SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
Accredited "A" Grade by NAAC | 12B Status by UGC | Approved by AICTE
www.sathyabama.ac.in

SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – I - ENDOCRINOLOGY – SBC3103

HORMONES

Definition, classification, biosynthesis and degradation. Mechanism of hormone action, class i and ii hormone receptors, steroids. Feedback regulation of hormones.

1. What is Endocrinology?

Endocrinology is the study of medicine that relates to the **endocrine system**, which is the system that controls **hormones**.

The word hormone is derived from the Greek *hormao* meaning 'I excite or arouse'. Hormones communicate this effect by their unique chemical structures recognized by specific receptors on their target cells, by their patterns of secretion and their concentrations in the general or localized circulation (Table 1).

The endocrine system uses hormones to control and coordinate body's internal metabolism (or homeostasis) energy level, reproduction, growth and development, and response to injury, stress, and environmental factors. Consider the following hormones and their role in the workings of the endocrine system

Table 1 List of hormones secreted from their respective gland

Endocrine Gland	**Hormone(s) secreted**	**Hormone function**
Adrenal glands	Aldosterone	Regulates salt, water balance, and blood pressure
Adrenal glands	Corticosteroid	Controls key functions in the body; acts as an anti-inflammatory; maintains blood sugar levels, blood pressure, and muscle strength; regulates salt and water balance

Pituitary gland	Antidiuretic hormone (vasopressin)	Affects water retention in kidneys; controls blood pressure
Pituitary gland	Adrenocorticotropic hormone (ACTH)	Controls production of sex hormones (estrogen in women and testosterone in men) and the production of eggs in women and sperm in men.
Pituitary gland	Growth hormone (GH)	Affects growth and development; stimulates protein production; affects fat distribution
Pituitary gland	Luteinizing hormone (LH) and follicle-stimulating hormone (FSH)	Controls production of sex hormones (estrogen in women and testosterone in men) and the production of eggs in women and sperm in men
Pituitary gland	Oxytocin	Stimulates contraction of uterus and milk ducts in the breast
Pituitary gland	Prolactin	Initiates and maintains milk production in breasts; impacts sex hormone levels
Pituitary gland	Thyroid-stimulating hormone (TSH)	Stimulates the production and secretion of thyroid hormones
Kidneys	Renin and angiotensin	Controls blood pressure, both directly and also by regulating aldosterone production from the adrenal glands
Kidneys	Erythropoietin	Affects red blood cell (RBC) production
Pancreas	Glucagon	Raises blood sugar levels
Pancreas	Insulin	Lowers blood sugar levels; stimulates metabolism of glucose, protein, and fat
Ovaries	Estrogen	Affects development of female sexual characteristics

		and reproductive development, important for functioning of uterus and breasts; also protects bone health
Ovaries	Progesterone	Stimulates the lining of the uterus for fertilization; prepares the breasts for milk production
Parathyroid glands	Parathyroid hormone (PTH)	Most important regulator of blood calcium levels
Thyroid gland	Thyroid hormone	Controls metabolism; also affects growth, maturation, nervous system activity, and metabolism
Adrenal glands	Epinephrine	Increases heart rate, oxygen intake, and blood flow
Adrenal glands	Norepinephrine	Maintains blood pressure
Testes (testicles)	Testosterone	Develop and maintain male sexual characteristics and maturation
Pineal gland	Melatonin	Releases melatonin during night hours to help with sleep
Hypothalamus	Growth hormone releasing hormone (GHRH)	Regulates growth hormone release in the pituitary gland
Hypothalamus	Thyrotropin releasing hormone (TRH)	Regulates thyroid stimulating hormone release in the pituitary gland
Hypothalamus	Gonadotropin releasing hormone (GnRH)	Regulates LH/FSH production in the pituitary gland
Hypothalamus	Corticotropin releasing hormone (CRH)	Regulates adrenocorticotropin release in the pituitary gland
Thymus	Humoral factors	Helps develop the lymphoid system

1.2 Chemical signaling

A chemical released by a specialized group of cells into the circulation and acting on a distant target tissue defines the 'classical' endocrine and neuroendocrine signalling mechanism. A paracrine mechanism is defined as chemical communication between neighboring cells within a tissue or organ. Autocrine signals are those in which a chemical acts on the same cell whilst an intracrine signal is generated by a chemical acting within the same cell (Fig 1).

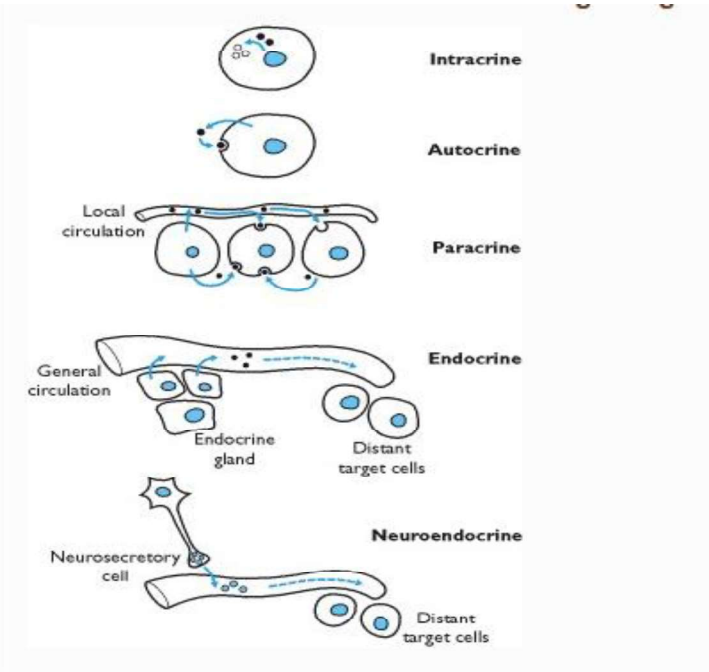


Figure 1 Mechanism of cell signalling

1.3 Chemical classification of hormones and their synthesis

Hormones are derived from amino acids, from cholesterol or from phospholipids. By far the most numerous are the protein or peptide hormones, ranging in size from just three to over 200 amino acids. Some hormones, such as insulin, are made up of two sub-units joined by disulfide bonds

between two cysteine molecules whilst the glycoprotein hormones of the anterior pituitary gland are not only made up of two protein sub-units but also have complex sugar moieties attached.

The steroid hormones, which include vitamin D and those secreted by the adrenal cortex and gonads, are derived from cholesterol. All adrenal and gonadal steroids have the same basic ring structure and despite superficial 2D structural similarity, the side chains and spatial orientation generate specificity.

The third group of hormones are those derived either from tyrosine or from tryptophan. A single tyrosine molecule yields the catecholamines, epinephrine and norepinephrine, the latter being both a neurotransmitter and a hormone. In the endo-crine system, these hormones are secreted by the adrenal medulla and are rapidly broken down once released into the circulation. The thyroid hormones are formed by the conjugation of two tyrosine molecules and resemble steroid hormones in binding to serum proteins and in the mechanism of action. Tryptophan is the precursor of serotonin (5-hydroxytryptamine) and melatonin synthesis. Finally, hormones derived from lipids and phospholipids include the major classes of eicosanoids including prostaglandins, prostacyclins, thromboxanes and leukotrienes.

1.4 Hormone synthesis

Most protein and peptide hormones require the transcription of a single gene though the α and β subunits of the glycoprotein hormones (TSH, LH and FSH) are derived from different genes. The initial RNA undergoes modifications such that the introns are excised from the molecule and there are modifications to the 3′ and 5′ ends of the messenger (m) RNA. The mature mRNA, containing only the exons, is then used as the template for the assembly of amino acids, through transfer (t) RNA, on the rough endoplasmic reticulum.

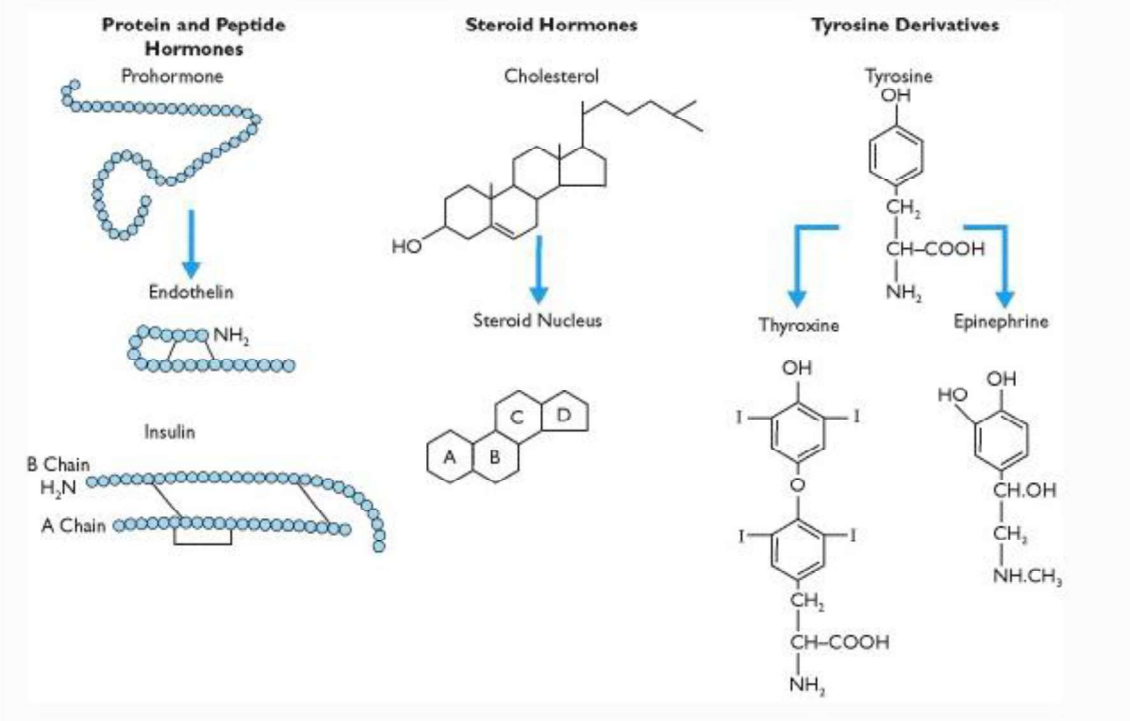


Figure 2 Chemical structures of the three major classes of hormones

Since protein and peptide hormones are stored in, and secreted from, secretory granules it is necessary for their synthesis and packaging to take place within membrane-bound structures of the cell. For this reason, the first amino acids that are translated from the mRNA template form a signal sequence. This signal sequence finds a docking protein, the signal recognition particle, on the rough endoplasmic reticulum so that as protein synthesis continues the assembled amino acids move into the membranes of the rough endoplasmic reticulum. The signal sequence is rapidly cleaved from the growing protein pre-prohormone and eventually a large pro-hormone is left within the membrane-bound rough endoplasmic reticulum(Fig 2).

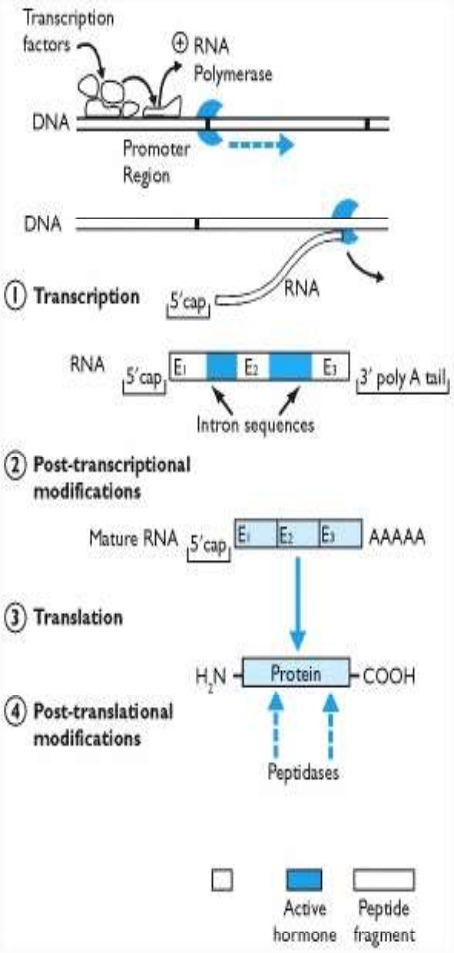
Inside the endoplasmic reticulum, the protein moves into the Golgi apparatus by fission and fusion of protein containing vesicles in which the large pro-hormone is cleaved by peptidases into the biologically active hormone and one or more fragments of the original molecule. Fragments are frequently co-secreted with the active hormone. Secretory granules are formed from budding of the

Golgi apparatus and hormones and their associated fragments are stored in these prior to their release.

Thus, protein and peptide hormone synthesis requires transcription of gene, post-transcriptional modification by exision of the introns, translation of the mRNA and post-translational modifications of the original amino acid sequence (Fig 3). As a result, more than one pro-hormone may be derived from a single gene. Furthermore, post-translational processing of a pro-hormone may result in the formation of different biologically active peptide fragments (e.g. pro-opiomelanocortin). These processes are typically tissue-specific.

In contrast, the synthesis of steroid hormones that occurs in the mitochondria and rough endoplasmic reticulum does not require immediate gene expression. It requires the presence of specific enzymes that convert cholesterol into the appropriate steroid. Different enzymes are expressed in different steroid secreting cells and their expression is controlled by trophic hormones and/or other factors. Cholesterol for steroid synthesis and the amino acid, tyrosine, for thyroid hormone synthesis are ubiquitous, but synthesis of thyroid hormones requires both specific enzymes (containing selenium) and iodine, both of which are trace elements (Fig 4).

The amine hormones such as the catecho-lamines, melatonin and serotonin are formed by side-chain modifications of either a single tyrosine or tryptophan molecule while the eicosanoid family of hormones is formed from lipids



① Transcription of the DNA sequence into RNA

② Excision of sequences (introns) from the initial DNA transcript and modifications of the 3′ and 5′ terminals

③ Translation of the mRNA into a protein (the signal sequence is rapidly cleaved)

④ The prohormone (Box 1.6) is cleaved into fragments, a process that normally occurs prior to secretion

Figure 3 Peptide and Protein hormone synthesis

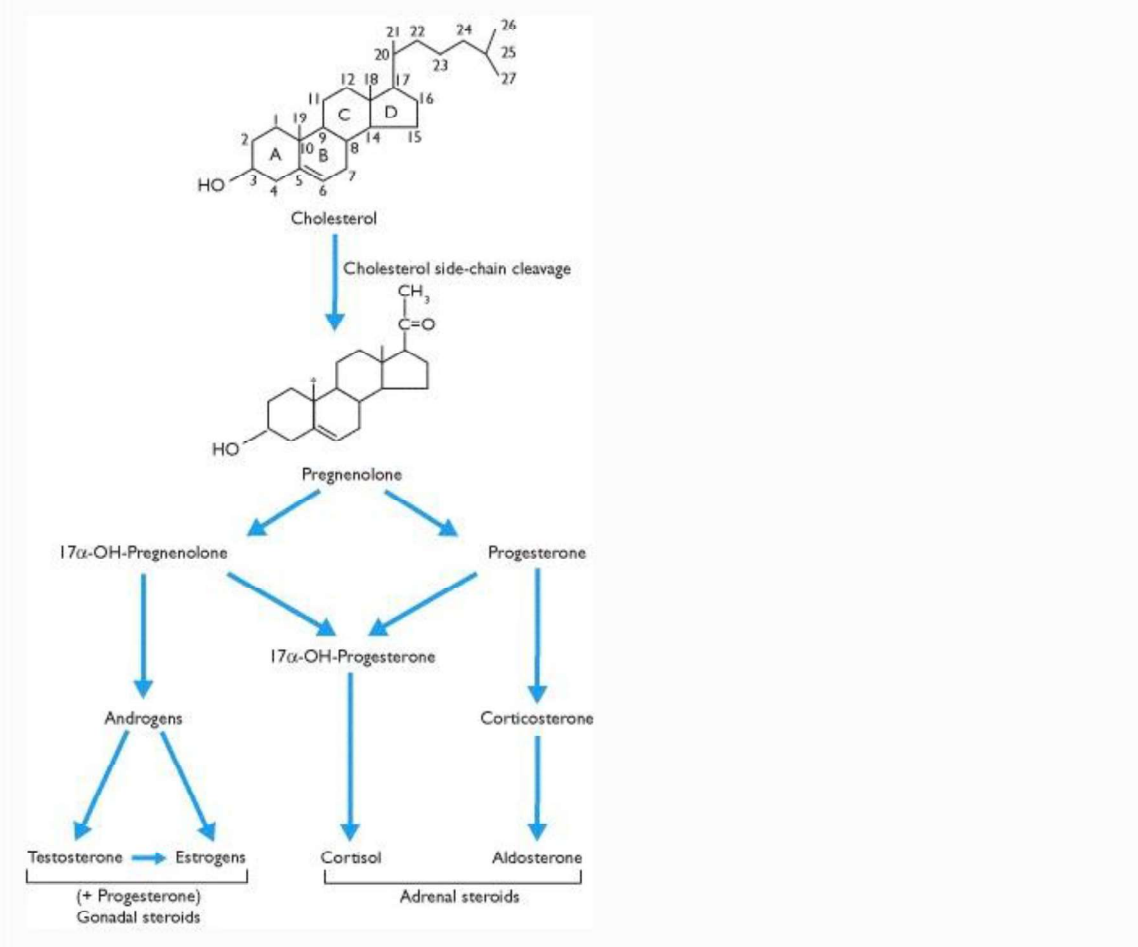


Figure 4 Steroid hormone synthesis

1.4 Transport of hormones

Steroid and thyroid hormones are less soluble in aqueous solution than protein and peptide hormones and over 90% circulate in blood as complexes bound to specific plasma globulins or albumin. Bound and free hormones are in equilibrium . More recently, binding proteins for several protein and peptide hormones (e.g. CRH, GH) as well as growth factors (e.g. IGF) have also been identified.

It is generally accepted that it is the unbound or free hormone that is biologically active and that hormone binding delays metabolism and provides a circulating reservoir of hormones. More recently, it has been suggested that the specific binding globulins are not just passive transporters

but may interact with membrane receptors and that hormone binding to the globulins initiates a signal transduction pathway.

