CHAPTER 13

HORMONES AND RELATED DRUGS

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PITUITARY HORMONES

Endocrine glands produce hormones. These glands secrete their contents directly into the extracellular fluid or blood stream. These substances can have an effect on adjoining cells or be transported through the bloodstream to act on various organ systems or specialised cells in the body, assisting in the maintenance of homeostasis. The pituitary gland is located in the hypophyseal fossa of the sphenoid bone and is connected to the brain by a stalk that is continuous with the hypothalamus.

Anterior Pituitary Hormones

As it produces peptide trophic hormones which affect the other ductless/endocrine glands, the anterior lobe of the pituitary is the master gland of the endocrine system as a whole. Hormones secreted by the anterior lobe include:

a) Growth hormone or somatotrophic hormone (GH & STH)
b) Thyroid stimulating hormone (TSH) or thyrotrophic hormone
c) Adrenocorticotrophic hormone (ACTH)
d) Follicle stimulating hormone (FSH)
e) Luteinising hormone (LH) or interstitial cell stimulating hormone (ICSH)
f) Lactogenic hormone or prolactin

a) Growth Hormone

Acidophil cells produce this substance. Human growth hormone is made up of 188 amino acids and has a single straight chain polypeptide structure with two intramolecular disulphide bridges. It promotes growth both on its own and in combination with other hormones. It increases the cartilage bone's length. Because of its direct effect on the tissues, there is an increase in body growth after administration. It promotes muscle development. During lactation, it also increases milk secretion. Protein metabolism is aided by growth hormone. It boosts protein and nucleic acid synthesis while lowering nitrogen excretion in the urine. It aids in tissue development. It causes the liver to mobilise peripheral fat depots. Its primary effect in carbohydrate metabolism is to stimulate storage. Hyperglycemia and glycosuria are side effects of growth hormone therapy. It boosts calcium absorption in the intestine. The hypothalamic hormone, the growth hormone-releasing factor, controls growth hormone secretion by acidophil cells (GHRF). Corticosteroids decrease and thyroxine increases GHRF levels in the hypothalamus. Insulin-induced hypoglycemia, fasting, physical activity, and amino acid administration are all stimuli that can boost growth hormone production. Growth hormone is released in response to stress and sleep. Hyposecretion of the pituitary

gland during childhood causes 'Dwarfism,' which is classified into two types: Lorain type and Frohlich's type, and is characterised by stunted skeletal growth and consequent 'dwarfism.'Simmond's disease' is characterised by dry, wrinkled skin, grey hair, atrophy of the sexual organs, and the cessation of the female menstrual cycle due to hyposecretion during adulthood. 'Gigantism,' or excessive skeletal growth, is caused by hypersecretion during childhood.

Poisoning and Drug Interaction

Hypersecretion during adulthood causes 'Acromegaly,' which is characterised by excessive facial bone growth, large and spade-like hands, thickening of facial and hand skin, and other symptoms. Human growth hormone is now produced using the recombinant DNA technique. Somatropin and Sometrem are two of the available preparations. The majority of these preparations are used to treat dwarfism. Somatostatin is a peptide that inhibits the pituitary's release of growth hormone, TSH, and prolactin, as well as the pancreas' release of insulin and glucagon. Its plasma half-life is extremely short. Its use in the treatment of acromegaly is limited due to its short duration of action and lack of specificity in inhibiting only GH secretion..

b) Thyroid Stimulating Hormone

The thyroid gland's growth and activity are regulated by this hormone. It affects the thyroid gland's iodine uptake, thyroxine (T4) and triiodothyronine (T3) synthesis, and release into the bloodstream. The chapter 'Thyroid and antithyroid agents' goes into more detail.

Adrenocorticotrophic Hormone (ACTH)

Basophil cells secrete it under the direction of CRF (corticotropin releasing factor) from the hypothalamus. ACTH is required for life because it regulates the growth of the adrenal cortex and the synthesis of corticosteroids. This hormone stimulates the adrenal gland's cortex to produce hormones. The amount of ACTH secreted is determined by the concentration of adrenal cortex hormones in the blood and hypothalamic stimulation. The glucocorticoids, mineralocorticoids, and sex hormones are all produced by the cortex of the adrenal gland.

Glucocorticoids

ACTH from the anterior lobe of the pituitary gland stimulates secretion. The main glucocorticoids are cortisone and hydrocortisone, and their main function is to regulate carbohydrate metabolism.

