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Unit 3
Unit 4
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Unit 2
Unit 3
Unit 4
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Unit 2
Unit 3
Unit 4
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PHARMACOLOGY - II

UNIT 4

TOPIC :

- **Pharmacology of drugs acting on endocrine system**

  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.

Drugs Acting on the Endocrine System

- The endocrine system consists of glands that secrete hormones directly into the blood.
- Hormones regulate metabolism, growth, reproduction, water-electrolyte balance, and stress response.
- Drugs acting on the endocrine system can either mimic, inhibit, or modulate hormone actions.

Basic Concepts in Endocrine Pharmacology

- The endocrine system is a network of ductless glands that secrete hormones directly into the bloodstream.
- These hormones act as chemical messengers that regulate the physiological activities of various organs and tissues to maintain homeostasis.
- Endocrine pharmacology is the branch of pharmacology that deals with drugs affecting the endocrine glands, hormones, and their synthetic analogues or antagonists.
- The drugs may act by:
    - Replacing deficient hormones
    - Stimulating or inhibiting hormone synthesis
    - Mimicking or blocking hormone actions at receptor sites.

Major Endocrine Glands and their Hormones

Endocrine Gland	Main Hormones Secreted	Major Functions
Pituitary gland (hypophysis)	Growth hormone (GH), ACTH, TSH, LH, FSH, Prolactin, ADH, Oxytocin	Regulates other endocrine glands and body growth
Thyroid gland	Thyroxine (T_4), Triiodothyronine (T_3), Calcitonin	Controls metabolism, growth, and calcium balance
Parathyroid gland	Parathyroid hormone (PTH)	Regulates calcium and phosphate metabolism
Adrenal cortex	Glucocorticoids (cortisol), Mineralocorticoids (aldosterone), Androgens	Stress response, electrolyte balance
Adrenal medulla	Adrenaline (epinephrine), Noradrenaline (norepinephrine)	Sympathetic (fight-or-flight) response
Pancreas (Islets of Langerhans)	Insulin, Glucagon, Somatostatin	Regulation of blood glucose
Gonads	Testosterone, Estrogen, Progesterone	Reproductive functions
Pineal gland	Melatonin	Regulation of circadian rhythm
Thymus	Thymosin	Development of immune system

General Principles of Endocrine Pharmacology

A. Hormone Synthesis and Secretion

- Hormones are synthesized by endocrine cells and secreted into the bloodstream.
- Their release is controlled by:
  1. Neural control (e.g., adrenaline release by sympathetic stimulation)
  2. Hormonal control (e.g., hypothalamus → pituitary → thyroid axis)
  3. Feedback mechanisms (negative or positive feedback)

B. Transport and Metabolism

- Many hormones (e.g., thyroid and steroid hormones) circulate bound to plasma proteins.
- Only the free fraction is biologically active.
- Hormones are metabolized mainly in the liver and kidneys.

C. Mechanism of Hormone Action

1. Binding to receptors on target cells (specificity).
2. Signal transduction inside the cell via:
   - Membrane receptors (for peptide hormones) activating second messengers like cAMP, IP_3, DAG.
   - Intracellular receptors (for steroid and thyroid hormones) that act on DNA to regulate gene transcription.

D. Feedback Regulation

- The endocrine system maintains hormone levels through negative feedback:
  - When hormone levels rise → they inhibit further secretion.
  - When levels fall → secretion increases.
    Example:
  - High T_3/T_4 levels inhibit TSH and TRH release.
  - High cortisol inhibits ACTH secretion.

Types of Hormones and their Classification

A. Based on Chemical Nature

Type	Examples	Mode of Action
Peptide/Protein hormones	Insulin, Growth hormone, ACTH, Oxytocin	Act on cell surface receptors via second messengers
Steroid hormones	Cortisol, Aldosterone, Estrogen, Testosterone	Act on intracellular receptors → gene transcription
Amino acid derivatives	Thyroxine, Epinephrine, Melatonin	May act on membrane or nuclear receptors
Fatty acid derivatives (Eicosanoids)	Prostaglandins, Leukotrienes	Act locally (paracrine/autocrine actions)

Therapeutic Approaches in Endocrine Pharmacology

A. Hormone Replacement Therapy (HRT)

- Used when hormone production is deficient or absent.
- Example:
  - Insulin for diabetes mellitus.
  - Levothyroxine for hypothyroidism.
  - Testosterone for male hypogonadism.
  - Estrogen + progesterone for menopausal symptoms.

B. Hormone Stimulation Therapy

- Drugs that stimulate natural hormone release.
  - Example: Clomiphene citrate stimulates ovulation by increasing gonadotropin release.

C. Hormone Suppression Therapy

- Used when hormone secretion is excessive.
  - Example:
    - Carbimazole inhibits thyroid hormone synthesis.
    - Ketoconazole inhibits cortisol synthesis.
    - GnRH analogues (e.g., leuprolide) suppress gonadotropins in prostate cancer.

D. Hormone Antagonism

- Drugs that block hormone receptors or inhibit hormone action.
  - Example:
    - Tamoxifen → estrogen receptor antagonist.
    - Spironolactone → aldosterone antagonist.
    - Mifepristone → progesterone receptor blocker.

