Oral hypoglycemic drugs

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Objectives

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

- Classify different categories of oral hypoglycemic drugs.
- Explain the mechanism of action, pharmacokinetics and pharmacodynamics of each class of oral hypoglycemics.
- Describe the clinical uses of oral hypoglycemics
- Know the side effects, contraindications of each class of oral hypoglycemics.

Types of diabetes mellitus

- **Type I**

  due to autoimmune or viral diseases

- **Type II**

  due to obesity, genetic factors

Pts with Type 11 diabetes have two physiological defects:

1. Abnormal insulin secretion.

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

Oral hypoglycemic drugs

Insulin secretagogues

- **Sulfonylurea drugs**
- **Meglitinide analogues**
- **Incretin mimetics**

Insulin sensitizers

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

Others

- **Alpha glucosidase inhibitors**

Insulin secretagogues

Are drugs which increase the amount of insulin secreted by the pancreas

Include:

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

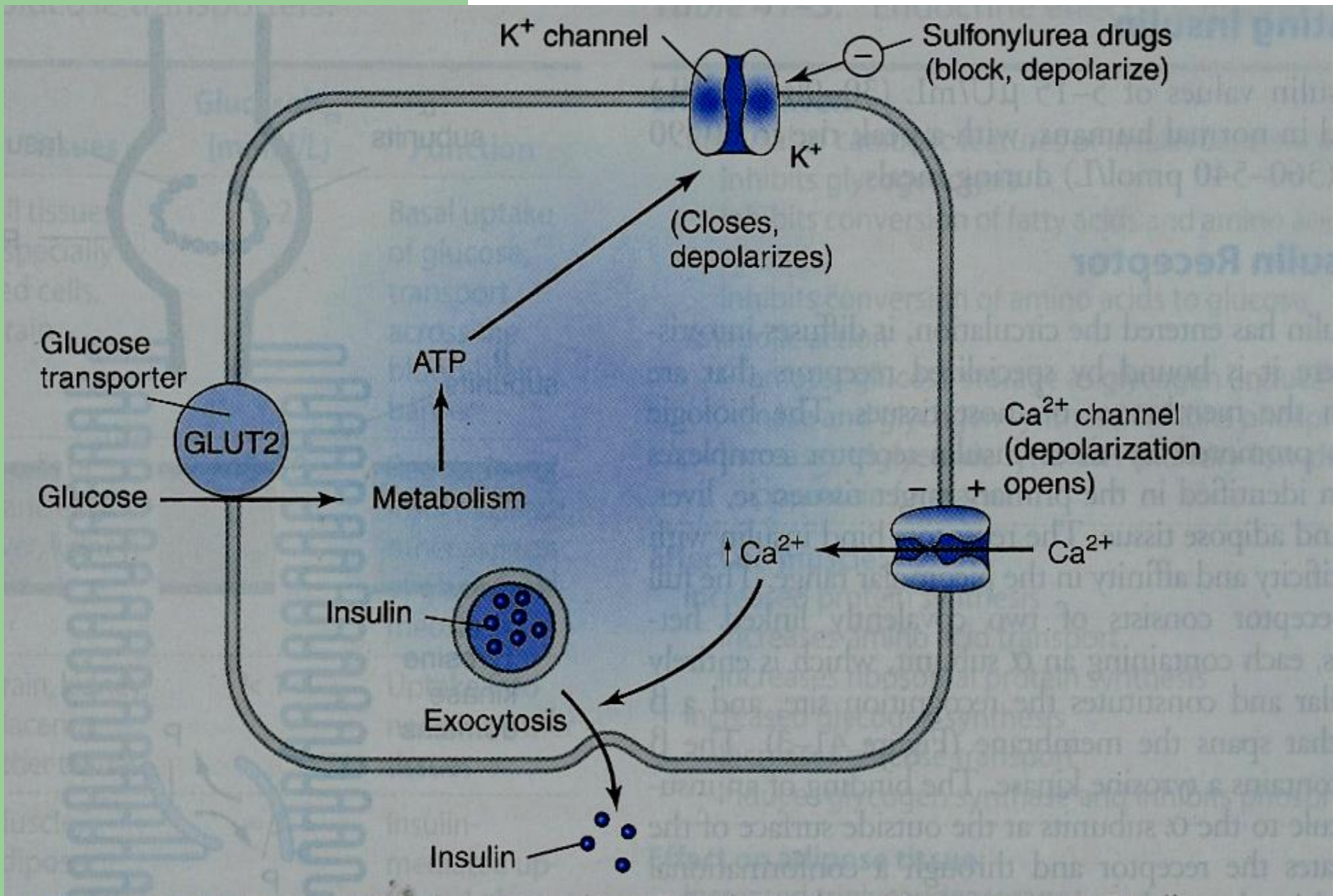
Sulfonylureas

- **Gliclazide(Diamicron)^{R} ,Glipizide(short acting)**
- **Glyburide (Glibenclamide)(long acting)**
- **Glimepiride(long acting)**

Mechanism of action of sulfonylureas:

- **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.**

Mechanisms of Insulin Release



Pharmacokinetics of Sulfonylureas

	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

Uses of sulfonylureas

- **Type II diabetes:**

monotherapy or in combination with other antidiabetic drugs.