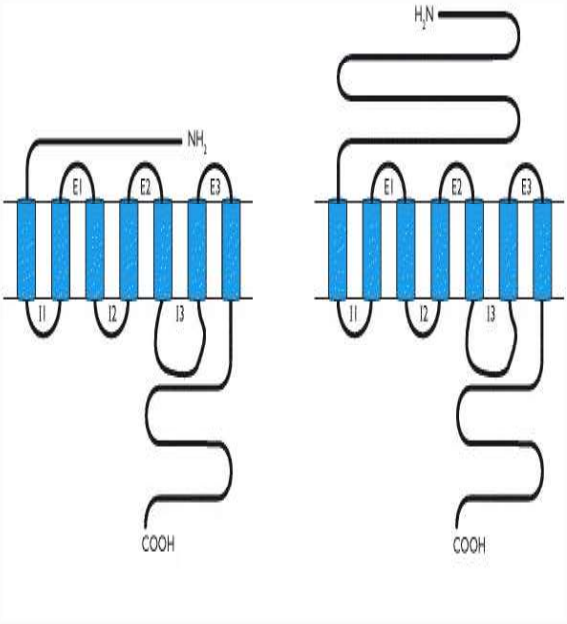
Most binding proteins are synthesized in the liver and alterations in the serum concentrations of these proteins alter total serum concentrations of a hormone but may have much less effect on the concentrations of free hormone. As a result, situations may arise in which assays of total hormone concentrations do not reflect changes in free hormone concentrations. Measurement of biologically relevant free hormone concentrations , however, is generally more difficult than measuring total hormone concentrations.

The rates of metabolism of hormones in the circulation vary but generally speaking the half life ($t_{½}$) of catecholamines from the adrenal medulla is in the order of seconds, minutes for protein and peptide hormones and hours for steroid and thyroid hormones.

1.5 Hormone receptor-cell surface

Proteins and peptides are water soluble and, hence, do not diffuse across hydrophobic lipid cell membranes. Thus, parts of their receptors lie extracellularly (where hormone-receptor interactions occur) and they couple with intracellular signal transducing molecules by traversing the cell membrane. The majority of classical protein and peptide hormone receptors are the G-protein linked receptors and these may either have a relatively short extracellular amino terminal domain (e.g. epinephrine, GnRH) or a much longer extracellular domain (e.g. TSH, LH, PTH). Extracellular hormone-receptor interactions induce dissociation of the associated intracellular trimeric G protein. This may either open ion channels in the membrane or activate a membrane bound enzyme that stimulates (or inhibits) the production of a second messenger such as cyclic AMP or diacylglycerol and inositol trisphosphate. These second messengers then activate serine/threonine kinases or phosphatases (Fig 5 and 6).

G-protein linked receptors that frequently activate serine/threonine kinases through second messengers such as cAMP, diacylglycerol, calmodulin



Receptors with inherent tyrosine kinase activity or associated with intracellular molecules possessing tyrosine kinase activity. Some intracellular kinases are attached to the membrane.

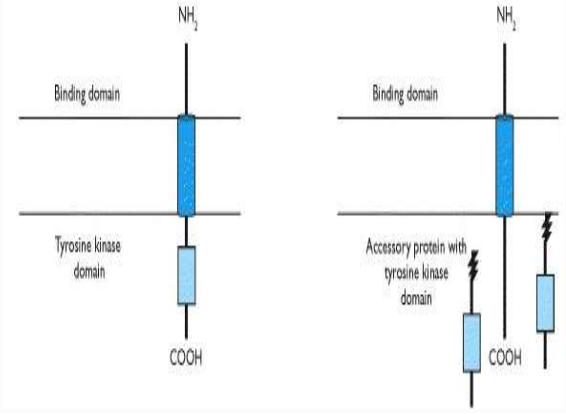
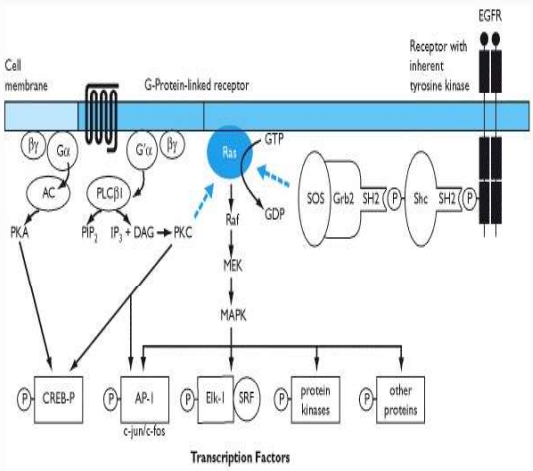


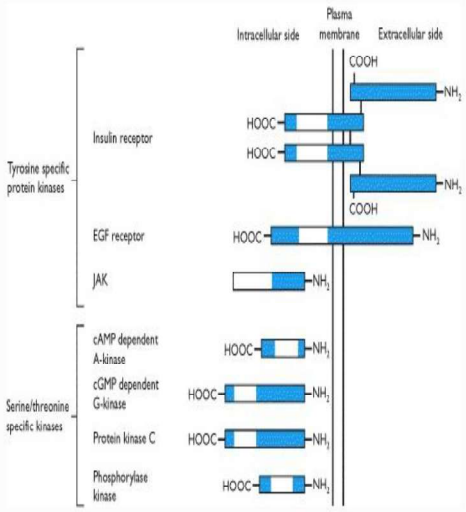
Figure 5 Protein and peptide hormone receptors



Protein and peptide hormones can activate a number of transcriptional factors by phosphorylation. This may involve the MEK-MAP pathway (serine-threonine kinases) or direct activation of transcription factors by protein kinase (PK) A, PKC or the Ca^{2+}-calmodulin activated CaM protein kinase (not shown).

Abbreviations: EGFR, epidermal growth hormone receptor; AC, adenylate cyclase; PLC, phospholipase; PIP_2, phosphatidylinositol 4,5-bisphosphate; IP_3, inositol 1,4,5-trisphosphate; DAG, diacylglycerol; Shc/Grb, accessory proteins with SH2 (src homology) domains; SOS, son-of-sevenless; Ras, monomeric G-protein; Raf/MEK, kinases; MAPK, mitogen activated protein kinase (serine/threonine kinase); CREB P, cyclic AMP response element binding protein; SRF, serum response factor.

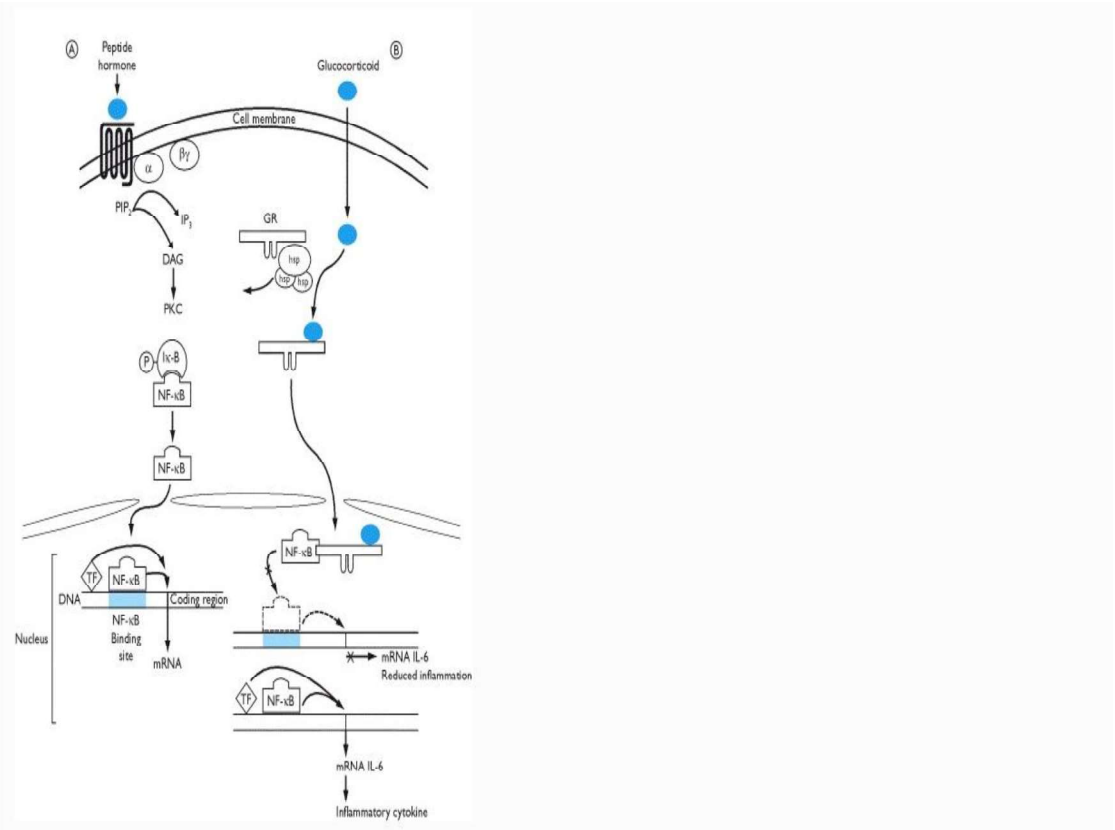
Figure 6 Signal transduction pathway and action of protein and peptide hormone



Some receptors possess inherent tyrosine kinase activity or are associated with intracellular molecules (e.g. JAK) that are activated upon hormone binding. G-protein linked receptors activate intracellular serine/threonine kinases via second messengers. The location of kinase activity is indicated by open (white) frames.

Figure 7 Protein kinase associated with peptide and protein hormone receptor

Activation of these protein kinases may have three consequences. It can lead to alterations in specific cytosolic enzyme activity, activation of nuclear transcription factors or initiation of a cascade of subsequent phosphorylations on the serine or threonine residues of protein kinases that can also regulate transcription (Fig 7).



Ⓐ Protein kinase C (PKC), activated by a peptide hormone via the inositol pathway, releases the transcription factor, NF-κB from its inhibitory subunit through phosphorylation. NF-κB moves into the nucleus where, along with other transcription factors (TF), initiates transcription.

Ⓑ The binding of an anti-inflammatory glucocortocoid to the glucocorticoid receptor (GR) induces release of the heat shock proteins and the hormone/receptor complex translocates to the nucleus. It binds with NF-κB preventing its transcriptional activity for pro-inflammatory proteins such as interleukin-6 (IL-6). This forms part of the anti-inflammatory effects of glucocorticoids.

Figure 8 Signal transduction pathway of peptide and steroid hormone

The second most common type of cell surface receptors is that used in the signalling of insulin, growth hormone, prolactin, most growth factors and cytokines. This type is a transmembrane receptor with either inherent protein tyrosine kinase activity on the intracellular domain (e.g. insulin and growth factor receptors) or associated intracellular molecules that have this activity (e.g.

receptors for growth hormone, prolactin and cytokines). Binding of the hormone or growth factor to the extracellular domain results in receptor dimerization with an adjacent receptor initiating either autophosphosphorylation (Fig 8) or phosphorylation of an associated enzyme. Subsequently, there are similar signal transduction events to those described above that involve both cytoplasmic and nuclear events.

1.6 Signal transduction pathways for cell surface receptors

These are complex processes and unfortunately dogged by terminology that is confusing and not always logical - a legacy from the periodic discovery of intracellular factors that were subsequently assembled into a relatively complete sequence of signal tranduction processes. It is not in the scope of this book to pursue all the molecular events but a broad outline is pertinent to understanding hormone action and genetic mutations that can cause endocrine disorders.

Receptors that have inherent tyrosine kinase activity bind molecules that have a specific SH2 domain (**s**rc **h**omology domain). In turn, another accessory protein may be activated such as SOS (**s**on-**o**f-**s**evenless). This can activate a monomeric G-protein known as Ras that essentially acts as a signal transduction switch. Its activation can lead to phosphorylation of Raf, MEK and eventually to mitogen activated protein kinase (MAPK) which can initiate transcription (termed the MEK-MAPK pathway).

Receptors for GH, prolactin, erythropoietin, insulin and a variety of cytokines and growth factors do not have inherent protein kinase activity but are associated with a protein that has tyrosine kinase activity. One of these proteins, known as JAK (**j**ust **a**nother **k**inase) may activate downstream effectors that include the STAT proteins - the JAK-STAT pathway. Binding of insulin to its receptor induces phosphorylation of insulin receptor substrate proteins (IRS) which activates further signal transduction pathways including activation of nuclear transcription factor κB (NF-

κB). In essence, there is a cascade of protein phosphorylations that ultimately end in the nucleus to induce transcription.

The transcription factor targets for kinases that are activated by protein and peptide hormones include c-jun and c-fos which make up the heterodimeric AP-1 complex, the serum response factor (often targeted by the MAP kinase dependent pathway), and nuclear CREB-P (**c**AMP **r**esponse **e**lement **b**inding **p**rotein) which is phosphorylated by protein kinase A and enhances transcriptional activity of closely positioned promoters.

1.7 Hormone receptor-intracellular

Steroid and thyroid hormones are lipophilic and readily diffuse across cell membranes. Their receptors are typically intracellular and are classified according to their cellular location, their dimerization and the sequences of DNA to which they bind. There is a large family of steroid receptors, all of which are transcription factors. They bind to DNA and with other transcription factors initiate RNA synthesis. Whilst receptors for the major steroid hormones have been identified other structurally similar molecules have been identified though their ligands have not. These have been termed orphan receptors.

The characteristic single polypeptide chain is structurally and functionally divided into six domains. At the amino terminus are the A/B domains that are variable both in sequence and length. The C domain, also called the DNA binding domain (DBD), is a highly conserved sequence across all steroid receptors and is characterized by possessing two zinc fingers which readily slot into the helix of the DNA molecule. The D domain is thought to represent a hinge region in the molecule whilst E represents the ligand binding domain and F a variable region in the carboxyl terminus. This end of the molecule is also the region where the heat shock proteins (hsps) are bound and where dimerization occurs.

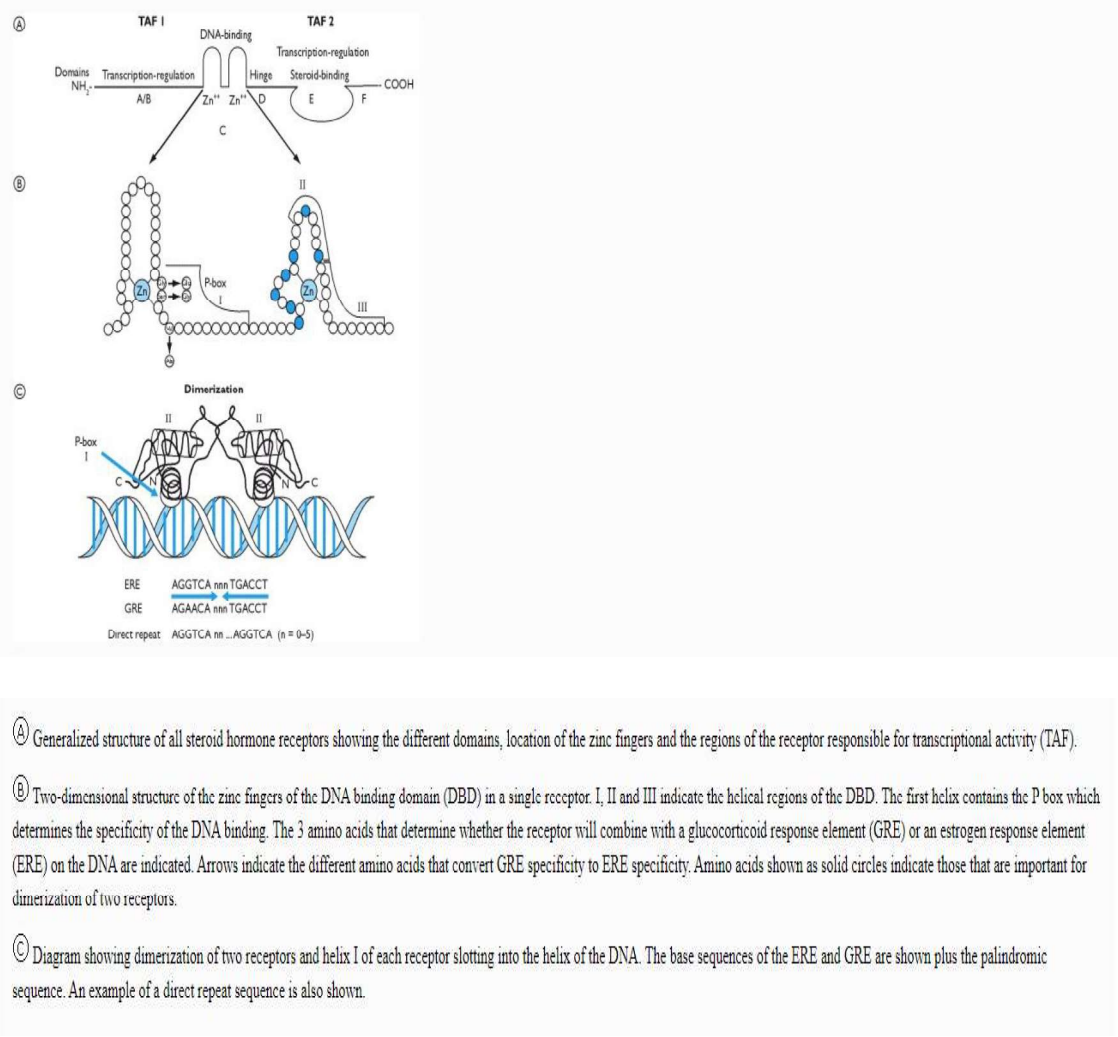
Receptors that exist predominantly in the cytoplasm are classified as Type 1 receptors and these include the glucocorticoid, mineralocorticoid, androgen and progesterone receptors. They are bound to heat shock proteins (e.g. hsp 90, hsp70 and hsp 56). Upon steroid binding the hsp complex is released and the receptor forms a dimer with another identical receptor

The homodimer translocates to the nucleus where it binds to a specific base sequence on the DNA. The estrogen receptor is also associated with hsps and whilst this receptor shuttles between the nucleus and cytoplasm, most are confined to the nuclear compartment. Type 2 receptors are typically located in the nucleus and may be bound to DNA. They characteristically form heterodimers (e.g. thyroid hormone receptor and retinoid X receptor) or may initiate transcription as monomers upon ligand binding.

The specific amino acid sequence of the zinc fingers in the DNA binding domain is important for determining the bases in the DNA helix to which the receptor binds and, thus, the specificity of the transcriptional activity of the receptor. This is determined through what is called the recognition helix that lies at the end of the first zinc finger and part of the amino acid sequence between the two zinc fingers. Amino acids in the second zinc finger make specific contacts with the phosphate backbone of the DNA (Fig 9).

Type 1 receptors recognize a base sequence AGAACA whilst Type 2 receptors and the estrogen receptors recognize a base sequence AGGTCA. These are known as hormone response elements on the DNA and can be further defined as a glucocorticoid response element (GRE) or estrogen response element (ERE), respectively. These, however, are half-site specificities of hormone receptors; the other half-site forms an inverted palindrome, as recognized by Type 1 and the estrogen receptors, or by a direct repeat of bases with variable number of bases between the half-site specificity. These are generally recognized by thyroid hormones, vitamin D, and retinoid receptors. The other way in which steroid hormones can alter transcription is not via interaction

with a GRE or ERE on the DNA but by binding to and activating/repressing other transcription factors that recognize a particular site on DNA .



Ⓐ Generalized structure of all steroid hormone receptors showing the different domains, location of the zinc fingers and the regions of the receptor responsible for transcriptional activity (TAF).