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Mineralocorticoids

It has something to do with the body's electrolyte balance. The mineralocorticoid aldosterone stimulates sodium reabsorption by the renal tubules, and as the amount of sodium reabsorbed increases, so does the amount of potassium excreted. Renin (from the kidneys) produces angiotensin, a vasopressor that stimulates aldosterone secretion.

Sex Hormones

ACTH regulates the adrenal cortex's secretion of estrogens in females and androgens in males. They are in charge of both male and female secondary sexual characters' development and maintenance. In males, they also increase protein deposition in muscles and decrease nitrogen excretion. Hypoglycemia, decreased basal metabolic rate, loss of appetite, weight loss due to water loss, muscular weakness, decreased blood sodium, subnormal body temperature, , inability to maintain normal protein deposition in the muscles and increased blood potassium are all symptoms of hyposecretion of hormones from the adrenal cortex. Hypersecretion from the adrenal cortex causes 'Cushing's syndrome,' which causes 'Feminism' in males, which is the tendency to develop female sex characteristics, and 'Virilism' in females, which is the tendency to develop male sex characteristics such as excessive hair growth on the chest and pubic region, increase and darkening of facial hair, atrophy of mammary glands (breasts), and menstrual cycle cessation (amenorrhoea). ACTH is a lyophilized powder that when reconstituted yields a 40 IU/ml solution. It is primarily used to diagnose pituitary adrenal axis disorders.

c) Follicle Stimulating Hormone (FSH)

The ovaries are the target organs in females, where it increases the number and size of Graffian follicles (maturation, development, and ripening) and prepares them for ovulation. The ovarian follicles secrete their own hormone oestrogen during development. It promotes spermatogenesis in males. Seminiferous tubules produce spermatozoa when this hormone is present..

d) Luteinising Hormone (LH)

It is responsible for the following in females: • Complete development of ovarian follicles to secretory stage and oestrogen secretion. • Promotes final maturation of ovarian follicles and ovulation, as well as the formation of the corpus luteum, which secretes progesterone.

The same hormone, known as ICSH, stimulates the development and functional activity of interstitial cells in males, leading to the production of the testicular androgen testosterone. Males with amenorrhoea, infertility, cryptorchidism, and hypogonadotrophic hypogonadism are treated with gonadotrophins. In vitro fertilisation is another application.

Gonadotrophins are divided into two categories:

Chorionic gonadotrophin is derived from the urine of pregnant women (powder form; can be used after reconstitution by parenteral route).

Menotrophin is a hormone derived from the urine of menopausal women (combination of FSH and LH).

For several years, gonadotrophin preparations have been used to treat infertility.

a) Lactogenic Hormone or Prolactin

It's a peptide hormone with only one chain. It has a direct effect on the breasts right after the baby is born, and it stimulates milk production when combined with other hormones. It also aids in the complete development of the breasts by stimulating the proliferation of glandular elements of the mammary glands during pregnancy. The hypothalamus inhibits prolactin secretion via prolactin inhibiting hormone (PRIH), which is dopamine and acts on the pituitary lactotrope dopamine receptor.

POSTERIOR LOBE OF PITUITARY GLAND

Antidiuretic and oxytocin hormones are secreted by the posterior lobe (ADH or vasopressin).

a) Vasopressin or ADH The unit 'Diuretics and Antidiuretics' goes over this in depth. Stimulants for Uterus (Oxytocics, Abortifacients)

b) Oxytocin

Oxytocin is an octapeptide produced in the hypothalamus and transported to the posterior lobe of the pituitary gland via axons. It causes the uterine muscle to contract. It also causes the lactating breast's myoepithelial cells to contract, forcing milk into the large ducts behind the nipple of the mammary gland. Oxytocin is involved in the onset of parturition, as well as the foetal and placental expulsion. It also aids sperm transport through the female genital tract. Induction of labour, postpartum haemorrhage, abortion, and breast engorgement are all treated with oxytocin. It is used by IM/IV route.

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Fill in the Blanks

i. Prolactin is secreted by the_____.

ii. Hyposecretion of pituitary during childhood leads to _____.

iii. _____ and _____ are the hormones secreted by the posterior pituitary gland.

iv. The anterior pituitary hormone that stimulated the thyroid is _____.

