Oral hypoglycemic drugs

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Objectives

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

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

Types of diabetes mellitus

- **Type I**

  due to autoimmune or viral diseases

- **Type II**

  due to obesity, genetic factors

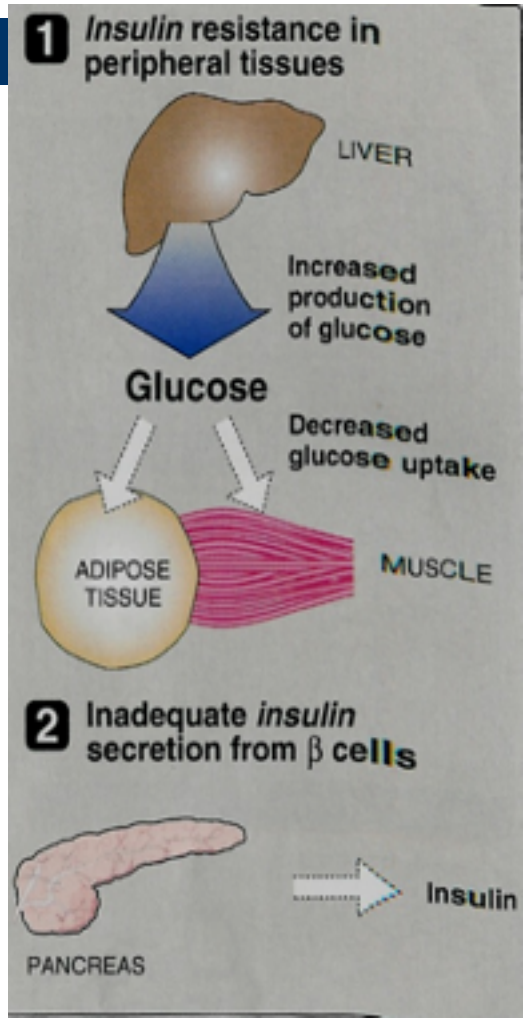
Type II Diabetes

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

Pts with Type II diabetes have two physiological defects

1. Abnormal insulin secretion.

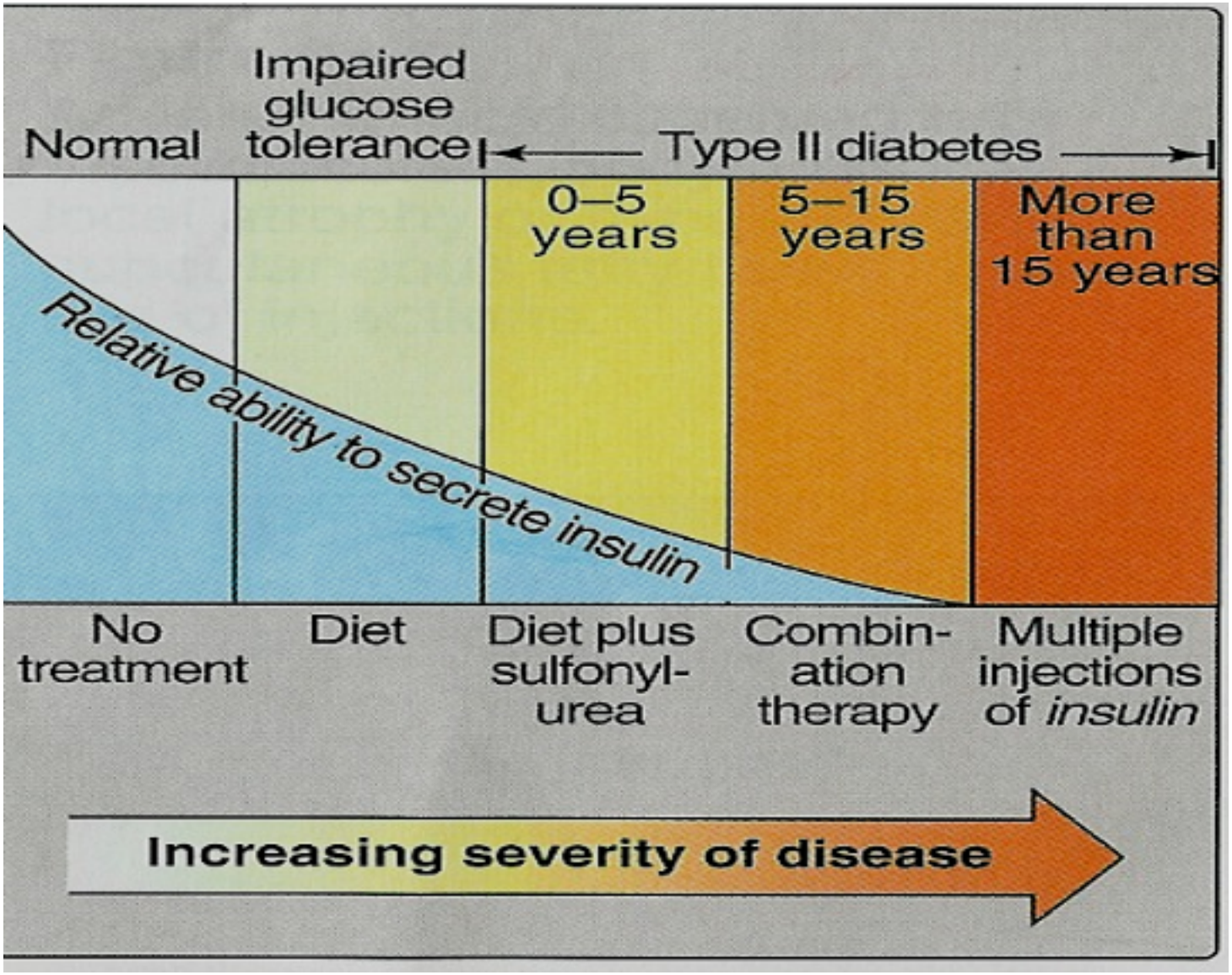
2. Resistance to insulin action in target tissues associated with decreased number of insulin receptors.



