The Endocrine System

PHARMACOLOGY

☑ Sheet ☐ Slide ☐ Handout

Number:	9
Subject:	Anti-Diabetic drugs
Done By:	Lina Mansour+ Amani Sharia
Corrected by:	Heba Al-lala
Doctor:	Yacoub Irshaid

Date: 00/0/2016

Price:

(Slides , Record-sec1), only things written in **BOLD** were mentioned by the doctor.

Anti-Diabetic drugs

This topic is Very long, and it has been updated a lot. So, in this lecture the doctor will only explain things that need explanations. However, we will mention everything in the slides –everything is required-.

Pathophysiology

*I really copied the slides in this section(were not mention), important things are indicated (bold).

The endocrine pancreas in the human consists of islets of Langerhans.

Within the islets, at least four hormone producing cells are present that produce:

- ✓ Insulin.
  [promotes the uptake and storage of glucose and other small, energy containing molecules.]
- ✓ **Amylin**
  which modulates appetite, gastric emptying, and glucagon and insulin secretion. Suppresses endogenous production of glucose in the liver. The physiologic effect of amylin may be to mediate negative feedback inhibition of insulin secretion.
  →At pharmacologic doses, amylin:
  a. reduces glucagon secretion
  b. slows gastric emptying by a vagally medicated mechanism.
  c. decreases appetite by a central action.

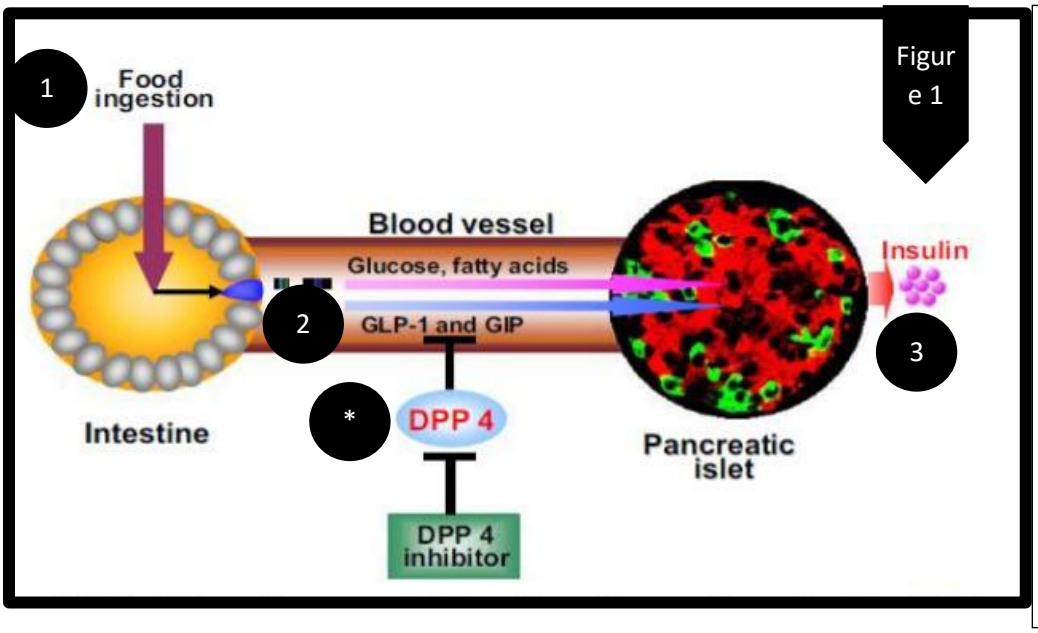
- ✓ Glucagon, mobilizes glucose from the liver by stimulating gluconeogenesis and glycogenolysis.
- ✓ Somatostatin, a universal inhibitor of secretory cells.
- ✓ Ghrelin, a peptide which increases pituitary growth hormone release.
- ✓ Pancreatic polypeptide, which facilitates digestive processes by yet unknown mechanism.

Glucagon-like peptide-1 (GLP-1) from the GIT:

figure 1

- ✓ Also called **incretin**
- ✓ It enhances insulin release in response to an ingested meal.
- ✓ It suppresses glucagon secretion.
- ✓ It delays gastric emptying.
- ✓ It decreases appetite.
- ✓ It is degraded by dipeptidyl peptidase-4 (DPP-4)

Note: in the figure you will notice sth. called GIP (Gastric inhibitory polypeptide or Glucose dependent insulino-tropic polypeptide), and actually this molecule along with GLP-1 are called collectively Incretins. Know more here.



Incretins Modulate Insulin secretion :

1:Ingestion of food.
2:food in gut stimulate incretin (GLP-1 , GIP) in blood vessels.
3: Incretins stimulate glucose-dependent Insulin secretion from the pancreas.
* : Incretins are subjected to degradation by DPP4 .

The counter-regulatory hormones

- ✓ Oppose the actions of insulin and prevent hypoglycemia, or produce hyperglycemia.
- ✓ These are :glucagon, epinephrine and norepinephrine,glucocorticoids and growth hormone

PPARγ (peroxisome proliferator activated receptor-γ)

- ✓ A nuclear receptor
- ✓ When activated It modulates the expression of the genes involved in:

a. lipid and glucose metabolism,

b. insulin signal transduction

c. adipocyte and other tissue differentiation.

ITS ACTVATION AND ACTION

Its activation by endogenous fatty acids, decreases serum fatty acid levels, increases lipogenesis in adipose tissue. The increased storage of fatty acids in adipose tissue allows other tissues-liver – to lower their fat content, lower their glucose production, and increase their insulin sensitivity.

Adenosine 5´- monophosphate activated protein kinase

In low-energy states (low ATP):The enzyme adenosine 5´- monophosphate activated protein kinase (AMPK) triggers a shift from anabolic to catabolic activities.
when this Kinase get activated?

- ✓ AMPK is activated by exercise, which increases muscle uptake of glucose to be used for energy production.

Action:

- ✓ Activated AMPK decreases glucose production and the synthesis of lipids and proteins by the liver.

Leptin

- ✓ It is secreted from adipocytes.(adipocytes are classified as endocrine tissue that secret adipokines , the most important adipokines is leptin)
- ✓ It suppresses appetite, which switches the body from an energy-accumulating state to a state of energy utilization.
- ✓ Insulin and leptin act in the brain as adiposity negative feedback signals.
- ✓ Insulin stimulates leptin secretion from adipose tissue.
- ✓ Leptin has the effect to normalize :hyperinsulinemia (reduce synthesis and secretion of insulin), and to increase insulin sensitivity, and thus corrects hyperglycemia.
- ✓ Lack of leptin (as in prolonged starvation)results in persistently increased appetite and suppression of energy-utilizingfunctions.

