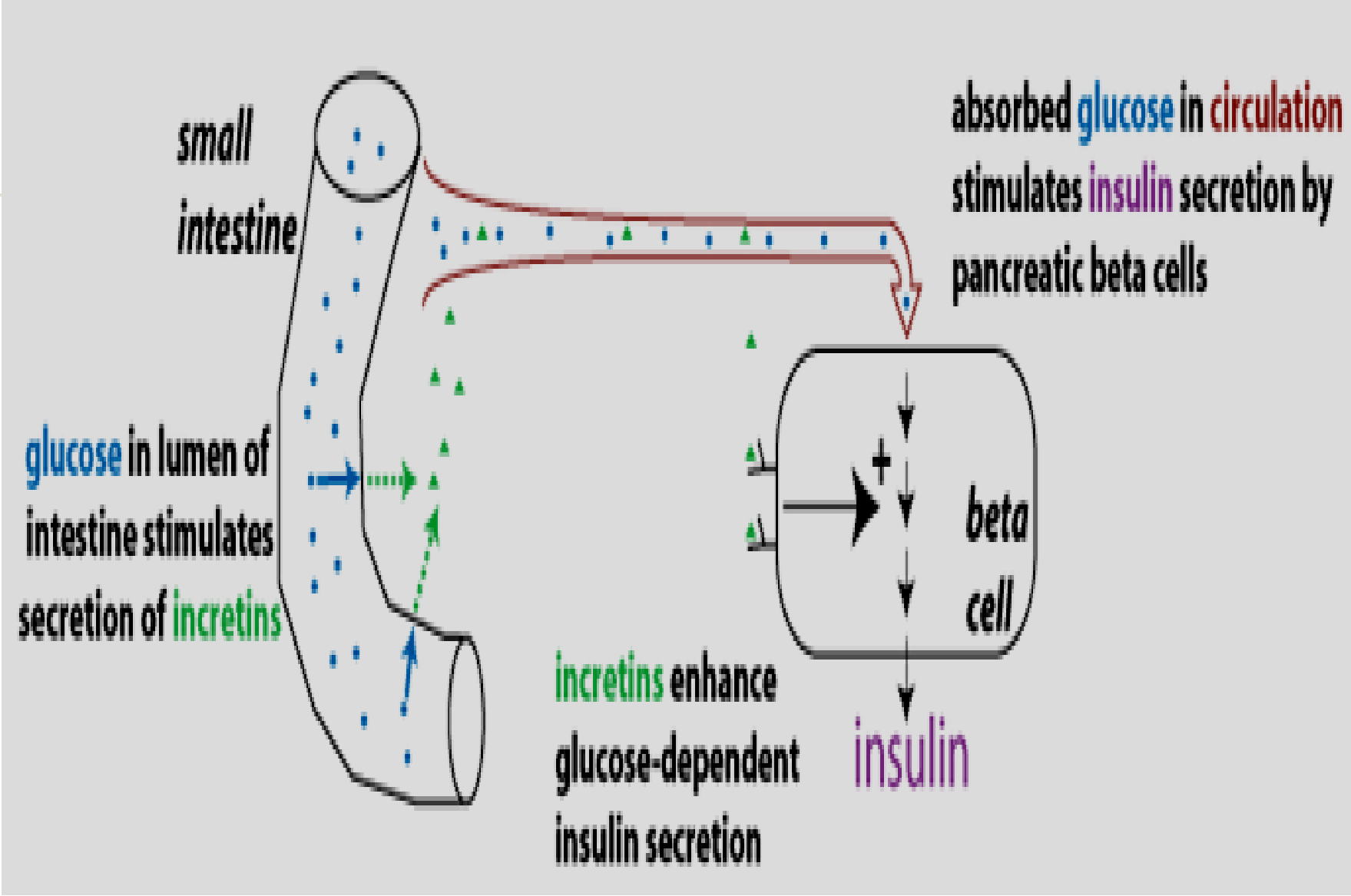
- **Incretins are GI hormones secreted from intestine in response to food even before blood glucose level becomes elevated. They are carried through circulation to pancreatic beta cells.**

