

# ***Anti-diabetic drugs***

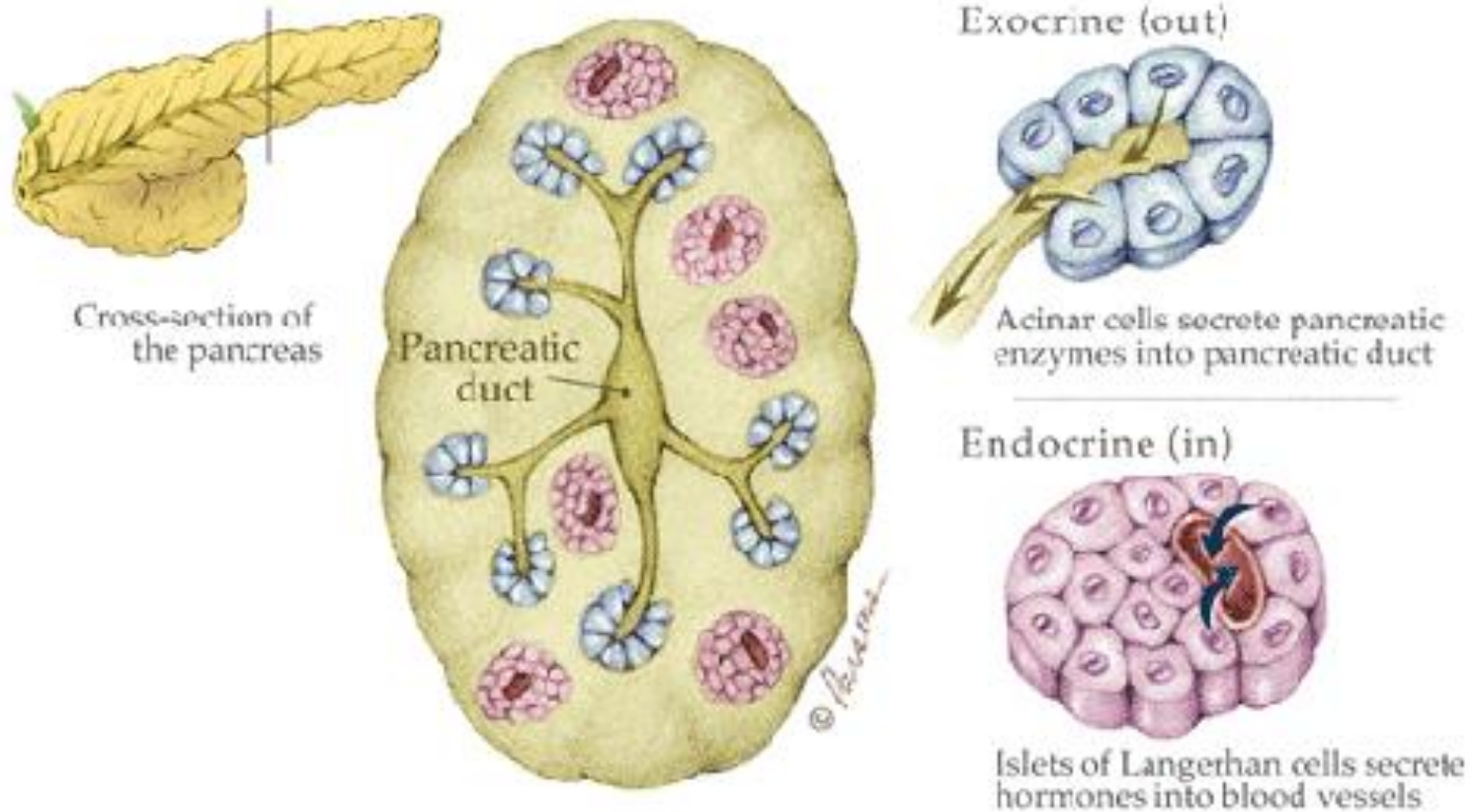
*Assistant lecturer*

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*MSc pharmacology & Toxicology*



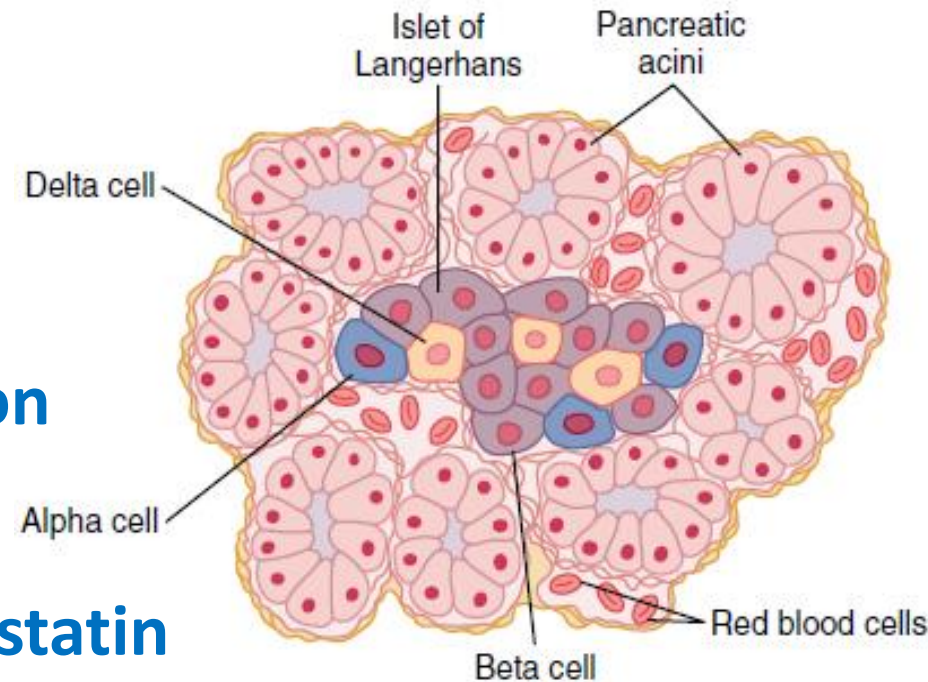
# ***Endocrine pancreas***

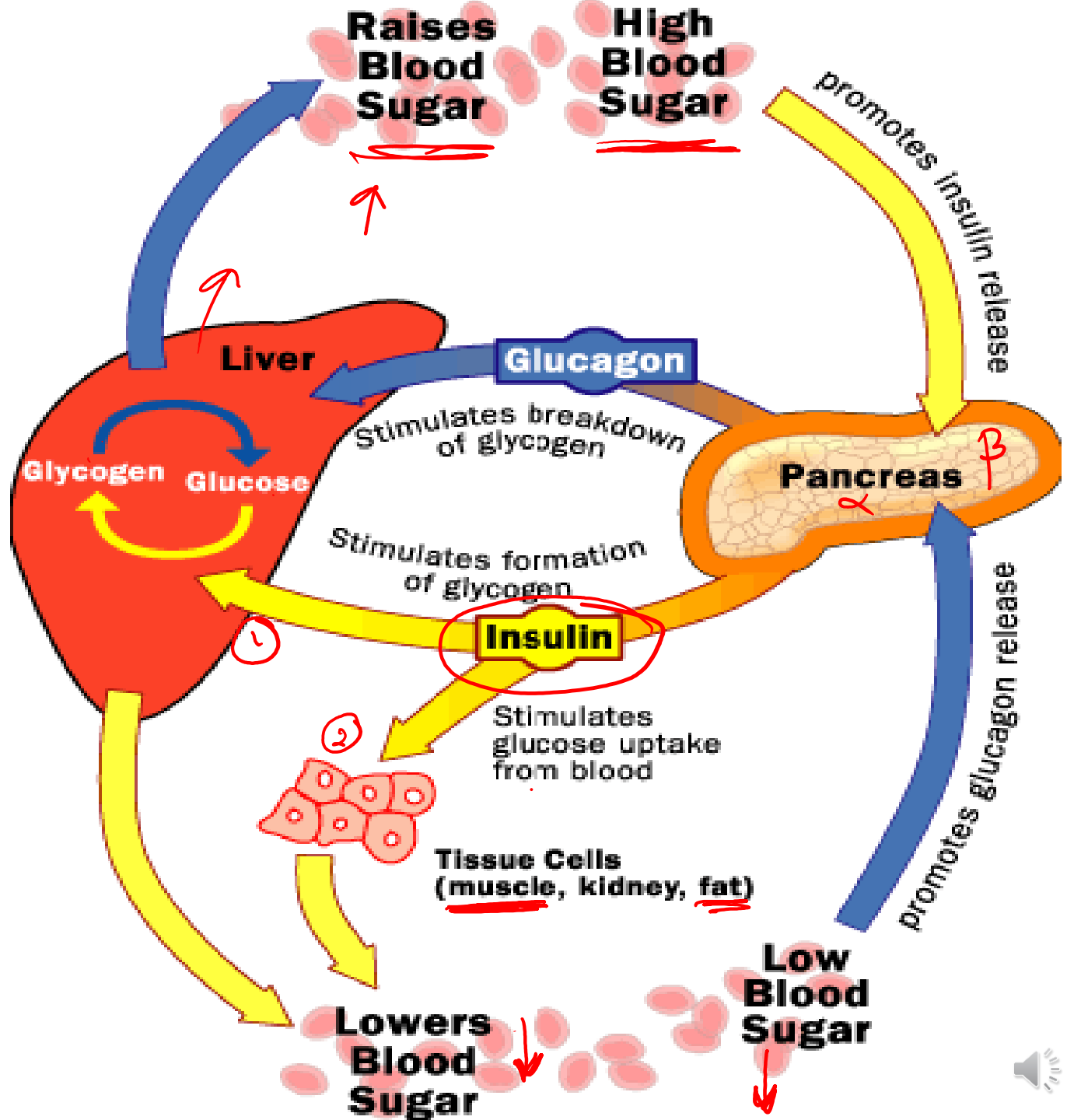
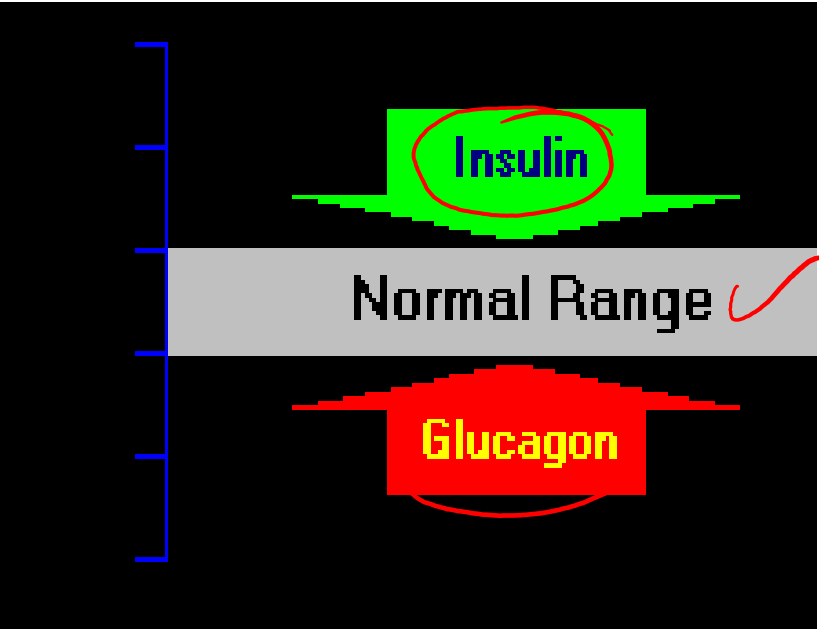


