Unit-4
Pharmacology- II

B.Pharma 5th Sem Notes

Unit: 4

- **Pharmacology of drugs acting on endocrine system**
    - Basic concepts in endocrine pharmacology. b. Anterior Pituitary hormones- analogues and their inhibitors.
    - **Thyroid hormones-** analogues and their inhibitors.
    - **Hormones regulating plasma calcium level-** Parathormone, Calcitonin and Vitamin-D.
    - Insulin, Oral Hypoglycemic agents and glucagon.
    - ACTH and corticosteroids.

Pharmacology of drugs acting on endocrine system:

- The endocrine system is a network of glands that produce hormones to regulate many functions in our body, like growth, metabolism, and reproduction.
- Drugs that affect the endocrine system can either increase or decrease the action of these hormones to help treat diseases or conditions caused by hormone imbalances.

Endocrine Gland:

- Endocrine glands are specialized organs in the body that produce and release hormones directly into the bloodstream.
- These hormones regulate important functions such as growth, metabolism, immune responses, mood, and reproduction.
- Unlike exocrine glands, which release their secretions through ducts (like sweat or saliva), endocrine glands release their hormones directly into the blood.

Anterior Pituitary Hormones: Analogues and Their Inhibitors

- The anterior pituitary gland, also known as the "master gland," plays important central role in regulating many physiological processes by secreting hormones that control the activity of other endocrine glands.
- These hormones are important for growth, metabolism, reproduction, and stress response. In clinical pharmacology, drugs that mimic (analogues) or block (inhibitors) the action of anterior pituitary hormones are used to treat various medical conditions.

1. Growth Hormone (GH)

- **Function**: Growth hormone (GH), also known as somatotropin, stimulates growth, cell reproduction, and cell regeneration. It plays a key role in childhood growth and continues to regulate metabolic functions throughout adulthood, such as fat metabolism, muscle growth, and bone density.
- **Analogues**:
    - **Somatropin**: This is a recombinant form of human growth hormone used to treat growth hormone deficiency in children and adults. It is used in conditions like *pituitary dwarfism* or short stature in children, and *adult GH deficiency*.
    - **Somatrem**: Another growth hormone analogue used for the treatment of growth hormone deficiency, similar to somatropin.
- **Inhibitors**:
    - **Octreotide**: An analogue of somatostatin, the natural inhibitor of growth hormone secretion. It is used to treat acromegaly (a condition caused by excess GH) by inhibiting GH release.
    - **Lanreotide**: Similar to octreotide, it is another somatostatin analogue used to treat acromegaly and other conditions associated with excessive GH production.

- **Pegvisomant**: A GH receptor antagonist used to treat acromegaly by blocking the effects of excess GH on tissues, particularly the liver's secretion of insulin-like growth factor 1 (IGF-1), which mediates many of GH's effects.

2. Thyroid-Stimulating Hormone (TSH)

- **Function**: TSH stimulates the thyroid gland to produce thyroid hormones (T3 and T4), which regulate metabolism, energy production, and overall growth. It plays a critical role in maintaining thyroid function.
- **Analogues**:
  - **Recombinant TSH (Thyrogen)**: This synthetic form of TSH is used in diagnostic tests to stimulate the thyroid gland in patients with thyroid cancer. It is also used in combination with radioactive iodine to scan for remnants of thyroid tissue after thyroid cancer treatment.
- **Inhibitors**:
  - **Thyroid Hormone Replacement (Levothyroxine)**: Levothyroxine (synthetic T4) and liothyronine (synthetic T3) are used to replace thyroid hormones in patients with hypothyroidism, effectively suppressing TSH production.
  - **Methimazole** and **Propylthiouracil (PTU)**: These are antithyroid medications that inhibit the production of thyroid hormones and can lead to suppressed TSH levels. They are used in the treatment of hyperthyroidism.

