Oral Antidiabetic Agents

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Oral Antidiabetic Agents

- Four categories of oral antidiabetic agents are now available:
  - insulin secretagogues (sulfonylureas, meglitinides, D-phenylalanine derivatives),
  - biguanides,
  - thiazolidinediones,
  - alpha- glucosidase inhibitors.

Oral Antidiabetic Agents

- The sulfonylureas and biguanides have been available the longest and are the traditional initial treatment choice for type 2 diabetes.
- Novel classes of rapidly acting insulin secretagogues, the D-phenylalanine derivatives and meglitinides, are alternatives to the short-acting sulfonylurea, tolbutamide.
- The thiazolidinediones are very effective agents that reduce insulin resistance.
- alpha-Glucosidase inhibitors have a relatively weak antidiabetic effect and significant adverse effects, and they are used primarily as adjunctive therapy in individuals who cannot achieve their glycemic goals with other medications.

Insulin Secretagogues

Sulfonylureas

Mechanism of Action

- The major action of sulfonylureas is to increase insulin release from the pancreas.
- Two additional mechanisms of action have been proposed:
  - a reduction of serum glucagon levels
  - and closure of potassium channels in extra pancreatic tissues (is of unknown clinical significance).

Regulation of Insulin Release in Humans

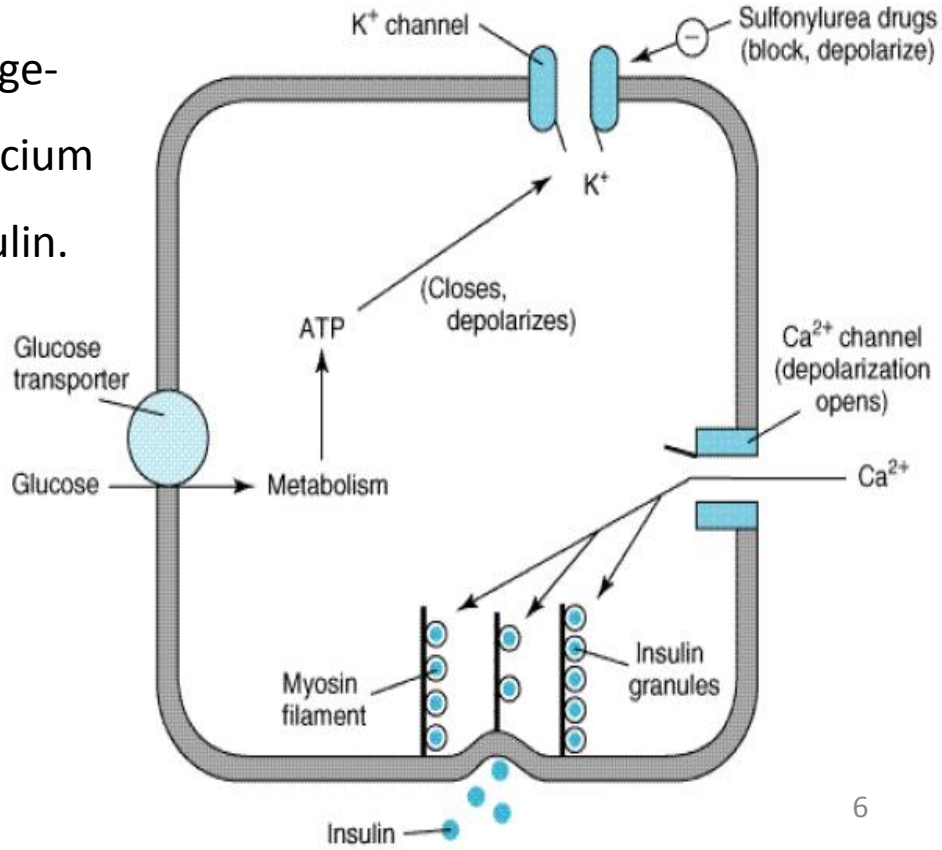
- **Stimulants of insulin release**
  - Glucose, mannose
  - Leucine
  - Vagal stimulation
  - Sulfonylureas

- **Amplifiers of glucose-induced insulin release**
  - Enteric hormones:
    - Glucagon-like peptide 1 (GLP-1)
    - Gastrin inhibitory peptide
    - Cholecystokinin
    - Secretin, gastrin
  - Neural amplifiers:
    - beta-Adrenoceptor stimulation
  - Amino acids:
    - Arginine

