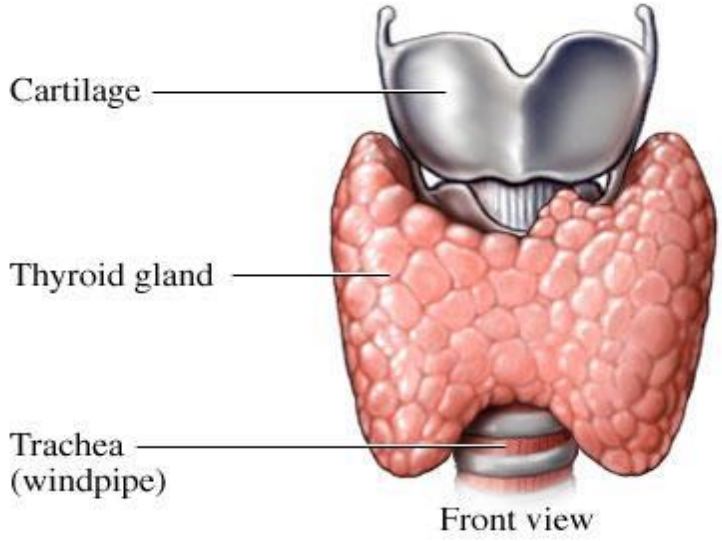
8. Pharmacology of Hormones and Hormones Antagonists

a) Thyroid drugs

Thyroid gland: It is one of the endocrine gland which synthesizes and secretes thyroid hormones. It is a butterfly shaped gland located just inferior to the larynx (voice box).It is composed of right and left lateral lobes. These lobes are connected by isthmus. The weight of thyroid gland is 30g. It is highly vascular and receives 80-120ml blood per minute. Each lobe consists of microscopic spherical sacs called thyroid follicles. The wall of each follicle consists of follicular cells with basement membrane.
These cells produce T4 and T3 hormones. Few cells called parafollicular (interfollicular cells) or C cells lie between follicles produce the hormone calcitonin.

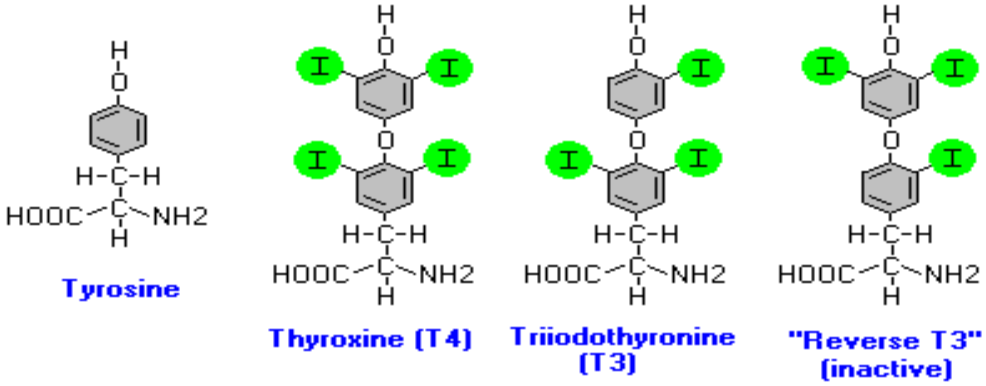


Thyroid gland

Thyroid hormones: These are three in number. Tetraiodothyronine (T4), triiodothyronine (T3) secreted by the follicular cells and thyrocalcitonine (calcitonin) secreted by the inter follicular (para follicular cells)'C' cells of the thyroid gland.

T4 and T3: The thyroxin and and triiodothyronine: **Chemistry of T3 and T4**

T3 and T4 are iodine containing aminoacids. They contain two phenyl rings linked with an ether (-O-) bridge. In thyroxine there are four iodine atoms at 3,5 (inner ring) and 3' and 5' (outer ring) positions and in T3 there are 3 iodine atoms at 3,5 (inner ring) and 3' (outer ring) positions. T3 is biologically very active. The reverse T3 is inactive.



Biosynthesis of thyroid hormones: Sea fish, eggs, and milk are good dietary sources of iodine. Dietary iodide is absorbed from the upper part of GIT and is carried in the plasma as inorganic iodide. Synthesis of thyroid hormones involves following steps.

1. Iodide trapping (uptake): The follicular cells of the thyroid gland trap the plasma iodide actively through Na+ I- symporter (sodium iodide symporter) which is a glycoprotein. This is activated by TSH. The TSH binds with TSH receptor (Gs type) increases cAMP concentration within the follicular cells. This activates the Na+ I- symporter. The iodide (I-) ions are trapped from the blood into the cytosol of the follicular cells.

2. Oxidation of iodide: The iodide is transported from the cytoplasm to the follicular lumen through the pendrin (sodium-independent chloride/iodide transporter) located in the luminal surface of the follicular cells. Then iodide is oxidized (2I- I2) to iodine by the peroxidase enzyme. The iodine also passes into lumen of the follicle.

3. Synthesis of TGB (thyroglobulin): TGB is a large glycoprotein synthesized ER of the follicular cells. The TGB gets released into the lumen of the follicle through the exocytosis.

The TGB is modified in the Golgi complex, and then it is stored in the secretory vesicles. The vesicles undergo exocytosis and TGB released into the lumen of the follicle.

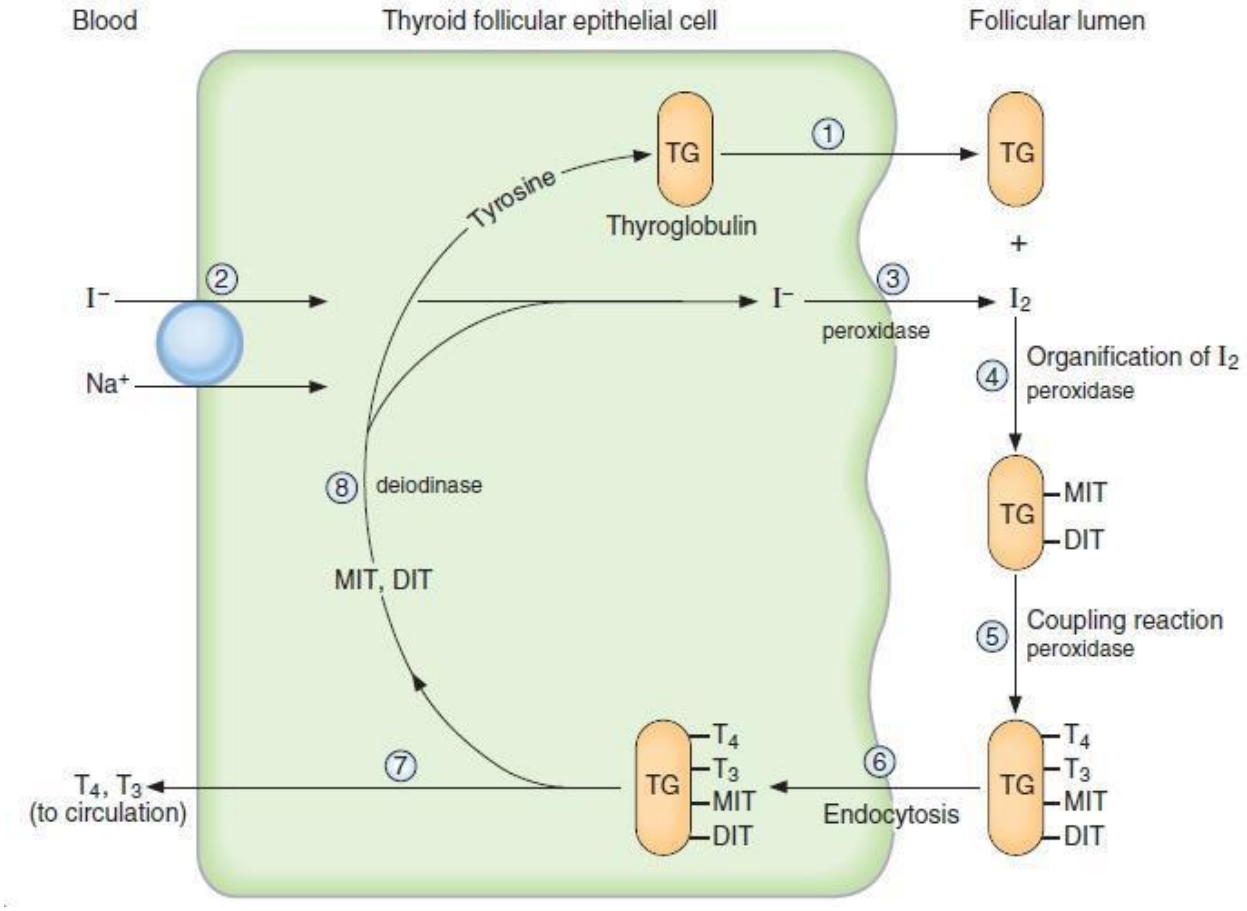
4.Organic binding of iodine: TGB contains tyrosine amino acids. Iodine binds with tyrosine. Binding of one iodine yields monoiodotyrosine (MIT), and a second iodination produces DIT.