Unwanted Effects:

1. **Hypoglycemia**
2. **Weight gain**

Meglitinide analogues

e.g. Repaglinide

Rapidly acting insulin secretagogues

Mechanism of Action:

Insulin secretagogue as sulfonylureas.

Pharmacokinetics 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 in combination with other antidiabetics).**
- **Patients allergic to sulfonylurea.**

Adverse effects :

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

Incretin mimetics

Incretins are GI hormones secreted in response to food, carried through circulation to the beta cells to stimulate insulin secretion & inhibit alpha cells &decrease glucagon secretion.

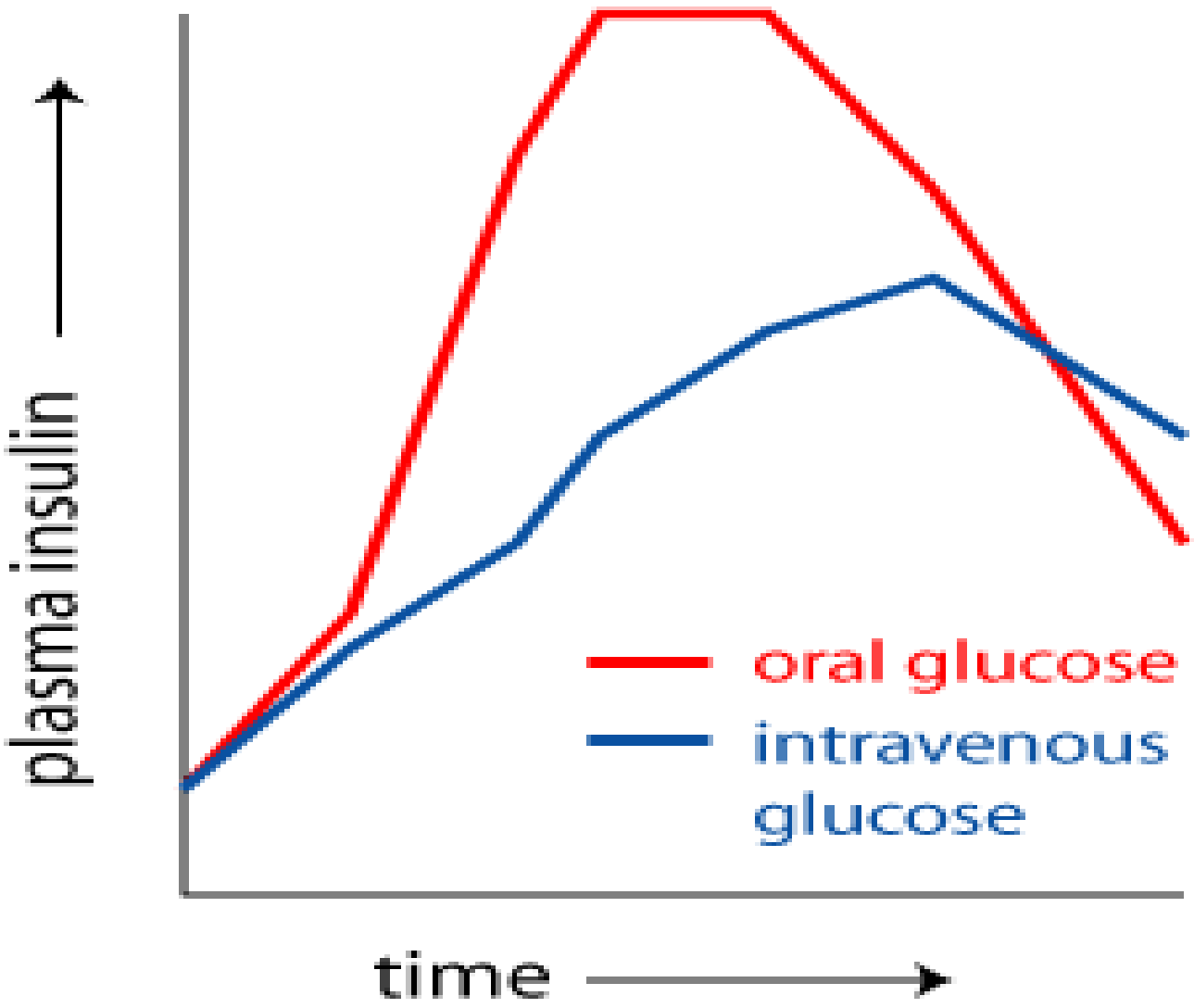
Main Incretin hormone:

- **GLP-1 (glucagon-like peptide-1)**

GLP-1 agonists, e.g. Liraglutide(Victoza, Saxenda)^{R}, Dulaglutide(Trulicity)^{R}, Exenatide.

Inactivated by dipeptidyl peptidase-4 (DPP-4) enzyme

DPP-4 Inhibitors, e.g. Sitagliptin, Vildagliptin


plasma insulin
oral glucose
intravenous glucose
time

GLP-1 agonists (Incretin mimetics)

e.g. Liraglutide

- **is glucagon-like peptide-1 (GLP-1) agonist.**
- **given s.c. once/week (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 1 diabetes.**

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.

Adverse efects

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

Dipeptidyl peptidase-4 (DPP- 4) inhibitors

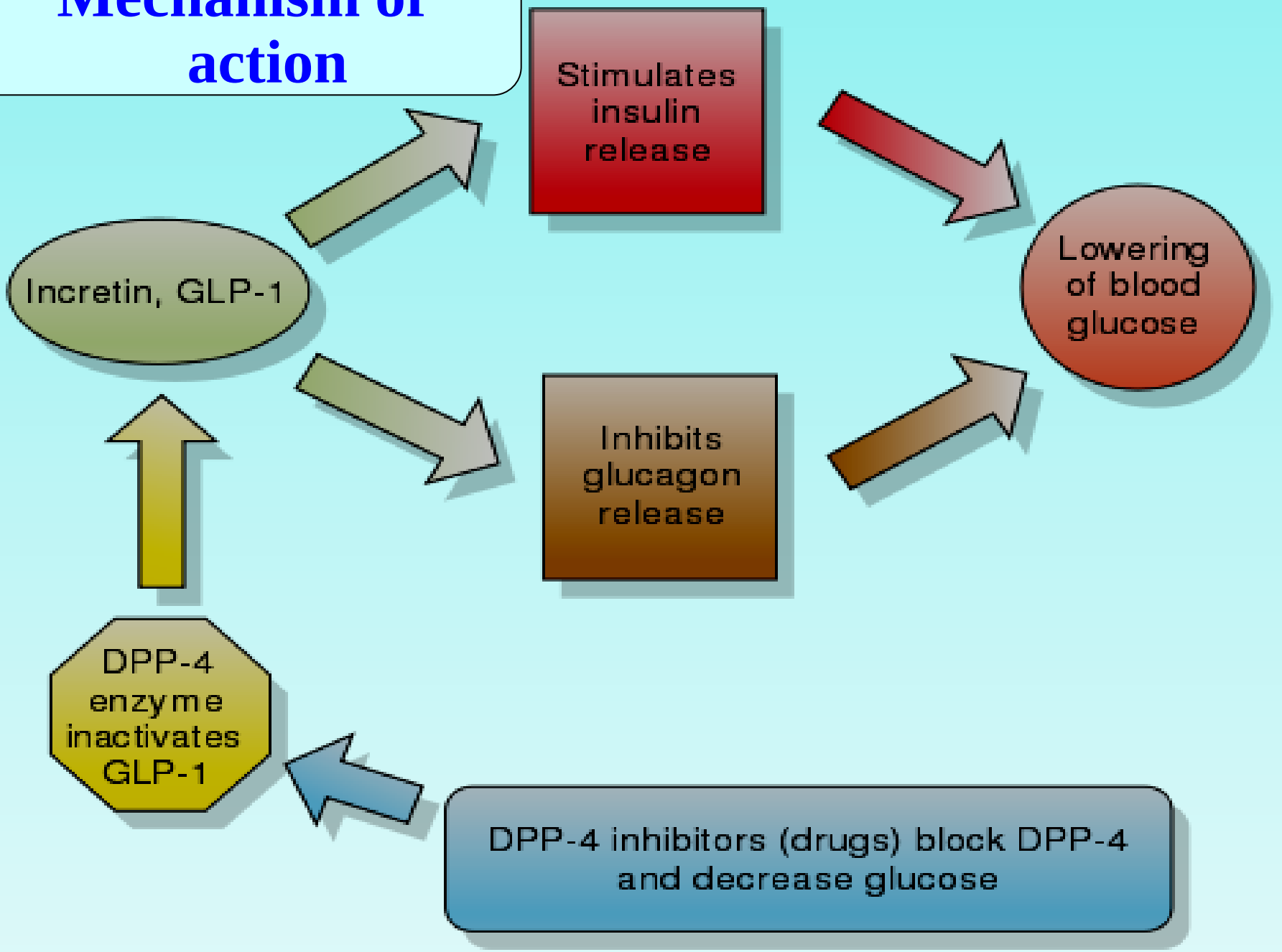
- **e.g. Sitagliptin(Januvia)®**
- **Orally**
- **half life 8-14 h**

