



# Drugs for Diabetes



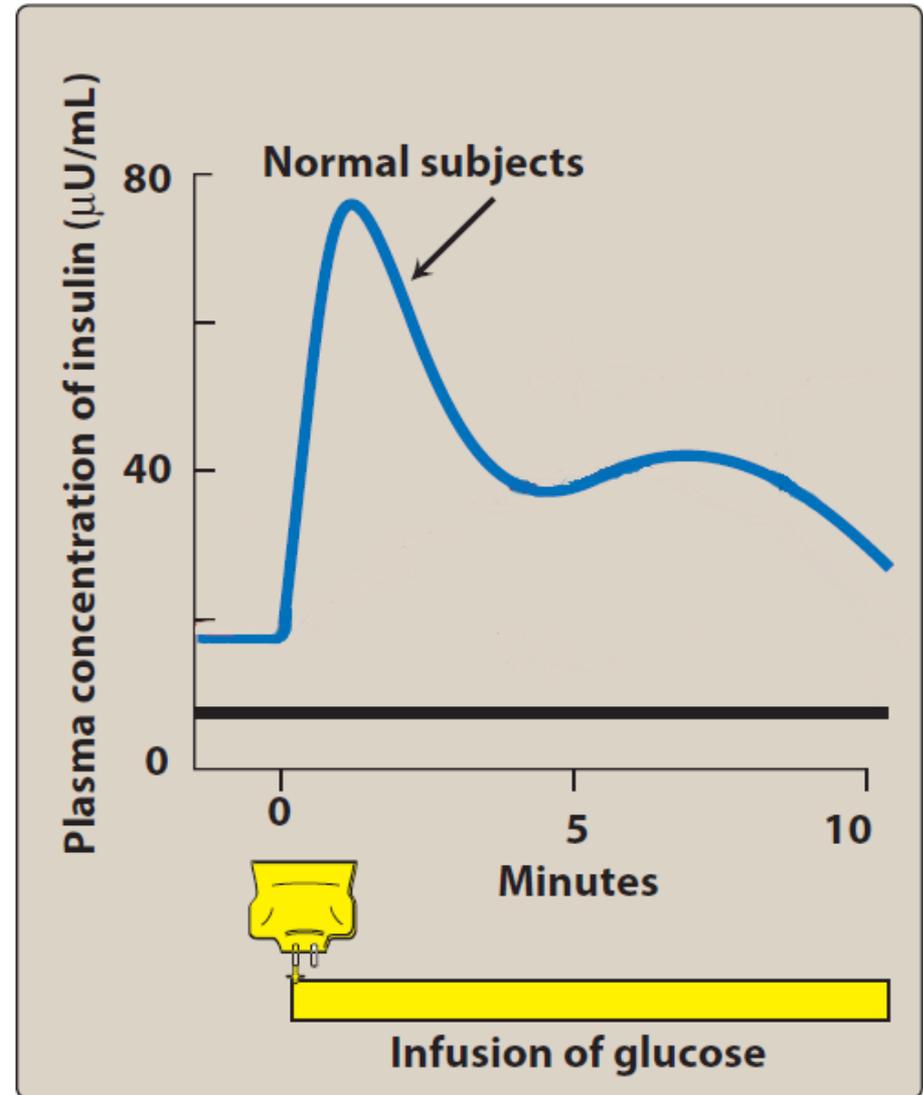
## Pharmacology Team

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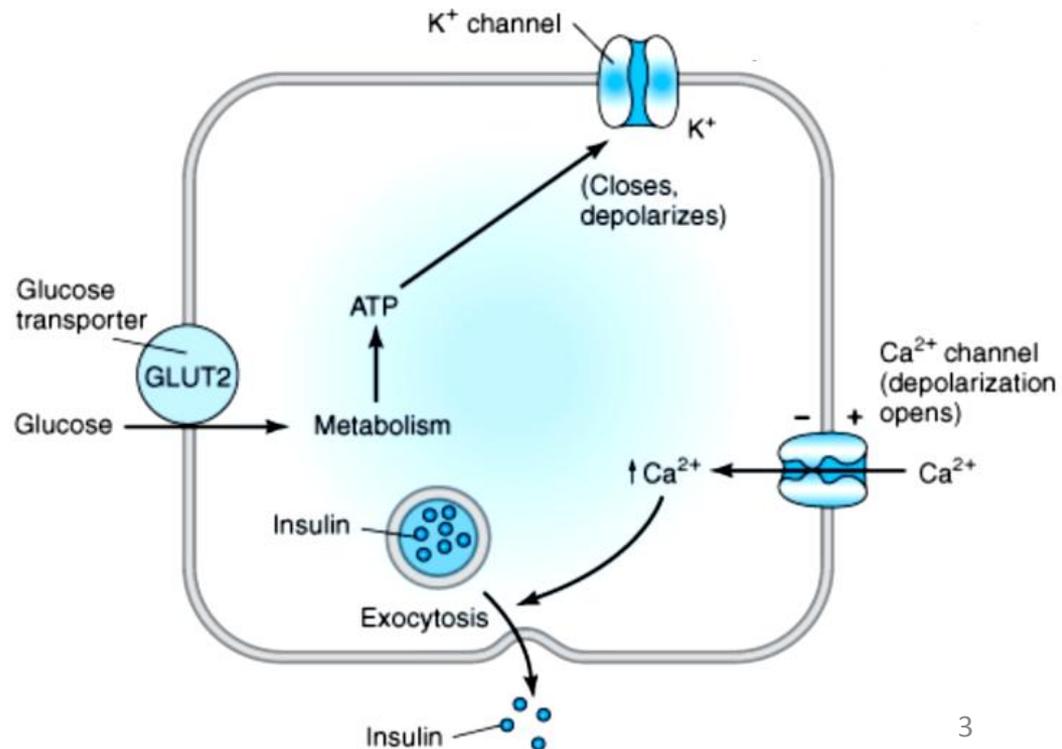
# Insulin

- During normal postabsorptive period, constant  $\beta$ -cell secretion maintains low basal levels of circulating insulin.
- This suppresses lipolysis, proteolysis, and glycogenolysis.
- A burst of insulin secretion occurs within 2 minutes after ingesting a meal, in response to transient increases in circulating glucose and amino acids.
- This lasts for up to 15 minutes, followed by the postprandial secretion of insulin