E. Diagnostic Uses

- Hormones and analogues are used in tests to assess endocrine function.
  - Example:
    - ACTH stimulation test (for adrenal insufficiency).
    - TSH test (for thyroid function).

Routes of Administration of Hormones

Route	Examples / Remarks
Oral	Thyroxine, Steroid hormones (resistant to digestion)
Parenteral (IM/IV)	Insulin, Growth hormone, Gonadotropins
Transdermal	Testosterone, Estrogen patches
Nasal / Inhalation	Desmopressin nasal spray
Implants	Long-acting contraceptive hormones (e.g., etonogestrel)

Factors Influencing Hormone Action

1. Concentration of hormone in blood.
2. Receptor sensitivity and number.
3. Rate of hormone metabolism and clearance.
4. Age, sex, nutritional status, and disease state.
5. Interactions with other hormones or drugs (e.g., steroids increasing glucose → antagonizing insulin action).

Disorders of Endocrine Function

Type of Disorder	Description	Example
Hypofunction	Decreased hormone secretion	Hypothyroidism, Addison's disease, Diabetes mellitus type 1
Hyperfunction	Excess hormone secretion	Hyperthyroidism, Cushing's syndrome, Acromegaly
Hormone resistance	Target tissues fail to respond	Type 2 diabetes mellitus (insulin resistance)

Clinical Importance of Endocrine Pharmacology

- Diagnosis and management of hormonal disorders.
- Therapeutic use of hormones and their analogues.
- Development of hormone antagonists for cancer, infertility, and metabolic diseases.
- Design of contraceptive agents.
- Understanding of adverse drug effects that alter endocrine balance (e.g., corticosteroid-induced diabetes).

Anterior Pituitary Hormones – Analogues and their Inhibitors

- The pituitary gland (also called the hypophysis) is a small endocrine gland located at the base of the brain, connected to the hypothalamus by the pituitary stalk.
- It consists of two main lobes:
    1. Anterior pituitary (adenohypophysis) – secretes tropic hormones that control other endocrine glands.
    2. Posterior pituitary (neurohypophysis) – stores and releases hormones synthesized by the hypothalamus (ADH and oxytocin).
- The anterior pituitary hormones are regulated by releasing and inhibiting hormones from the hypothalamus.
- These hormones control growth, metabolism, reproduction, and stress response.

Anterior Pituitary Hormones

Hormone	Target Organ	Main Function
Growth Hormone (GH)	Liver, bone, muscle	Stimulates growth and protein synthesis
Thyroid Stimulating Hormone (TSH)	Thyroid gland	Stimulates synthesis and secretion of thyroid hormones
Adrenocorticotropic Hormone (ACTH)	Adrenal cortex	Stimulates cortisol secretion
Follicle Stimulating Hormone (FSH)	Gonads	Stimulates gametogenesis (spermatogenesis, follicle development)
Luteinizing Hormone (LH)	Gonads	Stimulates sex hormone secretion (testosterone, estrogen, progesterone)
Prolactin (PRL)	Mammary glands	Stimulates milk production

Regulation of Pituitary Hormones

- Controlled by hypothalamic releasing and inhibiting hormones:

Hypothalamic Hormone	Effect on Pituitary	Target Pituitary Hormone
GHRH (Growth hormone-releasing hormone)	Stimulates GH release	GH
Somatostatin (GHIH)	Inhibits GH and TSH	GH, TSH
TRH (Thyrotropin-releasing hormone)	Stimulates TSH and prolactin	TSH, PRL
CRH (Corticotropin-releasing hormone)	Stimulates ACTH release	ACTH
GnRH (Gonadotropin-releasing hormone)	Stimulates LH and FSH release	LH, FSH
Dopamine (Prolactin-inhibiting factor)	Inhibits prolactin secretion	PRL

Growth Hormone (GH, Somatotropin)

A. Source and Function

- Secreted by somatotroph cells of the anterior pituitary.
- Promotes growth of bones and tissues, protein synthesis, and lipolysis.
- Mediates its effects through Insulin-like Growth Factors (IGF-1) produced by the liver.

B. Pharmacological Preparations (Analogues)

1. Somatropin – recombinant human GH
2. Somatrem – modified GH with an additional methionine residue

C. Therapeutic Uses

- Growth hormone deficiency in children (pituitary dwarfism)
- Turner's syndrome (female hypogonadism with short stature)
- Chronic renal failure–associated growth failure
- GH deficiency in adults (muscle wasting, fatigue)

D. Adverse Effects

- Edema, arthralgia, insulin resistance, gynecomastia
- In children: slipped capital femoral epiphysis, intracranial hypertension

- In adults: carpal tunnel syndrome

Growth Hormone Inhibitors

A. Somatostatin (GHIH)

- A natural peptide hormone produced by the hypothalamus.
- Inhibits GH, TSH, insulin, glucagon, and gastrin secretion.
- Short half-life (~2–3 min), so not useful therapeutically.

B. Somatostatin Analogues

1. Octreotide (long-acting synthetic analogue)
    - Duration: 8–12 hours
    - Uses:
        - Acromegaly (GH-secreting tumor)
        - Carcinoid tumors
        - VIPoma (vasoactive intestinal peptide-secreting tumor)
        - Bleeding esophageal varices
2. Lanreotide, Pasireotide – longer acting analogues

C. GH Receptor Antagonist

- Pegvisomant
    - Mechanism: binds to GH receptor but blocks signal transduction.
    - Use: resistant cases of acromegaly.