Antidiabetic Drugs

For type I DM we Use INSULIN primary. For type II DM we use Oral antidiabetic agents. However, 20% of DM type II patients also require Insulin. Knowing that The percentage of type I DM patients is 10%, that's make 30% of diabetic patients require "pure" insulin.

Oral antidiabetic agents

as said earlier these for type II DM. they are of many types:

- ✓ **Insulin secretagogues (stimulate Insulin secretion) : [Sulfonylureas, Meglitinides]**
- ✓ **Biguanides (manage Insulin resistance)**
- ✓ **Thiazolidinediones (manage Insulin resistance)**

- ✓ **α-Glucosidase inhibitors**

Others:

- ✓ **Amylin Analogues**
- ✓ **GLP-1 – based "incretin" therapies:**
  →GLP-1 analogues
  →DPP-4 inhibitors (drugs inhibit degradation of incretins)
- ✓ **Sodium-glucose Co-transporter 2(SGLT2) Inhibitors. The doctor thinks that this drug is foolish as it DO decrease glucose level in the blood but by increasing glucose level in urine (increase its execration), which is one of the causes that make us treat DM, we don't want Glucose in urine ,as a lot of Infections (UTIs) could occur (البكتيريا بتكيف).**
- ✓ **Other drugs are present.**

Now we will talk about each of these drugs in more details.

Insulin

Physiology : Insulin secretion figure2

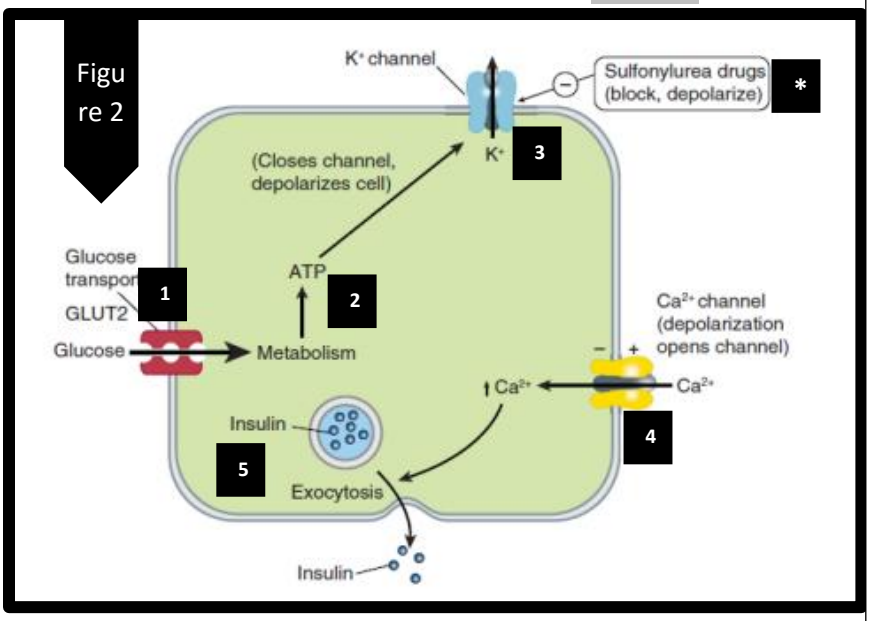


Figure 2: Insulin secretion
1:Glu. Enter beta cells of pancreas by GLUT2 transporter.
2: ATP is produced.
3:ATP close K+ channels , K+ will accumulate in the cell, the cell become +ve inside (depolarization)
4: Ca++ channels are opened.
5:Insulin is secreted by exocytosis

*** : Sulfonylurea mimic the action of ATP >>block K+ channels**
(all Insulin secretagogues do so) but they bind different place on this channel (not the ATP place)

(Mentioned in slides only)
Granules within the beta cells store the insulin in the form of crystals consisting of two atoms of zinc and six molecules of insulin.

The entire human pancreas contains up to 8 mg of insulin ~ 200 units.

Insulin secretion during the day

Insulin is always in our blood in certain quantities (base line), even when we are fasting, however insulin levels increase after meals.figure3

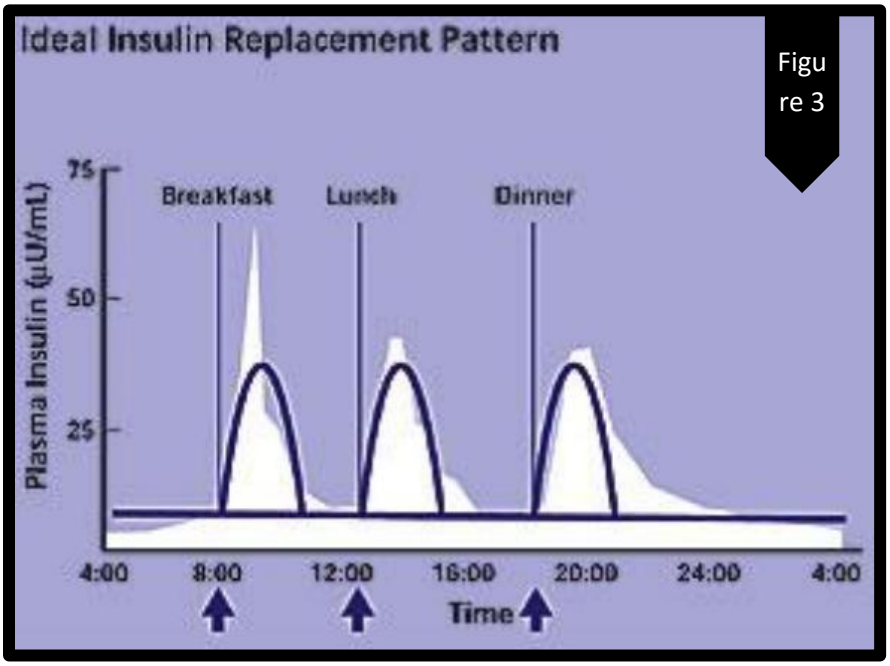


Figure 3: Insulin secretion during day .
Notice the base line , and the increase in insulin secretion after meals (arrows)

the solid lines represent the ideal release of insulin, while the white areas represent the actual physiological release.

the exact Mechanism of increase Insulin secretion after ingestion of food was mentioned earlier in this sheet figure1
[Food>> GLP-1 increase>>Insulin release]

by looking at figure3 we can conclude that insulin is secreted when needed. It's very High Yield to know this rhythm of secretion when treating Insulin deficient patients (you have to give them a base-line-Insulin (long acting Insulin) and short (or ultra-short) Insulin before each meal)

(things in slides only)

Secretion of Insulin is stimulated by:

1. Blood glucose and other sugars (mannose).
2. Amino acids (gluconeogenic amino acids,leucine, arginine).
3. High concentration of fatty acids.
4. **Parasympathetic activity.**
5. GLP-1, and glucose-dependent insulinotropic polypeptide (GIP).
6. Glucagon.
7. Cholecystokinin.
8. **β-adrenergic sympathetic activity.**
9. Drugs: sulfonylureas, meglitinide, nateglinide,isoproterenol, and acetylcholine.