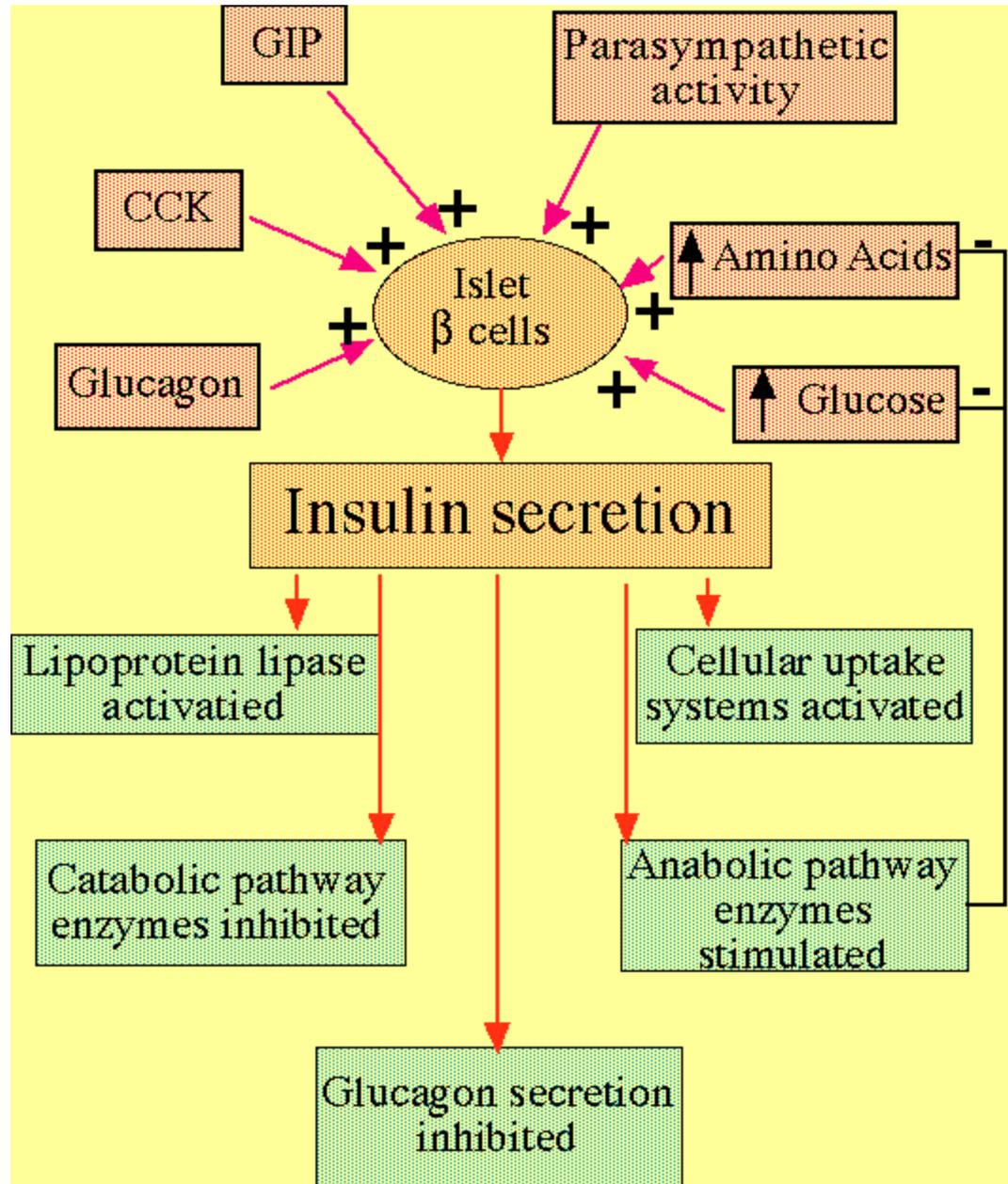


# Regulation of Insulin Secretion

- Secretion is most often triggered by increased blood glucose.
- Glucose is taken up by the glucose transporter into the  $\beta$  cells of the pancreas.
- There, it is metabolized to generate adenosine triphosphate (ATP).
- The rise in ATP levels causes a blockade of  $K^+$  channels, leading to membrane depolarization and an influx of  $Ca^{2+}$ .
- The increase in intracellular  $Ca^{2+}$  causes pulsatile insulin exocytosis



# Factors affecting secretion of Insulin and physiological effects of insulin



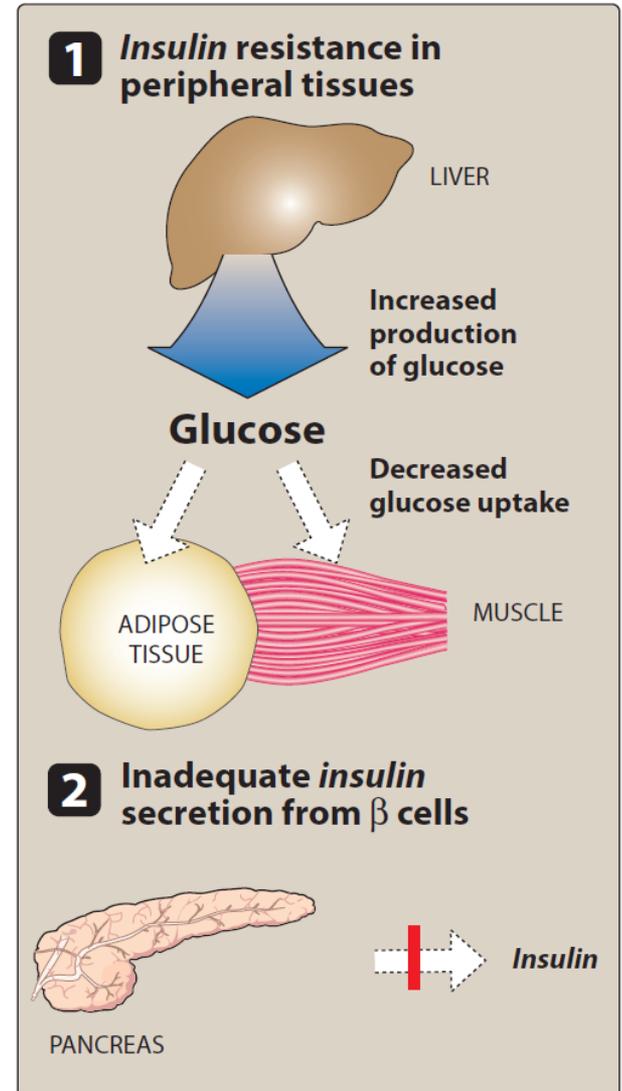
# Diabetes mellitus (DM)

- DM is characterized by elevated glucose levels due to absolute or relative lack of insulin functionality
- **Classification:**
  - Type 1, Type 2, gestational & diabetes due to other causes
- **Type 1 diabetes :**
  - $\beta$ -cell failure due to massive necrosis
  - May be autoimmune, viral or chemical induced
  - Classic symptoms of insulin deficiency
  - Treatment: Insulin dependent
  - Untreated: Life-threatening diabetic ketoacidosis

