Study Material

B.Pharm 5th Semester

Sub: PHARMACOLOGY-II (Theory)

Sub. Code: BP503T

UNIT-IV

Topic: 1. Pharmacology of drugs acting on endocrine system

Chapters:

a. Basic concepts in endocrine pharmacology.
b. Anterior Pituitary hormones- analogues and their inhibitors.
c. Thyroid hormones- analogues and their inhibitors.
d. Hormones regulating plasma calcium level- Parathormone, Calcitonin and Vitamin-D.
d. Insulin, Oral Hypoglycemic agents and glucagon.
e. ACTH and corticosteroids.

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a. Basic concepts in endocrine pharmacology

The word endocrine implies internal secretions poured directly into the blood; hence the endocrine glands are also called the ductless glands. The chemicals secreted by the endocrine glands are called hormones. Chemically hormones may be peptides, steroids, amines or derivatives of amino acids.

Characteristics of hormones:

1. Act in very low concentration
2. Synthesized and stored in glands (except posterior pituitary hormones)
3. Produce their effect at the target organ far away from the gland
4. Have a regulatory role on the physiological functions
5. Rapidly destroyed after their functions are over

Table.1. Endocrine glands, their hormone and their chemical nature

Endocrine gland	Hormone secretions
1. Pituitary (Anterior)	Growth hormone (GH), Prolactin Thyroid Stimulating Hormone (TSH) Follicle Stimulating Hormone (FSH) Leutenizing Hormone (LH) Adrenocorticotropic Hormone (ACTH)
Pituitary (Posterior)	Oxytocin, Vasopressin
2. Thyroid	Tri-iodo-thyronine (T3), Thyroxin (T4), Calcitonin
3. Parathyroid	Parathormone
4. Adrenal gland	Glucocorticoids, Mineralocorticoids, Sex-steroids (estrogen, progesterone and androgens), Adrenaline
5. Pancreas	Gluocagon, Insulin, Somatostatin
6. Testis	Testosterone
7. Ovary	Estrogen, Progesterone

Mechanism of action of hormones:

Many hormones bind to their specific receptors that may be nuclear or on the cell surface of the target cells and produce two effects:

1. Activation of genome and increase their protein synthesis
2. Activation of second messenger like cyclic AMP

b. Anterior Pituitary hormones- analogues and their inhibitors

1. Growth hormone:

Growth hormone (GH) or somatotropic hormone (STH) is secreted by acidophil cell of anterior pituitary gland. It is a polypeptide with 191 aminoacids residue. The secretion of GH from the anterior pituitary is controlled by hypothalamus through GH releasing factor.

Mechanism of action:

GH bind to growth hormone receptor located on cell surface and induces dimerization of a protein janus kinase 2 (JAK2). This JAK2 undergo autophosphorylation and activates signaling pathways involving various kinase, finally affects gene expression in the nucleus and increase synthesis of various proteins.

Functions of GH:

1. Increase body growth
2. Protein metabolism
3. Fat metabolism
4. Carbohydrate metabolism

Hypersecretion of GH in the young causes “Gigantasim” and in adult it causes “acromegali”. Hyposecretion of GH in young causes “Dwarfism”.

GH analogues:

There are three types of GH analogues:

1. Somatropin: DNA recombinant GH
2. Somatrem: Derivative of GH
3. Sermorelin acetate: Synthetic form of GH releasing factor

Use: These are used for replacement therapy in GH deficient children and for patients with Turner’s Syndrome to improve adult height.

Adverse effect: Intracranial hypertension, headache, nausea, vomiting and type-2 diabetes

GH inhibitors:

These are somatostatin analogues like Octeretide, Lanreoptide and Valpreotide, these analogues decrease GH secretion. GH antagonist like Pegvisomant have been developed for the treatment of acromegali.

Adverse effect: GI adverse effect like diarrhea, nausea, abdominal pain and gall stone

2. Prolactin:

It is a peptide hormone secreted by acidophilic cells of anterior pituitary. It is responsible for lactation in the post partum state of women. The secretion of prolactin is also controlled by hypothalamus through prolactin releasing factor.

