The endocrine system includes all of the glands of the body and the hormones produced by those glands.

The glands are controlled directly by stimulation from the nervous system as well as by hormones produced by other glands.

By regulating the functions of organs in the body, these glands help to maintain the body’s homeostasis.

Cellular metabolism, reproduction, sexual development, sugar and mineral homeostasis, heart rate, digestion etc among the many processes regulated by the actions of hormones.
Types of hormones in human body - steroid vs. nonsteroid hormones and their mechanisms of action

The endocrine system produces **two main types of hormone product:**

1. steroid hormones
2. nonsteroid hormones

**Steroid hormones**

Steroid hormones, such as cortisol, are manufactured from **cholesterol**. Each type of steroid hormone is composed of a central structure of four carbon rings attached to distinctive side chains that determine the hormone’s specific and unique properties. Within the endocrine cells, steroid hormones are synthesized in the **smooth endoplasmic reticulum** (ER).
Since steroid hormones are hydrophobic, they combine with a protein carrier that transports them through the bloodstream. Fat-soluble steroid hormones can pass through the membrane of a target cell. Once inside the target cell, steroid hormones attach to a protein receptor molecule in the cytoplasm. This hormone-receptor complex then enters the nucleus, where it binds with and activates a specific gene on the cell’s DNA molecule. The activated gene then produces an enzyme that initiates the desired chemical reaction within the cell.

**Non-steroid hormones**

Non-steroid hormones, such as adrenaline, are composed of either proteins, peptides, or amino acids. These hormone molecules are not fat-soluble, so they usually do not enter cells to exert their effect. Instead, they bind to receptors on the surface of target cells. This combination substance then triggers a specific chain of chemical reactions within the cell.
Hypothalamus:
The hypothalamus is located below the thalamus and above the pituitary gland & is part of the limbic system, it is the size of an almond.

Variety of functions including emotional expressions, controls body temperature, hunger, thirst, fatigue, sleep, and circadian rhythms. Its primary function is to maintain homeostasis (stability of the internal environment) in the body.

Most important functions of the hypothalamus is to link the nervous system to the endocrine system via the pituitary gland (hypophysis).

The hypothalamus exerts control of the anterior pituitary by secreting tropic hormones which regulate the secretion of other hormones by either stimulating or inhibiting their secretion.

The tropic hormones secreted by the neurosecretory cells of the hypothalamus reach the target cells of the anterior pituitary by the **hypothalamic-pituitary portal system.**
The hypothalamus secretes releasing hormones (RH) to stimulate hormone secretion from the anterior pituitary.

**Thyrotropin-releasing hormone (TRH)**
**Growth hormone-releasing hormone (GHRH)**
**Growth hormone-inhibiting hormone (GHIH)**
**Gonadotropin-releasing hormone (GnRH)**
**Corticotropin-releasing hormone (CRH)**

The anterior part of pituitary gland releases stimulating hormones (SH) including gonadotropins (FSH, LH), thyroid stimulating hormone (TSH), and adrenocorticotrophic (ACTH) all of which control the activity of peripheral endocrine glands such as the ovaries, testes, the thyroid gland, and the adrenal cortex. In addition, the anterior part of the pituitary gland produces growth hormone (GH) and prolactin (Prl).

The posterior lobe of the pituitary gland releases oxytocin and antidiuretic hormone (ADH), which are freed by nerve endings that stem from the hypothalamus.
Hypothalamic dysfunction

Causes of hypothalamic dysfunction include:
Anorexia, Bleeding, Genetic disorders, Growths (tumors), Head trauma, Infections and swelling (inflammation), Malnutrition, Radiation, Surgery, Too much iron, The most common tumors in the area are craniopharyngiomas in children.