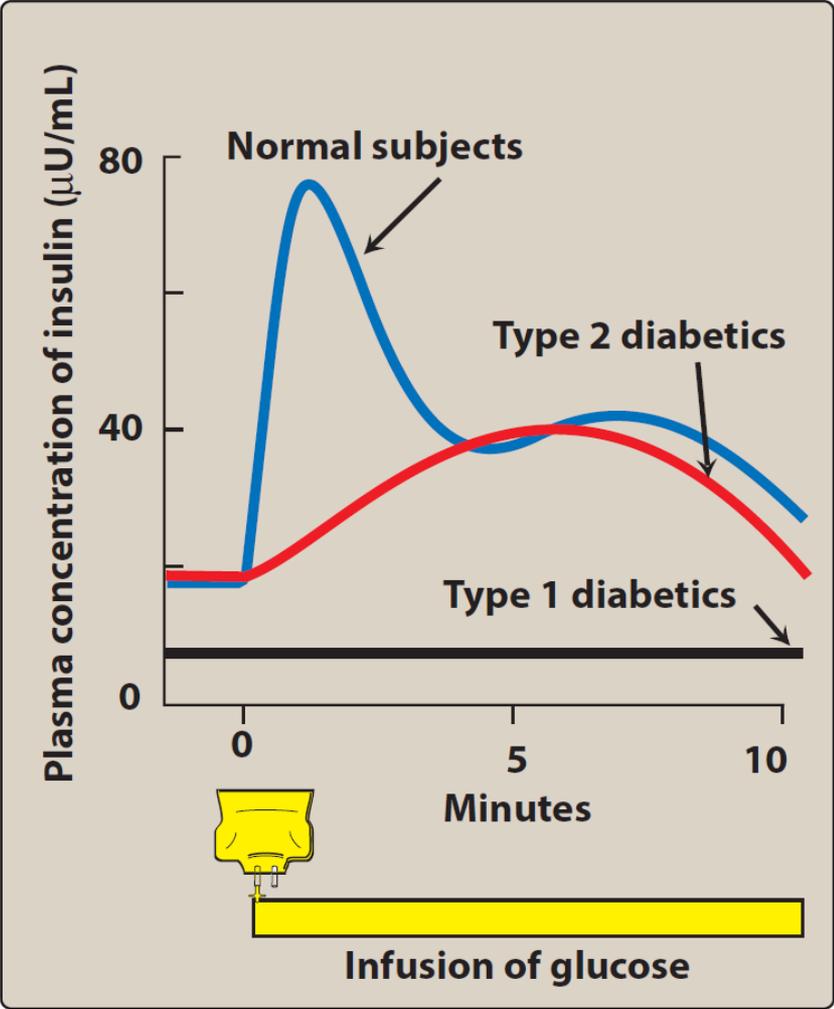
	Type 1	Type 2
Age of onset	Usually during childhood or puberty	Commonly over age 35
Nutritional status at time of onset	Commonly undernourished	Obesity usually present
Prevalence	5% to 10% of diagnosed diabetics	90% to 95% of diagnosed diabetics
Genetic predisposition	Moderate	Very strong
Defect or deficiency	$\beta$ cells are destroyed, eliminating the production of insulin	Inability of $\beta$ cells to produce appropriate quantities of insulin; insulin resistance; other defects

# Diabetes mellitus

- **Type 2 diabetes - Gradual  $\beta$ -cell deterioration**
  - Influenced by genetic factors, aging, obesity & peripheral insulin resistance.
  - Early stages: High levels of insulin, particularly in obese patients (insulin resistance)
  - Late-stage: the  $\beta$ -cell mass gradually decline over time, thus require insulin therapy



# Insulin level Profile for Healthy and Diabetic Individuals



## **Glycosylated hemoglobin Hb-A1c**

- Used to monitor the plasma glucose concentration over prolonged periods of time (4-6 weeks).
- Normal mean blood glucose is approximately 115 mg/dL or less (HbA1c < 5.7%)

## Insulin and insulin analogues

- Not active orally.
- Insulin is inactivated by insulinase (insulin transhydrogenase ) found mainly in liver and kidney.
- Insulin burst within 2 min, lasts for 15 min, then postprandial insulin secretion
- Dose reduced in renal insufficiency

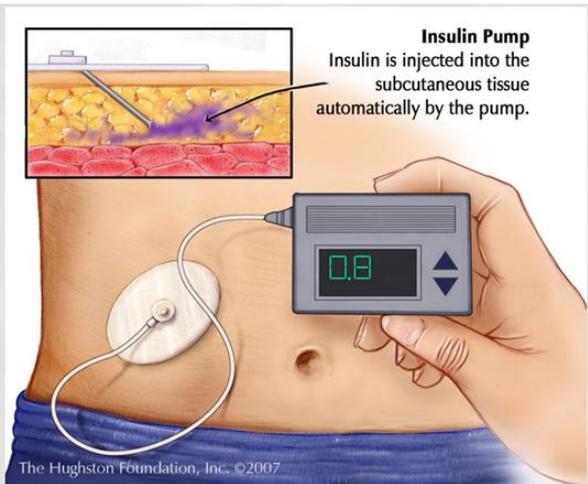
# Insulin Delivery system



Can you see the **Needle?**



You can hardly **feel** it too!





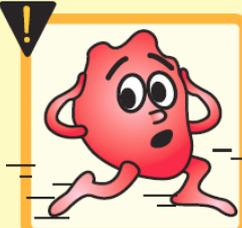
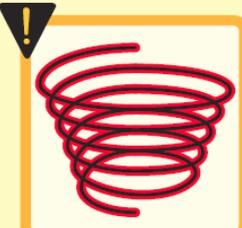
# Insulin Delivery Systems

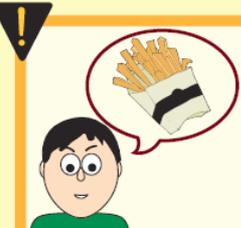
	<b>Advantages</b>	<b>Disadvantages</b>
Syringe	Ability to mix insulin and adjust to patient needs	Multiple injections Variable insulin absorption
Pen	Convenient Improves dosing accuracy	More expensive than syringe
Pump	Better glycemic control Less hypoglycemia	Expensive Requires motivated patient
Inhaled (under investigation)	Eliminates injections Glycemic control similar to subcutaneous	?

# Side effects of insulin

- Hypoglycemia is the most serious and common adverse reaction to insulin.

**Symptoms caused by hypoglycemia**

 Headache	 Anxiety
 Tachycardia	 Confusion
 Vertigo	 Diaphoresis

 Shaky	 Increased appetite
 Blurred vision	 Weakness/ fatigue

## Side effects of Insulin

- Hypoglycemia is the most serious and common adverse reaction to insulin (can result in Seizures and Coma)
- Other adverse reactions include: weight gain, local injection site reactions, and lipodystrophy.
- Lipodystrophy can be minimized by rotation of injection sites.



Insulin-induced Lipodystrophy

# Insulin and insulin analogues

- Human insulin is produced by recombinant DNA technology
- Modification of the amino acid sequence of human insulin produces insulins with different pharmacokinetic properties (onset and duration of action).
- Insulin preparations vary primarily in their onset and duration of action.
- **Factors influencing the onset and duration of action:** Dose, injection site, blood supply, temperature, and physical activity.