Prolactin (PRL)

A. Source and Function

- Secreted by lactotroph cells of anterior pituitary.
- Promotes lactation (milk production) after childbirth.
- Inhibited by dopamine (prolactin inhibitory hormone).

B. Hyperprolactinemia

- Causes: prolactin-secreting pituitary tumor (prolactinoma), antipsychotic drugs (dopamine blockers).
- Symptoms: galactorrhea, infertility, menstrual irregularities, decreased libido.

C. Prolactin Inhibitors (Dopamine Agonists)

1. Bromocriptine – ergot derivative, D_2 receptor agonist.
2. Cabergoline, Pergolide – newer agents, longer duration.

D. Therapeutic Uses:

- Hyperprolactinemia (restores ovulation and menstruation)
- Prolactinoma (reduces tumor size)
- Parkinson's disease (dopaminergic activity)
- Suppress postpartum lactation (rarely used now)

E. Adverse Effects:

- Nausea, vomiting, hypotension, dizziness, hallucinations.

Gonadotropins (FSH and LH)

A. Source and Function

- Secreted by gonadotroph cells of anterior pituitary.
- Regulated by GnRH (Gonadotropin-Releasing Hormone) from the hypothalamus.
- Functions:
  - FSH: stimulates spermatogenesis in males and follicular development in females.
  - LH: stimulates testosterone secretion in males and ovulation and corpus luteum formation in females.

B. Gonadotropin Analogues

1. Human Menopausal Gonadotropin (hMG) – contains FSH + LH; derived from postmenopausal urine.
2. Urofollitropin (FSH) – purified human FSH.
3. Recombinant FSH (Follitropin alfa, beta) – highly purified, consistent potency.
4. Human Chorionic Gonadotropin (hCG) – acts like LH; derived from pregnant women's urine.

C. Therapeutic Uses

- Infertility treatment (both in men and women).
- Anovulatory infertility due to hypogonadotropic hypogonadism.
- Cryptorchidism (undescended testes in boys).
- Male infertility due to pituitary insufficiency.

D. Adverse Effects

- Ovarian hyperstimulation, multiple pregnancies, gynecomastia in men, headache, mood changes.

Gonadotropin-Releasing Hormone (GnRH) Analogues and Inhibitors

A. GnRH Analogues

- Leuprolide, Goserelin, Nafarelin, Buserelin – synthetic analogues.
- Mechanism:
  - Pulsatile administration → stimulates FSH & LH (mimics physiology).
  - Continuous administration → suppresses gonadotropins (due to receptor downregulation).

Therapeutic Uses:

- Pulsatile: infertility (stimulates ovulation/spermatogenesis).
- Continuous: prostate cancer, endometriosis, uterine fibroids, precocious puberty.

B. GnRH Antagonists

- Cetrorelix, Ganirelix, Degarelix
  - Mechanism: directly block GnRH receptors → rapid suppression of FSH/LH.
  - Uses:
    - Prevention of premature ovulation during IVF.
    - Advanced prostate cancer.

Adverse Effects: headache, hot flashes, decreased libido, osteoporosis (with long-term use).

Adrenocorticotropic hormone (ACTH)

A. Source and Function

- Produced by corticotroph cells of anterior pituitary.
- Stimulates the adrenal cortex to secrete glucocorticoids (cortisol), mineralocorticoids (aldosterone), and androgens.

B. Analogues

- Cosyntropin – synthetic ACTH fragment (1–24 amino acids), retains full activity.

C. Therapeutic Uses

- Diagnostic test for adrenal insufficiency (to differentiate between primary and secondary).
- Infantile spasms (rarely used now due to steroid therapy).

D. Adverse Effects

- Same as glucocorticoids: sodium retention, edema, hypertension, Cushingoid symptoms.

Thyroid Stimulating Hormone (TSH)

A. Function

- Stimulates the thyroid gland to produce thyroxine (T_4) and triiodothyronine (T_3).
- Controlled by TRH and inhibited by negative feedback from T_3 and T_4.

B. Analogues

- Thyrotropin alfa – recombinant TSH.

C. Therapeutic Uses

- Thyroid cancer management – used to enhance radioactive iodine uptake.
- Diagnostic test for thyroid function evaluation.

D. Inhibitors

- Somatostatin, dopamine, and glucocorticoids inhibit TSH secretion.

Thyroid Hormones – Analogues and their Inhibitors

The thyroid gland is an important endocrine organ located in the neck region.
It synthesizes and secretes thyroid hormones, mainly:

- Thyroxine (T_4)
- Triiodothyronine (T_3)

These hormones play a crucial role in:

- Regulation of metabolism
- Growth and development
- Thermogenesis
- Protein synthesis
- CNS and skeletal maturation

Biosynthesis of Thyroid Hormones

1. Iodide uptake – Active transport of iodide (I^-) into thyroid follicular cells by Na^+/I^- symporter.
2. Oxidation and Iodination – Iodide is oxidized by thyroid peroxidase (TPO) to form active iodine.
   Iodination of tyrosine residues in thyroglobulin forms:
   - Monoiodotyrosine (MIT)
   - Diiodotyrosine (DIT)
3. Coupling reaction – Two DIT combine → T_4, and one MIT + one DIT → T_3.
4. Storage and Release – Thyroglobulin containing T_3 and T_4 is stored in follicles. Upon stimulation by TSH, T_3 and T_4 are released into circulation.
5. Peripheral conversion – T_4 is converted to T_3 (active form) in tissues by deiodinase enzymes.

