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.*

Type II Diabetes

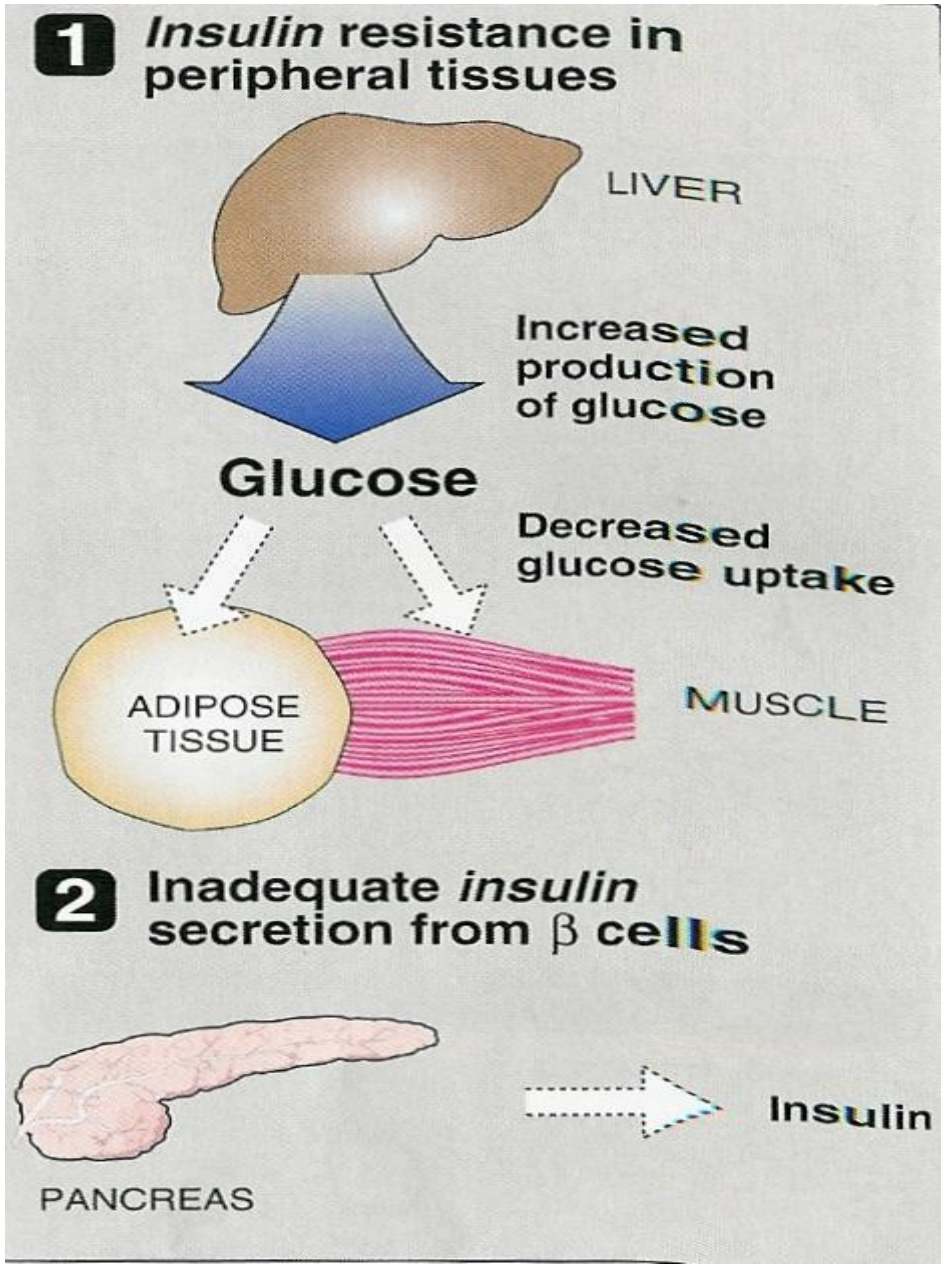
- 80-90% occurrence
- Over age 35
- Obesity is an important factor.

