ENDOCRINE SYSTEM

Pharmacology

Lec. 7

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*ما ينطق به الدكتور من شرح سيكون باللون الاحمر
*وما يكون مهم في شرح الدكتور يكون باللون البنفسجي
*ما يكون مهم في السلايدات يكون بخطين أو بخط

Pancreatic Hormones

- **Insulin (β-cells); Glucagon (α-cells)**
- **Diabetes Mellitus**

- A disease characterized by high blood sugar level?

Ans: agree with this definition

- A disease characterized by insulin deficiency?

Ans: completely wrong

- A metabolic disorder manifested by abnormalities in CHO, lipid and protein metabolism

Diabetes's complications:

- **Diabetes is a major cause of heart disease and stroke**
- **Diabetes is the leading cause of kidney failure, nontraumatic lower-limb amputations, and new cases of blindness among adults in the United States**
- **Diabetes is the seventh leading cause of death in the United States**

It's considered a severe type

No.1 approach is lifestyle modification

- Types of DM (2 types):
- Type I; juvenile-onset; IDDM

Insulin dependent, patients have no secreted endogenous insulin

- 10-20% of diabetics
- Most commonly occurs in childhood or adolescence but may occur at any age
- Mainly affects children at an age 10-14 (not reported in kids less than 6 months)

Insulin is the preferred therapy of diabetes in pregnancy, whether it's gestational or the pregnant woman is already diabetic (diabetes doesn't prevent pregnancy)

Additional: (3rd type of diabetes) Gestational diabetes (GD) is a type of diabetes that develops in pregnancy when blood sugar levels get too high. Developing GD doesn't mean you already had diabetes before you got pregnant. The condition appears because of the pregnancy and diasppears after delivery.

- Type I DM pts have little or no pancreatic function
- Often pts present with ketoacidosis (ketone bodies;acetone. You can even smell it from their bodies)
- Characterized by downhill course-severe type of DM (mortality is high)
- Easy to diagnose (pts usually present C/O wt. loss; easy fatigability; polyuria; polydipsia; polyphagia…)

Insulin independent, the doctor disagrees with considering it so, as some patients are treated with insulin "بس ماشي"

- **Type II; maturity or adult-onset; IIDM**

- Represents 80-90% of diabetics
- Usually discovered accidentally (symptoms are not that prominent)after an age of 30-40 yrs
- Most pts are obese and it is more common in females as compared to males
- Pts have strong family Hx (genetic background)

- Most cases of type II have mild polyuria and fatigue

- Ketoacidosis is rare in pts with type II DM unless in certain circumstances of unusual stress or in patients who don't follow instructions!

- Insulin blood levels could be low, normal or high

- Insulin resistance is common (pre-receptor; receptor; post-receptor (which means overactivity of insulin receptors as a result to an elevation in blood glucose levels, due to overproduction of some hormones; catecholamines, GH) mechanisms.

Specific autoanitibodies could damage insulin or by receptor downregulation

- **Symptomatology:**

- Early

- Late

- **Early manifestations:**

Polyuria

Polydipsia

Polyphagia

Ketoacidosis (type I)

Increase in patients with high and not well-controlled blood glucose levels and will appear earlier in non-compliant patients

- **Late manifestations or complications:**

Atherosclerosis & IHD

Retinopathy

Nephropathy

Neuropathy

**** Normalization of blood glucose level corrects immediately early manifestations… late complications???**

Good normalization of blood glucose level will not totally inhibit late complications but it could delay the onset of these late manifestations.

- **Diagnosis:**

- Clinical manifestations

- Lab. Tests:

Random blood sugar (RBS)

Fasting blood sugar

Glycosylated hemoglobin (HbA1c)

Glucose tolerance test

Can measure the glucose level over the past 3 months

The glucose tolerance test is the test which gives the definite answer to whether or not the patient is diabetic.

- **Management:**

- Type I:

Diet — Mandatory / very important, the first approach

+ Insulin therapy — Mandatory / very important

- Type II:

There are special diets for diabetic patients defined by the doctor.

