

**MUNI**  
**PHARM**

# **DRUGS IN PHARMACOTHERAPY OF DIABETES MELLITUS**

Assoc. Prof. PharmDr. Peter Kollár, Ph.D.  
Department of Pharmacology and Toxicology  
Faculty of Pharmacy MU

# Hormones that control body glucose

	Main actions	Main stimulus for secretion	Main effect
<b>Main regulatory hormone</b>			
Insulin	<ul style="list-style-type: none"> <li>↑Glucose uptake</li> <li>↑Glycogen synthesis</li> <li>↓Glycogenolysis</li> <li>↓Gluconeogenesis</li> </ul>	Acute rise in blood glucose	↓Blood glucose
<b>Main counter-regulatory hormones</b>			
Glucagon	↑Glycogenolysis	Hypoglycaemia (i.e. blood glucose < 3 mmol/l), (e.g. with exercise, stress, high protein meals), etc.	↑Blood <u>glucose</u>
Adrenaline (epinephrine)	<ul style="list-style-type: none"> <li>↑Gluconeogenesis</li> <li>↑Glycogenolysis</li> </ul>		
Glucocorticoids	↓Glucose uptake		
Growth hormone	<ul style="list-style-type: none"> <li>↑Gluconeogenesis</li> <li>↓Glucose uptake and utilisation</li> <li>↓Glucose uptake</li> </ul>		

# Proinsulin and Insulin

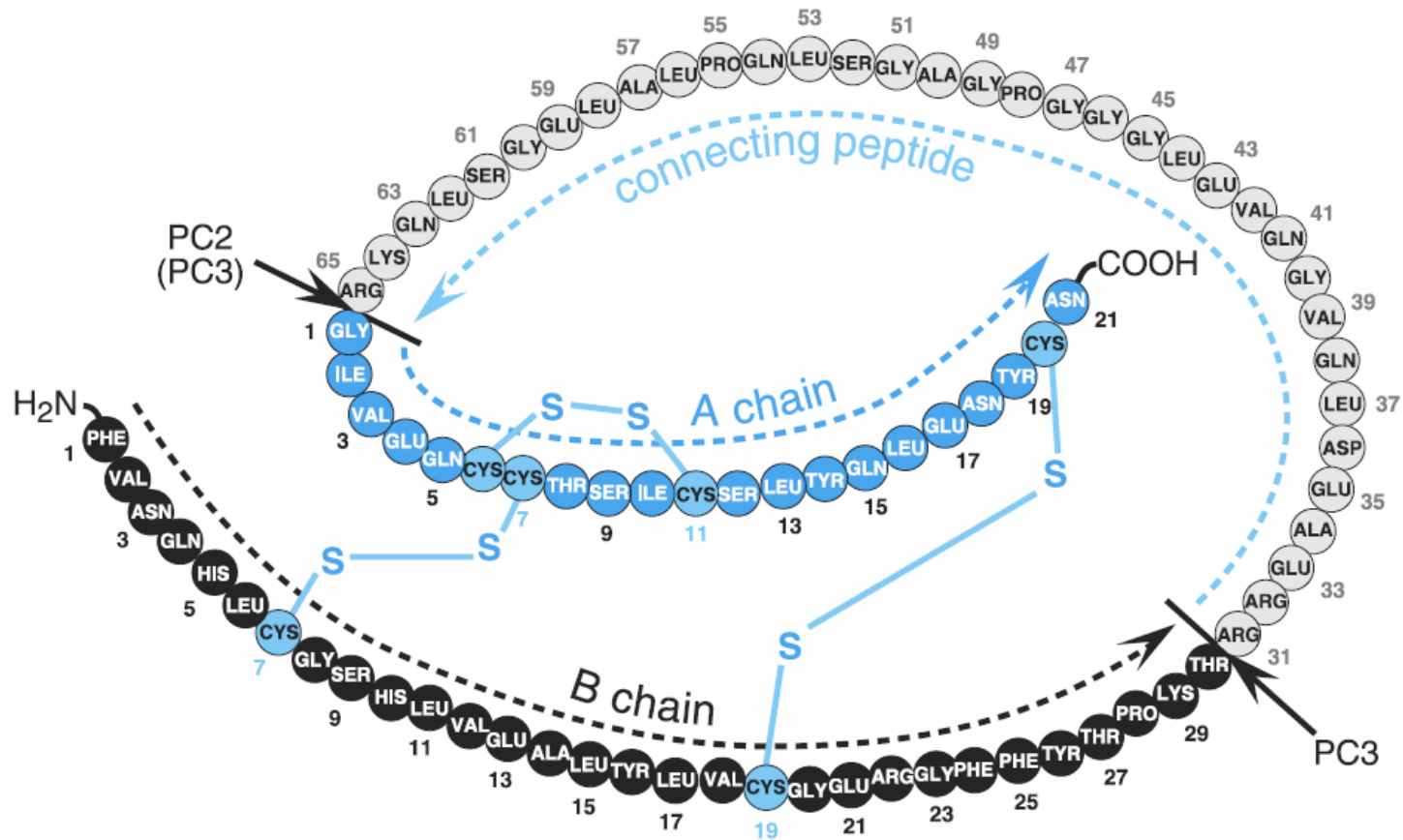
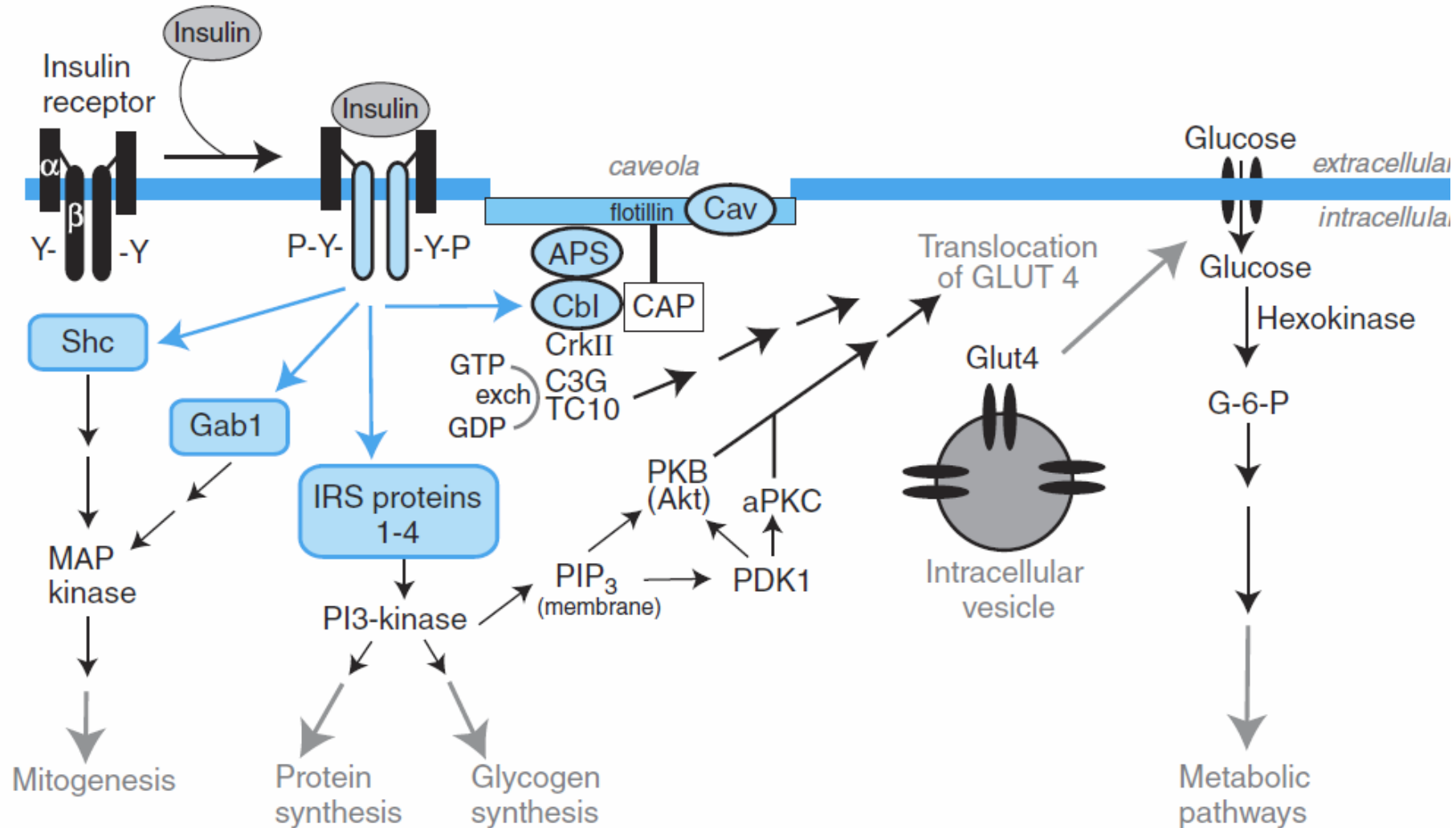