- **Incretins regulate blood glucose by:**
  - **Increase insulin secretion**
  - **Decrease glucagon secretion**

Incretins



Incretins


small
intestine
absorbed glucose in circulation
stimulates insulin secretion by
pancreatic beta cells
glucose in lumen of
intestine stimulates
secretion of incretins
+
beta
cell
incretins enhance
glucose-dependent
insulin secretion
insulin

Incretins

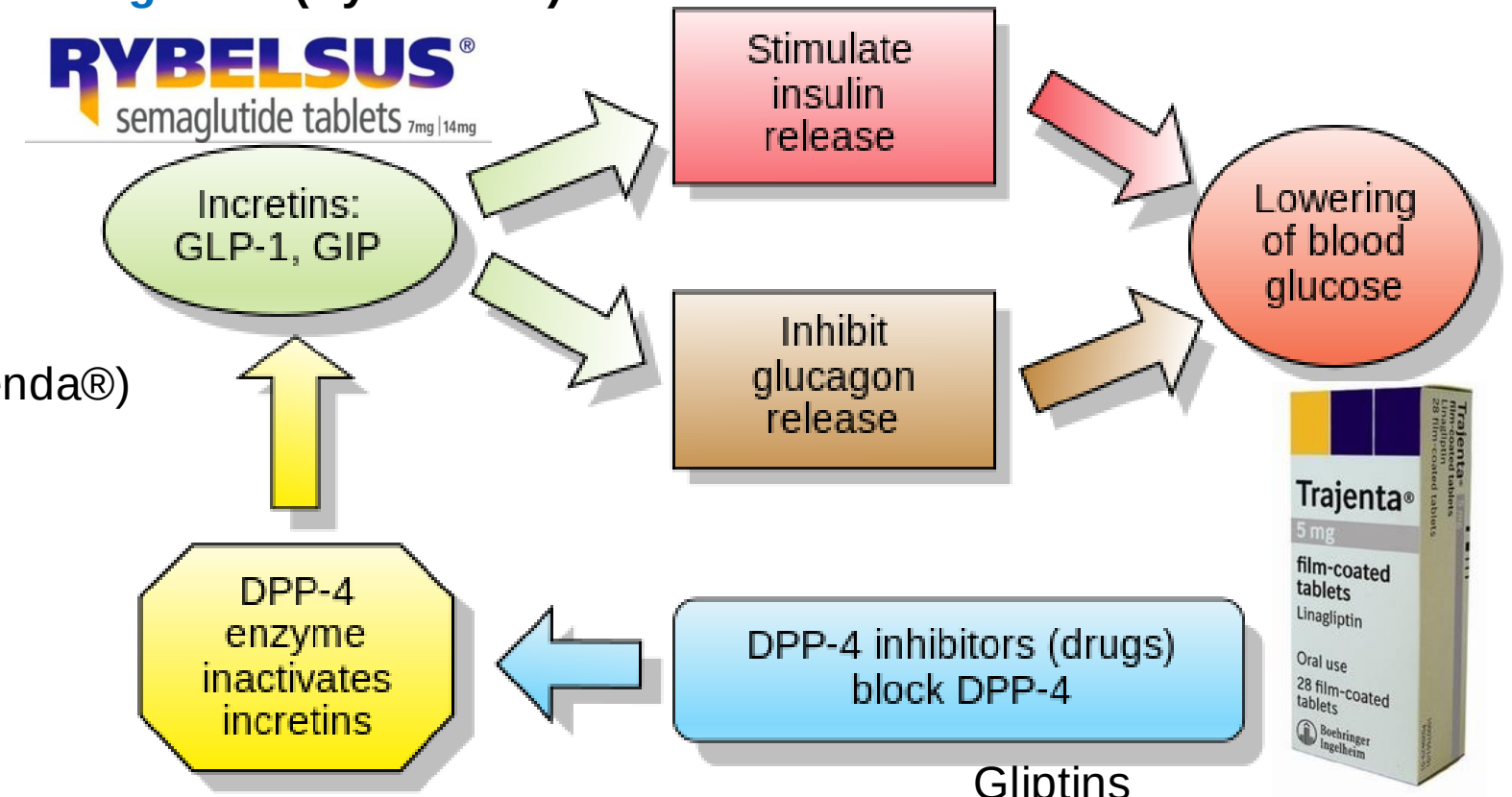
- **Incretins include:**
  - **GLP-1 (glucagon-like peptide-1)**
  - **GIP (gastric inhibitory peptide)**