Mechanism of Action

- T_3 binds to thyroid hormone receptors (TRα, TRβ) in the nucleus.
- The hormone-receptor complex binds to DNA → modulates gene transcription.
- This alters synthesis of enzymes and proteins involved in:
  - Energy metabolism
  - Growth and development
  - Oxygen consumption

Physiological Effects

System	Effect
Metabolic rate	Increases basal metabolic rate (BMR) and oxygen consumption
Carbohydrate metabolism	Increases glucose absorption and utilization
Lipid metabolism	Stimulates lipolysis and cholesterol degradation
Protein metabolism	Enhances protein synthesis
Cardiovascular system	Increases heart rate, cardiac output, and contractility
Growth and development	Essential for CNS and skeletal development in infants
Thermogenesis	Increases heat production

Disorders of Thyroid Function

Disorder	Description	Symptoms
Hypothyroidism	Deficiency of thyroid hormones	Fatigue, weight gain, cold intolerance, dry skin, myxedema
Cretinism	Congenital hypothyroidism	Mental retardation, stunted growth
Hyperthyroidism	Excess thyroid hormones	Weight loss, heat intolerance, tachycardia, tremors, anxiety
Graves' disease	Autoimmune hyperthyroidism	Goiter, exophthalmos, high BMR

Thyroid Hormone Analogues

These are synthetic or natural preparations used in the treatment of hypothyroidism.

A. Levothyroxine (T_4)

- Synthetic form of thyroxine
- Oral bioavailability: ~80%
- Half-life: 6–7 days
- Onset: Slow but long duration
- Uses:
  - Hypothyroidism (all types)
  - Myxedema coma (IV route)
  - Suppression of TSH in thyroid cancer or goiter
- Adverse effects:
  - Nervousness, insomnia
  - Palpitations, tachycardia
  - Angina (in cardiac patients)
- Contraindications:
  - Untreated adrenal insufficiency
  - Thyrotoxicosis

B. Liothyronine (T_3)

- Synthetic triiodothyronine
- Potent and faster-acting than T_4
- Half-life: 1–2 days
- Uses:
  - Myxedema coma (rapid action needed)
  - Short-term TSH suppression
- Adverse effects:
  - Same as levothyroxine but more severe due to higher potency

C. Liotrix

- Mixture of T_4 and T_3 in a fixed ratio (4:1)
- Mimics natural hormone secretion
- Use: Hypothyroidism (alternative to levothyroxine)
- Limitation: No major clinical advantage over levothyroxine

D. Thyroid Extract (Desiccated thyroid)

- Prepared from animal thyroid glands
- Contains both T_3 and T_4
- Obsolete now due to variable potency and stability

Thyroid Hormone Inhibitors (Antithyroid Drugs)

Used in hyperthyroidism and thyrotoxicosis.

A. Thioamides (Thioureylene Derivatives)

1. Propylthiouracil (PTU)

2. Methimazole

3. Carbimazole (Prodrug of methimazole)

Mechanism of Action:

- Inhibit thyroid peroxidase (TPO) enzyme
  → Prevent oxidation, iodination, and coupling steps.
- PTU also inhibits peripheral conversion of $T_4 \rightarrow T_3$.

Onset: Slow (takes 3–4 weeks as stored hormones are depleted).

Uses:

- Hyperthyroidism (Graves' disease)
- Preoperative preparation for thyroidectomy
- Thyrotoxic crisis (PTU preferred)

Adverse effects:

- Skin rash, urticaria
- Agranulocytosis (rare but serious)
- Hepatotoxicity (mainly PTU)
- Arthralgia

B. Iodide (Lugol's iodine, Potassium iodide)

Mechanism:

- Inhibits iodine organification and hormone release
- Decreases vascularity and size of thyroid gland

Uses:

- Short-term preoperative preparation
- Thyrotoxic crisis (rapid effect)
- Iodine prophylaxis after nuclear exposure

Adverse effects:

- Iodism (metallic taste, sore throat, salivation)
- Hypersensitivity reactions

Hormones Regulating Plasma Calcium Levels

(Parathormone, Calcitonin, and Vitamin D)

Calcium (Ca^{2+}) is a vital mineral required for:

- Bone and teeth formation
- Muscle contraction
- Blood coagulation
- Nerve transmission
- Enzyme activation and hormonal secretion

The normal plasma calcium level is maintained within a narrow range of 8.5–10.5 mg/dL.
Maintaining calcium homeostasis is crucial for neuromuscular excitability and bone integrity.