Prolactin inhibitor:

1. Pergolide and Cabergoline: These are ergot alkaloids.
2. Bromocriptine: A semisynthetic ergot alkaloid
3. Quinagolide: It is a non ergot

These are dopamine D2 receptor stimulant and used in the treatment of hyperprolactinemia, galactorrhoea and purperal lactation. It also induce ovulation and permits a women to become pregnant.

c. Thyroid stimulating hormones- analogues and their inhibitors

It is a glycoprotein released from the anterior pituitary and its secretion is controlled by hypothalamus through TSH releasing factor. TSH controls the activity of thyroid gland by regulating the uptake of iodide by the gland. It also affects the enzymes involved in the various stages of synthesis and release of the thyroid hormones. The blood level of TSH can be assessed by radioimmunoassay. The main use of TSH is as a diagnostic agent to differentiate primary hypothyroidism and secondary hypothyroidism.

Synthesis and release of thyroid hormones:

The synthesis and release of thyroid hormones from the thyroid gland takes place by following steps:

1. Uptake of iodide
2. Oxidation of iodide to free iodine and iodination of tyrosine
3. Formation of thyroxine (T4) and triodothyronine (T3) by coupling of iodotyrosines
4. Proteolysis of thyroglobulin and release of T4 and T3
5. Peripheral conversion of T4 to T3 by deiodination

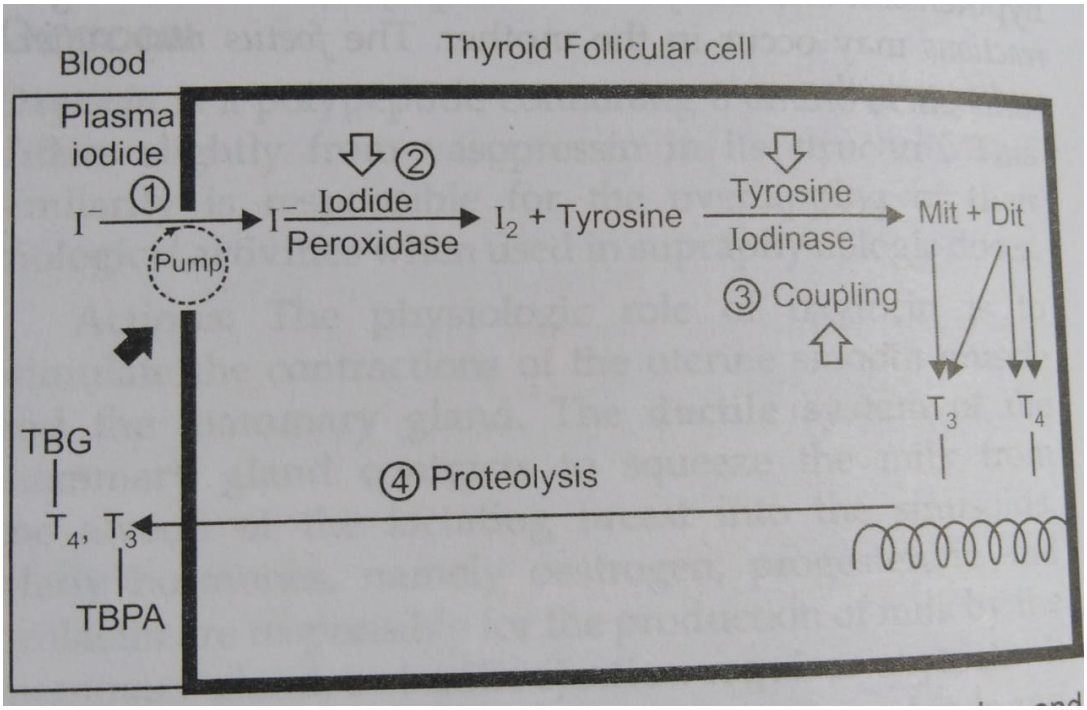

Fig.1. Biosynthesis and release of T3 and T4

1. Iodide trapping 2. Oxidation of iodide 3. Coupling of iodotyrosines
4. Proteolysis of thyroglobulin (Mit= Monoiodotyrosine; Dit= Diodotyrosine)

Function of Thyroid hormones:

1. Increase calorigenesis and raise basal metabolic rate (BMR)
2. Increase carbohydrate and protein metabolism
3. Hypolipidemic effect
4. Increase heart rate, contractility and cardiac output
5. Increase calcium mobilization from bone
6. Normal development of nervous system
7. Essential for normal body growth and development

Deficiency of thyroid hormones called hypothyroidism, the disease associated with hypothyroidism is called myxoedema. Excess secretion of thyroid hormones is called hyperthyroidism, it occurs in two major forms; (i) Diffuse toxic goiter (Graves' disease) and (ii) Toxic nodular goiter (Pulmmer's disease)

Thyroid hormones analogues:

1. Levothyroxine: This is a synthetic thyroxine (T4), readily absorbed from the gut and is the drug of choice for management of hypothyroid disorder. Average dose is 150 mcg daily.

2. Liothyronine: This is a synthetic triodothyronine (T3), it has rapid onset and short duration of action. It is the drug of choice in an emergency situation like myxoedema coma. Dose 5 to 10 mcg daily orally.
3. Liothrix: It is 4:1 mixture of synthetic T4 and T3. It is orally active.

Anti-thyroid drug or thyroid hormone inhibitor:

1. Inhibitors of thyroxine synthesis: Propylthiouracil, Methylthiouracil, Methimazole, Carbimazole
2. Drug that destroy thyroid tissue: Radioactive iodine (I^{131})
3. Drugs with uncertain mode of action: Potassium iodide, Sodium iodide, Lugol's solution

1. Propylthiouracil, Methylthiouracil, Methimazole, Carbimazole: These are thioamide, inhibits the synthesis of thyroid hormones. The antithyroid effect may range from several days to weeks. When thyroxine synthesis is diminished, the secretion of TSH is increased, this leads to thyroid hyperplasia.

MOA: The thioamides inhibit the formation of thyroxin mainly by interfering with: (i) the iodination of tyrosine and (ii) the coupling and condensation of iodotyrosine.

Adverse effect: Goitrogenic action, allergic reactions, leucopenia, and agranulocytosis

Therapeutic uses: Hypothyroidism (Graves' disease)

Contraindication: Use should be minimized in pregnancy and lactating mother

2. Radioactive iodine (I^{131}): I^{131} is mostly as antithyroid drug and accumulates in the thyroid gland, emits beta and gama radiation.

MOA: It emits beta and gama radiation, the biological activity is attributed to ionizing beta radiation, which destroy the thyroid cells within few weeks.

Adverse effect: Hypothyroidism, bone marrow depression, thyroid carcinoma and chromosomal abnormalities.

Therapeutic uses: Selected cases of hyperthyroidism, thyroid carcinoma

Contraindication: Pregnancy and lactation

3. Iodide: It is used in the treatment of iodine deficiency goiter but paradoxically, if iodide is administered to hyperthyroid patients, there is a reduction in the vascularity and swelling of glands. The gland shrinks and this response reaches its maximum in 10 to 15 days.

Therapeutic uses: Used to prepare hyperthyroid patients for surgery

d. Hormones regulating plasma calcium - Parathormone, Calcitonin and Vitamin-D

Calcium metabolism in the body is mainly controlled by two hormone, parathormone from the parathyroids and calcitonin from the parafolicular cells of the thyroid gland. In addition, vitamin-D also regulate plasma calcium level.

1. Parathormone (PTH): It is a large polypeptide hormone containing 84 amino acids secreted from the parathyroid gland present posterior to the thyroid gland. Release of PTH is stimulated by a fall and inhibited by a rise in the ionized Ca^{+2} level in plasma.

Action: Produce hypercalcemia by:

(i) Bone: PTH increase resorption of bone by promoting osteoclastic activity and decreasing osteoblastic activity.
(ii) Kidney: PTH decrease the calcium and phosphate clearance
(iii) Intestine: Promote intestinal calcium absorption in presence of Vit-D

Therapeutic use: Parathyroid injection 20 to 40 USP units twice daily subcutaneously or intramuscularly used for the early control of tetany due to hypoparathyroidism.

Adverse effect: Over dose with PTH causes hypercalcaemia, vomiting, diarrhea. Prolonged use of PTH can leads to demineralization of bone and metastatic calcification in the kidney.