FIGURE 60-1 *Human proinsulin and its conversion to insulin.* The amino acid sequence of human proinsulin is shown. By proteolytic cleavage, four basic amino acids (residues 31, 32, 64, and 65) and the connecting peptide are removed, converting proinsulin to insulin. The sites of action of the endopeptidases PC2 and PC3 are shown.

# Glucose transporters

- GLUT1
  - GLUT3
- } Non-insulin mediated glucose uptake
- GLUT2
    - Beta cell – Glucose sensors
  - GLUT4
    - Insulin mediated glucose uptake in muscle and adipose tissue

# Insulin induced IC pathways



# What goes wrong in diabetes?

– Multitude of mechanisms

- Insulin

  - Regulation

  - Secretion

  - Uptake or breakdown

- Beta cells

  - Damage

# Diabetes Mellitus

- Characterized by high levels of blood glucose resulting from defects in insulin production, insulin action, or both
- 20.8 million in US ( 7% of population)
- Estimated 14.6 million diagnosed (only 2/3)
- 3 types of DM:
  - Type 1 diabetes
  - Type 2 diabetes
  - Gestational diabetes

# Complications of Diabetes Mellitus

- Stroke
- Heart attack
- Kidney disease
- Eye Disease
- Nerve Damage



# Types of Diabetes Mellitus

## – Type 1 DM

- previously known as insulin-dependent diabetes mellitus-IDDM-or juvenile-onset diabetes

## – Type 2 DM

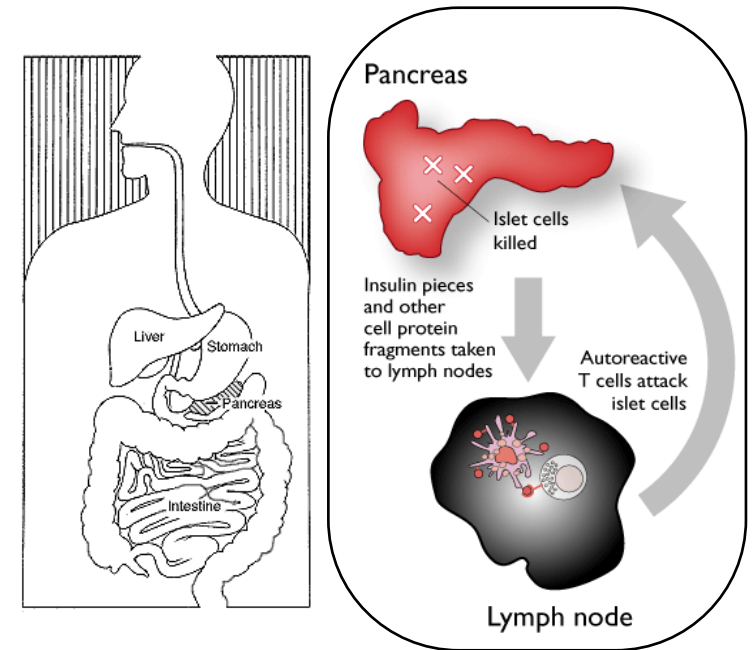
- previously known as non-insulin-dependent diabetes mellitus-NIDDM-or maturity-onset diabetes