5.Coupling: The next step is coupling of MIT and DIT. One MIT and one DIT join to form (T3 or triiodotyronine), one DIT and one DIT join to form T4 or thyroxin.

6.Pinocytosis and digestion of the colloid: Droplets of colloid reenter follicular cells by pinocytosis and merge with lysosomes. Digestive enzymes in the lysosomes (proteases) breakdown TGB, cleaving off molecules of T3 and T4.

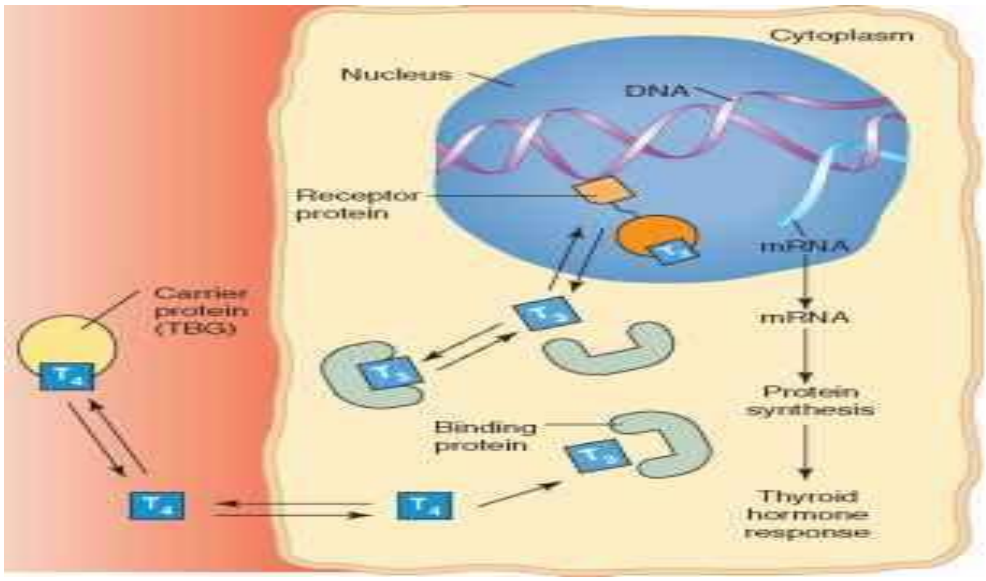
7. Secretion of thyroid hormones: T3 and T4 are lipid soluble, they diffuse through plasma membrane to interstitial fluid and then into the blood. T3 is more potent than T4. T4 is then converted into T3 with the removal of one iodine atom (deiodination)..

8. Transport in the blood: Both T3 and T4 combine with transport proteins in the blood mainly thyroxine-binding globulin (TBG).



Biosynthesis of thyroid hormones

Mechanism of action of T3 and T4



T3 and T4 are lipid soluble hormones. They diffuse from the blood after separating from the carrier protein (TBG). They enter the target cell through the cell membrane. T4 gets converted into T3. Then T3 enter the nucleus of the cell and bind with the T3 receptor. The hormone-receptor complex then leads to the alteration of the gene expression. The resultant DNA transcription leads to the formation of specific mRNA. The mRNA then enter the cytoplasm, where it bind with ribosomal RNA of the ribosomes, together with tRNA, specific proteins (enzymes) are formed. These are responsible for their effects.

Actions of thyroid hormones:

Actions of T3 and T4- 1.Increases the BMR 2.Stimulates the synthesis of Na+/K+ ATPase. 3.Increases the body temperature (calorigenic effect). 4.Stimulates the protein synthesis 5.Increase the use of glucose and fatty acids for ATP production. 6.Enhance some actions of adrenaline.7. Regulate development and growth of nervous tissue and bones. **Disorders of thyroid hormones-**

1.Congenital hypothyroidism in childrens leads to cretinism. It is characterized by mental retardation and stunted bone growth.

2. Hypothyroidism in adults leads to myxedema. It is characterized by puffy face, slow heart rate, low body temperature, weight gain.

3.The hyperthyroidism leads to Grave's disease. It is characterized by exophthalmos, increased heart rat, increased body temperature, weight loss.

Metabolism of thyroid hormones: Metabolized in the liver by deiodination, de-amination and conjugation. Free and conjugated metabolites are excreted through bile and urine.

Clinical uses of thyroid hormones:

1.As substitution therapy: They are used in cretinism (children) and myxedema (adults).

2. Non toxic goiter: In nontoxic simple goiter, in which size of the thyroid gland increases but secretion of thyroid hormones is low. It is corrected by administration of thyroid hormones.

3.Myxedema coma (myxedema crisis)- It is a rare life threatening clinical condition that represents severe hypothyroidism treated with thyroid hormones.

ADRs: They include diarrhea, weight loss, tremors, angina pain. Prolonged administration of thyroid hormones in large doses can cause osteoporosis especially in menopausal women.

Preparations:1. Levothyroxine sodium tablets (eltroxin) (50-300μg), 2.Liothyronine sodium tablet (tertroxin) (20-60 μg).

Anti thyroid drugs

Anti-thyroid drugs: An antithyroid agent is a hormone antagonist acting upon thyroid hormones. These are used in hyperthyroidism to inhibit the synthesis or release of thyroid hormones.

Classification: Four groups

1.Inhibitors of iodide trapping (Ionic inhibitors) e.g Sodium or potassium perchlorate, sodium or potassium thiocyanate.

2. Inhibitors of thyroid hormone synthesis: Thioamides (e.g. Carbimazole, methimazole and propylthiouracil.

3.Inhibitors of thyroid hormone release: (Iodides) e.g. Sodium or potassium iodide and Lugol's solution (5% Iodine in 10% KI).

4. Destroyers of thyroid tissue (Radioactive isotopes of iodine), e.g. I131 (commonly used), I125 (rarely used).

1. Inhibitors of iodide trapping (Ionic inhibitors) e.g Sodium or potassium perchlorate, sodium or potassium thiocyanate.

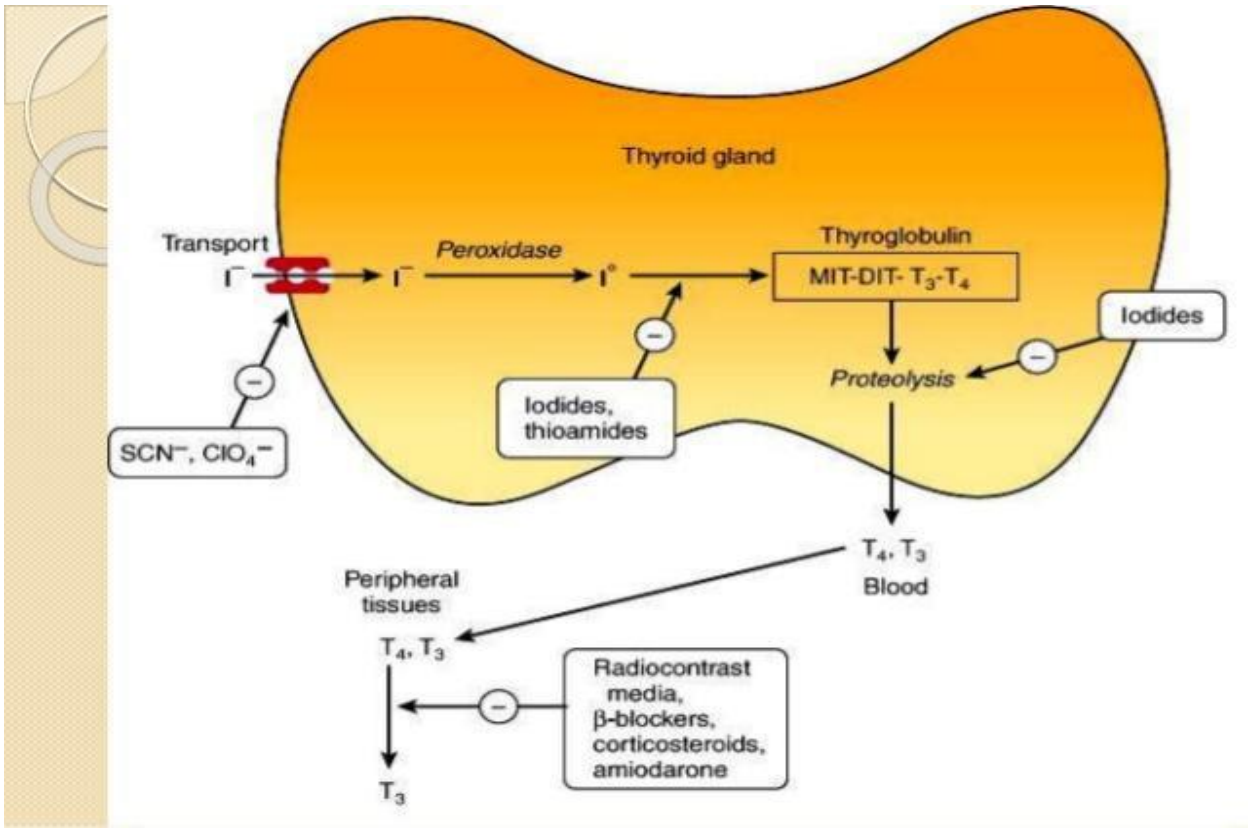
Mechanism of action- Iodide uptake is an active transport mechanism mediated by sodium-iodide symporter (NIS protein) found on the basolateral surface of thyroid follicular cells. As a result of this active transport, iodide (2I-) concentration inside the follicular cells is 20 to 50 times higher than in the plasma. They act by blocking competitively the sodium-iodide symporter (NIS protein) found on the basolateral surface of thyroid follicular cells. This prevents the entry of iodide into the follicular cells. This decreases the formation of thyroid hormones.