2. Calcitonin: Calcitonin is a small polypeptide hormone with 32 amino acids, synthesized and secreted by the parafollicular cells (C cells) of the thyroid gland. Calcitonin release is regulated by the ionized calcium concentration in the blood. Hypercalcaemia promotes its release and vice versa.

Action: Produce hypocalcemia by:

(i) Bone: Calcitonin inhibit bone resorption by decreasing osteoclastic activity and increasing osteoblastic activity
(ii) Kidney: Promoting urinary excretion of calcium and phosphate

Calcitonin Preparation: Synthetic compounds that resemble the polypeptide hormone is salmon calcitonin and human calcitonin.

Therapeutic Use: Salmon calcitonin 40 to 160 units daily, sc or im or iv and human calcitonin in a dose of 0.5 mg daily is used in hypercalcemic state, Paget's disease.

Adverse effect: Mild hypocalcemia

3. Vitamin-D: Vitamin-D designated as a group of related sterols (contain cyclopentano-perhydrophenanthrene ring). It has more than 6 components, of them Vit-D_2 and D_3 are most potent. Vit D_2 (ergocalciferol) an isomer of ergosterol and Vit-D_3 (cholecalciferol) are sources for Vit-D activity and are referred as provitamins. Both cholecalciferol and ergocalciferol are the substrate for both 25-hydroxylase enzyme of liver and α-hydroxylase enzyme of kidney to form 25(OH)D_3 (Calcifediol) followed by 1,25$(OH)_2$ D_3 (calcitriol). This conversion step is modulated by PTH.

Source: The source of Vit-D_2 (ergocalciferol) is vegetable where as Vit-D_3 (cholecalciferol) is produced in the skin from 7-dehydrocholesterol by the action of UV light from the sun and also from egg, milk, fish.

Action of calcitriol:

(i) Bone: Maintains the store of calcium in the mitochondria, thus is essential for PTH-induced bone resorption
(ii) Kidney: Increase calcium reabsorption
(iii) Intestine: Promote the absorption of calcium

Deficiency: Vit-D deficiency gives rise to rickets in children and osteomalacia in adults.

Therapeutic use: Treatment of rickets and osteomalaia

Adverse effect: Hypervitaminosis-D, hypercalcaemia, hyperphosphataemia and metastatic calcification.

e. Insulin, Oral Hypoglycemic agents and glucagon

The pancreas has both endocrine and exocrine functions. The exocrine secretions are mostly the digestive enzymes such as amylase, trypsine, chemotrypsine and lipase.The pancreas contains islets of Langerhans. The islets of Langerhans contain four types of secretory cells:

(i) Alpha cells-secrets glucagon
(ii) Beta cells-secrets insulin
(iii) Delta cells-secrets somatostatin and
(iv) PP (F) cells-secrets digestive enzymes

1. Glucagon: It is derived by the proteolytic cleavage of proglucagon (a large peptide). Its half life is 3-5 min. Decrease blood level of glucose, exercise, high protein diet stimulate glucagon release. Glucagon raise blood glucose by accelerating breakdown of glycogen into glucose in liver (glycogenolysis) and conversion of lactates and amino acid into glucose in the liver (gluconeogenesis), releasing glucose into blood.

   Therapeutic uses: To treat severe hypoglycaemia or hypoglycemic coma due to insulin in patients of type-1 diabetes.

2. Insulin: Insulin is a polypeptide, composed of an A-chain (acidic) made up of 21 amino acids and a B-chain (basic) of 30 amino acids, linked by two disulphide (-S-S-) bridges and both A and B-chain is joined by a connecting peptide (C-peptide) composed in man of 31 amino acids.The immediate precursor of insulin in beta cell is proinsulin.

   The most important factor controlling insulin secretion is glucose. An increase in blood glucose promotes insulin secretion from beta cell. The total insulin content of pancreas is about 200 units, normal man secrets about 50 units of insulin per day. Insulin produces its action through specific insulin receptors which consist of α and β sub unit.