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

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

Insulin sensitizers

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

Note: Antidiabetic drugs = oral hypoglycemic and others

Antidiabetic drugs

Reduce carbohydrate absorption

Alpha glucosidase inhibitors

Increase glucose excretion

Sodium-glucose transporter 2 (SGLT2) inhibitors

- **Canagliflozin**

Note: Antidiabetic drugs = oral hypoglycemic and others

Insulin secretagogues

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

Include:

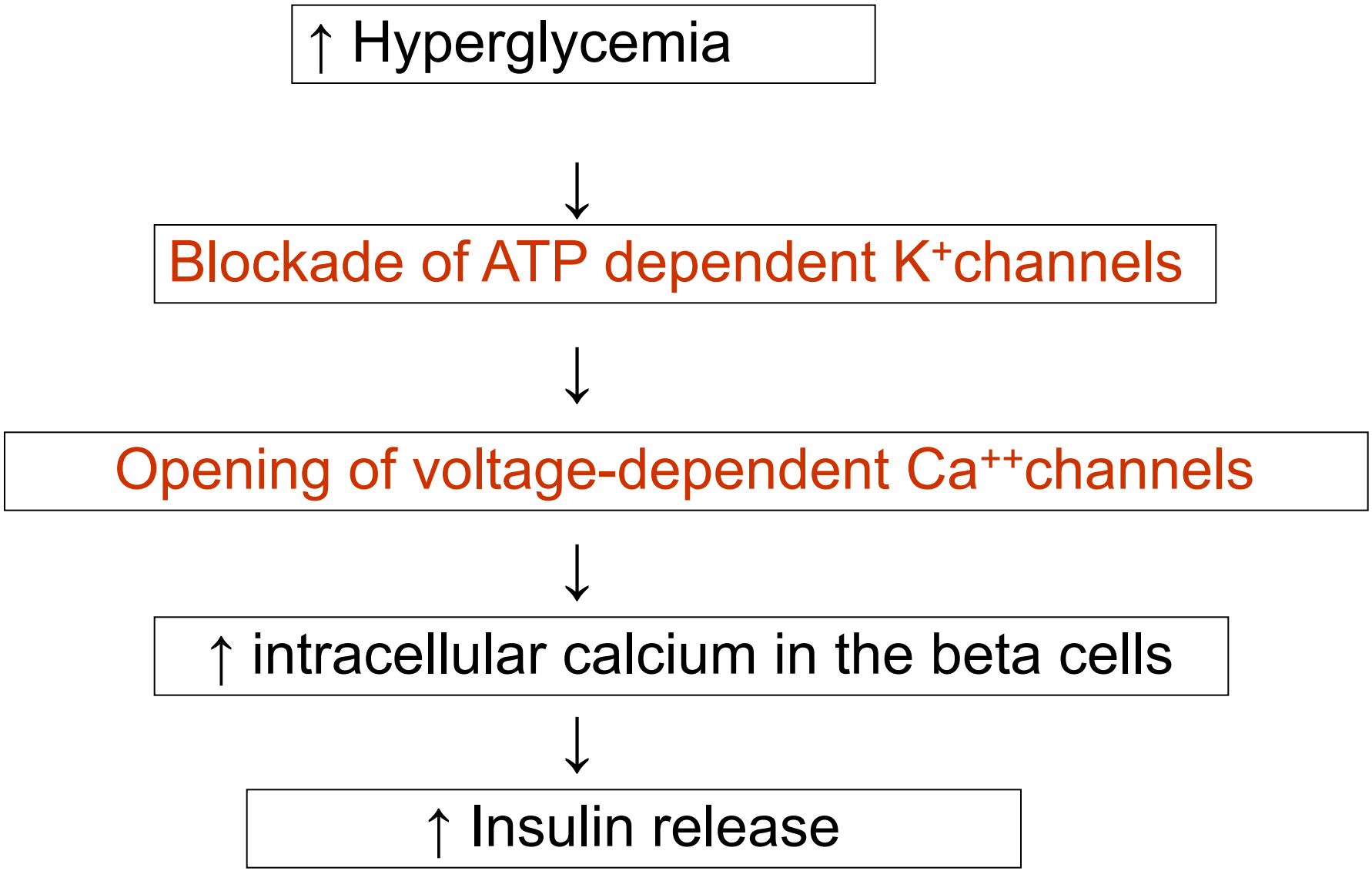
Sulfonylureas

- Meglitinides
- Incretin mimetics

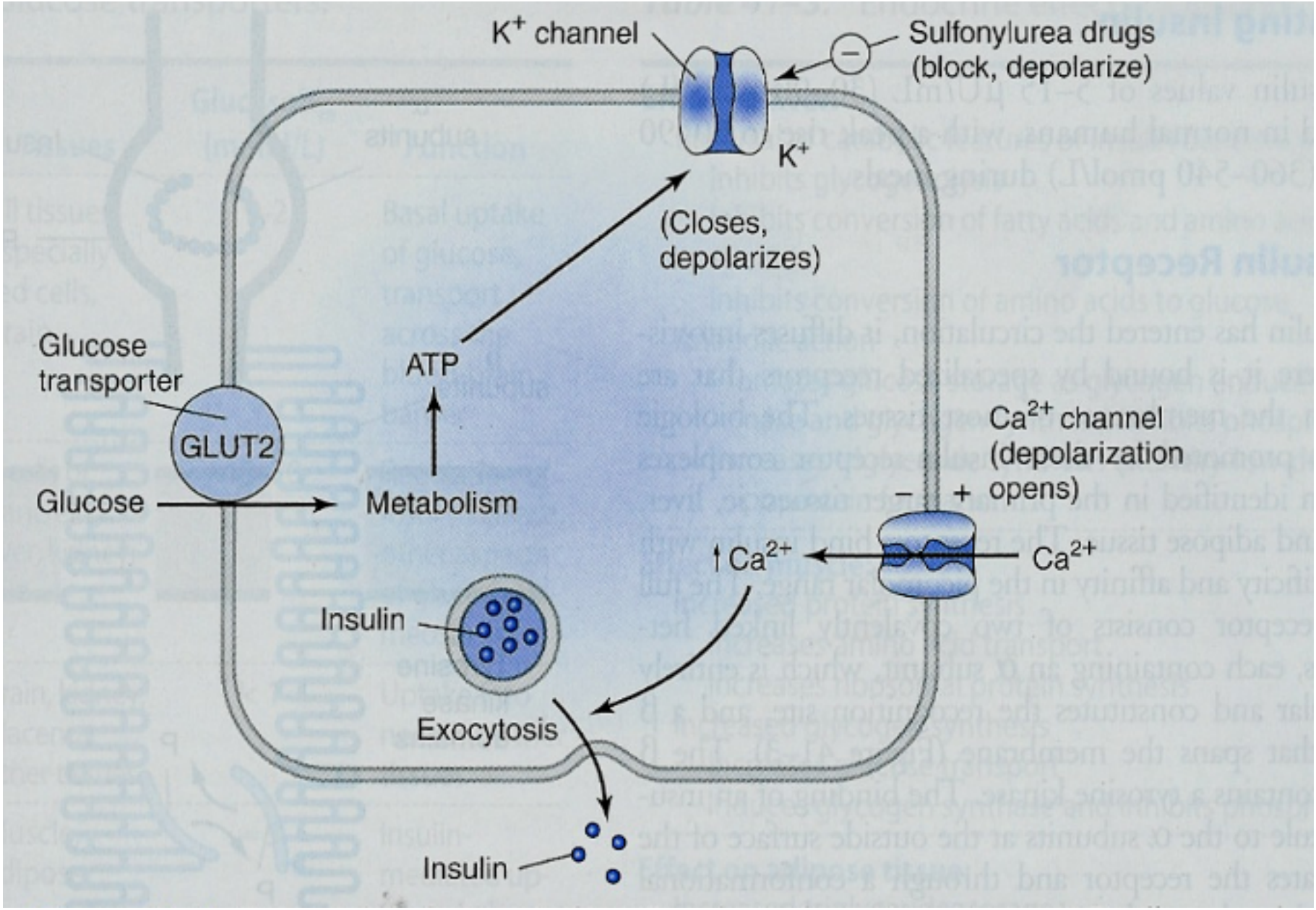
Mechanism of action of sulfonylureas:

- **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.**

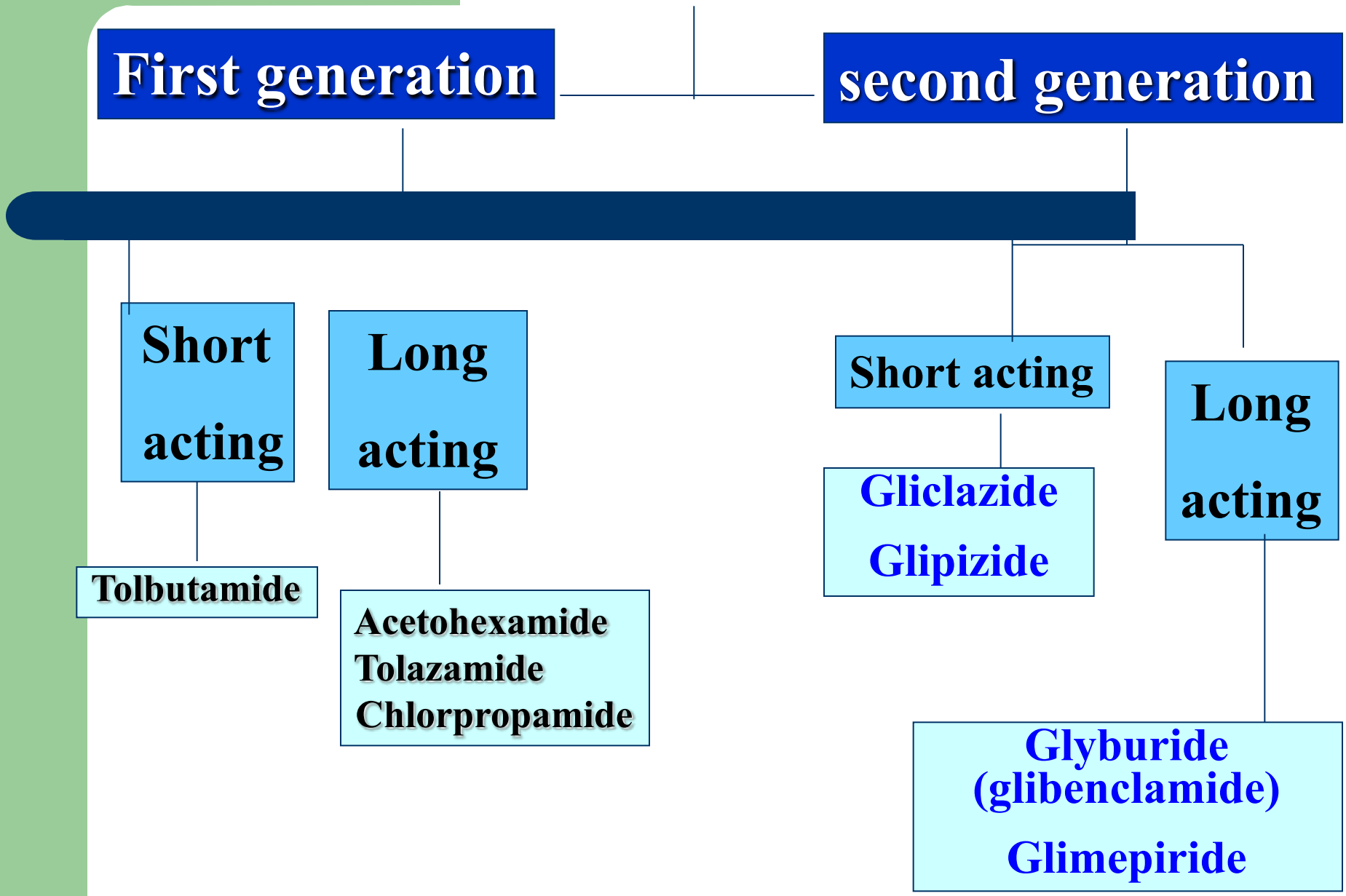
Insulin secretagogues (sulfonylureas)