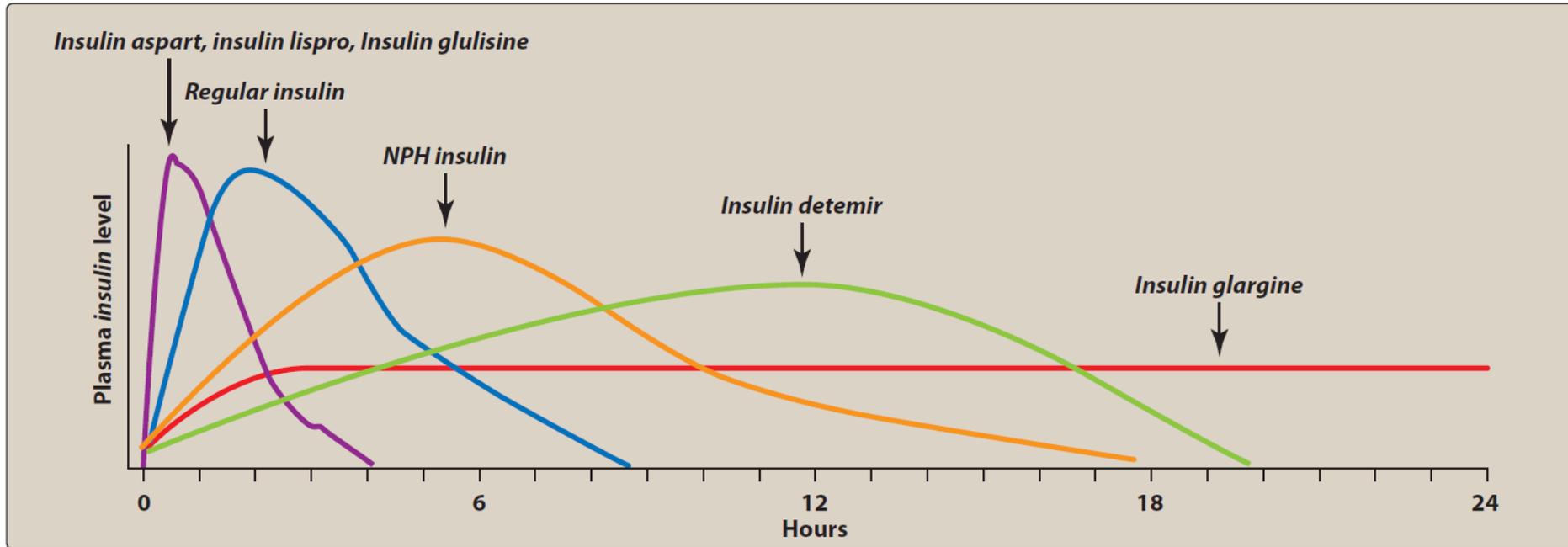
## Insulin preparations

- Rapid acting insulin : Lispro (Humalog<sup>®</sup>), Aspart and Glulisine, Human insulin (Actrapid<sup>®</sup>)
- Short acting insulin: Regular (crystalline) (Humulin R<sup>®</sup>)
- Intermediate acting insulin: NPH (isophane) and Lente (insulin zinc)
- Long acting insulin: Protamine—zinc , Ultralente, Detimir and Glargine (Lantus<sup>®</sup>)

Mixtard<sup>®</sup>: Regular and long-acting (isophane) insulin

Insulin	Duration	Route	Features
Lispro Rapid acting	3 – 5 hrs	I.V or S.C	Onset within 15 minutes
Regular (crystalline) Short acting	7 – 10 hrs	I.V or S.C	common
NPH (Neutral protamine hagedorn) Intermediate acting	16 – 20 hrs	S.C	NPH can mix with regular
Ultralente, Glargine Long acting Peakless	24 – 30 hrs	S.C	Basal level

# Insulin preparations



## Rapid-acting and short-acting insulin preparations

- Rapid- or short-acting insulins are administered to **mimic the prandial** (mealtime) release of insulin and to control **postprandial glucose**.
- They may also be used in cases where **swift correction** of elevated glucose is needed.
- Rapid- and short-acting insulins are usually **used in conjunction** with a longer-acting basal insulin that provides control of fasting glucose.

## Rapid-acting and short-acting insulin preparations

- Regular insulin should be injected SC **30 minutes** before a meal, whereas rapid-acting insulins are administered in the **15 minutes** preceding a meal or within 15 to 20 minutes after starting a meal.
- Rapid-acting insulins are commonly used in external **insulin pumps**, and they are suitable for IV administration.
- Regular insulin is most commonly used when the IV route is needed.

## Intermediate-acting insulin

- Neutral protamine Hagedorn (NPH) (isophane) insulin is an intermediate-acting insulin formed by the addition of zinc and protamine to regular insulin.
- It has less solubility, thus delayed absorption and a longer duration of action.
- It is used for **basal (fasting) control** in type 1 or 2 diabetes and is usually given along with rapid- or short-acting insulin for mealtime control.
- It should be given only subcutaneously (**never IV**)
- It should **not be** used when rapid glucose lowering is needed (for example, diabetic ketoacidosis).

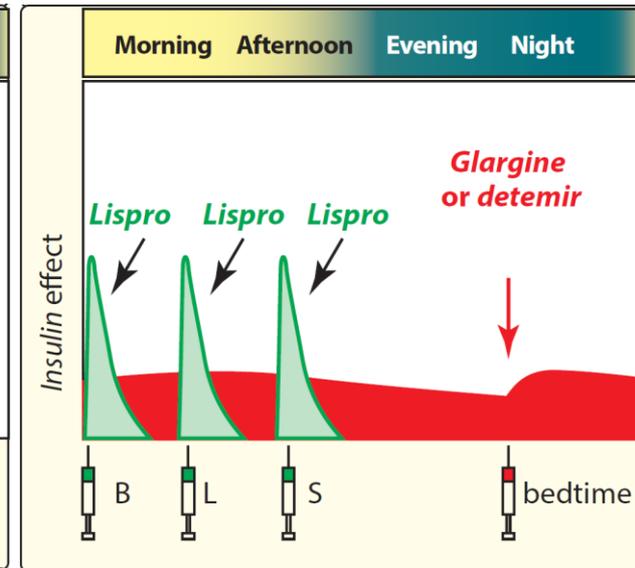
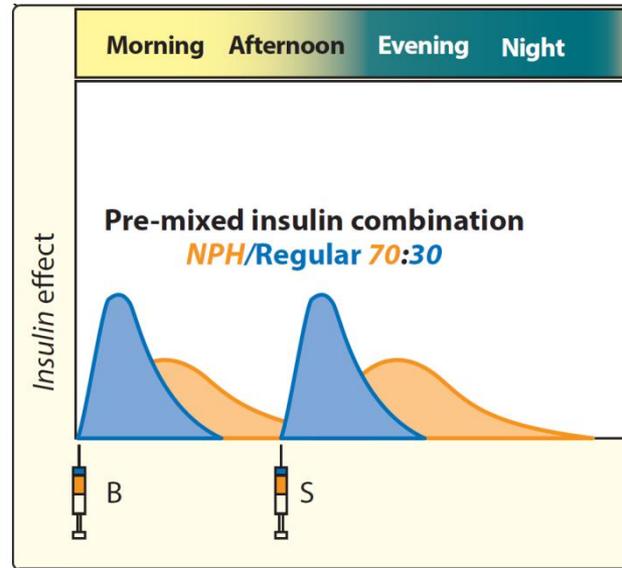
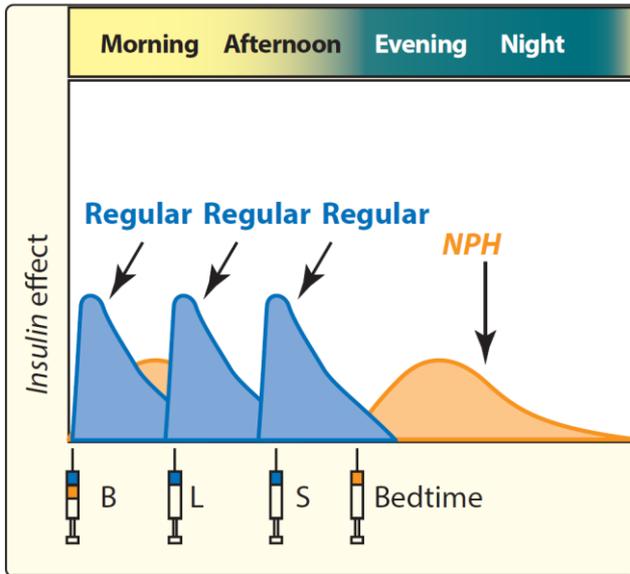
## Long-acting insulin preparations

- Insulin Glargine: has a slower onset than NPH insulin and a flat, prolonged hypoglycemic effect with no peak
- Insulin Detemir (association to albumin): Slow dissociation from albumin results in long-acting properties similar to those of insulin Glargine
- Both are used for basal control and should only be administered subcutaneously.
- Neither long-acting insulin should be mixed in the same syringe with other insulins

## Insulin combinations

- Examples of premixed combinations: 70% NPH insulin plus 30% regular insulin, or 50% of each.
- The use of premixed combinations decreases the number of daily injections but makes it more difficult to adjust individual components of the insulin regimen.