Three major hormones regulate plasma calcium and phosphate levels:

Hormone	Source	Effect on Plasma Ca^{2+}	Effect on Plasma Phosphate
Parathormone (PTH)	Parathyroid gland	↑ Increases	↓ Decreases
Calcitonin (CT)	Thyroid gland (C cells)	↓ Decreases	↓ Decreases
Vitamin D (Calcitriol)	Skin, Liver, Kidney (activated form)	↑ Increases	↑ Increases

Parathormone (PTH)

Source:

- Secreted by chief cells of the parathyroid glands (4 small glands located behind the thyroid).

Structure:

- It is a single-chain polypeptide with 84 amino acids.

Regulation of Secretion:

- Stimulus: Decrease in plasma Ca^{2+} concentration → stimulates PTH secretion.
- Inhibition: Increase in plasma Ca^{2+} → inhibits PTH release (negative feedback).

Mechanism of Action:

PTH acts through G-protein coupled receptors (PTH1 receptors) and increases cAMP formation in target tissues.

Target organs: Bone, Kidney, and indirectly Intestine.

Actions of Parathormone:

1. On Bone:

- Stimulates osteoclast activity (bone-resorbing cells).
- Increases breakdown of bone matrix → releases Ca^{2+} and phosphate into blood.

2. On Kidney:

- Increases Ca^{2+} reabsorption in distal tubules.

- Decreases phosphate reabsorption → increases phosphate excretion.
- Stimulates renal enzyme 1α-hydroxylase, which converts Vitamin D to its active form (calcitriol).

3. On Intestine (Indirect Action):

- By stimulating Vitamin D activation → increases intestinal absorption of calcium and phosphate.

Net Effect of PTH:

- Increases plasma calcium level
- Decreases plasma phosphate level

Disorders Associated with PTH:

Disorder	Cause	Features
Hypoparathyroidism	Deficient PTH secretion (e.g., after thyroid surgery)	Hypocalcemia, tetany, muscle spasms
Hyperparathyroidism	Overactive parathyroid gland or tumor	Hypercalcemia, bone demineralization, kidney stones ("stones, bones, and groans")

Therapeutic Uses of PTH and Analogues:

Drug	Use
Teriparatide (Recombinant PTH 1–34)	Treatment of osteoporosis (stimulates new bone formation)
Abaloparatide	Osteoporosis (PTHrP analogue)
PTH (1–84)	Replacement therapy for hypoparathyroidism

Calcitonin (CT)

Source:

- Secreted by parafollicular (C) cells of the thyroid gland.

Structure:

- Peptide hormone with 32 amino acids.

Regulation of Secretion:

- Stimulus: Increase in plasma calcium level → stimulates calcitonin release.
- Inhibition: Low plasma calcium → suppresses secretion.

Mechanism of Action:

- Acts through calcitonin receptors (GPCRs) on osteoclasts and kidneys.
- Increases cAMP and inhibits osteoclast activity → reduces bone resorption.

Actions of Calcitonin:

1. On Bone:

- Inhibits osteoclast-mediated bone resorption.
- Promotes calcium deposition in bone.
- Decreases calcium and phosphate release into plasma.

2. On Kidney:

- Increases urinary excretion of calcium and phosphate.

Net Effect of Calcitonin:

- Decreases plasma calcium and phosphate levels.
- Acts as a physiological antagonist of PTH.

Therapeutic Uses:

Drug	Source	Use
Salmon Calcitonin	Synthetic or recombinant	Osteoporosis, Paget's disease, hypercalcemia
Human Calcitonin	Recombinant	Less potent and short-acting

Adverse Effects:

- Nausea, flushing, tingling of hands

- Hypocalcemia (with prolonged use)

Vitamin D (Calcitriol)

Chemical Nature:

- Fat-soluble secosteroid
- Active form: 1,25-dihydroxycholecalciferol (Calcitriol)

Sources:

1. Endogenous (Skin):
   UV light converts 7-dehydrocholesterol → Cholecalciferol (Vitamin D_3).
2. Dietary:
   Fish oils, eggs, milk, butter, fortified foods.

Metabolism (Activation Pathway):

1. In Liver:
   Cholecalciferol → 25-hydroxycholecalciferol (Calcidiol)
2. In Kidney:
   Calcidiol → 1,25-dihydroxycholecalciferol (Calcitriol) (active form)
   (Enzyme: 1α-hydroxylase, stimulated by PTH)

Mechanism of Action:

- Binds to Vitamin D receptors (VDR), which act as nuclear transcription factors.
- Modulates gene expression → increases synthesis of calcium-binding proteins.

Actions of Vitamin D:

1. On Intestine:

- Increases absorption of calcium and phosphate from the gut by inducing synthesis of calbindin.

2. On Bone:

- Promotes bone mineralization (normal physiological levels).
- In high doses, mobilizes calcium from bone (bone resorption).

3. On Kidney:

- Increases reabsorption of calcium and phosphate in renal tubules.

Net Effect of Vitamin D:

- Increases both plasma calcium and phosphate levels.

