Mechanism of Action of Anti-diabetic Drugs

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Objective:

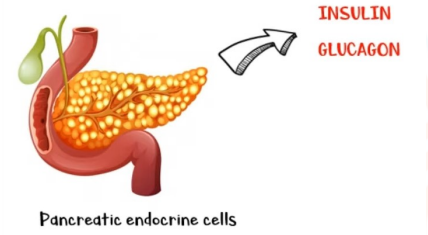
To understand how different classes of anti-diabetic drugs act at the molecular level

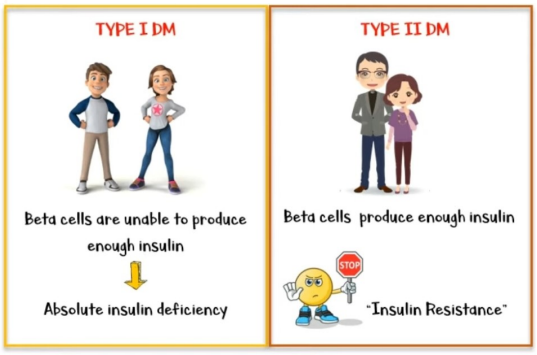
KhojisMorning

Q. **Before we talk about drugs, what exactly goes wrong in diabetes?**

Diabetes is a metabolic disorder characterized by **hyperglycemia** resulting from **defects in insulin secretion, insulin action, or both.**

1. Why does blood glucose rise in diabetes?
2. Which hormones control glucose homeostasis?





Insulin Secretagogues

Induce Pancreatic insulin secretion

1. Sulfonylureas
2. Meglitinides
3. Incretin – Based drugs
    1. GLP1 agonists
    2. DPP-4 inhibitors

Non - Insulin Secretagogues

1. Biguanides – Metformin
2. Thiazolidinediones
3. Alpha glucosidase inhibitors
4. Amylin analogues
5. SGLT-2 inhibitors

Mechanistic Group	Examples	Primary Target
Insulin & analogues	Lispro, Glargine	Insulin receptor
Secretagogues	Glibenclamide, Repaglinide	β-cell K^+ channels
Sensitizers	Metformin, Pioglitazone	AMPK, PPAR-γ
α-Glucosidase inhibitors	Acarbose, Miglitol	Intestinal enzymes
Incretin-based agents	Sitagliptin, Exenatide	GLP-1/DPP-4
SGLT2 inhibitors	Dapagliflozin	Kidney tubule transporter

Insulin and Analogues

Mechanism:
Bind to **insulin receptor (tyrosine kinase)** → activates **PI3K–Akt** pathway
↑ **GLUT4 translocation** → ↑ glucose uptake
Stimulates **glycogen, fat, and protein synthesis**
Clinical tip:
Rapid-acting analogues (Lispro, Aspart) act faster due to reduced self-association.

Sulfonylureas & Meglitinides (Secretagogues)

Mechanism:

Bind to **SUR1 subunit** of **ATP-sensitive K^+ channels (K_ATP)** on β-cell membranes.

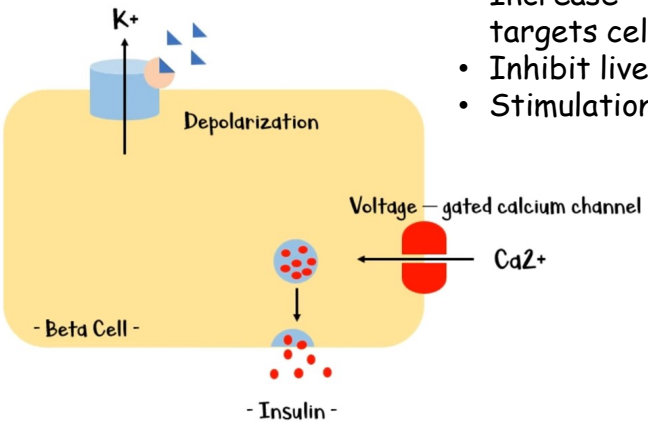
Channel closure → cell depolarization → **Ca^{2+} influx** → **insulin granule exocytosis**.

Examples:

Sulfonylureas: Glimepiride

Meglitinides: Repaglinide

⚠ **Note:** Require **functional β-cells** → ineffective in T1DM.



Extraapancreatic actions

- Increase insulin receptors on targets cells
- Inhibit liver gluconeogenesis
- Stimulation of appetite

First generation sulfonylureas :-

Tolbutamide

Tolazamide

Chlorpropamide

Second generation sulfonylureas :- More potent

Glipizide

Glyburide (Glibenclamide)

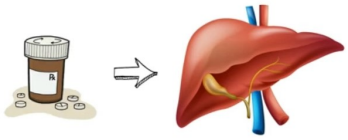
Glimepiride

Taken orally – before meals

Reduce blood glucose in type II diabetics

Monotherapy/combined with other oral anti – diabetics/with insulin

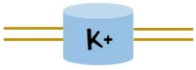
Glucose – independent action



INACTIVE METABOLITE

- Meglitinides -

Action is similar to sulfonylureas



Repaglinide

Nateglinide

Taken orally

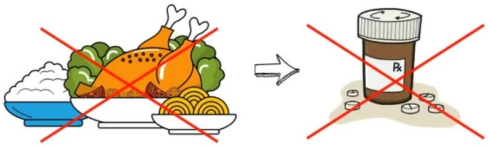
Rapid acting – shorter duration of action