# Examples of three regimens that provide both prandial and basal insulin replacement



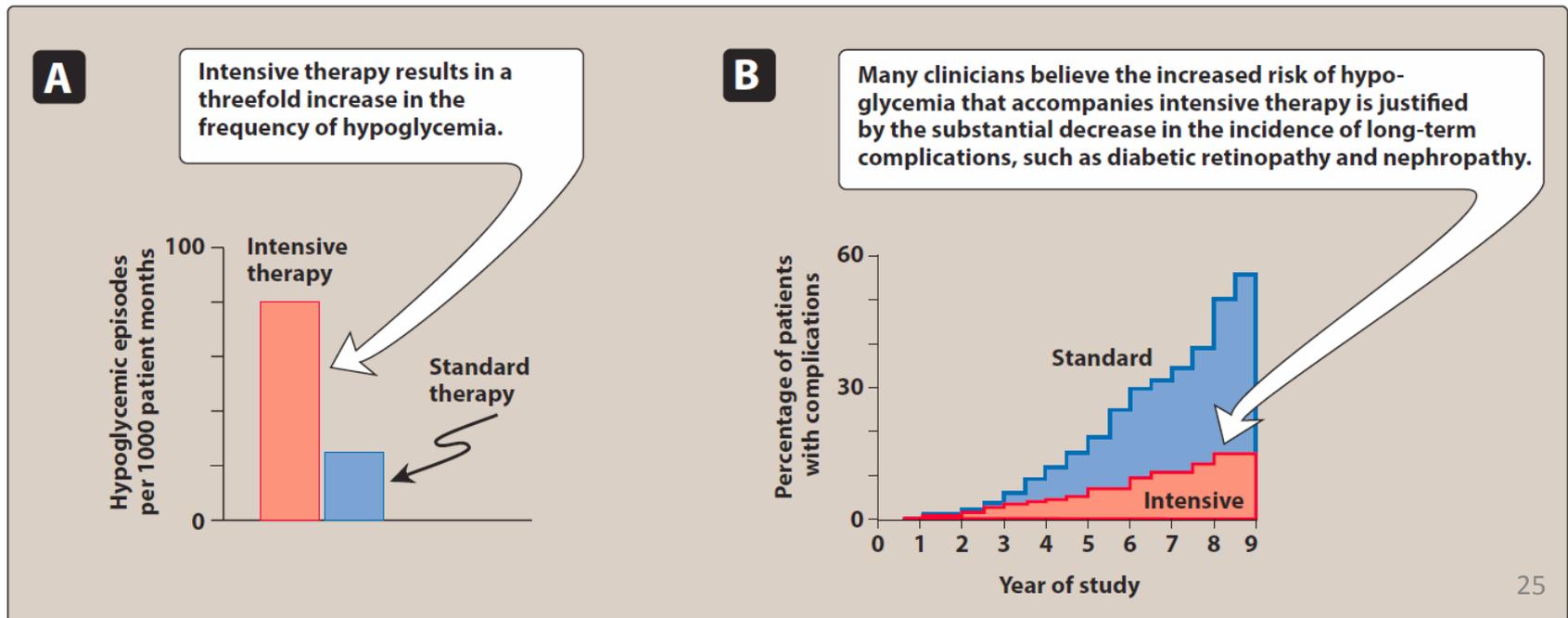
B = breakfast  
L = lunch  
S = supper

## Standard treatment versus intensive treatment

- **Standard insulin therapy:** involves twice-daily injections.
- **Intensive insulin therapy:** utilizes three or more injections daily with frequent monitoring of blood glucose levels.
- The recommended target **mean** blood glucose level of 154 mg/dL or less (HbA1c  $\leq$  7%)
- Intensive treatment is more likely to achieve this goal.

# Standard treatment versus intensive treatment

- The frequency of hypoglycemic episodes, coma, and seizures is higher with intensive *insulin regimens*.
- Patients on intensive therapy show a significant reduction in microvascular complications of diabetes such as retinopathy, nephropathy, and neuropathy compared to patients receiving standard care.



## Standard treatment versus intensive treatment

- Intensive therapy should not be recommended for patients with long-standing diabetes, significant microvascular complications, advanced age, and those with hypoglycemic unawareness

## Synthetic Amylin analog: Pramlintide

- Amylin is a peptide produced by beta cells and co-secreted with insulin.
- **Pharmacological (physiological) Effects:** Inhibits glucagon secretion, delay gastric emptying, suppress appetite, decreases postprandial glucagon secretion, improves satiety
- **Indication:** an adjunct to mealtime insulin therapy in patients with Type 1 or Type 2 diabetes.

## Synthetic Amylin analog: Pramlintide

- **Administration of Pramlintide:** subcutaneous injection immediately prior to meals.
- When pramlintide is initiated, the dose of rapid- or short-acting insulin should be decreased by 50% prior to meals to avoid a risk of severe hypoglycemia.
- **Adverse effects:** are mainly GI and consist of nausea, anorexia, and vomiting.

## Incretin mimetics

- Oral glucose results in a higher secretion of insulin than occurs when an equal load of glucose is given IV.
- This effect is referred to as the “incretin effect” and is markedly reduced in type 2 diabetes.
- The incretin effect occurs because the gut releases incretin hormones, notably glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) in response to a meal.
- GLP-1 is rapidly inactivated by the enzyme dipeptidyl peptidase 4 (DPP-4)

# Incretin mimetics

- Incretin hormones are responsible for 60% to 70% of postprandial insulin secretion.
- **Exenatide** and **Liraglutide** are injectable incretin mimetics used for the treatment of type 2 diabetes.
- Must be administered subcutaneously.
- **Indication:** Adjunct to therapy in patients with Type 2 diabetes who have failed to achieve adequate glycemic control on oral hypoglycemic agents.
- Exenatide has a shorter duration of action

# Mechanism of action and pharmacological effects of Incretin mimetics

- Analogs of GLP-1 that exert their activity by acting as GLP-1 receptor agonists.
- **Pharmacological effects:**
  1. Improve glucose-dependent insulin secretion
  2. Slow gastric emptying time
  3. Reduce food intake by enhancing satiety (a feeling of fullness)
  4. Decrease postprandial glucagon secretion by  $\alpha$ -cells
  5. Promote  $\beta$ -cell proliferation
- Consequently, weight gain and postprandial hyperglycemia are reduced, and HbA1c levels decline

# Adverse effects of Incretin mimetics

- Nausea and vomiting
- Diarrhea, and constipation
- Associated with pancreatitis