Disorders Related to Vitamin D Deficiency:

Disorder	Age group	Features
Rickets	Children	Bone deformities, bow legs, delayed growth
Osteomalacia	Adults	Bone softening, fractures, bone pain
Hypocalcemia	All ages	Muscle cramps, tetany

Therapeutic Uses of Vitamin D and Analogues:

Drug	Type	Use
Calcitriol ($1,25(OH)_2D_3$)	Active form	Hypocalcemia, chronic kidney disease
Cholecalciferol (D_3)	Natural form	Vitamin D deficiency, rickets
Ergocalciferol (D_2)	Plant form	Nutritional supplement
Alfacalcidol	1-hydroxy D_3 (requires hepatic activation)	Renal osteodystrophy
Dihydrotachysterol	Synthetic analogue	Hypoparathyroidism

Adverse Effects (Hypervitaminosis D):

- Hypercalcemia
- Nausea, vomiting, weakness
- Nephrocalcinosis, renal failure

Interrelation Between PTH, Calcitonin, and Vitamin D

Action	PTH	Calcitonin	Vitamin D
Bone resorption	↑ Increases	↓ Decreases	↑ (high dose)
Ca^{2+} absorption (Intestine)	Indirect (via Vit D)	–	↑ Increases
Ca^{2+} reabsorption (Kidney)	↑ Increases	↓ Decreases	↑ Increases
Phosphate excretion	↑ Increases	↑ Increases	↓ Decreases

Net effect on Plasma Ca^{2+}	↑ Increases	↓ Decreases	↑ Increases

Insulin, Oral Hypoglycemic Agents and Glucagon

The endocrine pancreas plays a vital role in regulating blood glucose levels through the secretion of different hormones:

Cell Type	Hormone Secreted	Function
α-cells	Glucagon	Increases blood glucose
β-cells	Insulin	Decreases blood glucose
δ-cells	Somatostatin	Inhibits insulin and glucagon release

Normal blood glucose level: 70–110 mg/dL (fasting).
Disturbances cause:

- Hyperglycemia → Diabetes mellitus
- Hypoglycemia → Insulin excess or fasting

INSULIN

Source:

- Secreted by β-cells of islets of Langerhans in the pancreas.

Structure:

- Peptide hormone of 51 amino acids arranged in two chains (A and B) linked by disulfide bonds.
- Synthesized as proinsulin → converted to insulin + C-peptide.

Mechanism of Secretion:

- Stimulated by high blood glucose (post-meal).
- Inhibited by low glucose, somatostatin, and α-adrenergic stimulation.

Mechanism of Action:

- Acts through insulin receptors (tyrosine kinase receptors) on target cells.
- Binding activates autophosphorylation, leading to:
  - ↑ glucose uptake by cells (via GLUT-4 transporter)
  - ↑ glycogen synthesis
  - ↑ protein and fat synthesis
  - ↓ gluconeogenesis

Metabolic Effects of Insulin:

Organ/System	Action
Liver	Promotes glycogen synthesis; inhibits gluconeogenesis
Muscle	Increases glucose uptake and glycogen formation; increases protein synthesis
Adipose tissue	Stimulates fat synthesis and inhibits lipolysis
Overall effect	Decreases blood glucose concentration

Therapeutic Preparations of Insulin

Insulins differ by onset and duration of action due to additives and formulation differences.

Type	Example	Onset (min)	Duration (hr)
Rapid-acting	Insulin Lispro, Aspart, Glulisine	10–20	3–5
Short-acting	Regular (soluble) insulin	30–60	6–8
Intermediate-acting	NPH (Isophane), Lente	60–120	18–24
Long-acting	Insulin Glargine, Detemir, Degludec	60–90	24–40

Routes of Administration:

- Subcutaneous injection (SC) – most common
- Intravenous (IV) – emergency use (regular insulin only)
- Inhalation/insulin pumps – advanced methods

Therapeutic Uses of Insulin:

- Type 1 Diabetes Mellitus (absolute insulin deficiency)
- Type 2 Diabetes Mellitus (when oral drugs fail)
- Diabetic ketoacidosis (DKA)
- Hyperkalemia (drives K^+ into cells)
- Gestational diabetes

Adverse Effects:

- Hypoglycemia (main danger): sweating, tremors, confusion, coma
- Lipodystrophy at injection site
- Allergic reactions (rare with human insulin)
- Weight gain

Management of Insulin-Induced Hypoglycemia:

- Mild: Oral glucose, sugar, fruit juice
- Severe: IV dextrose or IM/SC glucagon

Oral Hypoglycemic Agents (OHAs)

These are drugs used to lower blood glucose levels in Type 2 Diabetes Mellitus (non-insulin-dependent).

Classification:

A. Insulin Secretagogues (Increase Insulin Secretion)

1. Sulfonylureas
   - *First generation:* Tolbutamide, Chlorpropamide
   - *Second generation:* Glibenclamide (Glyburide), Glipizide, Gliclazide, Glimepiride

   Mechanism:

   - Block ATP-sensitive K^+ channels in β-cells → depolarization → Ca^{2+} influx → insulin release.
     Adverse effects: Hypoglycemia, weight gain, nausea.

2. Meglitinides (Rapid-acting Secretagogues)
   - Repaglinide, Nateglinide
     Mechanism: Same as sulfonylureas (different binding site).
     Use: Post-meal glucose control.
     Adverse effect: Hypoglycemia (less frequent).

B. Insulin Sensitizers (Improve Insulin Action)

1. Biguanides: Metformin
   Mechanism:
   - Decreases hepatic glucose production.
   - Increases glucose uptake in muscles.
   - Does not cause hypoglycemia.
     Uses: First-line drug for Type 2 DM; obesity-related diabetes; PCOS.
     Adverse effects: Lactic acidosis (rare), metallic taste, GI upset.