3. Adrenocorticotropic Hormone (ACTH)

- **Function**: ACTH stimulates the adrenal glands to release cortisol, a steroid hormone that helps regulate metabolism, the immune response, and stress adaptation.
- **Analogues**:
  - **Cosyntropin**: A synthetic form of ACTH, used in diagnostic tests to assess adrenal function. It is primarily used to test for *adrenal insufficiency* (e.g., Addison's disease) by stimulating the adrenal glands to release cortisol.
- **Inhibitors**:
  - **Corticosteroids (e.g., Prednisone, Hydrocortisone)**: These drugs mimic the action of cortisol and are used in the treatment of inflammatory and autoimmune conditions. Long-term use of corticosteroids can suppress ACTH production due to negative feedback on the hypothalamus and pituitary.
  - **Metyrapone**: This drug inhibits the enzyme responsible for cortisol synthesis and is used in certain diagnostic tests or in the treatment of Cushing's syndrome (excess cortisol).

4. Luteinizing Hormone (LH) and Follicle-Stimulating Hormone (FSH)

- **Function**:

- **LH** plays a key role in reproduction by triggering ovulation in women and stimulating testosterone production in men.
- **FSH** stimulates the growth and maturation of ovarian follicles in females and sperm production in males.

- **Analogues**:
  - **Gonadotropins** (e.g., **Human Chorionic Gonadotropin (hCG)**): Used in fertility treatments to mimic the action of LH. hCG is often used in women undergoing in vitro fertilization (IVF) or other assisted reproductive technologies to trigger ovulation.
  - **Recombinant FSH (e.g., Gonal-F, Puregon)**: Synthetic forms of FSH used in assisted reproduction to stimulate follicle development in women with infertility. These are often used in conjunction with LH analogues (e.g., hCG) for ovulation induction.
- **Inhibitors**:
  - **GnRH Agonists (e.g., Leuprolide, Goserelin)**: These drugs initially stimulate the release of LH and FSH but cause downregulation of GnRH receptors after prolonged use, leading to a decrease in the production of LH and FSH. Used in conditions like endometriosis, prostate cancer, and assisted reproductive treatments.
  - **GnRH Antagonists (e.g., Cetrorelix, Ganirelix)**: These drugs directly inhibit GnRH receptors, thus suppressing the release of LH and FSH. They are used in fertility treatments to prevent premature ovulation.

5. Prolactin

- **Function**: Prolactin primarily promotes milk production after childbirth. It also plays a role in reproductive health and the regulation of the immune system.
- **Analogues**:
  - Currently, there are no common analogues of prolactin in clinical use, but some drugs can affect prolactin levels.
- **Inhibitors**:
  - **Dopamine Agonists** (e.g., **Bromocriptine**, **Cabergoline**): These drugs decrease prolactin levels by stimulating dopamine receptors in the brain, which inhibit prolactin secretion. They are used to treat conditions like hyperprolactinemia, which can lead to infertility, irregular menstrual cycles, and galactorrhea (abnormal milk production).

6. Melanocyte-Stimulating Hormone (MSH)

- **Function**: MSH regulates the production of melanin in the skin, influencing pigmentation.

- **Analogues**:
    - **Melanotan I and II**: Synthetic analogues of MSH, used to stimulate tanning in the skin. Melanotan II has been studied for its potential to increase libido, but it is not widely used for medical purposes.
- **Inhibitors**:
    - There are no specific inhibitors of MSH commonly used in clinical practice.

Hormones Regulating Plasma Calcium Levels: Parathormone, Calcitonin, and Vitamin D

Calcium is an important mineral for our body. It helps build strong bones, allows muscles to work, helps blood clot when needed, and helps nerves send signals.

The body keeps the level of calcium in the blood in a very strict range through the action of different hormones. These hormones—parathyroid hormone (PTH), calcitonin, and vitamin D—control the amount of calcium in the blood, making sure it stays at the right level.