## – Gestational Diabetes

- 3-5% of pregnant women in the US develop gestational DM

# Type 1 Diabetes Mellitus

- Cells that produce insulin are destroyed
- Results in insulin dependence
- Commonly detected before 30
- Low or absent endogenous insulin
- Dependent on exogenous insulin for life
- 5-10% of cases of DM
- Onset sudden:
  - Symptoms: 3 P's: polyuria, polydipsia, polyphagia



# Type 1 Diabetes Mellitus

= absolute deficiency of insulin resulting from **autoimmune destruction of B cells**. Without insulin treatment – patients will ultimately die with diabetic ketoacidosis.

- Patients are usually **young** and **not obese** when they first develop symptoms
- The patient becomes overtly diabetic only when **more than 90%** of the B cells have been destroyed

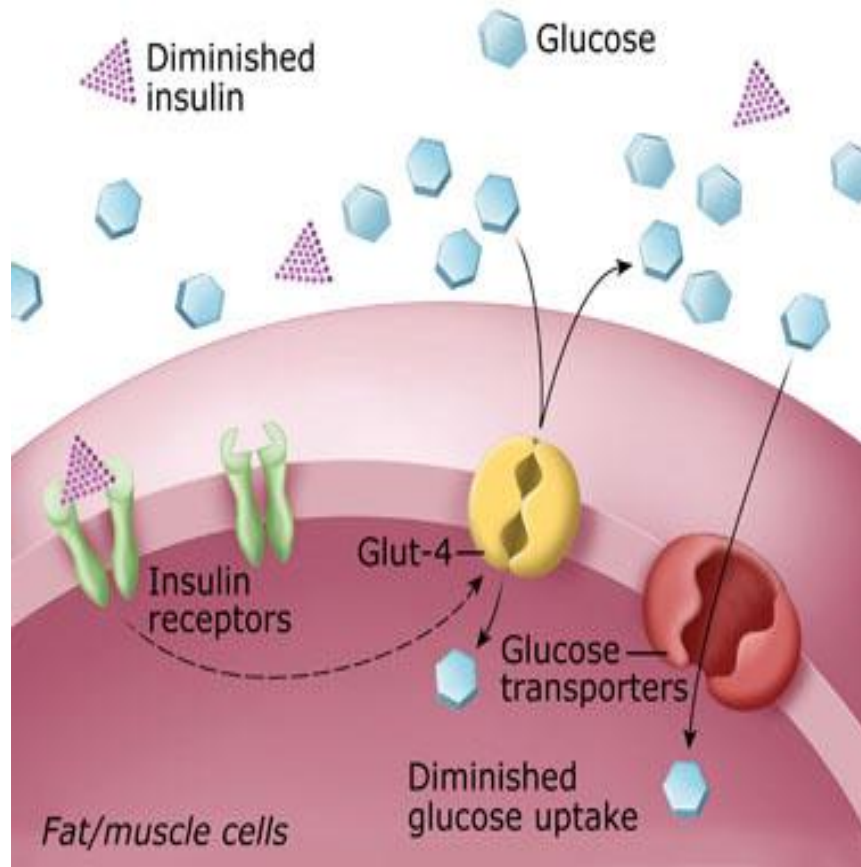
# Type 2 Diabetes Mellitus

- Blood glucose levels rise due to:
  - Lack of insulin production
  - Insufficient insulin action (resistant cells)
- Commonly occurs after 40
- Affects > 90%
- Eventually leads to  $\beta$ -cell failure (resulting in insulin dependence)
- Insulin levels may be normal, elevated or depressed
  - characterized by insulin resistance,
  - diminished tissue sensitivity to insulin,
  - impaired B-cell function (delayed or inadequate insulin release)