They are now obsolete drugs due to potential toxicity. The toxicity includes gastric irritation, fever, skin rashes, lymphadenopathy (lymph node disease abnormal increase in lymph node) agranulocytosis (deficiency of granulocytes) , aplastic anemia (deficiency of all types of blood cell caused by failure of bone marrow development), methenoglobinemia (metHb is a blood disorder in which an abnormal amount of methemoglobin is produced), hepatic and renal damage.

2. Inhibitors of thyroid hormone synthesis: Thiourea derivatives (e.g. Carbimazole, methimazole and propylthiouracil).

In India carbimazole alone is available.

Carbimazole: MOA: It is a prodrug, as after absorption it is converted into active form, methimazole. Thyroid peroxidase or thyroperoxidase (TPO) is an enzyme expressed mainly in the thyroid that liberates iodine (I2) for addition onto tyrosine residues on thyroglobulin for the production of T3 and T4 . Methimazole prevents the thyroid peroxidase enzyme from coupling and iodinating the tyrosine residues on thyroglobulin, hence reducing the production of the thyroid hormones T3 and T4.



ADME: Given orally, absorbed well and are concentrated into the thyroid. 40% is bound to plasma proteins. It crosses the placental barrier; hence it is given with caution if the patient is pregnant women and lactating women. It is metabolized in the liver and the metabolites are eliminated in the urine.

ADRs: Skin rash, uriticaria (hives) and fever. Agranulocytosis.

Uses: Used in Grave's disease, hyperthyroidism.

Propylthiouracil: Mechanism of action: It inhibits iodine and peroxidase from their normal interactions with thyroglobulin (TGB) to form T4 and T3. It also acts by inhibiting the enzyme deiodinase which converts T4 to the active form T3.

ADME: When administered orally, peak serum concentration is achieved within one hour and gets concentrated in the thyroid gland. About 70% get bound to plasma proteins. About 10% of the drug excreted in the free form. The remaining is metabolized in the liver by glucouronidation.

ADR- 1.Agranulocytosis 2.Thrombocytopenia- excessive bleeding. **3.Skin related**- Rash, itching, hives, abnormal hair loss, and skin pigmentation. **4.Other side effects**: Nausea, vomiting, heart burn, loss of taste, joint or muscle aches.

Uses: Used in Grave's disease, hyperthyroidism.

Preparations: 1.Carbimazole 5mg tab. 2.Propyl thiouracil 50mg tablets.

3. Inhibitors of thyroid hormone release: (Iodides) e.g. Sodium or potassium iodide and Lugol's solution.

Mechanism of action- These drugs (in large doses) act by inhibiting the release of preformed thyroid hormones probably by preventing the proteolysis of the thyroglobulin molecule. Iodide is also used in some selected cases of hyperthyroidism but not as a mono therapy. KI inhibits the iodide uptake by the follicular cells. KI also inhibits the peroxidase enzyme. This prevents the conversion of iodide to iodine. KI also act by reducing the size and vascularity of the thyroid gland.

ADME: They are well absorbed after oral administration and distributed throughout the body. They are selectively trapped by the thyroid gland, uptake being increased in hyperthyroidism and decreased in hypothyroidism. They can cross the placental barrier and may produce cretinism in the foetus.

Clinical uses:

1. Before partial thyroidectomy in hyperthyroidism:
2. In thyroid storm (acute thyroidism) together with other drugs it is used.

Preparations: Lugol's iodine solution: (5g of iodine in 100 ml of 10% potassium iodide)
Saturated solution of potassium iodide: (30g KI + 20ml water)

ADRs: Soreness of throat, lacrimation, rhinorrhea, increased salivation, gingivitis, swelling of eyelids and skin rashes. They cross the placental barrier and may cause critinism in foetus.

4. Destroyers of thyroid tissue (Radioactive isotopes of iodine), e.g. I131 (commonly used), I125 (rarely used).

Radioactive iodine I131. Radioactive isotope therapy is a treatment for hyperthyroidism. It is administered orally, in a liquid or capsule form. Most of it gets trapped by the thyroid gland. Very small amounts of iodine may also be taken up transiently by the cells of the stomach, salivary glands and ovaries/testicles.

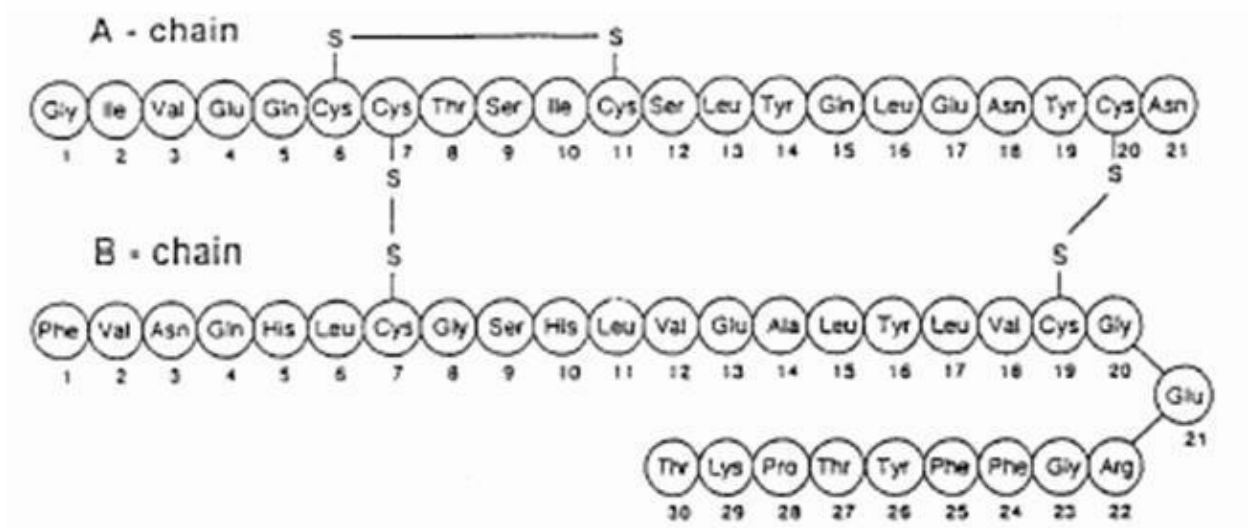
When it is given orally it is taken up by the thyroid gland by iodide trapping and concentrate within the thyroid follicles. It acts by emitting β and γ radiations. It has a t ½ of 8 days. Beta (β) rays are particles that penetrate and destroy cells of thyroid follicles up to 5mm distance producing fibrosis of tissues. Gamma (γ) rays are more penetrative.