Secretion of Insulin is inhibited by:

1. Insulin itself.
2. Somatostatin.
3. Leptin.
4. **α-Adrenergic sympathetic activity.**
5. Chronically elevated glucose.
6. Low concentrations of fatty acids.
7. Drugs: diazoxide, phenytoin, vinblastine, andcolchicine.

The doctor did mention this:

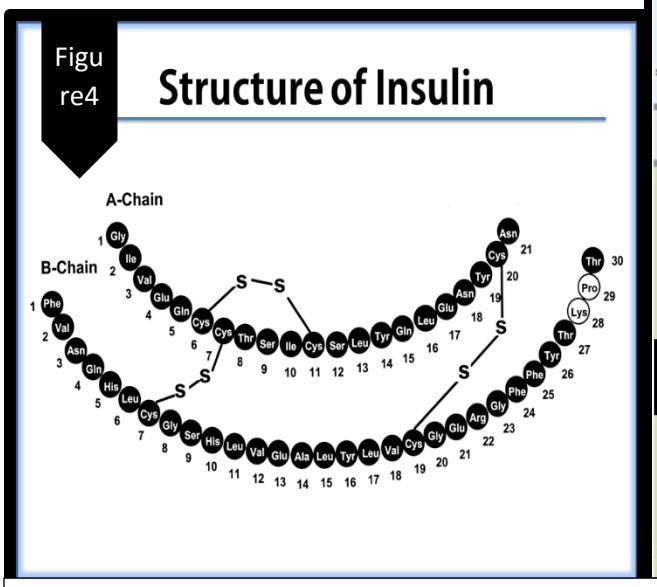
<u>The effect of Sympathetic and parasympathetic systems on Insulin secretion</u>

the parasympathetic system leads to stimulation of insulin secretion.
the sympathetic system may lead to stimulation or inhibition of insulin secretion , as follows:

- ✓ **if beta receptors were activated >>stimulation of insulin**
- ✓ **if alpha receptors were activated>> inhibition of insulin**

but actually (in general) if you stimulate the sympathetic system the dominant effect is inhibition of insulin secretion by the pancreas (when stimulating the Nerves) but say u are treating an asthma patient and u gave him B agonist (here u are not stimulating the nerves) >> then a net effect of insulin stimulation will occur. while if u give a patient alpha agonist the Insulin secretion is Inhibited. But collectively sympathetic system inhibits insulin secretion.

Insulin structure and its receptor



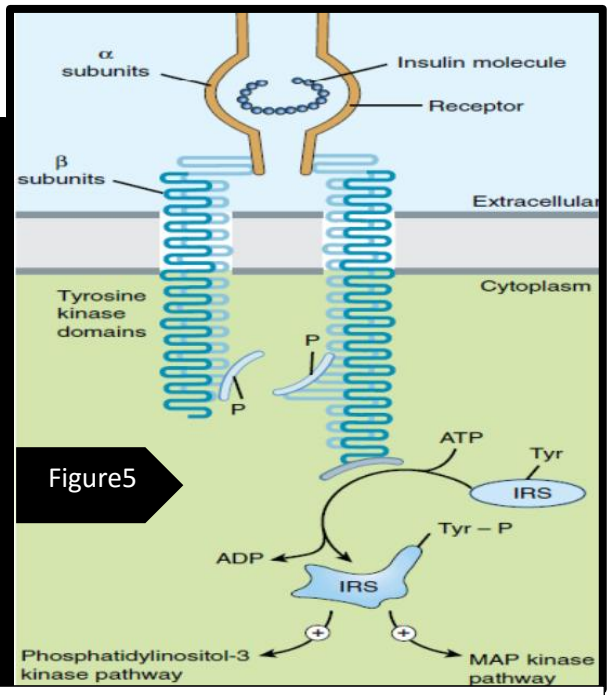


Figure4 : Insulin structure, a heterodimer protein consist of alpha and beta chains connected by 3 disulfide bridges. (insulin used to be 4 chains but it's been lysed)
figure5 : Insulin receptor, a tetramer consist of 2 beta domains (span membrane) and 2 alpha domains (outer /bind insulin). After binding of Insulin, the receptor is auto phosphorylated , and then it phosphorylate IRS (insulin receptor substrates) which will end by MAP Kinase pathway or IP3 Kinase pathway ..Notice how IRS are phosphorylated at Tyrosine residues.

Insulin Receptors:

- ✓ Found in the membranes of most tissues.
- ✓ Consist of 2 covalently linked heterodimers, each containing an α subunit, which is entirely extracellular, and constitutes the recognition site; and a β subunit that spans the membrane and contains tyrosine kinase.

Mechanismfigure5

Binding of insulin to α subunits activates the receptor through conformational change which facilitates mutual phosphorylation of tyrosine residues on the β subunits and tyrosine kinase activity directed at cytoplasmic proteins, called insulin receptor substrates (IRS). After tyrosine phosphorylation at several critical sites, the IRS molecules activate other kinases subserving energy metabolism -such as phosphatidylinositol-3kinase which produces further phosphorylation. Alternatively, IRS may stimulate an adaptor protein such as growth factor receptor binding protein-2 which translates the insulin signal to a guanine nucleotide releasing factor that ultimately activates the mitogen activated protein kinase (MAPK) system.
[Mitogen: is related to mitosis "cell division" remember Insulin is a growth factor]

This network of phosphorylation within the cells represents insulin's second message [Note: we consider phosphorylation as second messanger , just like cAMP , Ca++, cGMP..] and result in multiple effects, including translocation of glucose transporters (especially GLUT 4) to the cell membrane.

Action of insulin (post receptor binding):

1. Glucose uptake..this is obtained by inserting glucose transporters at the cell membrane.

2. Increased glycogen synthase activity and increased glycogen formation.(remember the glucose is trapped in cells, so don't we store it as glycogen)

3. Multiple effects on protein synthesis, lipolysis and lipogenesis.

Insulin act via both lipolysis and lipogenesis, HOW COME?!
the key point to understand this is to know that each of these actions occur in different places.
Lipolysis occurin BLOOD as insulin will hydrolyze lipid present in lipoproteins in plasma, converting them to free FAs -this action is mediated by lipase stimulation -now these FA are taken by the cells of the adipose tissue. In CELLs these FAs are re-built to TAG (fat)>>lipogenesis.