# ***Endocrine pancreas***

- **Islets of Langerhans** consist of 4 main cells. regulate glucose, fatty acid & amino acid metabolism

- 1- **Beta cells** (70%) secrete **Insulin** (↓ glucose) and **Amylin**
- 2- **Alpha cells** (20%) secrete **Glucagon** (↑ glucose)
- 3- **Delta cells** (<10%) secrete **somatostatin**
- 4- **F- cell (pp cell)** (2%) secrete pancreatic polypeptide regulate hormones above





# ***Diabetic mellitus***

***Chronic metabolic disorder cc. by high blood glucose***

- **Clinical features**
  - early signs due to high glucose level in blood
  - late signs due to irreversible damage of the blood vessels by consistent high blood glucose.



# *Early signs*

- Frequent urination. (polyuria)...
- Increased **thirst**. (polydipsia) ...
- Always feeling hungry. (polyphagia) ...
- Feeling very tired. ...
- Blurry vision. ...
- Slow healing of cuts and wounds. ...
- vaginal infection .



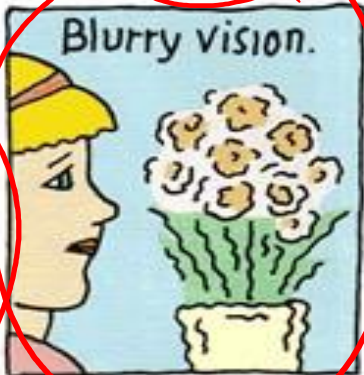
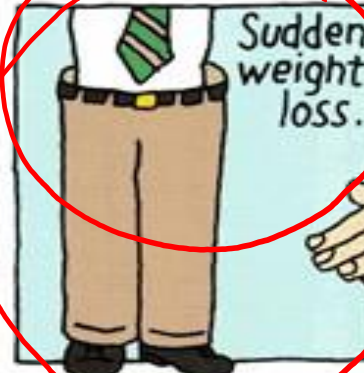


Type I

Insulin

# DIABETES

KNOW THE SYMPTOMS



# Late signs (complications) irreversible

- Macrovascular complications ( due to damage to large blood vessels)  
such as atherosclerosis [result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system]  
↳ MI , CVS , DVT
- Microvascular complications ( due to damage to small blood vessels)
  - ① – Diabetic Retinopathy (by small blood vessel damage to the back layer of the eye, the retina, leading to progressive loss of vision, even blindness.)
  - ② – Diabetic Nephropathy (damage to small blood vessels in the kidneys. This can cause kidney failure, and eventually lead to death.)
  - ③ – Diabetic Neuropathy (decreased blood flow to nerves by damaging small blood vessels)





# Diabetic mellitus

- Lab investigation

|  | <u>Normal</u>                              | <u>Pre-diabetic</u> | <u>D.M</u>            |
|--|--|---------------------|-----------------------|
| [1] Fasting<br>12hr  | <u>&lt; 100</u>                            | 100- 125            | <u>&gt;125 mg /dL</u> |
| [2] Post prandial<br>(75g glucose)<br>عين                              | <u>&lt; 140</u>                            | 140-200             | >200 mg /dL           |
| [3] <u>HbA1c</u><br><br>For control of<br>blood glucose<br>for 3 month | <u>&lt; 6 %</u> ✓<br><u>Hb + glucose</u> - | 6-6.5 %             | > <u>6.5 %</u> ✓      |



# ***Diabetic mellitus***

- **Types of Diabetes**

## **1- Type I (IDDM)**

autoimmune disease

before 30Yr of age

ttt by Insulin

*Handwritten:*  $Ab \rightarrow \beta \text{ cell} \rightarrow \text{dest} \rightarrow \downarrow \downarrow \text{Insulin}$   
*< 30 years*

