Pharmacology of Antidiabetic Drugs

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Diabetes mellitus

- An elevated blood glucose associated with
  - absent or inadequate pancreatic insulin secretion,
  - With or without concurrent impairment of insulin action
- Classified into four categories:
  - type 1, *insulin-dependent diabetes;*
  - type 2, *non–insulin-dependent diabetes;*
  - type 3, *other;* MODY
  - type 4, *gestational diabetes mellitus*

Type1

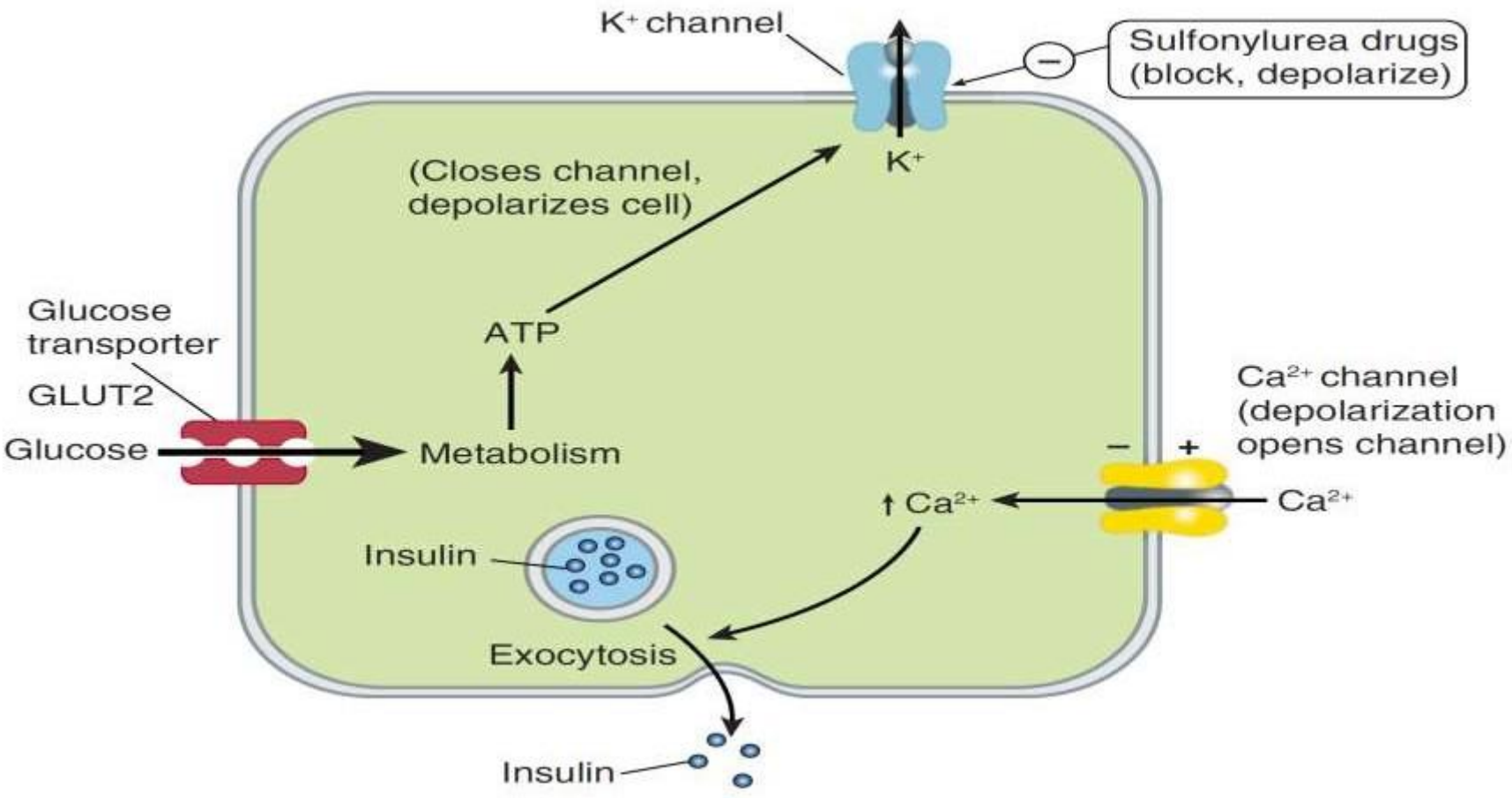
- For persons with type 1 diabetes, insulin replacement therapy is necessary to sustain life.
- Interruption of the insulin replacement therapy can be life-threatening and can result in **diabetic ketoacidosis** or death.
- Diabetic ketoacidosis is caused by insufficient or absent insulin and results from excess release of fatty acids and subsequent formation of toxic levels of ketoacids.