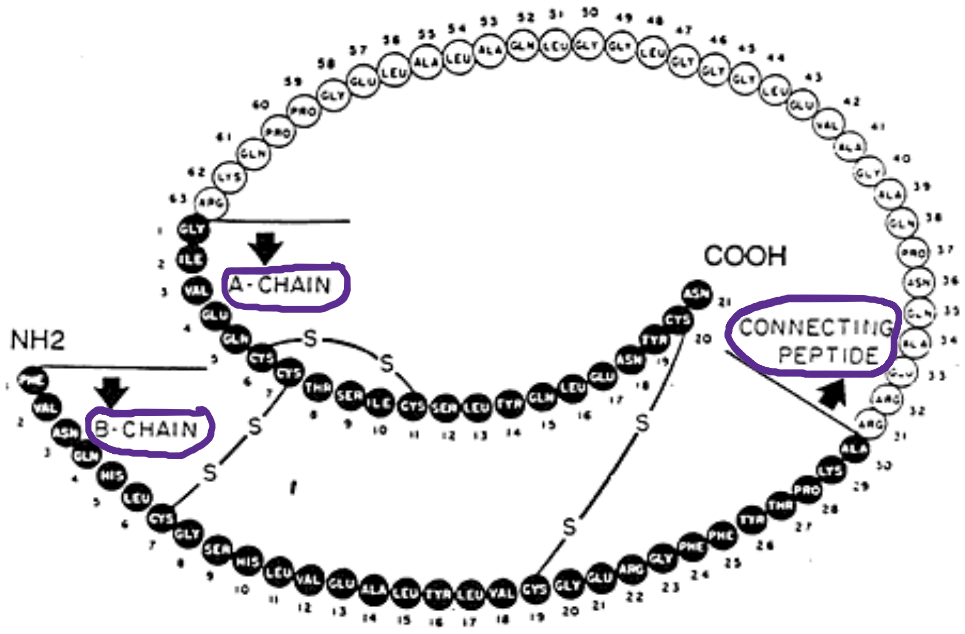
Diet + exercise

± Oral hypoglycemic agents

± Insulin

The sign ± means that people can take it or not depending on the case needs but diet and exercise are important despite compliance or not

Insulin



This is proinsulin, the precursor of insulin. It consists of insulin (2 chains in black) and a connecting 'C' peptide in white.

Insulin

Protein; A (21 aa) & B (30 aa) chains; disulfide bonds

- **Biosynthesis of insulin:**

Proinsulin has slight insulin-like activity (1/10 the potency of insulin)

Some cases of diabetes can be treated by recombinant proinsulin

C-peptide is devoid of any insulin-like activity

Insulin and C peptide are secreted normally in equal amounts, so each 1 insulin is accompanied by 1 C peptide (1:1)

C-peptide is used mainly to assess many pancreatic functions.

We can know the levels of insulin after treatment by measuring C-peptide, normal levels of it indicates that the pancreas (Beta cells) is functioning well, low levels mean low functioning and high levels mean overfunctioning which leads to suspicion of insulin resistance.

But not used for the diagnosis of diabetes.

Diabetes is diagnosed by glucose tolerance test.

- **Secretion of insulin:**

Ca^{++} dependent

[blood glucose] is the major regulator (low glucose 👉 low insulin , high glucose 👉 high insulin)

- **Factors/drugs ↑ release: (Some act directly by stimulating insulin secretion and some act indirectly by elevating glucose levels)**

1) Glucose;2) a.a's;3) F.A's;4) GH (recall from physiology that it causes insulin resistance through elevation of glucose levels) ;5) glucagon;6) ACTH;

7) Sulfonylureas ((hypoglycemic agent)) ;