Actually this thing is much more complicated as the insulin action on fat overlap with insulin action on glucose. For example, when Insulin mediate lipogenesis (ie. I want to build TAG in adipocytes : TAG= 3 FA + P-glycerol)FA are obtained from the hydrolysis of lipoproteins that occur in the blood –mentioned earlier- and glycerol is synthesized from glucose that Insulin mediate its trapping in cells earlier.
Note : when hydrolyzing lipoproteins we are lowering the content of Lipoproteins in the liver and muscles, this make these tissues <u>more sensitive</u> to Insulin..(Practically this point is very important)

4. Activation of transcription factors that enhance DNA synthesis, cell growth and division.

Notes :

- ✓ **Glucocorticoids lower the affinity of insulin to its receptors. [Recall : counter-regulatory hormones mentioned earlier]**
- ✓ Growth hormone in excess increases this affinity (slightly).
- ✓ **We said early that Tyrosine residues of IRS are phosphorylated, but what if other phosphorylatable residues (like serine and threonine) got phosphorylated.**
  Actually aberrant serine and threonine phosphorylation of β subunits or IRS molecules may result in insulin resistance and functional receptor down regulation.

- ✓ **[recall down regulation :reduction of the number of active receptors]**

Insulin protein figure4was extracted from animals, but now human insulin is available thanks to Recombinant DNA technology. But because first it was obtained from animals, they tend to use the "Unit of activity " system to measure how much insulin they obtained, not by "mg".. and they still use it tell now but it's more standardize [each 1 mg of insulin has 28 unit of activity]

Insulin Degradation (hepatic and renal)

- ✓ The liver clears 60% of endogenous insulin.(metabolized)
- ✓ The kidney removes 35-40% of endogenous insulin.(execrated)
  [so endogenous "physiological" insulin is metabolized more than excreted]
- ✓ In insulin-treated diabetics receiving subcutaneous insulin injections, this ratio is Reversed.
  [exogenous Insulin is excreted more than metabolized]
- ✓ t½ of circulating insulin is 3-5 minutes. But the duration of action is much longer, this depends on the sequence of events that occur post receptor action.

Again,

Action of Insulin summarized in table1 shown in figure6 (slides only)

I. <u>In the liver</u>:
   1. Trapping of glucose in hepatocytes which enhances glycogen synthesis, glycolysis, and fatty acid synthesis.
   2. Inhibition of glycogenolysis and gluconeogenesis enhance the anabolic processes.

II. <u>In skeletal muscle and adipose tissue</u>:
   Facilitates the movement of glucose into thecell.

III. In skeletal muscle:

1. Promotes glycogen synthesis.
2. Increases amino acid uptake
3. Stimulates protein synthesis.

IV. In adipose tissue:

Hydrolysis of triglycerides from circulating lipoproteins and uptake into fat cells wherethey are stored as triglyceride

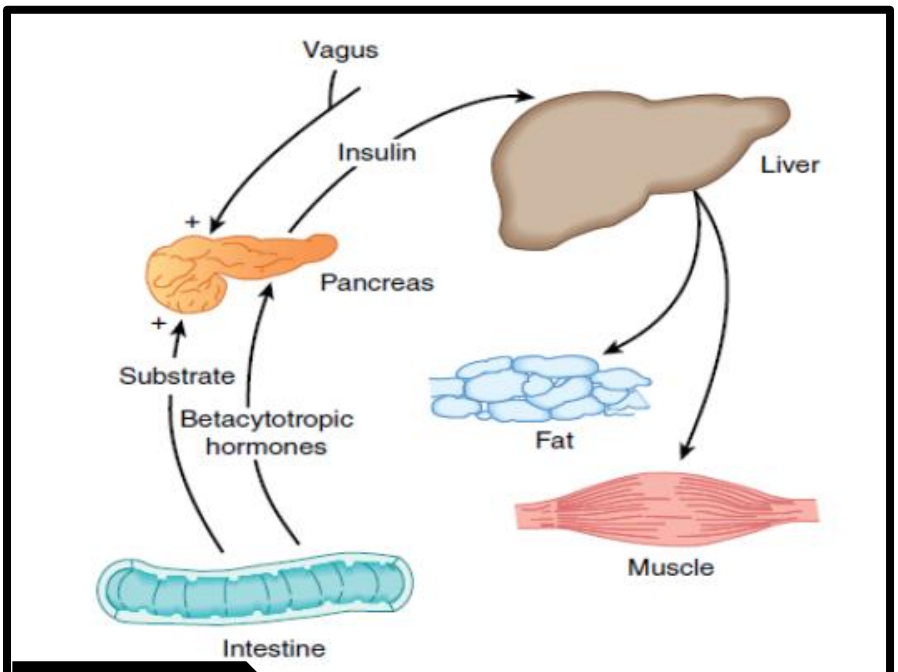


Figure 6 Insulin promotes synthesis (from circulating nutrients) and storage of glycogen, triglycerides, and protein in its major target tissues: liver, fat, and muscle. The release of insulin from the pancreas is stimulated by increased blood glucose, incretins, vagal nerve stimulation, and other factors (see text).

Table1 **Endocrine effects of insulin.**

Effect on liver:
Reversal of catabolic features of insulin deficiency
Inhibits glycogenolysis
Inhibits conversion of fatty acids and amino acids to keto acids
Inhibits conversion of amino acids to glucose
Anabolic action
Promotes glucose storage as glycogen (induces glucokinase and glycogen synthase, inhibits phosphorylase)
Increases triglyceride synthesis and very-low-density lipoprotein formation
Effect on muscle:
Increased protein synthesis
Increases amino acid transport
Increases ribosomal protein synthesis
Increased glycogen synthesis
Increases glucose transport
Induces glycogen synthase and inhibits phosphorylase
Effect on adipose tissue:
Increased triglyceride storage
Lipoprotein lipase is induced and activated by insulin to hydrolyze triglycerides from lipoproteins
Glucose transport into cell provides glycerol phosphate to permit esterification of fatty acids supplied by lipoprotein transport
Intracellular lipase is inhibited by insulin

Insulin Preparations

Now we go to insulin preparations, insulin preparations available changed in the last 15-20 years, in the past choices did not give us optimal therapy, now we have choices that you can optimize insulin use,, so there's no excuse for the doctor or the patient to not control diabetes very well…

- ☒ **In the past: - Regular (short acting) - Intermediate acting - Long acting**
- ☒ **Nowadays we have:**

►1. Rapid-acting insulin "Ultra short acting"(very fast onset & short duration): PEAK: 1 HOUR

A. Insulin lispro B. Insulin aspart C. Insulin glulisine

We want to know from where do the names came from? Insulin has 2 peptides alpha and beta, amino acids in them are numbered in a constant way, we know their order and names.