2. Thiazolidinediones (Glitazones): Pioglitazone, Rosiglitazone
   Mechanism:
   - Activate PPAR-γ receptors → increase insulin sensitivity in muscle and adipose tissue.
     Adverse effects: Weight gain, edema, heart failure, hepatotoxicity.

C. α-Glucosidase Inhibitors

- Acarbose, Miglitol, Voglibose
  Mechanism:
- Inhibit intestinal α-glucosidase enzyme, delaying carbohydrate digestion and glucose absorption.
  Adverse effects: Flatulence, diarrhea, abdominal pain.
  Use: Postprandial hyperglycemia.

D. DPP-4 Inhibitors (Incretin Enhancers)

- Sitagliptin, Vildagliptin, Saxagliptin, Linagliptin
  Mechanism:
- Inhibit Dipeptidyl Peptidase-4 enzyme → prolong action of GLP-1 and GIP → increase insulin release and decrease glucagon.
  Adverse effects: Nasopharyngitis, mild GI upset.
  Advantage: No weight gain or hypoglycemia.

E. GLP-1 Receptor Agonists (Incretin Mimetics)

- Exenatide, Liraglutide, Dulaglutide (injectable)
  Mechanism:
- Mimic GLP-1 → increase glucose-dependent insulin release, decrease glucagon, slow gastric emptying.
  Adverse effects: Nausea, pancreatitis, weight loss (useful in obese diabetics).

F. SGLT-2 Inhibitors (Renal Glucose Reabsorption Blockers)

- Dapagliflozin, Canagliflozin, Empagliflozin
  Mechanism:
- Inhibit Sodium-Glucose Cotransporter-2 in renal proximal tubules → increase urinary glucose excretion.
  Adverse effects: Genital infections, dehydration, ketoacidosis.
  Benefit: Weight reduction and BP lowering.

G. Other Agents

- Colesevelam (bile acid sequestrant): lowers glucose modestly.
- Pramlintide (amylin analogue): slows gastric emptying, reduces appetite.

Combination Therapy:

- Often used together for better glycemic control.
  Examples:
  - Metformin + Sulfonylurea
  - Metformin + DPP-4 inhibitor
  - Metformin + SGLT-2 inhibitor

GLUCAGON

Source:

- Secreted by α-cells of islets of Langerhans.

Structure:

- Single-chain polypeptide with 29 amino acids.

Mechanism of Action:

- Acts via G-protein coupled receptors → activates adenylyl cyclase → ↑ cAMP in liver.
- Promotes glycogenolysis and gluconeogenesis, raising blood glucose levels.

Physiological Actions:

Target	Effect
Liver	Increases glycogen breakdown → ↑ plasma glucose
Heart	Positive inotropic and chronotropic effect
Adipose tissue	Increases lipolysis

Therapeutic Uses of Glucagon:

1. Severe hypoglycemia (when patient unconscious and IV glucose unavailable).
2. Cardiac stimulant in β-blocker overdose.
3. Radiologic GI relaxation for bowel imaging.

Adverse Effects:

- Nausea and vomiting
- Transient rise in blood pressure
- Hypokalemia (rare)

ACTH and Corticosteroids

The adrenal cortex is a part of the adrenal gland, located above each kidney. It secretes steroid hormones, collectively known as corticosteroids, under the control of the pituitary hormone ACTH (Adrenocorticotropic Hormone).

These hormones are essential for:

- Regulation of metabolism
- Water and electrolyte balance
- Stress response
- Anti-inflammatory and immunosuppressive effects

Adrenocorticotropic Hormone (ACTH)

Source and Structure

- ACTH is a polypeptide hormone (39 amino acids) secreted by the anterior pituitary gland.
- It is derived from a larger precursor molecule pro-opiomelanocortin (POMC).

Regulation of ACTH Secretion

1. Stimulated by:
    - Corticotropin-releasing hormone (CRH) from the hypothalamus
    - Stress, trauma, hypoglycemia, or cold exposure
2. Inhibited by:
    - Negative feedback of plasma cortisol on both hypothalamus and pituitary.

Mechanism of Action

- ACTH acts on the adrenal cortex, specifically on melanocortin-2 receptors (MC2R).
- It activates adenylate cyclase → cAMP → protein kinase A, which stimulates:
    - Conversion of cholesterol → pregnenolone, the first step in corticosteroid synthesis.
- Result: Increased synthesis and secretion of glucocorticoids (cortisol), and to a lesser extent, mineralocorticoids and androgens.

Physiological Roles of ACTH

1. Stimulates adrenal cortex to produce cortisol and other steroids.
2. Trophic effect: Maintains the structural integrity of adrenal cortex.
3. In stress: Increases cortisol secretion to handle metabolic and physiological stress.