Mechanisms of Insulin Release



Classification of sulfonylureas



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.
- 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:

- are 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 in patients allergic to sulfonylureas.**

Adverse effects of Meglitinides

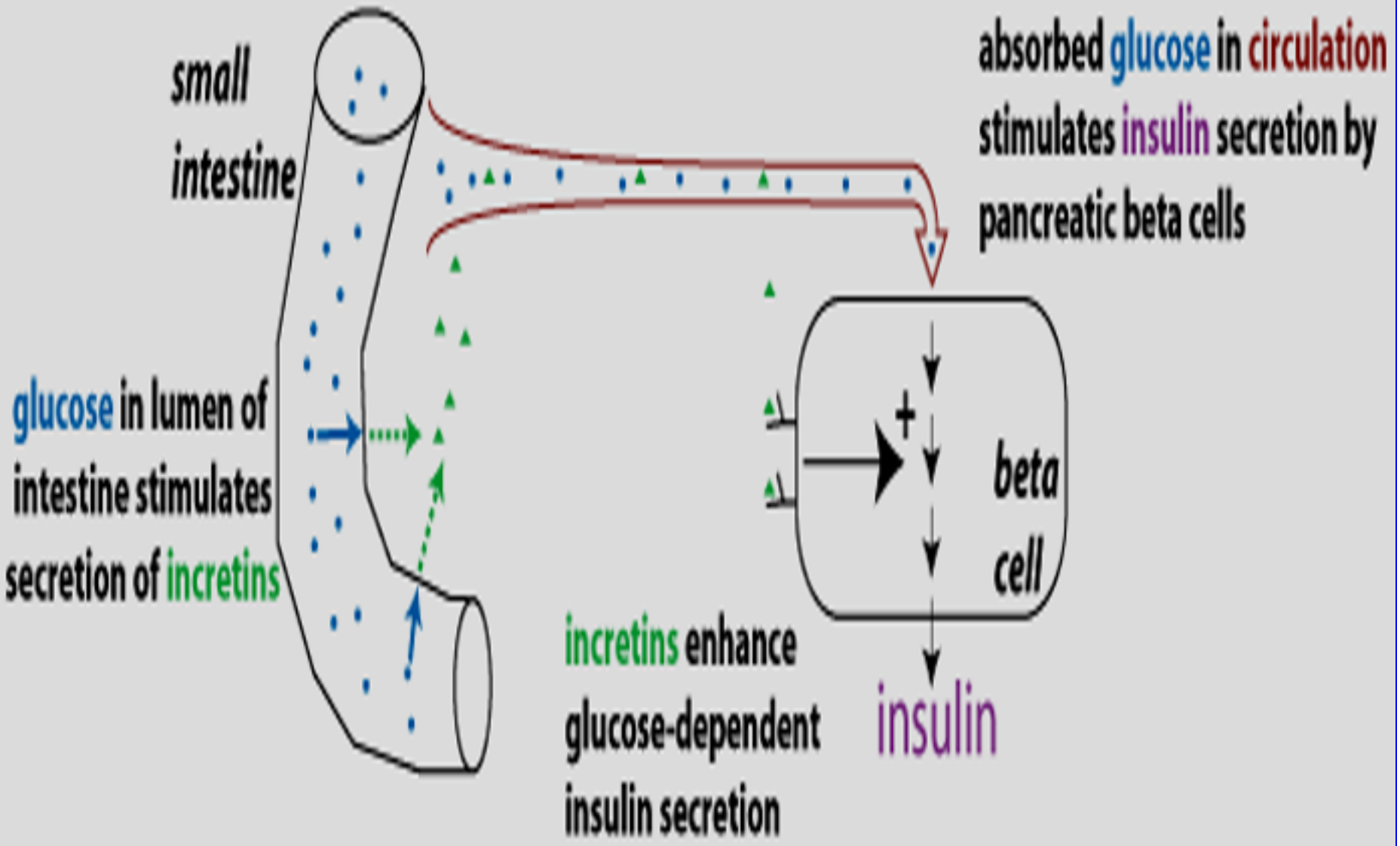
Less incidence than sulfonylureas

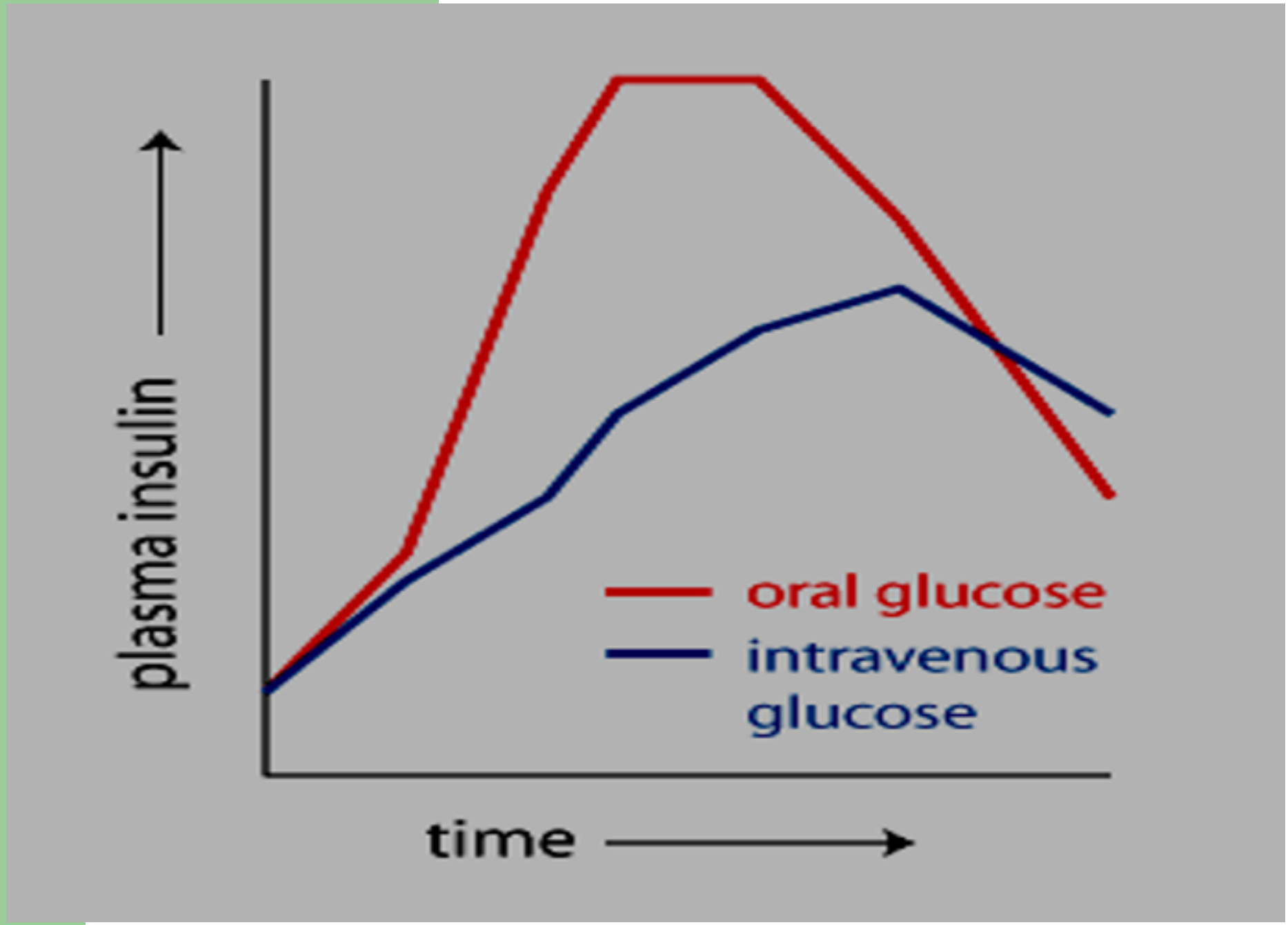
- **Hypoglycemia.**
- **Weight gain.**

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:**
  - **Increasing insulin secretion**
  - **Decreasing glucagon secretion**