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

Mechanism of Action of Incretin Mimetics

New FDA approved and 1st oral GLP-1 ago Semaglutide (Rybelsus®)

GLP-1 agonist
Liraglutide
(Victoza®/Saxenda®)



Gliptins
e.g. Linagliptin (Trajenta®)

GLP, glucagon-**l**ike **p**eptide; **DDP**, **di**pe**p**tidyl **p**eptidase
GIP, **g**astric **i**nhibitory **p**eptide (also called **g**lucose-dependent **i**nsulinotripic **p**eptide)

Incretins mimetics
Glucagon-like peptide-1 (GLP-1) agonists

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
GLP-1 agonists

Liraglutide (Victoza, Saxenda)[R]

Mechanism of action

- Binds to GLP-1 receptors & stimulates insulin secretion from β 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)

- **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)

- **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)

Adverse effects

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

First Oral GLP-1

- **Rybelsus® (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)®

- **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 ½ = 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_{12} 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 -γ (PPAR-γ).**
- **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**

α-Glucosidase inhibitors

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

α-Glucosidase inhibitors

- Reversible inhibitors of intestinal α-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).

α-Glucosidase inhibitors

Acarbose

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

Uses of α-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.**

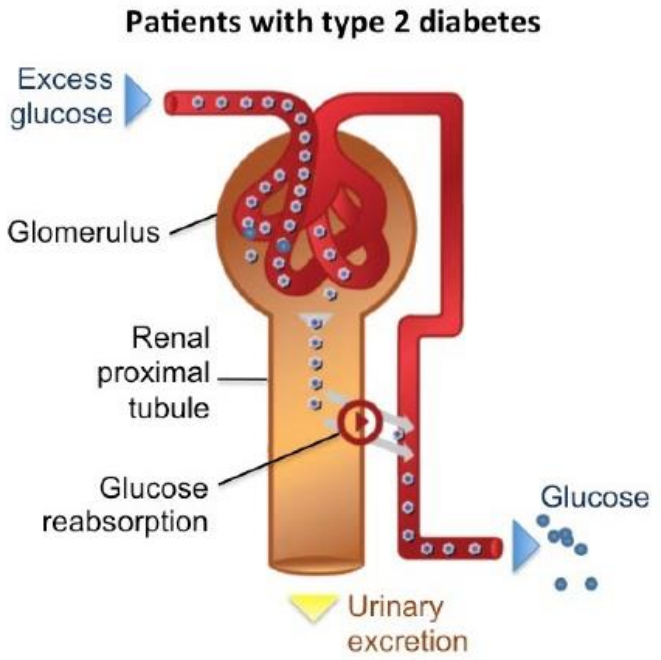
Adverse effects

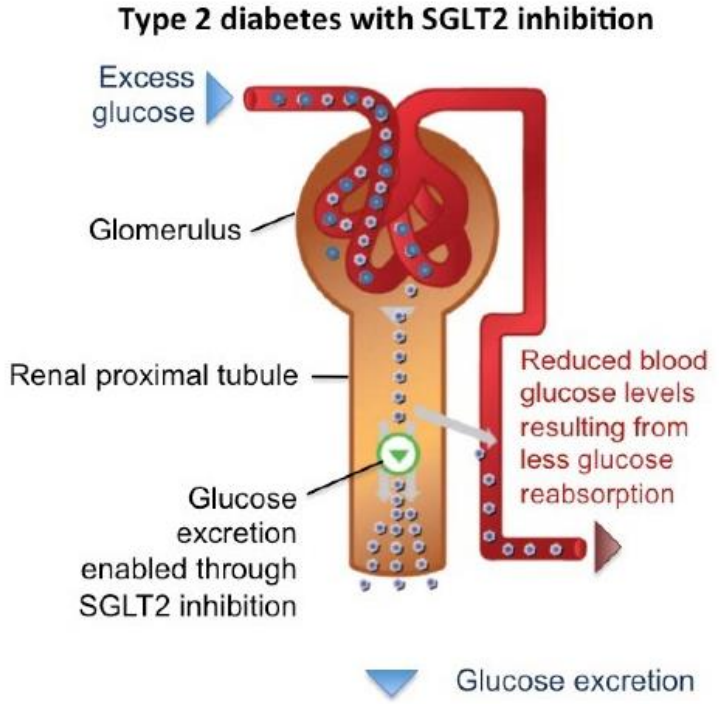
- **GIT side effects:** **Flatulence, bloating, diarrhea, abdominal pain.**

Contraindications of α-glucosidase inhibitors

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

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





Adapted from:

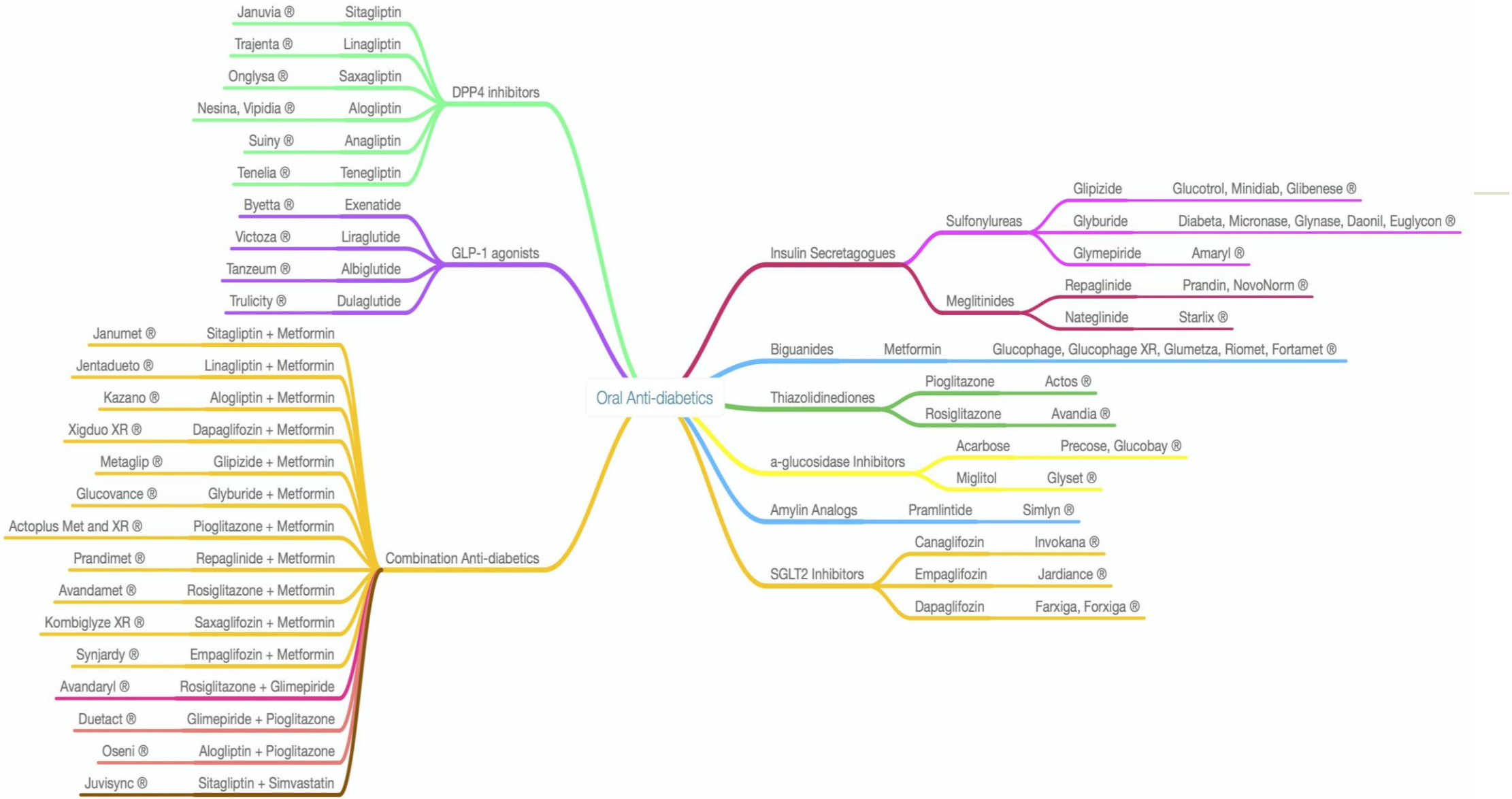
1. Chao EC & Henry RR. Nature Reviews Drug Discovery 2010;9:551-559.
2. DeFronzo RA, et al. Diab Obes Metab 2012;14:5-14.
3. Washburn WN. J Med Chem 2009;52:1785-1794.