8) β-adrenergics,9) cholinergic drugs…

- **Factors/drugs ↓ release (Doctor used them to induce diabetes in animals):**

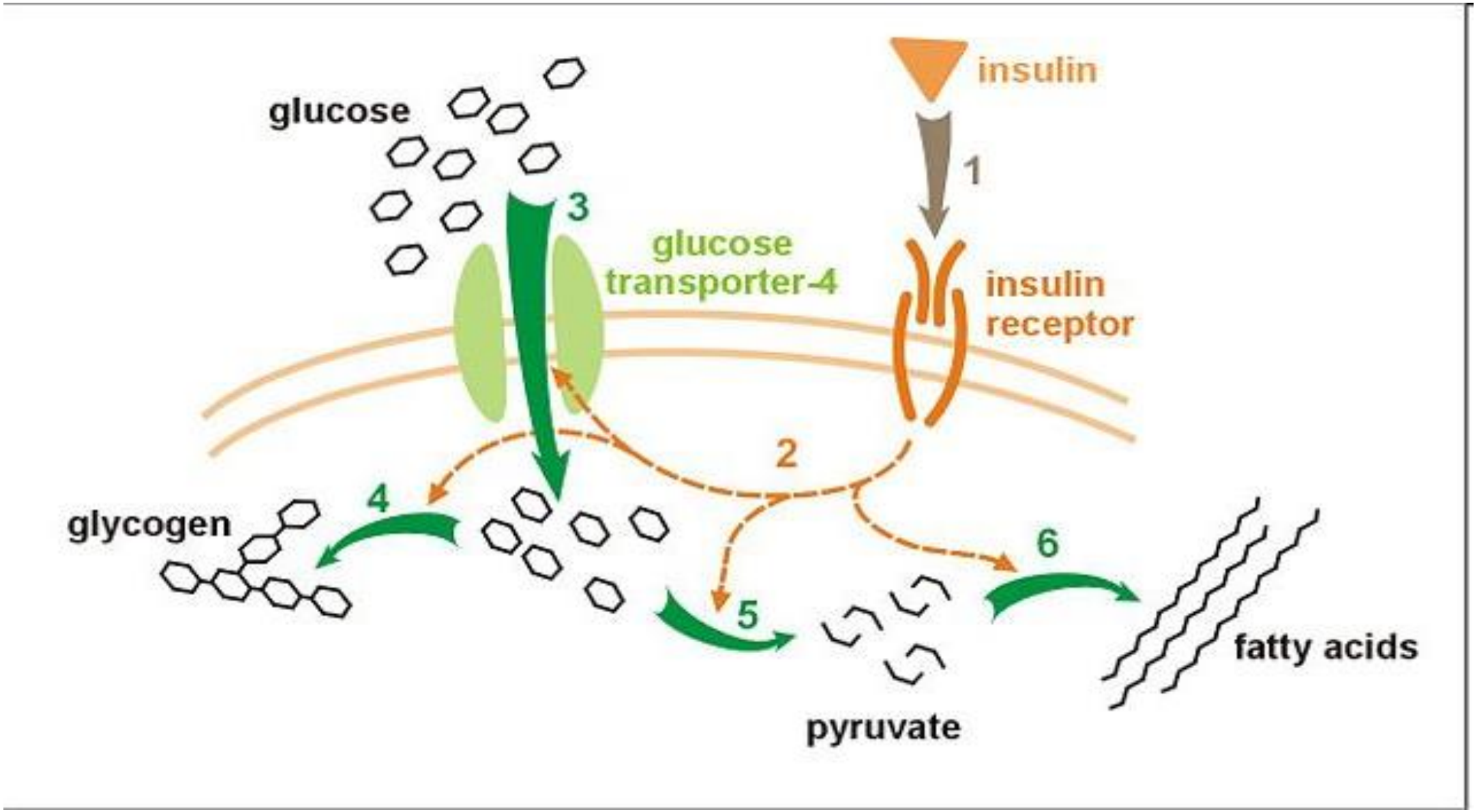
1)α-adrenergics;2) anticholinergics;3) phenytoin;

4) alloxan;5) streptozotocin (streptozocin) irreversibly damages beta cells, we could benefit from this feature by using it as an anti cancerous agent (insulinoma:tumor affecting beta cells) 😎

- **Insulin mechanism of action**

Effect of insulin on glucose uptake and metabolism. Insulin binds to its receptor leading to phosphorylation of insulin-receptor complex (1) which in turn starts many protein kinases activation cascades (2). These include: translocation of Glu transporter-4 to the plasma membrane and influx of glucose (3), glycogen synthesis (fuel of the cell) (4), glycolysis (5) and fatty acid synthesis (6).