## **2- Type II (NIDDM)**

insulin is not enough or insulin resistance

after 30Yr of age

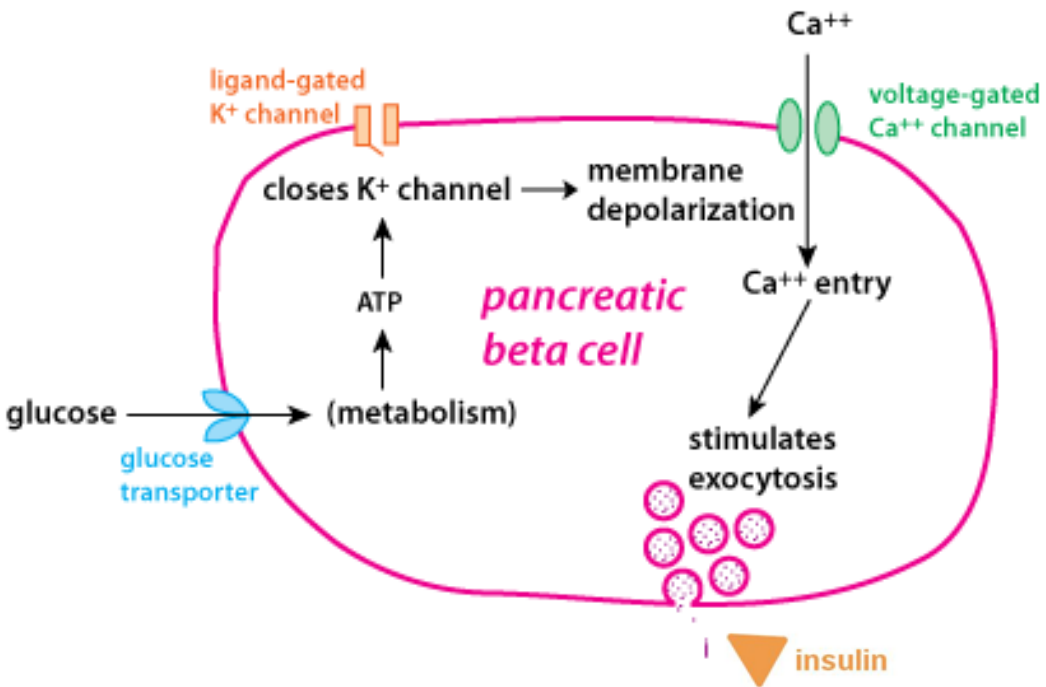
ttt by Oral drug and / or Insulin

*Handwritten:* Obesity

*Handwritten:* 11

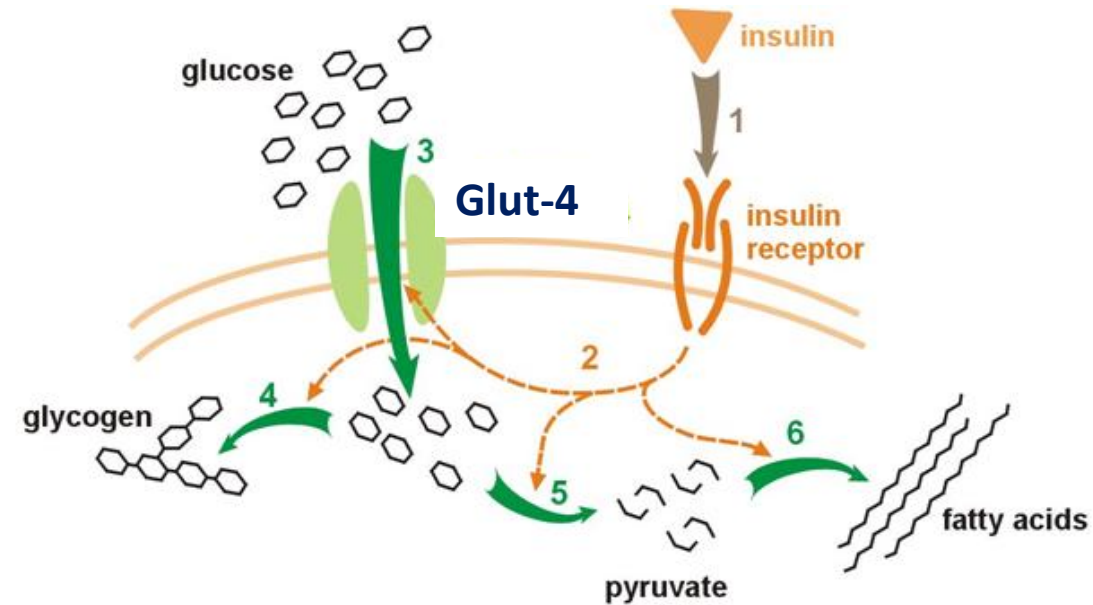


## Beta cell



*Problem of Type I*

## body cell



*Problem of Type II*



# Lines of treatment

- Diet
- Insulin
- Oral drugs

Diet

Caloric requirements

30 Kcal/Kg 70 Kg  
2100 2000 — 2500 Kcal

Child

50%  
15% prot  
55% CHO  
30% Fat  
Obese ptn

# Lines of treatment

x Diet

x Insulin

x Oral Dmg

Diet

Caloric requirement

30 kcal/kg

70 kg

2100 kcal/day

2000-2500

Child

40 kcal/kg

Adolesc 20 kcal/kg

15% protein

55% CHO

30% Fat

Natril-km







Glucose 100%  
↑

# Glycemic Index

تحتوی، سکر  
Food

Low GI (<55), Medium GI (56-69) and High GI (70>)

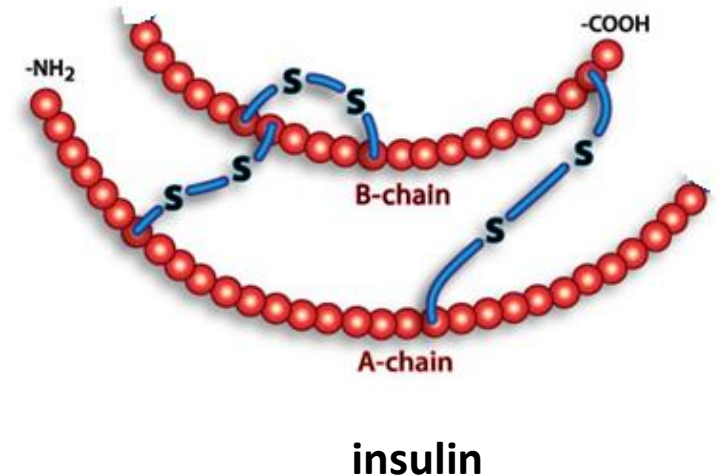
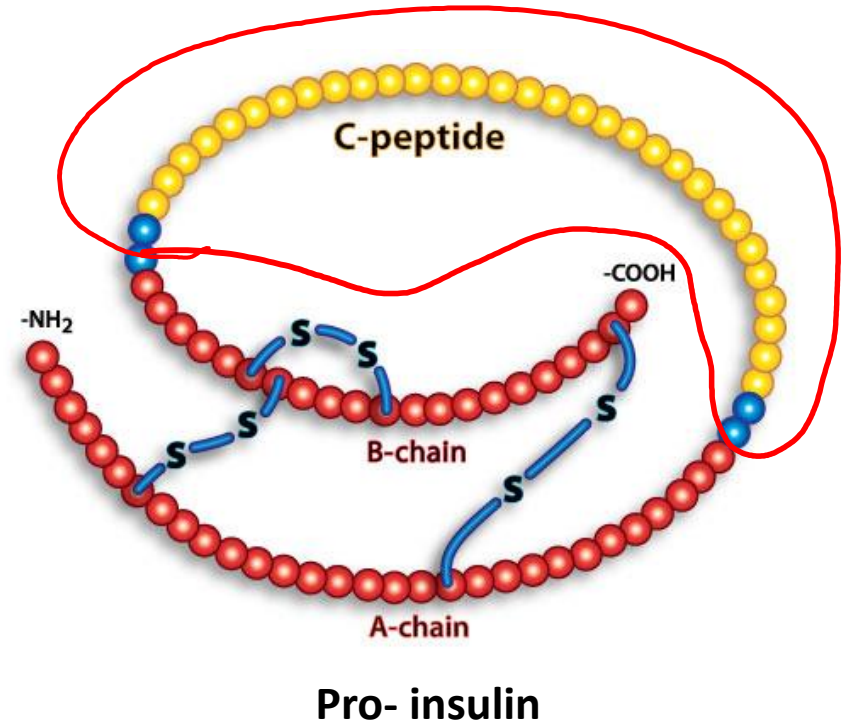
| Grains / Starchs   |           | Vegetables   |    | Fruits  |           | Dairy  |    | Proteins   |    |
|--------------------|-----------|--|----|---|-----------|--|----|--|----|
| Rice Bran          | 27        | Asparagus  | 15 | Grapefruit  | 25        | Low-Fat Yogurt   | 14 | Peanuts  | 21 |
| Bran Cereal        | 42        | Broccoli   | 15 | <u>Apple</u>  | <u>38</u> | Plain Yogurt   | 14 | Beans, Dried   | 40 |
| Spaghetti          | 42        | Celery   | 15 | <u>Peach</u>  | 42        | Whole Milk   | 27 | Lentils  | 41 |
| Corn, sweet        | 54        | Cucumber   | 15 | Orange  | 44        | Soy Milk   | 30 | Kidney Beans   | 41 |
| Wild Rice          | 57        | Lettuce  | 15 | Grape   | 46        | Fat-Free Milk  | 32 | Split Peas   | 45 |
| Sweet Potatoes     | 61        | Peppers  | 15 | Banana  | 54        | Skim Milk  | 32 | Lima Beans   | 46 |
| <u>White Rice</u>  | 64        | Spinach  | 15 | Mango   | 56        | Chocolate Milk   | 35 | Chickpeas  | 47 |
| Cous Cous          | 65        | Tomatoes   | 15 | Pineapple   | 66        | Fruit Yogurt   | 36 | Pinto Beans  | 55 |
| <u>Whole Wheat</u> | <u>71</u> | Chickpeas  | 33 | Watermelon  | 72        | Ice Cream  | 61 | Black-Eyed Beans   | 59 |
| Bread              |           | Cooked Carrots   | 39 |   |           |  |    |  |    |
| Muesli             | 80        |  |    |  |           |  |    |  |    |
| Baked Potatoes     | 85        |  |    |   |           |  |    |  |    |
| Oatmeal            | 87        |  |    |   |           |  |    |  |    |
| Taco Shells        | 97        |  |    |   |           |  |    |  |    |
| White Bread        | 100       |  |    |   |           |  |    |  |    |
| Bagel, White       | 103       |  |    |   |           |  |    |  |    |





## 2- insulin

peptide hormone of 51 a.a  
of 2 chains A & B attached  
by disulfide bonds (after  
cleaved of C peptide )



- what are the **Sources of Insulin** ?
  - **animal (beef (-3 a.a) ; pork (-1 a.a))** ; immunologic reaction & then resistance.
  - **rDNA (genetic engineering)**