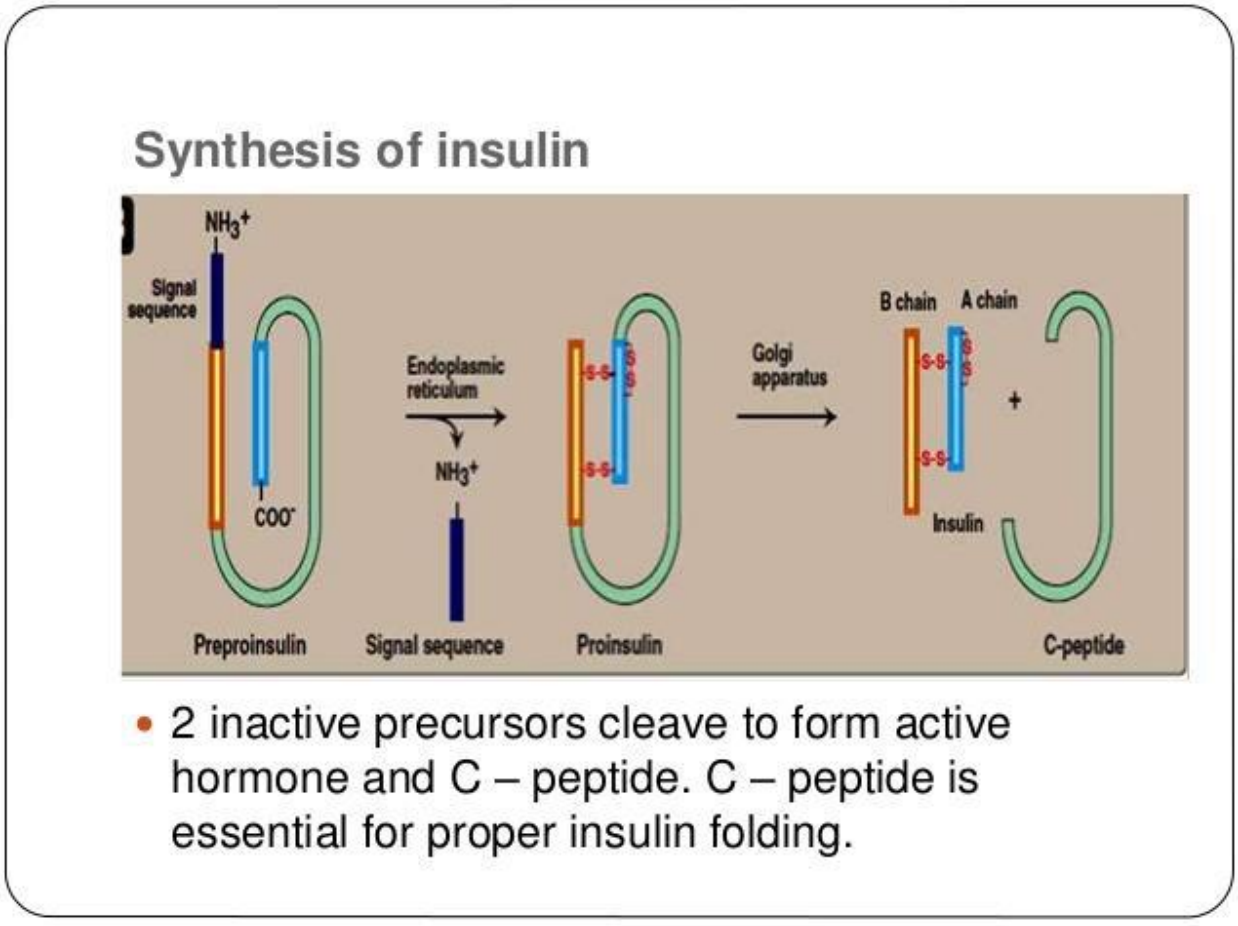
ADRs: It can produce hypothyroidism, thyroid carcinoma and damage to the foetal thyroid (if administered in pregnant woman), bone marrow depression, anemia, leucopenia, thrombocytopenia, etc.

Preparations: Radio iodine (I131) capsule, oral solution.

b. Anti-diabetic drugs- Insulin.

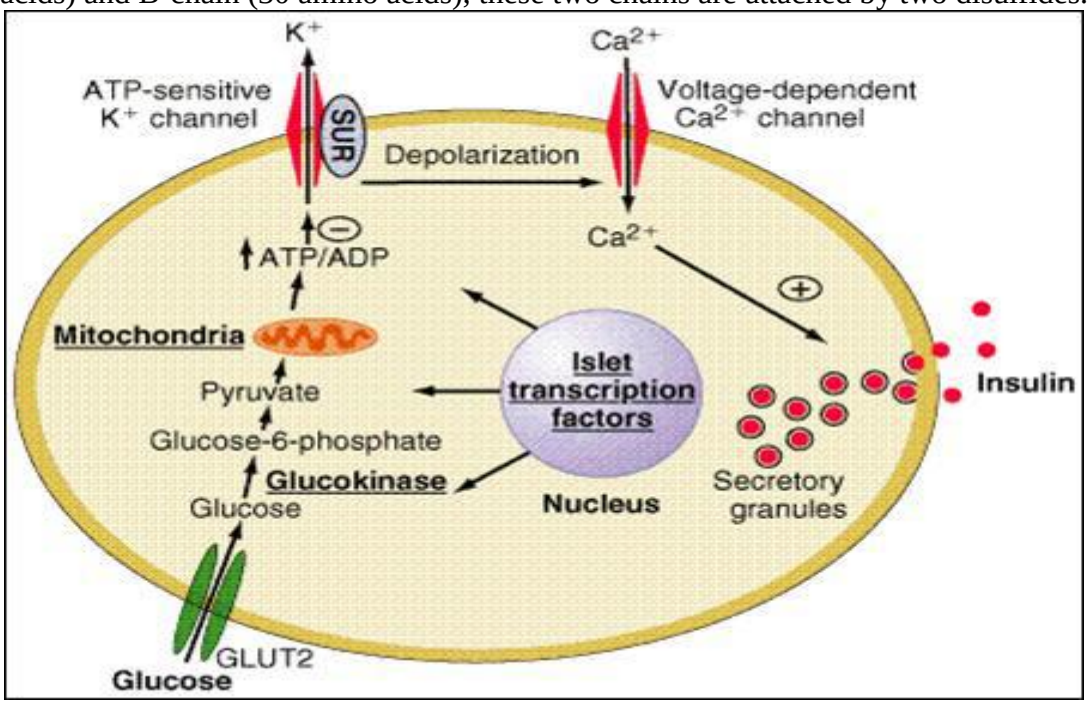
Insulin: It is a polypeptide hormone (containing 51 amino acids) secreted by the beta cells of islets of Langerhans of pancreas. It has two amino acid chains (A and B) joined together by disulfide linkages (-S-S-) which are essential for biological activity of insulin. It has disulfide linkage between 6th and 11th cystein amino acids within chain A. In between A and B chain there are two disulfide bonds. The first bond is in between 7th cystein amino acids of chain A and B. The second bond is in between 20th chain A and 19th chain B cystein amino acids. The insulin has a molecular weight of 5808Da. It was discovered by Banting and Best in 1922.





Synthesis of insulin: In mammals, insulin is synthesized in the pancreas within the beta cells of the islets of Langerhans. One million to three million islets of Langerhans form the endocrine part of the pancreas (2% of the total mass of the pancreas). Preproinsulin (containing 110 amino acids) is the primary translational product of the INS gene. Within 5-10min it is processed into proinsulin (containing 86 amino acids) in the ER of pancreatic beta cells. The proinsulin is then packed into Golgi complex, where it is converted into insulin(51 amino acids) by the actions of proteolytic enzymes prohormone convertase (PC1 and PC2) and carboxypeptidase E. C-peptide is a peptide composed of 31 amino acids. It is released from the pancreatic beta cells during cleavage of insulin from proinsulin. The C-peptide level in the plasma helps for the measurement

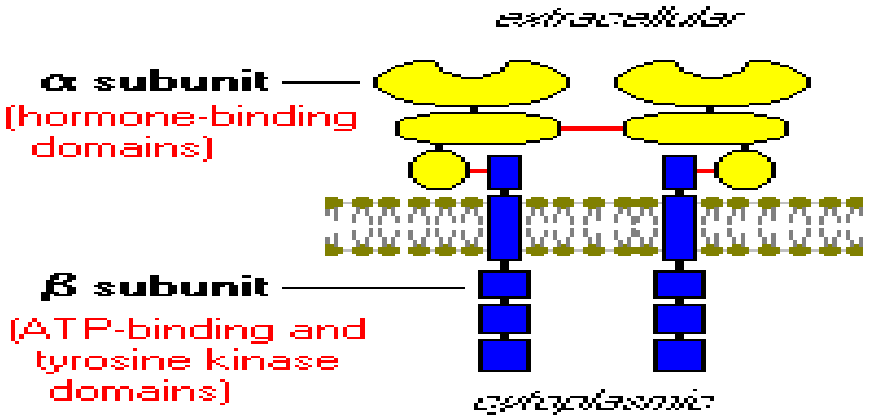
of extent of insulin secretion in DM patients. The mature insulin consisting of A chain (21 amino acids) and B-chain (30 amino acids), these two chains are attached by two disulfides.