No studies have shown the involvement of second messengers in Insulin's signaling


insulin
1
glucose
3
glucose
transporter-4
insulin
receptor
2
4
glycogen
6
5
fatty acids
pyruvate

- **Insulin effects:**

- ↑ glucose uptake or transport → muscles & adipocytes

- ↑ glucose oxidation by muscles

- ↓ hepatic gluconeogenesis

- ↑ hepatic glycogen synthesis and storage; ↓ glycogenolysis

- ↑ a.a uptake and protein synthesis by muscles and liver

- ↓ lipolysis

- ↓ ketogenesis

• Insulin preparations:

- **Natural (Not effective/Not used)**

Insulins of animal source are no more used and natural human insulin extracted from the pancreas is characterized by having low bioavailability and short $t_{1/2}$ due to problems with its stability

- Synthetic

rHI (recombinant human insulin) to all preparations are available

Insulins are classified according to duration of action (DOA)

They are used in insulin pumps

Don't memorize the onset of action and peak. But memorize 4 and 8 hrs of the DOA

** Ultra-rapid onset; very short acting:

	O (hr)	P (hr)	DOA (hr)
- Insulin Lispro (most common)	0.25-0.5	0.5-1	3-4
- Insulin Aspart	10-20 min		
- Insulin Glulisine			

** Rapid onset & short acting:

- Crystalline zinc (most common)	0.3-0.7	2-4	5-8
(regular; soluble; insulin injection)			
- Insulin zinc prompt	0.5-1	2-8	12-16
(Semilente)			

Regular insulin is widely used to treat severe DKA (Diabetic Ketoacidosis)

Don’t memorize any except for the number 24 and 36

** Intermediate onset & action:

- Insulin zinc suspension (Lente)	1-2	6-12	18-24
- Isophane insulin suspension (NPH; Humulin)	1-2	6-12	20-28

** Slow onset & action:

- Protamine zinc suspension	4-6	14-20	24-36
- Extended insulin zinc suspension (Ultralente)	4-6	16-18	24-36

Once they're injected subcutaneously and absorbed systematically, they produce sustained concentrations (steady states, don't reach the peak)

New insulins,less frequent incidence of hypoglycemia

Insulin Glargine	1-2	-	24-36
(peakless insulins)			
Insulin Detemir	1-2	-	24-36
** Mixed insulins:			
Int. + short	0.5-1	3-8	20-24
Int. + long	2-4	4-16	22-24