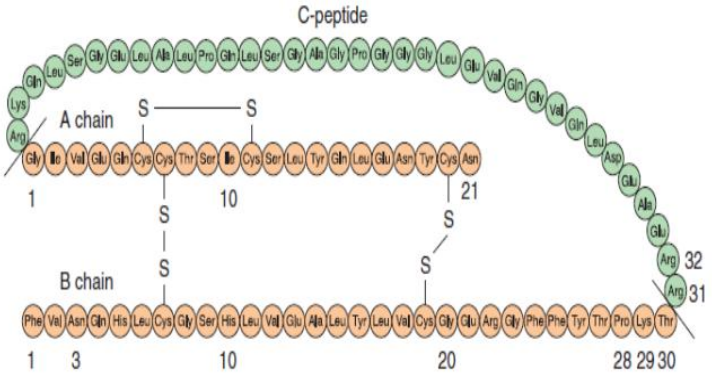


FIGURE 41-1 Structure of human proinsulin (C-peptide plus A and B chains) and insulin. Insulin is shown as the shaded (orange color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for the rapid-acting insulin analogs (aspart, lispro, and glulisine) and long-acting insulin analogs (glargine and detemir) are discussed in the text.

-INSULIN LISPRO: we EXCHANDED the position of lysine (29) and proline (28) (proline in the place of lysine and lysine on the place of proline).

-INSULIN ASPART: we removed an amino acid (proline) and put aspartic acid in its place (CHANGE not exchange).

- INSULIN GLULISINE: by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29.

***All of these are similar in: - They are rapid acting - The affinity of the receptor is the same and action and function of insulin is the same,, it ONLY made it faster (rapid-acting).**

♦Peak: 1 hr→ so food is still in the body at peak time → no hypoglycemia

♦The rapid-acting insulins permit more physiologic prandial insulin replacement.

***prandial: with meals *postprandial: after meals**

In the graph of insulin secretion we said we have to mimic physiologic insulin… so we always need basal insulin secretion, but with each meal we have to give insulin.

-Ultra-short (Rapid) acting is the most suitable to mimic real insulin, why? After injection within 10-15 min patient can eat because insulin will be ready at meal time.

♦They allow insulin to be taken immediately before the meal without sacrificing glucose control.

- Regular insulin which we used in the past, had to be taken 30 min before the meal; so when we eat and glucose raises, insulin had enough time to enter the body.

- What happens If we take Regular insulin immediately before meal?

we will have prandial hyperglycemia, why? because insulin did not have enough time to enter the body…

-Ultra-short (Rapid) acting insulin can be taken just before the meal.

♦ They have the lowest variability of absorption of all available commercial insulins.

-There is no variation in absorption between patients. The variation is very small.

♦Their duration of action is rarely more than 4- 5 hours, which decreases the risk of late postmeal hypoglycemia.

Patients using insulin in the past, always suffered from episodes of hyperglycemia or hypoglycemia through the day (not well controlled), <u>nowadays</u> we have little hypoglycemia? because duration of action is short.

♦They are preferred for use in continuous subcutaneous insulin infusion devices.

♦Insulin Pumps (like lispro and aspart) are the best, we have two types of pumps:

1)pumps that give regular doses

2)pumps that give dose according to glucose in blood(has sensor), the problem with this type is that:

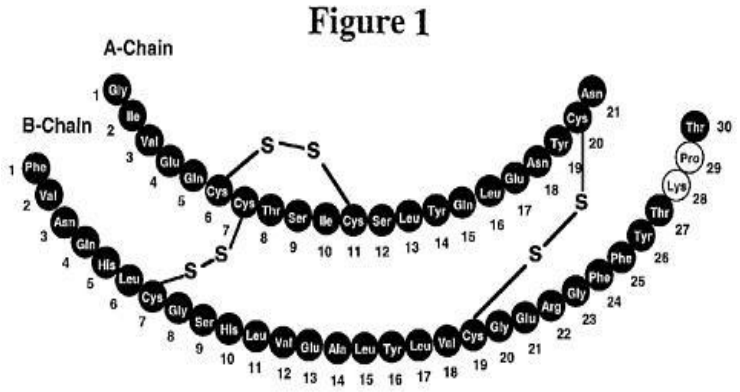
1-it needs someone smart enough to program it

2-people who work hard (like building houses,…) can hit and move the pump out of place so it will not release insulin

(hyperglycemia→ coma → death)

A) Insulin lispro is produced by recombinant technology, with 2 amino acids near the carboxy terminal of B chain have been **reversed (تبديل)** in position (**proline** at position **B28** has been moved to **B29**, and **lysine** at position **B29** has been moved to **B28**).

Figure 1



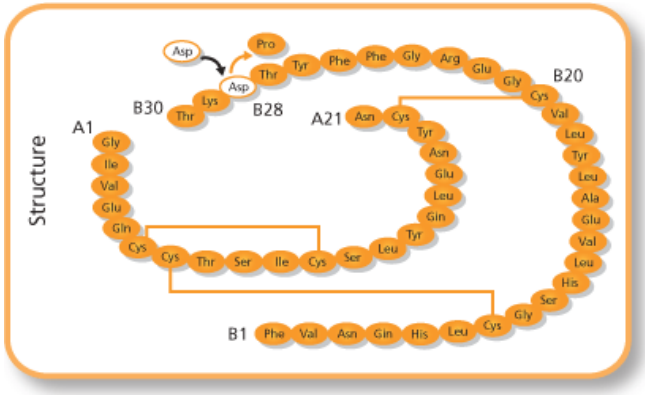
1. This change does not interfere with binding to insulin receptor, insulin's circulating half life, or its immunogenicity.

2. **The advantage (doctor said you should read all of this)** of this analog is its very low propensity – in contrast to human insulin – to self-associate in antiparallel fashion and form dimers.

3. To enhance shelf-life it is stabilized into hexamers by a cresol preservative, which quickly dissociate into monomers after subcutaneous injection.

4. Onset of action 5-15 minutes, peak activity 1 hour.

B) Insulin aspart is a **substituted (تغيير وليس تبديل) B28 proline** with a negatively charged **aspartic acid**.