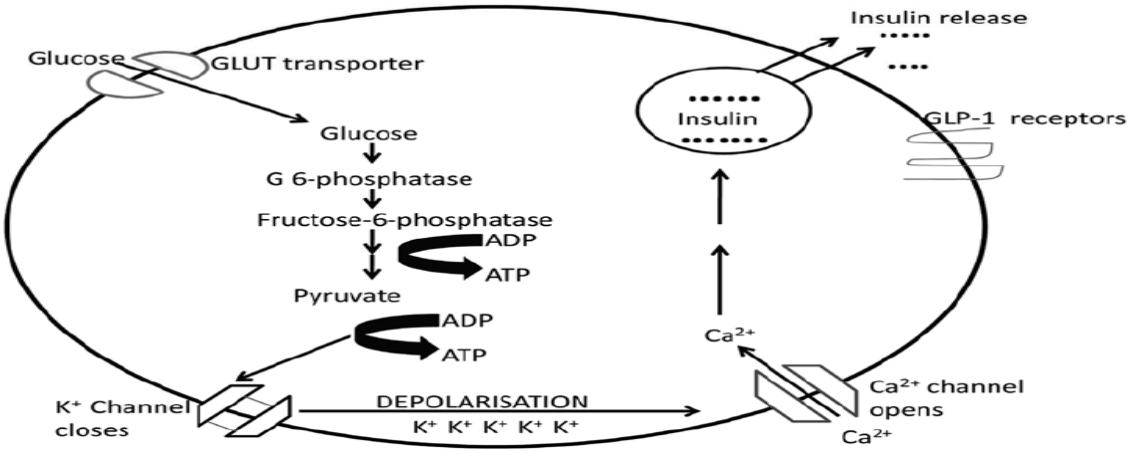

Fig.2. Mechanism of insulin secretion

Function of insulin:

1. Carbohydrate metabolism: It stimulates transport of glucose into the cell, increase glycogen synthesis in muscle and liver, reduce glucogenolysis in liver. The net result is decrease blood glucose.
2. Protein metabolism: It stimulates protein synthesis, increase amino acid uptake in muscle and decrease gluconeogenesis in liver.
3. Lipid metabolism: In adipose tissues insulin increases fatty acid synthesis, glycerol phosphate synthesis and triglyceride deposition. Also decrease lypolysis.
4. Miscellaneous: Insulin prevents ketone body formation.

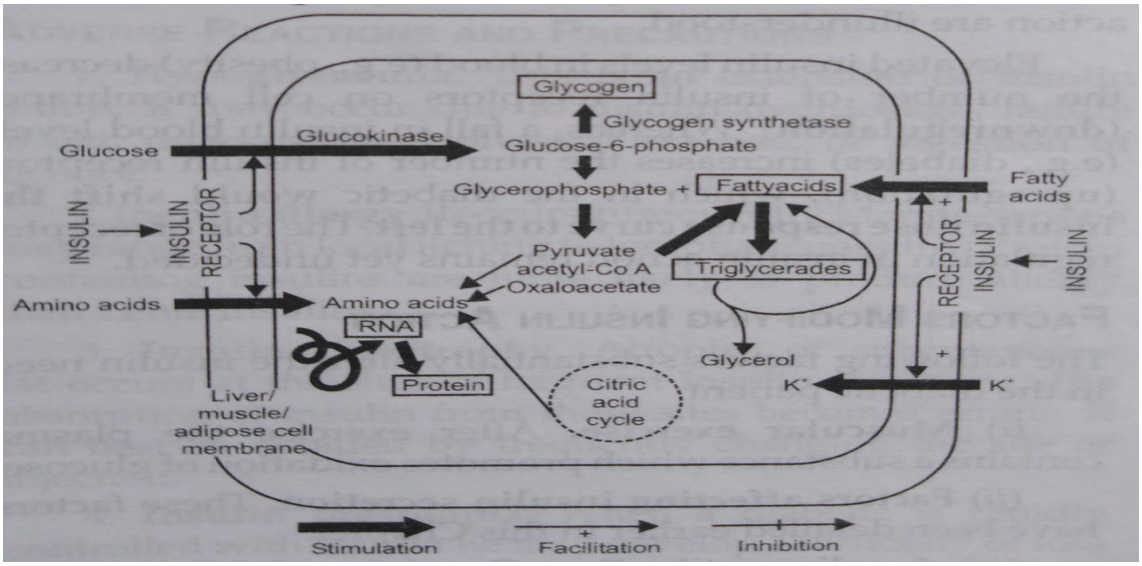

Fig.2. Action of insulin, It stimulates the formation of glycogen, protein, fatty acid and triglycerides from their precursors

Deficiency of insulin leads to type-1 diabetes mellitus, known as insulin dependent diabetes mellitus. The treatment for type-1 diabetes mellitus is administration of insulin.