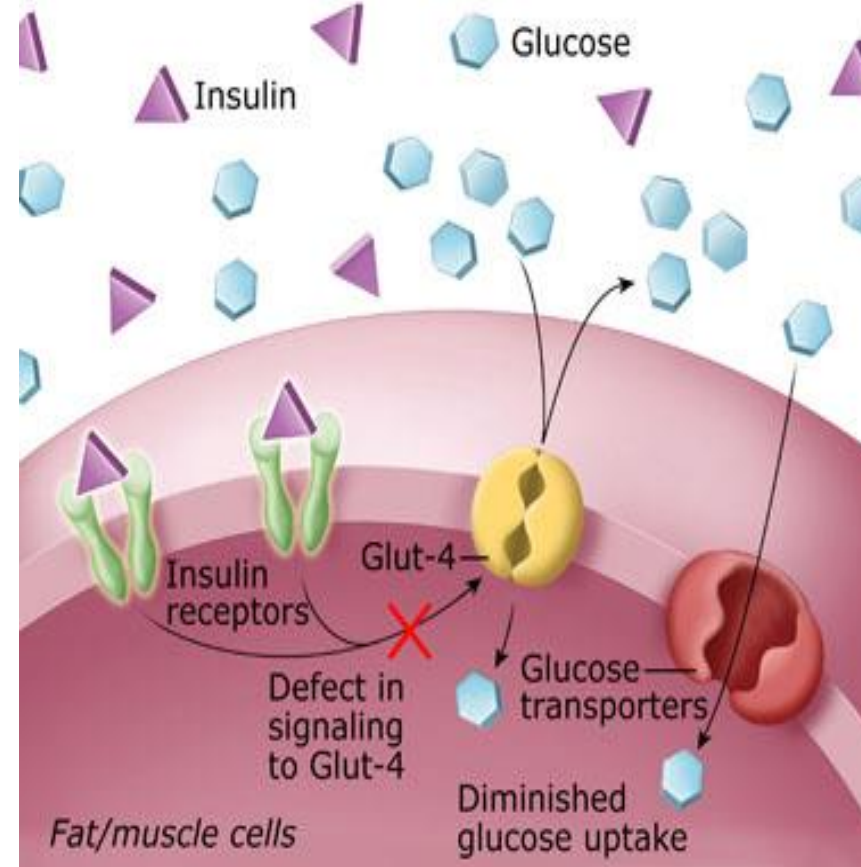
# Type 2 Diabetes Mellitus

- Accompanied by both **insulin resistance** and by **impaired insulin secretion**
- Such patients are **often obese**, the incidence rising progressively with age as B-cell function declines
- Treatment is initially dietary, although oral hypoglycaemic drugs usually **become necessary**, and about one-third of patients ultimately **require insulin**

## Type 1 Diabetes: Insufficient Insulin



## Type 2 Diabetes: Insulin Resistance



# Diagnosis of Diabetes Mellitus

- ADA criteria for the diagnosis of DM include:
  - symptoms (e.g., polyuria, polydipsia, and unexplained weight loss),
  - random plasma glucose conc. of greater than 11 mmol/L,
  - fasting plasma glucose conc. of greater than 7mmol/L, or
  - plasma glucose conc. of greater than 11 mmol/L 2 hours after the ingestion of oral glucose load

# Treatment of Diabetes Mellitus

- The major components of the treatment of diabetes are:
  - Diet and exercise
  - Insulin (essential for the treatment of type 1 diabetes)
  - Oral antidiabetics



# Antidiabetic Medications

- Insulin
- Sensitizers
  - Biguanides
  - Thiazolidinediones
- Secretagogues
  - Sulfonylureas
  - Nonsulfonylurea secretagogues (Meglitinides)
- Alpha-glucosidase inhibitors
- Peptide analogs
  - Injectable (s.c.) Incretin mimetics

**Glucagon-like peptide (GLP-1) agonists:** *exenatide, liraglutide...*

**Dipeptidyl Peptidase-4 (DPP-4) Inhibitors:** *sitagliptin, vildagliptin...*

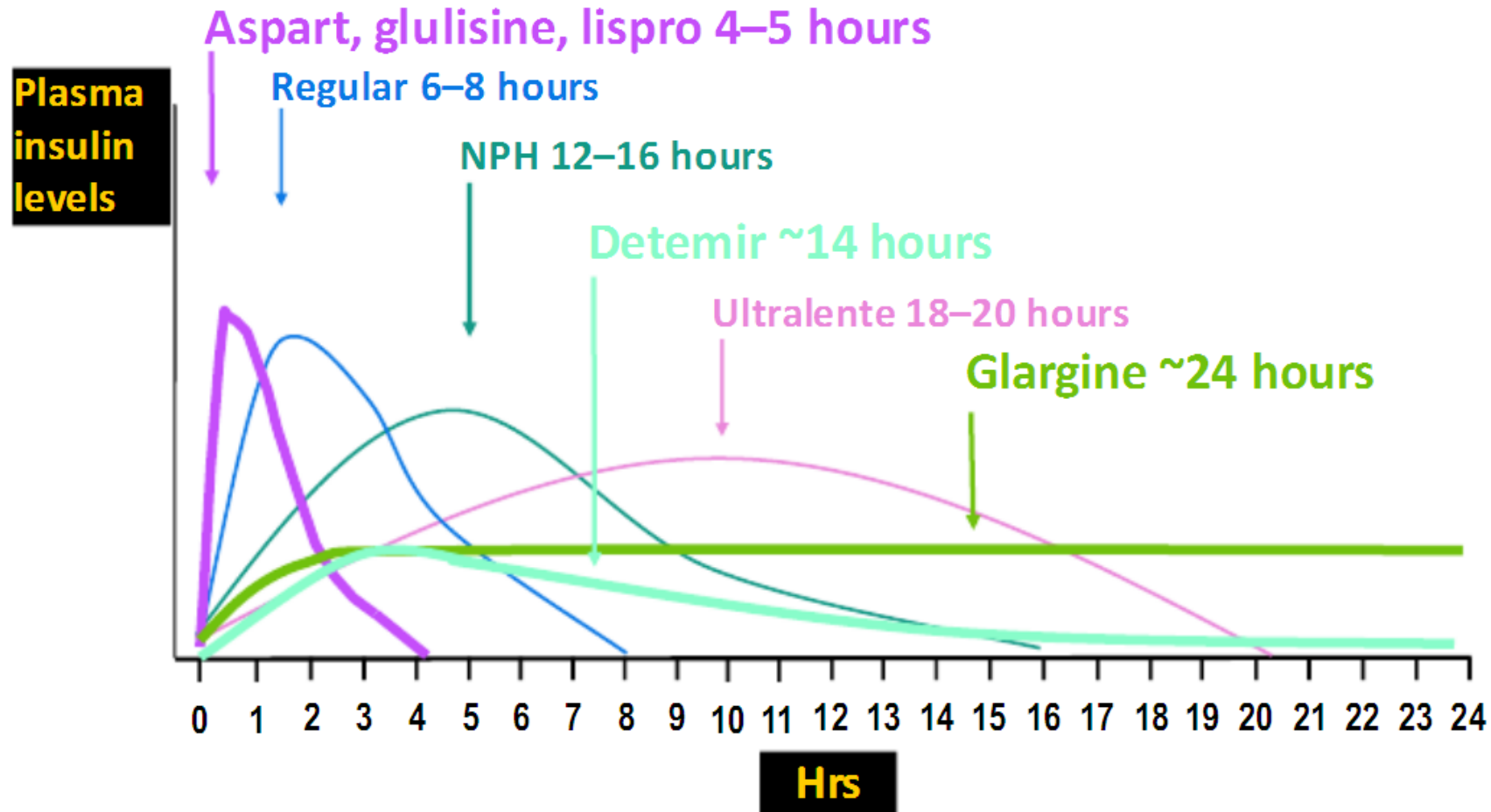
## Properties of Currently Available Insulin Preparations

