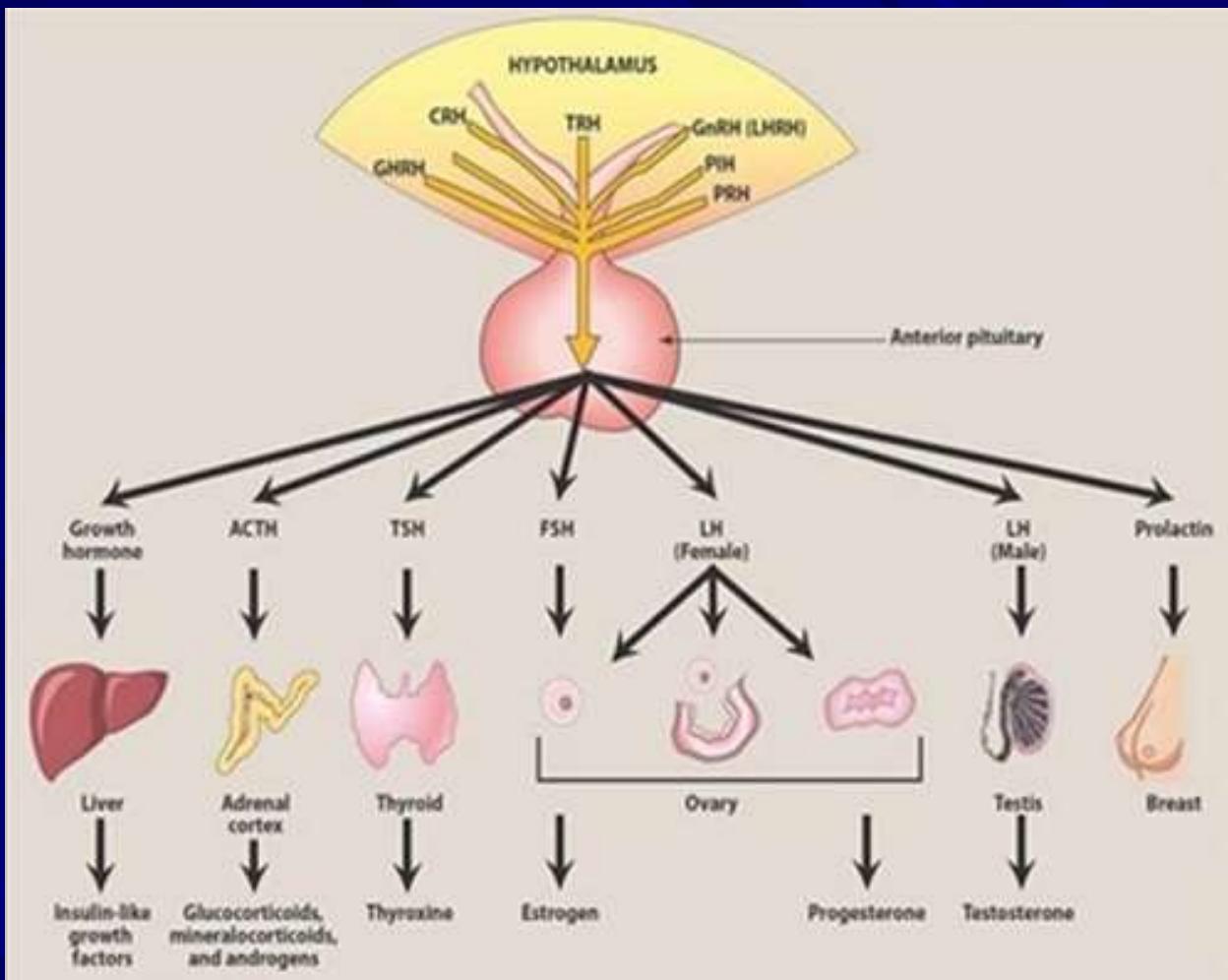




Antidiabetic Drugs

Insulin, Non Insulin Antidiabetic Drugs

Assistant Prof. Dr. Najlaa Saadi
PhD Pharmacology
Faculty of Pharmacy
University of Philadelphia



Pancreas is both an endocrine gland that produce insulin, glucagons and somatostatin and exocrine gland that produce digestive enzymes

Pancreatic Islet cells and their secretory products

Cell Types	Approximate Percent of Islet Mass	Secretory Products
A cell (alpha)	20	Glucagon, proglucagon
B cell (beta)	75	Insulin, C-peptide, proinsulin, amylin
D cell (delta)	3-5	Somatostatin
F cell (PP cell) ¹	< 2	Pancreatic polypeptide (PP)

These hormones play an important role in regulating the metabolic activities of the body, particularly the homeostasis of blood glucose.

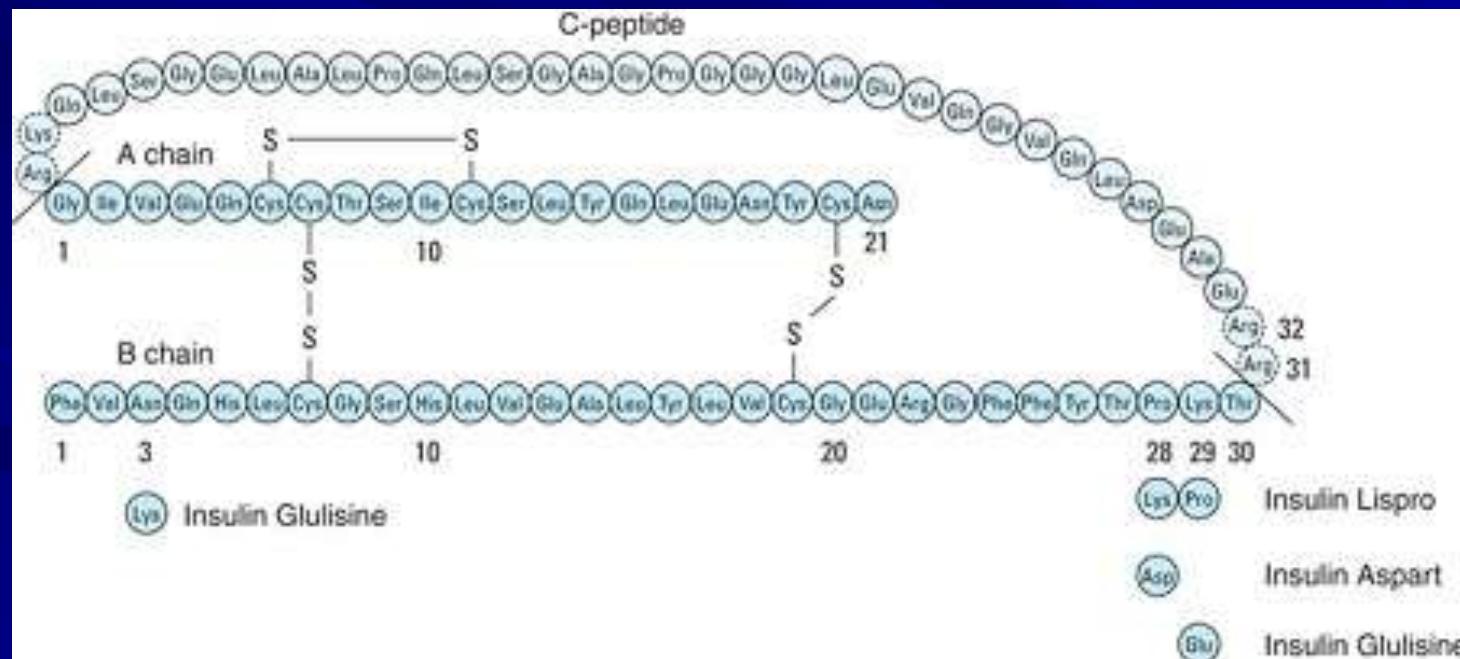
Examples:

- Hyperinsulinemia (due to an insulinoma) can cause severe hypoglycemia.
- A relative or absolute lack of insulin, in diabetes mellitus, can cause serious hyperglycemia

Insulin

- Hormone consist of 2 peptide chains that are connected by disulfide bonds
- It is synthesized as a precursor (pro-insulin) that undergoes proteolysis to from insulin and C peptide, both of which are secreted by the β cells of the pancreas.
- Measurement of circulating C peptide provides a index of insulin levels.

Structure of human proinsulin and some commercially available insulin analogs. Insulin is shown as the shaded (darker color) peptide chains, A and B. Differences in the A and B chains and amino acid modifications for insulin aspart, lispro, and glulisine are noted



Factors Stimulate Insulin Secretion:

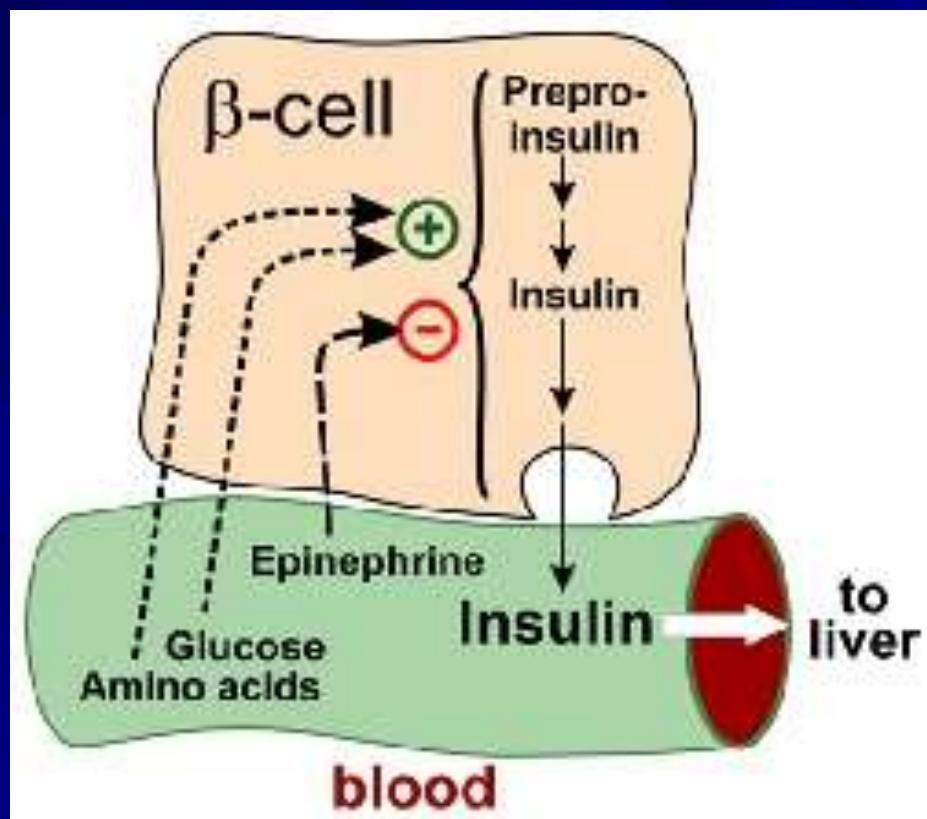
- Glucose
- Amino acids (leucine, arginine)
- Hormones such as glucagon-like polypeptide-1 (GLP-1), glucose-dependent insulinotropic polypeptide (GIP), glucagon, high concentrations of fatty acids and β -adrenergic sympathetic activity
- Stimulatory drugs are sulfonylureas, meglitinide, nateglinide, isoproterenol and acetylcholine

Mechanism stimulated insulin secretion

Hyperglycemia results in increased intracellular ATP levels, which close the ATP-dependent potassium channels. Decreased outward potassium efflux results in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone.

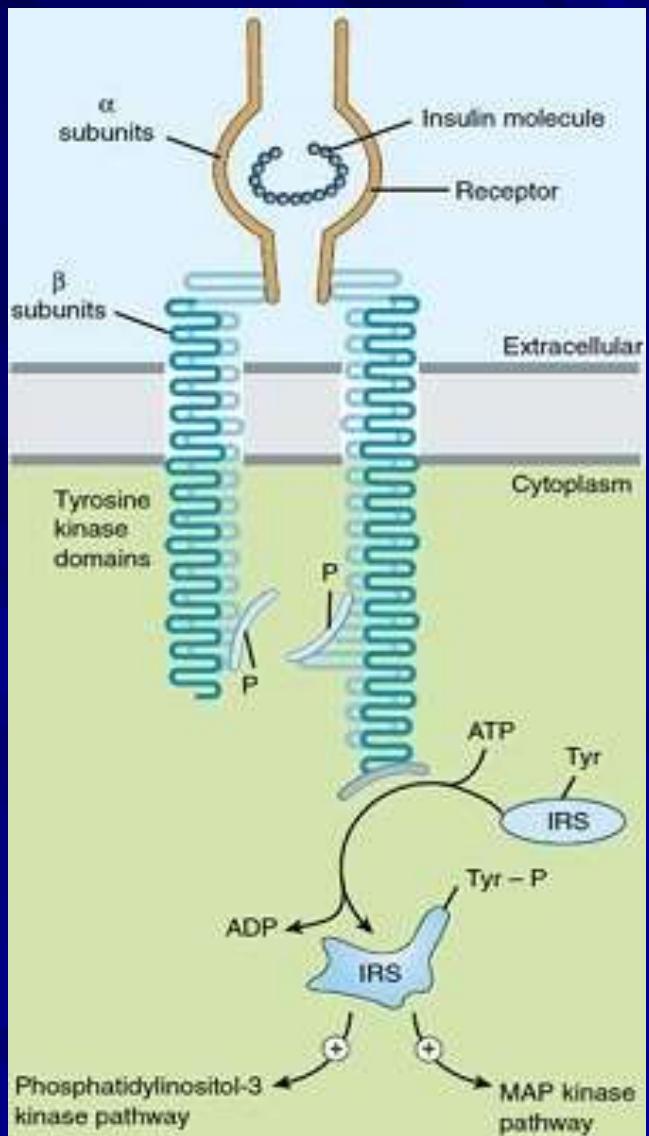
Factors Inhibit Insulin Secretion:

Epinephrine is the most important inhibitor, in emergency situations like stress, exercise and trauma, the nervous system stimulate adrenal medulla to release epinephrine and suppress insulin secretion.