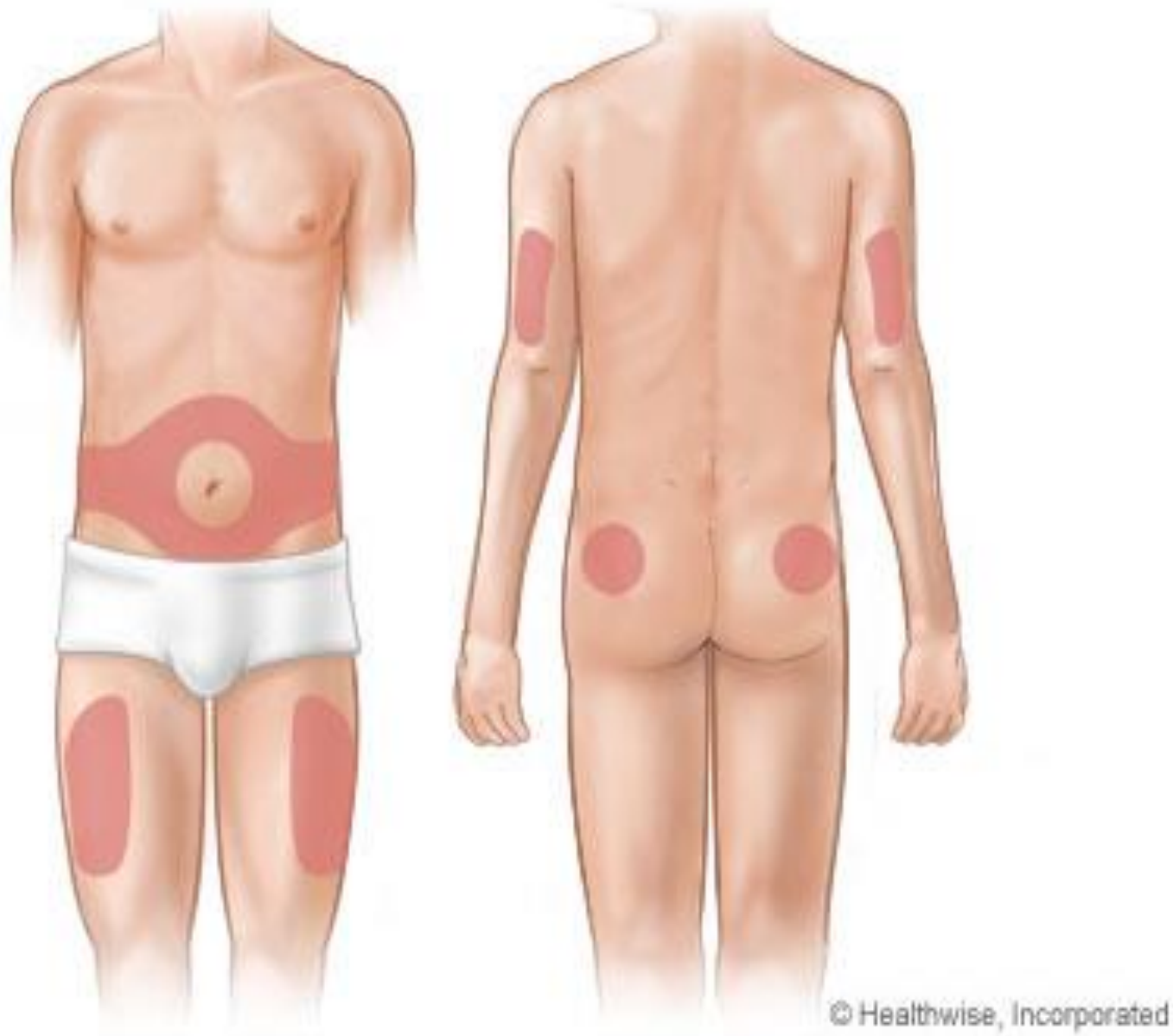
All insulin preparations are mainly given S.C except regular insulin, insulin Glulisine & insulin Aspart (SC & I.V)… Instructions to pt

- **Advantages of peakless insulins over intermediate-acting insulins:**

- **Constant circulating insulin over 24hr with no pronounced peak**

- **More safe than NPH & Lente insulins due to reduced risk of hypoglycemia (esp. nocturnal hypoglycemia)**

- Clear solution that does not require resuspension before administration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- **Factors affecting insulin absorption:**

- Site of injection:

abdomen > arm > buttocks > thigh

- Exercise = blood flow at site

- Depth of injection ↑ **bioavailability**

- Concentration and dose of insulin

- Addition of protamine or isophane to insulin preparations to form a complex delaying absorption and hence alter DOA

- **Insulin is metabolized in tissues (liver, muscles and kidneys) and metabolites are excreted renally**

Most widely used


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Pen injector, it is easy to use