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.

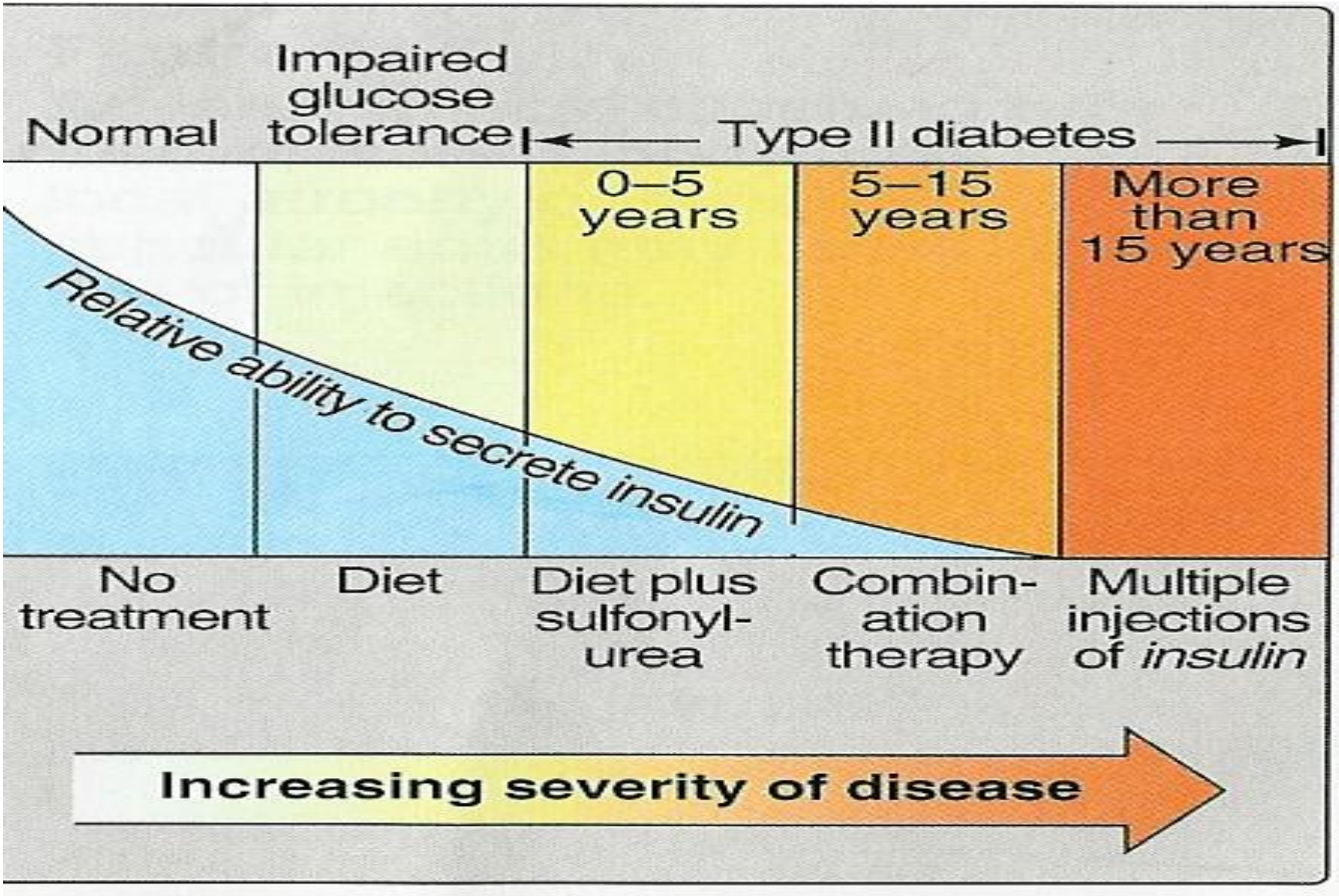
Types II diabetes



Treatment of Type II Diabetes (NIDDM)