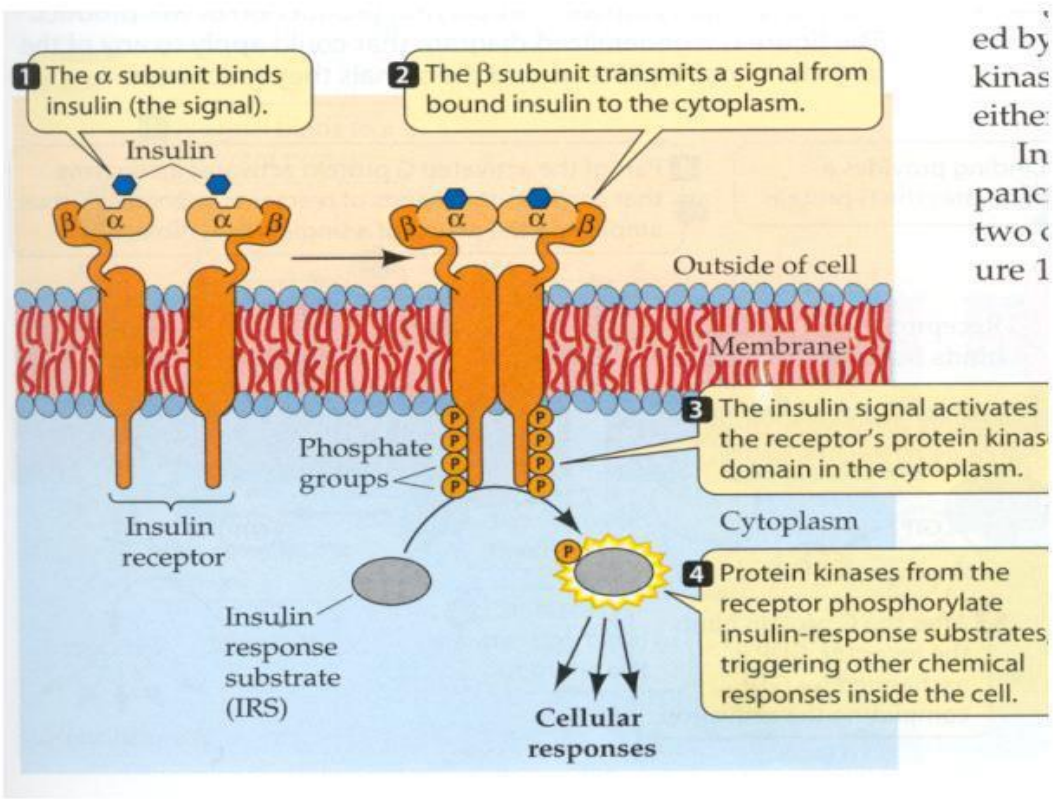
Storage and release of insulin: Insulin is packaged within the granules and stored in the β cells, from which it is released at a slow rate by exocytosis into circulation. The plasma concentration of insulin shows fluctuations throughout the day and peak plasma concentrations are produced after meals. In the basal state, the plasma membrane of beta cell is hyperpolarized, and the rate of insulin secretion from the beta cell is low. When glucose is available, glucose enters the cell via GLUT2 transporters in the plasma membrane. The glucose gets converted into glucose-6-phosphate by glucokinase. Then G6PO4 converted in to pyruvate. The pyruvate enters the mitochondria and ATPs are generated through respiratory cycle. This increases intracellular ATP concentration. ATP binds to ATP sensitive K+ channel (an ion channel made up of 8 sub units-octamer). This inhibits the K+/ATP channel and K+ conductance (out flux) decrease. This increases potential within the beta cells due to the accumulation of K+ ions. This results in depolarization of the membrane of the beta cell. This activates the voltage gated Ca2+ channels and thereby stimulates an influx of Ca2+. Calcium ions mediate exocytosis of insulin-containing secretory vesicles leading to insulin secretion.

Regulation of insulin secretion; Insulin secretion is regulated by many factors including blood glucose concentration, certain hormones and CNS. High blood sugar level stimulates insulin secretion. GIT hormones like gastrin, CCK (cholecystokinin) and secretin, which are secreted after meals, stimulates insulin secretion. CNS regulates the insulin secretion via ANS (α2 adrenergic stimulation) inhibits insulin secretion, whereas β2 stimulation and vagal stimulation increase insulin secretion. Drugs like sulfonyl urea and xanthins stimulate insulin release and thiazides, frusemide and phenytoin inhibit the insulin release.

MOA of insulin: The insulin receptors are expressed on the energy storing tissues like liver, muscle, and adipose tissue. The insulin receptor is a glycoprotein consisting of four disulfide linked sub-units, including two extracellular α subunits and two β subunits. Each of the β sub units is composed of a short extracellular domain, a trans membrane domain, and an intracellular tail that contains a tyrosine kinase domain.



The binding of insulin to the extracellular portion of the insulin receptor activates the intracellular tyrosine kinase, resulting in "autophosphorylation" of tyrosine on the nearby β subunit and in phosphorylation of several other intracellular proteins- insulin receptor-substrate proteins (IRS-proteins). Phosphorylated IRS proteins interact with many other signaling proteins to effect changes in cellular function, including glucose transport (via the translocation of GLUT4 glucose transport to the cell surface), protein synthesis and glycogen synthesis. Glucose that enters the cell is rapidly phosphorylated by hexokinase and subsequently used for metabolism or stored in the cell as glycogen or triglyceride.



Actions of insulin on target tissues: **Liver**; Insulin decreases glycogenolysis, gluconeogenesis, ketogenesis and increases the glucose uptake into the hepatocytes. Insulin increases protein synthesis and decreases protein breakdown.

Adipose tissue cells: Insulin increases glucose uptake and utilization of glucose. Insulin increases lipogenesis (increases fatty acid synthesis and triglycerides synthesis), but decreases lipolysis.

Skeletal muscle cells- Insulin increase glucose uptake and utilization. Insulin increases the glycogen synthesis. Insulin increase protein synthesis, but decreases its breakdown.

Effects of insulin deficiency: 1. Hyperglycemia and glycosurea, 2.Diabetic ketoacidosis- This is due to increased lipolysis especially triglycerides leading to increased levels of free fatty acids and ketones like acetoacetic acid and β hydroxybutyric acid in the blood.

3. Abnormal blood lipid pattern- Hypercholesteremia, hypertriglyceridemia and high LDL level with susceptible to atherosclerosis. 4. Muscle wasting. 5. Nephropathy, retinopathy, neuropathy, etc. 6.Suceptible to bacterial infections.

Clinical uses of insulin:

1. In all cases of type I DM.
2. In those cases of type II DM where-

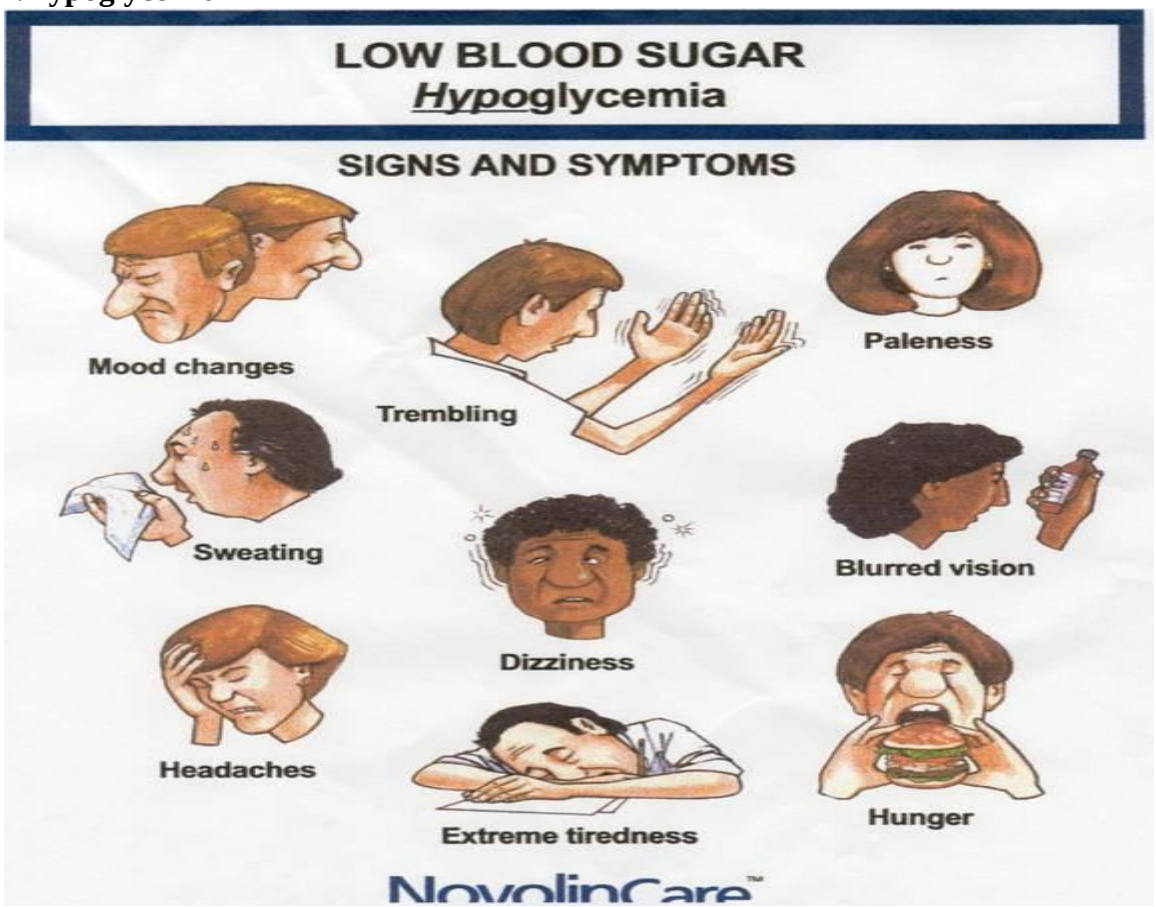
a. Diet, exercise- oral anti-diabetic drugs fail to control hyperglycemia.