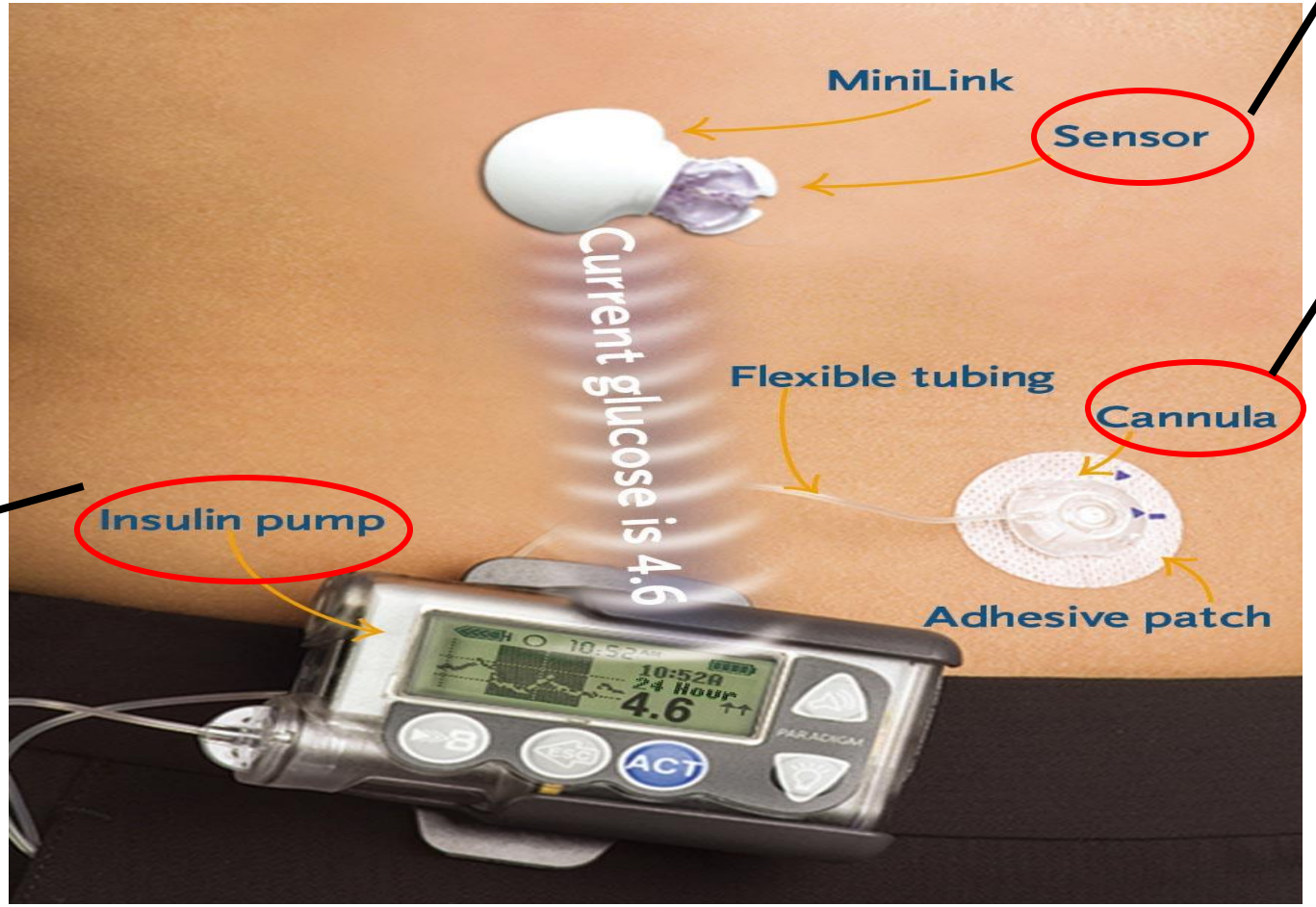
Pregnant women can take insulin

The jet injector, without a needle.

The jet injector

This system acts as an artificial pancreas. Very expensive !

1.Senses blood sugar levels



3. Delivers insulin according to blood glucose levels

2. Sends a message to the pump

We start with low doses and then measure glucose levels to adjust the dose accordingly

- **Dose of insulin:**

Insulin is given in units and its need varies tremendously

- **Side effects to Insulin therapy:**

- Hypoglycemia; ↑ sympathetic activity (instructions to pts)

- Lipodystrophy

- Allergy

- Induration (hardening of the skin, that's why we advice them to switch the injection site frequently ' the abdomen واسع يا جماعة')

**** Diabetic → to E.R with coma; management?!!!!**

The Most frequent and dangerous side effect to insulin therapy is HYPOGLYCEMIA
It will come in the exam Very important **بجيبه من ٣٨ سنة'**

** Diabetic → to E.R with coma; management?!!!!

Coma in diabetics could be due to 2 scenarios, let's see them throughly..