Insulin Receptor:

- Two α subunit (extracellular) and two β subunit (trans membrane)
- The β subunit contains a tyrosine kinase.
- The binding of an insulin molecule to the α subunits at the outside surface of the cell activates the receptor and lead to conformational change of the opposing cytoplasmic β subunits , this facilitates phosphorylation of tyrosine residues on the β subunits and activation of a variety of intracellular proteins.



The major Target Organs for Insulin Action Include:

1. Liver
2. Skeletal muscle
3. Adipose tissue

Metabolic Effects of Insulin

Carbohydrate Metabolism:

- In liver, inhibits gluconeogenesis and glycogen breakdown
- In muscle and liver, increases glycogen synthesis
- In muscle and adipose tissue (& other tissues), increases glucose uptake by increasing number of glucose transporters in the cell membrane
- Overall effect is to decrease glucose concentration in plasma

Effects on Carbohydrate Metabolism:

About half of ingested glucose is utilized to meet energy demand through the process of glycolysis, the other half is either converted to fat40% or glycogen 10%.

Glucagon:

- It is secreted from α cells of the pancreas, oppose the action of insulin, it is a polypeptide hormone composed of 29 amino acids in a single chain, it is actually synthesized as proglucagon which on sequential degradation release active Glucagon together with cortisol, epinephrine and norepinephrine, it opposes the actions of insulin
- Glucagon maintains blood glucose levels by activating gluconeogenesis and glycogen degradation in liver

Regulation of Glucagon secretion:

- The secretion of glucagon is stimulated by low blood glucose concentration, amino acids derived from dietary protein and low level of epinephrine.
- Increased blood glucose level markedly inhibit glucagon secretion.

Metabolic Effects:

- Effects on carbohydrate: Glucagon is the most potent hormone that enhances the blood glucose level (hyperglyemic), primarily glucagon acts on the liver to cause increase synthesis of glucose (gluconeogenesis) and enhanced degradation of glycogen (glycogenolysis).

Effects on Lipid Metabolism:

- Glucagon promotes fatty acid oxidation resulting in energy production and ketone body synthesis (ketogenesis).

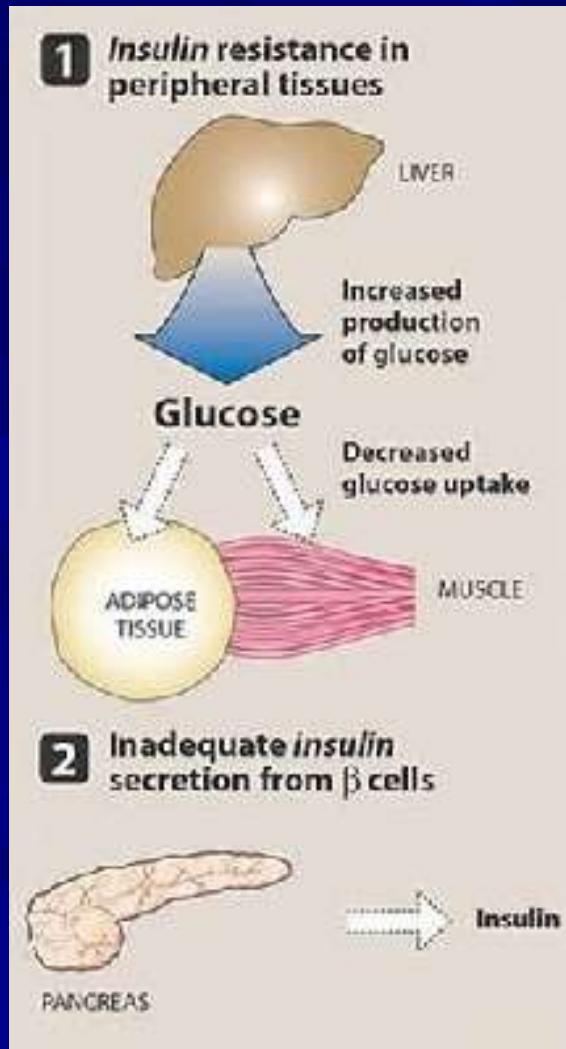
Effects on Protein Metabolism:

- Glucagon increase the amino acid uptake by liver which in turn promotes gluconeogenesis, thus glucagon lower plasma amino acids

Diabetes Mellitus

- Diabetes mellitus, affecting 171 million people worldwide as of 2000, a number expected to be more than double, up to 366 million, by 2030. The majority 90% have T2DM, which is linked to westernized diets, obesity, and inactivity
- Type 2 diabetes mellitus is a complex of metabolic condition characterized by elevated levels of serum glucose, caused mainly by impairment in both insulin action and insulin secretion.

Major factors contributing to hyperglycemia observed in Type 2 diabetes.



The Classification of Diabetes

Classification

1. Type 1 Diabetes mellitus, it results from β -cell destruction, usually leading to absolute insulin deficiency.
2. Type 2 Diabetes mellitus, it ranges from predominant insulin resistance with relative insulin deficiency to predominant insulin secretory defect with insulin resistance.
3. Other specific types of diabetes: genetic defects of the β -cells, genetic defects in insulin action, diseases of the exocrine pancreas, endocrinopathies, drug or chemical induced diabetes, infections.
4. Gestational Diabetes (GDM), it is diagnosed during pregnancy