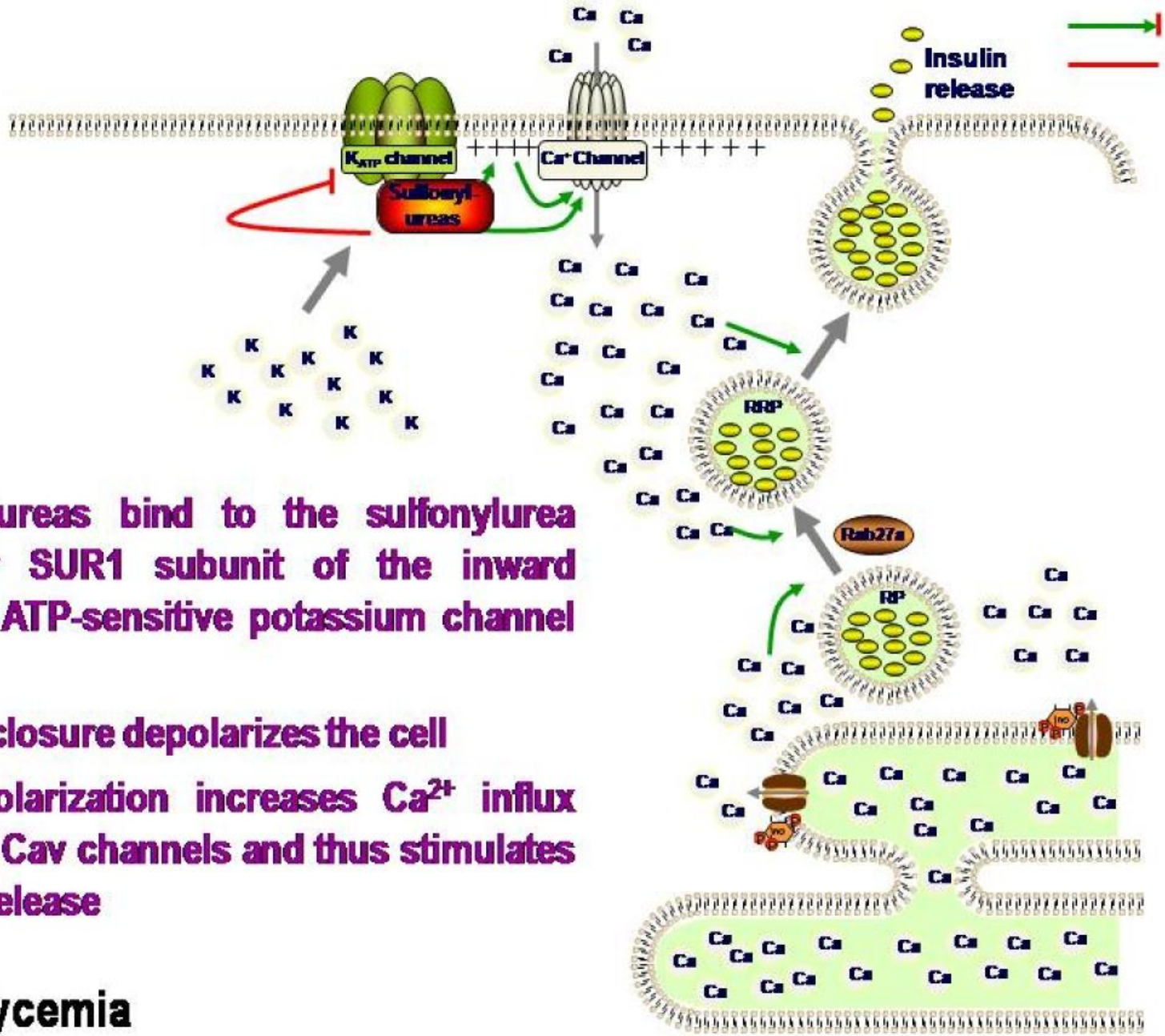
- **Inhibitors of insulin release**
  - Neural: alpha-Sympathomimetic effect of catecholamines
  - Humoral: Somatostatin
  - Drugs: Diazoxide, phenytoin, vinblastine, colchicine

Insulin Release from Pancreatic B Cells

- Sulfonylureas bind to a high-affinity sulfonylurea receptor that is associated with a B cell inward rectifier ATP-sensitive potassium channel.
- Binding of a sulfonylurea inhibits the efflux of potassium ions through the channel and results in depolarization.
- Depolarization, in turn, opens a voltage-gated calcium channel and results in calcium influx and the release of preformed insulin.



Sulfonylureas increase insulin release



Sulfonylureas bind to the sulfonylurea receptor SUR1 subunit of the inward rectifier ATP-sensitive potassium channel Kir6.2

→ K_{ATP} closure depolarizes the cell

→ Depolarization increases Ca^{2+} influx through Cav channels and thus stimulates insulin release

Hypoglycemia

Reduction of Serum Glucagon Concentrations

- Chronic administration of sulfonylureas to type 2 diabetics reduces serum glucagon levels, which may contribute to the hypoglycemic effect of the drugs.
- The mechanism for this suppressive effect of sulfonylureas on glucagon levels is unclear but appears to involve indirect inhibition due to enhanced release of both insulin and somatostatin, which inhibit A cell secretion.

Potassium Channel Closure in Extrapancreatic Tissues

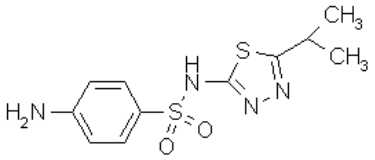
- Insulin secretagogues bind to sulfonylurea receptors in potassium channels in extrapancreatic tissues but the binding affinity varies among the drug classes and is much less avid than for the B cell receptors.
- The clinical significance of extrapancreatic binding is not known.

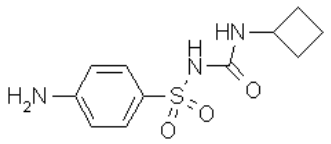
Efficacy & Safety of the Sulfonylureas

- They are conventionally divided into first-generation and second-generation agents, which differ primarily in their potency and adverse effects.
- The second-generation agents become generic and less expensive, so the earlier compounds (first-generation sulfonylureas) probably will be discontinued.

Sulfonylureas :

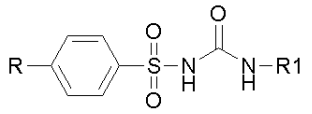
stimulate β cells to produce more insulin





2-(p-aminobenzenesulfonamido)-5-isopropyl -thiadiazole **(IPTD)** was used in treatment of typhoid fever in 1940's → hypoglycemia

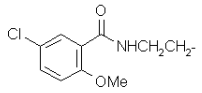
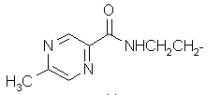
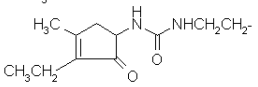
Currently > 12,000

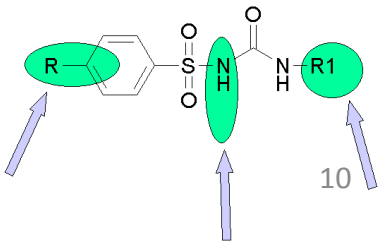


Rel. Potency

- 1st generation
  - bind to protein
  - (1)Orinase (tolbutamide)
  - (3)Tolinase (tolazamide)
  - (6)Diabinese (chlorpropamide)
  - ∴ **may become dislodged → delayed activity**

- 2nd generation
  - (75)Glucotrol (glipizide)
  - (150)Glucotrol XL (ex. rel. glipizide)
  - (150)Micronase, Diabeta (glyburide)
  - (250)Glynase (micronized glyburide)
  - (350)Amaryl (glimepiride)

name	R	R1
Tolbutamide	$-CH_3$	$-CH_2CH_2CH_2CH_3$
Chlorpropamide	$-Cl$	$-CH_2CH_2CH_3$
Tolazamide	$-CH_3$	
Acetohaxamide		
Glyburide		
Glipizide		
Glimepiride		