Type II

- Individuals with type 2 diabetes may not require insulin to survive, but 30% or more will benefit from insulin therapy to control blood glucose.
- It is likely that 10–20% of individuals in whom type 2 diabetes was initially diagnosed actually have both type 1 and type 2 or a slowly progressing type 1 called latent autoimmune diabetes of adults (LADA), and they ultimately require full insulin replacement.
- Dehydration in individuals with untreated or poorly controlled type 2 diabetes can lead to a life-threatening condition called **nonketotic hyperosmolar coma** .

INSULIN

- Insulin is a small protein with a molecular weight in humans of 5808.
- It contains 51 amino acids arranged in two chains (A and B) linked by disulfide bridges
- Proinsulin, a long single-chain protein molecule, is processed within the Golgi apparatus of beta cells and packaged into granules, where it is hydrolyzed into insulin and a residual connecting segment called C-peptide by removal of four amino acids



Secretion of Insulin

Pharmacokinetics and fate

- Human *insulin* is produced by recombinant DNA technology
- Modification of the amino acid sequence of human *insulin* produces insulins with different pharmacokinetic properties.
- *Insulin* preparations vary primarily in their onset and duration of activity.
- Dose, injection site, blood supply, temperature, and physical activity can also affect the onset and duration of various *insulin* preparations.
- Because *insulin* is a polypeptide generally administered by subcutaneous injection.
- Continuous subcutaneous insulin infusion (also called the insulin pump) is another method of insulin delivery.

Adverse reactions to insulin

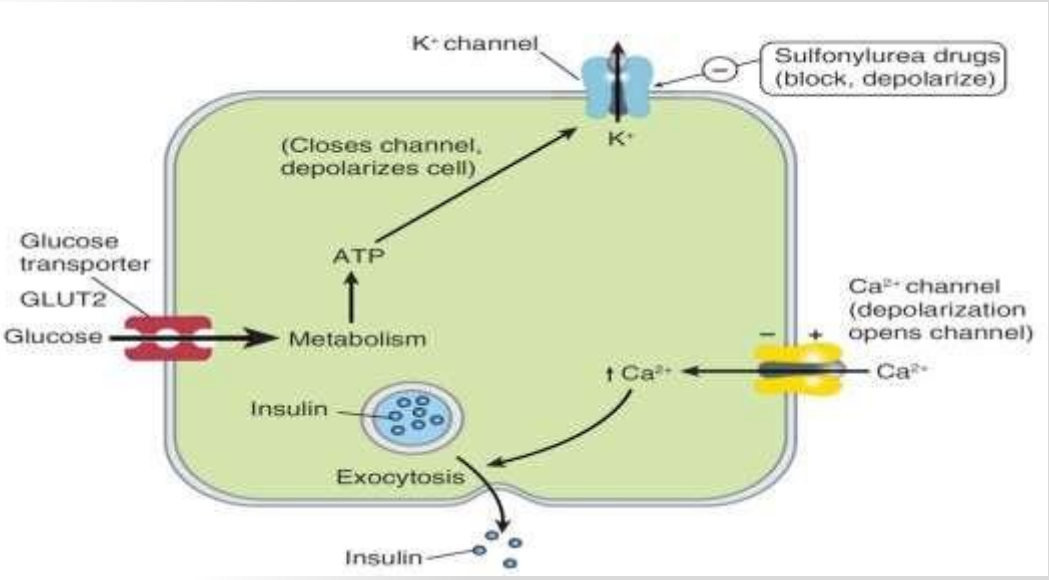
- Hypoglycemia
- Weight gain,
- Local injection site reactions
- Lipodystrophy
- Diabetics with renal insufficiency may require a decrease in *insulin* dose.

Drug classification

- Insulin secretagogues
  - sulfonylureas, meglitinides, D-phenylalanine derivatives
- biguanides,
- thiazolidinediones,
- α-glucosidase inhibitors,
- incretin-based therapies,
- an amylin analog,
- a bile acidbinding sequestrant

Mechanism of action

- Increase insulin release from the pancreas
- A reduction of serum glucagon levels
- Closure of potassium channels in extrapancreatic tissue



Insulin Release from PancreaticBeta Cells

Sulfonylureas

⬇

bind to a 140-kDa high-affinity sulfonylurea receptor

⬇

inhibits the efflux of potassium ions

⬇

depolarization.