SGLT-2, **S**odium/**gl**ucose co**t**ransporter 2

https://www.deutsche-apotheker-zeitung.de/_Resources/Persistent/2ce1262efc49b38c414755d167176b4e67eefcd9/P513_jardiance-4483x2523-637x358.jpg:
http://www.international-diabetes-association.com/wp-content/uploads/2015/10/4dae138c620f89f5f2486133601378d9167de1db.jpg

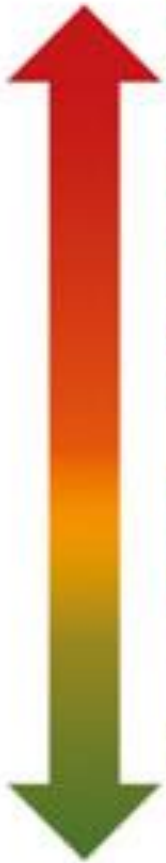
SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas Gliclzide	Stimulates insulin secretion	Pancreatic beta cells	• Effective • Inexpensive	• Hypoglycemia • Weight (Wt) gain
Meglitinides Repaglinide		Pancreatic beta cells	Sulfa free	•Hypoglycemia •Wt gain
Biguanides Metformin	Decreases insulin resistance	Liver	• mild weight loss • No hypoglycemia	• GIT symptoms, • Lactic acidosis • Metallic taste
Thiazolidinediones pioglitazone		Fat, muscle	No hypoglycemia	Hepatoxicity Edema, mild wt gain
Incretins mimetics Dulaglutide	Increase incretin	GI tract	Once/week, s.c.	Nausea & vomiting
DPP-4 inhibitors Sitagliptin	Inhibit incretin breakdown	GI tract	orally	Nausea & abdominal pain
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	•GI symptoms, flatulence
SGLT-2 inhibitors Dapagliflozin	Inhibit renal SGLT-2	Kidney	Orally Reduced Na (CV benefits)	Genital yeast/UTI Increased urination



https://i1.wp.com/ecuadoctors.com/wp-content/uploads/2018/03/Oral-Antidiabetic-Drugs.jpg?zoom=2&ssl=1

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.

https://diabetes-ayurveda.com/HTML/12_album.jpg