*Hydroxylation of the aromatic ring appears to be the most favored metabolic pathway
*Hydroxylated derivatives have much lower hypoglycemic activity

First-Generation Sulfonylureas

- **Tolbutamide**
  - Its duration of effect is relatively short, with an elimination half-life of 4–5 hours.
  - Because of its short half-life, it is the safest sulfonylurea for use in elderly diabetics.
  - Prolonged hypoglycemia has been reported rarely.
- **Chlorpropamide**
  - has a half-life of 32 hours and is slowly metabolized in the liver to products that retain some biologic activity.
  - is contraindicated in patients with hepatic or renal insufficiency.
  - Prolonged hypoglycemic reactions are more common in elderly patients, and the drug is contraindicated in this group.
- **Tolazamide**
  - is comparable to chlorpropamide in potency but has a shorter duration of action.
  - is more slowly absorbed than the other sulfonylureas. Its half-life is about 7 h.
  - is metabolized to several compounds that retain hypoglycemic effects.

Second-Generation Sulfonylureas

- The second-generation sulfonylureas are more frequently prescribed than the first generation agents because they have fewer adverse effects and drug interactions.
- These potent sulfonylurea compounds - glyburide, glipizide, and glimepiride - should be used with caution in patients with cardiovascular disease or in elderly patients, in whom hypoglycemia would be especially dangerous.

- **Glyburide**
  - is metabolized in the liver into products with very low hypoglycemic activity.
  - has few adverse effects other than its potential for causing hypoglycemia.
  - is contraindicated in the presence of hepatic impairment and in patients with renal insufficiency.

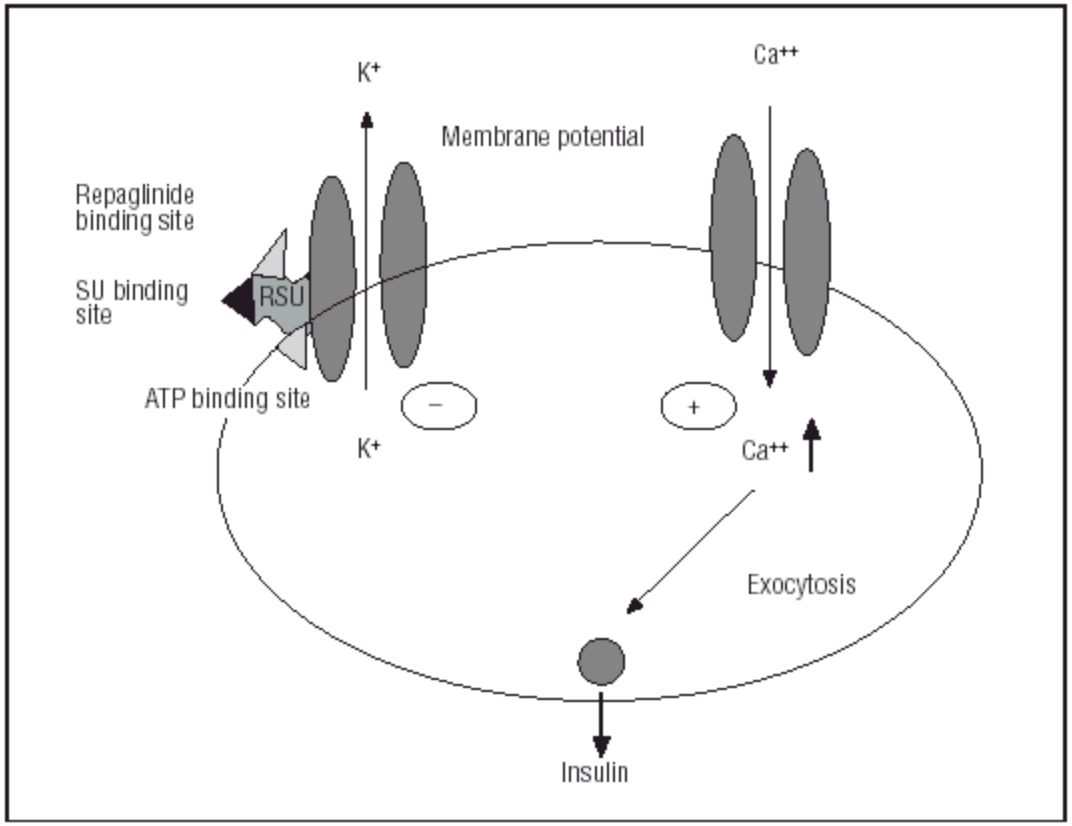
- **Glipizide**
  - Has the shortest half-life (2–4 hours) of the more potent agents, therefore, glipizide is much less likely than glyburide to produce serious hypoglycemia.
  - For maximum effect in reducing postprandial hyperglycemia, this agent should be ingested 30 minutes before breakfast.
  - Glipizide therapy is contraindicated in patients with significant hepatic or renal impairment, who would therefore be at high risk for hypoglycemia.

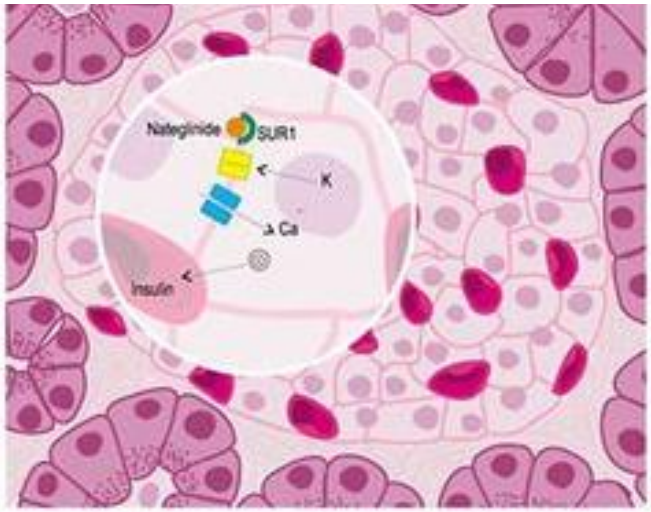
- **Glimepiride**
  - Is approved for once-daily use as monotherapy or in combination with insulin.
  - Lowers blood glucose with the lowest dose of any sulfonylurea compound.
  - It has a long duration of effect, allowing once-daily dosing and thereby improving compliance.
  - It is completely metabolized by the liver to inactive products.