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.

Mechanism of action



Clinical uses

Type 2 DM as an adjunct to diet & exercise as a monotherapy or in combination with other antidiabetics.

Adverse effects

Nausea, abdominal pain, diarrhea

Runny nose

Joint and muscle pain

Insulin sensitizers

- 1. Biguanides, e.g. Metformin
- 2. Thiazolidinediones, e.g. pioglitazone

BIGUANIDES E.g. Metformin

Mechanism of action of metformin

- Does not stimulate insulin release.
- Increasesliver,muscle&adiposetissues sensitivity to insulin & increase peripheral glucose utilization.
- Inhibits gluconeogenesis.
- Impairsglucose absorption from GIT.

Pharmacokinetics 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 with other antidiabetics.**

Advantages:

- **No risk hypoglycemia when used alone or weight gain (anorexia).**

Adverse effects of metformin

- **Metallic taste in the mouth**
- **GIT disturbances: nausea, vomiting, diarrhea**
- **Lactic acidosis(rare 1:30,000)**
- **Vitamin B_{12} deficiency(Long term use) .**

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.**

Pharmacokinetics 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 in combination with other antidiabetics.**
- **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.**

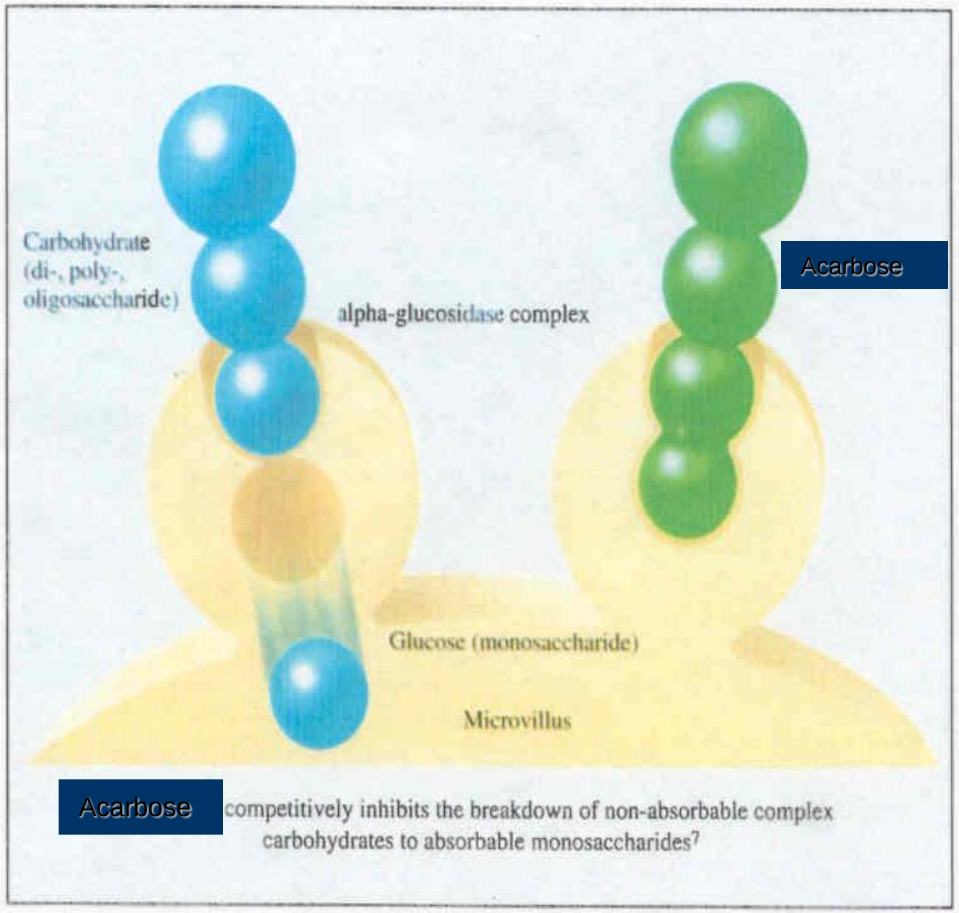