1. Parathyroid Hormone (PTH)

- **Source**: PTH is secreted by the **parathyroid glands**, which are small glands located behind the thyroid gland in the neck.
- **Function**: PTH plays a crucial role in increasing plasma calcium levels when they drop too low. It does this through several mechanisms:
    1. **Bone Resorption**: PTH increases the activity of osteoclasts (bone-resorbing cells), which break down bone tissue and release calcium into the bloodstream.
    2. **Renal (Kidney) Reabsorption**: PTH stimulates the kidneys to reabsorb calcium from urine, reducing calcium loss.
    3. **Activation of Vitamin D**: PTH promotes the conversion of inactive vitamin D (in the liver) to its active form (calcitriol) in the kidneys. Active vitamin D enhances calcium absorption in the intestines.
- **Overall Effect**: PTH **raises** blood calcium levels by increasing calcium release from bones, reabsorption in the kidneys, and absorption in the intestines.
- **Regulation**: PTH secretion is regulated by the calcium-sensing receptors on the parathyroid glands. When blood calcium levels are low, PTH secretion increases; when calcium levels are high, PTH secretion is inhibited.

2. Calcitonin

- **Source**: Calcitonin is produced by the **C-cells** (parafollicular cells) of the **thyroid gland**.
- **Function**: Calcitonin is essentially the antagonist to PTH. Its primary role is to **lower** blood calcium levels when they are too high. It does this through the following mechanisms:
    1. **Bone Formation**: Calcitonin inhibits the activity of osteoclasts, reducing bone resorption and thus preventing the release of calcium into the bloodstream.
    2. **Renal Calcium Excretion**: It enhances the excretion of calcium in urine by the kidneys, further reducing blood calcium levels.

- **Overall Effect**: Calcitonin **lowers** blood calcium levels by inhibiting bone resorption and increasing calcium excretion through the kidneys.
- **Regulation**: Calcitonin secretion is stimulated by high blood calcium levels and inhibited when calcium levels are low.

3. Vitamin D (Calcitriol)

- **Source**: Vitamin D is synthesized in the skin through exposure to sunlight (specifically UVB rays) as **vitamin D3 (cholecalciferol)**. It is then converted into its active form, **calcitriol**, in the liver and kidneys.
- **Function**: Vitamin D enhances the body's ability to absorb calcium from the intestines into the bloodstream, helping to maintain adequate calcium levels. It has several actions:
    1. **Increased Intestinal Absorption**: Calcitriol increases the intestinal absorption of calcium and phosphate, promoting the mineralization of bones and maintaining calcium levels.
    2. **Bone Resorption**: In combination with PTH, calcitriol also enhances the activity of osteoclasts in bone, contributing to calcium release when necessary.
    3. **Renal Calcium Reabsorption**: Calcitriol also works on the kidneys to increase calcium reabsorption, reducing calcium loss in urine.
- **Overall Effect**: Vitamin D **raises** blood calcium levels by increasing calcium absorption from the gut, promoting bone resorption, and enhancing kidney reabsorption of calcium.
- **Regulation**: The production of calcitriol is regulated by PTH. When calcium levels are low, PTH stimulates the kidneys to convert inactive vitamin D into its active form (calcitriol). Additionally, calcitriol's synthesis is inhibited when calcium levels are sufficiently high.

Summary of the Effects of Parathormone, Calcitonin, and Vitamin D

Hormone	Source	Action on Blood Calcium	Mechanism of Action
Parathyroid Hormone (PTH)	Parathyroid glands	**Raises** calcium levels	Stimulates bone resorption (osteoclasts), increases renal calcium reabsorption, activates vitamin D (calcitriol)
Calcitonin	Thyroid gland (C-cells)	**Lowers** calcium levels	Inhibits osteoclast activity (reduces bone resorption), increases renal calcium excretion
Vitamin D (Calcitriol)	Skin (via sunlight), liver, kidneys	**Raises** calcium levels	Increases calcium absorption in the intestines, promotes bone resorption, enhances renal calcium reabsorption