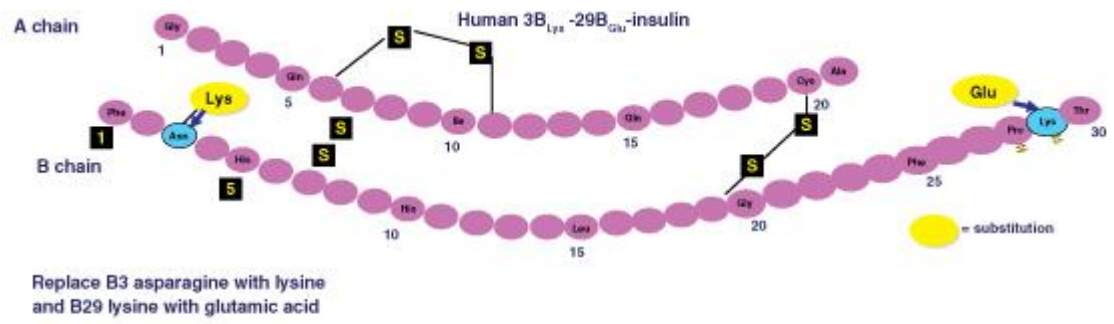


1. This modification reduces the normal ProB28 and GlyB23 monomer-monomer interaction, thereby inhibiting insulin self aggregation.

2. Its absorption and activity profile is similar to insulin lispro.

3. It has similar binding, activity, mitogenicity characteristics and immunogenicity to regular insulin.

C) Insulin glulisineis formulated by substituting a lysine for asparagine at B3 and glutamic acid for lysine at B29.



Adapted from Becker RH. Diabetes Technol Ther 2007;9:109-21. Reproduced with permission.

- Its absorption, action and immunologic characteristics are similar to the above.

►2. Short-acting insulin (rapid onset): (Regular Insulin)

(زمان لكن لا يزال يستعمل)

♦**Still used**

♦It is a short-acting soluble crystalline zinc insulin made by **recombinant DNA technique (human insulin)**.

♦**Effects appear within 30 min, peak 2-3 hours** after sc injection and **Duration of action : last for 5-8 hours.**

♦In high concentrations (in vials), it self-aggregates in an antiparallel fashion to form dimers that stabilize around zinc ions to create insulin hexamers.

♦After sc injection it dissociates ultimately to monomers.

♦**If administered at meal times, blood glucose rises faster than insulin → early postprandial hyperglycemia and an increased risk of late postprandial hypoglycemia.**

- **What happens if administered at meal time? blood glucose will rise faster than insulin.**

-Why? because glucose is absorbed easier and faster, while insulin is a protein (large molecule) it needs time to diffuse from subcutaneous tissue to circulation through capillaries.

♦**Therefore, it should be injected 30-45 minutes (mostly 30 min) before meals to minimize this mismatching. →to prevent early postprandial hyperglycemia and late postprandial hypoglycemia**.

-Diabetics patients should always carry sweets with them, why? To eat it when they feel signs of hypoglycemia (late postprandial hypoglycemia) ; immediately it will be absorbed from the mouth.

(but disaccharides like sucrose→ not absorbed by the mouth, needs digestion, takes time)

-Most patient who are treated with insulin are type 1, children and adults who were born with type 1.

♦**This is the only type of insulin that should be administered IV** in the management of diabetic ketoacidosis, and when the insulin requirement is changing rapidly after surgery or acute infections.

-The only one used to treat Ketoacidosis? because it is the only which can be given IV, (ketoacidosis needs IV)

♦ **Rapid-acting and short-acting insulins are dispensed as clear solutions at neutral Ph (7.4)and contain small amount of zinc (to stabilize insulin) to increase their stability and shelf-life.**

-If you see turbid insulin (like milk)→ it NOT Rapid-acting nor short-acting.

-How Zinc helps stabilize insulin?

1)Insulin tends to aggregate in <u>antiparallel</u> fashion.

(Aggregation = activity loss) so zinc prevents that.

2)Increases shelf life.

►3. Intermediate-acting and Long-acting insulins:

A-NPH (neutral protamine Hagedorn, or isophane insulin)(Intermediate acting)

***Hagedorn: name of the lab**

♦ NPH is an ***<u>intermediate-acting</u>*** insulin with **delayed absorption and onset of action.**

♦It is mixed with Protamine, why? to stabilize insulin

(Protamine : insulin ratio by <u>weight</u> is 1:10)

(representing 6 <u>molecules</u> of insulin per 1 <u>molecule</u> of protamine (hexamer))

♦It is neutral and stabilized by protamine.

♦After sc injection, proteolytic enzymes degrade protamine and permit absorption of insulin.

proteolytic cleavage (hydrolysis) by proteolytic ezymes in tissues→ will release insulin from this insulin-protamime molecules.

♦Onset of action 2-5 hours and duration of 4- 12 hours.

-Does 4-12 hours mean 8? No! it is variable and unpredictable, so any number is possible, it is not the average! So you should titrate your patient, and find the duration.

----"Doctor said you should memorize : onset of action, duration, peak of all drugs in this lecture. Doses are not required----

-Like when the dose is 200-400 mg, it doesn't mean "give the patient 300mg", it means some people need 200 and some 400 and some in between.

♦Can be mixed with regular, lispro, aspart or glulisine insulin.

-At morning half hour before breakfast we can mix ultra-shot acting and intermediate acting to reduce injection numbers..So we should know which can be mixed.

-Ultra-short and Rapid acting (Regular) CAN be mixed with NPH.

♦ **Dispensed as turbid suspension** at neutral pH with protamine in phosphate buffer.

Clear=solution
Turbid=suspension (not diluted)

-Suspension: not diluted so some of it is precipitated at bottom → we should mix Gently to make suspension homogenous.

-Don't mix vigorously (بقوة), why? You will break insulin and oxidiation by O2 will occur.

B- Insulin glargine: (long acting)

♦Glaragine : name indicates that -> Glycine instead of Asparagine.

♦It is a soluble, "peakless", and "long-acting" insulin analog. Dispensed as clear solutions.

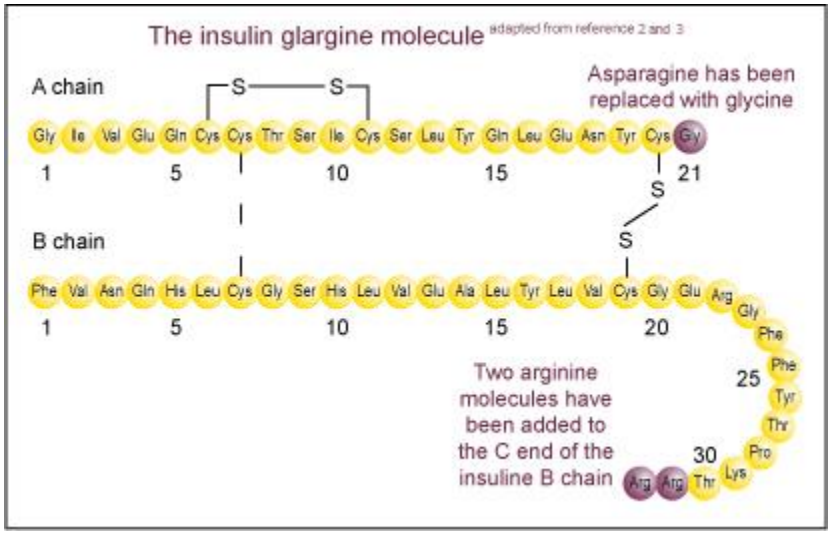
-Peakless: negligible peak, so it is suitable for baseline insulin.