Ⓑ Two-dimensional structure of the zinc fingers of the DNA binding domain (DBD) in a single receptor. I, II and III indicate the helical regions of the DBD. The first helix contains the P box which determines the specificity of the DNA binding. The 3 amino acids that determine whether the receptor will combine with a glucocorticoid response element (GRE) or an estrogen response element (ERE) on the DNA are indicated. Arrows indicate the different amino acids that convert GRE specificity to ERE specificity. Amino acids shown as solid circles indicate those that are important for dimerization of two receptors.

Ⓒ Diagram showing dimerization of two receptors and helix I of each receptor slotting into the helix of the DNA. The base sequences of the ERE and GRE are shown plus the palindromic sequence. An example of a direct repeat sequence is also shown.

Figure 9 Steroid receptors, zinc fingers and DNA binding

Many steroids and thyroid hormones can stimulate rapid responses in target cells that are clearly non-genomic and may be explained by interaction with cell surface receptors. Such receptors may initiate the opening of ion channels or activate classical second messenger systems. The difficulty of isolating such receptors has hampered their investigation but it is clear that steroids exert membrane effects.

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
Accredited "A" Grade by NAAC | 12B Status by UGC | Approved by AICTE
www.sathyabama.ac.in

SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – II - ENDOCRINOLOGY – SBC3103

HYPOTHALAMUS AND PITUITARY HORMONES

HYPOTHALAMIC RELEASING FACTORS VASOPRESSIN, OXYTOCIN; BIOSYNTHESIS, SECRETION, TRANSPORT, REGULATION AND BIOLOGICAL EFFECTS OF GROWTH HORMONES.FSH, LH, TSH, ACTH AND PROLACTIN.

2.1 PITUITARY

The pituitary is a pea-sized gland that is housed within a bony structure (sella turcica) at the base of the brain. The sella turcica protects the pituitary but allows very little room for expansion.

The pituitary controls the function of most other endocrine glands and is therefore sometimes called the master gland. In turn, the pituitary is controlled in large part by the hypothalamus, a region of the brain that lies just above the pituitary. By detecting the levels of hormones produced by glands under the pituitary's control (target glands), the hypothalamus or the pituitary can determine how much stimulation the target glands need (Fig 10).

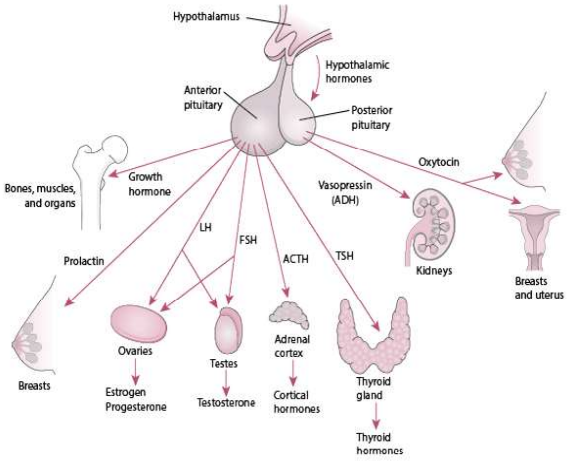


Fig 10 Pituitary and its target organs

The pituitary has two distinct parts:

- Front (anterior) lobe, which accounts for 80% of the pituitary gland's weight
- Back (posterior) lobe

The lobes are connected to the hypothalamus by a stalk that contains blood vessels and nerve cell projections (nerve fibers, or axons). The hypothalamus controls the anterior lobe by releasing hormones through the connecting blood vessels. It controls the posterior lobe through nerve impulses (Fig 11).

The hormones produced by the pituitary are not all produced continuously. Most are released in bursts every 1 to 3 hours, with alternating periods of activity and inactivity. Some of the hormones, such as adrenocorticotropic hormone (ACTH), growth hormone, and prolactin, follow a circadian rhythm: The levels rise and fall predictably during the day, usually peaking just before awakening and dropping to their lowest levels just before sleep. The levels of other hormones vary according to other factors. For example, in women, the levels of luteinizing hormone and

follicle-stimulating hormone, which control reproductive functions, vary during the menstrual cycle.

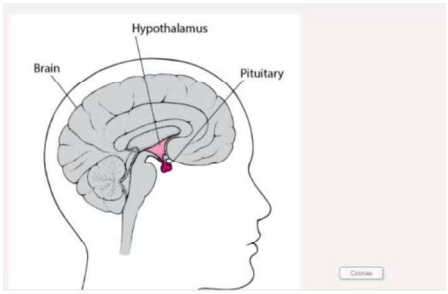


Fig 11 Position of pituitary

2.1.1 Anterior lobe hormones

The anterior lobe of the pituitary produces and releases (secretes) six main hormones:

- Growth hormone, which regulates growth and physical development and has important effects on body shape by stimulating muscle formation and reducing fat tissue
- Thyroid-stimulating hormone, which stimulates the thyroid gland to produce thyroid hormones
- Adrenocorticotropic hormone (ACTH), also called corticotropin, which stimulates the adrenal glands to produce cortisol and other hormones
- Follicle-stimulating hormone and luteinizing hormone (the gonadotropins), which stimulate the testes to produce sperm, the ovaries to produce eggs, and the sex organs to produce sex hormones (testosterone and estrogen)
- Prolactin, which stimulates the mammary glands of the breasts to produce milk

The anterior lobe also produces several other hormones, including one that causes the skin to darken (beta-melanocyte–stimulating hormone) and ones that inhibit pain sensations (enkephalins and endorphins) and help control the immune system (endorphins).

2.1.2 Posterior lobe hormones

The posterior lobe of the pituitary produces only two hormones:

- Vasopressin
- Oxytocin

Vasopressin (also called antidiuretic hormone) regulates the amount of water excreted by the kidneys and is therefore important in maintaining water balance in the body.

Oxytocin causes the uterus to contract during childbirth and immediately after delivery to prevent excessive bleeding. Oxytocin also stimulates contractions of the milk ducts in the breast, which move milk to the nipple (the let-down) in lactating women. Oxytocin has some additional roles in both men and women.

2.1.3 Pituitary gland malfunction

The pituitary gland can malfunction in several ways, usually as a result of developing a noncancerous tumor (adenoma). The tumor may overproduce one or more pituitary hormones, or the tumor may press on the normal pituitary cells, causing underproduction of one or more pituitary hormones.

The tumor may also cause enlargement of the pituitary gland, with or without disturbing hormone production. Sometimes there is overproduction of one hormone by a pituitary tumor and underproduction of another at the same time due to pressure.

Sometimes excess cerebrospinal fluid can fill the space around the pituitary gland and compress it (resulting in empty sella syndrome). The pressure may cause the pituitary to overproduce or underproduce hormones.

Too little or too much of a pituitary hormone results in a wide variety of symptoms.

2.1.4 Disorders that result from overproduction of pituitary hormones include

- Acromegaly or gigantism: Growth hormone
- Cushing disease: Adrenocorticotropic hormone (ACTH),
- Galactorrhea (the secretion of breast milk by men or by women when not pregnant): Prolactin
- Erectile dysfunction: Prolactin
- Infertility (particularly in women): Prolactin

2.1.5 Disorders that result from underproduction of pituitary hormones include

- Central diabetes insipidus: Vasopressin
- Hypopituitarism: Multiple hormones

Doctors can diagnose pituitary gland malfunction using several tests. Imaging tests, such as a computed tomography (CT) or magnetic resonance imaging (MRI), can show whether the pituitary has enlarged or shrunk. Such tests can usually determine whether a tumor exists in the gland.

Doctors can measure the levels of pituitary hormones, usually by a simple blood test. Doctors select which pituitary hormone levels they want to measure depending on the person's symptoms. Sometimes, levels of pituitary hormones are not easy to interpret because the levels vary greatly during the day and according to the body's needs. For these hormones, measuring a random blood sample does not provide useful information.

For some of those hormones, doctors give a substance that would normally affect hormone production and then they measure the level of the hormone. For example, if a doctor injects insulin, the levels of ACTH, growth hormone, and prolactin should increase. Rather than measuring growth hormone levels directly, doctors often measure another hormone, insulin-like growth factor 1 (IGF-1). Growth hormone is produced in bursts and its levels quickly fall, but

IGF-1 levels reflect the overall daily production of growth hormone. For all of these reasons, interpreting the results of blood tests for pituitary hormones is complex.

2.2 GROWTH HORMONE

2.2.1 Introduction

Human growth hormone (HGH), also known as somatotropin, is a 191 amino acid single-chain polypeptide produced by somatotropic cells within the anterior pituitary gland. As its name implies, scientists originally found it to be responsible for growth regulation during childhood. However, research has determined that HGH is also responsible for the regulation of many of the body's other basal metabolic functions and operates as an acute phase stress reactant.

Human growth hormone is produced via the anterior pituitary of the brain in the acidophilic, somatotrophic cells. Its production is tightly regulated through several complex feedback mechanisms in response to stress, exercise, nutrition, sleep, and growth hormone itself. The primary regulation factors are growth hormone-releasing hormone (GHRH) produced in the hypothalamus, somatostatin, produced in various tissues throughout the body, and ghrelin, which is produced in the gastrointestinal tract. GHRH functions to promote HGH production and release. Somatostatin inhibits the release of GHRH as well as the HGH release response to GHRH stimulus and increases in hypoglycemia. Ghrelin is a hormone produced by the stomach as part of the hunger response. Functionally, the ghrelin response is protective against hypoglycemia. When elevated, ghrelin binds to somatotrophs to stimulate HGH secretion. Insulin-like growth factor-1 also acts to inhibit HGH by both directly inhibiting somatotrophic HGH release and indirectly through synergistically increasing the release of somatostatin. Additionally, HGH will negatively feedback into the hypothalamus, thus decreasing GHRH production. The net effect of this regulatory mechanism produces a pulsatile release of HGH into circulation that varies hourly. In general, HGH levels will

be increased in childhood, spike to their highest levels during puberty, and subsequently decrease with increased age.

2.2.2 Function

HGH has two mechanisms of effect: direct action and indirect action. The direct effects of HGH on the body are through its action on binding to target cells to stimulate a response. The indirect effects occur primarily by the action of insulin-like growth factor-1, which hepatocytes primarily secrete in response to elevated HGH binding to surface receptors. Once activated, the Janus activating tyrosine kinases (JAKs) 1 and 2 will bind to the latent cytoplasmic transcriptions factors STAT1, STAT3, and STAT5, and be transported into the nucleus inducing increased gene transcription and metabolism to produce insulin-like growth factor-1 for release into the circulation. Insulin-like growth factor-1 then has an impact on the growth and metabolism of peripheral tissues. One can think of the effects of HGH as a combined effect of both HGH and insulin-like growth factor-1.

2.2.3 Growth

HGH induces growth in nearly every tissue and organ in the body. However, it is most notorious for its growth-promoting effect on cartilage and bone, especially in the adolescent years. Chondrocytes and osteoblasts receive signals to increase replication and thus allow for growth in size via HGH's activation of the mitogen-activated protein (MAP) kinases designated ERKs (extracellular signal-regulated kinases) 1 and 2 cellular signaling pathways. Activation of this phosphorylation intracellular signaling cascade results in a cascade of protein activation, which leads to increased gene transcription of the affected cells and ultimately causes increased gene replication and cellular growth.

Insulin-like growth factor-1 binds to its receptor, IGF-1R, on the cellular surface and activates a tyrosine kinase-mediated intracellular signaling pathway that phosphorylates various proteins

intracellularly leading to increased metabolism, anabolism, and cellular replication and division. Furthermore, it acts to inhibit apoptosis of the cell, thus prolonging the lifespan of existing cells. The net result is to encourage the growth of tissue and to create a hyperglycemic environment in the body.

2.2.4 Metabolic Effects

HGH impacts metabolism primarily by up-regulating the production of insulin-like growth factor-1 and its subsequent effect on peripheral cells. The intracellular signaling activation that occurs, as stated above, also has a significant impact on the basal metabolic functions of organ tissues. In general, cells enter an anabolic protein state with increased amino acid uptake, protein synthesis, and decreased catabolism of proteins. Fats are processed and consumed by stimulating triglyceride breakdown and oxidation in adipocytes. Additionally, HGH suppresses the ability of insulin to stimulate the uptake of glucose in peripheral tissues and causes an increased rate of gluconeogenesis in the liver leading to an overall hyperglycemic state.

2.2.5 Clinical significance

As stated previously, HGH is extremely important for modulating growth during adolescence. Therefore, the major aberrations in the regulation of HGH may result in growth defects. HGH hypersecretion results in gigantism or acromegaly, whereas HGH deficiency will result in a growth deficit in children and the GH deficiency syndrome in adults.

2.2.5.1 Acromegaly

Acromegaly typically results from an HGH secreting pituitary adenoma with an onset after the closure of the epiphyseal growth plates, typically in adulthood. Therefore, bone growth primarily affects flat bones such as the skull, mandible, sternum, hands, and feet. Often the presenting complaint is of hats or gloves not fitting anymore due to swelling of the hands and head. Because

the illness is due to a pituitary mass, hypopituitarism may also develop with secondary reproductive disorders and visual symptoms. In addition to bony growth, there is the growth of myocardium resulting in biventricular concentric hypertrophy and subsequent heart failure in later disease. Because HGH counteracts the effects of insulin on glucose and lipid metabolism, diabetes mellitus type 2 and hyperlipidemia are strongly associated with this disease. Treatment consists of surgery and radiation therapy targeting the underlying adenoma as well as symptomatic relief of the secondary effects of HGH as above.

2.2.5.2 Gigantism

This illness is very similar to acromegaly in all aspects, except the underlying pituitary adenoma develops before the closure of long bone epiphysis. Therefore, bone growth occurs in long bones such as tibia, fibula, femur, humerus, radius, and ulna. Since epiphyseal closure occurs before adulthood, this is typically an illness with an onset seen in children. The organ and metabolic impacts are similar to acromegaly.

2.2.5.3 HGH Deficiency

In children, idiopathic HGH deficiency is most common. In adult-onset, HGH deficiency typically presents as a constellation of hypopituitary deficiencies. The triggering incident is typically a pituitary adenoma, most likely a prolactinoma. However, other treatments, such as radiation therapy or surgery, might be the culprit. Childhood-onset is associated with decreased growth of all skeletal structures leading to dwarfism. Adult-onset HGH deficiency is less easily diagnosed as it has no single identifying feature that is pathognomonic. Typically adults have decreased skeletal muscle and increased fat mass in visceral tissue as well as decreased bone density and remodeling, which leads to osteoporosis. Dyslipidemia and insulin resistance are prevalent, which lead to secondary cardiovascular dysfunction, depressed mood, increased anxiety, and a lack of energy.

2.3 FOLLICLE STIMULATING HORMONE

Follicle stimulating hormone is produced by the pituitary gland. It regulates the functions of both the ovaries and testes. Lack or insufficiency of it can cause infertility or subfertility both in men and women.

2.3.1 Alternative names for follicle stimulating hormone

FSH; follitropin (pharmaceutical preparations)

2.3.2 What is follicle stimulating hormone?

Follicle stimulating hormone is one of the gonadotrophic hormones, the other being luteinising hormone. Both are released by the pituitary gland into the bloodstream. Follicle stimulating hormone is one of the hormones essential to pubertal development and the function of women's ovaries and men's testes. In women, this hormone stimulates the growth of ovarian follicles in the ovary before the release of an egg from one follicle at ovulation. It also increases oestradiol production. In men, follicle stimulating hormone acts on the Sertoli cells of the testes to stimulate sperm production (spermatogenesis).

2.3.3 How is follicle stimulating hormone controlled?

The production and release of follicle stimulating hormone is regulated by the levels of a number of circulating hormones released by the ovaries and testes. This system is called the hypothalamic–pituitary–gonadal axis. Gonadotrophin-releasing hormone is released from the hypothalamus and binds to receptors in the anterior pituitary gland to stimulate both the synthesis and release of follicle stimulating hormone and luteinising hormone. The released follicle stimulating hormone is carried in the bloodstream where it binds to receptors in the testes and ovaries. Using this

mechanism follicle stimulating hormone, along with luteinising hormone, can control the functions of the testes and ovaries.

In women, when hormone levels fall towards the end of the menstrual cycle, this is sensed by nerve cells in the hypothalamus. These cells produce more gonadotrophin-releasing hormone, which in turn stimulates the pituitary gland to produce more follicle stimulating hormone and luteinising hormone, and release these into the bloodstream. The rise in follicle stimulating hormone stimulates the growth of the follicle in the ovary. With this growth, the cells of the follicles produce increasing amounts of oestradiol and inhibin. In turn, the production of these hormones is sensed by the hypothalamus and pituitary gland and less gonadotrophin-releasing hormone and follicle stimulating hormone will be released. However, as the follicle grows, and more and more oestrogen is produced from the follicles, it simulates a surge in luteinising hormone and follicle stimulating hormone, which stimulates the release of an egg from a mature follicle – ovulation.

Thus, during each menstrual cycle, there is a rise in follicle stimulating hormone secretion in the first half of the cycle that stimulates follicular growth in the ovary. After ovulation the ruptured follicle forms a corpus luteum that produces high levels of progesterone. This inhibits the release of follicle stimulating hormone. Towards the end of the cycle the corpus luteum breaks down, progesterone production decreases and the next menstrual cycle begins when follicle stimulating hormone starts to rise again.

In men, the production of follicle stimulating hormone is regulated by the circulating levels of testosterone and inhibin, both produced by the testes. Follicle stimulating hormone regulates testosterone levels and when these rise they are sensed by nerve cells in the hypothalamus so that gonadotrophin-releasing hormone secretion and consequently follicle stimulating hormone is decreased. The opposite occurs when testosterone levels decrease. This is known as a 'negative

feedback' control so that the production of testosterone remains steady. The production of inhibin is also controlled in a similar way but this is sensed by cells in the anterior pituitary gland rather than the hypothalamus.

2.3.4 What happens if I have too much follicle stimulating hormone?

Most often, raised levels of follicle stimulating hormone are a sign of malfunction in the ovary or testis. If the gonads fail to create enough oestrogen, testosterone and/or inhibin, the correct feedback control of follicle stimulating hormone production from the pituitary gland is lost and the levels of both follicle stimulating hormone and luteinising hormone will rise. This condition is called **hyper**gonadotrophic-**hypo**gonadism, and is associated with primary ovarian failure or testicular failure. This is seen in conditions such as Klinefelter's syndrome in men and Turner syndrome in women.

In women, follicle stimulating hormone levels also start to rise naturally in women around the menopausal period, reflecting a reduction in function of the ovaries and decline of oestrogen and progesterone production.

There are very rare pituitary conditions that can raise the levels of follicle stimulating hormone in the bloodstream. This overwhelms the normal negative feedback loop and can (rarely) cause ovarian hyperstimulation syndrome in women. Symptoms of this include enlarging of the ovaries and a potentially dangerous accumulation of fluid in the abdomen (triggered by the rise in ovarian steroid output), which leads to pain in the pelvic area.