Insulin Secretagogues

Meglitinides

- The meglitinides are a relatively new class of insulin secretagogues.
- Repaglinide, the first member of the group.
- These drugs modulate B cell insulin release by regulating potassium efflux through the potassium channels.
- There is overlap with the sulfonylureas in their molecular sites of action since the meglitinides have two binding sites in common with the sulfonylureas and one unique binding site.
- Unlike the sulfonylureas, they have no direct effect on insulin exocytosis.


K+
Ca++
Membrane potential
Repaglinide binding site
SU binding site
RSU
ATP binding site
K+
Ca++
Exocytosis
Insulin


Nateglinide
SUR1
K
Ca
Insulin

➢ Repaglinide

- Has a very fast onset of action, with a peak concentration and peak effect within approximately 1 hour after ingestion, but the duration of action is 5–8 hours.
- It is hepatically cleared by CYP3A4 with a plasma half-life of 1 hour.
- Because of its rapid onset, repaglinide is indicated for use in controlling postprandial glucose excursions.
- It should be taken just before each meal; hypoglycemia is a risk if the meal is delayed or skipped or contains inadequate carbohydrate.
- It should be used cautiously in individuals with renal and hepatic impairment.
- It is approved as monotherapy or in combination with biguanides.

Insulin Secretagogue

D-Phenylalanine Derivative

- **Nateglinide,**
  - Is a D-phenylalanine derivative, is the latest insulin secretagogue to become clinically available.
  - Stimulates very rapid and transient release of insulin from B cells through closure of the ATP-sensitive K+ channel.
  - May have a special role in the treatment of individuals with isolated postprandial hyperglycemia, but it has minimal effect on overnight or fasting glucose levels.
  - Nateglinide is ingested just prior to meals.
  - The overall duration of action is less than 4 hours.
  - It is efficacious when given alone or in combination with nonsecretagogue oral agents (such as metformin).

- **Nateglinide**,
  - Nateglinide amplifies the insulin secretory response to a glucose load but has a markedly diminished effect in the presence of normoglycemia.
  - The incidence of hypoglycemia may be the lowest of all the secretagogues, and it has the advantage of being safe in individuals with very reduced renal function.

Biguanides

- Metformin is the only biguanide used for the treatment of type 2 diabetes .
- Phenformin (an older biguanide) was discontinued in the USA because of its association with lactic acidosis and because there was no documentation of any long-term benefit from its use.

Metabolism & Excretion

- Metformin has a half-life of 1.5–3 hours, is not bound to plasma proteins, is not metabolized, and is excreted by the kidneys as the active compound.
- As a consequence of metformin's blockade of gluconeogenesis, the drug may impair the hepatic metabolism of lactic acid.
- In patients with renal insufficiency, biguanides accumulate and thereby increase the risk of lactic acidosis, which appears to be a dose-related complication.

Biguanides

Mechanisms of Action

- A full explanation of the biguanides' mechanism of action remains elusive.
- These agents are therefore more appropriately termed "euglycemic" agents.
- Currently proposed mechanisms of action include:

(1) direct stimulation of glycolysis in tissues;

(2) reduced hepatic gluconeogenesis;

(3) slowing of glucose absorption from the GIT;

and (4) reduction of plasma glucagon levels.

Clinical Use

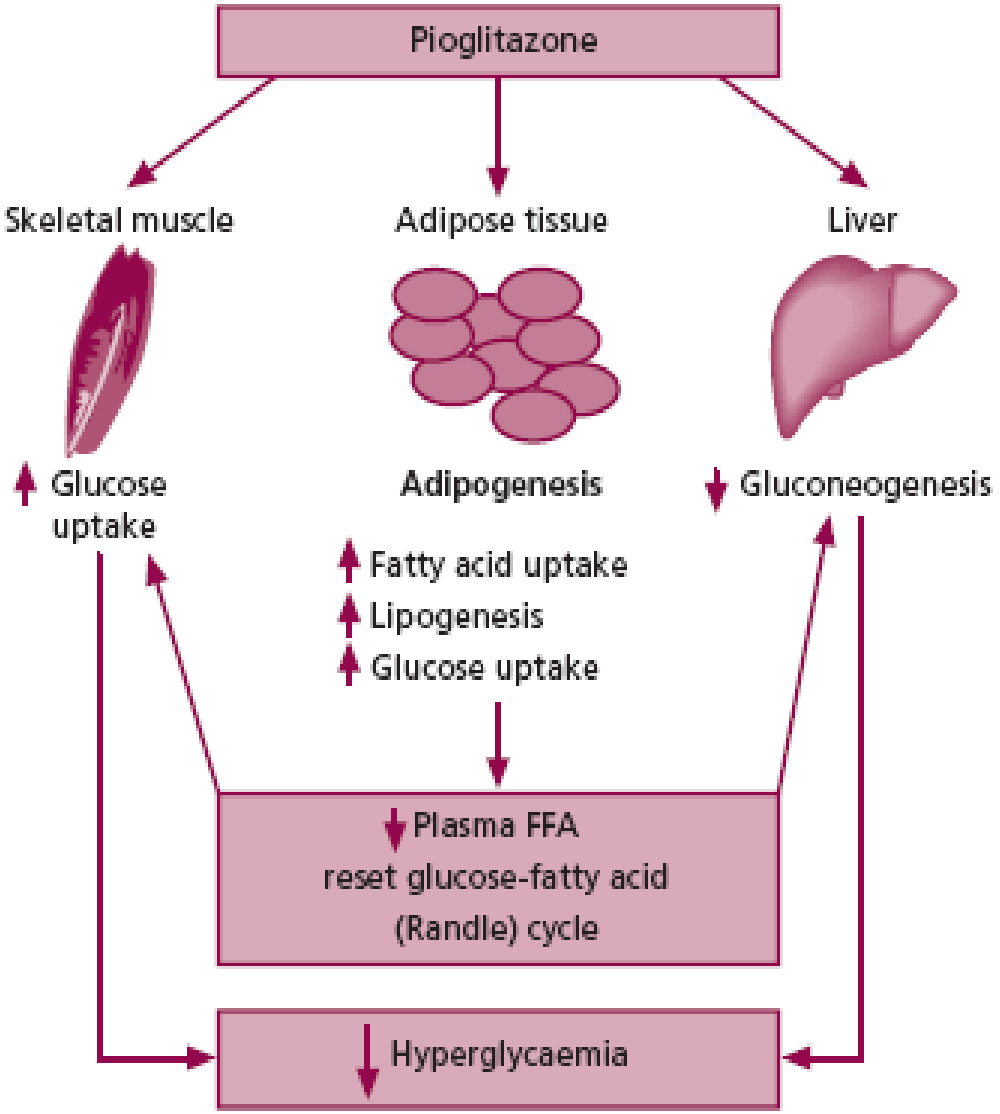
- Biguanides have been most often prescribed for patients whose hyperglycemia is due to ineffective insulin action, ie, insulin resistance syndrome.
- Metformin does not increase weight or provoke hypoglycemia, it offers obvious advantages over insulin or sulfonylureas in treating hyperglycemia in such individuals.
- Metformin therapy decreases the risk of macrovascular as well as microvascular disease; this is in contrast to the other therapies.
- Metformin is efficacious in preventing the new onset of type 2 diabetes in middle-aged, obese individuals with impaired glucose tolerance and fasting hyperglycemia.