Insulin, Oral Hypoglycemic Agents, and Glucagon

1. Insulin

- **Source**:
  - **Insulin** is a hormone secreted by the **beta cells** of the **pancreas** in response to elevated blood glucose levels (after eating).
- **Function**:
  - Insulin's primary role is to **lower blood glucose levels** by facilitating the uptake of glucose into cells, where it is used for energy or stored as glycogen (in the liver and muscles).
  - Insulin also promotes the conversion of glucose to **fat** in adipose tissue and inhibits the release of glucose from the liver.
- **Mechanism of Action**:
  - **Increased glucose uptake**: Insulin binds to receptors on cell membranes, allowing glucose to enter cells (muscle, fat, and liver).
  - **Glycogen synthesis**: It stimulates the liver and muscle cells to convert glucose into glycogen (the storage form of glucose).
  - **Fat storage**: Insulin helps store excess glucose as fat in adipose tissue.
- **Clinical Use**:
  - Insulin is primarily used in the treatment of **Type 1 diabetes mellitus** (where the body does not produce insulin) and **Type 2 diabetes** (where the body does not respond properly to insulin).
  - It is administered **subcutaneously** (via injection) or sometimes via an **insulin pump**.
- **Types of Insulin**:
  - **Rapid-acting insulin** (e.g., Insulin lispro, insulin aspart)
  - **Short-acting insulin** (e.g., Regular insulin)
  - **Intermediate-acting insulin** (e.g., NPH insulin)
  - **Long-acting insulin** (e.g., Insulin glargine, insulin detemir)
- **Adverse Effects**:
  - **Hypoglycemia (low blood sugar)** is the most common side effect of insulin therapy.
  - Weight gain, injection site reactions, and possible allergic reactions.

2. Oral Hypoglycemic Agents (Oral Antidiabetic Drugs)

- Oral hypoglycemic agents are medications used to help manage blood glucose levels in **Type 2 diabetes**, where the body either resists the action of insulin or doesn't produce enough insulin.
- These drugs work by improving insulin sensitivity, stimulating insulin production, or slowing the absorption of glucose.

Classes of Oral Hypoglycemic Agents:

1. **Biguanides** (e.g., **Metformin**):
    - **Mechanism**: Reduces hepatic glucose production and increases insulin sensitivity in peripheral tissues (especially muscles).
    - **Indication**: First-line treatment for **Type 2 diabetes**.
    - **Adverse Effects**: Gastrointestinal upset (e.g., nausea, diarrhea), lactic acidosis (rare but serious).
2. **Sulfonylureas** (e.g., **Glibenclamide, Glimepiride**):
    - **Mechanism**: Stimulate the beta cells in the pancreas to secrete more insulin.
    - **Indication**: Used in Type 2 diabetes when blood sugar control is inadequate with diet alone.
    - **Adverse Effects**: Hypoglycemia, weight gain.
3. **Thiazolidinediones (TZDs)** (e.g., **Pioglitazone, Rosiglitazone**):
    - **Mechanism**: Increase insulin sensitivity in muscle and fat tissues by acting on PPAR-gamma receptors.
    - **Indication**: Can be used as an adjunct to other oral agents or in combination with insulin.
    - **Adverse Effects**: Weight gain, fluid retention, possible heart failure risk, and bone fractures.
4. **DPP-4 Inhibitors** (e.g., **Sitagliptin, Saxagliptin**):
    - **Mechanism**: Inhibit the enzyme DPP-4, which inactivates incretin hormones (like GLP-1), leading to increased insulin secretion and decreased glucagon levels after meals.
    - **Indication**: Used to control blood sugar levels in Type 2 diabetes, often combined with other agents.
    - **Adverse Effects**: Generally well tolerated, but can cause headaches, upper respiratory infections, and rare pancreatitis.
5. **SGLT-2 Inhibitors** (e.g., **Empagliflozin, Canagliflozin**):

- **Mechanism**: Block sodium-glucose cotransporter 2 (SGLT-2) in the kidneys, preventing glucose reabsorption and promoting its excretion in urine.
- **Indication**: Used in Type 2 diabetes, especially in patients with heart disease or kidney problems.
- **Adverse Effects**: Urinary tract infections, dehydration, risk of ketoacidosis.