2.3.5 What happens if I have too little follicle stimulating hormone?

In women, a lack of follicle stimulating hormone leads to incomplete development at puberty and poor ovarian function (ovarian failure). In this situation ovarian follicles do not grow properly and

do not release an egg, thus leading to infertility. Since levels of follicle stimulating hormone in the bloodstream are low, this condition is called **hypo**gonadotrophic-**hypo**gonadism. This is seen in a condition called Kallman's syndrome, which is associated with a reduced sense of smell.

Sufficient follicle stimulating hormone action is also needed for proper sperm production. In the case of complete absence of follicle stimulating hormone in men, lack of puberty and infertility due to lack of sperm (azoospermia) can occur. Partial follicle stimulating hormone deficiency in men can cause delayed puberty and limited sperm production (oligozoospermia), but fathering a child may still be possible. If the loss of follicle stimulating hormone occurs after puberty, there will be a similar loss of fertility.

2.4 LUTEINISING HORMONE

Luteinising hormone is produced by the pituitary gland and is one of the main hormones that control the reproductive system.

2.4.1 Alternative names for luteinising hormone

Interstitial cell stimulating hormone; luteinizing hormone; lutropin; LH

2.4.2 What is luteinising hormone?

Luteinising hormone, like follicle stimulating hormone, is a gonadotrophic hormone produced and released by cells in the anterior pituitary gland. It is crucial in regulating the function of the testes in men and ovaries in women.

In men, luteinising hormone stimulates Leydig cells in the testes to produce testosterone, which acts locally to support sperm production. Testosterone also exerts effects all around the body to generate male characteristics such as increased muscle mass, enlargement of the larynx to generate a deep voice, and the growth of facial and body hair.

In women, luteinising hormone carries out different roles in the two halves of the menstrual cycle. In weeks one to two of the cycle, luteinising hormone is required to stimulate the ovarian follicles in the ovary to produce the female sex hormone, oestradiol. Around day 14 of the cycle, a surge in luteinising hormone levels causes the ovarian follicle to tear and release a mature oocyte (egg) from the ovary, a process called ovulation. For the remainder of the cycle (weeks three to four), the remnants of the ovarian follicle form a corpus luteum. Luteinising hormone stimulates the corpus luteum to produce progesterone, which is required to support the early stages of pregnancy, if fertilisation occurs.

2.4.3 How is luteinising hormone controlled?

The secretion of luteinising hormone from the anterior pituitary gland is regulated through a system called the hypothalamic-pituitary-gonadal axis. Gonadotrophin-releasing hormone is released from the hypothalamus and binds to receptors in the anterior pituitary gland to stimulate both the synthesis and release of luteinising hormone (and follicle stimulating hormone). The released luteinising hormone is carried in the bloodstream where it binds to receptors in the testes and ovaries to regulate their hormone secretions and the production of sperm or eggs.

The release of hormones from the gonads can suppress the secretion of gonadotrophin-releasing hormone and, in turn, luteinising hormone from the anterior pituitary gland. When levels of hormones from the gonads fall, the reverse happens and gonadtrophin-releasing hormone and hence luteinising hormone rise. This is known as negative feedback.

In men, testosterone exerts this negative feedback and in women oestrogen and progesterone exert the same effect except at the midpoint in the menstrual cycle. At this point, high oestrogen secretions from the ovary stimulate a surge of luteinising hormone from the pituitary gland, which triggers ovulation.

The fine tuning of luteinising hormone release is vital to maintaining fertility. Because of this, compounds designed to mimic the actions of gonadotrophin-releasing hormone, luteinising hormone and follicle stimulating hormone are used to stimulate gonadal function in assisted conception techniques such as in vitro fertilisation (IVF). Measuring the levels of luteinising hormone present in urine can be used to predict the timing of the luteinising hormone surge in women, and hence ovulation. This is one of the methods employed in ovulation prediction kits used by couples wishing to conceive.

2.4.4 What happens if I have too much luteinising hormone?

Too much luteinising hormone can be an indication of infertility. Since the secretion of luteinising hormone is tightly controlled by the hypothalamic-pituitary-gonadal axis, high levels of luteinising hormone in the bloodstream can indicate decreased sex steroid production from the testes or ovaries (for example, as in premature ovarian failure).

Polycystic ovary syndrome is a common condition in women associated with high levels of luteinising hormone and reduced fertility. In this condition, an imbalance between luteinising hormone and follicle stimulating hormone can stimulate inappropriate production of testosterone.

Genetic conditions, such as Klinefelter's syndrome and Turner syndrome, can also result in high luteinising hormone levels. Klinefelter's syndrome is a male-only disorder and results from carrying an extra X chromosome (so that men have XXY, rather than XY chromosomes). As a result of this, the testes are small and do not secrete adequate levels of testosterone to support sperm production. Turner syndrome is a female-only disorder caused by a partial or full deletion of an X chromosome (so that women have XO, rather than XX). In affected patients, ovarian function is impaired and therefore luteinising hormone production increases to try to stimulate ovarian function.

2.4.5 What happens if I have too little luteinising hormone?

Too little luteinising hormone will also result in infertility in both men and women, as a critical level of luteinising hormone is required to support testicular or ovarian function.

In men, an example of a condition where low levels of luteinising hormone are found is Kallmann's syndrome, which is associated with a deficiency in gonadotrophin-releasing hormone secretion from the hypothalamus.

In women, a lack of luteinising hormone means that ovulation does not occur and menstrual periods may not occur regularly. An example of a condition which can be caused by too little luteinising hormone is amenorrhoea.

2.5 TSH

Thyrotropin, also called **thyroid-stimulating hormone (TSH)**, substance produced by cells called thyrotrophs in the anterior pituitary gland.

Thyrotropin binds to specific receptors on the surface of cells in the thyroid gland. This binding stimulates the breakdown of thyroglobulin (a large protein that is cleaved to form the thyroid hormones and that is stored within the follicles of the thyroid gland). The result is the secretion of the thyroid hormones thyroxine (T_4) and triiodothyronine (T_3) into the circulation. Thyrotropin also stimulates the synthesis of additional thyroglobulin and thyroid hormone and the growth of thyroid cells. Thyrotropin is secreted by the pituitary gland upon the command of thyrotropin-releasing hormone (TRH). When thyrotropin causes the manufacture and secretion of excess thyroid hormone, the secreted hormone can travel to the pituitary gland and act on receptors that slow down the release of thyrotropin and hence TRH. This negative feedback contributes to the body's ability to maintain appropriate levels of thyroid hormones.

Serum thyrotropin concentrations are high in patients with thyroid deficiency (hypothyroidism) because there is decreased negative feedback inhibition of thyrotropin release by the low serum thyroid hormone concentrations. Conversely, serum thyrotropin concentrations are low in patients with hyperthyroidism (except in the case of a thyrotropin-secreting pituitary tumour) because there is increased negative feedback inhibition of thyrotropin secretion by the high serum thyroid hormone concentrations. The changes in serum thyroid hormone concentrations need not be large to produce notable symptoms, and measurement of serum thyrotropin is useful for detecting both hypothyroidism or hyperthyroidism when those disorders are caused by thyroid disease. Hypothalamic or pituitary disease may cause low serum thyrotropin and low serum thyroid hormone concentrations, also known as central hypothyroidism.

2.6 Adrenocorticotropic hormone

Adrenocorticotropic hormone (ACTH) is made in the pituitary gland. It is needed for your adrenal glands to work properly and help your body react to stress. ACTH stimulates the release of another hormone called cortisol from the cortex (outer part) of the adrenal gland.

2.6.1 Alternative names for adrenocorticotropic hormone

ACTH; adrenocorticotrophin; corticotropin

2.6.2 What is adrenocorticotropic hormone?

ACTH is made in the corticotroph cells of the anterior pituitary gland, where it is released in bursts into the bloodstream and transported around the body. Like cortisol, levels of adrenocorticotropic hormone are generally high in the morning when we wake up and fall throughout the day (reaching their lowest level during sleep). This is called a diurnal (circadian) rhythm. Once adrenocorticotropic hormone reaches the adrenal glands, it binds on to receptors causing the adrenal

glands to secrete more cortisol, resulting in higher levels of cortisol in the blood. It also increases production of the chemical compounds that trigger an increase in other hormones such as adrenaline and noradrenaline.

2.6.3 How is adrenocorticotropic hormone controlled?

Secretion of ACTH is controlled by three regions of the body, the hypothalamus, the pituitary gland and the adrenal glands. This is called the hypothalamic–pituitary–adrenal (HPA) axis. When adrenocorticotropic hormone levels in the blood are low, a group of cells in the hypothalamus release a hormone called corticotrophin-releasing hormone which stimulates the pituitary gland to secrete ACTH into the bloodstream. High levels of ACTH are detected by the adrenal gland receptors which stimulate the secretion of cortisol, causing blood levels of cortisol to rise. As the cortisol levels rise, they start to slow down the release of corticotrophin-releasing hormone from the hypothalamus and ACTH from the pituitary gland. As a result, the ACTH levels start to fall. This is called a negative feedback loop.

Stress, both physical and psychological, also stimulates ACTH production and hence increases cortisol levels.

2.6.4 What happens if I have too much adrenocorticotropic hormone?

The effects of too much ACTH are mainly due to the increase in cortisol levels. Higher than normal levels of adrenocorticotropic hormone may be due to:

- Cushing's disease – this is the most common cause of increased ACTH. It is caused by a non-cancerous tumour called an adenoma located in the pituitary gland, which produces excess amounts of ACTH. (Please note, Cushing’s disease is just one of the numerous

causes of Cushing's syndrome).

- A tumour, outside the pituitary gland, producing ACTH (also called ectopic ACTH tumour).

- Adrenal insufficiency including Addison's disease (although cortisol levels are low, ACTH levels are raised).

- Congenital adrenal hyperplasia (a genetic disorder with inadequate production of cortisol, aldosterone or both).

Other chemical compounds secreted with ACTH can also lead to hyper-pigmentation.

2.6.5 What happens if I have too little adrenocorticotropic hormone?

Lower than normal levels of adrenocorticotropic hormone may be due to:

- Cushing's syndrome related to an adrenal tumour.

- Cushing's syndrome due to steroid medication.

- Conditions affecting the pituitary gland, e.g. hypopituitarism.

- Side-effect of pituitary surgery or radiation therapy.

2.7 PROLACTIN

Prolactin is a hormone produced in the pituitary gland, named because of its role in lactation. It also has other wide ranging functions in the body, from acting on the reproductive system to influencing behaviour and regulating the immune system.

2.7.1 Alternative names for prolactin

In everyday language, prolactin is referred to as the 'milk hormone'; PRL; luteotropic hormone; LTH

2.7. 2 What is prolactin?

Prolactin is a hormone named originally after its function to promote milk production (lactation) in mammals in response to the suckling of young after birth. It has since been shown to have more than 300 functions in the body. These can be divided into a number of areas: reproductive, metabolic, regulation of fluids (osmoregulation), regulation of the immune system (immunoregulation) and behavioural functions.

In humans, prolactin is produced both in the front portion of the pituitary gland (anterior pituitary gland) and in a range of sites elsewhere in the body. Lactotroph cells in the pituitary gland produce prolactin, where it is stored and then released into the bloodstream. Human prolactin is also produced in the uterus, immune cells, brain, breasts, prostate, skin and adipose tissue.

2.7.3 How is prolactin controlled?

One of the main regulators of the production of prolactin from the pituitary gland is the hormone called dopamine, which is produced by the hypothalamus, the part of the brain directly above the pituitary gland. Dopamine restrains prolactin production, so the more dopamine there is, the less

prolactin is released. Prolactin itself enhances the secretion of dopamine, so this creates a negative feedback loop.

Oestrogen is another key regulator of prolactin and has been shown to increase the production and secretion of prolactin from the pituitary gland. Studies have shown small increases in prolactin in the blood circulation of women during stages of their reproductive cycle where oestrogen levels are at their highest. This is also the case during and after pregnancy, which makes sense, since a higher level of circulating prolactin is needed to cause lactation to start.

In addition to dopamine and oestrogen, a whole range of other hormones can both increase and decrease the amount of prolactin released in the body, with some examples being thyrotropin-releasing hormone, oxytocin and anti-diuretic hormone.

2.7.4 What happens if I have too much prolactin?

The condition of having too much prolactin circulating in the blood is called hyperprolactinaemia. The most common causes of hyperprolactinaemia include pregnancy, medications that reduce dopamine action in the body, thyroid underactivity and benign pituitary tumours (known as prolactinomas). Symptoms can include the unwanted production of milk, disturbances to the menstrual cycle and symptoms due to oestrogen deficiency (in women) or testosterone deficiency (in men). The vast majority of patients with a prolactinoma can be treated successfully using drugs which mimic the action of dopamine. The most commonly used is cabergoline.

2.7.5 What happens if I have too little prolactin?

The condition of having too little prolactin circulating in the blood is called hypoprolactinaemia. This condition is very rare and may occur in people with pituitary underactivity.

A decrease in the amount of prolactin secreted can lead to insufficient milk being produced after giving birth. Most people with low prolactin levels do not have any specific medical problems, although preliminary evidence suggests they might have reduced immune responses to some infections.

2.8 OXYTOCIN

Oxytocin is a hormone that acts on organs in the body (including the breast and uterus) and as a chemical messenger in the brain, controlling key aspects of the reproductive system, including childbirth and lactation, and aspects of human behaviour.

2.8.1 Alternative names for oxytocin

Alpha-hypophamine; manufactured versions – carbetocin, syntocinon and pitocin

2.8.2 What is oxytocin?

Oxytocin is produced in the hypothalamus and is secreted into the bloodstream by the posterior pituitary gland. Secretion depends on electrical activity of neurons in the hypothalamus – it is released into the blood when these cells are excited.

The two main actions of oxytocin in the body are contraction of the womb (uterus) during childbirth and lactation. Oxytocin stimulates the uterine muscles to contract and also increases production of prostaglandins, which increase the contractions further. Manufactured oxytocin is

sometimes given to induce labour if it has not started naturally or it can be used to strengthen contractions to aid childbirth. In addition, manufactured oxytocin is often given to speed up delivery of the placenta and reduce the risk of heavy bleeding by contracting the uterus. During breastfeeding, oxytocin promotes the movement of milk into the breast, allowing it to be excreted by the nipple. Oxytocin is also present in men, playing a role in sperm movement and production of testosterone by the testes.

More recently, oxytocin has been suggested to be an important player in social behaviour.

In the brain, oxytocin acts as a chemical messenger and has been shown to be important in human behaviours including sexual arousal, recognition, trust, anxiety and mother–infant bonding. As a result, oxytocin has been called the 'love hormone' or 'cuddle chemical'.

Many research projects are undertaken, looking at the role of oxytocin in addiction, brain injury, anorexia and stress, among other topics.

2.8.3 How is oxytocin controlled?

Oxytocin is controlled by a positive feedback mechanism where release of the hormone causes an action that stimulates more of its own release. When contraction of the uterus starts, for example, oxytocin is released, which stimulates more contractions and more oxytocin to be released. In this way, contractions increase in intensity and frequency.

There is also a positive feedback involved in the milk-ejection reflex. When a baby sucks at the breast of its mother, the stimulation leads to oxytocin secretion into the blood, which then causes milk to be let down into the breast. Oxytocin is also released into the brain to help stimulate further oxytocin secretion. These processes are self-limiting; production of the hormone is stopped after the baby is delivered or when the baby stops feeding.

2.8.4 What happens if I have too much oxytocin?

At present, the implications of having too much oxytocin are not clear. High levels have been linked to benign prostatic hyperplasia, a condition which affects the prostate in more than half of men over the age of 50. This may cause difficulty in passing urine.

It may be possible to treat this condition by manipulating oxytocin levels; however, more research is needed before any possible treatments are available.

2.8.5 What happens if I have too little oxytocin?

Similarly, it is not fully understood at present if there are any implications of having too little oxytocin in the body. A lack of oxytocin in a nursing mother would prevent the milk-ejection reflex and prevent breastfeeding.

Low oxytocin levels have been linked to autism and autistic spectrum disorders (e.g. Asperger syndrome) – a key element of these disorders being poor social functioning. Some scientists believe oxytocin could be used to treat these disorders. In addition, low oxytocin has been linked to depressive symptoms and it has been proposed as a treatment for depressive disorders. However, there is not enough evidence at present to support its use for any of these conditions.

2.9 ANTI-DIURETIC HORMONE

Anti-diuretic hormone acts to maintain blood pressure, blood volume and tissue water content by controlling the amount of water and hence the concentration of urine excreted by the kidney.

2.9.1 Alternative names for anti-diuretic hormone

Vasopressin; arginine vasopressin; AVP; ADH

2.9.2 What is anti-diuretic hormone?

Anti-diuretic hormone is made by special nerve cells found in an area at the base of the brain known as the hypothalamus. The nerve cells transport the hormone down their nerve fibres (axons) to the pituitary gland where the hormone is released into the bloodstream. Anti-diuretic hormone helps to control blood pressure by acting on the kidneys and the blood vessels. Its most important role is to conserve the fluid volume of your body by reducing the amount of water passed out in the urine. It does this by allowing water in the urine to be taken back into the body in a specific area of the kidney. Thus, more water returns to the bloodstream, urine concentration rises and water loss is reduced. Higher concentrations of anti-diuretic hormone cause blood vessels to constrict (become narrower) and this increases blood pressure. A deficiency of body fluid (dehydration) can only be finally restored by increasing water intake.

2.9.3 How is anti-diuretic hormone controlled?

The release of anti-diuretic hormone from the pituitary gland into the bloodstream is controlled by a number of factors. A decrease in blood volume or low blood pressure, which occurs during dehydration or a haemorrhage, is detected by sensors (receptors) in the heart and large blood vessels. These stimulate anti-diuretic hormone release. Secretion of anti-diuretic hormone also occurs if the concentration of salts in the bloodstream increases, for example as a result of not drinking enough water on a hot day. This is detected by special nerve cells in the hypothalamus which simulate anti-diuretic hormone release from the pituitary. If the concentration of salts reaches abnormally low levels, this condition is called hyponatraemia. Anti-diuretic hormone is also released by thirst, nausea, vomiting and pain, and acts to keep up the volume of fluid in the bloodstream at times of stress or injury. Alcohol prevents anti-diuretic hormone release, which causes an increase in urine production and dehydration.

2.9.4 What happens if I have too much anti-diuretic hormone?

High levels of anti-diuretic hormone cause the kidneys to retain water in the body. There is a condition called Syndrome of Inappropriate Anti-Diuretic Hormone secretion (SIADH; a type of hyponatraemia) where excess anti-diuretic hormone is released when it is not needed (see the article on hyponatraemia for more information). With this condition, excessive water retention dilutes the blood, giving a characteristically low salt concentration. Excessive levels of anti-diuretic hormone might be caused by drug side-effects and diseases of the lungs, chest wall, hypothalamus or pituitary. Some tumours (particularly lung cancer), can produce anti-diuretic hormone.