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

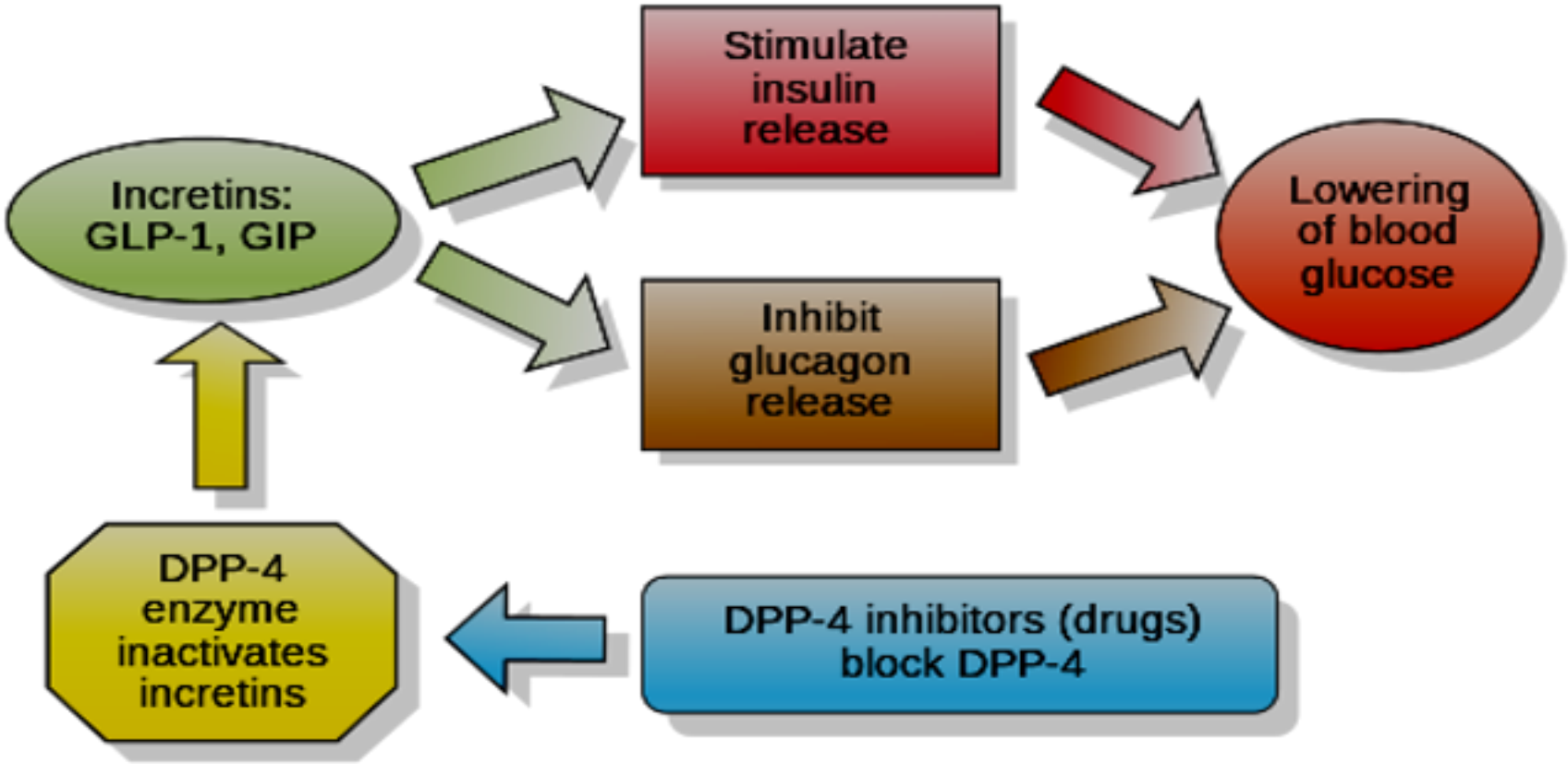

plasma insulin
oral glucose
intravenous glucose
time

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



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

GLP-1 drugs are non-insulin treatments for people with type 2 diabetes.

Include:

- **Exenatide**
- **Dulaglutide (Trulicity)®**
- **Liraglutide (Victoza, Saxenda)®,**
- **Semaglutide (Rybelsus®) 1st oral GLP-1 agonist**

GLP-1 agonists
Liraglutide (Victoza, Saxenda)[R]

Mechanism of action

- Binds to GLP-1 receptors & stimulates insulin secretion from β cells.
- Inhibits alpha cells of the pancreas.
- Reduces glucagon secretion
- Decreases appetite & decreases body weight gain.

GLP-1 agonists
Liraglutide (Victoza, Saxenda)[R]

- Liraglutide
  - Victoza®, is the lower dose for diabetes
  - Saxenda®, is the higher dose for obesity
- given s.c. once/day
- given as 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
Liraglutide (Victoza, Saxenda)[R]

Liraglutide (saxenda) used for treatment of obesity in adults who are 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

- **Semaglutide (Rybelsus®) 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 inhibitors (DPP- 4 inhibitors)
Gliptins

e.g. Sitagliptin, vildagliptin, Linagliptin

- **Gliptins inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1) leading to increase in insulin secretion & decrease in glucagon secretion.**

- **Sitagliptin (Januvia)^{R} Is given orally / once daily.**

Clinical uses of DPP- 4 inhibitors

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

- are effective alone in the earliest stages of impaired glucose tolerance
- are not recommended alone as therapy for moderate to severe hyperglycemia
- are 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.**