- what are the **preparations of Insulin ??**

| preparations  | <u>Onset</u>        | <u>Duration</u> | remarks   |
|---|---------------------|-----------------|---|
| 1- short acting insulin (regular; soluble) <span>الصابني</span> | <u>30min</u><br>S.C | <u>4-6 hr.</u>  | <u>I.V</u> & s.c. { mostly used in <u>emergency</u> } |
| 2- NPH (protamine ) <u>1950</u><br>by Hagidurn                  | <u>1hr</u>          | <u>12 h</u>     | <u>S.C</u> only<br>slow onset & long duration         |

protamin

Neutral protamin Hagidurn



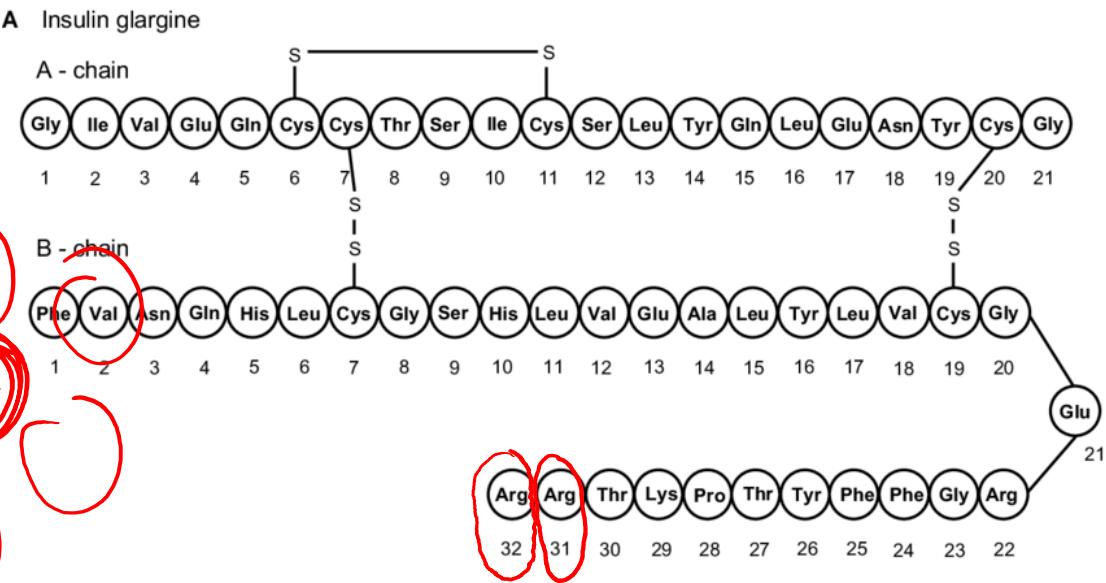
- **preparations of Insulin** continue...

| preparations   | Onset       | Duration   | remarks                     |
|--|-------------|------------|-----------------------------|
| <b>3- Lispro (monomer switching of lysine then proline) 1996 by Lilly.</b> | <b>5min</b> | <b>3hr</b> | <b>S.C<br/>Rapid acting</b> |
| <b>4- Aspart (aspart instead of proline ) 2000 by holland</b>              | <b>5min</b> | <b>3hr</b> | <b>S.C<br/>rapid acting</b> |



# preparations of Insulin continue...

| preparations                                    | Onset | Duration  | remarks                         |
|---|-------|-----------|---------------------------------|
| 5- Glargine (2 arginine a.a with monomer)       | 1-2hr | 16-24 hr. | S.C Long acting <span>٢٥</span> |
| 6- Insulin zinc suspension (more Zn in hexamer) | 1-2hr | 16-24 hr. | S.C Long acting                 |



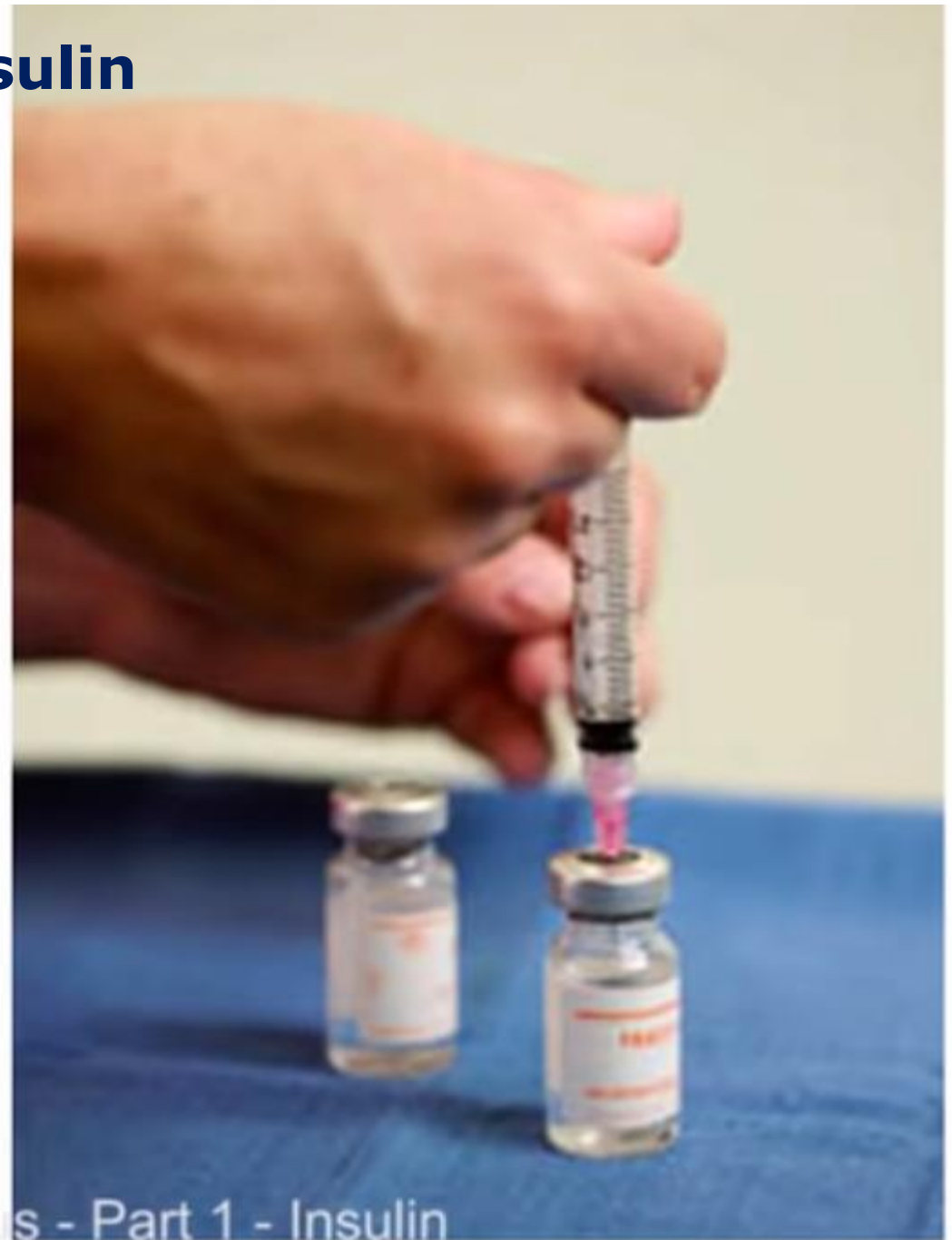
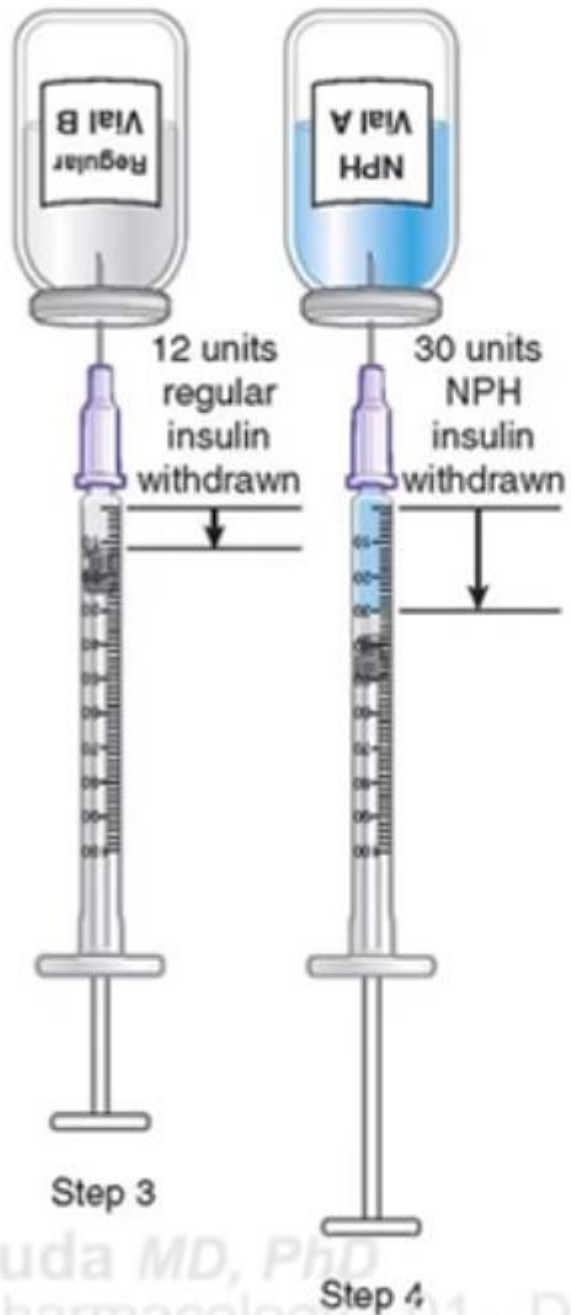