2.9.5 What happens if I have too little anti-diuretic hormone?

Low levels of anti-diuretic hormone will cause the kidneys to excrete too much water. Urine volume will increase leading to dehydration and a fall in blood pressure. Low levels of anti-diuretic hormone may indicate damage to the hypothalamus or pituitary gland, or primary polydipsia (compulsive or excessive water drinking). In primary polydipsia, the low level of anti-diuretic hormone represents an effort by the body to get rid of excess water. Diabetes insipidus is a condition where you either make too little anti-diuretic hormone (usually due to a tumour, trauma or inflammation of the pituitary or hypothalamus), or where the kidneys are insensitive to it. Diabetes insipidus is associated with increased thirst and urine production.

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
Accredited "A" Grade by NAAC | 12B Status by UGC | Approved by AICTE
www.sathyabama.ac.in

SCHOOL OF BIO AND CHEMICAL ENGINEERING

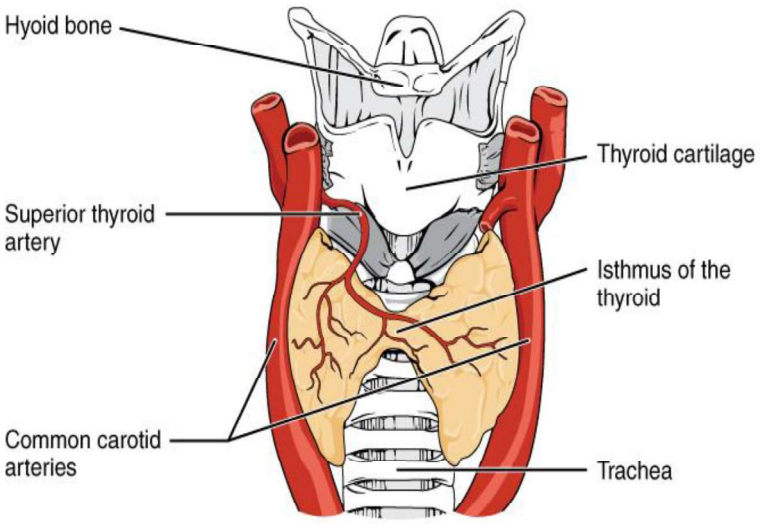
DEPARTMENT OF BIOTECHNOLOGY

UNIT – III - ENDOCRINOLOGY – SBC3103

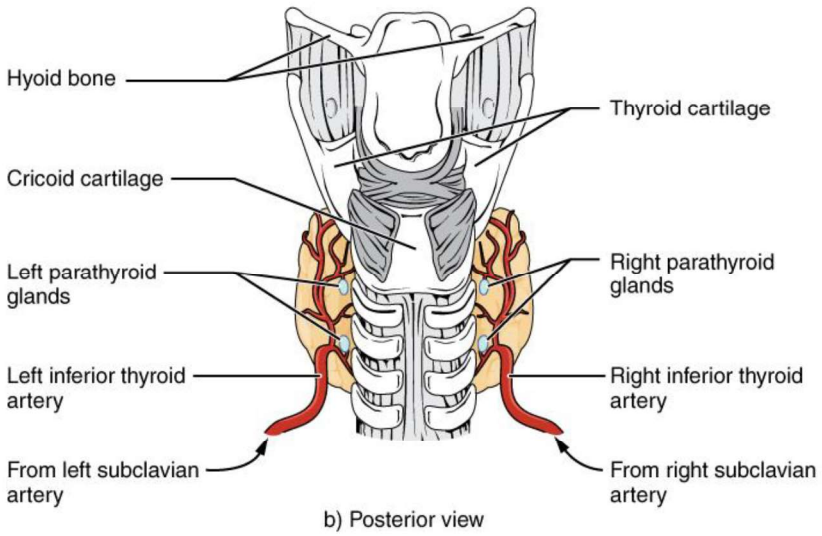
THYROID HORMONES

3.1 THYROID GLAND

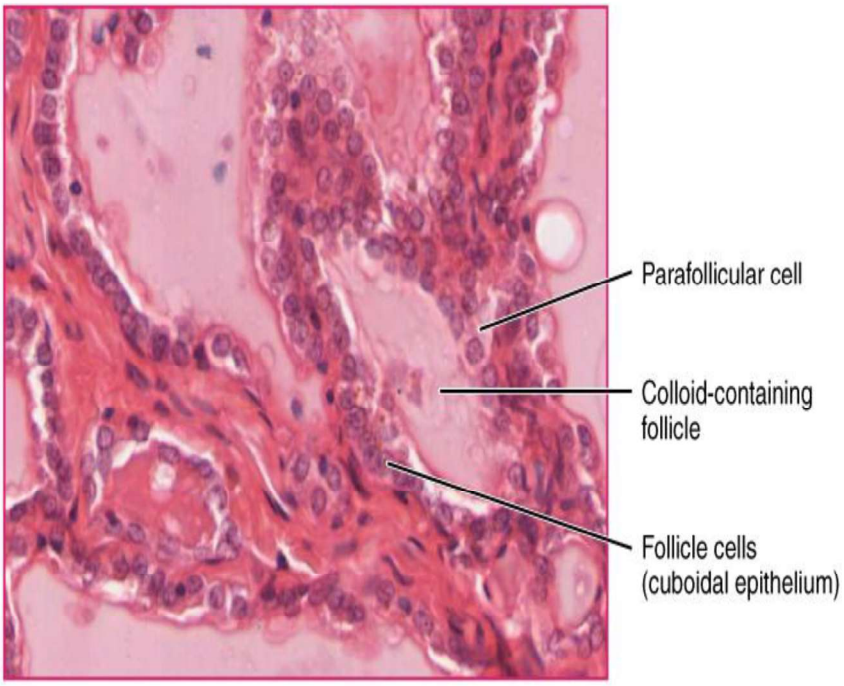
A butterfly-shaped organ, the **thyroid gland** is located anterior to the trachea, just inferior to the larynx (Fig 12). The medial region, called the isthmus, is flanked by wing-shaped left and right lobes. Each of the thyroid lobes are embedded with parathyroid glands, primarily on their posterior surfaces. The tissue of the thyroid gland is composed mostly of thyroid follicles. The follicles are made up of a central cavity filled with a sticky fluid called **colloid**. Surrounded by a wall of epithelial follicle cells, the colloid is the center of thyroid hormone production, and that production is dependent on the hormones' essential and unique component: iodine.



a) Anterior view



b) Posterior view



c) Thyroid follicle cells

Figure 12. Thyroid Gland. The thyroid gland is located in the neck where it wraps around the trachea. (a) Anterior view of the thyroid gland. (b) Posterior view of the thyroid gland. (c) The glandular tissue is composed primarily of thyroid follicles. The larger parafollicular cells often appear within the matrix of follicle cells.

3.1.1 SYNTHESIS AND RELEASE OF THYROID HORMONES

Hormones are produced in the colloid when atoms of the mineral iodine attach to a glycoprotein, called thyroglobulin, that is secreted into the colloid by the follicle cells. The following steps outline the hormones' assembly:

1. Binding of TSH to its receptors in the follicle cells of the thyroid gland causes the cells to actively transport iodide ions (I^-) across their cell membrane, from the bloodstream into the cytosol. As a result, the concentration of iodide ions "trapped" in the follicular cells is many times higher than the concentration in the bloodstream.
2. Iodide ions then move to the lumen of the follicle cells that border the colloid. There, the ions undergo oxidation (their negatively charged electrons are removed). The oxidation of two iodide ions ($2\ I^-$) results in iodine (I_2), which passes through the follicle cell membrane into the colloid.
3. In the colloid, peroxidase enzymes link the iodine to the tyrosine amino acids in thyroglobulin to produce two intermediaries: a tyrosine attached to one iodine and a tyrosine attached to two iodines. When one of each of these intermediaries is linked by covalent bonds, the resulting compound is **triiodothyronine** (T_3), a thyroid hormone with three iodines. Much more commonly, two copies of the second intermediary bond, forming tetraiodothyronine, also known as **thyroxine** (T_4), a thyroid hormone with four iodines.

These hormones remain in the colloid center of the thyroid follicles until TSH stimulates endocytosis of colloid back into the follicle cells. There, lysosomal enzymes break apart the thyroglobulin colloid, releasing free T_3 and T_4, which diffuse across the follicle cell membrane and enter the bloodstream.

In the bloodstream, less than one percent of the circulating T_3 and T_4 remains unbound. This free T_3 and T_4 can cross the lipid bilayer of cell membranes and be taken up by cells. The remaining 99 percent of circulating T_3 and T_4 is bound to specialized transport proteins called thyroxine-binding globulins (TBGs), to albumin, or to other plasma proteins. This "packaging" prevents their free diffusion into body cells. When blood levels of T_3 and T_4 begin to decline, bound T_3 and T_4 are released from these plasma proteins and readily cross the membrane of target cells. T_3 is more potent than T_4, and many cells convert T_4 to T_3 through the removal of an iodine atom.

3.1.2 REGULATION OF TH SYNTHESIS

The release of T_3 and T_4 from the thyroid gland is regulated by thyroid-stimulating hormone (TSH). As shown in Fig 13, low blood levels of T_3 and T_4 stimulate the release of thyrotropin-releasing hormone (TRH) from the hypothalamus, which triggers secretion of TSH from the anterior pituitary. In turn, TSH stimulates the thyroid gland to secrete T_3 and T_4. The levels of TRH, TSH, T_3, and T_4 are regulated by a negative feedback system in which increasing levels of T_3 and T_4 decrease the production and secretion of TSH.

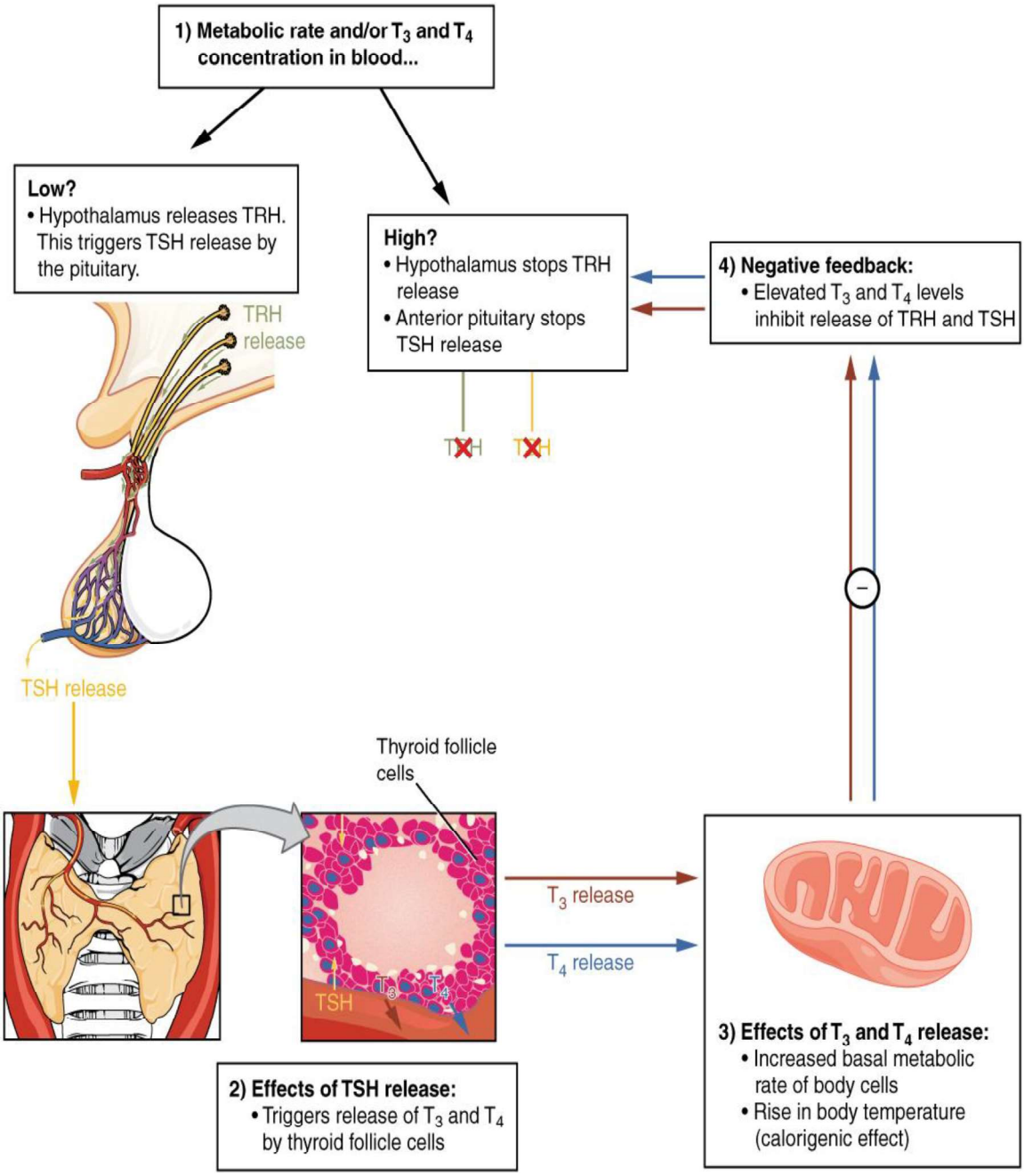


Figure 13. Classic Negative Feedback Loop. A classic negative feedback loop controls the regulation of thyroid hormone levels.

3.1.3 FUNCTIONS OF THYROID HORMONES

The thyroid hormones, T_3 and T_4, are often referred to as metabolic hormones because their levels influence the body's basal metabolic rate, the amount of energy used by the body at rest. When T_3 and T_4 bind to intracellular receptors located on the mitochondria, they cause an increase in nutrient breakdown and the use of oxygen to produce ATP. In addition, T_3 and T_4 initiate the transcription of genes involved in glucose oxidation. Although these mechanisms prompt cells to produce more ATP, the process is inefficient, and an abnormally increased level of heat is released as a byproduct of these reactions. This so-called calorigenic effect (calor- = "heat") raises body temperature.

Adequate levels of thyroid hormones are also required for protein synthesis and for fetal and childhood tissue development and growth. They are especially critical for normal development of the nervous system both in utero and in early childhood, and they continue to support neurological function in adults. As noted earlier, these thyroid hormones have a complex interrelationship with reproductive hormones, and deficiencies can influence libido, fertility, and other aspects of reproductive function. Finally, thyroid hormones increase the body's sensitivity to catecholamines (epinephrine and norepinephrine) from the adrenal medulla by upregulation of receptors in the blood vessels. When levels of T_3 and T_4 hormones are excessive, this effect accelerates the heart rate, strengthens the heartbeat, and increases blood pressure. Because thyroid hormones regulate metabolism, heat production, protein synthesis, and many other body functions, thyroid disorders can have severe and widespread consequences.

3.1.4 Iodine Deficiency, Hypothyroidism, and Hyperthyroidism

As discussed above, dietary iodine is required for the synthesis of T_3 and T_4. But for much of the world's population, foods do not provide adequate levels of this mineral, because the amount varies according to the level in the soil in which the food was grown, as well as the irrigation and fertilizers used. Marine fish and shrimp tend to have high levels because they concentrate iodine

from seawater, but many people in landlocked regions lack access to seafood. Thus, the primary source of dietary iodine in many countries is iodized salt. Fortification of salt with iodine began in the United States in 1924, and international efforts to iodize salt in the world's poorest nations continue today.

Dietary iodine deficiency can result in the impaired ability to synthesize T_3 and T_4, leading to a variety of severe disorders. When T_3 and T_4 cannot be produced, TSH is secreted in increasing amounts. As a result of this hyperstimulation, thyroglobulin accumulates in the thyroid gland follicles, increasing their deposits of colloid. The accumulation of colloid increases the overall size of the thyroid gland, a condition called a **goiter** (Fig 14). A goiter is only a visible indication of the deficiency. Other iodine deficiency disorders include impaired growth and development, decreased fertility, and prenatal and infant death. Moreover, iodine deficiency is the primary cause of preventable mental retardation worldwide. **Neonatal hypothyroidism** (cretinism) is characterized by cognitive deficits, short stature, and sometimes deafness and muteness in children and adults born to mothers who were iodine-deficient during pregnancy.

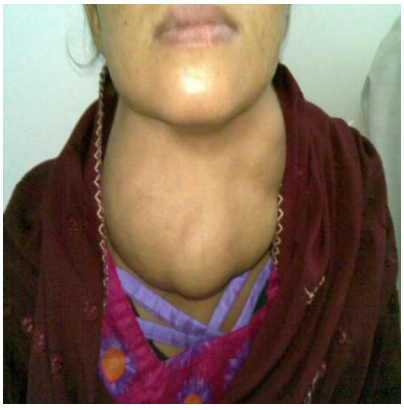


Figure 14. Goiter

In areas of the world with access to iodized salt, dietary deficiency is rare. Instead, inflammation of the thyroid gland is the more common cause of low blood levels of thyroid hormones.

Called **hypothyroidism**, the condition is characterized by a low metabolic rate, weight gain, cold extremities, constipation, reduced libido, menstrual irregularities, and reduced mental activity. In contrast, **hyperthyroidism**—an abnormally elevated blood level of thyroid hormones—is often caused by a pituitary or thyroid tumor. In Graves' disease, the hyperthyroid state results from an autoimmune reaction in which antibodies overstimulate the follicle cells of the thyroid gland. Hyperthyroidism can lead to an increased metabolic rate, excessive body heat and sweating, diarrhea, weight loss, tremors, and increased heart rate. The person's eyes may bulge (called exophthalmos) as antibodies produce inflammation in the soft tissues of the orbits. The person may also develop a goiter.

3.2 CALCITONIN

The thyroid gland also secretes a hormone called **calcitonin** that is produced by the parafollicular cells (also called C cells) that stud the tissue between distinct follicles. Calcitonin is released in response to a rise in blood calcium levels. It appears to have a function in decreasing blood calcium concentrations by:

- Inhibiting the activity of osteoclasts, bone cells that release calcium into the circulation by degrading bone matrix
- Increasing osteoblastic activity
- Decreasing calcium absorption in the intestines
- Increasing calcium loss in the urine

However, these functions are usually not significant in maintaining calcium homeostasis, so the importance of calcitonin is not entirely understood. Pharmaceutical preparations of calcitonin are

sometimes prescribed to reduce osteoclast activity in people with osteoporosis and to reduce the degradation of cartilage in people with osteoarthritis

3.3 Parathyroid hormone

Parathyroid hormone is secreted by the parathyroid glands and is the most important regulator of blood calcium levels.

3.3.1 Alternative names for parathyroid hormone

PTH; parathormone; parathyrin

3.3.2 What is parathyroid hormone?

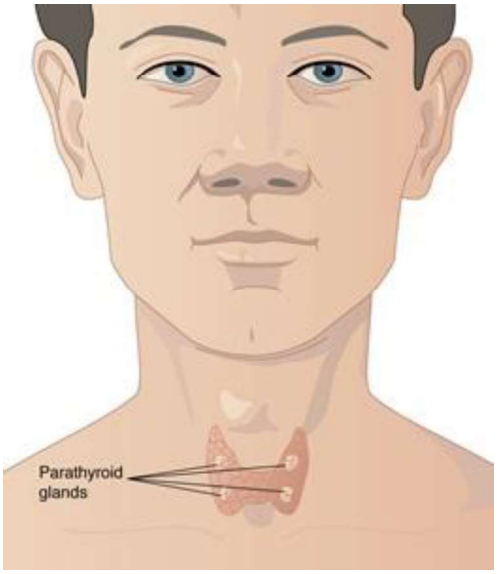


Figure 15 Parathyroid gland

The parathyroid glands (Fig 15) are located in the neck, just behind the butterfly-shaped thyroid gland.