Comparison of Type 1 and Type 2 diabetes

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

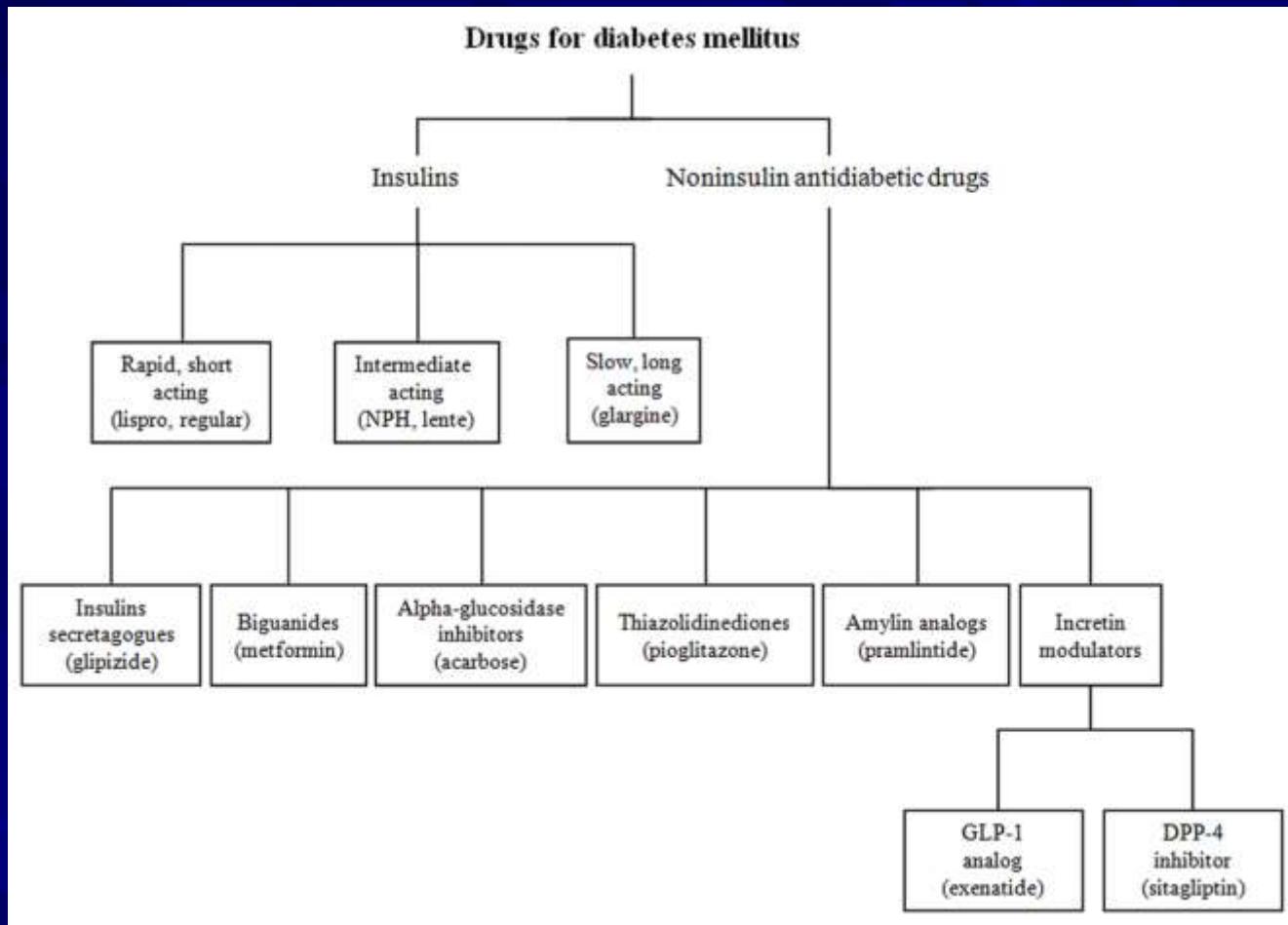
Diabetes Mellitus Complications

- Macro- and micro- vascular damage
- The complication of diabetes affect eye, kidney and nervous system.
- Diabetes is a major cause of blindness, renal failure, heart attack and stroke

Treatment of Type 2 Diabetes :

The Goal in Treating Type 2 Diabetes is to:

- Maintain blood glucose concentrations within normal limits
- Prevent the development of long-term complications of the disease.



Sources of Insulin

- Human insulin is manufactured by bacterial recombinant (Deoxyribonucleic acid) DNA technology.
- Modifications of the amino acid sequence of human insulin have produced insulins with different pharmacokinetic properties.
- The onset of action, peak effect and duration of action determined by insulin type and by physical and chemical form of the insulin.
- The available forms range from rapid-acting to long-acting

Types of Insulin Preparations

- Rapid-onset and ultrashort-acting insulin Preparations
- Intermediate-acting insulin
- Long-acting insulin preparations

Note:

- Insulin preparations vary in their times of onset of activity and in their durations of activity. This is due to differences in the amino acid sequences of the polypeptides.
- Dose, site of injection, blood supply, temperature, and physical activity can affect the duration of action of the various preparations

- Injected rapid-acting and short-acting insulins are dispensed as clear solutions at neutral pH and contain small amounts of zinc to improve their stability
- Injected intermediate-acting NPH insulins have been modified to provide prolonged action and are dispensed as a turbid suspension at neutral pH with protamine in phosphate buffer
- An inhaled form of rapid-acting insulin is available as a powder for alveolar absorption

Current regimens generally use long-acting insulins to provide basal or background coverage and rapid-acting insulin to meet the mealtime requirements

Rapid-onset and Ultrashort-acting Insulin Preparations

1. Regular insulin
2. Insulin lispro
3. Insulin aspart
4. Insulin glulisine

Regular Insulin

- It is a short-acting, soluble, crystalline zinc insulin.
- It is usually given subcutaneously (or intravenously in emergencies)
- It rapidly lowers blood sugar
- It is safely used in pregnancy

Insulin Lispro, Insulin Aspart and Insulin Glulisine

- Classified as ultrashort-acting insulins
(Because of their rapid onset and short duration of action).
- These agents offer more flexible treatment regimens and lower the risk of hypoglycemia
- Used in pregnancy only if clearly needed

Intermediate-acting Insulin Preparations

1. Lente insulin

- Its onset of action and peak effect are slower than those of regular insulin, but are sustained for a longer period.
- Not suitable for intravenous administration.

2. Isophane NPH Insulin Suspension: Neutral Protamine Hagedorn Insulin

- It is a suspension of crystalline zinc insulin combined at neutral pH with a positively charged polypeptide, protamine.
- Its duration of action is intermediate(due to delayed absorption of the insulin because of its conjugation with protamine, forming a less-soluble complex).
- Should only be given subcutaneously
- It is useful in treating all forms of diabetes except diabetic ketoacidosis or emergency hyperglycemia.

Long-acting Insulin Preparations

1. Insulin glargine

- The isoelectric point of insulin glargine is lower than that of human insulin, leading to precipitation at the injection site (extending its action)
- It is slower in onset than NPH insulin and has prolonged hypoglycemic effect
- It has no peak.

2. Insulin Detemir

- Most recently developed long-acting insulin analog.
- It is associated with than NPH insulin.
- Has a dose-dependend hypoglycemic effect.
- Onset of action of 1-2 hours.
- Duration of action of more than 24 hours.
- It is given twice daily.