Pharmacokinetics:

Insulin cannot be given orally because it is destroyed in the gastrointestinal tract. Injection of soluble crystalline insulin is given by subcutaneous injection and is quickly absorbed. Peak effect achieved quickly and excreted quickly within a few hours. Whereas zinc suspensions, protein and globulin insulin preparations like semilente, lente and ultralente are absorb slowly. The peak is reached slowly and sustained, their excretion is also slow.

Table.2. Insulin preparations

Type/Names	Onset (hours)	Peak (hours)	Duration (hours)
I. Short acting insulin			
Crystalline zinc insuline	0.5-1	2	5-8
Prompt zinc insulin suspension	0.5-1	2	5-8
II. Intermediate acting insulin			
Insulin zinc suspension (Lente)	1-3	6-8	16-20
Neutral protamine hagedorn	1-2	10-12	16-20
III. Long acting insulin			
Insulin glargine	1.5-2	14-16	15-24
Extended insulin zinc crystalline (Ultralente)	4-6	14-16	20-36

Resistance:

Insulin resistance develops in course of time and hence doses have to be increased. This occurs because of development of insulin antibodies.

Therapeutic use:

1. It is used as the specific replacement therapy in diabetes mellitus.
2. For emergency treatment of diabetic ketoacidosis (diabetic coma)
3. For emergency treatment of hyperkalaemia

Adverse effect: Hypoglycemia, lipodystrophy, allergic manifestations, insulin resistance

3. Oral hypoglycemic agent:

Oral hypoglycemic agents are agents used to treat type-2 diabetes mellitus, they are of two type:
(i) Agent which promote insulin secretion: Sulfonylureas and meglitinides
(ii) Antihyperglycemic agent: Biguanides, Alpha glucosidase inhibitor and Thiazolidinediones

1. Sulfonylureas: These are chemically related to sulfonamides but are deprived of antibacterial activity. The examples of sulfonylureas are Tolbutamide, Tolzamide, Chlorpropamide, Glibenclamide, Glipizide, Glyburide. These are readily absorbed from the

gastrointestinal tract, appear in the blood within 1-2 hrs and peak levels are attained within 4-6 hrs. They are partially protein bound and metabolized in liver.

MOA: 1. It blocks the ATP dependant K^+ channel in the beta cell of the pancreas and cause degranulation of beta cell to release insulin.
2. Inhibits hepatic glycogenolysis.

Therapeutic uses: (i) Maturity onset diabetes mellitus
(iii) Insulin resistant diabetes mellitus

Adverse effect: Hypoglycemia, allergic skin reaction, bone marrow depression, cholestatic jaundice, Chlorpropamide may produce disulfiram like reaction.

2. Meglitinides: These are quick and short acting insulin secretion enhancer, examples are Repaglinide, Nateglinide. Their mode of action is similar to sulfonylureas. Because of their rapid onset of action, these drugs are administered shortly before a meal to reduce the post-prandial glucose rise in type-2 diabetic patient.

Adverse effect: Hypoglycemia is a great risk if the meal is delayed or skipped.

3. Biguanides: The examples are: Phenformin and Metformin, it do not lower blood glucose level in normal non-diabetic person.

MOA: The action of biguanides is extrapancreatic, and does not depend on presence of endogenous insulin in the body. They stimulate the peripheral utilization of glucose and reduce the intestinal absorption of glucose. Also lower LDL, VLDL and elevates HDL.

Therapeutic uses: Phenformin is used for the treatment of maturity onset diabetes mellitus and it may be combined with sulfonylureas.

Adverse effect: Phenformin induce a metallic taste, nausea, anorexia, and diarrhea. Phenformin may cause ketonuria and lactic acidosis.

4. Alpha-glucosidase inhibitors: Example of α-glucosidase inhibitor is acarbose and miglitol. It inhibits intestinal α-glucosidase and inhibits the digestion and absorption of starch and sucrose from the gut, therefore reduces post-prandial digestion and absorption of carbohydrate and lower post meal hyperglycemia. Regular use also tends to lower HbA1c, body weight and serum triglycerides.