-So we should give long acting (baseline) PLUS at meal times → to mimic physiological pattern of insulin secretion.

…but will never be exactly like physiological when you take insulin from outside…

♦It is designed to provide reproducible, convenient, background insulin replacement.

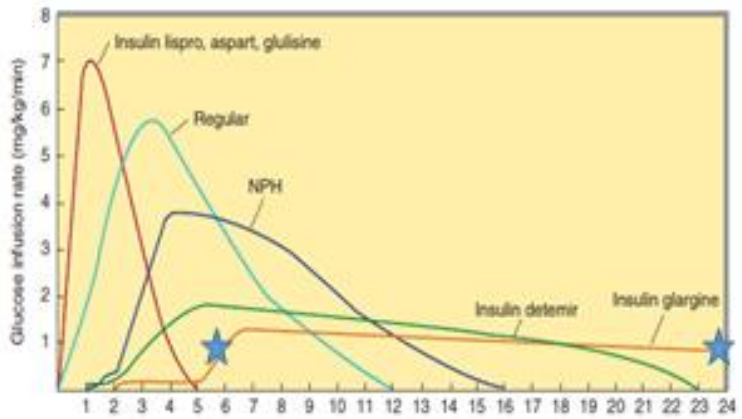
♦Two arginine molecules are attached to the B chain carboxyl terminal, and a glycine is substituted for asparagine at the A21 position (we put glycine instead of asparagine at position A21) →it gives us an analog that is soluble in an acidic solution but precipitates in the more neutral body pH after sc injection.



-Because body pH is more alkaline->Glargine will precipitate and insulin will be released slowly. "Glargine is soluble in acidic solution, so it will precipitate at neutral body pH"

♦ Insulin molecules slowly dissolve away from the crystalline depot and provide a low, continuous level of circulating insulin.

♦Onset of action 1-1.5 hours, peak effect occurs at 4-6 hours (no real peak)and maximal activity is maintained for 11-24 hours or longer.



from ★ to ★ is the duration of action

♦Usually given once daily.

♦ Insulin glargine should NOT be mixed with other insulins,Why? They well become like it (long acting); so they should be given with different syringes in different places (very important).

♦ May be less immunogenic than human insulin (based on animal studies).

♦ Interaction with insulin receptor is similar to that of native insulin.

♦It has no increase in mitogenic activity.

♦It has 6-7 fold greater binding than native insulin to insulin-like growth factor-1 (IGF-1) receptor.

Isnulin glargine affinity to (IGF-1) receptor is more than to native normal physiologic insulin receptor.

C- Insulin detemir:

♦The most recently developed long-acting insulin analog.

♦The terminal threonine is dropped from the B30 position and myristic acid (FA) is attached to the terminal B29 lysine in B subunits. That changed it to become long acting insulin.

♦These modifications prolong the availability of the injected analog by increasing both self-aggregation in subcutaneous tissue and reversible albumin binding.

<u>Long</u> availability <u>after modification</u>is <u>due to</u> both:

-incresed self-aggregation in subcutaneous tissue

-increased reversible albumin binding

♦Its use is associated with LESS hypoglycemia than NPH insulin.

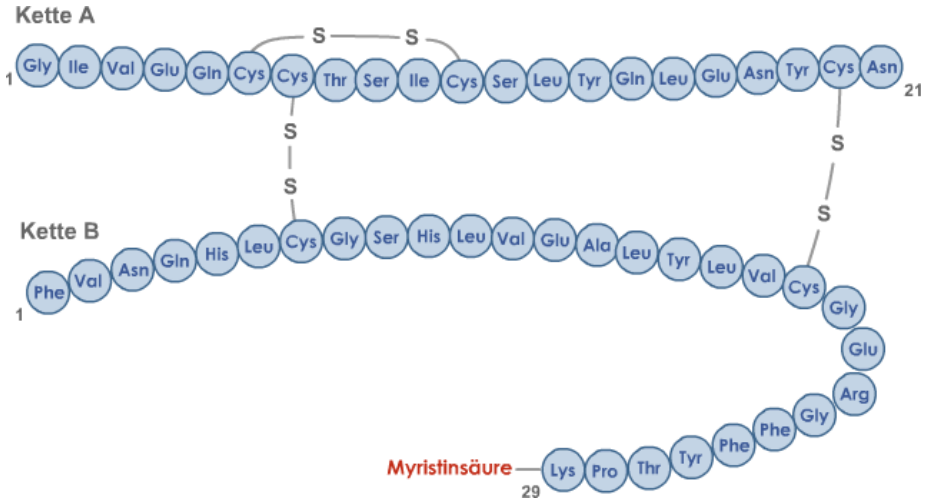
-LESS doen't mean no hypoglycemia, it means that percentage of people who develop hypoglycemia is less than NPH (epidemiologically).

In general Hypoglycemia is important because it can be fatal.

♦Onset of action is dose dependent, 1-2 hours, and duration of action of more than 24 hours (long acting). Can be given <u>one dose once daily</u> OR <u>half dose two times daily</u>.

♦Given twice daily (two half doses), why?to produce smooth background (baseline) insulin level.

♦Dispensed as clear soluble solution.



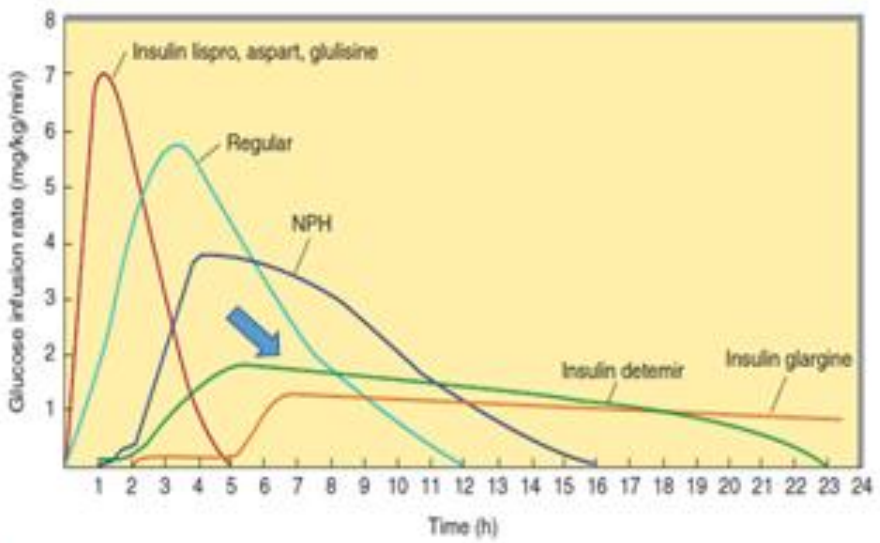


FIGURE 41-5 Extent and duration of action of various types of insulin as indicated by the glucose infusion rates (mg/kg/min) required to maintain a constant glucose concentration. The durations of action shown are typical of an average dose of 0.2–0.3 U/kg. The durations of regular and NPH insulin increase considerably when dosage is increased.