Sodium-glucose transporter- 2 (SGLT2) inhibitors

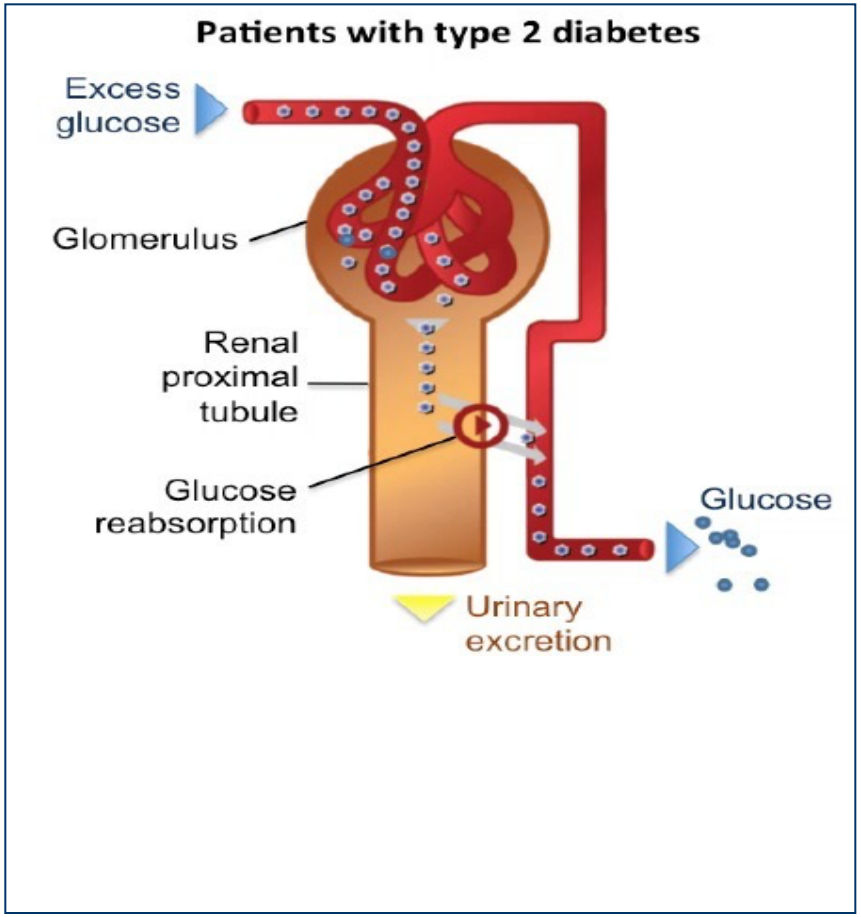
Drugs as

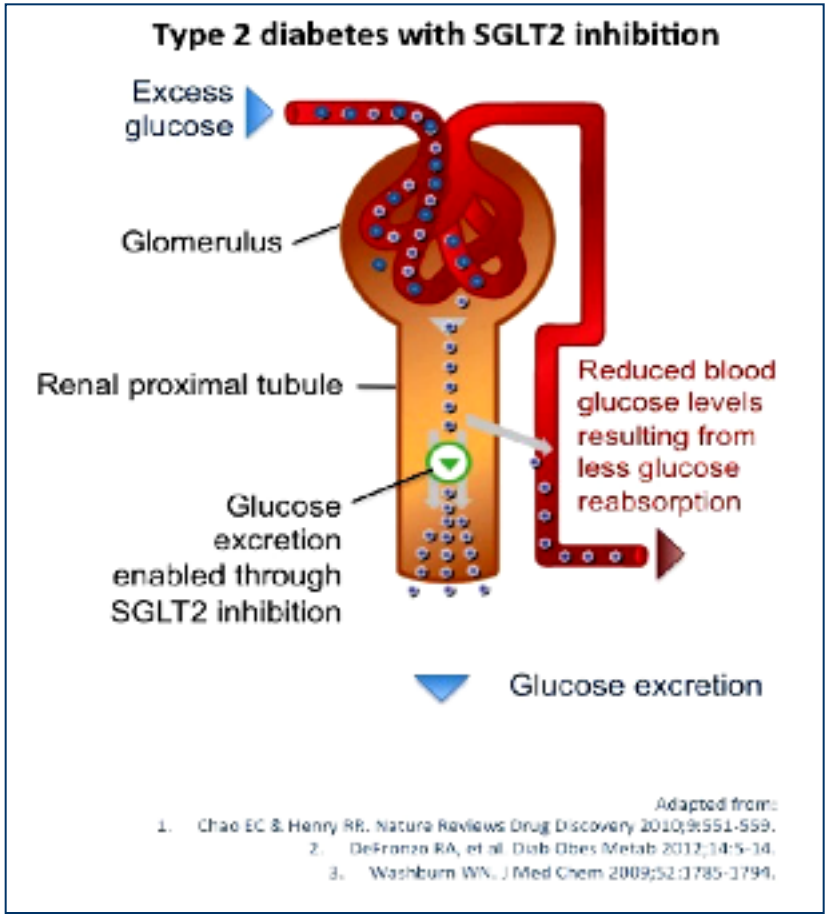
Canagliflozin, Dapagliflozin, Empagliflozin

Mechanism of action:

Inhibit SGLT2 in the kidneys. This allows excess glucose to be excreted in the urine. This will reduce blood sugar levels

Mechanism of action of (SGLT2) inhibitors





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.