Type	Appearance	Added Protein	Zinc Content, mg/100 units	Buffer*	Action, Hours <sup>†</sup>		
					Onset	Peak	Duration
<b>Rapid/Short</b>							
Regular soluble (crystalline)	Clear	None	0.01–0.04	None	0.5–0.7	1.5–4	5–8
Lispro	Clear	None	0.02	Phosphate	0.25	0.5–1.5	2–5
Aspart	Clear	None	0.0196	Phosphate	0.25	0.6–0.8	3–5
Glulisine	Clear	None	None	None	—	0.5–1.5	1–2.5
<b>Intermediate</b>							
NPH (isophane)	Cloudy	Protamine	0.016–0.04	Phosphate	1–2	6–12	18–24
Lente	Cloudy	None	0.2–0.25	Acetate	1–2	6–12	18–24
<b>Slow</b>							
Ultralente	Cloudy	None	0.2–0.25	Acetate	4–6	16–18	20–36
Protamine zinc	Cloudy	Protamine	0.2–0.25	Phosphate	4–6	14–20	24–36
Glargine	Clear	None	0.03	None	2–5	5–24	18–24
Detemir	Clear	None	0.065	Phosphate	1–2	4–14	6–24

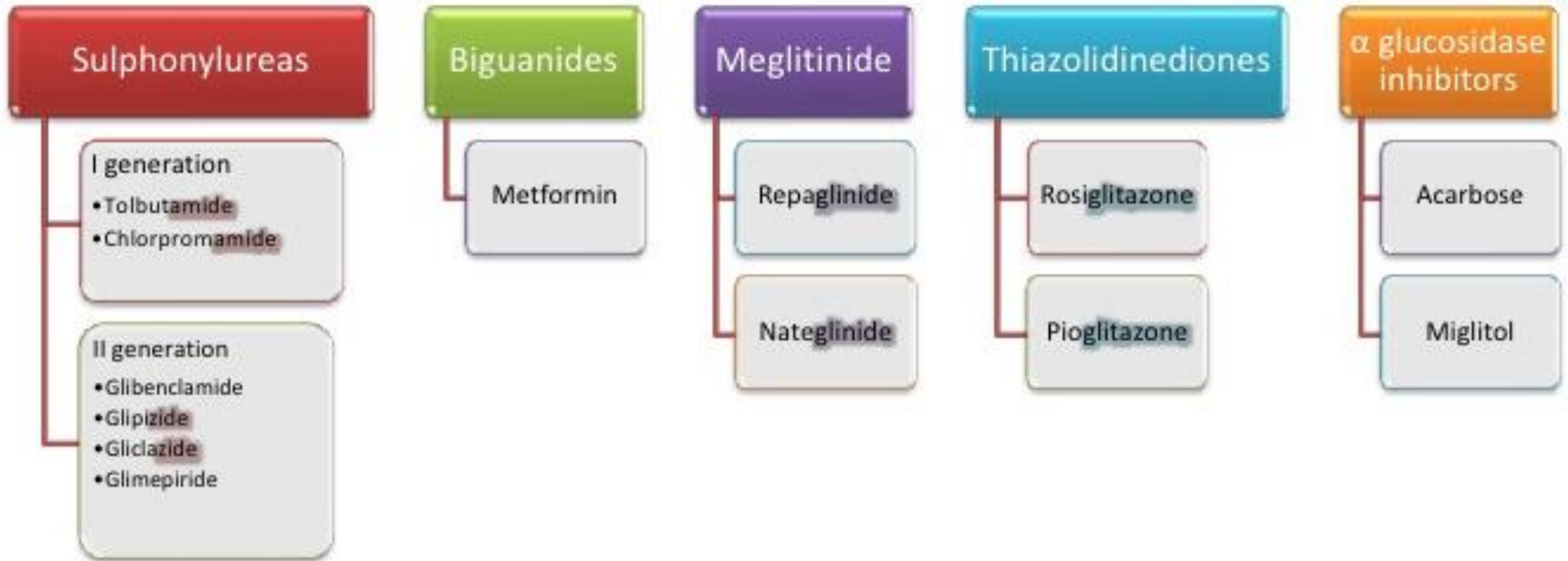
\*Most insulin preparations are supplied at pH 7.2–7.4. Glargine and Detemir are supplied at a pH of 4.0.

<sup>†</sup>These are approximate figures. There is considerable variation from patient to patient and from time to time in a given patient.

# Action profiles of various insulins



# Classification of Antidiabetic Drugs



# Antidiabetic Agents and Mechanisms of Actions

Drug Class	Drug Name	Brand Name	Mechanism of Action
Biguanides	Metformin	Glucophage®	Inhibit glucose production by the liver
Sulfonylureas (second-generation)	Glimepiride Glipizide Glyburide	Amaryl® Glucotrol® Diabeta®, Glynase PresTab®, Micronase®	Increase insulin secretion by pancreatic beta cells
Meglitinides	Repaglinide Nateglinide	Prandin® Starlix®	Increase insulin secretion by pancreatic beta cells
Thiazolidinediones (TZDs)	Pioglitazone Rosiglitazone	Actos® Avandia®	Increase glucose uptake by skeletal muscle
Alpha-glucosidase inhibitors	Acarbose Miglitol	Precose® Glyset®	Inhibit carbohydrate absorption in the small intestine