1. Hypoglycemia (very very dangerous)

2.Hyperglycemia(dangerous)

Now, we give them glucose ASAP , whether they're hypo or hyperglycemic because hypoglycemia is immediately fatal. Then we measure blood glucose levels , if it's hyperglycemia then we replace glucose with saline and regular insulin to lower blood glucose levels.Along with insulin, K+ 'Potassium' must be given because insulin increases the uptake of glucose and K+, thus K+ levels will decrease so we replace it.

Oral hypoglycemic agents (non-insulin therapy)

** Biguanides:

Metformin, Buformin

The Metformin is a Glucophage that is widely used

Possible MOA:

- ↓ CHO absorption
- ↓ hepatic gluconeogenesis; ↑ glycolysis
- ↓ glucagon release
- ↑ peripheral utilization of glucose
- ↑ response to insulin

These enhance the activity of Insulin and require insulin to act

Metformin is only effective in type II DM (effects require insulin)

?? Other uses: Obesity (↓ fat deposition) and polycystic ovarian syndrome (↓ androgen production by ovaries and adrenals)

Side effects:

- N & V, metallic taste

- Abdominal pain and diarrhea

- Hypoglycemia (rare)

- Lactic acidosis

- ↓ vitamin B_{12} absorption

** Sulfonylureas

- Classification

* First generation

Read only

	$t_{1/2}$	DOA	Metabolic fate
Tolbutamide	7	6-12	-
Chlorpropamide	34	24-72	+
Tolazamide	7	12-16	+
Acetohexamide	5	12-18	+

Read only

* Second generation

	$t_{1/2}$	DOA	Metabolic fate
Glyburide (Glibenclamide)	4	20-24	±
Glipizide	3	14-16	–
Gliclazide	8	10-15	–
Glimeperide	5	18-22	±

These are more potent so they’re more commonly used.

- **Sulfonylureas:**

- ↑ insulin release ‘main mechanism’ (insulin is in their pancreas, but not released due to some reasons) (major MOA) (Receptor-mediated effect)

- ↑ no. of β-cells, ↑ no. of insulin receptors

- ↑ peripheral cells sensitivity to insulin effect

- ↑ insulin binding to its receptors

- ↑ insulin affinity to its receptors

- ↓ hepatic gluconeogenesis

- ↓ glucagon release, ↑ somatostatin release…

- **Mechanism of action of sulfonylureas:**

Doctor didn't focus on it!

- **High affinity sulfonylurea receptors found on beta cells linked to ATP-ase sensitive K^+ ion channel**

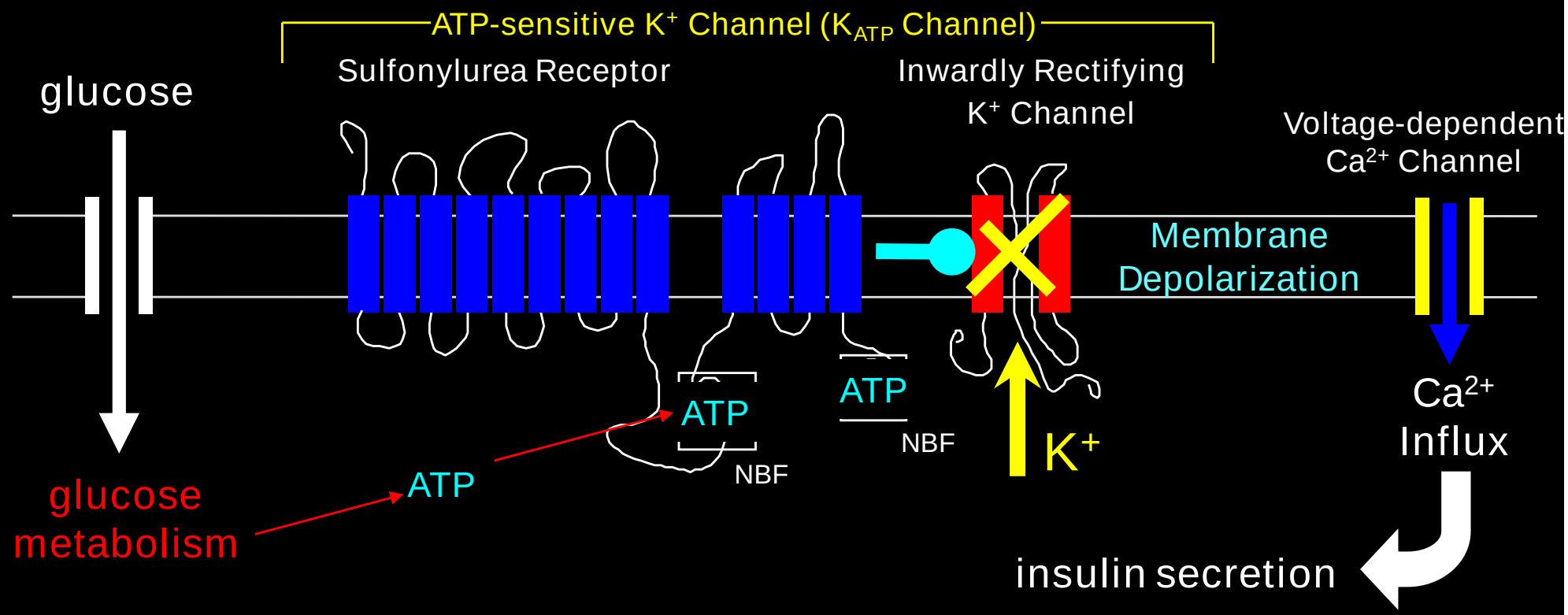
- **Following binding, voltage dependent Ca^{++} channels open in response to depolarization and allow influx of Ca^{++}**