- **Proper dietary management.**
- **Caloric restriction and weight loss are important in obese diabetic patients.**
- **Increase physical activity.**
- **Oral antidiabetic drugs.**

Types II diabetes



Oral hypoglycemic drugs

Insulin secretagogues

- **Sulfonylurea drugs**
- **Meglitinides**

Insulin sensitizers

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

Agents that reduce carbohydrate absorption

(Alpha glucosidase inhibitors).

Newer agents: Gastrointestinal hormones.

Insulin secretagogues

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

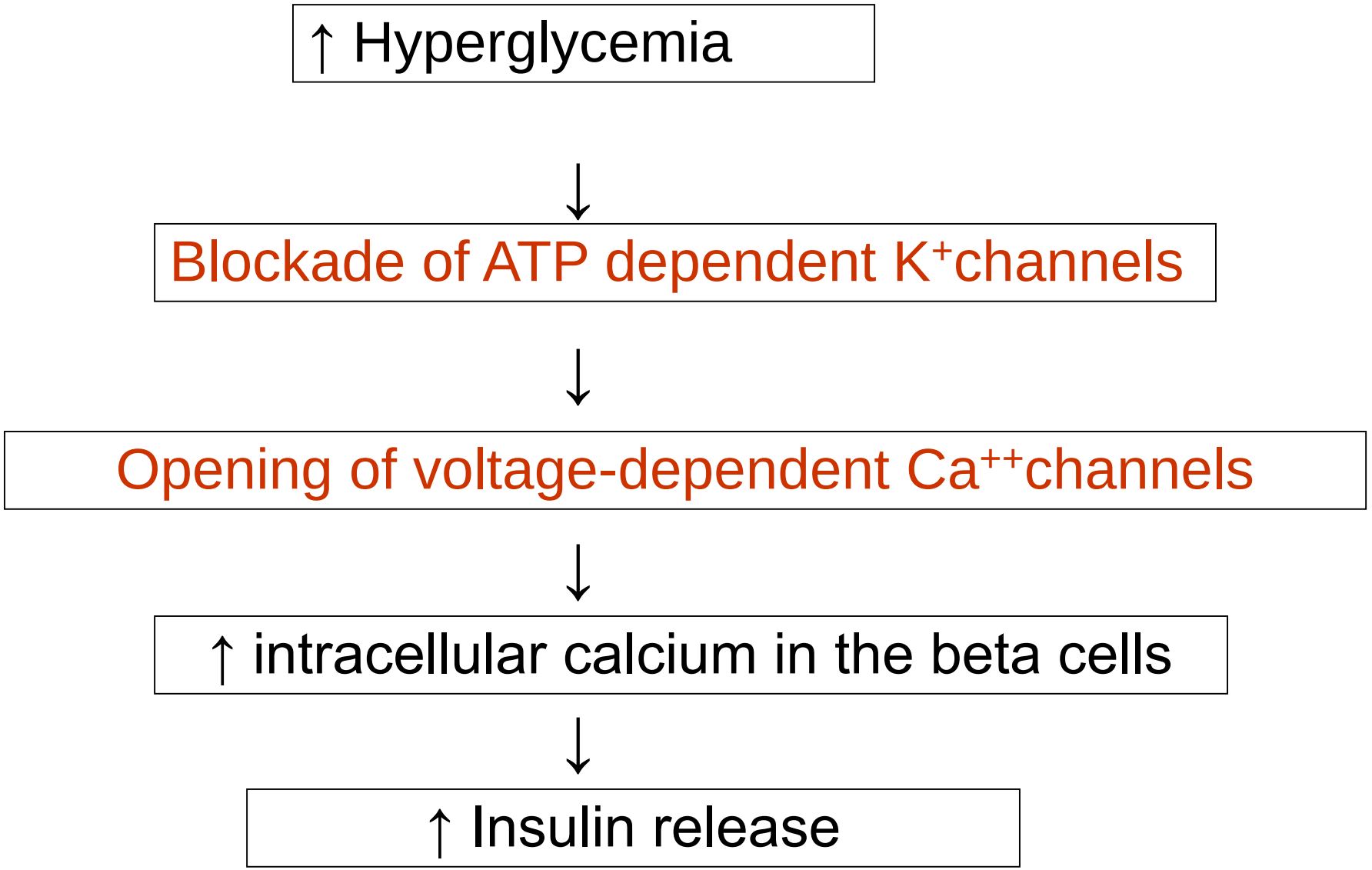
Include:

- Sulfonylureas
- Meglitinides

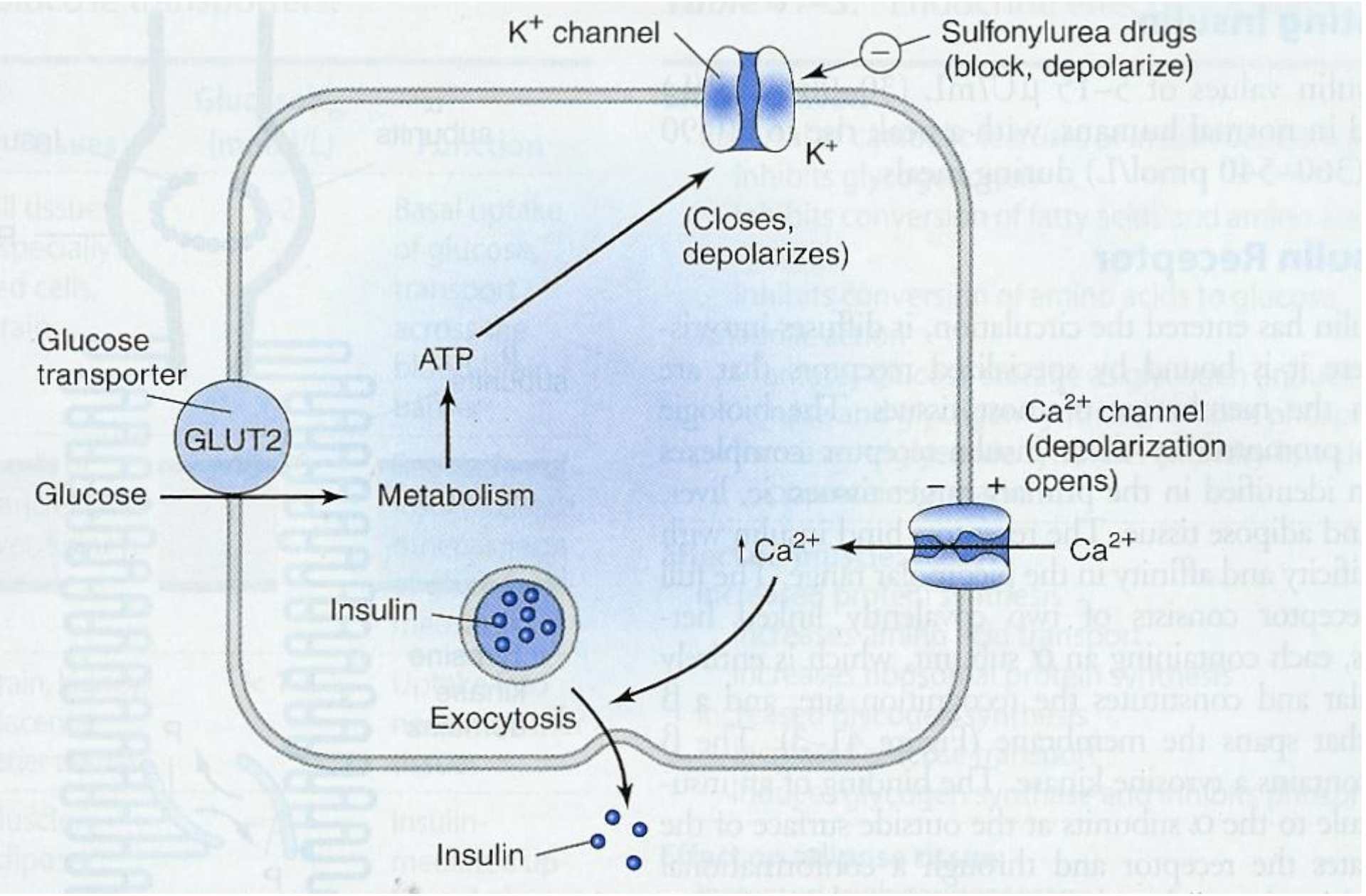
Mechanism of action of sulfonylureas:

- **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.**

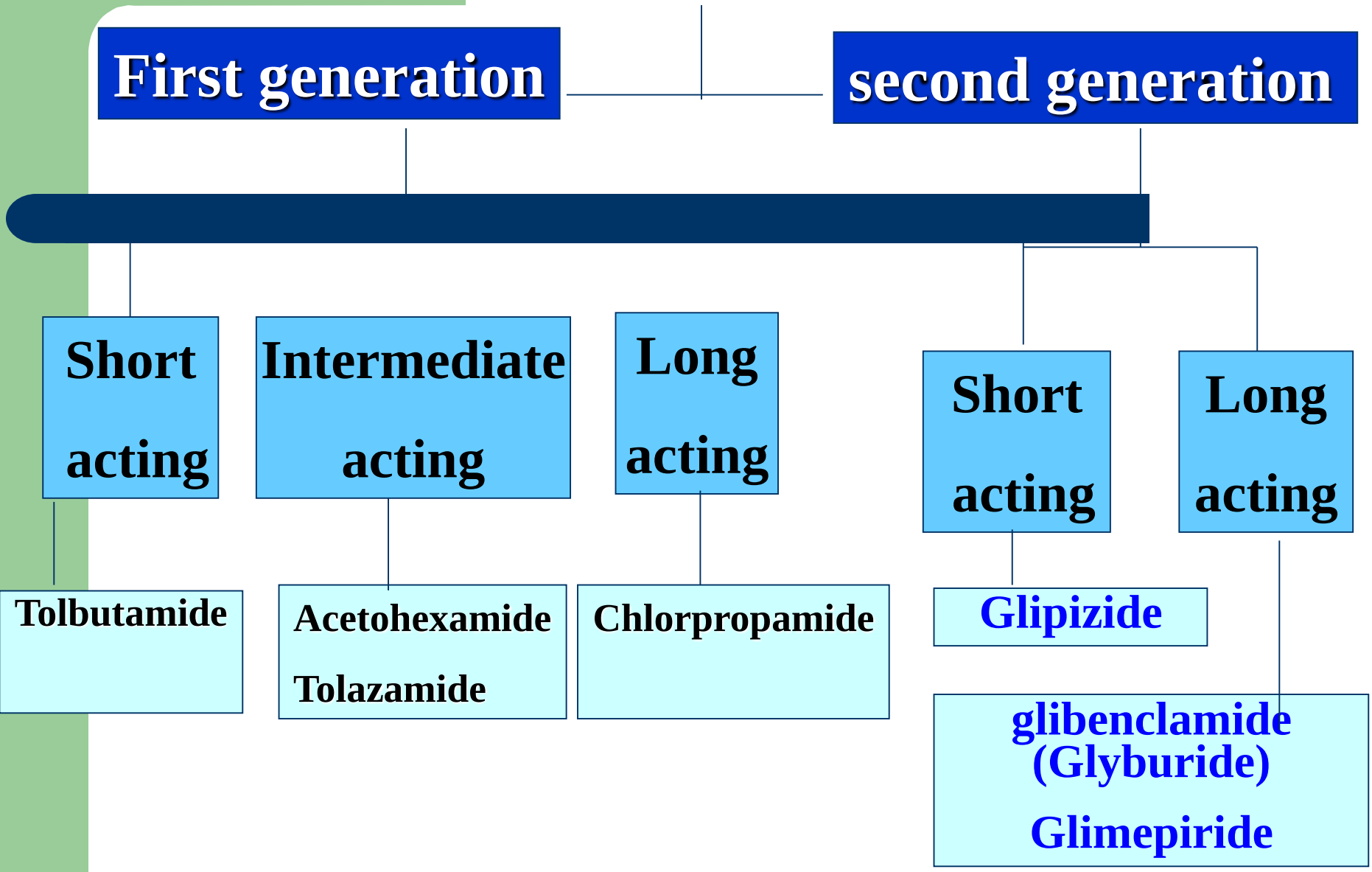
Insulin secretagogues (sulfonylureas)