Toxicities

- The most frequent toxic effects of metformin are gastrointestinal (anorexia, nausea, vomiting, abdominal discomfort, diarrhea).
- Absorption of vitamin B12 appears to be reduced during long-term metformin therapy.
- In the absence of hypoxia or renal or hepatic insufficiency, lactic acidosis is less common with metformin therapy than with phenformin therapy.
- Biguanides are contraindicated in patients with renal disease, alcoholism, hepatic disease, because of an increased risk of lactic acidosis induced by biguanide drugs in the presence of these diseases.

Thiazolidinediones

- Thiazolidinediones (Tzds) act to decrease insulin resistance.
- Their primary action is the nuclear regulation of genes involved in glucose and lipid metabolism and adipocyte differentiation.
- Tzds are ligands of peroxisome proliferator-activated receptor-gamma (PPAR- γ), part of the steroid and thyroid superfamily of nuclear receptors.
- These PPAR receptors are found in muscle, fat, and liver.
- In addition to targeting adipocytes, myocytes, and hepatocytes, Tzds also have significant effects on vascular endothelium, the immune system, the ovaries, and tumor cells. Some of these responses may be independent of the PPAR- γ pathway.
- In persons with diabetes, a major site of Tzd action is adipose tissue, where the drug promotes glucose uptake and utilization and modulates synthesis of lipid hormones or cytokines and other proteins involved in energy regulation.



Key: FFA = free fatty acids

Adapted with permission from Bailey CJ, Feher MD, Therapies for Diabetes, Sherborne Gibbs, Birmingham UK, 2004

- Two thiazolidinediones are currently available: pioglitazone and rosiglitazone.

Pioglitazone

- It is absorbed within 2 hours of ingestion; although food may delay uptake, total bioavailability is not affected.
- Pioglitazone may be taken once daily.
- The TGs lowering effect is more significant than that observed with rosiglitazone.
- Pioglitazone is approved as a monotherapy and in combination with metformin, sulfonylureas, and insulin for the treatment of type 2 diabetes.