Insulin Combinations

Various premixed combinations of human insulins:

- 70% NPH insulin + 30% regular insulin
- 50% NPL insulin + 50% lispro insulin
- 75 % NPL insulin + 25% lispro insulin

Insulin Administration

(not given orally, why?)

- It is administered by subcutaneous injection ,insulin is a polypeptide (it is degraded in the gastrointestinal tract if taken orally).
- I.V. injection (in a hyperglycemic emergency, regular insulin)
- I.V. infusion (to avoid multiple injections)

➤ Insulin pumps (open-loop pumps):
Continuous subcutaneous administration ,
not require multiple daily injections .The
devices have a user-programmable pump
that delivers individualized basal and bolus
insulin replacement doses based on blood
glucose self-monitoring results.

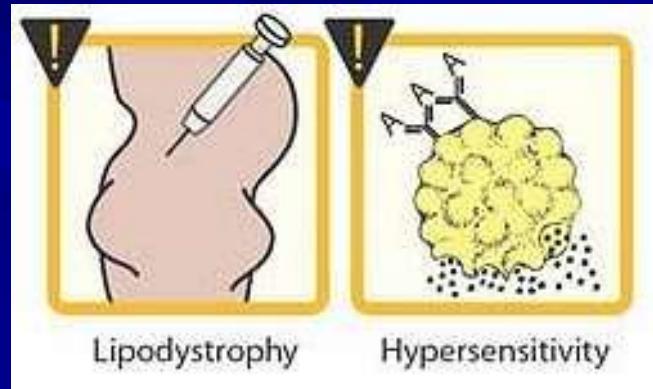
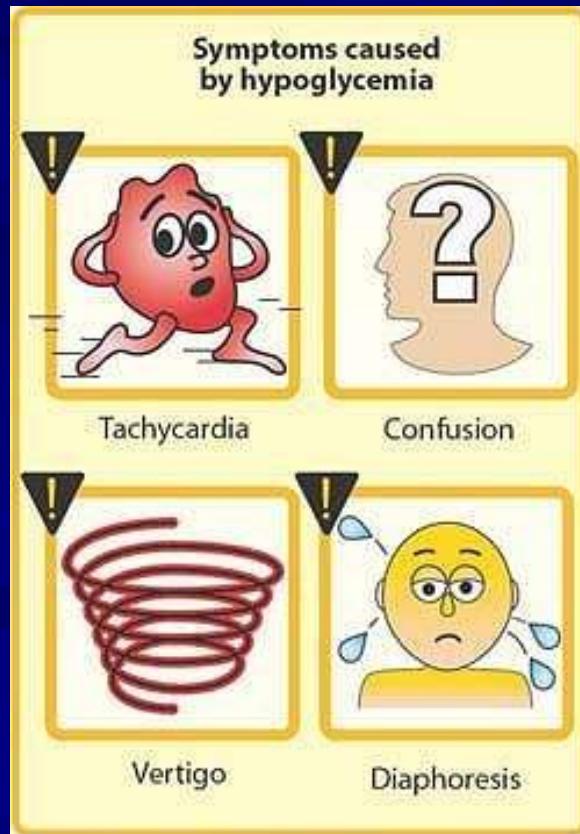
- Portable pen injectors: These contain cartridges of insulin and replaceable needles.
- Aerosol preparation: Inhaled insulin preparation of finely powdered, Insulin is absorbed into the bloodstream through alveolar walls, but the challenge has been to create particles that are small enough to pass through the bronchial tree without being trapped.



- Insulin is inactivated by insulin-degrading enzyme (also called insulin protease, which is found mainly in the liver and kidney).

Adverse Effects Observed With Insulin.

Note: Lipodystrophy is a local atrophy or hypertrophy of subcutaneous fatty tissue at the site of injections.



Adverse Reactions to Insulin

- 1. Hypoglycemia** (more common) due to over dose (tachycardia, confusion, vertigo and diaphoresis)

Treatment of Hypoglycemia:

- Conscious patient:
 - Orange juice, glucose, Suger containing beverage and food.
- Unconsciousness patient (severe hypoglycemia)
 - Intravenous infusion of 20-50 mL of 50% glucose solution over a 2-3 minute.
 - In the absence of intravenous infusion, 1 mg of glucagon (subcutaneous or intramuscular administration), restore consciousness within about 15 minutes then food consumption

2. lipodystrophy

- Atrophy of subcutaneous fat due to availability of more highly concentrated insulin preparations of neutral pH.
- Hypertrophy of subcutaneous fatty tissue (if insulin is injected repeatedly at the same site)

3. Allergic Reactions and Local Injection Site Reactions

- Immediate type hypersensitivity, rare urticaria follows histamine release from tissue mast cells (sensitized by anti-insulin IgE antibodies)
- Treatment by antihistamines, corticosteroids common.

4. Weight Gain

5. Insulin Immune Resistance

- Due to high titer circulating IgG anti-insulin antibodies

Note: Diabetics with renal insufficiency may require adjustment of the insulin dose

Non Insulin Antidiabetic Drugs

- Insulin secretagogues
 1. Sulfonylureas
 2. Meglitinide analogs
- Insulin Sensitizers
 1. Biguanides
 2. Thiazolidinediones or glitazones
- Alpha - Glucosidase Inhibitors
 1. Acarbose
 2. Miglitol
- Amylin analog
Pramlintide
- Gastrointestinal Hormones
 1. Incretins analoge (Incretins Mimetics)
 2. Dipeptidyl Peptidase-4 Inhibitors (DPP-4 inhibitor)

Non Insulin Antidiabetic Drugs

- For treatment of patients who have Type 2 Diabetes but cannot be managed by diet alone.
- A combination of hypoglycemic drugs with or without insulin to control the hyperglycemia (for Patients with long-standing disease).
- Oral hypoglycemic agents should not be given to patients with Type 1 diabetes

Note: The patient respond well to oral hypoglycemic agents if diabetes occurs after age fourty and has had diabetes less than five years

Insulin Secretagogues

1. Sulfonylureas

Tolbutamide (First-Generation Sulfonylureas)

Glyburide, glipizide, and glimepiride (second-
Generation derivatives)

Mechanisms of Action of the Sulfonylureas

1. Stimulate insulin release from β cells of pancreas by blocking the ATP-sensitive K⁺ channels, resulting in depolarization of the beta cell and opening of voltage-gated calcium channels. The resulting increased intracellular calcium triggers secretion of the hormone.
2. Reduction of serum level of glucagons
3. Increase binding of insulin to receptors

Pharmacokinetic of the sulfonylureas

- Given orally
- Bind to serum proteins
- Tolbutamide duration of action is 6-12 hours
- Second-generation agents last about 24 hours.
- Metabolized by liver
- The drugs and its metabolites excreted by kidney

Adverse Effects of Sulfonylureas

- Weight gain
- Hyperinsulinemia
- Hypoglycemia
- Can deplete insulin from fetal pancreas (cross the placenta), so pregnant women with type 2 DM should be treated with insulin.