Taken before each meal to control post prandial blood glucose

Adverse effects :-

Hypoglycemia

Weight gain



Biguanides (Metformin)

Mechanism:

Activates **AMPK (AMP-activated protein kinase)** in liver and muscle

↓ **Hepatic gluconeogenesis**

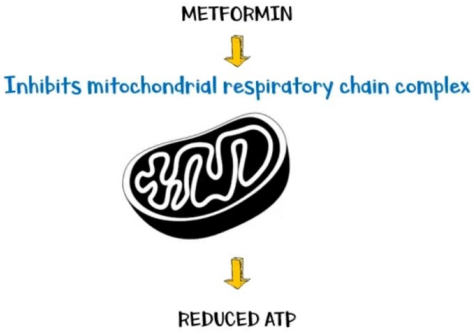
↑ **Peripheral glucose uptake**

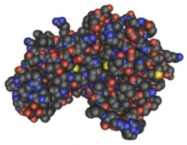
↓ **Intestinal glucose absorption**

Unique points:

No hypoglycemia

May promote weight loss





AMPK

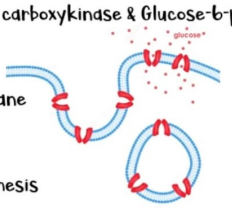
Increases the cellular catabolism & reduces anabolism

Reduces gluconeogenesis by :-

→Inhibiting genes responsible for the synthesis of "PEP carboxykinase & Glucose-6-phosphatase"

Increases glucose uptake by :-

→Inducing translocation of GLUT-4 in to the cell membrane



Increases fatty acid oxidation

Decreases glycogen, protein, fatty acid and cholesterol synthesis

Decreases intestinal absorption of glucose

Reduces LDL cholesterol & increases HDL cholesterol ➡ Reduces cardiovascular disease risk in T2DM patients

Most of the time, treatment of T2DM is started with metformin alone (monotherapy)

Later, metformin is given in combination with other oral hypoglycemic agents (combined therapy)

Available in immediate & slow release formulations

Also used in the treatment of PCOS & GDM

Pharmacokinetics :-

Oral bioavailability – 50 - 60%

Very low plasma protein binding

Duration of action :- 6 – 8 hours

Adverse effects :-

Metformin is a well – tolerated drug by most individuals

Weight loss (most common)

GI disturbances :-

→ Abdominal discomfort

→ Nausea & vomiting

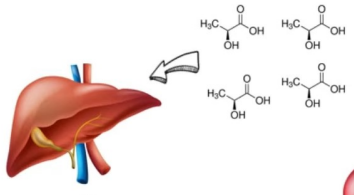
→ Diarrhea

Anorexia

Metallic taste

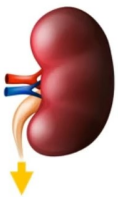
"Hypoglycemia does not occur with metformin"

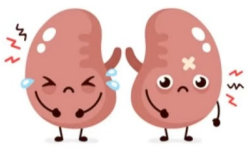
"Lactic Acidosis"



GLUCONEOGENESIS

"Metformin inhibits gluconeogenesis"



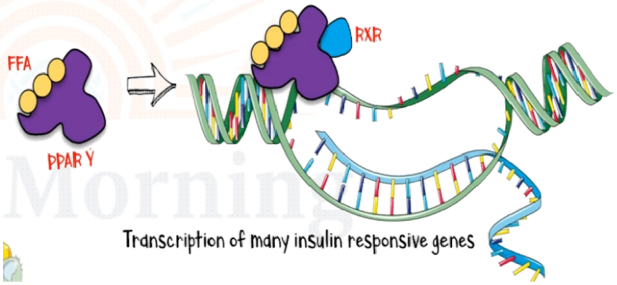


Lactic acid accumulates

Thiazolidinediones (Pioglitazone, Rosiglitazone)

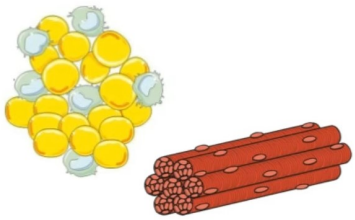
Mechanism:

Activate **PPAR-γ (a nuclear receptor)** in adipose tissue
↑ **Insulin sensitivity**, ↑ **Glucose transporter expression**



Side effects:

Fluid retention
Weight gain



Increased insulin sensitivity in muscle and adipose tissue

Reduce hepatic gluconeogenesis

Regulate fatty acid metabolism

→ Reduce TG
→ Increase HDL & LDL

Weight gain

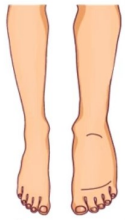
Cardiovascular disease

Pharmacokinetics :-

Good oral bioavailability
99% of the drug is plasma protein bound → Slow onset of action
Half – life :- 3 -4 hours
Metabolized by the liver in to active metabolites
70% excretion :- Bile
Remainder