**Symptoms**
Symptoms are usually due to the hormones that are missing. In children, there may be growth problems -- either too much or too little growth -- or puberty that occurs too early or too late.
Tumor symptoms: Headaches, Loss of vision
Hypothyroidism symptoms:
Low adrenal function symptoms:
Kallmann's syndrome (a type of hypothalamic dysfunction that occurs in men)
symptoms: Lowered function of sexual hormones (hypogonadism)
Exams and Tests
Blood or urine tests to determine levels of hormones such as: Cortisol, Estrogen, Growth hormone, Pituitary hormones, Prolactin Testosterone, Thyroid,

Other possible tests:
Hormone injections followed by timed blood samples
MRI or CT scans of the brain

Treatment
Treatment depends on the cause of the hypothalamic dysfunction.
Tumors -- surgery or radiation
Hormonal deficiencies -- replace missing hormones
Pituitary Gland

Also known as the hypophysis, is a small pea-sized lump of tissue connected to the inferior portion of the hypothalamus of the brain. Many blood vessels surround the pituitary gland to carry the hormones it releases throughout the body. Made of 2 completely separate structures: the posterior and anterior pituitary glands.

Posterior Pituitary: Actually not glandular tissue, but nervous tissue. The posterior pituitary is a small extension of the hypothalamus through which the axons of some of the neurosecretory cells of the hypothalamus extend. These neurosecretory cells create 2 hormones in the hypothalamus that are stored and released by the posterior pituitary:

- **Oxytocin** triggers uterine contractions during childbirth and the release of milk during breastfeeding.
- **Antidiuretic hormone (ADH)** prevents water loss in the body by increasing the re-uptake of water in the kidneys and reducing blood flow to sweat glands.
Anterior Pituitary: True glandular part, its functions is controlled by the tropic hormones of the hypothalamus. The anterior pituitary produces 6 important hormones:

TSH- stimulates thyroid gland.

ACTH- stimulates the adrenal cortex, the outer part of the adrenal gland, to produce its hormones.

FSH- stimulates the follicle cells of the gonads to produce gametes, ova in females and sperm in males.

LH- stimulates the gonads to produce the sex hormones—estrogens in females and testosterone in males.

HGH- affects many target cells throughout the body by stimulating their growth, repair, and reproduction.

PRL- has many effects on the body, chief of which is that it stimulates the mammary glands of the breast to produce milk.
<table>
<thead>
<tr>
<th>Hormone Deficiency</th>
<th>Symptoms</th>
<th>Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Growth hormone</td>
<td>Anergia, poor quality of life</td>
<td>Osteoporosis, visceral obesity, reduced lean body mass, dyslipidemia</td>
</tr>
<tr>
<td>LH/FSH (sex steroids)</td>
<td>Oligomenorrhea or amenorrhea, sexual dysfunction, mood disorders, reduced vigor</td>
<td>Loss of secondary hair, reduced muscle mass and exercise tolerance (men), osteoporosis, infertility (men and women)</td>
</tr>
<tr>
<td>Corticosteroids</td>
<td>Life-threatening adrenal crisis (weakness, nausea, fever, shock), poor energy, weight loss</td>
<td>Hypotension, hypoglycemia, hyponatremia, myopathy, anemia, eosinophilia</td>
</tr>
<tr>
<td>Thyroid hormones</td>
<td>Poor energy, neuropsychiatric problems, weight gain</td>
<td>Bradycardia, hypotension, myopathy, neuropathy, skin, hair, and voice changes</td>
</tr>
</tbody>
</table>

Abbreviations: FSH, follicle-stimulating hormone; LH, luteinizing hormone.
Pineal Gland

It produces the hormone melatonin that helps to regulate the human sleep-wake cycle known as the circadian rhythm.

The activity of the pineal gland is inhibited by stimulation from the photoreceptors of the retina.

This light sensitivity causes melatonin to be produced only in low light or darkness. Increased melatonin production causes humans to feel drowsy at nighttime when the pineal gland is active.
The adrenal glands are endocrine glands located just above the kidneys and produce a variety of hormones including adrenaline and the steroids aldosterone and cortisol.