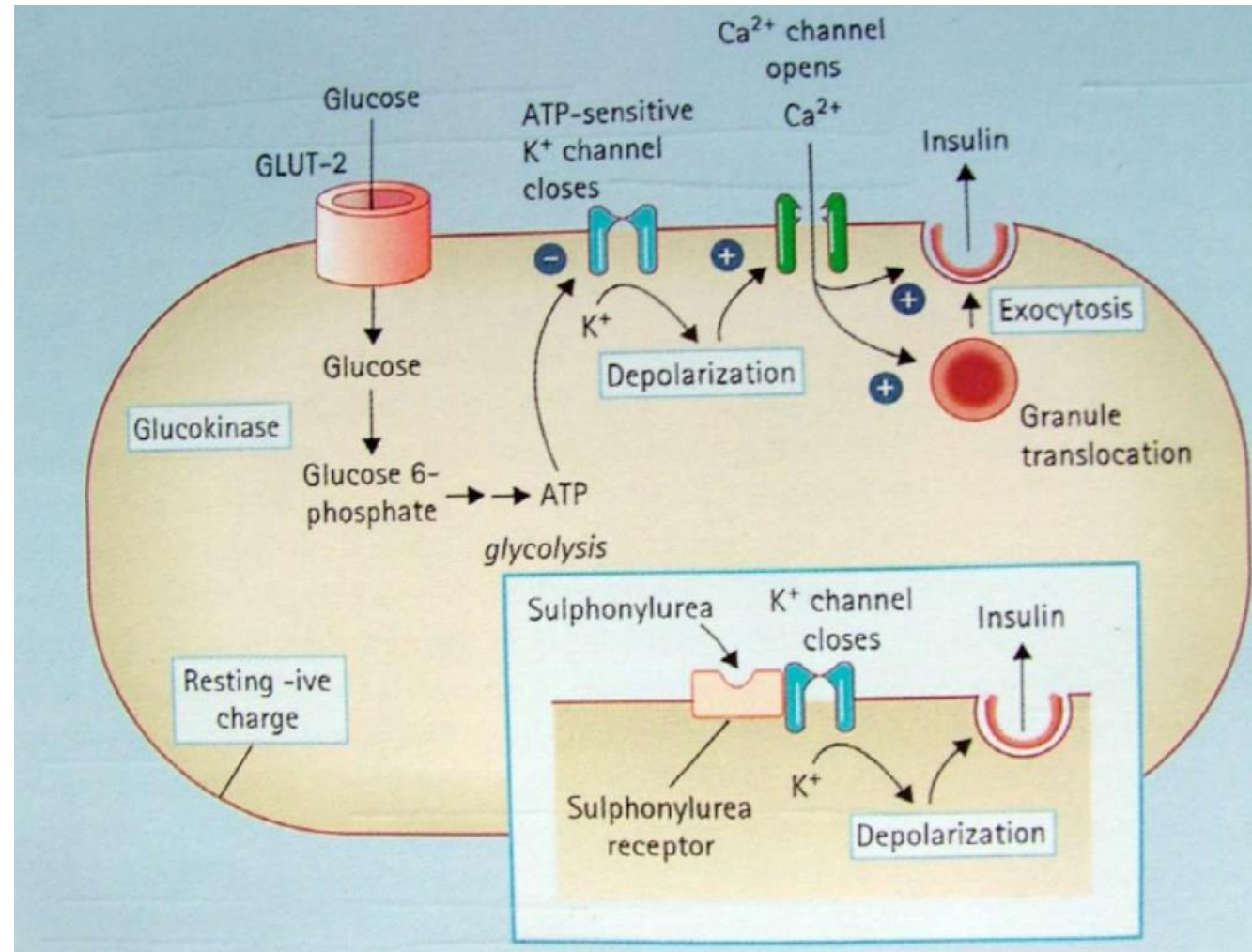
Medications	Action	Advantages	Possible Side Effects
<b>Meglitinides</b> Repaglinide (Prandin) Nateglinide (Starlix)	Stimulate the release of insulin	Works quickly	Severely <b>low blood sugar</b> (hypoglycemia), weight gain, nausea, back pain, headache
<b>Biguanides</b> Metformin (Fortamet, Glucophage, others)	Inhibit the release of glucose from the liver; improve sensitivity to insulin	May promote modest weight loss and modest decline in low-density lipoprotein (LDL), or "bad," cholesterol	Well tolerated- weight loss or weight neutral, nausea, <b>diarrhea</b> , rarely, the harmful buildup of lactic acid (lactic acidosis)
<b>Thiazolidinediones</b> Rosiglitazone (Avandia) Pioglitazone (Actos)	Improve sensitivity to insulin; inhibit the release of glucose from liver	May slightly increase HDL ("good" cholesterol)	Heart failure, heart attack, stroke, liver disease
<b>Alpha-glucosidase inhibitors</b> Acarbose (Precose) Miglitol (Glyset)	Slow the breakdown of starches and some sugars	Doesn't cause weight gain	<b>Stomach pain, gas</b> , diarrhea

# BIGUANIDES = Metformin

- Metformin is **antihyperglycemic**, not hypoglycemic. It does not stimulate insulin release from the pancreas and generally **does not cause hypoglycemia**, even in large doses
- MofA: Reduces glucose levels primarily by **decreasing hepatic glucose production** and by **increasing insulin action in muscle and fat**. This is mediated at least partly by activation of AMP-activated protein kinase
- The mechanism by which metformin reduces hepatic glucose production is most likely due to **reducing gluconeogenesis**

# SULPHONYLUREAS

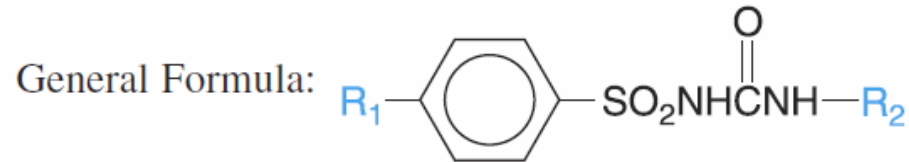
- They stimulate insulin release by blocking ATP-sensitive  $K^+$  channels resulting in depolarization with  $Ca^{2+}$  influx which promotes insulin secretion