Sulfonylureas

*Phenylbutazone
Salicylates
Sulfonamides*

*Allopurinol
Probenecid
Phenylbutazone
Salicylates
Sulfonamides*

↓
Displace sulfonyl-
ureas
from plasma
proteins

↓
Decrease urinary
excretion of
sulfonylureas or
their metabolites

↑
Increased hypoglycemic action
of sulfonylurea drugs

↑
Reduce hepatic metabolism
of sulfonylureas

↑
*Dicumarol
Chloramphenicol
Monoamine oxidase inhibitors
Phenylbutazone*

Sulfonylureas

2. Meglitinide Analogs (Repaglinide, Nateglinide)

- They are postprandial glucose regulators (effective in early release of insulin that occurs after a meal).
- Their action is dependent on functioning of pancreatic B cells.
- They bind to distinct site of on sulfonylurea receptor of ATP-sensitive potassium channels, thereby initiating a series of reactions resulting in insulin secretion.
- In contrast to sulfonylureas, meglitinide has a rapid onset and short duration of action.
- Combination therapy with metformin or the glitazones better than monotherapy

Pharmacokinetic of Meglitinides

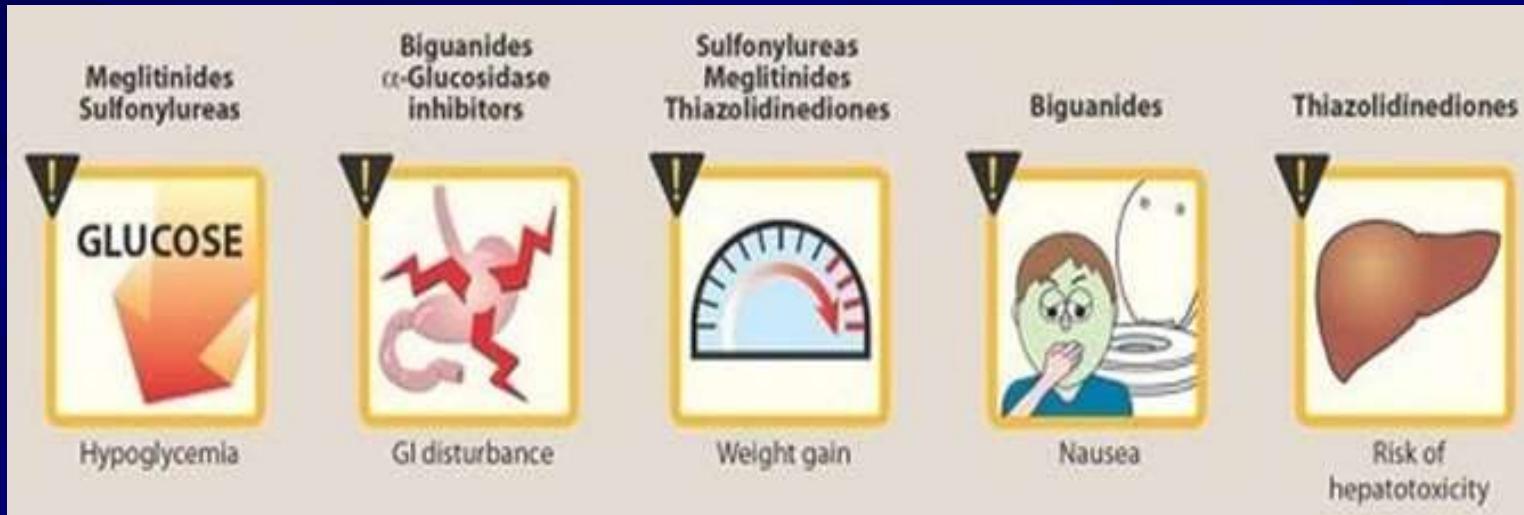
- Well absorbed orally
- Taken 1- 30 minutes before meals
- Meglitinides are metabolized by CYP3A4 to inactive products in the liver
- Excreted through the bile.

Adverse Effects of Meglitinides

- Hypoglycemia (the incidence Hypoglycemia lower than that with the sulfonylureas)
- These agents must be used with caution in patients with hepatic impairment
- Weight gain is less with the meglitinides than with the sulfonylureas.

Drug Interaction With Meglitinide

1. Enzyme inhibitor (ketoconazole, itraconazole, erythromycin, and clarithromycin) enhance the effect of repaglinide
2. Enzyme inducer (barbiturates, carbamazepine, and rifampin, decrease the glucose-lowering effect of repaglinide)
3. Repaglinide cause severe hypoglycemia in patients who are also taking the lipid-lowering drug gemfibrozil.



Insulin Sensitizers

1. Biguanides (Metformin)
2. Thiazolidinediones or glitazones

These agents lower blood sugar by improving target cell response to insulin without increase pancreatic insulin secretion

Biguanides (Metformin)

- Metformin is only available biguanide
- It require insulin for it is action
- It will increase glucose uptake and decrease insulin resistance
- It will not increase insulin secretion
- Hypoglycemia is less than that with sulfonylurea agents.

Action of Metformin

- Reduce hepatic glucose out put (inhibiting hepatic gluconeogenesis)
 - It slows intestinal absorption of sugars.
 - Reduces hyperlipidemia (LDL and VLDL) cholesterol concentrations
 - Raises HDL cholesterol
- These effects may not be apparent until 4 -6 weeks of use.

- Metformin may be used alone or in combination with other oral agent or with insulin
- It Is decrease cardiovascular mortality.
- The patient often loses weight because of loss of appetite
- Hypoglycemia has occurred when metformin was taken in combination.

Note: If used with insulin, the dose of the hormone must be adjusted, because metformin decreases the production of glucose by the liver

Pharmacokinetic of Metformin

- Well absorbed orally
- Not bound to serum proteins
- Not metabolized
- Highest concentration are in saliva and intestinal wall
- Excretion via urine

Adverse Effects of Metformin

1. GIT disturbance
2. Interfere with vitamin B12 absorption (Long-term use)
3. Fatal lactic acidosis (Rarely).

Note: Lactic acidosis is type of metabolic acidosis caused by accumulation of lactic acid due to tissue hypoxia, drug effect, or unknown etiology.

Contraindications of Metformin

- Renal disease
- Hepatic disease
- Cardiac or respiratory insufficiency
- A history of alcohol abuse
- Severe infection
- Pregnancy

Drug-drug Interactions

- Metformin may be enhanced by cimetidine, furosemide and nifedipine.