# Oral hypoglycemic agents

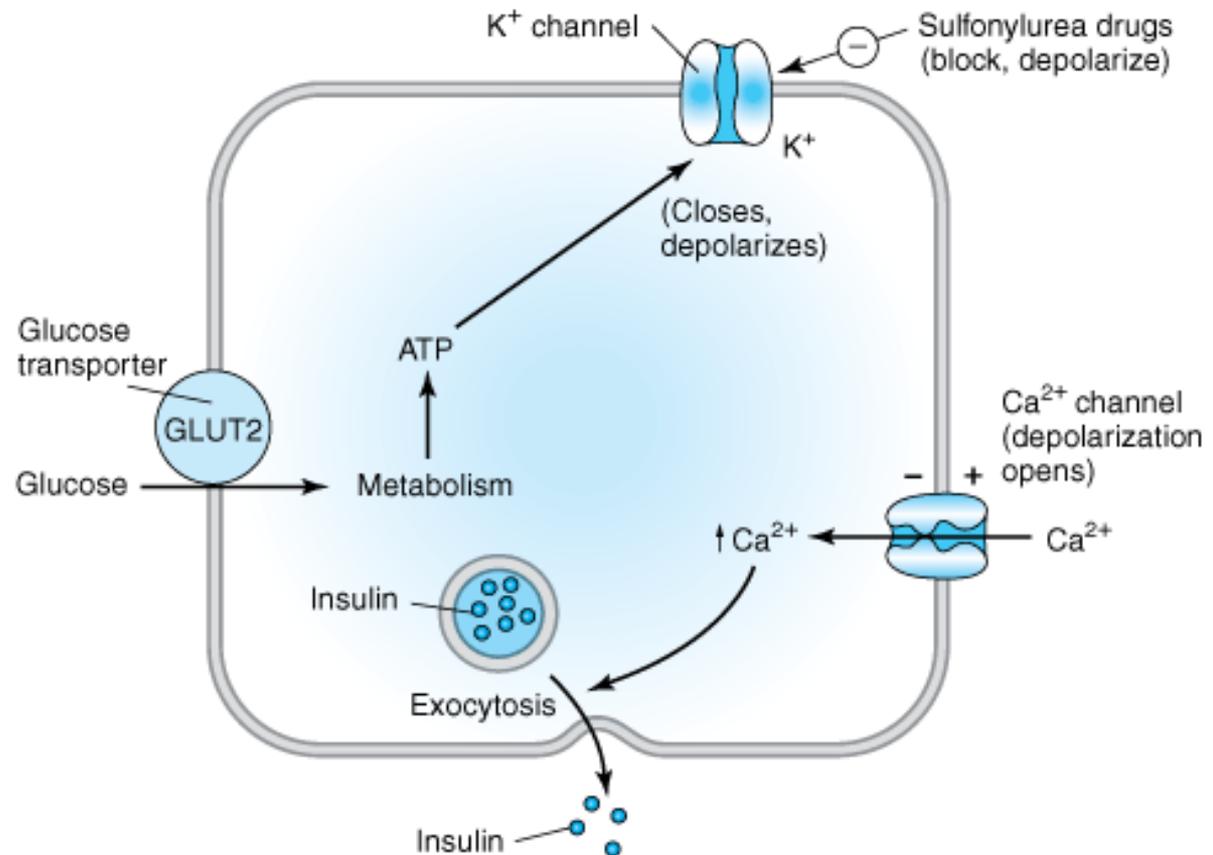
- Sulfonylureas
- Meglitinides (Glinides)
- Biguanides
- Thiazolidinediones
- $\alpha$ -Glucosidase inhibitors
- Dipeptidyl peptidase-4 inhibitors

# Sulfonylureas

- Insulin secretagogues: They induce insulin secretion
- **Three generations:**
  - First generation : Acetohexamide, Chlorpropamide, Tolbutamide, Tolazamide (no longer used)
  - Second generation : Glipizide, Glyburide (Glibenclamide)
  - Third generation : Glimiperide (*more potent, more efficacious , fewer adverse effects*).

# Mechanism of action of Sulfonylureas

- They may reduce hepatic glucose production and increase peripheral insulin sensitivity.



## Adverse effects of Sulfonylureas

- Hyperinsulinemia and Hypoglycemia
- Cholestatic jaundice
- Weight gain
- Cross placenta – fetal hypoglycemia

Notes: Glyburide has minimal transfer across the placenta and may be an alternative to insulin for diabetes in pregnancy.

Use with caution in hepatic or renal insufficiency to avoid accumulation

<b>Sulfonylureas</b>	<b>Dose (mg)</b>	<b>Duration (h)</b>
<b>First Generation</b>		
Tolbutamide	1000-1500	6-8
Chlorpropamide	250-375	24-60
Tolazamide	250-375	12-24
<b>Second generation</b>		
Glipizide	10	10-24
Glyburide (Glibenclamide)	5	16-24
<b>Third generation</b>		
Glimepiride	1-2	24

# Meglitinides (glinides)

## Repaglinide, Nateglinide :

- Insulin enhancers with shorter duration than sulfonylurea (mealtime anti-diabetic drugs)
- These are insulin secretagogues that act by blocking ATP-dependent K<sup>+</sup> channels.
- This leads to increased insulin secretion by pancreatic  $\beta$ -cells.
- Hypoglycemia is the common adverse effect.
- Less weight gain
- The drug has minimal renal excretion thus useful in patients with DM and impaired renal function.

## Meglitinides (glinides)

### Repaglinide, Nateglinide :

- By inhibiting hepatic metabolism, the lipid-lowering drug *Gemfibrozil* may significantly increase the effects of repaglinide, and concurrent use is contraindicated.
- These agents should be used with caution in patients with hepatic impairment

# Biguanides (Metformin)

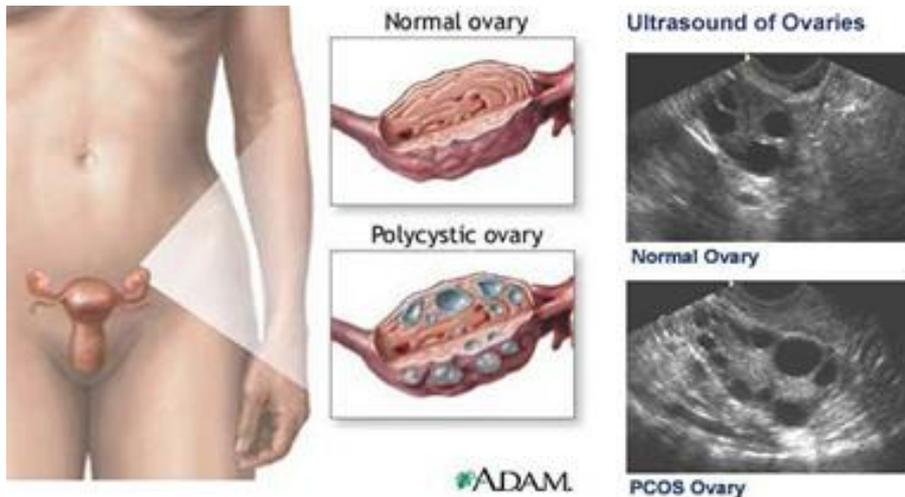
- **Pharmacological actions:**
  - Insulin sensitizer: It increase the sensitivity of liver and muscle to insulin (increase uptake of glucose)
  - Inhibits glucose output (gluconeogenesis)
  - Slows intestinal absorption of sugars
  - Does not promote insulin secretion
  - It causes modest weight loss: loss of appetite
  - It does **not** cause hypoglycemia.
  - It produces a significant ↓TG and LDL, and ↑HDL.

## Biguanides (Metformin)

- Contraindicated for patients with renal dysfunction due to the risk of lactic acidosis.
- It should be discontinued in disorders that can cause acute renal failure: e.g. acute MI, exacerbation of heart failure and sepsis.
- *Metformin should be used with caution* in patients older than 80 years and in those with heart failure.
- Should be temporarily discontinued in patients undergoing procedures requiring IV radiographic contrast

## Other uses of Metformin

- Metformin is effective in the treatment of polycystic ovary syndrome
- It lowers *insulin* resistance seen in this disorder and can result in ovulation and, therefore, possibly pregnancy



# Thiazolidinediones (TZDs) (glitazones)

- Insulin sensitizers
- Enhance sensitivity to insulin in muscle and fat by increasing the GLUT 4 glucose transporters.
- Enhance glucose and lipid metabolism through action on Peroxisome Proliferator Activated Receptor (PPAR- $\gamma$ )
- Beneficial effects on serum lipid;  $\downarrow$ TG and  $\uparrow$ HDL.