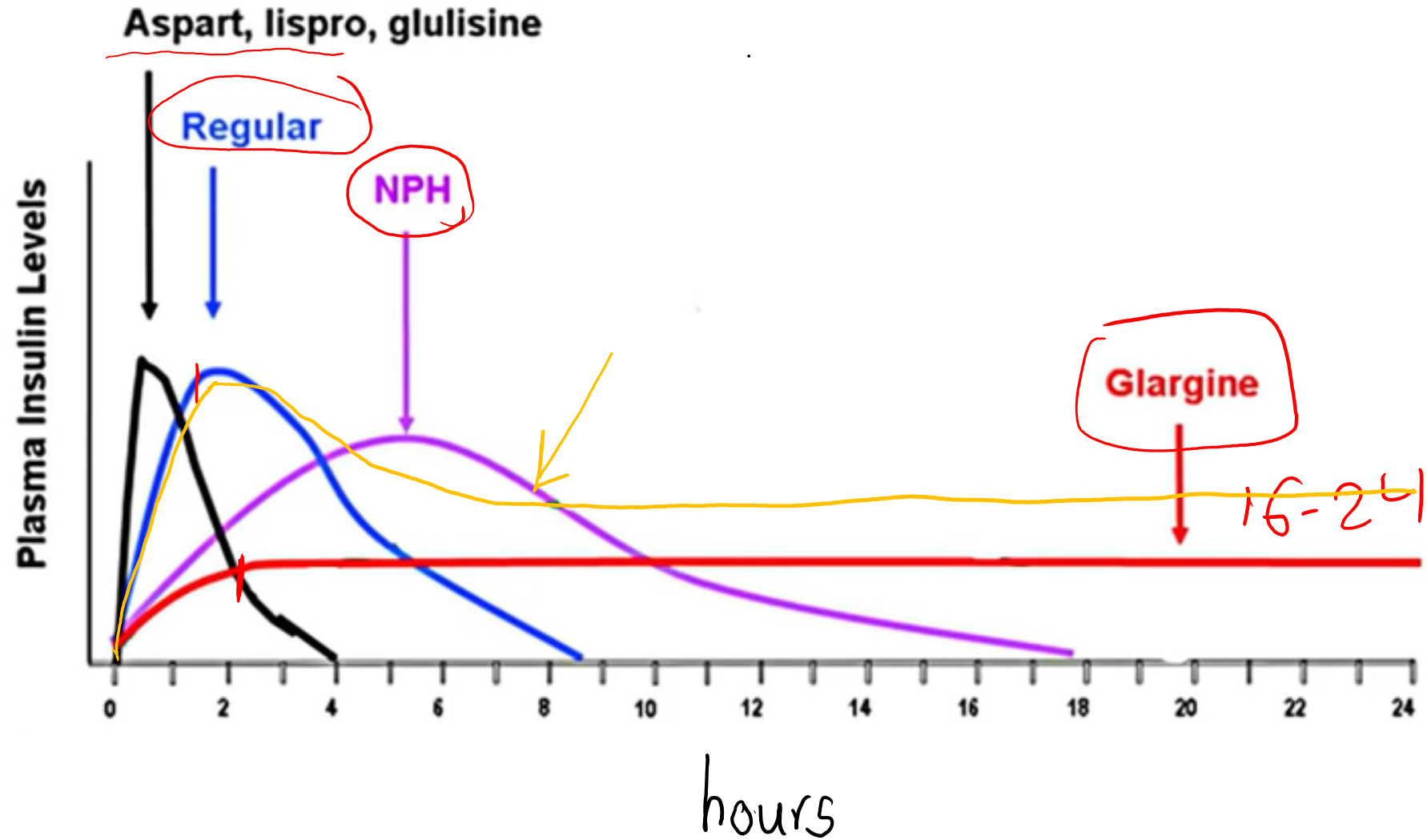
| preparations                       | Onset        | Duration     | Remarks                                    |
|------------------------------------|--------------|--------------|--|
| 7- Mixtard (30% regular + 70% NPH) | <u>30min</u> | <u>16 hr</u> | <u>S.C</u><br><u>Rapid + long duration</u> |

30% regular ←  
+  
70% NPH ←



## Mixtard insulin





- How do you administer insulin ??
  - **Dose** (starting ) 0.4u-0.5u /kg/day
  - **method of administration** by s.c  
(unless DKA given IV).

e.g. **ptn need 60u .. Two strategy:**

**1- 30u long acting once and 10u short acting before each Meal....or**

**2- 40u mixtard at mornings and 20u mixtard at evening.**

**another Auto-injection pump (lispro or aspart because same physiological secretion of insulin = within 5min)**



- who need insulin ?

**1- Type I**

**2- Type II (IR , 20% of them need insulin +oral drugs)**

**3- Type II with stress conditions**

- Surgery
- Infection
- pregnancy

**4- Diabetic Ketoacidosis**

**5- Hyperkalemia (insulin enter K into the cell. You must give Glucose with insulin to avoid hypoglycemia )**



# Insulin side effects

## ✓ Local:

- 1- SC lipodystrophy → Insulin Resistance.
- 2- Allergy & Arthus reaction (deposition of antigen/antibody complexes at localized site)



lipodystrophy

## ✓ Systemic:

- 1- Hypoglycemia due to too much insulin, too little food.



2- Insulin resistance

3- Hypokalemia


↓ K



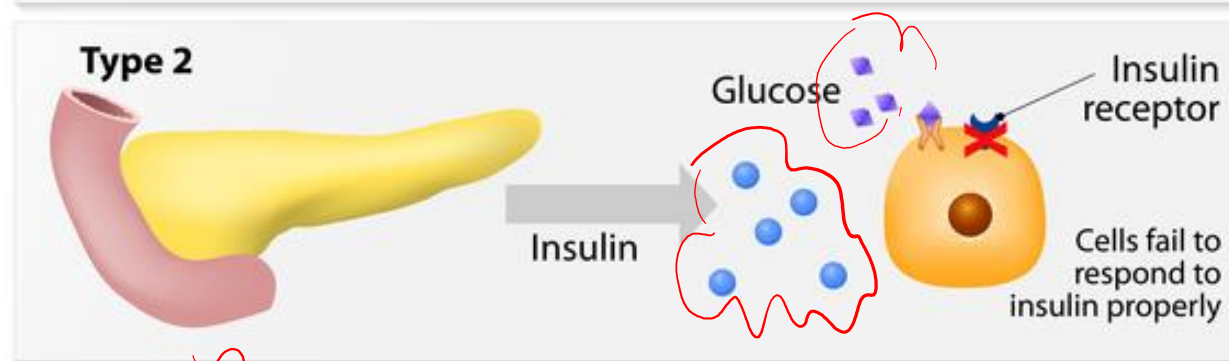
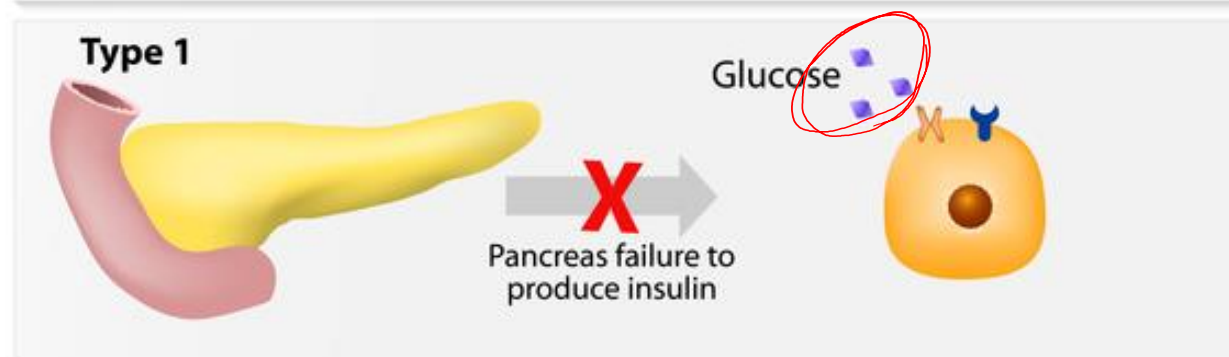
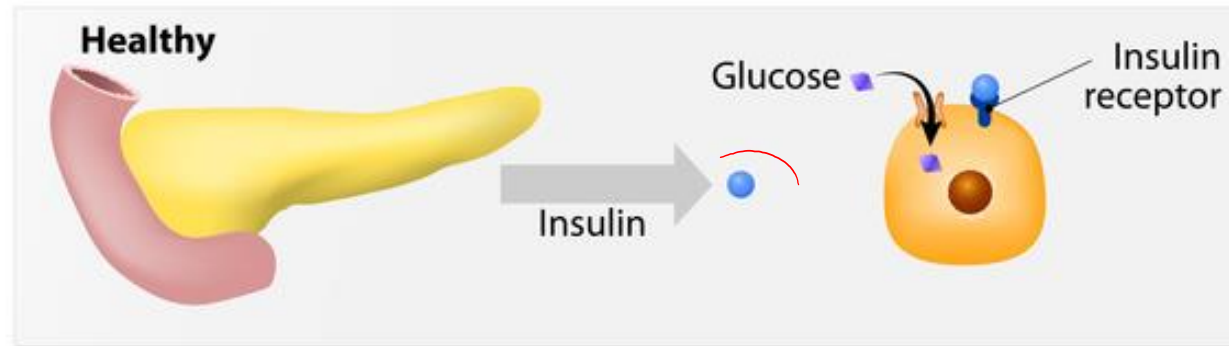


- what is the Insulin resistance?