α-Glucosidase inhibitors

E.g. Acarbose, Meglitol

- **Reversible inhibitors of intestinal α- glucosidases responsible for degradation of oligosaccharides to monosaccharides.**
- **decrease carbohydrate digestion and absorption in small intestine.**
- **Decrease postprandial hyperglycemia.**
- **Taken just before meals.**
- **No hypoglycemia if used alone.**

α-GLUCOSIDASE INHIBITORS (Contd.)

MECHANISM OF ACTION

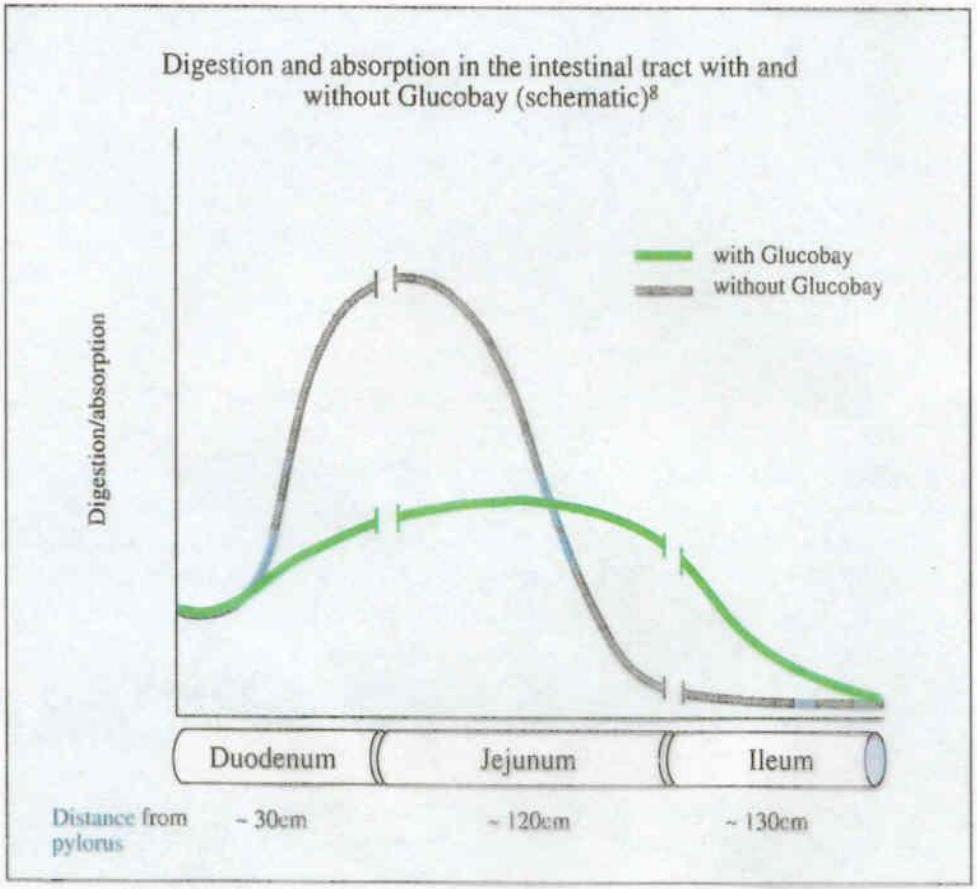


Competitively inhibits the digestion of carbohydrates

- Acarbose binds to carbohydrate-splitting enzymes (alpha-glucosidases) at receptor sites[1,2]
- By blocking these sites, Glucobay competitively and reversibly inhibits the digestion of carbohydrates in the small intestine[1,2]

α-GLUCOSIDASE INHIBITORS (Contd.)

MECHANISM OF ACTION



Delayed absorption of carbohydrates

- Absorption of glucose into the blood is slowed and the rise in postprandial blood glucose diminished[1,2]
- The portion of carbohydrate that remains undigested in the jejunum is transported to the ileum, prolonging intestinal digestion[1,2]

Kinetics of α-glucosidase inhibitors

Acarbose

- Given orally, poorly absorbed.
- Metabolized by intestinal bacteria.
- Excreted in stool and urine.

Adverse effects :

- GIT: Flatulence, diarrhea, abdominal pain.
- No hypoglycemia when used alone.