DRUGS ACTING ON ENDOCRINE SYSTEM

THYROID HORMONE AND ANTITHYROID AGENTS

a. Thyroid Hormone

Thyroxine (T4) and tri-iodothyronine (T3) are two important hormones secreted by the thyroid gland. Calcitonin, a hormone secreted by interstitial cells and responsible for calcium metabolism regulation, is a physiologically different hormone. Thyroid hormones have an effect on target organs by binding to nuclear receptors. After oral administration, both thyroid hormones are well absorbed. In the liver, they are conjugated with sulfuric acid and excreted in the bile. Thyroxine, Liothyronine sodium, and Thyroglobulin are among the medications used.

Thyroid hormones are used to treat the following conditions:

- Infant hypothyroidism (cretinism).
- Hypothyroidism in adults (myxoedema).
- Myxoedema coma: This is a life-threatening situation. Liothyronine 100 µg IV can be used sand maintained by thyroxine 500 µg IV.
- In the treatment of benign goitre.
- Papillary thyroid carcinoma: It is often responsive to thyroid stimulating hormone (TSH).

b. Antithyroid Agents

These are used to stop the hypersecretory thyroid gland from working properly. Thyrotoxicosis develops as a result of hypersecretion. Antithyroid drugs work by interfering with thyroid hormone synthesis and release.

They are as follows:

i) Drugs which inhibit hormone synthesis
ii) Drugs which inhibit iodide trapping
iii) Drugs which inhibit hormone release
iv) Drugs which destroy thyroid gland tissue

i. Drugs which Inhibit Hormone Synthesis

The main drugs used to treat thyrotoxicosis are propyl thiouracil and methimazole. Carbamazepine is the most commonly prescribed drug in India. These medications are used to treat hyperthyroidism caused by Graves' disease before undergoing thyroid surgery. It's also used to treat intractable congestive cardiac failure and paroxysmal tachycardia. It's also used to treat intractable congestive cardiac failure and paroxysmal tachycardia.

ii. Drugs which Inhibit Iodide Trapping

Through competitive inhibition of the iodide transport mechanism, monovalent anions such as thiocyanates, perchlorates, and pertechnetate can block iodide uptake by the gland. However, because it requires a higher dose, which can cause aplastic anaemia, it is not used clinically.

iii. Drugs which Inhibit Hormone Release

Iodine prevents hormone production. On a regular basis, they inhibit organification and hormone release, as well as shrink the size and vascularity of the hyperplastic gland. After two weeks, the antithyroid effect peaks, and thyrotoxicosis may recur. Iodine is used to treat thyroid storm, hyperthyroidism, thyroid surgery preparation, and endemic goitre prevention. Antiseptics and expectorants both contain iodine. Hyperthyroidism is treated with iodinated contrast agents such as ipodate and iopanic acid.

iv. Drugs which Destroy Thyroid Gland Tissue

The only radioisotope of iodine used to treat thyrotoxicosis is 131I. The other isotopes, 123I and 125I, are only used for diagnostic purposes. Gamma and beta radiation are emitted by 131I. It's sold as a sodium solution. Hyperthyroidism caused by Graves' disease or toxic nodular goitre is treated with radioactive iodine, which is also used as palliative therapy after thyroid surgery for papillary carcinoma of the thyroid.

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Fill in the blanks

i. The hormones secreted by the thyroid are _____, _____ and _____.

ii. Hypersecretion of thyroid gland leads to the development of_____.

iii. Agents inhibiting thyroid hormone synthesis act on the enzyme _____.

iv. Radioactive isotopes of _____ are used to destroy the thyroid gland in thyrotoxicosis.

INSULIN AND ORAL AGENTS

Diabetes mellitus (DM) is a chronic disease marked by abnormal carbohydrate, protein, and fat metabolism. Diabetes mellitus prevalence rates vary between two and four percent in different population groups, according to epidemiological surveys conducted in several developing countries. Diabetes mellitus affects roughly 2% of the world's population.

There are two types of diabetes mellitus i.e.