•This curve should be memorized. It is important because you will depend on it to treat patients, when you monitor glucose for a diabetic patient, you will see the time glucose raises; some patient after lunch.

•Regular food intake is important (the best is breakfast at 6 am lunch at 12 pm and dinner at 6pm), why?to not change the pattern.

•You should see glucose pattern according to the day in relation to meals and fasting.

•Key points of blood sugar measure: -fasting glucose -postprandial glucose

•Fasting glucose normal and high postprandial glucose, what it means?
Pancreas cannot cope with stress (meals contain glucose so it's a stress for pancreas because it has so secrete insulin)

•Which is more important fasting or postprandial? Postprandial, because fasting is not regular it depends on many things like how much you sleep that changes from day to day.

•It should be regular

•**Insulin lispro, aspart, glulisine:the onset is fast, peak is high, short duration.**

•**insulin detemir and insulin glargine, look at the graph, we give them at night, why? So when morning comes we are at plateu(↘)**look at graph

•**we use this curve to select the suitable treatment for you patient, according to their pattern.**

•**You can control patient when he's at hospital, but when he is not under you control he may change the pattern.**

►4. Mixtures of insulin:

♦ Because intermediate-acting insulins (NPH) require several hours to reach adequate therapeutic levels, their use in type 1 diabetic patients require supplements of rapid- or short-acting insulin before meals.

♦ For convenience, these are often mixed in the same syringe acutely before injection.

♦ Premixed preparations are unstable, but some are available.

♦ Insulin glargine and detemir must be given as separate injections. They are not miscible acutely or in a premixed preparations with any other insulin preparation.

♦**All insulins are available in a concentration of 100 U/mL (U100).**

-A limited supply of U500 regular human insulin is available for use in severe insulin resistance.

-It means numbering of syringes and vials of U100 insulin is different from that of U500.

……

<u>example</u> the u100 syringe has 10 divisions each division has 10 little divisions**

so you should direct your patient on how to use it according to meal intake.

"The picture bellow is for understanding only not in dr's slides"

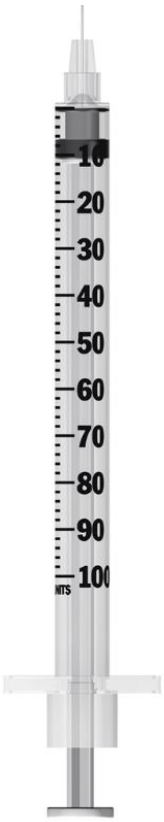
One syringe full= 100U

One large division= 10U

One small division= 1U

In this image one small division is 2U don't care about that,,

500u is for insulin resistant patients



► Insulin Delivery Systems:(you should read it)

1. The standard mode is subcutaneous injection using conventional disposable needles and syringes.
2. Portable pen injectors: prefilled, with replaceable needles.
3. Continuous subcutaneous insulin infusion devices (pumps).
4. **Inhaled insulin:**

   It is not that better than other insulins + inhalation makes problems to lungs

   • A dry powder formulation of human insulin to be absorbed through the alveolar wall.

   • Available as small, single use device.

   • Peak levels are reached in 12 -15 minutes and decline to baseline in 3 hours, faster in onset and shorter in duration than subcutaneous insulin.

• Inhaled insulin combined with injected basal insulin was as effective in lowering glucose as injected rapid-acting insulin combined with basal insulin.

• Adverse effects include cough (27%)

• Pulmonary function should be monitored.

• The drug is contraindicated in smokers and patients with chronic obstructive pulmonary disease.

►Complications of Insulin Therapy:

1. Hypoglycemia:

is the most common and serious complication.

• Usually results from **inadequate carbohydrate consumption**, **unusual physical exertion**, or **too large a dose of insulin**.

• **Manifested by signs** of autonomic hyperactivity, both sympathetic (tachycardia, palpitations, sweating, tremulousness) and parasympathetic (nausea, hunger), which may progress to convulsions and coma if untreated.

-We have to teach him manifestations of hypoglycemia, within the first sign he must eat sweets.

• **Frequent hypoglycemic episodes** during tight glycemic control**, lead to "hypoglycemic unawareness"**, (inadequate autonomic signals).

-If patient has frequent hypoglycemia he will not know that he is having hypoglycemia when it happens→give New doses and Educate him.

(you should read rest of adverse effects)

• An identification bracelet, necklace, or card in the wallet or purse, as well as some form of rapidly absorbed glucose, should be carried by every diabetic person who is receiving hypoglycemic drug therapy.

• All the manifestations of hypoglycemia are relieved by glucose administration.

2. Immune disorders:

• Many classes of insulin antibodies may be produced during the course of therapy (IgA, IgD, IgG, IgE and IgM) →

A. Insulin allergy: immediate type hypersensitivity reaction, anaphylaxis, IgE-mediated. Mainly due to noninsulin protein contaminants.

B. Immune insulin resistance: IgG anti-insulin antibodies neutralize action of insulin.

• May be associated with other systemic autoimmune processes such as lupus erythematosus.

3. Lipodystrophy at injection sites:

A. Atrophy of subcutaneous fat at site of injection of old animal insulins. Almost never seen with human insulin.

B. Hypertrophy of subcutaneous fatty tissue at sites of repeated injections.

END OF TEXT

الطبيعيون يقولون :
ولقد بلغتُ من التفاؤلِ أوجَهُ
وقلائلٌ من يفعلونَ قلائلُ
حتى تفاعيلُ البحورِ قرأتُها
متفائلٌ متفائلٌ متـــفائلُ

أما أولئك المعذَّبون، فيقولون:
ولقدْ بلغتُ من الطبِّ أوجَهُ
وقلائلٌ من يفعلونَ قلائلُ
حتى تعاليمُ الشّيتِ قرأتُهــا
متسائلٌ متسائلٌ متسائــل