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.
- 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

Glipizide, Glyburide, Glimepiride

- **More potent than first generation**
- **Have longer duration of action.**
- **Less frequency of administration**
- **Have fewer adverse effects**
- **Have fewer drug interactions**

SECOND GENERATION SULPHONYLUREAS

	Glipizide	Glyburide (Glibenclamide)	Glimepiride
Absorption	Well reduced by food	Well	Well
Metabolism	Yes	Yes	Yes
Metabolites	Inactive	Inactive	Inactive
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

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**
- **Nateglinide**

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 sulfur.**

Adverse effects of Meglitinides

Less incidence than sulfonylureas

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

Insulin sensitizers

- **Are drugs which increase the sensitivity of peripheral target organs to insulin.**

Include

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

Biguanides

e.g. Metformin

Mechanism of action of metformin

- **Increases glucose uptake and utilization by peripheral tissues (tissue glycolysis)**
- **Reduces insulin resistance.**
- **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**

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 glucose uptake and utilization in muscle and adipose tissue.**
- **Increase sensitivity of target tissues to insulin.**

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. If hypoglycemia occurs should be corrected with glucose tablets or gel.**

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

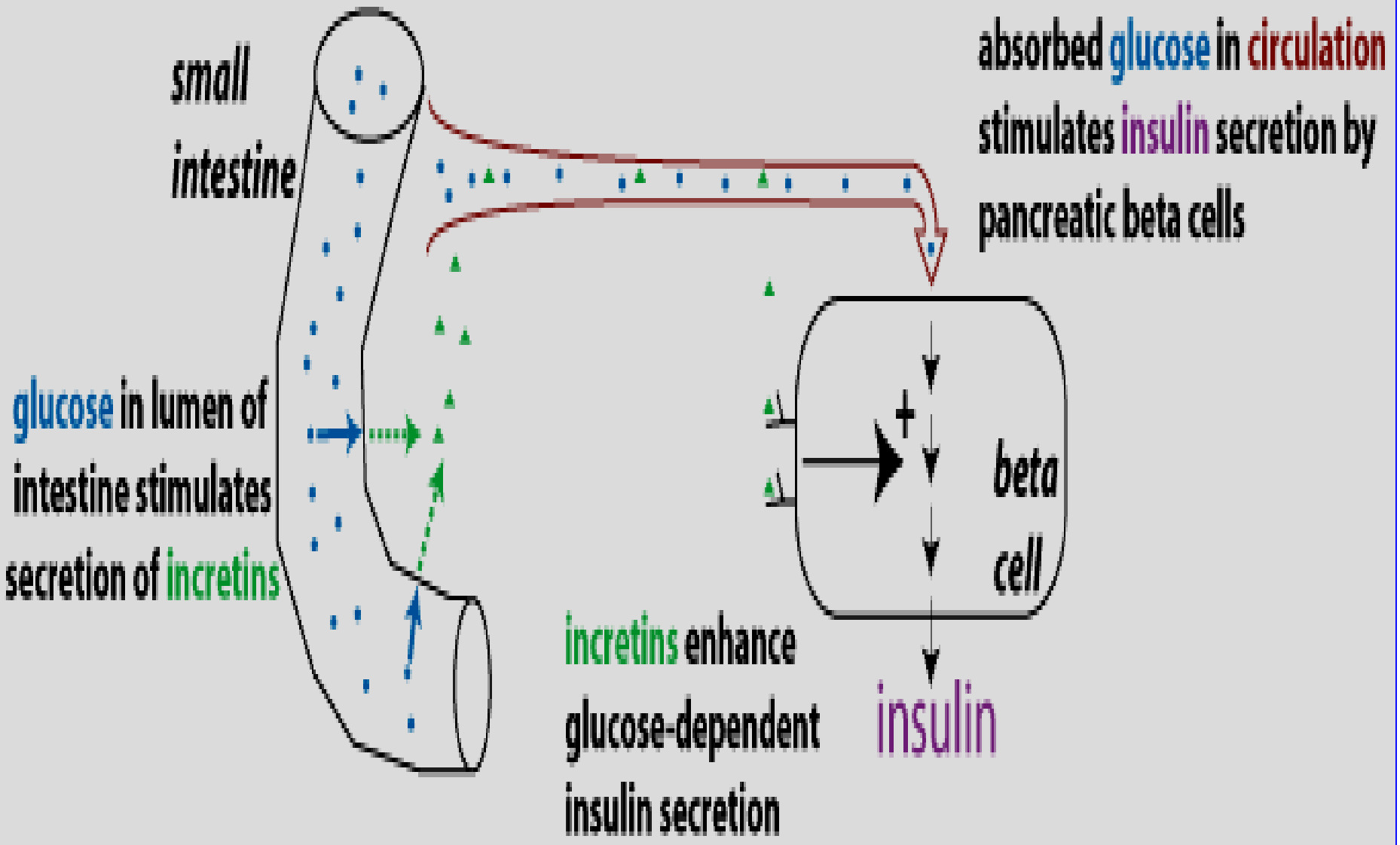
- **GIT side effects: Flatulence, bloating, diarrhea, abdominal pain.**