⬇

opens a voltage-gated calcium channel

⬇

calcium influx

⬇

the release of preformed insulin.

Pharmacokinetics and fate

- Given orally
- Bind to serum proteins,
- Metabolized by the liver
- Excreted in the urine and feces
- The duration of action ranges from 12 to 24 hours

- **Tolbutamide**
  - Well absorbed but rapidly metabolized in the liver.
  - Its duration of effect is relatively short, with an elimination half-life of 4–5 hours
  - Dicumarol, phenylbutazone, some sulfonamides that inhibit the metabolism of tolbutamide.

- **Glipizide**
  - Shortest half-life (2–4 hours)
  - ingested 30 minutes before breakfast
  - starting dosage is 5 mg/d, with up to 15 mg/d
  - 90% of glipizide is metabolized
  - 10% is excreted unchanged in the urine
  - Contraindicated in patients with significant hepatic or renal impairment, who would be at high risk for hypoglycemia.

- **Glimepiride**
  - approved for once-daily use as monotherapy or in combination with insulin.
  - 1 mg has been shown to be effective, and the recommended maximal daily dose is 8 mg.
  - Long duration of effect with a half-life of 5 hours,
  - Completely metabolized by the liver to metabolites with weak or no activity.

Repaglinide

- The first member of the meglitinide group
- Mechanism of action is similar to sulfonylureas
- Two binding sites in common with the sulfonylureas and one unique binding site.

Pharmacokinetics

- Very fast onset of action
- Peak effect within 1 h
- Duration of action is 4–7 hours
- Metabolism by CYP3A4
  - Indicated for use in controlling postprandial glucose excursions.
  - Doses of 0.25–4 mg (maximum 16 mg/d);
  - Hypoglycemia is a risk
- C/I in renal and hepatic impairment.

BIGUANIDES

- *Metformin*
- *Insulin* sensitizer.
- It increases glucose uptake and use by target tissues,
- decreasing *insulin* resistance.

Mechanism of action

Metformin

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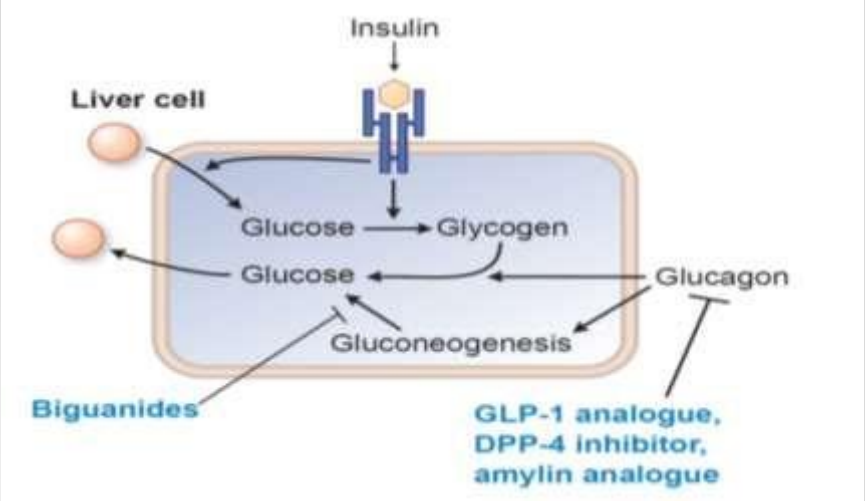
Activate AMP activated protein kinase (AMPA-PK)

↓

Reduce hepatic glucose production

↓

Lower blood glucose level



THIAZOLIDINEDIONES

- **Pioglitazone and rosiglitazone**
- Decrease insulin resistance.
- Ligands of **peroxisome proliferator-activated receptor gamma (PPAR-f),**
- Found in muscle, fat, and liver.
- Modulate the expression of the genes involved in
  - lipid and glucose metabolism,
  - insulin signal transduction,
  - adipocyte and other tissue differentiation.