**Insulin resistance:** failure of body cell to response to insulin either endogenous or exogenous insulin.

- Can **be sure** by measure insulin in blood ( > normal value 5-15U ).
- **Causes** : either by > 15
  - 1- **pre-receptor** (antibody to insulin) ✓
  - 2- **receptor** (down regulation of receptor = **Obesity**; infection; pregnancy; genetic )
  - 3- **post-receptor** (problem in tyrosine kinase...) 
  - 4- **local** (change site of administration)
- **Management:** by Diet; Metformin ; insulin sensitizer (TZD)





IR



# 3- Oral Antidiabetic drugs

for type II Diabetic patients

- ✓ **sulphonyl urea** ✓
- ✓ **meglitinide** ✓
- ✓ **Biguanide** ✓
- ✓ **thiozolidendion** ✓
- ✓ **starch blocker** ✓
- ✓ **Na-GLUT2 co- transporter inhibitor**



# 1- sulphonyl urea drugs

| generation                 | Drugs   | Remarks  |
|----------------------------|---|--|
| 1 <sup>st</sup> generation | <b>Chloropropamide;<br/>tolbutamide</b>                               | <b>Long duration 72hr<br/>(hypoglycemia); less<br/>potent ; adverse effect</b> |
| 2 <sup>nd</sup> generation | <b>Glibenclamid (<u>Daonil</u>),<br/>gliclazid (<u>Diamicron</u>)</b> | <b>6-12 hr<br/>High potent than 1st</b>  |
| 3 <sup>rd</sup> generation | <b>Glimepride (<u>Amaryl</u>)</b>                                     | <b><u>More potent ;</u></b>  |

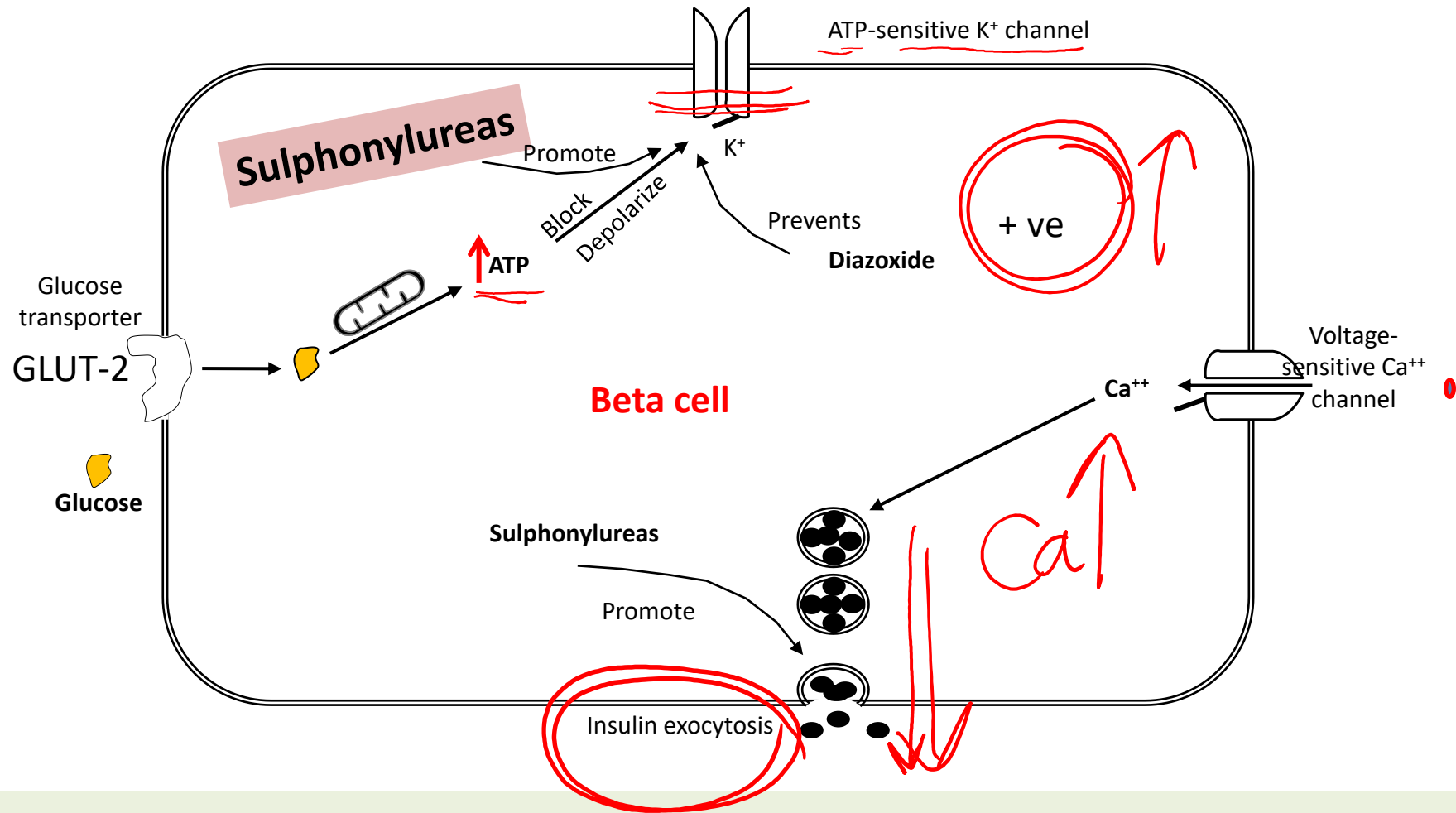


# Sulphonyl urea mechanisms of action

- 1 • promote insulin release by blocking of  $K_{ATP}$  channel
- 2 • Reducing serum glucagon levels.
- 3 • Increasing binding of insulin to target tissue receptors (↑ insulin sensitivity ).



+ BK of ATP sen K ch.



**sulphonyl urea inhibit K<sub>ATP</sub> → promote insulin release**





# Adverse effect of sulphonyl urea

- **hypoglycemia** (esp. with 1<sup>st</sup> generation )
- wt gain ✓ long t<sub>1/2</sub>
- pharmacological failure (exhaustion of beta cells)
- hypersensitivity reaction (sulpha)
- hepatotoxicity



# Sulphonylurea Drugs interaction

## Drugs potentiate the hypoglycemic effect:

- Microsomal enzyme inhibitors.
- **$\beta$ -blockers:** ↓ hepatic glycogenolysis
- **Salicylates:** displacement of sulphonylureas from plasma proteins.

## Drugs antagonize the hypoglycemic effect:

- Microsomal enzyme inducers.
- **$\beta$ -agonists:** ↑ hepatic glycogenolysis.
- **Thiazides** and **diazoxide:** they open ATP sensitive K<sup>+</sup> channels → ↓ insulin release and ↓ peripheral glucose utilization.
- Anti-insulin hormones: e.g. steroids and glucagon.



## 2- Meglitanides



- **Repaglinide & Nateglanide**
- same mechanism of sulphonyl urea ✓
- But has not sulphonyl gp
- Rapid acting & short duration (therefore take immediately before meal )
- alternative for ptn. has sensitivity for Sulphonyl urea
- main side effect is Hypoglycemia



# 3- Biguanides (metformin)

- mechanism of action of metformin
  - ✓ mainly by ↓ intestinal glucose absorption
  - ✓ ↑ insulin sensitivity
  - ✓ ↑ **anaerobic** glucose utilization (not depend on insulin) but produce lactic acid (problem)

**Biguanides** not cause hypoglycemia because not increase insulin release as sulphonylurea



# Who take **metformin**?

- **Type II diabetic** ✓
- Obesity ✓
- Polycystic ovary syndrome (multiple cyst causes infertility ... 6-10% of women.. insulin resistance and high androgen).



# Adverse effect of **metformin**?

- GIT upset, abdominal diarrhea, distension.
- Reducing vitamin B12 absorption (megaloblastic anaemia) →
- Due to anaerobic glycolysis → lactic acidosis in ptn with renal impairment, old age, with Alcohol

**NB:** metformin with iodinated contrast media is **contraindicated** >>> sever lactic acidosis and acute kidney failure.