## Thiazolidinediones (TZDs) (glitazones)

- TZDs do not promote its release from the  $\beta$  cells, so hyperinsulinemia is not a risk.
- Troglitazone, was withdrawn in 1990s from the market due to an increased incidence of drug-induced hepatitis. Pioglitazone , Rosiglitazone: suspended from the EU market due to elevated cardiovascular risks
- The main side effect of all thiazolidinediones is water retention, leading to edema .

# Adverse effects of Oral Anti-diabetic drugs

Meglitinides  
Sulfonylureas



Hypoglycemia

Biguanides  
 $\alpha$ -Glucosidase  
inhibitors



GI disturbance

Sulfonylureas  
Meglitinides  
Thiazolidinediones



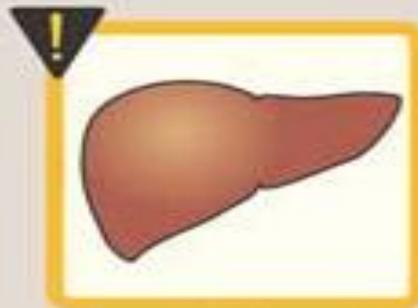
Weight gain

Biguanides



Nausea

Thiazolidinediones



Risk of  
hepatotoxicity

# Alpha-Glucosidase Inhibitors

- Acarbose and Miglitol
- Taken at the beginning of the meal
- They inhibit  $\alpha$ -glucosidase which converts dietary starch and complex carbohydrates into simple sugars
- It reduces absorption of glucose after meals.
- The main side effects includes flatulence and diarrhea.
- Not recommended in patients with inflammatory bowel disease (IBDs), colonic ulceration or intestinal obstruction

Agent	Mechanism	Site of action	Main advantages	Main side effects
<b>Sulfonylureas</b>	Stimulating insulin production by inhibiting the $K_{ATP}$ channel	Pancreatic beta cells	<ul style="list-style-type: none"> <li>• Effective</li> <li>• Inexpensive</li> </ul>	<ul style="list-style-type: none"> <li>• Hypoglycemia</li> <li>• Weight gain</li> </ul>
<b>Metformin</b>	Decreases insulin resistance	Liver	<ul style="list-style-type: none"> <li>• May result in mild weight loss</li> <li>• Does not cause hypoglycemia</li> </ul>	<ul style="list-style-type: none"> <li>• GI symptoms, including diarrhea, nausea, abdominal pain</li> <li>• Lactic acidosis</li> <li>• Metallic taste</li> </ul>
<b>Acarbose</b>	Reduces intestinal glucose absorption	GI tract	<ul style="list-style-type: none"> <li>• Low risk</li> </ul>	<ul style="list-style-type: none"> <li>• GI symptoms, including diarrhea, abdominal cramping, flatulence</li> </ul>
<b>Thiazolidinediones</b>	Reduce insulin resistance by activating PPAR- $\gamma$	Fat, muscle		<ul style="list-style-type: none"> <li>• Hepatotoxicity</li> </ul>

## **Dipeptidyl peptidase-4 inhibitors**

- Alogliptin, Linagliptin, Saxagliptin, and Sitagliptin
- Orally active dipeptidyl peptidase-4 (DPP-4) inhibitors
- Used for the treatment of type 2 diabetes

## Mechanism of action of Dipeptidyl peptidase-4 inhibitors

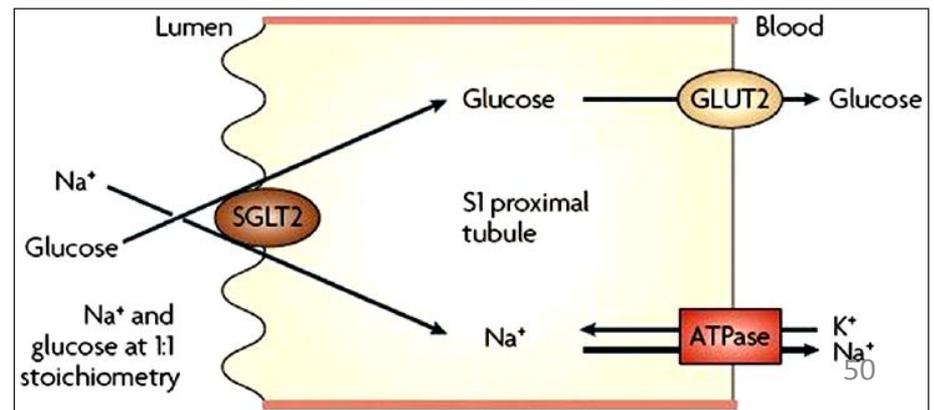
- They inhibit the enzyme DPP-4, which is responsible for the inactivation of incretin hormones such as GLP-1.
- Prolonging the activity of incretin hormones increases insulin release in response to meals and reduces inappropriate secretion of glucagon.
- DPP-4 inhibitors may be used as monotherapy or in combination with other drugs.
- Unlike incretin mimetics, these drugs do not cause satiety, or fullness, and are weight neutral

# Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Canagliflozin and Dapagliflozin)

## Mechanism of action:

- (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.
- Inhibition of SGLT2 also decreases reabsorption of sodium and causes osmotic diuresis.
- Therefore, SGLT2 inhibitors may reduce systolic blood pressure.
- They are not indicated for the treatment of hypertension.