b. If oral anti-diabetic drugs are contraindicated,

3. Insulin is used in hyperkalemia: Insulin with glucose (10%) IV drip is used to promote intracellular influx of potassium.
4. Insulin shock therapy is indicated in schizophrenia
5. Diagnostic test: Insulin tolerance test is used to test anterior pituitary function.

ADRs of insulin: **1.Allergy:** Local itching, redness, swelling and pain at the site of injection or generalized uriticaria and lymphadenopathy. It may be due to protamine (protein) in the preparation. Non protein insulin such as lente insulin is thus preferred than protamine insulin. Human insulin is devoid of antigenecity.

2.Hypoglycemia-



3. Lipotrophy: (localized loss of fat tissue).
4. Presbyopia: (eye loses its ability to focus on near objects)
5. Obesity: Insulin may increase the body weight, by anabolic action and preventing lipolysis.

8. Pharmacology of Hormones and Hormones Antagonists: Insulin preparations

1.Insulin aspart (Novolog)- It is a manufactured form of human insulin. It is a fast acting insulin analog marketed by Novo Nordisk.

Structure same as human insulin except the proline amino acid at position B-28 replaced by aspartic acid. Onset of action 15min, duration 2-4h

2.Insulin Lispro (Humalog)- It is another human insulin prepared by DNA recombinant technology. In normal human insulin – B-28 Proline and B-29 Lysine. But in insulin Lispro it is reversed- B-28 Lysine and B-29 Proline. Onset of action -15 min, duration 2-4h.

3.Insulin glulisine (Apidra) - It is another insulin analog.

B-3 Asparagine is replaced by lysine

B-29 Lysine is replaced by glutamic acid.

Onset of action -15 min, duration 2-4h.

4. Regular Insulin (Humulin or Novolin) - The only insulin that is approved to be administered via IV route. Its sources are pork (porcine), beef (bovine) , human pancreas or genetically engineered by DNA recombinant technology using *E.Coli*. Onset of action- 30-60min, duration- 6-8h.

5.Isophane Insulin Suspension or Neutral Protamine Hagedorn (NPH)- (Humulin N or Novolin N)

It is a sterile suspension of insulin zinc crystals and protamine sulfate a protein from the sperm of fish. Onset of action – 1-2h duration -10-16h

6.Insulin zinc suspension(Lente)-

It is a sterile suspension of insulin modified by the addition of Zinc chloride. It has fewer allergic reactions than NPH. Onset of action – 1-2h duration -10-16h

7.Glargine (Lanctus)-

A-21 Asparagine is replaced by glycine and addition of two arginine residues to B-30. Onset of action – 2h and duration- 24h

8. Extended insulin Zinc suspension (Ultra Lente) - It is a sterile suspension of insulin modified by the addition of Zinc chloride. Onset 4-8h duration -36h

9.Insulin Detemir-It is an analog of insulin. B-30 amino acid is replaced by myristic acid (a 14 carbon atom fatty acid chain). Duration -24h

10.Insulin combinations-

a.Novolin 70/30 (70 % NPH 30% regular insulin).

b.Humulin 50/50 (50% NPH 50% regular insulin).

Oral hypoglycemic agents:

Classification, mechanism of action, salient features of oral anti-diabetics including newer agents.

Oral hypoglycemic agents are given orally to reduce blood sugar in DM type II. OCPs are classified as follows

1.Insulin secretagogues-

a.Sulfonylurea- First generation- tolbutamide, chlorpropamide, Second generation – glibenclamide, glipizide, gliclazide, glimiperide.

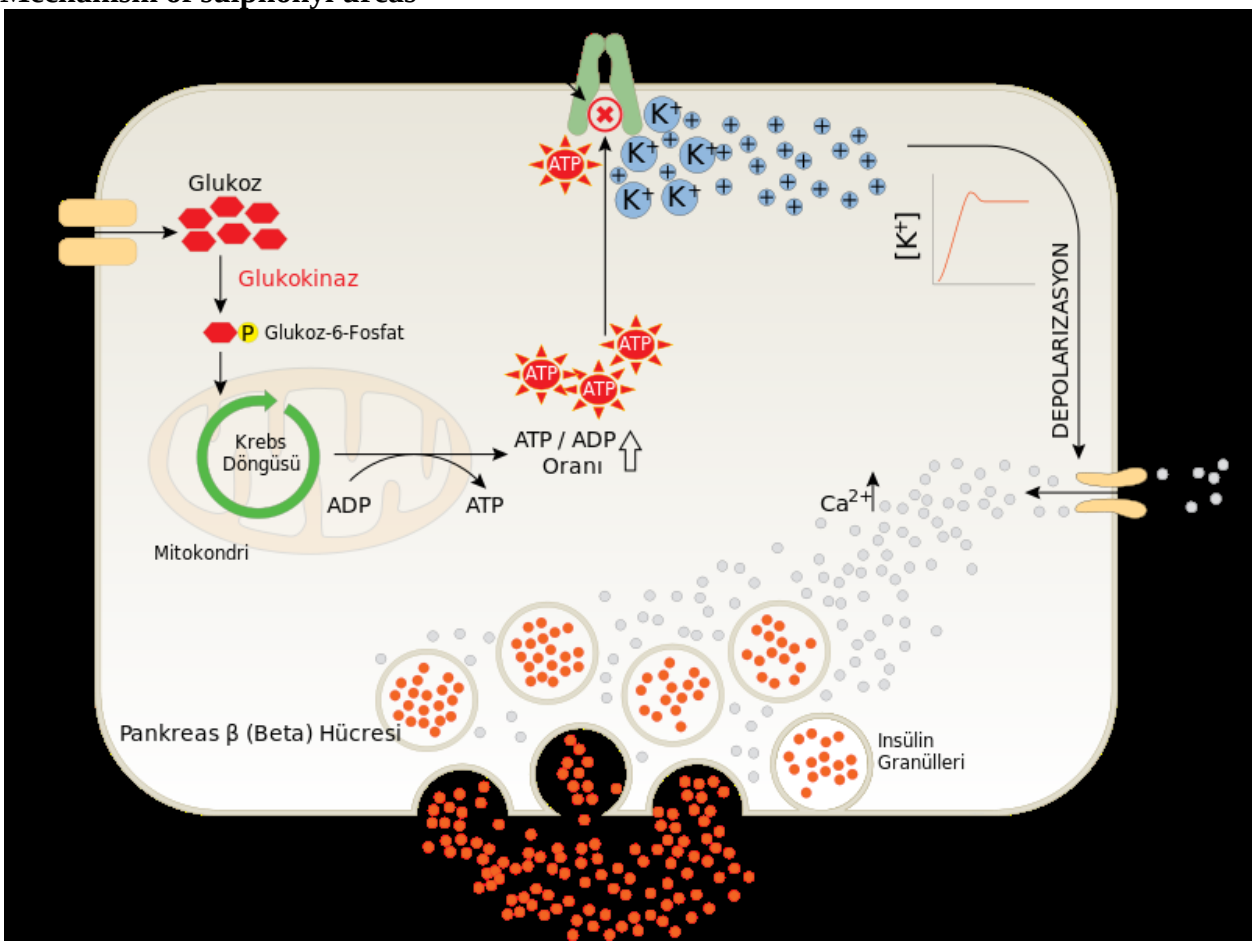
b.Maglitinide analogue-Repaglinide, nateglinide.