# 3-Thiazolidenediones

**insulin sensitizer**



**rosiglitazone; pioglitazone**

These drugs activate **Peroxisome proliferator-activated receptor delta**

(*PPAR $\delta$* ) >> DNA transcription >>

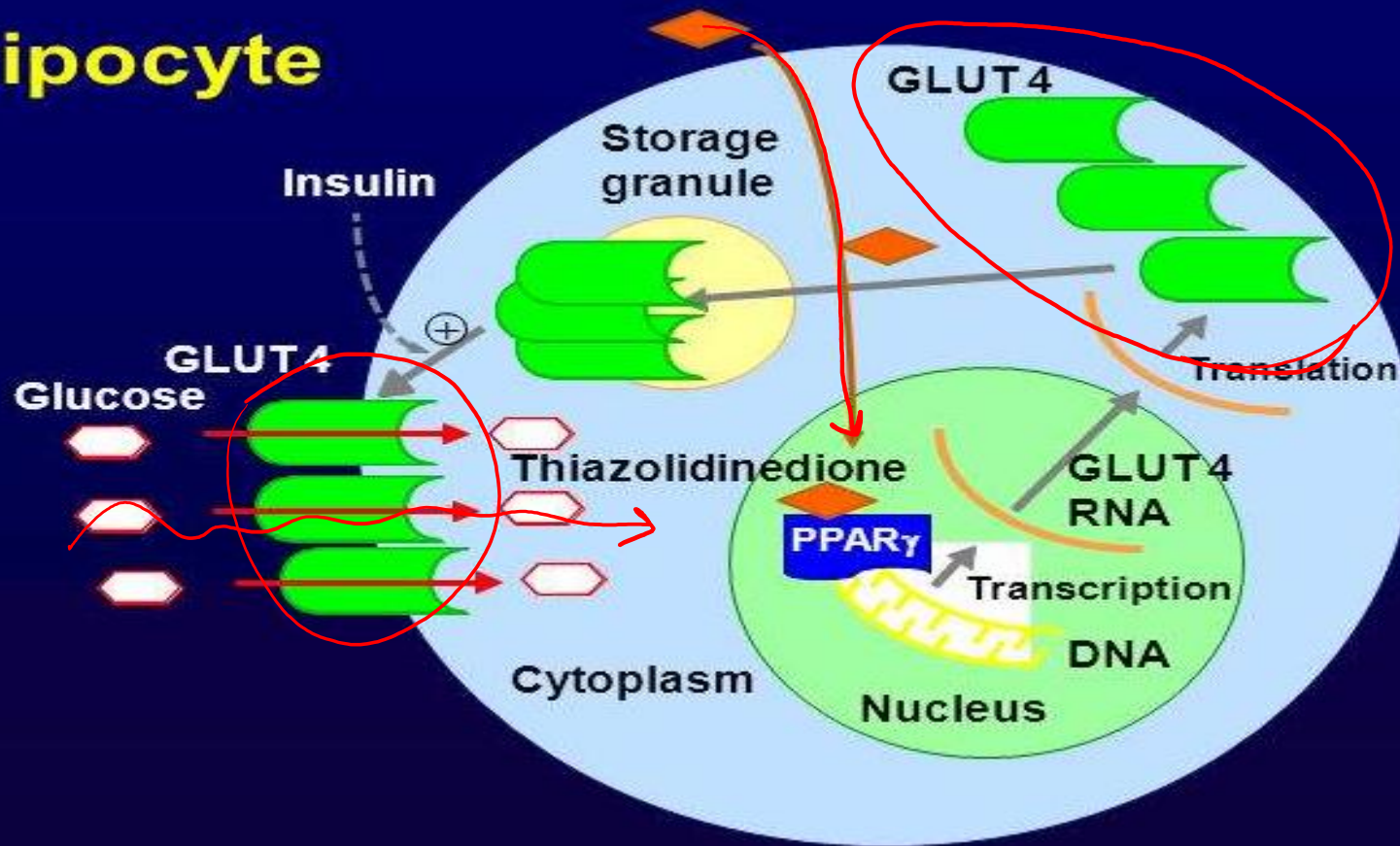
*produce more GLUT4 receptors* >>

increase insulin mediated glucose uptake by adipocyte





# Adipocyte



# Adverse effect of Thiazolidinedione

- hepatotoxic
- fluid retention
- wt. gain
- pioglitazone → may cause bladder cancer
- rosiglitazone → fracture of upper limb

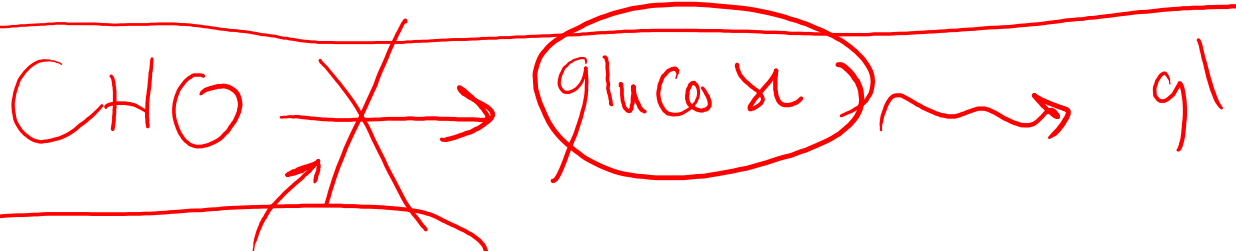
*liver f test*

CHF



# 4- $\alpha$ -Glucosidase Inhibitors

**Acarbose**



Inhibition of  $\alpha$ -glucosidase reduces postprandial rise of glucose resulting in an insulin sparing action.

**Adverse effect**



**Flatulence** (20-30%, caused by lower bowel undigested carbohydrate).



## 5- Na-GLUT2 co- transporter inhibitor

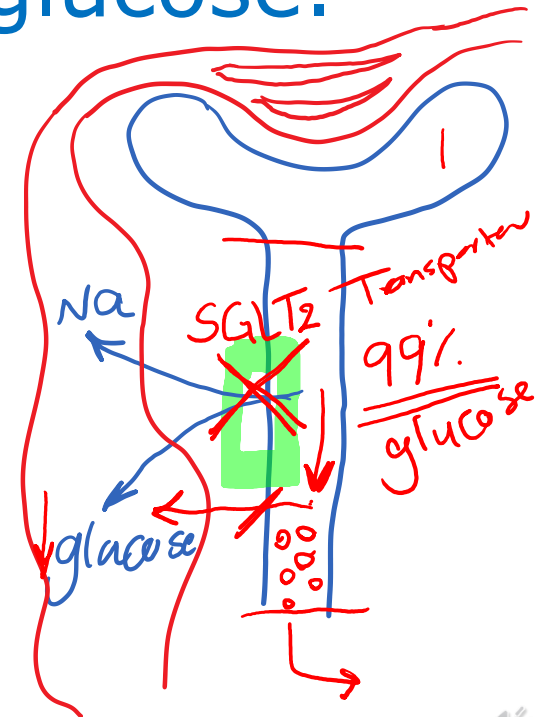
# Canagliflozin & Dapagliflozin

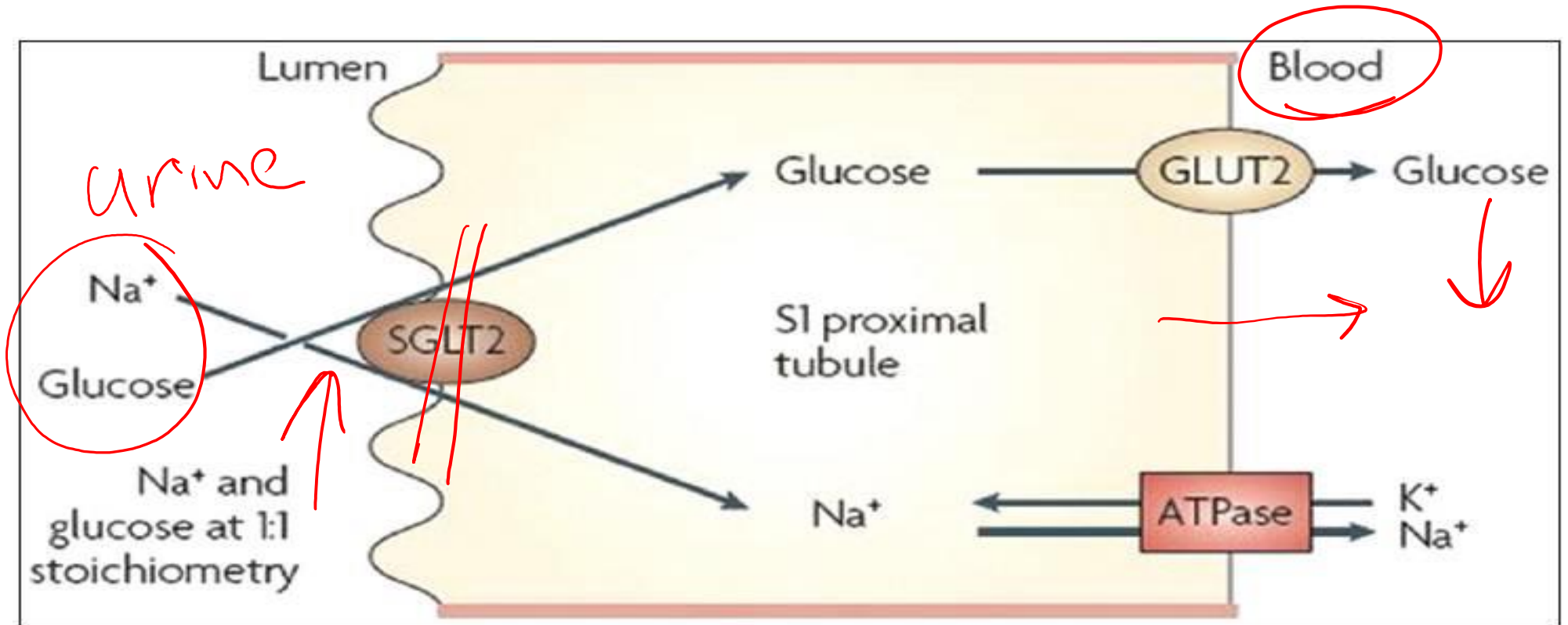
Inhibit **SGLT2** in proximal tubules →  
↓ reabsorption of glucose → ↓ blood glucose.