Parathyroid hormone is secreted from four parathyroid glands, which are small glands in the neck, located behind the thyroid gland. Parathyroid hormone regulates calcium levels in the blood,

largely by increasing the levels when they are too low. It does this through its actions on the kidneys, bones and intestine:

1. Bones – parathyroid hormone stimulates the release of calcium from large calcium stores in the bones into the bloodstream. This increases bone destruction and decreases the formation of new bone.

2. Kidneys – parathyroid hormone reduces loss of calcium in urine. Parathyroid hormone also stimulates the production of active vitamin D in the kidneys.

3. Intestine – parathyroid hormone indirectly increases calcium absorption from food in the intestine, via its effects on vitamin D metabolism.

3.3.3 How is parathyroid hormone controlled?

Parathyroid hormone is mainly controlled by the negative feedback of calcium levels in the blood to the parathyroid glands. Low calcium levels in the blood stimulate parathyroid hormone secretion, whereas high calcium levels in the blood prevent the release of parathyroid hormone.

What happens if I have too much parathyroid hormone?

A primary problem in the parathyroid glands, producing too much parathyroid hormone causes raised calcium levels in the blood (hypercalcaemia) and this is referred to as primary hyperparathyroidism. There is a similar but much rarer condition called tertiary hyperparathyroidism that causes hypercalcaemia due to excess parathyroid hormone production on the back drop of all four glands being overactive. Secondary hyperparathyroidism occurs in

response to low blood calcium levels and is caused by other mechanisms, for example, kidney disease and vitamin D deficiency.

Mild primary hyperparathyroidism often causes few if any symptoms and is frequently diagnosed by finding a high calcium concentration on a routine blood test. Treatment may be by surgical removal of the affected gland(s) (parathyroidectomy). Further information on the symptoms for each condition can be found in the individual articles.

3.3.4 What happens if I have too little parathyroid hormone?

Too little parathyroid hormone or hypoparathyroidism, is a rare medical condition. It can result in low levels of calcium in the blood (hypocalcaemia). It is usually treated medically with oral calcium and vitamin D analogues but the availability of parathyroid hormone replacement therapy may change the approach to treatment for some patients.

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
Accredited "A" Grade by NAAC | 12B Status by UGC | Approved by AICTE
www.sathyabama.ac.in

SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – IV - ENDOCRINOLOGY – SBC3103

Pancreatic hormones

4.1 Pancreas

- The pancreas is a glandular organ in the upper mid-region, however, it fills in as two organs in one: a stomach related exocrine organ and a hormone-delivering endocrine organ.
- Working as an exocrine organ, the pancreas discharges catalysts to separate the proteins, lipids, sugars, and nucleic acids in nourishment.
- Working as an endocrine organ, the pancreas secretes the hormones insulin and glucagon to control glucose levels for the duration of the day.
- Both of these different capacities are essential to the body's endurance.
- These are created by a specific tissue in the pancreas and afterward discharged to the slim framework and arrived at the liver by the entry venous dissemination.
- The specific tissue is called islets of Langerhans. Islets of Langerhans speak to around 1-2 % of the pancreas.

Three kinds of cells are recognized in these islets (Fig 16).

- **A cells–** responsible for glucagon production (25% of all islet cells).
- **B cells–** responsible for insulin production(60% of all islet cells).
- **D cells–** responsible for somatostatin production (10% of all islet cells).
- **F cells–** responsible for pancreatic polypeptide production(5% of all islet cells).

Islets of Langerhans assume an essential job in starch digestion thus in a plasma glucose absorption. It involves:

- **Glycolysis–** the anaerobic transformation of glucose into lactate. Takes place in the RBCs, renal medulla and skeletal muscles.
- **Glycogenesis–** the synthesis of glycogen from glucose. Glucose is stored (in the liver, muscle) in the form of glycogen and this serves to maintain a constant plasma glucose concentration.
- **Glycogenolysis–** the breakdown of glycogen to glucose.
- **Gluconeogenesis–** the production of glucose from non-sugar molecules (amino acids, lactate, glycerol)
- **Lipolysis–** the breakdown of triacylglycerols into glycerol and free fatty acids.
- **Lipogenesis–** the synthesis of triacylglycerols.

4.1.1 Function

- Pancreatic hormones are responsible for the storage of fat and glucose, as glycogen, after the meal.
- Enables the mobilization of energy reserves due to food deprivation, stress, and physical activity.
- Maintain the constant plasma glucose concentration.
- Promote growth.

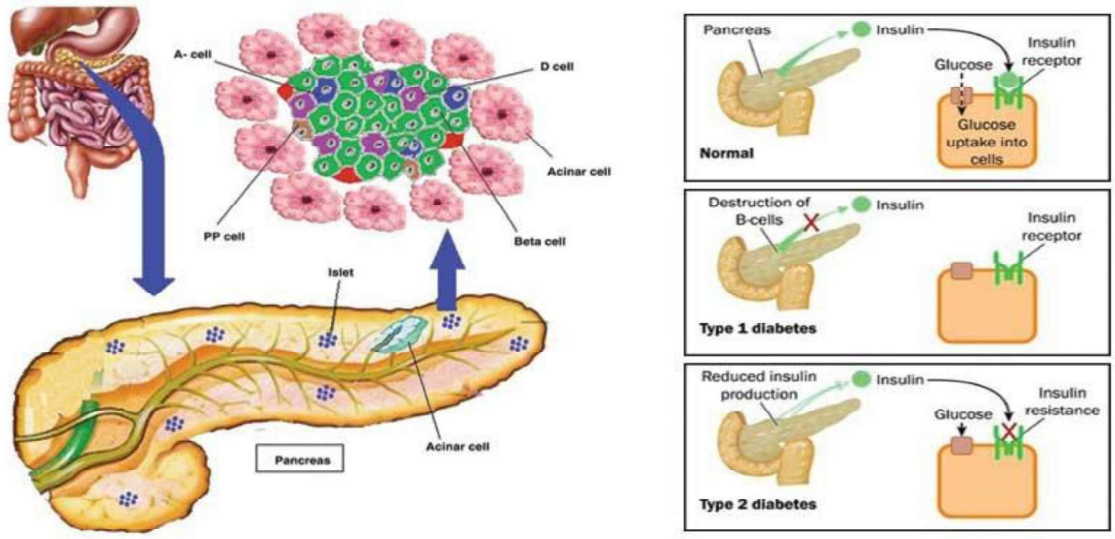


Figure 16 Pancreatic Hormones and Control of Blood Glucose: A Glance and An Overview of the Pancreas

4.1.2 Insulin

4.1.2.1 Structure

Insulin is a peptide that contains an α-chain 21 amino acids long linked to a 30 amino acid β-chain via two disulfide bridges. The precursor to insulin is preproinsulin, which contains a signal sequence that is further removed in the endoplasmic reticulum converting the precursor into its pro-hormone referred to as proinsulin. Proinsulin is changed into insulin after removal of a C-peptide from the pro-hormone.

The insulin receptor comprises of 2 extracellular α-subunits and two transmembraneous β-subunits. When insulin is near the receptor, it binds to the α-subunits of the receptor. This binding leads to the auto-phosphorylation of the β-subunits of the insulin receptor. These β-subunits then act as receptor tyrosine kinases that phosphorylate insulin receptor subunits. The signal then travels downstream to intracellular proteins.

4.1.2.2 Regulation

Insulin is mainly secreted in a response to increases in the blood levels of glucose. The higher level of glucose causes that glucose enters the B cells and is converted to a glucose-6-phosphate. This creates the cytosolic ATP and leads to a closure of ATP-gated K+ channels leading towards depolarization which results in voltage-gated Ca^{2+} channels opening & the level of cytosolic Ca^{2+} rises and recruits exocytosis of insulin & re-opening of K+ channels.

Insulin secretion is stimulated during digestion via acetylcholine (vagus nerve), gastrin, secretin. Certain amino acids as arginine and leucine also stimulate secretion as well as free fatty acids and some steroid hormones. The secretion is inhibited via epinephrine and norepinephrine. These are activated when hypoglycemia is detected by central chemoreceptors channels and then to depolarization.

Depolarization causes an opening of voltage-gated Ca^{2+} channels and the level of cytosolic Ca^{2+} rises and initiates exocytosis of insulin and re-opening of K^{+} channels. Insulin secretion is stimulated during digestion via acetylcholine (vagus nerve), gastrin, secretin.

Certain amino acids as arginine and leucine also stimulate secretion as well as FFAs and some steroid hormones. The secretion is repressed via epinephrine and norepinephrine. These are enacted when hypoglycemia is recognized by focal chemoreceptors channels and afterward to depolarization which results in voltage-gated Ca^{2+} channels opening and the level of cytosolic Ca^{2+} rises and initiates exocytosis of insulin and re-opening of K^{+} channels.

Insulin secretion is stimulated during digestion via acetylcholine (vagus nerve), gastrin, secretin. Insulin secretion is stimulated during digestion via acetylcholine (vagus nerve), gastrin, secretin.

4.1.2.3 Function

Insulin has anabolic and lipogenic effects. The storage of glucose in the liver is stimulated & also activates enzymes to promote glycolysis and glycogenesis. In addition, it promotes the uptake and

storage of amino acids in the kind of proteins and promotes growth. Insulin also increases the amount of GLUT-4.

(Glucose transporters are present in skeletal myocytes so that glucose can enter the cell. Glucose can move into the cell in two different ways. One is with sodium as a secondary active transport and the other one is through glucose transports, facilitated diffusion).

Insulin affects many organs. It

- stimulates skeletal muscle fibers to
- take up glucose & change it into glycogen;
- take up amino acids from the blood & change them into protein.
- acts on liver cells
- stimulating them to take up glucose from the blood & change it into glycogen while
- inhibiting enzymes production that is involved in breaking glycogen back down inhibiting "gluconeogenesis"; that is, the conversion of fats & proteins into glucose.
- acts on fat (adipose) cells to stimulate the uptake of glucose & the synthesis of fat.
- acts on cells in the hypothalamus to reduce appetite.

In such circumstances, insulin activates these effects by binding to the insulin receptor a transmembrane protein embedded in the cell membrane of the reacting cells.

To sum up, the end product of these reactions is:

- the capacity of the dissolvable supplements retained from the digestive system into insoluble, vitality rich items (glycogen, protein, fat)
- a drop in the level of blood sugar

4.1.3 Glucagon

4.1.3.1 Structure

Glucagon is a peptide derived from proglucagon (glicentin). Glucagon secretion is stimulated by amino acids, arginine, and alanine, from digested proteins and furthermore by hypoglycemia because of physical exercise and sympathetic driving forces. The discharge is hindered by glucose, somatostatin and high plasma concentrations of free fatty acids.

4.1.3.2 Function

Glucagon mainly antagonizes insulin. The signal from the glucagon receptor is spread via cAMP. Glucagon increases glycogenolysis in the liver, stimulates gluconeogenesis from lactate, protein degradation and lipolysis. Its main role is to maintain the regular concentration of glucose between meals to ensure constant energy supply.

4.1.4 Somatostatin

Somatostatin is a hormone that inhibits the secretion of several other hormones, including growth hormone, thyroid stimulating hormone, cholecystokinin and insulin.

4.1.4.1 Alternative names for somatostatin

SS, SST or SOM; growth hormone inhibitory hormone (GHIH); somatotropin release inhibiting factor (SRIF); somatotropin release inhibiting hormone (SRIH)

4.1.4.2 What is somatostatin?

Somatostatin is a hormone produced by many tissues in the body, principally in the nervous and digestive systems. It regulates a wide variety of physiological functions and inhibits the secretion of other hormones, the activity of the gastrointestinal tract and the rapid reproduction of normal and tumour cells. Somatostatin may also act as a neurotransmitter in the nervous system.

The hypothalamus is a region of the brain that regulates secretion of hormones from the pituitary gland located below it. Somatostatin from the hypothalamus inhibits the pituitary gland's secretion of growth hormone and thyroid stimulating hormone.

In addition, somatostatin is produced in the pancreas and inhibits the secretion of other pancreatic hormones such as insulin and glucagon. Somatostatin is also produced in the gastrointestinal tract where it acts locally to reduce gastric secretion, gastrointestinal motility and to inhibit the secretion of gastrointestinal hormones, including gastrin and secretin.

Chemically altered equivalents of somatostatin are used as a medical therapy to control too much hormone secretion in patients with acromegaly and other endocrine conditions, and to treat some gastrointestinal diseases and a variety of tumours.

4.1.4.3 How is somatostatin controlled?

In the same way that somatostatin controls the production of several hormones, these hormones feed back to control the production of somatostatin. This is increased by raised levels of these other hormones and reduced by low levels.

Somatostatin is also secreted by the pancreas in response to many factors related to food intake, such as high blood levels of glucose and amino acids.

4.1.4.4 What happens if I have too much somatostatin?

Excessive somatostatin levels in the bloodstream may be caused by a rare endocrine tumour that produces somatostatin, called a 'somatostatinoma'. Too much somatostatin results in extreme reduction in secretion of many endocrine hormones. An example of this is suppression of insulin secretion from the pancreas leading to raised blood glucose levels (diabetes). As somatostatin inhibits many functions of the gastrointestinal tract, its overproduction may also result in the formation of gallstones, intolerance to fat in the diet and diarrhoea.

4.1.4.5 What happens if I have too little somatostatin?

Since somatostatin regulates many physiological processes, too little somatostatin production would lead to a variety of problems, including too much secretion of growth hormone. However, there are very few reports of somatostatin deficiency.

4.1.5 Pancreatic polypeptide

he F cells of the islets secrete a 36-amino-acid pancreatic polypeptide, which reduces appetite. The function of PP is to self-regulate pancreatic secretion activities (endocrine and exocrine); it also has effects on hepatic glycogen levels and gastrointestinal secretions. Its secretion in humans is increased after a protein meal, fasting, exercise, and acute hypoglycemia and is decreased by somatostatin and intravenous glucose.

4.1.6 Diabetes mellitus

Diabetes mellitus is an endocrine disorder characterized by many signs and symptoms. Primary among these are:

- failure of the kidney to proficiently recover glucose all together that glucose overflows into the urine
- resulting rise in the level of urine due to the osmotic effect of glucose

There are three categories of diabetes mellitus:

- Type 1
- Type 2
- Inherited Forms of Diabetes Mellitus

4.1.6.1 Type 1 Diabetes mellitus (Also known as Insulin-Dependent Diabetes Mellitus or IDDM)

- is portrayed by pretty much low or no flowing insulin;
- most generally shows up in youth.

- It results from the obliteration of the beta cells of the islets.
- The annihilation results from a cell-intervened immune system assault against the beta cells.
- What triggers this assault stays a riddle.

One prospect: peptides got from insulin may attach to random peptides to make a “neoantigen”; that is, an antigen that was absent when resilience to self-antigens was being built up.

Type 1 diabetes is constrained via cautiously managed infusions of insulin. (Insulin can’t be taken by mouth since being a protein, it would be processed. On the other hand, the U.S. FDA has endorsed an insulin inhaler that conveys insulin through the lungs and may lessen the quantity of every day infused dosages required).

For a long time, insulin removed from the organs of cows and pigs was utilized. Notwithstanding, pig insulin varies from human insulin by one amino corrosive; meat insulin by three. Albeit both work in people to bring down glucose, they are seen by the insusceptible framework as “foreign” and initiate a counteracting agent reaction in the patient that blunts their impact and requires higher dosages.

This can be solved by:

- Convert pig insulin into human insulin by evacuating the one amino corrosive that recognizes them and supplanting it with the human adaptation. This methodology is costly, so now the supported methodology is to
- Insert the human gene for insulin into *E. coli* and grow recombinant human insulin in culture tanks. Insulin is not a glycoprotein so E. coli can make a completely useful particle (trade name = Humulin). Yeast is also utilized (trade name = Novolin).
- Recombinant DNA innovation has additionally made it potential to make marginally changed types of human insulin that work quicker (Humalog® and NovoLog®) or slower (Lantus®) than standard human insulin.

Injections of insulin must be done cautiously. Injections after overwhelming activity or long after dinner may drive the glucose level down to a hazardously low worth causing an insulin response.

The patient gets bad-tempered, exhausted, and may lose awareness. In the event that the patient is as yet cognizant, giving a wellspring of sugar (e.g., sweet) by mouth typically takes care of the issue rapidly. Injections of glucagon are sometimes used.

4.1.6.2 Type 2 Diabetes mellitus

Type 2 is also known as Non-Insulin-Dependent Diabetes Mellitus (NIDDM) and adult-onset diabetes. However, this sort, in the end, prompts insulin reliance and furthermore is presently showing up in numerous kids so those terms are never again proper.

Many people develop Type 2 diabetes mellitus without a drop in insulin levels (in any event from the start). As a rule, the issue gives off an impression of being an inability to communicate an adequate number of glucose transporters in the plasma membrane (and T-system) of their skeletal muscles.

Normally at the point insulin ties to its receptor on the cell surface and starts a chain of occasions that prompts the inclusion in the plasma film of expanded quantities of a transmembrane glucose transporter (called GLUT4). This transporter formulates a network that allows the facilitated diffusion of glucose into the cell.

Skeletal muscle is the main "sink" for expelling abundance glucose from the blood (and changing over it into glycogen). In T2D, the patient's capacity to expel glucose from the blood and convert it into glycogen might be just 20% of typical. This is called insulin resistance.

Curiously, excessive vital exercise appears to build the statement of the glucose transporter on skeletal muscle and this may clarify why T2D is progressively regular in individuals who live lavish lives.

T2DM usually occurs in adults & mainly in obese people. However, throughout the most recent couple of years in the U. S., the frequency of type 2 diabetes in kids has developed to where they currently represent 20% of all recently analyzed cases (and, similar to their grown-up partners, are normally obese).

A few medications, which can all be taken by mouth, are helpful in reestablishing better command over glucose in patients with T2D.

In any case, late over the span of malady, patients may need to start to take insulin. It is just as following quite a while of siphoning out insulin with an end goal to defeat the patient's insulin obstruction, the β-cells become depleted.

4.2 ADRENAL GLANDS

The **adrenal glands** are wedges of glandular and neuroendocrine tissue adhering to the top of the kidneys by a fibrous capsule (Figure 17). The adrenal glands have a rich blood supply and experience one of the highest rates of blood flow in the body. They are served by several arteries branching off the aorta, including the suprarenal and renal arteries. Blood flows to each adrenal gland at the adrenal cortex and then drains into the adrenal medulla. Adrenal hormones are released into the circulation via the left and right suprarenal veins.