Therapeutic Uses

- Diagnostic test for adrenal cortical function:
    - ACTH stimulation test helps distinguish primary adrenal insufficiency (Addison's disease) from secondary (pituitary) insufficiency.
- Therapeutic use (limited due to corticosteroid availability):
    - Infantile spasms (West syndrome)
    - Multiple sclerosis (acute attack)

Adverse Effects

Similar to prolonged corticosteroid use:

- Sodium and water retention
- Hypertension
- Cushingoid appearance (moon face, obesity)
- Peptic ulcers

- Osteoporosis

CORTICOSTEROIDS

Corticosteroids are steroid hormones produced by the adrenal cortex and are divided into:

1. Glucocorticoids – mainly cortisol (hydrocortisone)
   → Affect carbohydrate, protein, and fat metabolism
2. Mineralocorticoids – mainly aldosterone
   → Regulate electrolyte and water balance

Classification of Corticosteroids

Type	Examples	Major Function
Natural	Cortisol, Corticosterone, Aldosterone	Physiological functions
Synthetic Glucocorticoids	Prednisolone, Dexamethasone, Betamethasone, Triamcinolone	Anti-inflammatory, immunosuppressive
Synthetic Mineralocorticoids	Fludrocortisone, Deoxycorticosterone acetate	Electrolyte balance, BP maintenance

GLUCOCORTICOIDS

Mechanism of Action

1. Glucocorticoids diffuse through cell membrane → bind to cytoplasmic glucocorticoid receptor (GR).
2. The complex enters the nucleus → binds to glucocorticoid response elements (GREs) on DNA.
3. Alters gene transcription, increasing or decreasing protein synthesis.
4. Results in:
   - Anti-inflammatory, anti-allergic, immunosuppressive actions
   - Metabolic effects

Physiological and Pharmacological Actions

1. Metabolic Effects

Metabolism	Effect
Carbohydrate	↑ Gluconeogenesis → ↑ Blood glucose (hyperglycemia)
Protein	↑ Protein catabolism → muscle wasting
Fat	↑ Lipolysis → redistribution of fat (moon face, buffalo hump)

2. Anti-inflammatory Effects

- Inhibit phospholipase A_2 → ↓ prostaglandins and leukotrienes
- Decrease capillary permeability and migration of immune cells
- Suppress cytokine release (IL-1, TNF-α)

3. Immunosuppressive Effects

- Decrease lymphocyte count (T-cell suppression)
- Inhibit antibody formation

4. Other Effects

- CNS stimulation (mood elevation, insomnia)
- ↑ Gastric acid secretion (risk of ulcers)
- ↓ Calcium absorption → osteoporosis
- Negative feedback on ACTH → adrenal suppression

Therapeutic Uses

1. Replacement therapy
    - Addison's disease (adrenal insufficiency) → Hydrocortisone + Fludrocortisone
    - Congenital adrenal hyperplasia
2. Anti-inflammatory & immunosuppressive
    - Rheumatoid arthritis
    - Asthma and allergic disorders
    - Autoimmune diseases (SLE, ulcerative colitis)
    - Organ transplantation (to prevent rejection)
3. Anti-cancer therapy
    - Lymphomas, leukemias (due to lympholytic action)
4. Diagnostic uses

- Dexamethasone suppression test (for Cushing's syndrome)

5. Miscellaneous
   - Cerebral edema
   - Shock (as supportive therapy)
   - Skin diseases (eczema, psoriasis)

Adverse Effects of Glucocorticoids

System	Adverse Effect
Metabolic	Hyperglycemia, diabetes mellitus
Musculoskeletal	Osteoporosis, muscle wasting
GI tract	Peptic ulcer, GI bleeding
CNS	Insomnia, euphoria, psychosis
Endocrine	Adrenal suppression, Cushingoid features
Immunity	Increased infection risk
Eye	Glaucoma, cataract
Growth	Growth retardation in children

Withdrawal Effects

- Abrupt stoppage → acute adrenal insufficiency
- Symptoms: fatigue, hypotension, vomiting, shock
- Therefore, taper dose gradually after long-term therapy.

MINERALOCORTICOIDS

A. Principal Hormone – Aldosterone

Functions:

- Acts on renal distal tubules
- Promotes:
  - Na^+ and water reabsorption
  - K^+ and H^+ excretion
    → Maintains blood pressure and volume

Regulation:

- Renin–angiotensin–aldosterone system (RAAS)
- Hyperkalemia and ACTH also stimulate secretion.

B. Synthetic Mineralocorticoid – Fludrocortisone

Uses:

- Replacement therapy in Addison's disease
- Orthostatic hypotension

Adverse Effects:

- Sodium and water retention → edema
- Hypertension
- Hypokalemia

Comparison of Glucocorticoids and Mineralocorticoids

Feature	Glucocorticoids	Mineralocorticoids
Main Hormone	Cortisol	Aldosterone
Main Action	Metabolic, anti-inflammatory	Electrolyte balance
Sodium Retention	Mild	Strong
Potassium Excretion	Moderate	High
Anti-inflammatory	Potent	Absent

Example	Prednisolone	Fludrocortisone

Contraindications of Corticosteroids

- Peptic ulcer disease
- Diabetes mellitus
- Hypertension
- Tuberculosis or active infections
- Osteoporosis
- Psychotic disorders

Drug Interactions

- NSAIDs → ↑ Risk of ulcers
- Antidiabetic drugs → Reduced efficacy (hyperglycemia)
- Diuretics + corticosteroids → Hypokalemia
- Vaccines → Decreased immune response