Contraindications of α-glucosidase inhibitors

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

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**

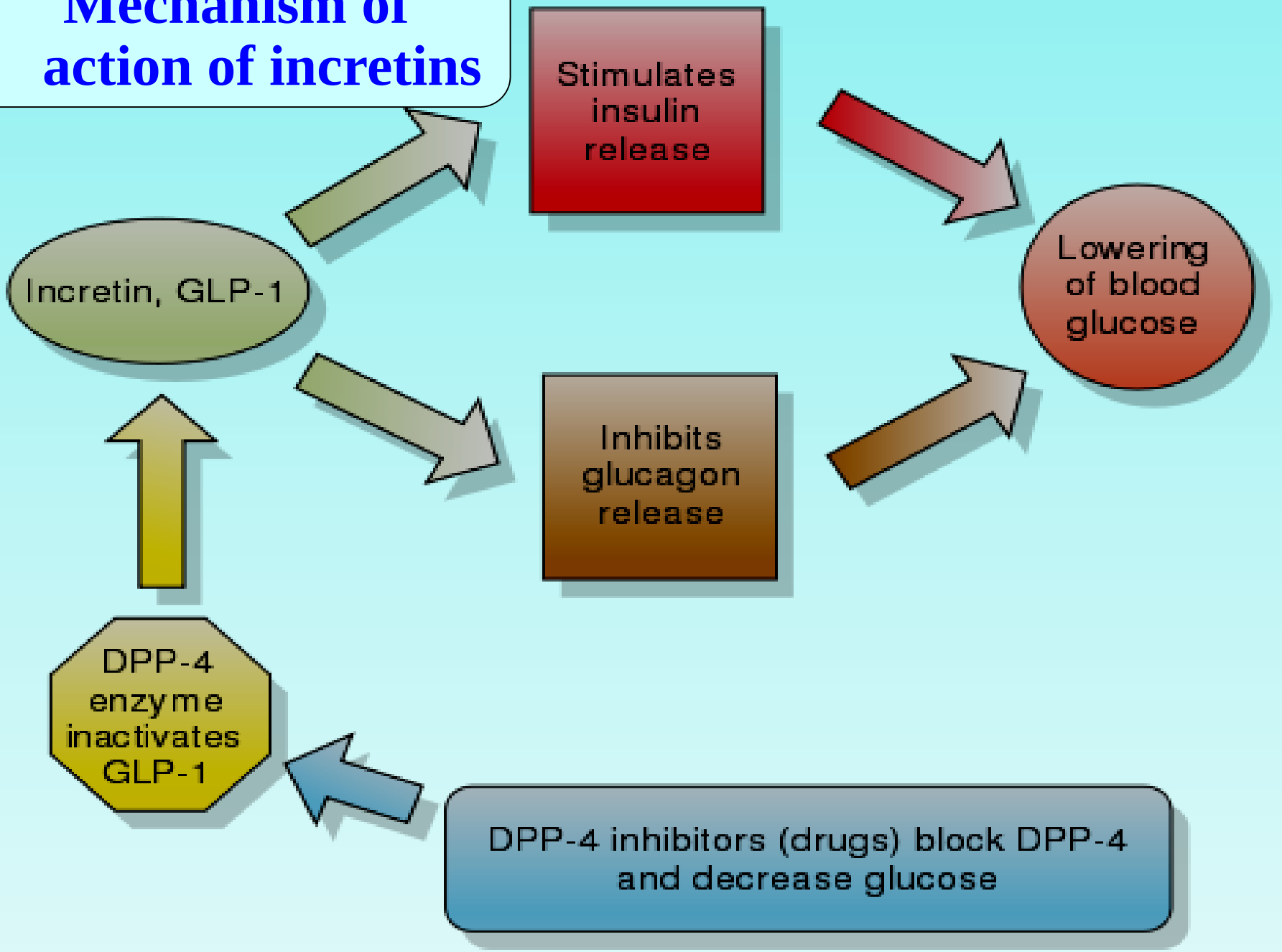

small intestine
absorbed glucose in circulation stimulates insulin secretion by pancreatic beta cells
glucose in lumen of intestine stimulates secretion of incretins
+
beta cell
incretins enhance glucose-dependent insulin secretion
insulin

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 incretins



Incretins mimetics
GLP-1 agonists

e.g. Dulaglutide, Exenatide.

GLP-1 agonists (Incretin mimetics)

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

Dulaglutide

Adverse effects

Nausea & vomiting (most common).

Abdominal pain, decreased appetite & fatigue.

Dipeptidyl peptidase-4 inhibitor (DPP- 4 inhibitors)

e.g. Sitagliptin, vildagliptin

Sitagliptin

- **Inhibit DPP-4 enzyme thus increase incretin hormone (GLP-1).**
- **Is given orally.**
- **Is given once daily.**

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.

SUMMARY

Class	Mechanism	Site of action	Main advantages	Main side effects
Sulfonylureas	Stimulates insulin secretion	Pancreatic beta cells	• Effective • Inexpensive	• Hypoglycemia • Weight gain
Meglitinides repaglinide		Pancreatic beta cells	Sulfa free	•Hypoglycemia •Weight 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 weight gain
α-Glucosidase inhibitors Acarbose	Inhibits α-glucosidase	GI tract	Low risk	•GI symptoms, flatulence
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