2.Insulin Sensitizers- a.Biguanides- Metformin

b.Thiazolinediones (TZD)- Troglitazone, pioglitazone, and rosiglitazone.
3.α-glucosidase inhibitors--
4. Dipeptidyl peptidase IV inhibitors-

1.Insulin secretagogues- Useful in patients, with DM type II, cannot be managed by diet alone. It is useful in patients if DM occurs above 40 years. These should not be given to patients with type I DM. These drugs promote the release of insulin from beta cells of pancreas.

Mechanism of sulphonyl ureas



- a.Sulphonylureas act by blocking the ATP sensitive K+ channels on the beta cells of the islets. This decreases the efflux of potassium ions (cat ions). This increases the accumulation of K+ within the cells. The voltage increases. The increased voltage leads to the opening of voltage gated calcium channels. The rise in intracellular calcium leads to exocytosis of insulin containing vesicles causing insulin release from the beta cells.
b. Sulphonylurea drugs also act by reducing the glucose production in the liver.
c. Sulphonylurea drugs also act by increasing peripheral insulin sensitivity.

ADME- Given orally, binds to plasma proteins, metabolized in the liver and metabolites are eliminated through urine.

Tolbutamide has shortest duration of action -6 to 12h. The second generation agents last about 24h.

ADRs- Hyperinsulinemia, hypoglycemia, weight gain. These drugs used with caution in renal or hepatic in-sufficiency patients, because delayed excretion leading to its accumulation results in hypoglycemia.

b.Maglitinide analogue-Repaglinide, nateglinide. They are not sulfonyl ureas, but they have common actions. They have rapid action but shorter duration. These should not be given along with sulfonylureas due to overlapping mechanism of action.

ADME- These are given orally. These drugs absorbed better if given 1-30min before meals. In the liver both repaglinide and nateglinide are metabolized by CYP3A4 enzymes to inactive metabolite. These metabolites are excreted through bile.

ADRs- Incidence of hypoglycemia is lower than that of sulfonylureas. Repaglinide has been reported to shown severe hypoglycemia in patients who are also taking lipid lowering drug-gemfibrozil. Weight gain problem is less compared to sulfonylureas.

Preparations- Repaglinide- 1, 2mg tabs, Nateglinide tabs- 60, 120mg tabs.

2.Insulin Sensitizers- Biguanides and thiazolinediones (TZD)

These drugs lower the blood sugar level by improving target cell response to insulin without increasing the insulin secretion.

a.Metformin- This is only currently available biguanide. It increases the glucose uptake and utilization by the target tissues- adipose tissue, liver and skeletal muscles. It act by decreasing the insulin secretion. These drugs do not cause hyperinsulinemia, hence no hypoglycemic effect.

Mechanism- Metformin decreases hepatic glucose production, decreases intestinal absorption of glucose, and improves insulin sensitivity by increasing peripheral glucose uptake and utilization. Unlike sulfonylureas metformin does not produce hypoglycemia in either patients with type 2 DM or normal subjects and does not cause hyperinsulinemia. Metformin requires insulin for its action but it does not promote the insulin secretion. Metformin may be used alone or in combination. Hypoglycemia may occur if given in combination.

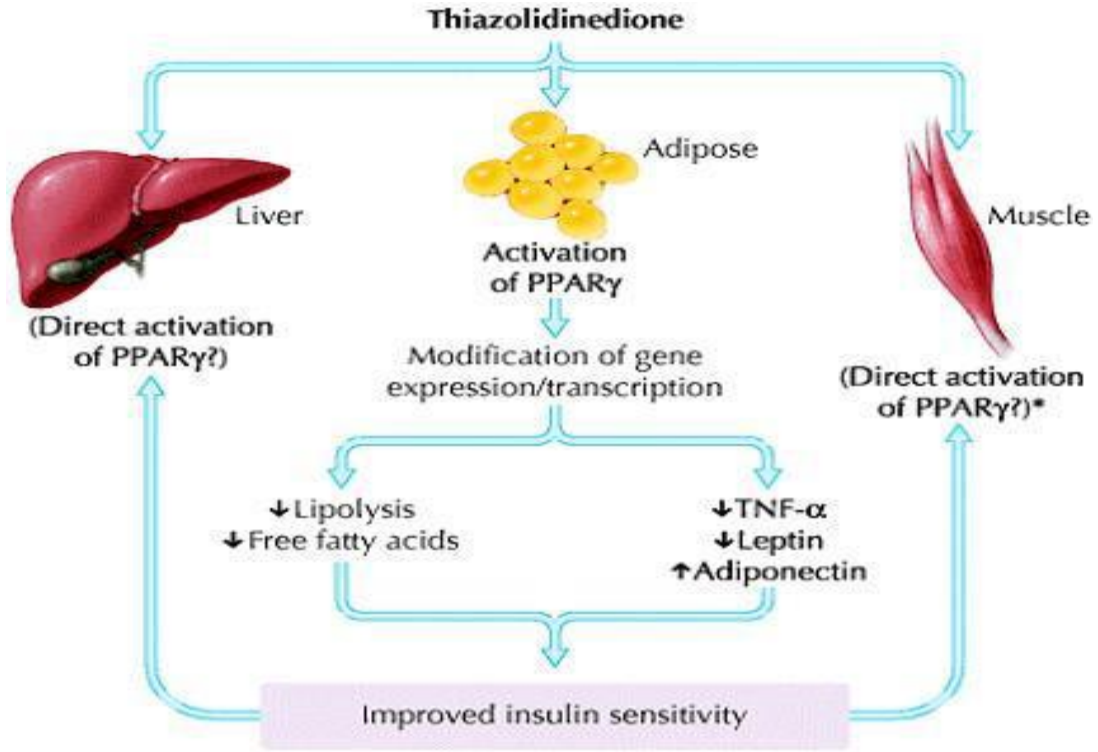
ADME- It is well absorbed orally. It is not bound to plasma proteins. It is not metabolized and excreted in the urine.

ADRs- Long term use may leads to vit B12 deficiency. It should be given with caution to diabetic patients with hepatic and renal disease, acute MI, severe infection, or diabetic keto acidosis. It should be given with caution to diabetic patients with age more than 80 years.

Thiazolinediones (TZD)-Troglitazone, pioglitazone, and rosiglitazone.

Troglitazone was withdrawn after a number of deaths due to hepato toxicity were reported.

TZDs act by activating peroxisome proliferative activated receptors, a group of nuclear receptors, with greatest specificity for PPAR-gamma or PPAR-γ. They are thus the PPAR-γ agonists. The endogenous ligands for these receptors are free fatty acids and eicosanoids. When TZD binds to the receptors, the activated receptors binds to another receptors- retinoid X receptors and this complex binds to the specific genes of the DNA. This interaction increases the transcription of a number of specific genes and decreasing the transcription of others. The main effect of expression and repression of specific genes is an increase in the storage of fatty acids in adipocytes, thereby decreasing the amount of fatty acids present in the circulation. As a result, cells become more dependent on the oxidation of carbohydrates (glucose), to yield ATPs. Thus glucose utilization increases. TZD also act by increasing insulin sensitivity in adipose tissue, skeletal muscle and liver.



ADME- Both pioglitazone, and rosiglitazone are absorbed well after oral route of administration and are extensively bound to plasma proteins- albumin. Both undergo metabolism by different CYP-450 isoenzymes. Pioglitazone (free form) and its metabolite are eliminated mainly through bile and in the feces. The rosiglglitazone (free form) and its metabolites are mainly eliminated through urine.

ADRs- Headache, anemia, ostopenia (decreased bone density), increased fracture risk, weight gain.

3.α-glucosidase inhibitors- Acarbose, miglitol.

α-glucosidase inhibitors (Acarbose) are saccharides that act as competitive inhibitors of enzymes needed to digest carbohydrates; specifically alpha-glucosidase enzymes in the brush border of the small intestines. The membrane bound intestinal alpha-glucosidases hydrolyze oligosaccharides (2-10 manosaccharides), trisaccharides, and disaccharides to glucose and other monosaccharides in the small intestine.

Acarbose also blocks pancreatic alpha-amylase enzyme in addition to inhibiting membrane bound alpha-glucosidases. Pancreatic alpha-amylase hydrolyses complex starches to this use Aoligosaccharides in the lumen of the small intestine.

Inhibition of these enzyme systems reduces the rate of digestion of carbohydrates. Less glucose is absorbed because the carbohydrates are not broken into glucose molecules. These drugs do not stimulate insulin release or increase the sensitivity of insulin on the target tissues.

ADME- These drugs are administered orally and are taken at the beginning of meals.

ADRs- As mono therapy, they do not cause hypoglycemia. However, when used in combination with the sulfonylureas or with insulin, hypoglycemia may develop. Other ADRs include- flatulence, diarrhea, and intestinal cramping. Patients with inflammatory bowel disease (IBD), colonic ulceration, or intestinal obstruction should not use these drugs.