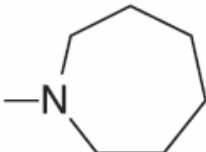
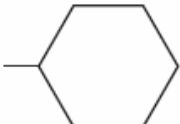




# Types and structures of Sulfonylureas

- High bonding to blood proteins – interactions!!
- 1st generation – low effect, tolbutamide also short acting



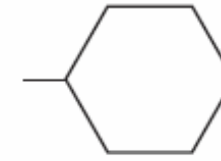
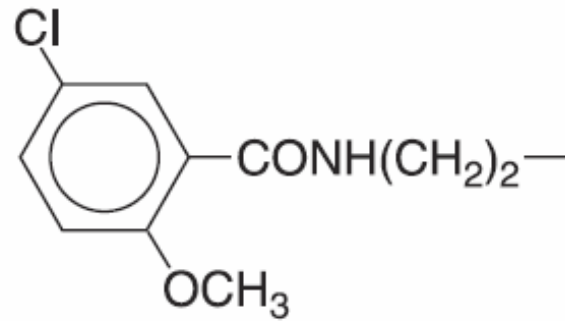
First-Generation Agents	R <sub>1</sub>	R <sub>2</sub>
Tolbutamide (ORINASE, others)	H <sub>3</sub> C—	—C <sub>4</sub> H <sub>9</sub>
Chlorpropamide (DIABINESE, others)	Cl—	—C <sub>3</sub> H <sub>7</sub>
Tolazamide (TOLINASE, others)	H <sub>3</sub> C—	
Acetohexamide (DYMELOR, others)	H <sub>3</sub> CCO—	

Second-Generation Agents

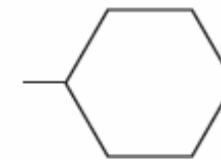
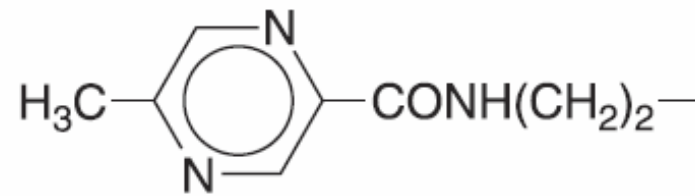
R<sub>1</sub>

R<sub>2</sub>

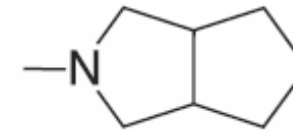
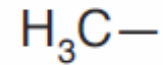
Glyburide  
(Glibenclamide, MICRONASE,  
DIABETA, others)



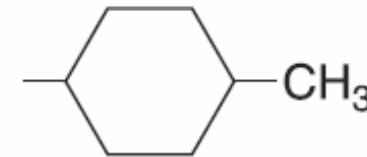
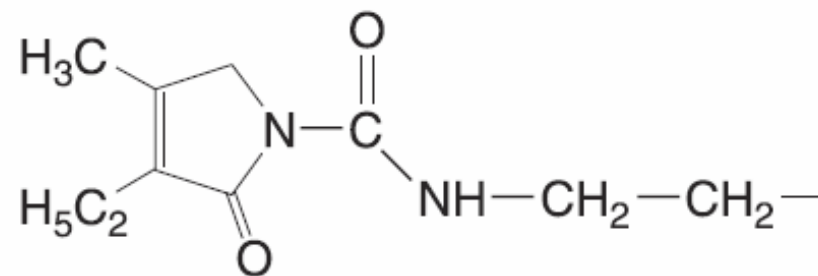
Glipizide (GLUCOTROL, others)



Gliclazide (DIAMICRON, others;  
unavailable in the U.S.)



Glimepiride (AMARYL)



# SULPHONYLUREAS

- *SE*: weight gain, hyperinsulinemia and hypoglycemia. Hepatic or renal insufficiency causes accumulation of these agents promoting the risk of **hypoglycemia**. There are a number of drug-drug interactions.
- Bind to plasma **proteins**, are MTB in the liver and excreted by the liver or kidney
- Tolbutamide has the shortest duration of action (6-12 hrs), the other agents are effective for cca 24 h

# MEGLITINIDES -- Repaglinide

- Repaglinide is an oral insulin secretagogue of the meglitinide class
- MofA: Like sulfonylureas, repaglinide stimulates insulin release by closing ATP-dependent K<sup>+</sup> channels in pancreatic cells
- Major substrate of CYP3A4 → hypoglycemia

# MEGLITINIDES -- Nateglinide

- Derivative of D-phenylalanine that **stimulates insulin secretion** by blocking ATP-sensitive K<sup>+</sup> channels in pancreatic cells
- Promotes a **more rapid but less sustained** secretion of insulin than do other available oral antidiabetic agents
- Major therapeutic effect is **reducing postprandial glycemc elevations** in type 2 DM patients
- Most effective if **administered** in a dose of 120 mg, **1–10 minutes before a meal**

# THIAZOLIDINEDIONES

- Act as insulin sensitizers
- Enter the cell, bind to the nuclear receptors (PPAR $\gamma$ ), and affect the expression of DNA  $\rightarrow$  reduce glucose, fatty acid, and INS blood conc.
- *Rosiglitazone* and *pioglitazone* can be combined with insulin or other classes of oral glucose lowering agents

# THIAZOLIDINEDIONES

- Agonists for the peroxisome proliferator activated receptor - *PPAR*, that regulate *carbohydrate* and *lipid* metabolism
- Principally act by increasing insulin sensitivity in peripheral tissues—and thus are effective only when insulin is present—but also may lower hepatic glucose production

# THIAZOLIDINEDIONES

- Some peripheral actions may be secondary to the **stimulation of adiponectin** release by adipocytes
- **Adiponectin** increases insulin sensitivity by elevating AMP kinase, which stimulates glucose transport into muscle and increases fatty acid oxidation