- type I diabetes or Insulin dependent (IDDM).
- type II diabetes or Non-insulin dependent (NIDDM).

a. Insulin

Insulin is a polypeptide hormone produced by beta cells in the Langerhans islets. It is made up of two peptide chains (A with 21 amino acid residues and B with 30) that are linked by a disulphide bond. Insulin binds to insulin receptors on cell membranes to work. Insulin deficiency or insulin resistance in peripheral tissues causes hyperglycemia and glycosuria in people with diabetes. Insulin acts on various tissues to correct various abnormalities in carbohydrate metabolism. Hypoglycemia is the most common and dangerous side effect, characterised by neuroglucopenic symptoms such as confusion, dizziness, behavioural changes, visual disturbances, fatigue, muscle incoordination, and a drop in blood pressure.

The important insulin preparations available in market are given below:

I. Conventional preparations

Regular (soluble) insulin, Insulin zinc suspension 'prompt' (Semilente), Protamine zinc insulin (PZI), Insulin zinc suspension (Lente insulin), Globin zinc insulin, Insulin zinc suspension 'extended' (Ultralente), Isophane or Neutral Protamine Hagedorn (NPH) insulin

II. Newer purified insulin preparations

i) Regular-ILETIN, ii) Regular-ILETIN-II

ii) Single peak insulins

Pork regular insulin

Pork lente insulin

Pork regular and isophane insulin

Monocomponent insulin

III. Biosynthetic human insulins (by recombinant DNA technique)

Human regular insulin

Human soluble insulin

Human lente insulin

b. Oral Antidiabetic Drugs

These are medications that can be taken orally and help to lower blood glucose levels. They are divided into four categories.

i) Sulfonylureas

ii) Biguanides

iii) Meglitinides

iv) Thiazolidinediones

i) Sulfonylureas

Neoglucogenesis and glycogenolysis are inhibited by sulfonylureas. Chlorpropamide is used to treat nonketotic diabetes mellitus that is not responsive to diet and neurogenic diabetes insipidus. Tolbutamide is a short-acting, less potent oral hypoglycemic agent that is quickly metabolised in the liver after administration. Glibenclamide is used to treat non-insulin-dependent diabetes mellitus (type II, maturity-onset diabetes) when diet alone is ineffective. Glipizide is a fast-acting insulinemic agent that continues to work even after prolonged use. It's used to treat type 2 diabetes when diet control alone isn't enough to keep hyperglycemia under control. Glimeperide has a long half-life and is used to treat non-insulin-dependent diabetes (type II).

ii. Biguanides

They lower blood sugar levels in all types of diabetes, but they do not lower blood sugar levels in healthy people like sulfonylureas do. They work by stimulating peripheral anaerobic glycolysis (glucose utilisation), inhibiting carbohydrate absorption in the gut, and suppressing hepatic gluconeogenesis. Metformin improves NIDDM patients' glucose tolerance by lowering both basal and postprandial plasma glucose levels. Metformin lowers hepatic glucose production, lowers glucose absorption in the intestine, and improves insulin sensitivity (increases peripheral glucose uptake and utilization).

iii. Meglitinides

Repaglinide is an insulin secretagogue that is new. By acting on the beta cells of the pancreas, it lowers both postprandial and fasting blood glucose in patients with type 2 diabetes mellitus. Only during mealtime does it stimulate insulin release. It's used to treat type 2 diabetes in people who aren't responding to diet and exercise. Nateglinide is primarily used to treat postprandial hyperglycemia in people with type 2 diabetes.

iv. Thiazolidinediones

Both rosiglitazone and pioglitazone work by lowering insulin resistance. They increase insulin sensitivity in muscle and adipose tissue while also inhibiting hepatic gluconeogenesis. They also improve glycemic control while lowering insulin levels in the blood.

Fill in the blanks

_____is secreted from β-cells of islets of Langerhans.

The most frequent and serious adverse reaction of insulin therapy is_____.

Thiazolidinediones primary act by decreasing _____.

Sulfonylureas primarily act on _____ on the pancreatic β-cells.

HORMONAL CONTRACEPTIVES AND ANABOLIC STEROIDS

Hormonal Contraceptives

The most effective spacing methods of contraception are hormonal contraceptives. They are used to suppress fertility in a reversible manner. Oral contraceptives work through a variety of mechanisms.

- Blocking the release of follicle stimulating hormone and luteinizing hormone from the anterior lobe of the pituitary gland, which prevents ovulation.
- Progestins increase the thickness of cervical mucus, creating an unfavourable environment for sperm penetration and subsequent conception.
- Inducing other changes in the uterine mucosa that could make it difficult for fertilised ovum to implant. In minipills and postcoital pills, this action is critical.

a) Oral Contraceptives

Oral hormonal contraceptives are divided into six categories, each of which contains oestrogen, progestins, or both in varying amounts.