6. **GLP-1 Agonists** (e.g., **Exenatide, Liraglutide**):
   - **Mechanism**: Mimic the action of the natural incretin hormone GLP-1, which stimulates insulin secretion, suppresses glucagon release, and slows gastric emptying.
   - **Indication**: Used for Type 2 diabetes and may help with weight loss.
   - **Adverse Effects**: Nausea, vomiting, and risk of pancreatitis.

3. Glucagon

- **Source**:
  - **Glucagon** is a hormone secreted by the **alpha cells** of the **pancreas** in response to low blood glucose levels (hypoglycemia).
- **Function**:
  - The primary function of glucagon is to **increase blood glucose levels** when they are too low, acting in the opposite manner of insulin.
  - It promotes the **release of glucose** from the liver by stimulating **glycogenolysis** (the breakdown of glycogen into glucose) and **gluconeogenesis** (the formation of glucose from non-carbohydrate sources).
- **Mechanism of Action**:
  - **Liver Glycogen Breakdown**: Glucagon stimulates the liver to break down glycogen into glucose and release it into the bloodstream.
  - **Gluconeogenesis**: Glucagon promotes the synthesis of glucose from amino acids and other precursors in the liver.
- **Clinical Use**:
  - **Emergency treatment of hypoglycemia**: Glucagon is used in emergency situations when someone with diabetes experiences severe hypoglycemia and is unable to consume oral glucose. It is administered via **injection** or **intranasal spray**.
  - In hospital settings, glucagon can also be used to treat **beta-blocker overdose** and other conditions where blood glucose is dangerously low.
- **Adverse Effects**:

- Common side effects are nausea and vomiting, especially if the patient eats soon after receiving glucagon.
- Rarely, allergic reactions may occur.

Summary of Insulin, Oral Hypoglycemic Agents, and Glucagon

Substance	Source	Primary Action	Mechanism	Clinical Use
Insulin	Pancreas (Beta cells)	Lowers blood glucose	Facilitates glucose uptake, promotes storage as glycogen, inhibits glucose release from liver	Used in Type 1 & Type 2 diabetes to regulate blood glucose
Oral Hypoglycemic Agents	Various (pancreatic, kidney, liver, and intestinal targets)	Lowers blood glucose	Increases insulin secretion, improves insulin sensitivity, inhibits glucose absorption	Primarily used in Type 2 diabetes
Glucagon	Pancreas (Alpha cells)	Raises blood glucose	Stimulates glycogen breakdown and glucose release from liver	Used in emergency treatment of hypoglycemia

ACTH and Corticosteroids

- **Adrenocorticotropic hormone (ACTH)** and **corticosteroids** are important components of the body's response to stress and help regulate several physiological processes, including immune response, metabolism, and inflammation. Here's a detailed explanation of each:

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1. ACTH (Adrenocorticotropic Hormone)

- **Source**:
  - ACTH is a **peptide hormone** secreted by the **anterior pituitary gland** in response to signals from the hypothalamus.
- **Synthesis**:
  - ACTH is derived from a larger precursor protein called **pro-opiomelanocortin (POMC)**. When POMC is cleaved, ACTH is released into the bloodstream.
- **Function**:
  - The primary role of ACTH is to stimulate the **adrenal cortex**, which is the outer portion of the adrenal glands, to produce and release **corticosteroids**, particularly **cortisol**.
  - ACTH is part of the **hypothalamic-pituitary-adrenal (HPA) axis**, which is activated in response to stress (either physical or emotional). It helps in regulating the body's response to stress and maintaining homeostasis.
- **Regulation**:
  - The release of ACTH is regulated by the **hypothalamus** through the secretion of **corticotropin-releasing hormone (CRH)**.
  - ACTH secretion follows a **diurnal rhythm**, with the highest levels in the early morning and the lowest levels at night.
  - **Negative feedback**: When cortisol levels are sufficiently high, they signal the hypothalamus and pituitary gland to reduce the production of CRH and ACTH.
- **Clinical Significance**:
  - **Addison's disease**: In this condition, there is insufficient production of corticosteroids due to adrenal gland failure. As a result, ACTH levels are elevated as the body tries to stimulate the adrenal glands.
  - **Cushing's syndrome**: This occurs when there is an overproduction of ACTH, leading to excess cortisol production and its associated effects, such as weight gain, high blood pressure, and skin changes.