# ALPHA-GLUCOSIDASE INHIBITORS

- Reduce intestinal absorption of starch, dextrin, and disaccharides by **inhibiting the action of  $\alpha$ -glucosidase** in the intestinal brush border
- Postprandial rise in plasma glucose is weakened in both normal and diabetic subjects
- May be used as monotherapy in elderly patients or in patients with predominantly postprandial hyperglycemia
- Used **in combination** with other oral antidiabetic agents and/or insulin
- Should be administered at the **start of a meal**

# ALPHA-GLUCOSIDASE INHIBITORS

- ***acarbose***, an oligosaccharide, and ***miglitol*** also competitively inhibit glucoamylase and sucrase but have weak effects on pancreatic amylase
- They **reduce** postprandial plasma glucose levels in type 1 and type 2 DM subjects
- However, in patients with mild-to-moderate hyperglycemia, the glucose-lowering potential of  $\alpha$ -glucosidase inhibitors is about 30–50% of that of other oral antidiabetic agents

# INCRETIN MIMETICS

- **Glucagon-like peptide (GLP-1) agonists:**

- exenatide, liraglutide, albiglutid, ...

- **Dipeptidyl peptidase-4 (DPP-4) inhibitors:**

- sitagliptin, vildagliptin, saxagliptin, alogliptin, linagliptin, ...

# INCRETINS

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

**GIP (glucose-dependent insulinotropic peptide)**

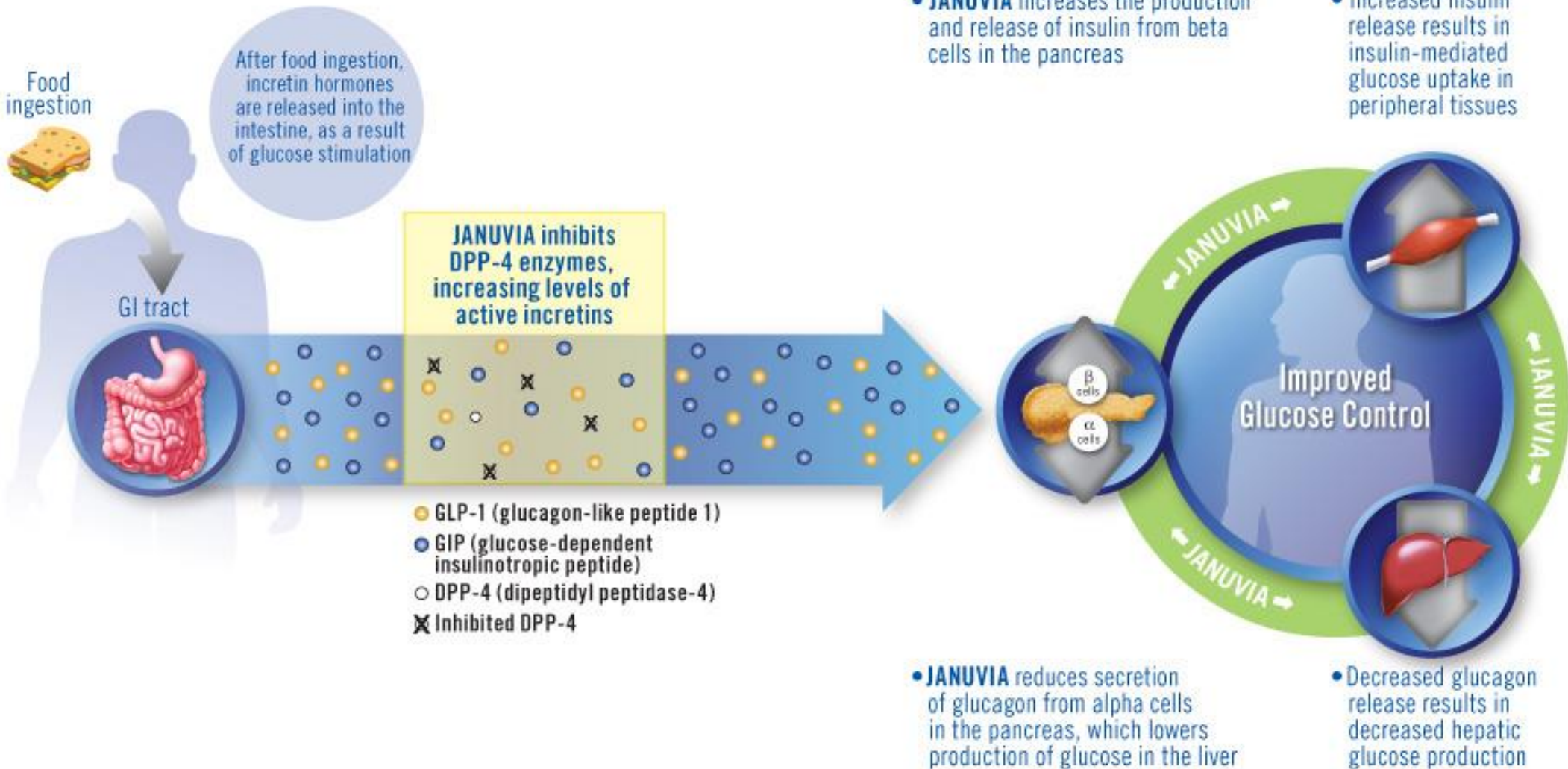
- are released from the gut in response to ingestion of food and contribute to glucose control by:
  - stimulating insulin release from pancreatic  $\beta$ -cells
  - decreasing glucagon production from pancreatic  $\alpha$ -cells when glucose levels are elevated
- Physiologic activity is limited by the enzyme dipeptidyl peptidase-4 (DPP-4), which rapidly degrades active incretins after their release

# DPP-4 Inhibitors MOA



Selective inhibition of DPP-4 increases plasma GLP-1 levels, resulting in reduction in glycemia

# Sitagliptin (Januvia) therapy



# Thank you for your attention

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