Mechanism of actions

Thiazolidinediones

↓

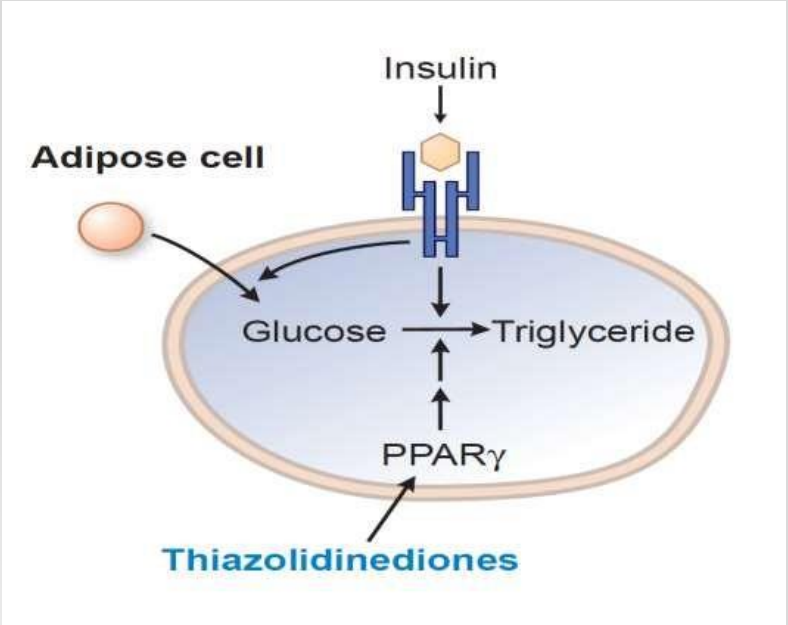
Activates peroxisome proliferator–activated receptor-γ (PPARγ)

↓

Regulates the transcription of several *insulin* responsive genes

↓

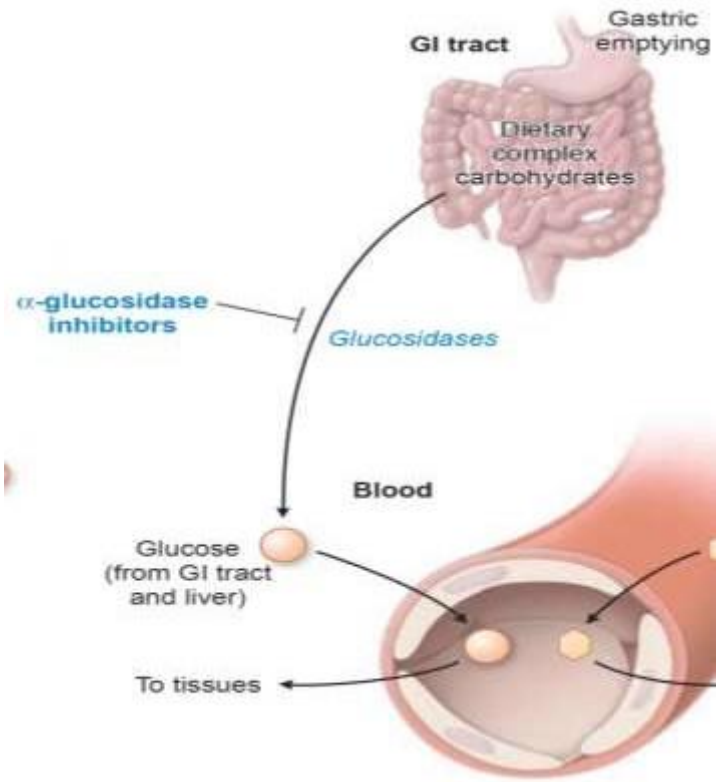
increased *insulin* sensitivity



α-Glucosidase inhibitors

- *Acarbose*
- *miglitol*

Mechanism of action



Liraglutide

- Long-acting synthetic GLP-1 analog with 97% homology to native GLP-1
- Peak levels are obtained in 8–12 hours
- Elimination half-life is about 13 hours
- Prolonged half-life that permits once-daily dosing.

Sitagliptin

- Orally well absorbed
- Bioavailability 85%
- Reach PPC with in 1-4 h
- Half life is 12 h
- Oral dose is 100 mg
- Metabolized via CYP3A4
- Excreted via urine by tubular secretion

Sexagliptin

- Orally well absorbed
- Dose is 2.5 to 5 mg daily
- Less protein binding
- Reach peak plasma conc within 2 h
- Undergo metabilosm by CYP3A4/5 to form active molecule
- Peak plasma conc of metabolite is 4 h
- Both are excreted via urine