2. Corticosteroids

- Corticosteroids are a class of hormones produced by the **adrenal cortex** in response to ACTH stimulation.
- There are two major types of corticosteroids: **glucocorticoids** and **mineralocorticoids**.

A. Glucocorticoids

- **Primary Hormone**: **Cortisol**
  - **Source**: Cortisol is produced by the **zona fasciculata**, a layer of the adrenal cortex.
- **Function**:
  - **Metabolic regulation**: Cortisol helps regulate the body's metabolism by increasing glucose production (through gluconeogenesis) and reducing insulin sensitivity (leading to increased blood glucose levels).
  - **Immune system suppression**: Cortisol has potent **anti-inflammatory and immunosuppressive** effects, making it important in controlling inflammation and the immune response.
  - **Stress response**: During stress, cortisol helps prepare the body for a "fight or flight" response by increasing glucose availability, improving cardiovascular function, and suppressing unnecessary physiological processes.
- **Clinical Use**:
  - **Corticosteroids** (such as **prednisone, hydrocortisone, dexamethasone**) are commonly used to treat conditions like **inflammatory diseases** (e.g., rheumatoid arthritis, asthma, inflammatory bowel disease), **autoimmune diseases**, and **allergic reactions**.
  - They are also used in **adrenal insufficiency** (such as in **Addison's disease**) to replace the deficient cortisol.
- **Adverse Effects**:
  - Long-term use of glucocorticoids can lead to significant side effects such as **weight gain**, **osteoporosis**, **hypertension**, **diabetes**, and **immune suppression**.
  - Sudden withdrawal can lead to **adrenal insufficiency**, where the body cannot produce enough cortisol.

B. Mineralocorticoids

- **Primary Hormone**: **Aldosterone**
  - **Source**: Aldosterone is produced by the **zona glomerulosa**, the outermost layer of the adrenal cortex.

- **Function**:
    - **Sodium and water balance**: Aldosterone plays a crucial role in regulating **blood pressure** and maintaining **electrolyte balance** by increasing the reabsorption of **sodium** and **water** in the kidneys and promoting the excretion of **potassium**.
    - **Blood volume regulation**: By increasing sodium retention, aldosterone also increases blood volume, which helps maintain blood pressure.
- **Clinical Use**:
    - Mineralocorticoid therapy (e.g., **fludrocortisone**) is used in conditions like **Addison's disease**, where aldosterone production is insufficient.
- **Adverse Effects**:
    - Excessive aldosterone can cause **high blood pressure** (hypertension), **low potassium levels** (hypokalemia), and **fluid retention**.

3. Clinical Implications of ACTH and Corticosteroid Imbalance

- **Addison's Disease**:
    - **Cause**: Primary adrenal insufficiency, where the adrenal glands do not produce enough cortisol and aldosterone.
    - **Symptoms**: Fatigue, muscle weakness, weight loss, low blood pressure, and hyperpigmentation (due to elevated ACTH levels).
    - **Treatment**: Corticosteroid replacement therapy (hydrocortisone, fludrocortisone).
- **Cushing's Syndrome**:
    - **Cause**: Overproduction of cortisol, often due to excessive ACTH secretion (pituitary adenoma) or long-term use of corticosteroid medications.
    - **Symptoms**: Weight gain, moon face, thinning skin, hypertension, hyperglycemia, and easy bruising.
    - **Treatment**: Treatment may involve surgery to remove the pituitary tumor or discontinuing corticosteroid medications (gradually).
- **Congenital Adrenal Hyperplasia (CAH)**:
    - **Cause**: Genetic disorders that result in enzyme deficiencies in the adrenal cortex, leading to impaired corticosteroid production and excess ACTH secretion.
    - **Symptoms**: Virilization (masculinization) in females, ambiguous genitalia, and salt-wasting crises in newborns.
    - **Treatment**: Lifelong corticosteroid replacement therapy.

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