Each gland has an outer cortex which produces steroid hormones and an inner medulla.
Adrenal medulla

- Core of the adrenal glands.
- Surrounded by the adrenal cortex.
- Responsible for the production of catecholamines, derived from the amino acid tyrosine.
Chromaffin cells, also pheochromocytes, are neuroendocrine cells found mostly in the medulla of the adrenal glands in mammals.

Serve a variety of functions such as serving as a response to stress, monitoring carbon dioxide and oxygen concentrations in the body, maintenance of respiration and the regulation of blood pressure.

They are in close proximity to pre-synaptic sympathetic ganglia of the sympathetic nervous system which releases acetylcholine which further excites post-synaptic sympathetic neurons/chromaffin cells and releases the neurotransmitter noradrenaline (also called norepinephrine). The action of noradrenaline on a particular gland or muscle in excitatory is some cases, inhibitory in others.
ADRENAL CORTEX  Situated along the perimeter of the adrenal gland, mediates stress response

Layers of Adrenal cortex

<table>
<thead>
<tr>
<th>Tissue area</th>
<th>Hormones released</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zona glomerulosa</td>
<td>Mineralcorticoids (regulate mineral balance)</td>
<td>Aldosterone</td>
</tr>
<tr>
<td>(adrenal cortex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zona fasciculata</td>
<td>Glucocorticoids (regulate glucose metabolism)</td>
<td>Cortisol, Corticosterone, Cortisone</td>
</tr>
<tr>
<td>(adrenal cortex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Zona reticularis</td>
<td>Androgens (stimulate masculinization)</td>
<td>Dehydroepiandrosterone</td>
</tr>
<tr>
<td>(adrenal cortex)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Adrenal medulla</td>
<td>Stress hormones (stimulate sympathetic ANS)</td>
<td>Epinephrine, Norepinephrine</td>
</tr>
</tbody>
</table>
Synthesis of Norepinephrine and Epinephrine

Begins in the axoplasm of the terminal nerve endings of adrenergic nerve fibers but is completed inside the secretory vesicles. The basic steps are the following:

In the adrenal medulla, this reaction goes still one step further to transform about 80 per cent of the norepinephrine into epinephrine, as follows:
Ordinarily, the norepinephrine secreted directly into a tissue remains active for only a few seconds, demonstrating that its reuptake and diffusion away from the tissue are rapid.

However, the norepinephrine and epinephrine secreted into the blood by the adrenal medullae remain active until they diffuse into some tissue, where they can be destroyed by catechol-O-methyl transferase; this occurs mainly in the liver.

These catcholamines target the adrenergic receptors (or adrenoceptors), a class of G protein-coupled receptors present on many cells and stimulate the sympathetic nervous system. The sympathetic nervous system is responsible for the fight-or-flight response, which includes dilating the pupil, increasing heart rate, mobilizing energy, and diverting blood flow from non-essential organs to skeletal muscle.
Adrenergic Receptors

Two major types of adrenergic receptors:

- **alpha receptors**: alpha1 and alpha2
- **beta receptors**: beta1, beta2 and beta3

Majorly excited by NOREPINEPHRINE.

EPINEPHRINE excites both receptors equally.