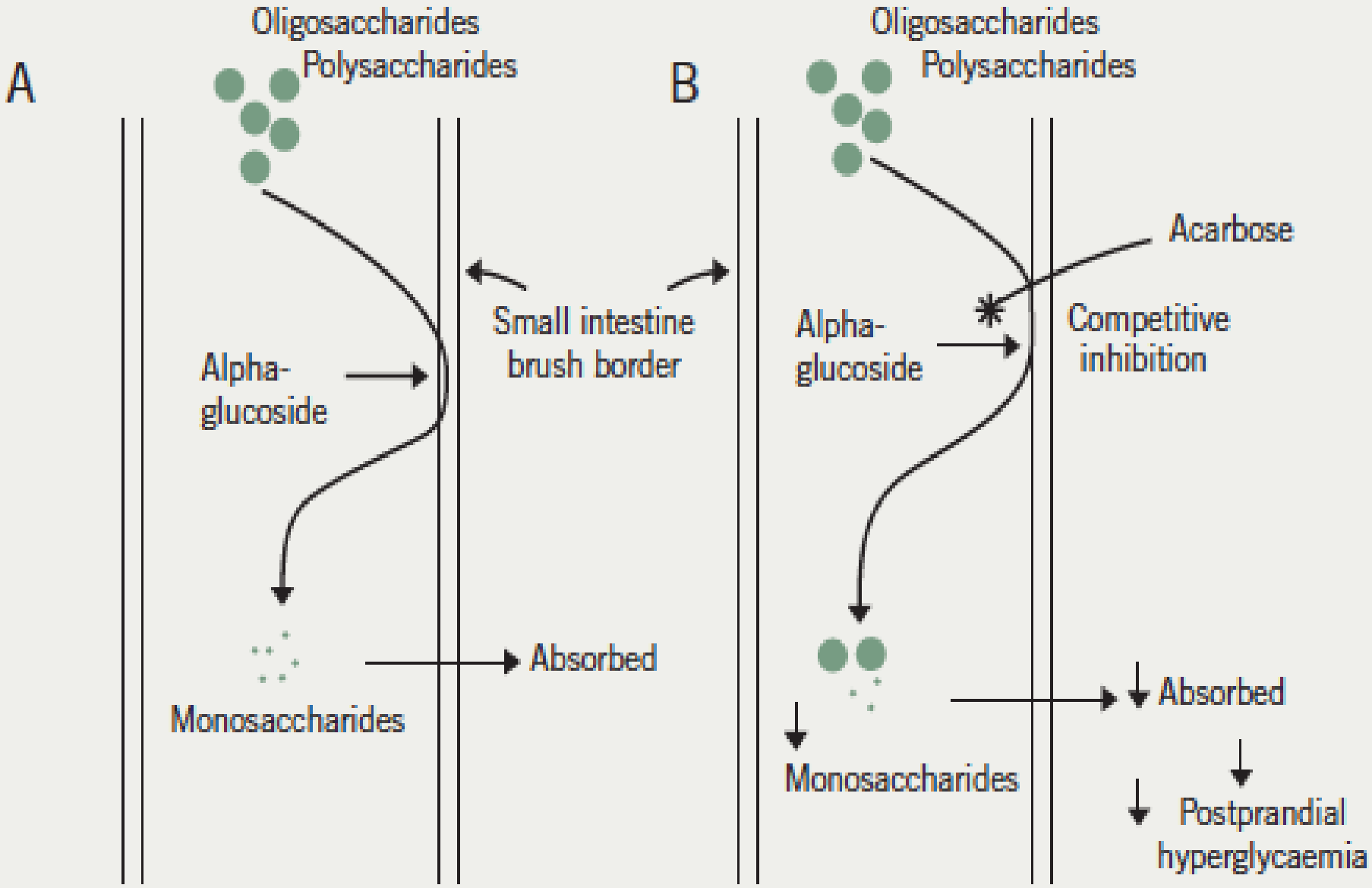
Rosiglitazone

- Is rapidly absorbed and highly protein bound.
- It is administered once or twice daily.
- The drug is approved for use in type 2 diabetes as monotherapy or in combination with a biguanide or sulfonylurea.

- Tzds are considered "euglycemics" and are efficacious in about 70% of new users.
- Individuals experiencing secondary failure to other oral agents should benefit from the addition (rather than substitution) of a Tzd.
- Because their mechanism of action involves gene regulation, the Tzds have a slow onset and offset of activity over weeks or even months.
- Combination therapy with sulfonylureas and insulin can lead to hypoglycemia and may require dosage adjustment.
- An adverse effect common to both Tzds is fluid retention especially when used in combination with insulin or insulin secretagogues.
- Many users have a dose-related weight gain, which may be fluid-related.
- These agents should not be used during pregnancy, in the presence of significant liver disease, or if there is a concurrent diagnosis of heart failure.

Alpha Glucosidase Inhibitors

- Only monosaccharides, such as glucose and fructose, can be transported out of the intestinal lumen and into the bloodstream.
- The digestion of complex starches, oligosaccharides, and disaccharides is facilitated by enteric enzymes, including pancreatic α -amylase, and α-glucosidases.
- Acarbose and miglitol are competitive inhibitors of the intestinal α -glucosidases and reduce the postprandial digestion and absorption of starch and disaccharides, thereby lowering postmeal glycemic excursions as much as 45–60 mg/dL.
- Acarbose and miglitol are taken just prior to ingesting the first portion of each meal.
- Although the binding affinity of the two compounds differs, acarbose and miglitol both target the α -glucosidases: sucrase, maltase, glycoamylase, dextranase.

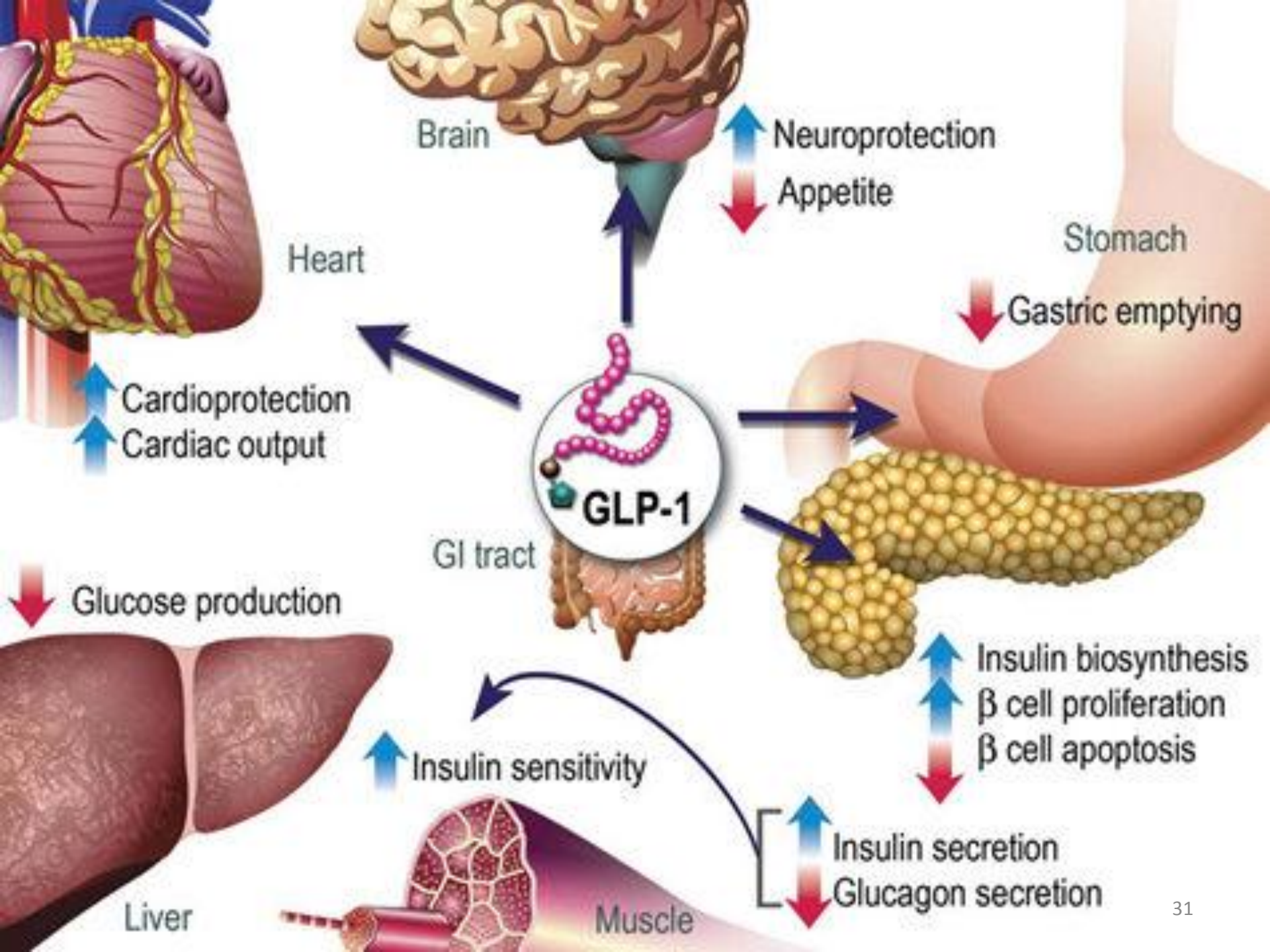

A
Oligosaccharides
Polysaccharides
Small intestine
brush border
Alpha-
glucoside
Absorbed
Monosaccharides
B
Oligosaccharides
Polysaccharides
Acarbose
Alpha-
glucoside
Competitive
inhibition
Absorbed
Monosaccharides
Postprandial
hyperglycaemia