Sodium-glucose transporter- 2 (SGLT2) inhibitors

USES

- Used with diet and exercise to control high blood sugar in patients with type 2 diabetes.
- To reduce risk of major adverse cardiovascular events in adults with T2DM and established cardiovascular disease.

Side effects

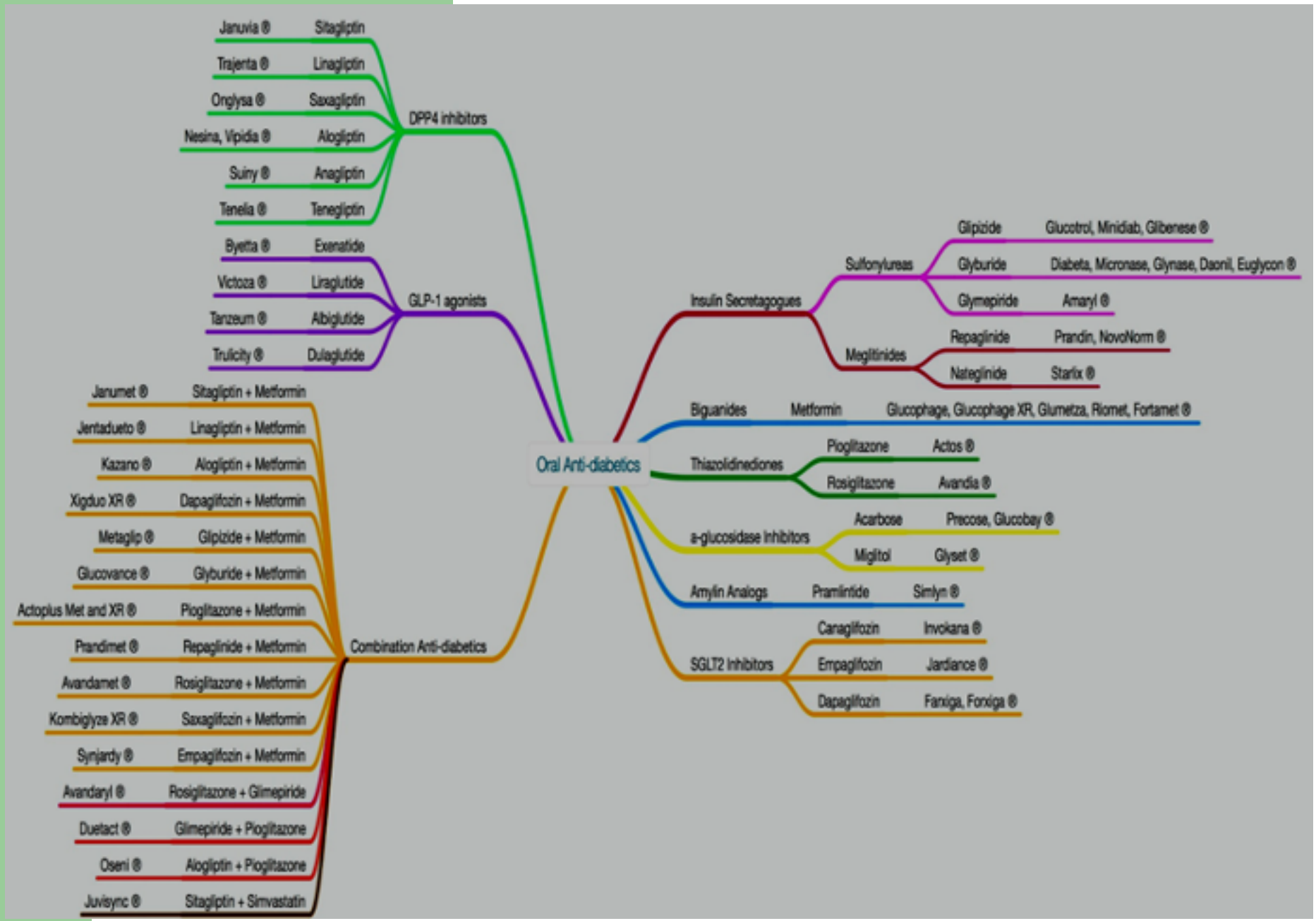
1) Urinary tract infections
2) Increased urination and dry mouth
3) Yeast infections (vagina or penis)
4) Itching (vagina or penis)
5) Thirst
6) Fatigue