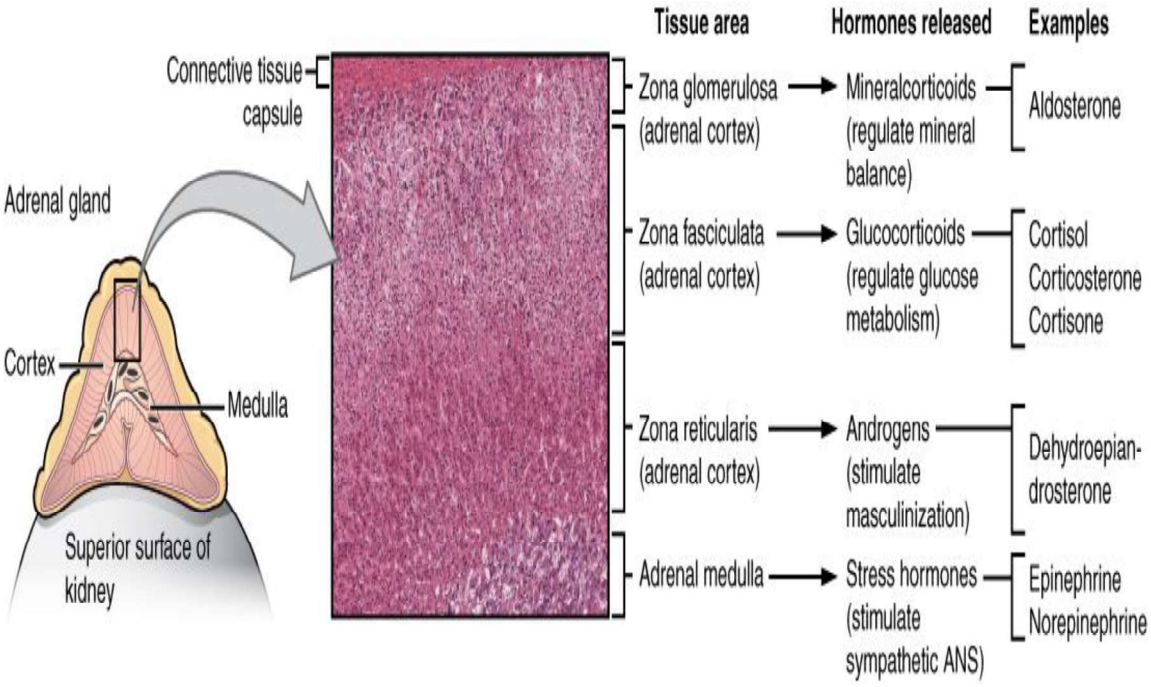


Figure 17. Adrenal Glands. Both adrenal glands sit atop the kidneys and are composed of an outer cortex and an inner medulla, all surrounded by a connective tissue capsule. The cortex can be subdivided into additional zones, all of which produce different types of hormones.

The adrenal gland consists of an outer cortex of glandular tissue and an inner medulla of nervous tissue. The cortex itself is divided into three zones: the **zona glomerulosa**, the **zona fasciculata**, and the **zona reticularis**. Each region secretes its own set of hormones.

The **adrenal cortex**, as a component of the hypothalamic-pituitary-adrenal (HPA) axis, secretes steroid hormones important for the regulation of the long-term stress response, blood pressure and blood volume, nutrient uptake and storage, fluid and electrolyte balance, and inflammation. The HPA axis involves the stimulation of hormone release of adrenocorticotropic hormone (ACTH) from the pituitary by the hypothalamus. ACTH then stimulates the adrenal cortex to produce the hormone cortisol. This pathway will be discussed in more detail below.

The **adrenal medulla** is neuroendocrine tissue composed of postganglionic sympathetic nervous system (SNS) neurons. It is really an extension of the autonomic nervous system, which regulates homeostasis in the body. The sympathomedullary (SAM) pathway involves the stimulation of the medulla by impulses from the hypothalamus via neurons from the thoracic spinal cord. The medulla is stimulated to secrete the amine hormones epinephrine and norepinephrine.

One of the major functions of the adrenal gland is to respond to stress. Stress can be either physical or psychological or both. Physical stresses include exposing the body to injury, walking outside in cold and wet conditions without a coat on, or malnutrition. Psychological stresses include the perception of a physical threat, a fight with a loved one, or just a bad day at school.

The body responds in different ways to short-term stress and long-term stress following a pattern known as the **general adaptation syndrome (GAS)**. Stage one of GAS is called the **alarm reaction**. This is short-term stress, the fight-or-flight response, mediated by the hormones epinephrine and norepinephrine from the adrenal medulla via the SAM pathway. Their function is to prepare the body for extreme physical exertion. Once this stress is relieved, the body quickly returns to normal. The section on the adrenal medulla covers this response in more detail.

If the stress is not soon relieved, the body adapts to the stress in the second stage called the **stage of resistance**. If a person is starving for example, the body may send signals to the gastrointestinal tract to maximize the absorption of nutrients from food.

If the stress continues for a longer term however, the body responds with symptoms quite different than the fight-or-flight response. During the **stage of exhaustion**, individuals may begin to suffer depression, the suppression of their immune response, severe fatigue, or even a fatal heart attack.

These symptoms are mediated by the hormones of the adrenal cortex, especially cortisol, released as a result of signals from the HPA axis.

Adrenal hormones also have several non–stress-related functions, including the increase of blood sodium and glucose levels, which will be described in detail below.

4.2.1 ADRENAL CORTEX

The adrenal cortex consists of multiple layers of lipid-storing cells that occur in three structurally distinct regions. Each of these regions produces different hormones.

4.2.1.1 HORMONES OF THE ZONA GLOMERULOSA

The most superficial region of the adrenal cortex is the zona glomerulosa, which produces a group of hormones collectively referred to as **mineralocorticoids** because of their effect on body minerals, especially sodium and potassium. These hormones are essential for fluid and electrolyte balance.

Aldosterone is the major mineralocorticoid. It is important in the regulation of the concentration of sodium and potassium ions in urine, sweat, and saliva. For example, it is released in response to elevated blood K^+, low blood Na^+, low blood pressure, or low blood volume. In response, aldosterone increases the excretion of K^+ and the retention of Na^+, which in turn increases blood volume and blood pressure. Its secretion is prompted when CRH from the hypothalamus triggers ACTH release from the anterior pituitary.

Aldosterone is also a key component of the renin-angiotensin-aldosterone system (RAAS) in which specialized cells of the kidneys secrete the enzyme renin in response to low blood volume or low blood pressure. Renin then catalyzes the conversion of the blood protein angiotensinogen, produced

by the liver, to the hormone angiotensin I. Angiotensin I is converted in the lungs to angiotensin II by **angiotensin-converting enzyme** (ACE). Angiotensin II has three major functions:

1. Initiating vasoconstriction of the arterioles, decreasing blood flow
2. Stimulating kidney tubules to reabsorb NaCl and water, increasing blood volume
3. Signaling the adrenal cortex to secrete aldosterone, the effects of which further contribute to fluid retention, restoring blood pressure and blood volume

For individuals with hypertension, or high blood pressure, drugs are available that block the production of angiotensin II. These drugs, known as ACE inhibitors, block the ACE enzyme from converting angiotensin I to angiotensin II, thus mitigating the latter's ability to increase blood pressure.

4.2.1.2 HORMONES OF THE ZONA FASCICULATA

The intermediate region of the adrenal cortex is the zona fasciculata, named as such because the cells form small fascicles (bundles) separated by tiny blood vessels. The cells of the zona fasciculata produce hormones called **glucocorticoids** because of their role in glucose metabolism. The most important of these is **cortisol**, some of which the liver converts to cortisone. A glucocorticoid produced in much smaller amounts is corticosterone. In response to long-term stressors, the hypothalamus secretes CRH, which in turn triggers the release of ACTH by the anterior pituitary. ACTH triggers the release of the glucocorticoids. Their overall effect is to inhibit tissue building while stimulating the breakdown of stored nutrients to maintain adequate fuel supplies. In conditions of long-term stress, for example, cortisol promotes the catabolism of glycogen to glucose, the catabolism of stored triglycerides into fatty acids and glycerol, and the catabolism of muscle proteins into amino acids. These raw materials can then be used to synthesize additional glucose and ketones for use as body fuels. The hippocampus, which is part of the

temporal lobe of the cerebral cortices and important in memory formation, is highly sensitive to stress levels because of its many glucocorticoid receptors.

You are probably familiar with prescription and over-the-counter medications containing glucocorticoids, such as cortisone injections into inflamed joints, prednisone tablets and steroid-based inhalers used to manage severe asthma, and hydrocortisone creams applied to relieve itchy skin rashes. These drugs reflect another role of cortisol—the downregulation of the immune system, which inhibits the inflammatory response.

4.2.1.3 HORMONES OF THE ZONA RETICULARIS

The deepest region of the adrenal cortex is the zona reticularis, which produces small amounts of a class of steroid sex hormones called androgens. During puberty and most of adulthood, androgens are produced in the gonads. The androgens produced in the zona reticularis supplement the gonadal androgens. They are produced in response to ACTH from the anterior pituitary and are converted in the tissues to testosterone or estrogens. In adult women, they may contribute to the sex drive, but their function in adult men is not well understood. In post-menopausal women, as the functions of the ovaries decline, the main source of estrogens becomes the androgens produced by the zona reticularis.

4.2.2 ADRENAL MEDULLA

As noted earlier, the adrenal cortex releases glucocorticoids in response to long-term stress such as severe illness. In contrast, the adrenal medulla releases its hormones in response to acute, short-term stress mediated by the sympathetic nervous system (SNS).

The medullary tissue is composed of unique postganglionic SNS neurons called **chromaffin** cells, which are large and irregularly shaped, and produce the neurotransmitters **epinephrine** (also called adrenaline) and **norepinephrine** (or noradrenaline). Epinephrine is produced in greater quantities—approximately a 4 to 1 ratio with norepinephrine—and is the more powerful hormone. Because the chromaffin cells release epinephrine and norepinephrine into the systemic circulation, where they travel widely and exert effects on distant cells, they are considered hormones. Derived from the amino acid tyrosine, they are chemically classified as catecholamines.

The secretion of medullary epinephrine and norepinephrine is controlled by a neural pathway that originates from the hypothalamus in response to danger or stress (the SAM pathway). Both epinephrine and norepinephrine signal the liver and skeletal muscle cells to convert glycogen into glucose, resulting in increased blood glucose levels. These hormones increase the heart rate, pulse, and blood pressure to prepare the body to fight the perceived threat or flee from it. In addition, the pathway dilates the airways, raising blood oxygen levels. It also prompts vasodilation, further increasing the oxygenation of important organs such as the lungs, brain, heart, and skeletal muscle. At the same time, it triggers vasoconstriction to blood vessels serving less essential organs such as the gastrointestinal tract, kidneys, and skin, and downregulates some components of the immune system. Other effects include a dry mouth, loss of appetite, pupil dilation, and a loss of peripheral vision.

4.2.3 DISORDERS INVOLVING THE ADRENAL GLANDS

Several disorders are caused by the dysregulation of the hormones produced by the adrenal glands. For example, Cushing's disease is a disorder characterized by high blood glucose levels and the accumulation of lipid deposits on the face and neck. It is caused by hypersecretion of cortisol. The most common source of Cushing's disease is a pituitary tumor that secretes cortisol or ACTH in abnormally high amounts. Other common signs of Cushing's disease include the development of a

moon-shaped face, a buffalo hump on the back of the neck, rapid weight gain, and hair loss. Chronically elevated glucose levels are also associated with an elevated risk of developing type 2 diabetes. In addition to hyperglycemia, chronically elevated glucocorticoids compromise immunity, resistance to infection, and memory, and can result in rapid weight gain and hair loss.

In contrast, the hyposecretion of corticosteroids can result in Addison's disease, a rare disorder that causes low blood glucose levels and low blood sodium levels. The signs and symptoms of Addison's disease are vague and are typical of other disorders as well, making diagnosis difficult. They may include general weakness, abdominal pain, weight loss, nausea, vomiting, sweating, and cravings for salty food.

SATHYABAMA
INSTITUTE OF SCIENCE AND TECHNOLOGY
(DEEMED TO BE UNIVERSITY)
Accredited "A" Grade by NAAC | 12B Status by UGC | Approved by AICTE
www.sathyabama.ac.in

SCHOOL OF BIO AND CHEMICAL ENGINEERING

DEPARTMENT OF BIOTECHNOLOGY

UNIT – V - ENDOCRINOLOGY – SBC3103

5.1 Nervous System

1 - Receives stimuli from receptors & transmits information to effectors that respond to stimulation

2 - Regulates behavior by integrating incoming sensory information with stored information (the results of past experience) & translating that into action by way of effectors

3 - Includes billions of nerve cells (or neurons), each of which establishes thousands of contacts with other nerve cells

4 - Also includes neuroglia cells that support, nourish, & insulate neurons

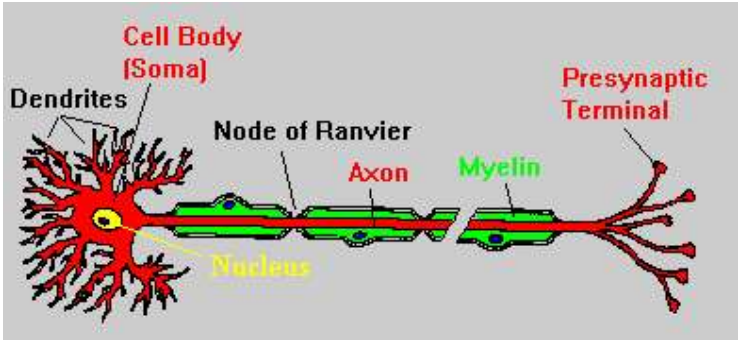


Figure 18 Nervous System

Subdivisions of the Vertebrate Nervous System:

1 - Central Nervous System - including the brain & spinal cord

2 - Peripheral Nervous System - including cranial nerves, spinal nerves, & all branches of cranial & spinal nerves

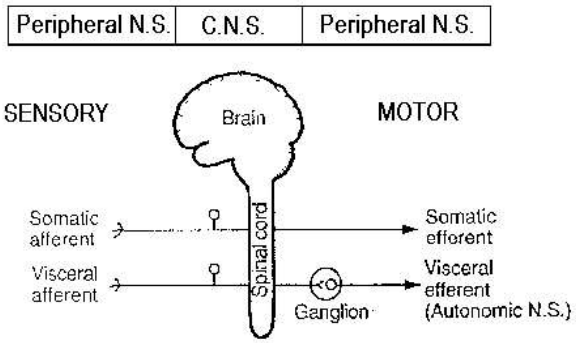
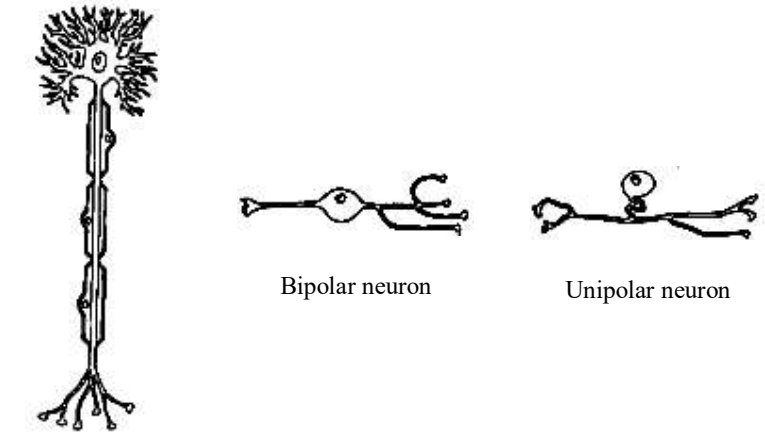


Figure 19 Divisions of Nervous System

Neurons (or nerve cells):

- Respond to stimuli & conduct impulses
- 3 types - all with cell body & processes (axons & dendrites):
  - multipolar
  - bipolar
  - unipolar



Multipolar neuron

Bipolar neuron

Unipolar neuron

Figure 20 Nerves = bundles of nerve cell processes; may be sensory, motor, or mixed

5.2 Spinal cord:

- located in vertebral canal
- anatomical beginning is the foramen magnum of the skull
- length varies among vertebrates:

- in vertebrates with abundant tail musculature, the spinal cord extends to the caudal end of the vertebral column
- in vertebrates without tails or without much tail musculature, the spinal cord extends to about the lumbar region of the vertebral column

- a cross-section of the spinal cord reveals gray matter & white matter. The gray matter consists of nerve cell bodies, while the white matter consists of nerve cell processes (axons). These processes make up ascending (sensory) and descending (motor) fiber tracts.