Adverse effects :-

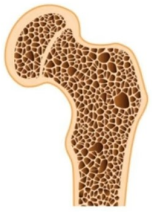
Weight gain



Fluid retention & edema

→ May worsen the symptoms of HF

→ Esp. with concurrent insulin therapy



Osteopenia & fractures

"ROSIGLITAZONE"

→ Not used now

→ Increased risk of cardiovascular events – MI, stroke

"PIOGLITAZONE"

→ Increased risk of bladder cancer

Hepatitis & liver failure

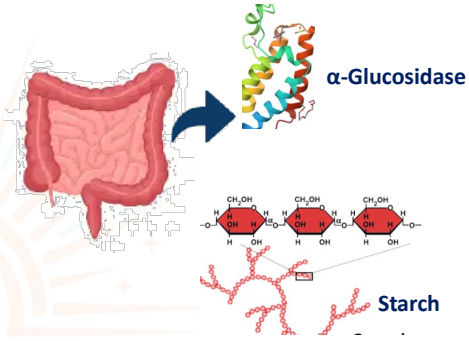
α-Glucosidase Inhibitors

Mechanism:

Inhibit **α-glucosidase enzyme** in intestinal brush border

Slow digestion of carbohydrates → delay glucose absorption

Examples: Acarbose, Miglitol



Side effects: Flatulence, bloating (due to undigested carbs)

Works **locally** in intestine → minimal systemic absorption.

Incretin-Based Therapies

A group of hormones secreted by GI tract in response to high glucose levels → increase the secretion of insuline from the pancrease

Glucagon-like peptide-1(GLP-1) Receptor Agonists

Mimic **GLP-1** → ↑ insulin (glucose-dependent), ↓ glucagon
Delay gastric emptying, promote satiety
Examples: **Exenatide, Liraglutide**

DPP-4 Inhibitors

Block **DPP-4 enzyme** → ↑ endogenous GLP-1 & GIP
Examples: **Sitagliptin, Vildagliptin**

Adverse effects :-

- GI disturbances :- Nausea & vomiting
- Loss of appetite
- Weight loss
- Fatigue
- Hypoglycemia
- Risk of pancreatitis

DPP-IV inhibitors

Sitagliptin, Vildagliptin saxagliptin → inhibit → DPP-IV → Break dwon GLP-1

GLP-1 Excets its effects longer

Stimulate insulin Secretion

Reduce Glucagon relese

Slow down gastric emptying

Improve satiety

Adverse effects –

- GI disturbances – Nausea & vomiting
- Nasopharyngitis
- Headache
- Mild Urinary & respiratory infectins

Contraindications – Hepatic & renal impairment, Pregnancy, Breastfeeding

Do not cause weight gain or weight loss

Taken orally

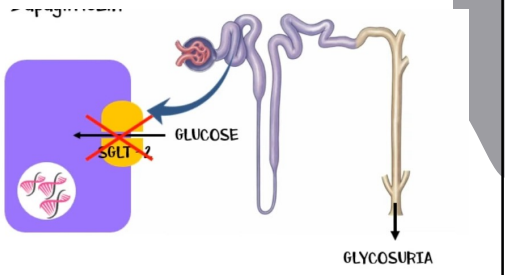
SGLT2 Inhibitors

Mechanism:

Inhibit **SGLT2 transporter** in kidney proximal tubule

↓ glucose reabsorption → ↑ glucosuria → ↓ plasma glucose

Examples: Dapagliflozin, Empagliflozin



- Increased risk of urinary infections
- Hypotension
- Canagliflozin- Moderately increases LDL

No risk of hypoglycemia

Combined with other oral agents/Monotherapy

Moderate weight loss

Amylin Analogues

Mechanism:

Mimic **amylin**, co-secreted with insulin

↓ Glucagon release

↓ Gastric emptying

↑ Satiety

Example: Pramlintide

Used as adjunct with insulin in T1DM & T2DM.

Summary

Site of Action	Drug Class	Key Mechanism
Pancreas	Sulfonylureas, Meglitinides	↑ Insulin secretion
Liver	Metformin	↓ Gluconeogenesis
Muscle/Adipose	TZDs	↑ Insulin sensitivity
Intestine	Acarbose	↓ Carbohydrate absorption
Kidney	SGLT2 inhibitors	↑ Glucose excretion
Gut hormones	GLP-1 analogues, DPP-4 inhibitors	↑ Incretin effect

1. Which drug activates AMPK?
2. Which class inhibits glucose reabsorption in the kidney?
3. Why are DPP-4 inhibitors less likely to cause hypoglycemia?
4. What is the main difference between Sulfonylureas and Meglitinides?

5. Which anti-diabetic class acts independently of insulin secretion?
6. How does AMPK activation contribute to the glucose-lowering effect of metformin?
7. Why might combination therapy be advantageous in T2DM management?
8. Which class offers both glycemic and cardiovascular benefits?