## Adverse effect

# Polyuria, UTI, Hypotension &

# ?? Bladder cancer



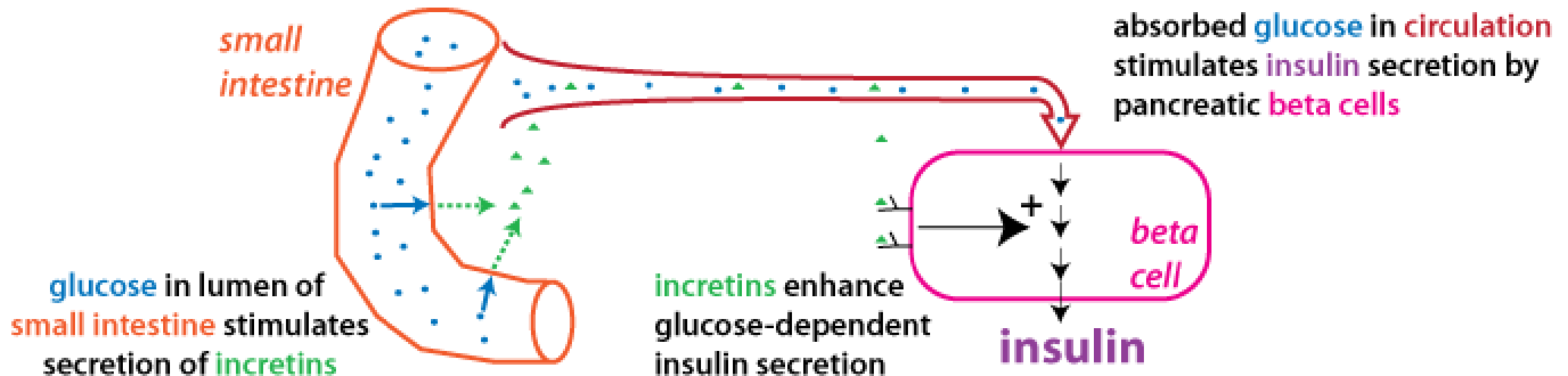


# New Antidiabetic drugs

- ✓ **incretin mimetic drugs**
- ✓ **DPP-4 inhibitor drugs**
- ✓ **amylin analogue**



**Incretin** peptides secreted from SI in response to CHO and stimulate beta cell to release insulin and inhibit glucagon and inhibit appetite and slows gastric emptying e.g. **Glucagon like peptide-1**





# 1-Incretin mimetic

- **GLP-1 (Glucagon like peptide-1 ) receptor agonist**
  - **Exenatide**, **injection**.  
**before meal twice a day**
  - **Liraglutide** **longer acting once weekly**

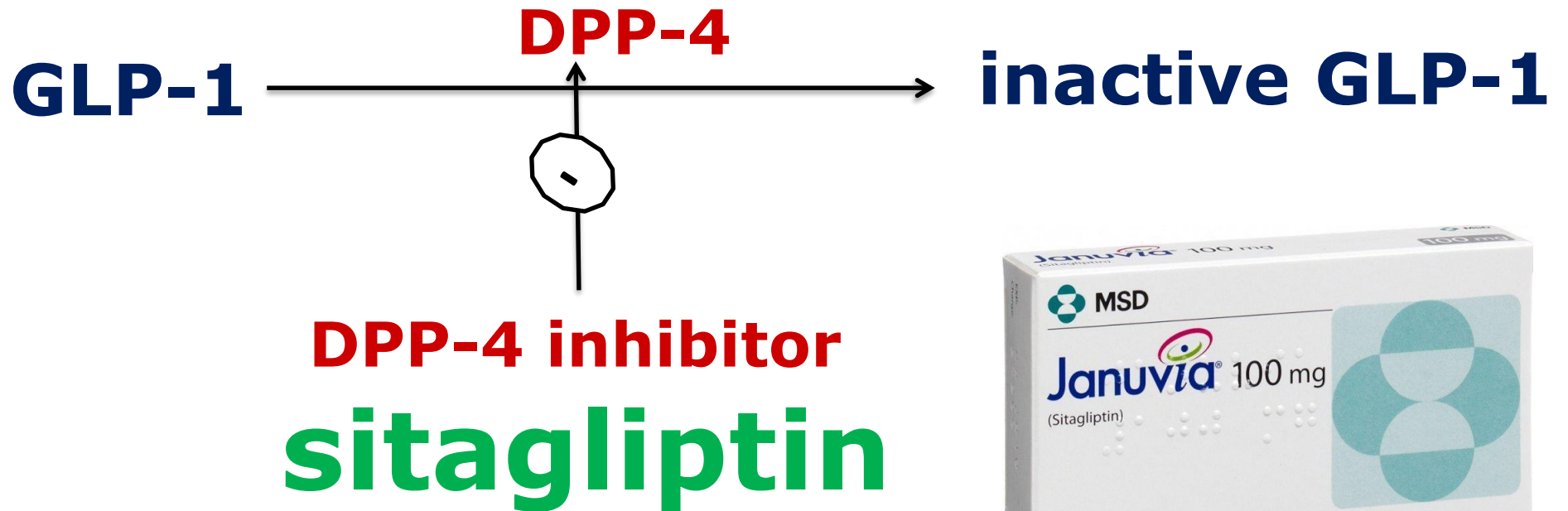


**Side effect :** **pancreatitis**



## 2- DPP-4 inhibitor

- DPP-4 (Dipeptidyl Peptidase -4) : enzyme responsible for incretin degradation 



# 3- amylin analogue

- **pramlinitid** act by increase insulin receptor sensitivity , ↑ satiety feeling , and ↓ gastric emptying rate.
- Therefore, can be given in combination with insulin.



# Diabetic complication



## Acute complication

- Hypoglycemia.. Coma
- Hyperglycemia .. DKA
- Hyperosmolar-hyperglycemia state (HHs)

## Chronic complication

- Neuropathy
- Retinopathy
- Nephropathy

# Hypoglycaemia

Hypoglycaemia caused by excessive insulin dosage, a missed or late meal or by excessive exercise.

Therefore, the diabetic should always carry quick-acting oral glucose tablets. The unconscious patient should be given 20 ml of **50% dextrose** i.v., together with **glucagon**. Prolonged severe hypoglycaemia reactions may require 10-20% dextrose infusions over 24-48 hours or longer, together with high-dose steroids, e.g. **dexamethasone** (2 mg i.m. 4 hourly) and 20% **mannitol** i.v. over 20 minutes, to reduce

**cerebral oedema**. Unfortunately, if treatment is delayed, some diabetics may develop irreversible brain damage and death may occur.

# Diabetic ketoacidosis

- **causes:** too much diet; inadequate ttt ; sever stress
  - **manifestation :**
    - ✓ sever dehydration due to osmotic diuresis
    - ✓ ketone bodies (acetone, acetoacetic acid; alpha ketoglutyric acid) in smell, ↓ pH (<7.3).
  - **management**
    - **I.V fluid** 4-5 L ; saline 0.9% .. **dose** : 2L in 1st 2 hr then 3L (0.5 L /1hr).
    - **Kcl** 20 meq in each liter of fluid for hypokalemia (fluid loss or dilution due to fluid replacement)
    - **Insulin** regular I.V, 0.1u/kg then 0.1u/kg infusion per hr until normal glucose level , serum electrolyte , pH
- NB:** if blood glucose become <250mg/dL → cerebral edema give G/S fluid instead of saline.
- **I.V Bicarbonate** if high acidosis.

# Hyperosmolar-hyperglycemic state

- State (no coma)
- old age .. Glucose > 600mg /dL ..Causes **osmotic diuresis only** → v. sever dehydration :loss 8-10 L of fluid (without loss of Na).
- **No ketone bodies**
- **pH > 7.3**
- Management
  - **Saline** 8-10 L in aggressive way
  - **insulin** in same way of DKA

**NB: MUST** saline before Insulin



# Neuropathy

- **Irreversible** nerve inflammation: high glucose for long time causes glucose bind with protein of body cell (nerve tissue).
- **sensory**: Numbness, tingling, back pain, leg pain.
- **Motor**; weakness
- **autonomic** : irregular heart beat , constipation , ED (in male).
- **management** : symptomatic
  - ✓ tight **glycemic control**
  - ✓ **duloxetine or pregabalin** (Lyrica).





Thank You  
For Your  
Attention