Adverse effect: Flatulence, diarrhea and abdominal pain.

5. Thiazolidinediones (Glitazones): Examples are Rosiglitazone, Pioglitazone and Troglitazone are a newer class of antihyperglycemic agents.

MOA: These are agonist of nuclear receptor called Peroxisome Proliferator-Activated Receptor-gamma (PPAR-γ). The PPAR-γ receptor is expressed mainly in adipose tissue but also in muscle

and liver. Activation of PPAR-γ receptor by glitazones increases lipogenesis and promote uptake of fatty acid and glucose. It also reduce hepatic glucose output by inhibiting hepatic gluconeogenesis, promote glucose uptake into muscle by decreasing insulin resistance and decrease HbA1c level.

Adverse effect: Weight gain, fluid retention, oedema and hepatotoxicity.

f. ACTH and corticosteroids

Corticosteroids are the hormone secreted by the adrenal cortex under the control of ACTH released from the anterior pituitary into the circulation in response to corticotrophin releasing hormone (CRH) secreted from hypothalamus.

Table.3. Hormones of adrenal cortex

Sl	Layer of adrenal cortex	Hormones
1	Zona glomerulosa	Aldosterone (Mineralocorticoids)
2	Zona fasciculate	Cortisone, cortocosterone (Glucocorticoids)
3	Zona reticularis	Androgen, estrogen and progesterone (Sex hormones)

All the hormones of adrenal cortex have a common basic structure cyclopentanoperhydro-phenanthrene or steroid ring. All steroid hormones are derived from cholesterol. Cholesterol under the influence of ACTH is converted into pregnenolone, the precursor of all steroid hormones. The steroid hormones can be divided into three major groups on the basis of no of carbon atoms in their structure. These are:

1. The C-21 steroids: Progesterone, glucocorticoids, and mineralocorticoids
2. The C-19 steroids: Androgen
3. The C-18 steroids: estrogen

1. Glucocorticoids: They are classified into:
   - (i) Natural: Cortisol,
   - (ii) Synthetic: (a) Short acting e.g. Cortisone, Hydrocortisone
     - (b) Intermediate acting e.g. Prednisone, Prednisolone
     - (c) Long acting e.g. Betamethasone, Dexamethasone

Physiological action:

1. Carbohydrate metabolism: Stimulate the formation of glycogen in liver and muscles and increase gluconeogenesis in liver.
2. Protein metabolism: It increases the rate of deamination and breakdown of tissue proteins into amino acids. Thus body proteins are lost, increasing nitrogen excretion.
3. Fat metabolism: They act directly to breakdown triglycerides to fatty acid (lipolysis). However, they also indirectly increase the formation and storage of fat (lipogenesis).
4. Other metabolism: Glucocorticoids have minimal action on mineral metabolism causing sodium and water retention and increased excretion of K^+ and PO_4.

Pharmacological action:

1. Anti-inflammatory: Glucocorticoids inhibits the inflammatory responses of body tissue to all kind of noxious stimuli.
2. Immunosupressant: The corticosteroids inhibit antibody formation and antibody reaction.
3. Anti-allergic activity: They suppress immediate hypersensitivity reaction by interfearing the release of histamine and bradykinins.

Effect on organ system:

1. Cardiovascular system: Corticosteroids exerts positive inotropic effect.
2. Central nervous system: Increases CNS excitability, euphoria, psychosis
3. Gastrointestinal system: Increase secretion of gastric hydrochloric acid, pepsinogen and pancreatic trypsinogen
4. Skeletal muscle: Excess corticosteroid leads to skeletal muscles weakness and fatigue rapidly
5. Body growth: Large dose of glucocorticoids retard growth of children

Mode of action: The natural and synthetic glucocorticoids bind to specific intracellular receptors located on the cytoplasm of the target cells to form steroid receptor complex. The complex is then entering to the nucleus where it binds to the nuclear acceptor site. In the nucleus the complex interacts with the DNA and alters transcription and translation of proteins that produce various pharmacological effects.