<table>
<thead>
<tr>
<th>Alpha Receptor</th>
<th>Beta Receptor</th>
</tr>
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<tbody>
<tr>
<td>Vasoconstriction</td>
<td>Vasodilation (β2)</td>
</tr>
<tr>
<td>Iris dilation</td>
<td>Cardioacceleration (β1)</td>
</tr>
<tr>
<td>Intestinal relaxation</td>
<td>Increased myocardial strength (β1)</td>
</tr>
<tr>
<td>Intestinal sphincter contraction</td>
<td>Intestinal relaxation (β2)</td>
</tr>
<tr>
<td></td>
<td>Uterus relaxation (β2)</td>
</tr>
<tr>
<td>Pilomotor contraction</td>
<td>Bronchodilation (β2)</td>
</tr>
<tr>
<td>Bladder sphincter contraction</td>
<td>Calorigenesis (β2)</td>
</tr>
<tr>
<td>Inhibits neurotransmitter release (α2)</td>
<td>Glycogenolysis (β2)</td>
</tr>
<tr>
<td></td>
<td>Lipolysis (β1)</td>
</tr>
<tr>
<td></td>
<td>Bladder wall relaxation (β2)</td>
</tr>
<tr>
<td></td>
<td>Thermogenesis (β3)</td>
</tr>
</tbody>
</table>
The autonomic nervous system (involuntary) consists of sensory neurons and motor neurons that run between the central nervous system (especially the hypothalamus and medulla oblongata) and various internal organs such as the: Heart, lungs, viscera, glands (both exocrine and endocrine).

All our conscious awareness of the external environment and all our motor activity to cope with it operate through the sensory-somatic division of the PNS (SSN-12 pairs of cranial nerves, 31 pairs of spinal nerves).
The autonomic nervous system has two subdivisions, the **sympathetic nervous system** and the **parasympathetic nervous system**.

Anatomically the **preganglionic** motor neurons of the sympathetic system arise in the spinal cord whereas the main nerves of the parasympathetic system are the tenth (X) cranial nerves, the vagus nerves. They originate in the medulla oblongata.

Activation of the sympathetic system is quite general because a single preganglionic neuron usually synapses with many postganglionic neurons; the release of adrenaline from the adrenal medulla into the blood ensures that all the cells of the body will be exposed to sympathetic stimulation even if no postganglionic neurons reach them directly.
Stimulation of the sympathetic branch of the autonomic nervous system prepares the body for emergencies: for "**fight or flight**", the parasympathetic system returns the body functions to normal after they have been altered by sympathetic stimulation.
**Fight or Flight Response**

*Amygdala*, an area of the brain that contributes to emotional processing, **perceives danger** and instantly sends a distress signal to the **hypothalamus**.

The hypothalamus activates the **sympathetic** nervous system by sending signals through the autonomic nerves to the **adrenal glands**.

Activation of the sympathetic NS and release of hormones by the adrenal medullae set in motion a series of physiological responses collectively called the **fight-or-flight response**.
Function of physiological changes

- Increased blood flow to the muscles.

- Increased blood pressure, heart rate, blood sugars, and fats in order to supply the body with extra energy.

- The blood clotting function of the body speeds up in order to prevent excessive blood loss in the event of an injury sustained during the response.

- Increased muscle tension in order to provide the body with extra speed and strength.
Once a sensory input is received, the stress response may take either or both of two forms, which act via different systems one acting quickly (within seconds) via sympathetic nervous impulses and the monoamines adrenaline and noradrenaline, and the second acting more slowly (within minutes or hours) via corticosteroids.

**sympatho-adrenomedulary (SAM) axis**

**hypothalamic-pituitary-adrenal (HPA) axis**

<table>
<thead>
<tr>
<th>Short-term stress response</th>
<th>Long-term stress response</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Glycogen broken down to glucose; increased blood glucose</td>
<td><strong>Mineralocorticoids</strong></td>
</tr>
<tr>
<td>2. Increased blood pressure</td>
<td>1. Retention of sodium ions and water by kidneys</td>
</tr>
<tr>
<td>3. Increased breathing rate</td>
<td>2. Increased blood volume and blood pressure</td>
</tr>
<tr>
<td>4. Increased metabolic rate</td>
<td></td>
</tr>
<tr>
<td>5. Change in blood-flow patterns, leading to increased alertness and decreased digestive and kidney activity</td>
<td>1. Proteins and fats broken down and converted to glucose, leading to increased blood glucose</td>
</tr>
<tr>
<td></td>
<td>2. Immune system may be suppressed</td>
</tr>
</tbody>
</table>
As the initial surge of epinephrine subsides, the hypothalamus activates HPA axis.