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas	**Insulin Secretagougues** Stimulate insulin secretion	**Pancreatic beta cells**	• **Effective** • **Inexpensive**	• **Hypoglycemia** • **Weight gain**
Meglitinides **repaglinide**		**Pancreatic beta cells**	**Sulfa free**	•**Hypoglycemia** •**Weight gain**
Incretins mimetics Glucagon-like peptide-1 agonists (GLP-1 agonists) **Dulaglutide** **Liraglutide** **Exenatide**	**Increase incretin thus**	**GI tract**	**Once/day, s.c.**	**Nausea & vomiting**
DPP-4 inhibitors **Sitagliptin** **vildagliptin**	**Inhibit incretin breakdown**	**GI tract**	**orally**	**Nausea & abdominal pain**

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
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 weight gain
α-Glucosidase inhibitors Acarbose	Decrease glucose absorption in small intestine	GI tract	Low risk	•GI symptoms, flatulence
Sodium-glucose transporter 2 (SGLT2) inhibitors Canagliflozin	Increase renal glucose excretion	Kidney	Orally Reduced Na (CV benefits)	▪ UTI ▪ Increased urination and dry mouth ▪ Yeast infection ▪ Itching (vagina or penis)



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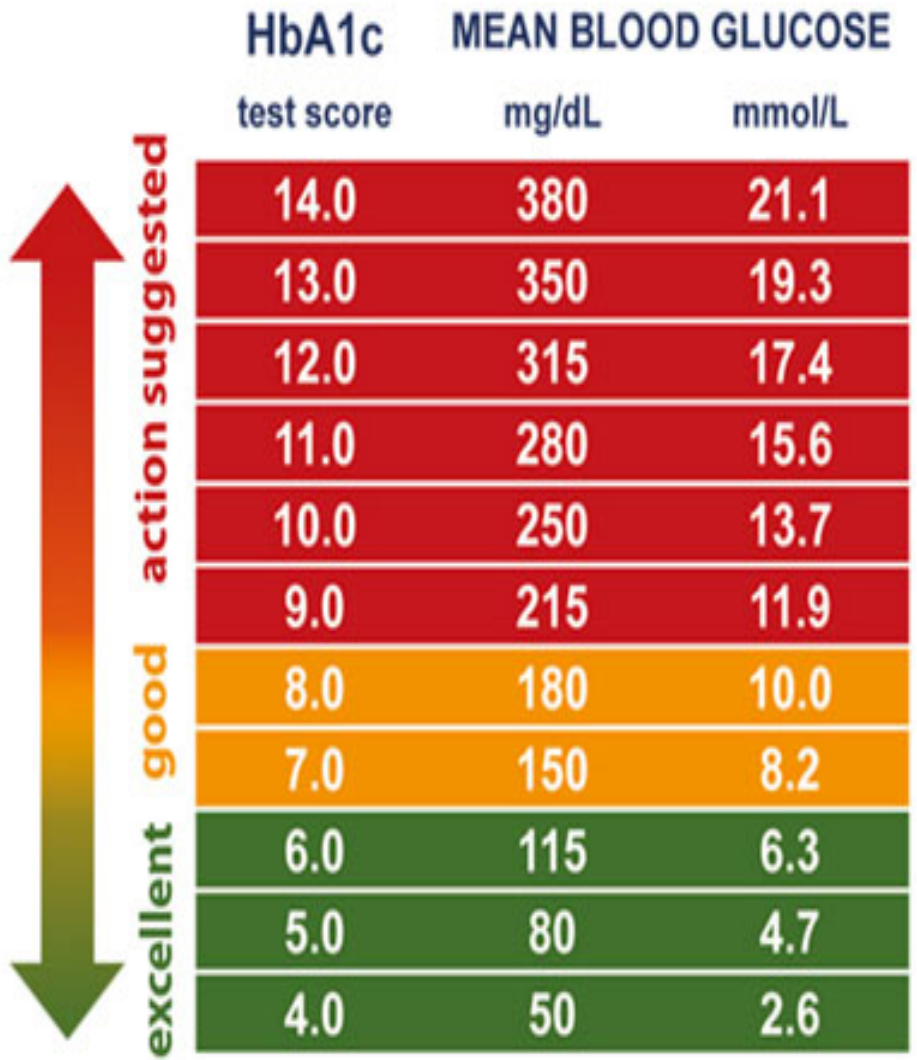
Supplementary Slide



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