Other Uses of Metformin

- Metformin is effective in the treatment of polycystic ovary disease.
- Its ability to lower insulin resistance in these women can result in ovulation, possibly and pregnancy

Thiazolidinediones or glitazones

Troglitazone withdrawn (due to hepatotoxicity)

Pioglitazone

Rosiglitazone

- They are insulin sensitizers
- Not promote insulin release from the pancreatic β-cells (hyperinsulinemia not occurs)
- Insulin is required for their action
- Pioglitazone and rosiglitazone can be used as monotherapy or in combination with other hypoglycemics or with insulin

Mechanism of Action of Thiazolidinediones

- They target a nuclear hormone receptor, the peroxisome proliferator activated receptor (PPAR- γ)
- Pioglitazone has PPAR- α as well as PPAR- γ
- Peroxisome proliferator-activated receptor gamma is a nuclear transcription factor which triggers the expression of multiple genes involved in glucose and lipid metabolism
- They increase insulin sensitivity
- These agents improve Hyperglycemia, hyperinsulinemia, hypertriacylglycerolemia and improve elevated levels HbA1c

Pharmacokinetics of Thiazolidinediones

- They are very well absorbed after oral administration
- Extensively bound to serum albumin.
- Metabolism by cytochrome P450 isozymes.
- Their metabolites are excreted in the urine
- The parent agent eliminated via the bile.
- These agents not used in nursing mothers

Adverse Effects of Thiazolidinediones

- Fluid retention, mild anemia and peripheral edema (when used in combination with insulin or insulin secretagogues)
- Increased risk of heart failure.
- Weight gain (due to fluid-retention).
- Hepatotoxicity with troglitazone, ,monitoring of liver function tests before initiation of therapy and during therapy

Note: To date hepatotoxicity has not been associated with Rosiglitazone or Pioglitazone

- Increased risk of pregnancy (Reduce plasma concentrations of the estrogen-containing Contraceptives)

Contra Indication of Thiazolidinediones

- Pregnancy
- Liver disease
- Heart failure

Other Uses of Thiazolidinediones

Improve insulin sensitivity, can cause ovulation in premenopausal women with polycystic ovarian syndrome

Alpha - Glucosidase Inhibitors

Acarbose

Miglitol

- Orally active drugs
- Taken at the beginning of meals
- Hypoglycemia may Develop when used in combination with the sulfonylureas or with insulin
- Glucose not sucrose should be given to patients treated by alpha-glucosidase inhibitor in case of hypoglycemia (because sucrase is also inhibited by these drugs)

Mechanism of Action of Acarbose and Miglitol

- They are reversible competitive inhibitors of the intestinal α -glucosidases (enzyme responsible for hydrolysis of oligosaccharides to glucose) and reduce the postprandial digestion and absorption of starch and disaccharides
- Miglitol differs structurally from acarbose and is six times more potent in inhibiting sucrase.

Pharmacokinetics of Alpha - Glucosidase Inhibitors

- Acarbose is poorly absorbed , It is metabolized primarily by intestinal bacteria, some of the metabolites are absorbed and excreted into the urine.
- Miglitol is very well absorbed but has no systemic effects. It is excreted unchanged by the kidney.

Adverse Effects of Alpha - Glucosidase Inhibitors

flatulence, diarrhea and abdominal cramping.

Contra Indication of Alpha - Glucosidase Inhibitors

- Patients with inflammatory bowel disease
- Colonic ulceration
- Intestinal obstruction.

Amylin Analog Pramlintide

Pramlintide is an injectable synthetic analog of amylin, a 37-amino acid hormone produced by pancreatic B cells.

Amylin Contributes to Glycemic Control Actions:

Suppresses glucagon release, slows gastric emptying, works in the CNS to reduce appetite.

Pharmacokinetic of Amylin Analog (Pramlintide)

- Subcutaneous injection
- Rapidly absorbed
- Short duration of action.
- Combine with insulin to control Postprandial glucose levels.

Adverse Effects Amylin Analog (Pramlintide)

1. Hypoglycemia
2. Gastrointestinal disturbances

Gastrointestinal Hormones Modulators

1. Incretins analoge (Exenatide)
2. Dipeptidyl Peptidase-4 Inhibitors (DPP-4 inhibitor)

Gastrointestinal Hormones (INCRETINS)

1. Gastric inhibitory polypeptide (GIP)
2. Glucagon-like peptide-1 (GLP-1)
 - Hormones produced by the gastrointestinal tract in response to incoming nutrients
 - In T2DM circulatory GLP-1 levels significantly reduced (rapid inactivation)

Incretins Analoge (Incretins Mimetics) Exenatide

- Polypeptide homologous to GLP-1, mediates its effect through the GLP-1 receptor

Incretin Mimetics

Exenatide

liraglutide

- Incretin effect occurs because the gut releases Incretin hormones (GLP-1) in response to a meal, and these hormones are responsible for 60 to 70 percent of postprandial insulin secretion.
- Incretin effect is markedly reduced in type 2 diabetes
- Exenatide and liraglutide are injectable incretin mimetics used for the treatment of patients with type 2 diabetes.

Mechanism of Action of The Incretin Mimetics

These Agents are Analogs of GLP-1 by Acting as

- GLP-1 receptor agonists
- Improve glucose-dependent insulin secretion
- Slow gastric emptying time
- Decrease food intake
- Decrease postprandial glucagon secretion,
- Promote β -cell proliferation
- Reduce weight gain and postprandial, Hyperglycemia and HbA1c levels

Pharmacokinetics of the Incretin Mimetics

- Administered subcutaneously.
- Liraglutide has a long half life, once-daily dosing
Exenatide has a much shorter half life. twice daily.
- Should be avoided in patients with severe renal impairment.

Adverse Effects of The Incretin Mimetics

- Nausea, vomiting, diarrhea, and constipation.
- Exenatide and liraglutide have been associated with pancreatitis.
- Liraglutide causes thyroid C-cell tumors in rodents. However, it is unknown if it causes these tumors or thyroid carcinoma in humans

Dipeptidyl Peptidase-4 Inhibitors (DPP-4 Inhibitor)