- **Ca^{++} binds to Calmodulin which activates kinases that cause exocytosis of insulin containing secretory granules**

- **Beta cells sense glucose more efficiently, producing more insulin**

Calcium is required for insulin release.

K_{ATP} Channel Structure and Function



NBF
Nucleotide Binding Fold = site of ATP/ADP binding

Four copies of each subunit combine to form an active K_{ATP} channel

They bind to albumin, if the patient has to take them both, then you have to adjust the dose!

- Sulfonylureas differ in potency, bioavailability, DOA, tolerance, extent of protein binding and metabolic fate
- Drug-drug interactions (many):

Propranolol, sulfa drugs, oral anticoagulants, aspirin…etc
↑ effects of sulfonylureas

- Clinical uses to sulfonylureas:

- DM

- Nocturnal enuresis (Glyburide → ↑ ADH release)

It means bed wetting and is best managed by one of the synthetic analogues to ADH that is given intranasally

- **Side effects to sulfonylureas:**

- Hypoglycemia

- N & V, dizziness

- Allergy

- Agranulocytosis → **Additional: a condition in which the absolute neutrophil count (ANC) is less than 100 neutrophils per microliter of the blood**

- Hepatic dysfunction

- **Other orally effective drugs in DM:**

- α-glucosidase inhibitors

Acarbose; Miglitol (more potent)

Effective in type II DM

↓ CHO absorption

Inhibits α-glucosidase , an enzyme in the brush border of intestine responsible for breakdown of CHO, and hence ↑ glucose absorption

Such inhibitors ↓ fasting and postprandial hyperglycemia

اللهم نستودعك أهالي غزّة وفلسطين فانصرهم واحفظهم بعينك التي لا تنام، واربط على قلوبهم وأمدهم بجُندك وأنزل عليهم سكينتك وسخر لهم الأرض ومن عليها.

اللهم بقوتك، وبغوثك، وبغيرتك على حرماتك، وبحمايتك لمن احتمى بآياتك، نسألك يا الله يا سميع يا قريب، يا مجيب يا منتقم يا جبار، يا قهار يا شديد البطش، يا عظيم القهر يا من لا يعجزه قهر الجبابرة، ولا يعظم عليه هلاك المتمردين من الملوك والأكاسرة، أن تجعل كيد المحتلين في نحرهم، واجعل مكرهم عائداً إليهم.

اللهم اجعل للمرابطين النّصرة والعزّة والغلبة والقوة والهيبة في قلوب أعدائهم يا أكرم الأكرمين.