- Prominent adverse effects include diarrhea, and abdominal pain and result from the appearance of undigested carbohydrate in the colon that is then fermented.
- Although not a problem with monotherapy or combination therapy with a biguanide, hypoglycemia may occur with concurrent sulfonylurea treatment.
- Hypoglycemia should be treated with glucose (dextrose) and not sucrose, whose breakdown may be blocked.
- These drugs are contraindicated in patients with inflammatory bowel disease or any intestinal condition that could be worsened by gas and distention.
- Diabetes prevention may become a further indication for this class of medications.

Combination Therapy with Oral Antidiabetic Agents & Insulin

Combination Therapy in Type 2 Diabetes Mellitus

- Bedtime insulin has been suggested as an adjunct to oral antidiabetic therapy in patients with type 2 diabetes who have not responded to maximal oral therapy.
- Clinical practice has evolved to include sulfonylureas, meglitinides, D-phenylalanine derivatives, biguanides, thiazolidinediones, or alpha-glucosidase inhibitors given in conjunction with insulin.
- Individuals unable to achieve glycemic control with bedtime insulin generally require full insulin replacement and multiple daily injections of insulin.
- When oral agents are added to the regimen of someone already taking insulin, the blood glucose should be closely monitored and the insulin dosage decreased as needed to avoid hypoglycemia.


Brain
Neuroprotection
Appetite
Heart
Stomach
Gastric emptying
Cardioprotection
Cardiac output
GLP-1
GI tract
Glucose production
Insulin biosynthesis
β cell proliferation
β cell apoptosis
Insulin sensitivity
Insulin secretion
Glucagon secretion
Liver
Muscle

Dipeptidyl peptidase-4 (DPP-4) inhibitors (Alogliptin, linagliptin, saxagliptin, and sitagliptin.)

1. **Mechanism of action:**

➢ These drugs inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1.

➢ Prolonging the activity of incretin hormones increases *insulin release in response to meals* and *reduces inappropriate* secretion of glucagon.

➢ DPP-4 inhibitors may be used as monotherapy or in combination with sulfonylureas, *metformin, TZDs, or insulin.*

➢ *Unlike incretin mimetics, these drugs do not cause satiety,* or fullness, and are weight neutral.

2. Pharmacokinetics and fate:

- The DPP-4 inhibitors are well absorbed after oral administration.
- Food does not affect the extent of absorption.
- *Alogliptin and sitagliptin are mostly* excreted unchanged in the urine.
- *Saxagliptin is metabolized* via CYP450 3A4/5 to an active metabolite.
- The primary route of elimination for *saxagliptin and the metabolite is renal.*
- *Linagliptin* is primarily eliminated via the enterohepatic system.
- All DPP-4 inhibitors except linagliptin require dosage adjustments in renal dysfunction.

3. Adverse effects:

- In general, DPP-4 inhibitors are well tolerated, with the most common adverse effects being nasopharyngitis and headache.
- Strong inhibitors of CYP450 3A4/5, such as *ritonavir, atazanavir, itraconazole, and clarithromycin, may* increase levels of *saxagliptin. Therefore, reduced doses of saxagliptin* should be used.

Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Canagliflozin and dapagliflozin)

1. Mechanism of action:

- The sodium–glucose cotransporter 2 (SGLT2) is responsible for reabsorbing filtered glucose in the tubular lumen of the kidney.

- By inhibiting SGLT2, these agents
  - decrease reabsorption of glucose, increase urinary glucose excretion, and lower blood glucose.
  - decreases reabsorption of sodium and causes osmotic diuresis. Therefore, SGLT2 inhibitors may reduce systolic blood pressure. However, they are not indicated for the treatment of hypertension.

2. Pharmacokinetics and fate:

- Given once daily in the morning.
- *Canagliflozin should be taken before the* first meal of the day.
- Both drugs are mainly metabolized by glucuronidation to inactive metabolites.
- While the primary route of excretion for *canagliflozin is via the feces, about one-third of a* dose is renally eliminated.
- These agents should be avoided in patients with renal dysfunction.

3. Adverse effects:

- The most common adverse effects are female genital mycotic infections (for example, candidiasis), urinary tract infections, and urinary frequency.
- Hypotension has also occurred, particularly in the elderly or patients on diuretics. Thus, volume status should be evaluated prior to starting these agents.