Sitagliptin

Vildagliptin

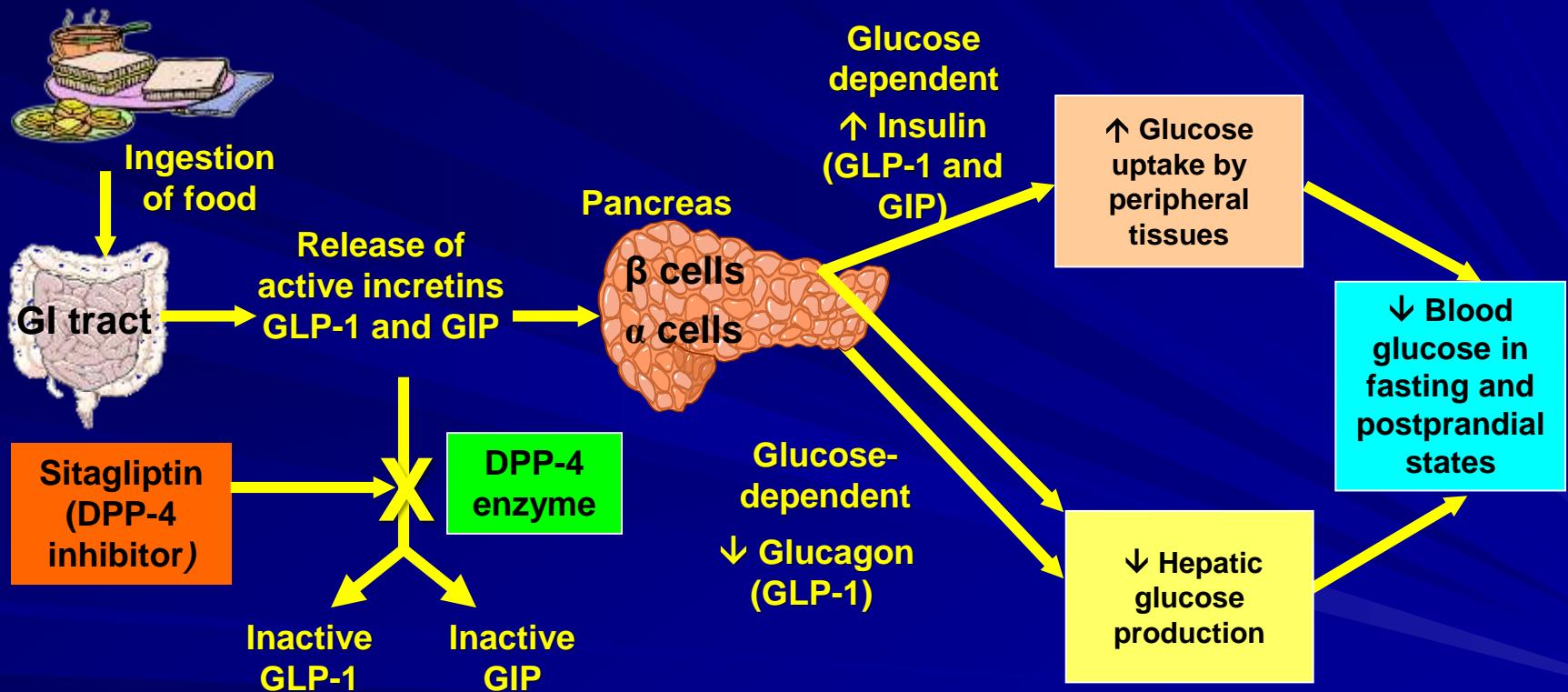
Saxagliptin

- Inhibit the DPP-4 enzyme
- Inhibition of the DPP-4 enzyme prolongs and enhances the activity of incretins that play an important role in Insulin secretion and blood glucose control regulation

Mechanism of Action of (DPP-4 inhibitor) These Drugs Inhibit the Enzyme

- DPP-IV, which is responsible for the inactivation of incretin hormones such as glucagon-like peptide-1 (GLP-1). Prolonging the activity of incretin hormones results in increased insulin release in response to meals and a reduction in inappropriate secretion of glucagon.
- DPP-4 inhibitors used as monotherapy or in combination with a sulfonylurea, metformin, glitazones, or insulin.

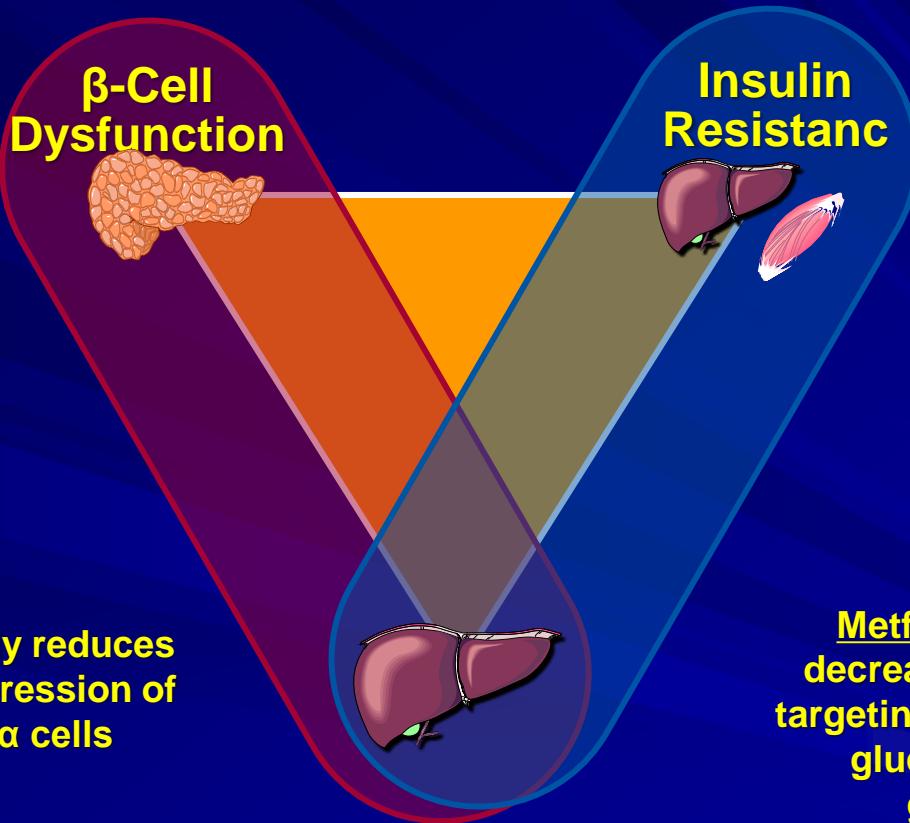
Mechanism of Action of Sitagliptin



Pharmacokinetic of (DPP-4 inhibitor)

- Orally administered
- High oral bioavailability
- Small fraction of Sitagliptin undergoes hepatic metabolism via CYP 450 3A4, 79% excreted in an unchanged form in the urine
- Saxagliptin is metabolized via CYP 3A4

Sitagliptin improves markers of β -cell function and increases insulin synthesis and release



Sitagliptin indirectly reduces HGO through suppression of glucagon from α cells

Metformin acts as an insulin sensitiser (liver>muscle/fat)

Metformin significantly decreases HGO by directly targeting the liver to decrease gluconeogenesis and glycogenolysis

Side Effect of DPP-4 Inhibitors

- Upper respiratory tract infections, sore throat
- Very rare case of pancreatitis (especially with saxagliptin)

Note: DPP-4 inhibitors not have the side effects that tend to follow type -2 diabetes treatment, e.g. weight gain and hyperglycemia

Drug Interaction of DPP-4 Inhibitors

Strong CYP3A4/5 inhibitors like ketoconazole, clarithromycin, increased concentrations of saxagliptin