- Used for type 2 diabetes



# **Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Canagliflozin and Dapagliflozin)**

## **Pharmacokinetics**

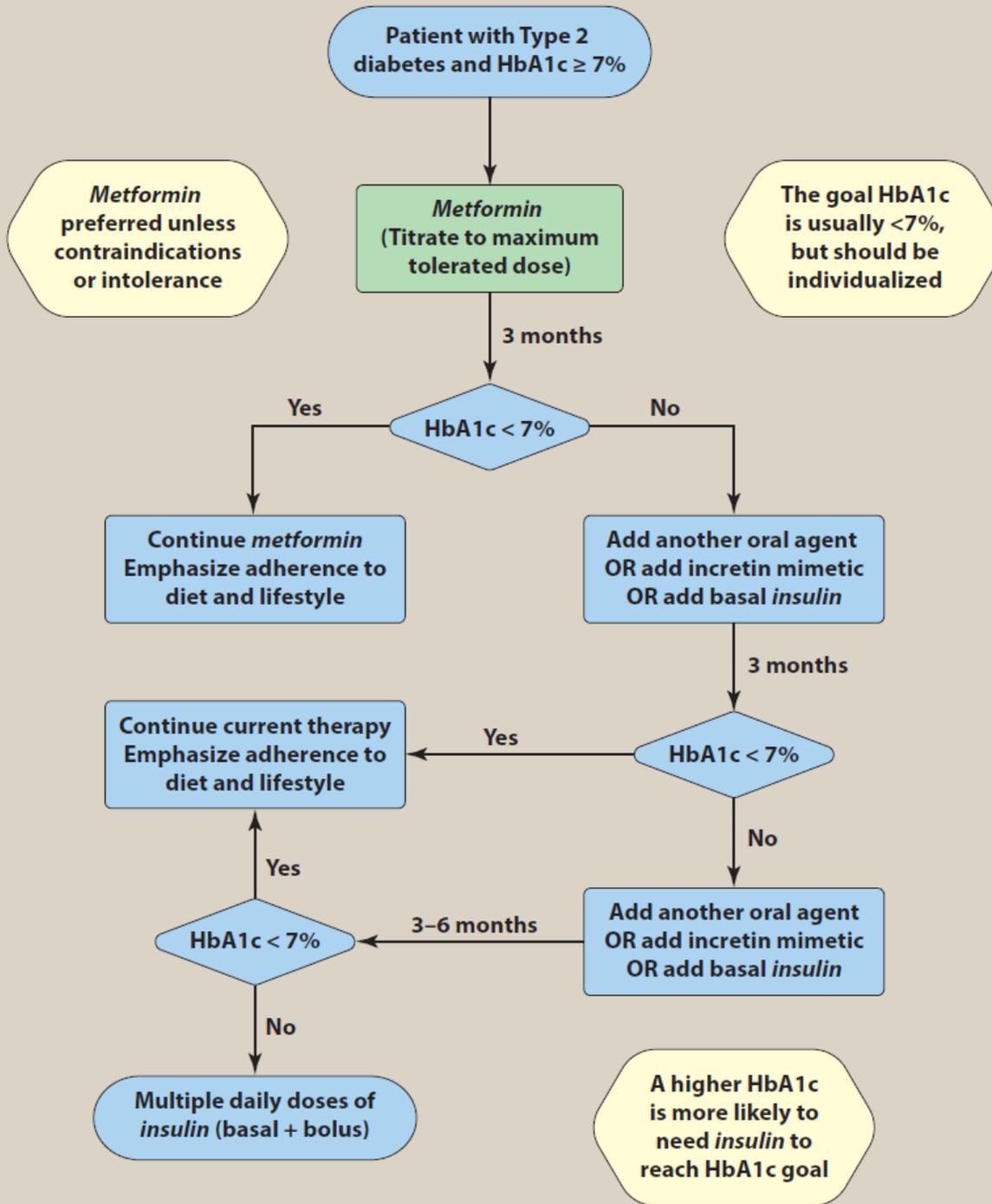
- These agents are given once daily in the morning before the first meal.
- About one-third of a dose is renally eliminated.
- These agents should be avoided in patients with renal dysfunction

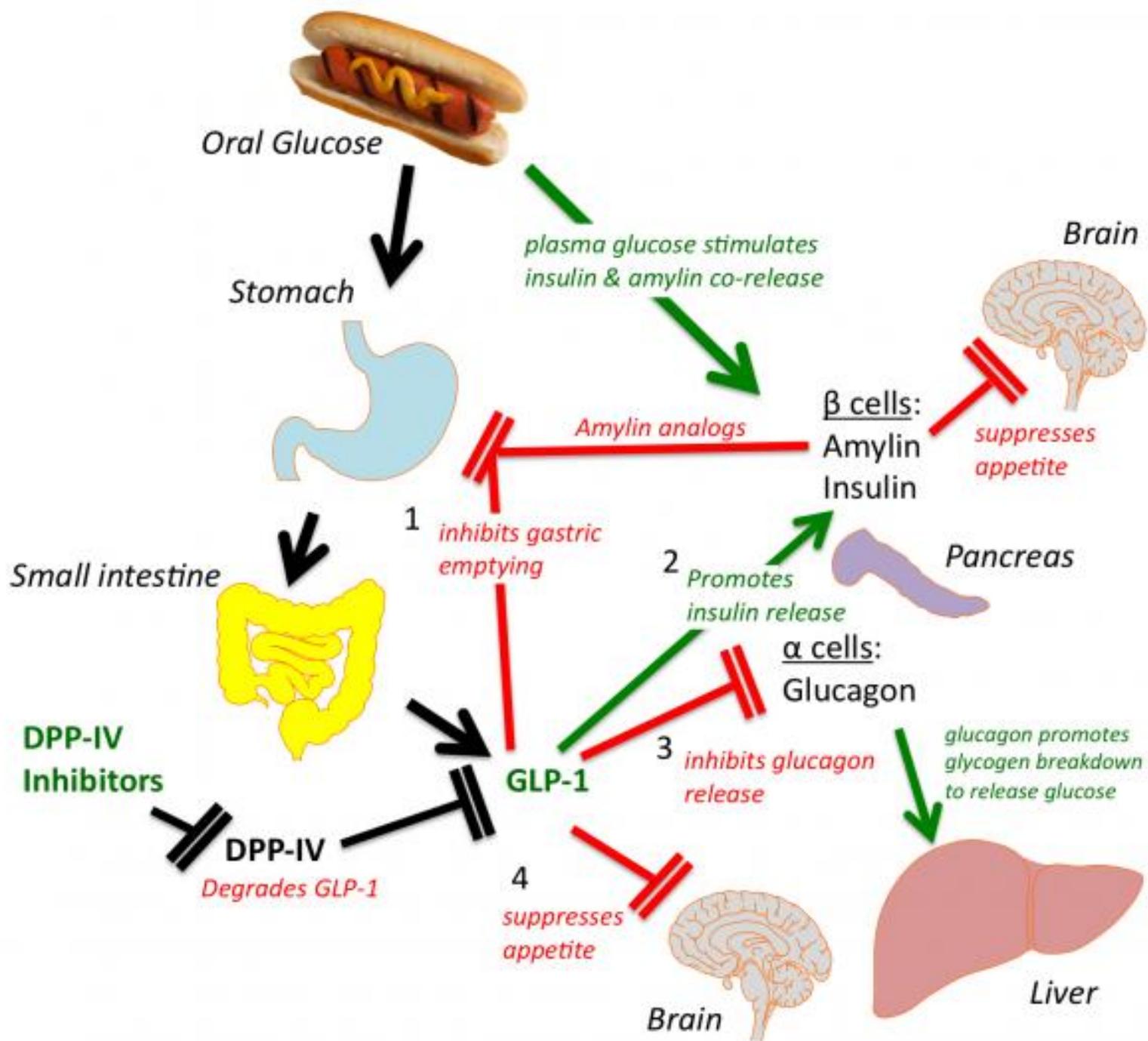
# **Sodium–glucose cotransporter 2 (SGLT2) inhibitors (Canagliflozin and Dapagliflozin)**

## **Side effects:**

- Female genital mycotic infections (for example, vulvovaginal candidiasis)
- Urinary tract infections
- Urinary frequency
- Hypotension, particularly in the elderly or patients on diuretics.

# Treatment guidelines for type 2 diabetes





# Agents that increase blood glucose (hyperglycemics)

## Glucagon : Uses

- A. First aid in cases of severe hypoglycemia when the victim is unconscious or for other reasons cannot take glucose orally.
  
- B. Treatment of overdose with beta blockers
  - It has positive inotropic action and chronotropic action on the heart.
  - It acts by stimulation of glucagon receptors and not through beta 1 receptors.

## Agents that increase blood glucose (hyperglycemics)

### Diazoxide

- A. Diazoxide is a nondiuretic thiazide that promptly increases blood glucose levels by direct inhibition of insulin secretion.
- B. Diazoxide is useful in cases of insulinoma or leucine-sensitive hypoglycemia
- C. Diazoxide may cause sodium retention, gastrointestinal irritation, and changes in circulating white blood cells.