Prolonged activation of HPA axis can cause ATROPHY of Hippocampus

Increased blood pressure, blood sugar, and suppression of the immune system
Hypothalamus

- Pituitary Gland
- Adrenal Medulla

Adrenal Cortex
- Corticosteroids
  - Liver releases energy

Adrenaline
- Fight or Flight
  - Physiological Reactions

HPA (Chronic)

SAM (Acute)
The first step in the activation of this pathway is the innervation of the parvocellular sections of the paraventricular nucleus (PVN) of the hypothalamus, which is achieved by several processes.

The primary regulators of the hypothalamus are the amygdala – which stimulates the PVN and secondly the hippocampus which inhibits it.

Sensory information from the prefrontal cortex (PFC) is received by the basolateral amygdala, processed and sent on to the amygdala central nucleus, which innervates and stimulates the PVN.

Corticotropin-releasing hormone (CRH)- and arginine vasopressin (AVP)-expressing Parvocellular neurons in PVN project to pituitary where they stimulate adrenocorticotropic hormone (ACTH) synthesis and secretion, subsequently triggering corticosteroid synthesis and release from the adrenal cortex.

Besides acting in the brain to regulate various behaviours, corticosteroids fine-tune the amplitude and duration of corticosteroid secretion; they activate their cognate receptors (GR) in the pituitary, hypothalamus and hippocampus and bed nucleus of the stria terminalis (BNST) to restrain, and in the amygdala to enhance, adrenocortical secretion. Monoaminergic transmitters, namely, norepinephrine, serotonin and dopamine released from midbrain nuclei (the locus coeruleus [LC], raphé and ventral tegmental area [VTA] and substantia nigra [SN], respectively) exert modulatory effects on all brain regions involved in the control of the HPA axis.
Disturbances in the hypothalamic–pituitary–adrenal (HPA)-axis disturbances leads to severe hormonal imbalances

- Tight regulation of GC levels is essential as prolonged exposure to high concentrations alters numerous cellular processes potentially damaging the brain. Neuronal activity is directly influenced by GC levels through its regulation of the alpha subunit of the active Na+ channel.

- Administration of high doses of GCs led to atrophy in the hippocampus of rats and monkeys, as well as neuronal atrophy and volume reduction in the prefrontal cortex.

- Dysregulation of the HPA-axis is also strongly implicated in the pathology of major depressive disorder.

- HPA-axis activity is altered in neurodegenerative disorders AD, PD, and HD.

**Dexamethasone suppression test (DST):** To evaluate HPA-axis function. It is based on the administration of dexamethasone (DEX), a synthetic GC that binds with high affinity to GR. This simulates the molecular cascade for negative feedback with the end result being a suppression of cortisol release. Blood is collected from the subject to determine their cortisol suppression response with the expectation that most individuals would have diminished serum/plasma cortisol levels.
Lifestyle Interventions
- Increase engagement in pleasurable activities
- Reduce exposure to stressors
- Maintain appropriate levels of physical activity/exercise
- Improve sleep patterns
- Decrease drug and alcohol use
- Increase social support
- Decrease toxic exposure

Psychological Treatments
- Stress management
- Breathing retraining
- Coping skills training
- Biofeedback training
- Past Trauma therapy
- Interpersonal skills training
- Meditation

Treating HPA Dysfunction
(high or low stress response)

Nutritional Treatments
- Improve diet
- Increase meal frequency
- Reduce exposure to intolerant/allergic foods
- Nutritional supplementation and herbal remedies
- Increase anti-inflammatory and high antioxidant foods
- Improve digestive function and treat digestive disturbances

Medical / Physical
- Treat underlying medical/physical conditions
- Appropriate use of medications
- Identify and decrease inflammatory response
- Treat neurotransmitter imbalances
- Improve liver and detoxification function
- Maintain a healthy weight