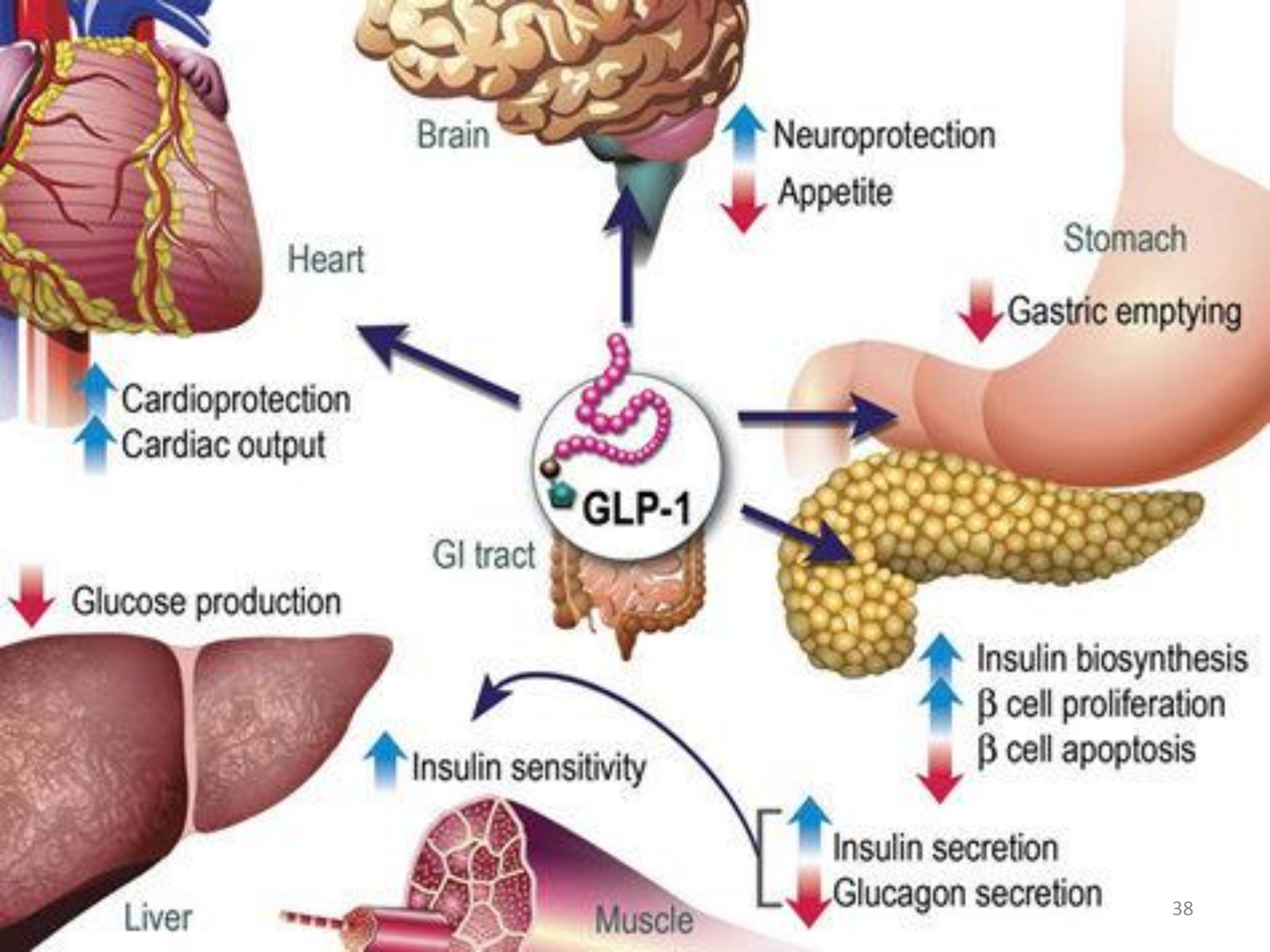
Combination Therapy in Type 1 Diabetes Mellitus

- There is no indication for combining insulin with insulin secretagogues in individuals with type 1 diabetes.
- Type 1 diabetics with diets very high in starch may benefit from the addition of alpha-glucosidase inhibitors, but this is not typically practiced.

Glucagon

Chemistry & Metabolism

- Glucagon is synthesized in the A cells of the pancreatic islets of Langerhans.
- Glucagon is a peptide consisting of a single chain of 29 amino acids.
- Glucagon is extensively degraded in the liver and kidney as well as in plasma, and at its tissue receptor sites.
- Its half-life in plasma is between 3 and 6 minutes, which is similar to that of insulin.
- The intestinal cells secrete enteroglucagon, a family of glucagon-like peptides, along with glucagon-like peptides 1 and 2 (GLP-1 and GLP-2).
- A derivative of GLP-1 **Exenatide** is a potent stimulant of insulin release and has been termed "insulinotropin" .
- It has been considered as a potential therapeutic agent in type 2 diabetes.
- However, it requires continuous subcutaneous infusion to produce a sustained lowering of both fasting and postprandial hyperglycemia in type 2 diabetic patients; therefore, its clinical usefulness is limited.


Brain
Neuroprotection
Appetite
Heart
Stomach
Gastric emptying
Cardioprotection
Cardiac output
GLP-1
GI tract
Glucose production
Insulin biosynthesis
β cell proliferation
β cell apoptosis
Insulin sensitivity
Insulin secretion
Glucagon secretion
Liver
Muscle

Pharmacologic Effects of Glucagon

Metabolic Effects

- The first six amino acids at the amino terminal of the glucagon molecule bind to specific receptors on liver cells.
- This leads to a Gs protein-linked increase in adenylyl cyclase activity and the production of cAMP, which facilitates catabolism of stored glycogen and increases gluconeogenesis and ketogenesis.
- The immediate pharmacologic result of glucagon infusion is to raise blood glucose at the expense of stored hepatic glycogen.
- There is no effect on skeletal muscle glycogen, presumably because of the lack of glucagon receptors on skeletal muscle.
- Pharmacologic amounts of glucagon cause release of insulin from normal pancreatic B cells, catecholamines from pheochromocytoma, and calcitonin from medullary carcinoma cells.

Cardiac Effects

- Glucagon has a potent inotropic and chronotropic effect on the heart, mediated by the cAMP mechanism.
- Thus, it produces an effect very similar to that of β-adrenoceptor agonists without requiring functioning β -receptors.

Effects on Smooth Muscle

- Large doses of glucagon produce profound relaxation of the intestine.
- In contrast to the above effects of the peptide, this action on the intestine may be due to mechanisms other than adenylyl cyclase activation.

Clinical Uses

Severe Hypoglycemia

- The major use of glucagon is for emergency treatment of severe hypoglycemic reactions in patients with type 1 diabetes when unconsciousness precludes oral feedings and use of intravenous glucose is not possible.
- Recombinant glucagon is currently available in 1 mg vials for parenteral use.
- Nasal sprays have been developed for this purpose.

Beta-Blocker Poisoning

- Glucagon is sometimes useful for reversing the cardiac effects of an overdose of beta-blocking agents because of its ability to increase cAMP production in the heart.

Adverse Reactions

- Transient nausea and occasional vomiting can result from glucagon administration.
- These are generally mild, and glucagon is relatively free of severe adverse reactions.