Combined Pills - This is a combination of oestrogen and progestin that is given together for exceptional efficacy, safety, and ease of use. It consists of 21 pills, each of which is taken orally for 21 days starting on the 5th day of the menstrual cycle (when the bleeding occurs this is considered the first day of cycle). The pill should be taken at a set time each day, preferably before going to bed.

b) Phased Pills

This is a combined pill that is biphasic or triphasic in nature, meaning the oestrogen level is constant but the progestin level is low in the early stages of the menstrual cycle and increases as the cycle progresses. The fifth to tenth days of the menstrual cycle (ethinyl estradiol 30 g + levonorgestrel 50 g), the eleventh to fifteenth days (ethinyl estradiol 30 g + levonorgestrel 75 g), and the sixteenth to twenty-fifth days (ethinyl estradiol 30 g + levonorgestrel 125 g). They come in a single pack of different coloured pills that last from the fifth to the twenty-fifth day of the menstrual cycle, and the next pack can be started after a seven-day gap, just like combined pills.

c) Minipill

It's also referred to as a progestin-only pill (POP). It only contains progestins (Norgestrel, Norethindrone), which are given in small doses throughout the menstrual cycle (without interruption), but it is not widely used due to its low efficacy rate.

d) Postcoital Contraception

Within 48 hours of an unprotected intercourse, rape, or contraceptive failure, postcoital (morning after) contraception is recommended. A combination of ethinyl estradiol 0.1 mg and levonorgestrel 0.5 to 1 mg has also been used. Within three days of intercourse, two tablets are taken 12 hours apart. Levonorgestrel 0.75 mg (1 tablet) is

also used, with the first tablet being taken as soon as possible (within 72 hours) and the second tablet being taken 12-24 hours later. Within 3-7 days, withdrawal bleeding occurs.

e) Injectable Formulations

They are usually administered via intramuscular route. Menstrual irregularities and amenorrhoea are more common as a result of them.

• Once every two months, norethindrone enanthate 200 mg

• Depot medroxyprogesterone acetate 150 mg once every three months and 400 mg once every six months. Progesterone implants prepared in biodegradable polymeric matrices have also been used subcutaneously and intrauterinally.

f) Centchroman

It is a non-steroidal estrogen antagonist that prevents implantation due to embryo-uterine asynchrony, accelerated tubal transport, and decasualization suppression. Pituitary and ovarian functions are unaffected. It is taken 30 mg twice weekly for 12 weeks, then once a week for as long as fertility suppression is required.

Male Contraceptive

Different approaches, such as preventing spermatogenesis, interfering with sperm storage and maturation, and preventing sperm transport in the vas deferens, are the main research focus. Hormones that suppress sperm production, on the other hand, tend to lower testosterone, affecting potency and libido. Although Gossypol, a non-hormonal selective spermatogenesis suppressant derived from cottonseed oil, is effective in producing azoospermia or severe oligospermia, it is not widely used as a male contraceptive. The exact mechanism of action is unknown.

Antabolic Steroids

Anabolic steroids are testosterone-like substances with a higher anabolic/androgenic ratio. These drugs have a similar mechanism of action to testosterone, but they have a greater impact on body anabolic growth. The most important medications are listed below:

Nandrolone

It's very similar to testosterone, but it's less androgenic and more anabolic. It's used to treat debilitating illnesses like postmenopausal osteoporosis, burns, and major

illnesses like postmenopausal metastatic mammary carcinoma, as well as haemolytic, hypoplastic, and cancer-related anemias.

a) Stanozolol

It's a synthetic steroid that's both anabolic and androgenic. Hereditary angioedema and vascular manifestations of Behcet's syndrome are treated with this drug as a preventative measure.

b) Mesterolone

It is an oral therapy that does not harm the liver. It's used to treat hypogonadism and infertility in men. Priapism and frequent erection of the penis are two side effects.

Fill in the blanks:

i. _____is a fixed dose combination of estrogen and progestin.

ii. _____ is a non-hormonal selective spermatogenesis suppressant.

iii. The injectable contraceptive preparations are administered by the _____ route.

iv. Anabolic steroids have greater _____ ratio than testosterone.