ADME- It is administered orally at the beginning of meals. It is poorly absorbed and excreted through the urine. Miglitol is very well absorbed but has no systemic effects. It is excreted unchanged through the urine.

Uses- It is used in DM type II to reduce postprandial hyperglycemia. It may be used as monotherapy along with diet and exercise or in conjugation with other antidiabetic drugs.
It may also be useful in DM type I but this use not has been approved by FDA.
Preparations- Acarbose 50, 100mg tabs, Meglitol 25, 50, 100mg tabs **4. Dipeptidyl peptidase IV inhibitors- (Gliptins)- Sitagliptin**
DPP-4 or gliptins are a class of oral hypoglycemic drugs that block DPP_4. They can be used to treat DM type 2. The first agent of the class- sitagliptin was approved by the FDA in 2006.
Mechanism- Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) are the two primary incretin hormones secreted from the intestine on ingestion of glucose or nutrients to stimulate insulin secretion from pancreatic β cells. Sitagliptin act by competitively inhibiting the enzyme dipeptidyl peptidase 4 (DPP-4). This enzyme breaks down the incretins GLP-1 (glucagon like peptide) and GIP, the GIT hormones released in response to a meal. By preventing GLP-1 and GI(gastric inhibitory peptide) inactivation, they are able to increase the secretion of insulin and suppress the release of glucagon by the alpha cells of the pancreas. This drives blood sugar level to normal level. Sitagliptin may be used as monotherapy or in combination with metformin or pioglitazone.
ADME- It is well absorbed after oral administration. The majority of sitagliptin is excreted unchanged in the urine.
ADRs- Nasopharyngitis, headache, hypoglycemia (if given along withother antidiebetic drugs).
Preparations- Sitagliptin (Januvia)- 50, 100mg tab

Pharmacology of oxytocin, other uterine stimulants and relaxants (tocolytics).

Uterine stimulants (Ecbolics, abortificients) are the drugs which cause contraction and increase the motility of the uterus.
1.Posterior pituitary hormone- Oxytocin
2.Ergot alkaloids- Ergometrine, methyergometrine.
3.Prostaglandins- PGE2, PGF2α, 15-methyl PGF2α, misopristol.
4.Miscellaneous- Ethacridine, quinine.

Oxytocin-
Oxytocin is an octapeptide, structurally similar to vasopressin. It is synthesized by the paraventricular nucleus of the hypothalamus and stored in the synoptic vesicles of the posterior pituitary gland. It is synthesized as a large precursor molecule rapidly broken down to the active enzyme. After synthesis they get packed in the granules of the synoptic vesicles of the posterior pituitary gland.

Actions of oxytocin-
1.Uterus- Oxytocin causes contraction of uterus during child birth. Oxytocin also increase the synthesis of prostaglandins. The released PGs also increase the contractions of the uterus.
Mechanism- The oxytocin receptors are expressed on the pregnant uterus and mammary glands. These receptors belong to G-protein coupled receptors (Gq type). The oxytocin binds to the OT receptors, the alpha-GTP binds to the PLC. The stimulated PLC leads to the formation of second messengers- IP3 and DAG. These second messengers trigger the calcium concentration within the cell. The calcium binds to calmodulin protein. The Ca-Cam complex activates MLCK. The activated MLCK phosphorylates MLC to MLC-P. The MLC-P causes contraction of the myometrium of the uterus.
2.Breast- Oxytocin also causes contraction of myoepethelial cells of the mammary glands leading to milk ejection.
3.CVS- The conventional dosage used in obstetrics have no effect. But higher doses cause vasodilation, decrease of BP, reflex tachycardia, flushing.
4.Kidney- Conventional doses no effect. But higher doses cause ADH like effect (antidiuretic effect).

Physiological roles of oxytocin-

1.Labour- Oxytocin released in excess during labour to facilitate baby delivery. Increased secretion of PGs and PAF also facilitate the labour. 2. Milk ejection reflex is initiated by oxytocin.

3. Oxytocin acts as a neurotransmitter in the hypothalamus and brain stem.

ADME- Administered by iv or im routes. About 30 % of the administered drug bound to plasma proteins. Oxytoci is metabolized in the liver and the plasma by the enzyme oxytocinase. To the small extent it is also metabolized by the mammary glands.The metabolites and free form eliminated through both bile and urine.

Uses-

1.Induction of labour

2.In uterine inertia (absence of effective uterine contractions during labour)

3.Used in postpartum hemorrhage (PPH) (PPH is defined as the loss of more than 500ml or 1000ml of blood within first 24 h following child birth).

4.In breast engorgement (painfully overfull of milk in the breast).

5.Oxygen challenge test- (used to check utero-placental adequacy in high risk pregnancies)

Oxytocin is used for induction of labor, controlling bleeding after child birth, and treatment of incomplete or inevitable aborption.

ADRs- Nausea, vomiting, severe allergic reactions, repture of the uterus, high BP, abnormal heart rate, water intoxication due to its ADH like action.

Drug interactions- Severe elevations in BP may occur if combined with vasoconstrictors used for anesthesia.

Preparations- Oxytocin, syntocinon 2IU/ml, and 5IU/ml.

Ergometrine- It is a ergot alkaloid. Its actions are

1.Uterus- It increases force, frequency and duration of uterine contractions.

2.CVS- weaker vasoconstriction effect.

3. CNS- No effects at normal doses. But higher doses may interact with some receptors in the brain.

4.GIT- High doses may increase peristalsis.

Uses- 1.It is used to control and prevent PPH. 2.Used to prevent uterine atony.

Preparations- Ergometrine 0.25, 0.5mg tabs, 0.5mg/ml inj

Pharmacology uterine relaxants (tocolytics)

Tocolytics are the drugs which reduce or stop uterine contractions and decrease uterine motility. These are used to delay or postpone labour. Tocolytics can delay labour and give more time for fetal growth and for the fetal lungs to mature. They are also used to arrest threatened abortion (a threatened abortion is vaginal bleeding that occurs in the first 20 weeks of pregnancy) and in dysmenorrhoea (painful periods).

Classfication of tocolytics

1.Adrenergic agonists- Ritodrine.

2.Magnesium sulfate-

3.Calcium channel blockers- Nifedepine

4.Prostaglandin synthesis inhibitors- Aspirin, diclofenac and indomethacin.

5.Alcohol- Ethyl alcohol-

6.Sex hormones- Progesterone-

7.Miscellaneous- Nitrites, atropine and general anesthetics

1.Adrenergic agonists- Ritodrine.

Ritodrine is a tocolytic agent used for the treatment and prevention of premature labour. β2 receptors are located in the uterus. Ritodrine is a β2 receptor agonist. It stimulates β2 receptors.

The α-GTP stimulates the adenylyl cyclase enzyme. The stimulated adenylyl cyclase increases cAMP level and decreases intracellular calcium concentration. The decrease of calcium contraction leads to a relaxation of uterine smooth muscle and, therefore a decrease in premature uterine contractions.

ADME- Administered orally and parenterally. It is bound to plasma proteins (56%). It is metabolized in the liver both in mother and fetus.

ADRs- Increase in heart rate, BP, arrhythmia, water retention, hyper glycemia (due to concurrent beta 1 agonistic effects), post partum hemorrhage (PPH). It should be given caution to DM patients and patients with hypertension and cardiac problems.

Uses- It is used for the treatment and prevention of premature labour.

Preparations- Ritodrine 10mg tab, 10mg/ml inj.

2.Magnesium sulfate- It is a tocolytic agent. It inhibits the uterine contractions by inhibiting calcium uptake by the smooth muscles of uterus. Continuous administration of magnesium sulfate is an unapproved treatment for premature labour. The safety and efficacy of such use have not been established.

3.Calcium channel blockers- Nifedepine

The influx of calcium ions in the smooth muscles of uterus is important for the uterine contractions. Calcium channel blockers (nifedepine) act by blocking the calcium channels present on the smooth muscles of uterus. This causes relaxation of the uterine smooth muscles. Oral administration of nifedipine 10 mg every 20-30 min till uterine contractions subside, followed by 10mg once in six hours has been used.

ADR- Hypotension and tachycardia.

4.Prostaglandin synthesis inhibitors- Aspirin, diclofenac and indomethacin.

These are effective in dysmenorrhoea, because prostaglandins are produced locally in the uterus are responsible for this condition.

5.Ethyl alcohol- If alcohol if given by iv infusion it prevents labour. But it causes maternal CNS depression, foetal hypoxia. Hence it is not recommended.

6.Progesterone- It decreases the sensitivity of oxytocin. It is used in threatened/habitual abortion.

7.Miscellaneous- Nitrites, atropine and general anesthetics also reduce uterine contractions, but have poor efficacy.