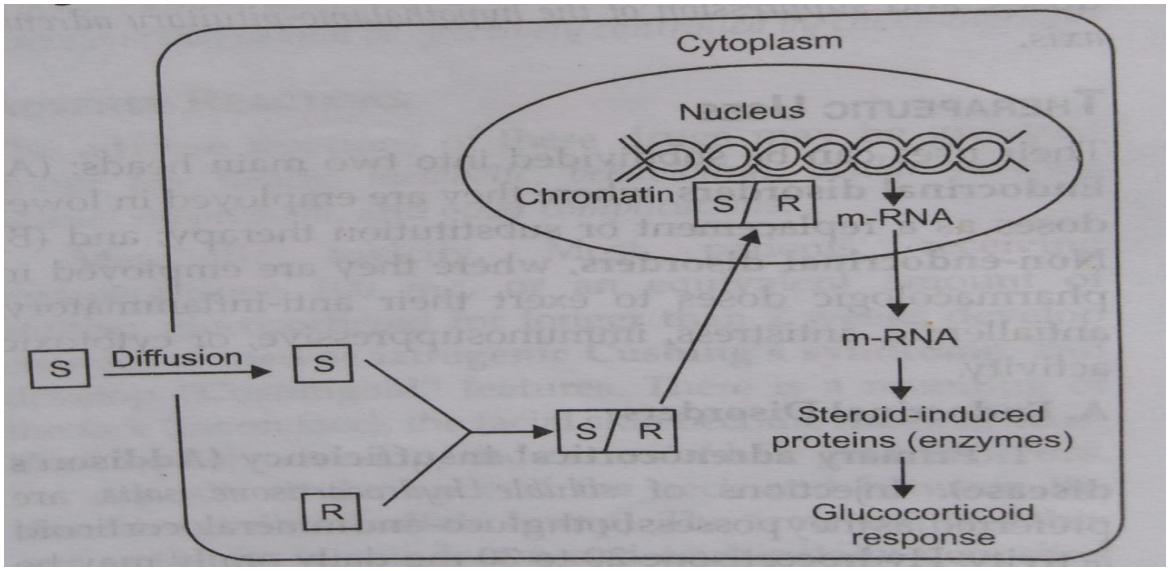

Fig.3. Cellular mechanism of glucocorticoids

Therapeutic uses: Primary adrenocortical insuffiency, Rheumatoid arthritis, Allergic disorders, Bronchial asthma.

Adverse effects: Prolong use for more than 2 weeks produce iatrogenic Cushing's syndrome, steroid induced glaucoma, adrenal suppression, superinfection.

Contraindications: Peptic ulcer, infection, hypertension, psychosis, diabetes mellitus, osteoporosis, glaucoma, pregnancy.

2. Mineralocorticoids: Aldosterone is the natural mineralocorticoid in man, but unsuitable for medical use as it is inactivated when given orally. Fludrocortisone, a synthetic corticosteroid, is the most often used compound when mineralocorticoid treatment is required. It is the only compound available for oral use, and is employed for the management of chronic primary adrenocortical insufficiency and salt losing forms of congenital adrenal hyperplasia.

   MOA: It produces its effect by binding to the cytosolic aldosteron receptor, a nuclear receptor. The drug receptor complex then enters into the nucleus and binds to the specific site of the DNA and alters transcription and translation of the protein. The protein produces desired pharmacological activity.

   Adverse effect: Oedema, hypertension and hypokalaemia.

   Aldosterone antagonist: e.g. Spironolactone is used clinically as a potassium sparing diuretics.

3. Adrenocortical antagonist: e.g. Metyrapone, Aminoglutethamide and Trilostane.

   Metyrapone blocks the biosynthesis of corticosteroids by inhibiting the enzyme 11-β-hydroxylase. It decrease the synthesis of hydrocortisone, corticosterone, and aldosterone. It is used as a diuretic in case of resistant oedema associated with excess aldosterone.

   Aminoglutethamide blocks the conversion of cholesterol to pregnenolone, thus reduce synthesis of adrenocorticosteroids. It is used in case of adrenocortical malignancy.

   Trilostane is a synthetic steroid, a competitive inhibitor of the 3-β-hydroxysteroid dehydrogenase. It is used for the treatment of Cushing's disease.

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