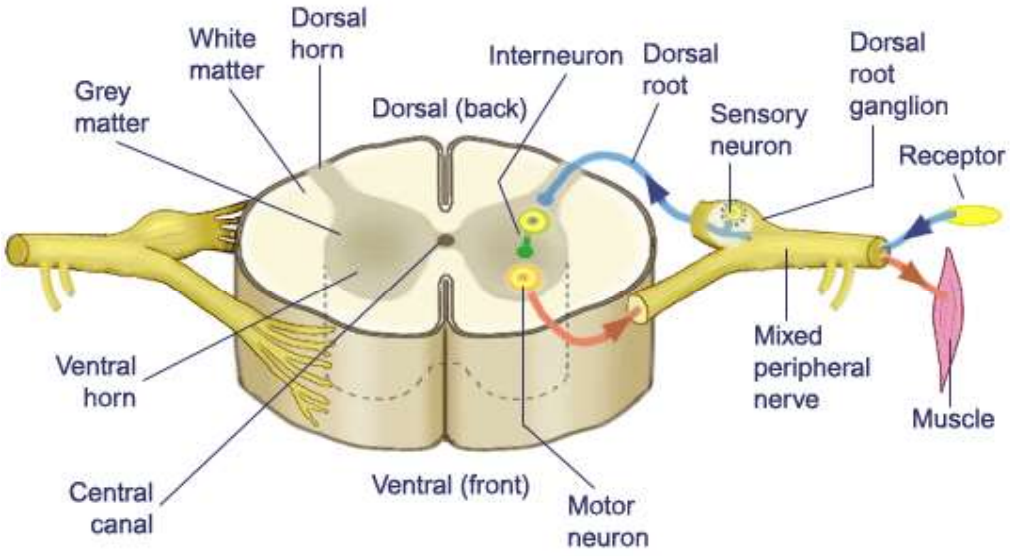


Figure 21 Spinal Cord

5.3 Spinal nerves

- arise from spinal cord by dorsal & ventral roots. The dorsal root exhibits a ganglion & is sensory, while the ventral root has no ganglion & is motor.
- early vertebrates:
  - dorsal & ventral roots did not unite
  - dorsal roots were mixed (contained both sensory & motor fibers)
  - no dorsal root ganglion

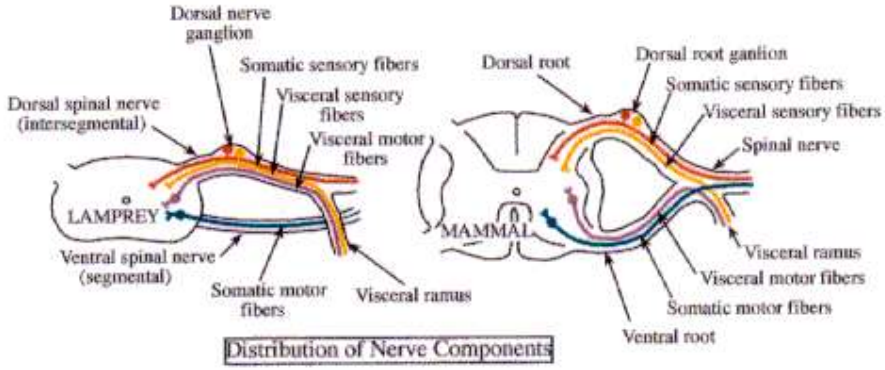
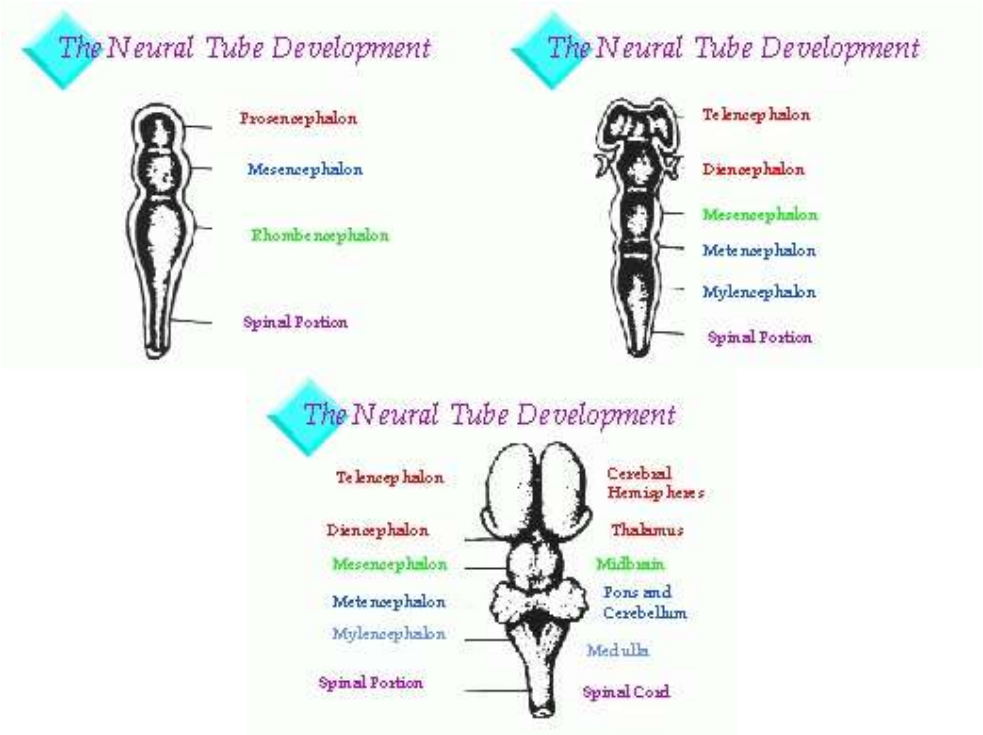


Figure 22 Distribution of nerve

- Rami - 2 branches of each spinal nerve:
  - dorsal ramus - supplies epaxial muscles & skin of the dorsal part of the body
  - ventral ramus - supplies hypaxial muscles & skin of the side & ventral part of the body
- Functional types of neurons in spinal nerves (& other nerves):
  - somatic afferent - sensory from general cutaneous receptors (in the skin) & proprioceptors (in skeletal muscles, tendons, & joints)
  - somatic efferent - motor to skeletal muscles
  - visceral afferent - sensory from receptors in the viscera (smooth muscle, cardiac muscle, & glands)
  - visceral efferent - motor to smooth muscle, cardiac muscle, & glands

5.4 Brain

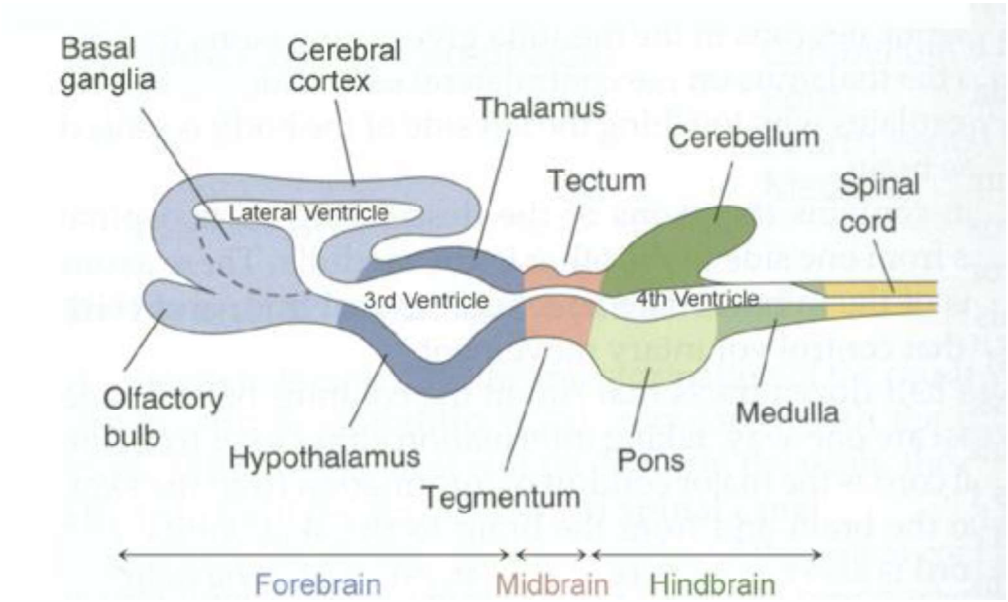
- the anterior end of the embryonic central nervous system exhibits 3 primary sections:
  - prosencephalon (forebrain) - subsequently divides into the telencephalon (cerebrum) & diencephalon (epithalamus, thalamus, & hypothalamus)
  - mesencephalon (midbrain) - develops without further subdivision & forms the tectum
  - rhombencephalon (hindbrain) - subdivides into the metencephalon (pons & cerebellum) and myelencephalon (medulla oblongata)



Source: http://brainmuseum.org/development/index.html

Figure 23 Brain

- Phylogenetic trend in vertebrate brains is for enlargement of forebrain:
  - increasingly complex behaviors & muscle control:
    - coordination of limb movements more complicated (e.g., bipedal dinosaurs & birds)
    - increased input of sensory information & increased output of motor responses



Source: http://www.colorado.edu/epob/epob3730rlynch/image/figure5-1.jpg

Figure 24 Basic plan of brain

5.4.1 Myelencephalon - consists of the medulla oblongata & its major functions include:

- origin of cranial nerves (VII - X or VII - XII)
- pathway for ascending & descending fiber tracts
- contains centers important in regulating respiration, heartbeat, & intestinal motility

5.4.2 Metencephalon - consists of the pons & cerebellum:

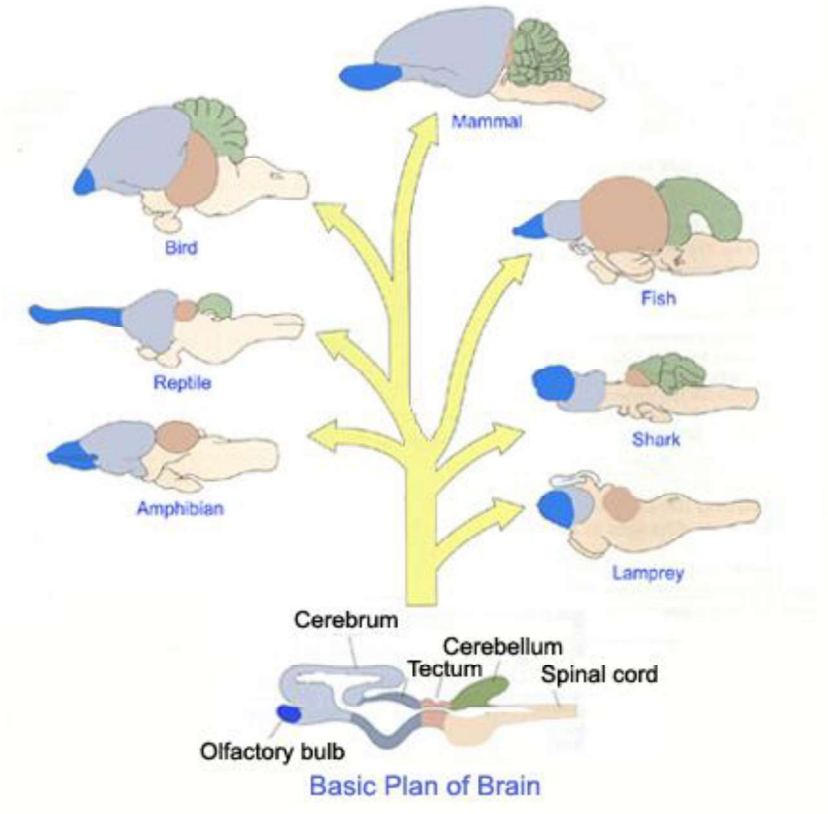
- Pons - pathway for ascending & descending fiber tracts & origin of cranial nerves V, VI, & VII
- Cerebellum - modifies & monitors motor output:
  - important in maintaining equilibrium
  - coordinates & refines motor action

5.4.3 Mesencephalon - consists of the tectum which includes the optic lobes & auditory lobes:

- optic lobes - receive fibers from retina; vary in size with relative importance of vision
- auditory lobes - receive fibers from inner ear

5.4.4 Diencephalon - consists of the epithalamus, hypothalamus, & thalamus:

- epithalamus - includes pineal gland (epiphysis) that affects skin pigmentation (by acting on melanocytes) in lower vertebrates & plays a role in regulating biological rhythms in higher vertebrates
- hypothalamus - regulates body temperature, water balance, appetite, blood pressure, sexual behavior, & some aspects of emotional behavior
- thalamus - major coordinating, or relay, center for sensory impulses from all parts of the body



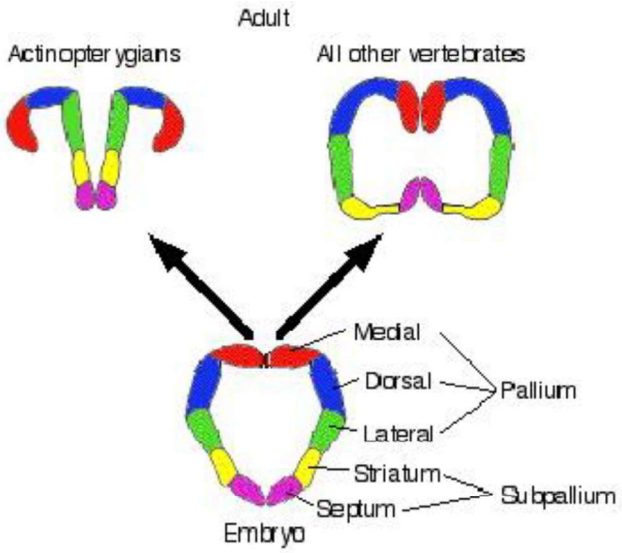
Source: http://www.colorado.edu/epob/epob3730rlynch/image/figure5-4.jpg

Figure 25 Brain

5.4.5 Telencephalon - consists of the cerebrum which, in turn, consists of 2 cerebral hemispheres

- cerebrum has 2 regions: a dorsal PALLIUM (with medial, dorsal, & lateral divisions) & a ventral SUBPALLIUM (consisting of a striatum & a septum)
- **all vertebrates have a cerebrum based on the same basic plan**; major phylogenetic changes are due to loss, fusion, or enlargement of the various regions.
    - medial pallium receives olfactory information
    - dorsal & lateral pallia receive other sensory input (including visual & auditory information relayed from the thalamus)

- **agnathans, fish, & amphibians** - pallia are similar



Source: http://www.auburn.edu/academic/classes/zy/0301/Topic19/Topic19.html
Figure 26 Adult Brain

- **reptiles** - pallium has 3 main divisions (medial, dorsal, & lateral) but also has a large DORSAL VENTRICULAR RIDGE (DVR), derived from lateral pallium; DVR may be higher association area
- **birds** - DVR expands further; dorsal part increases in size & is called the WULST; as in reptiles, the DVR appears to serve as a higher association area

- **mammals** - do not have enlarged DVR but DORSAL PALLIUM is enlarged & is called the CEREBRAL CORTEX; cortex receives & analyzes sensory information & initiates motor activity

- **subpallium:**
  - septum - important part of the limbic system (regulates emotions & plays vital role in short-term memory)
  - striatum - also called basal ganglia; present in all vertebrates & controls sequence of actions in complex movements

5.5 **Cranial nerves** - agnathans, most fish, & living amphibians have 10 cranial nerves; crossopterygians & amniotes have 12:

- Olfactory nerve (I) - sensory nerve; sense of smell
- Optic nerve (II) - sensory 'nerve'; sense of vision
- Oculomotor nerve (III) - motor nerve to extrinsic eye muscles

- Trochlear nerve (IV) - motor to extrinsic eye muscles
- Trigeminal (V) - mixed nerve; sensory from skin of head & mouth (including teeth) & motor to muscles of 1st pharyngeal arch (muscles of jaw)
- Abducens (VI) - motor to extrinsic eyeball muscles
- Facial (VII) - mixed nerve; sensory from lateral line of head, ampullae of Lorenzini, & taste buds; motor to muscles of hyoid arch
- Auditory (VIII) - sensory from inner ear (balance & hearing)
- Glossopharyngeal (IX) - mixed nerve; sensory from taste buds & lateral line; motor to muscles of 3rd arch
- Vagus (X) - mixed nerve; sensory from & motor to heart, anterior digestive system, mouth, gill pouches 2 - 5, & lateral line
- Accessory nerve (XI) - motor to derivatives of cucullaris muscle (cleidomastoid, sternomastoid, & trapezius)
- Hypoglossal nerve (XII) - motor to hyoid & tongue muscles

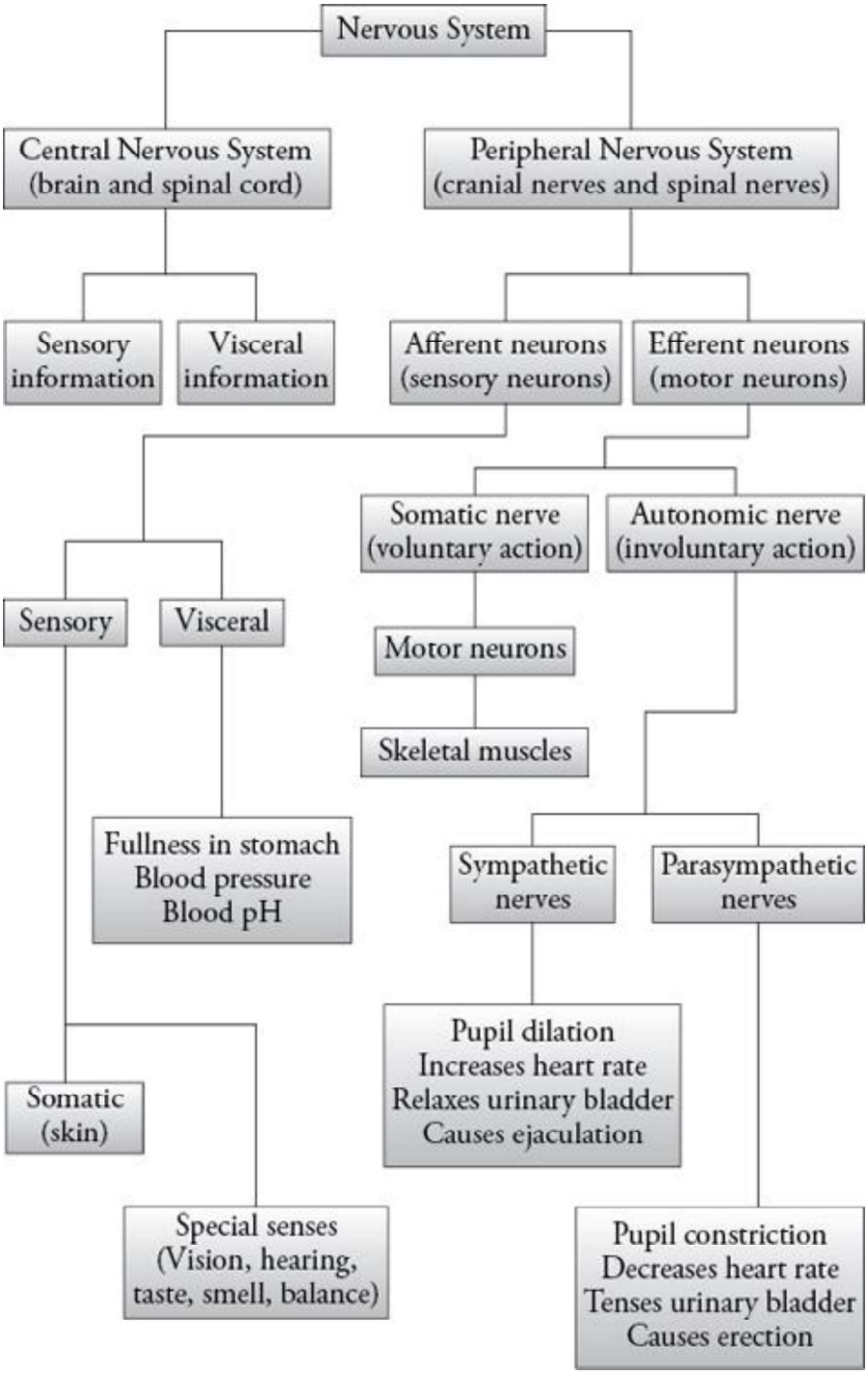


Figure 27 Nervous system

The nervous system comprises of two group of cells, **glial cells** and **neurons**. Neurons are responsible for sensing change and communicating with other neurons. Glial cells work to support, nourish, insulate neurons and remove waste products. This article will discuss the function of neurons and glial cells.

Neurons The neuron is made up of several components as follows (Fig 28):

Cell body or Soma – this contains the nucleus, the neuron's intracellular organelles (such as the mitochondria and golgi apparatus) and it is the location for cellular metabolism. It is also contains the Nissl Substance. These are granules containing rough endoplasmic reticulum and free ribosomes, making it the site of protein synthesis.

Dendrites – these originate from the soma and extend outwards. They transmit signals they receive from other neurons to the soma.

Axon – It arises from the soma from an area called the axon hillock, where action potentials are initiated. The action potentials are conducted through the axon to the axon terminal.

Schwann cells – These insulate the axon which aids with rapid transmission of action potentials through the axon.

Axon terminal – Distally the axon branches to form axon terminals. These make synaptic connection with other neurons. They contain various neurotransmitters which is released into the synapse to allow signals to be transmitted from one neuron to the next.

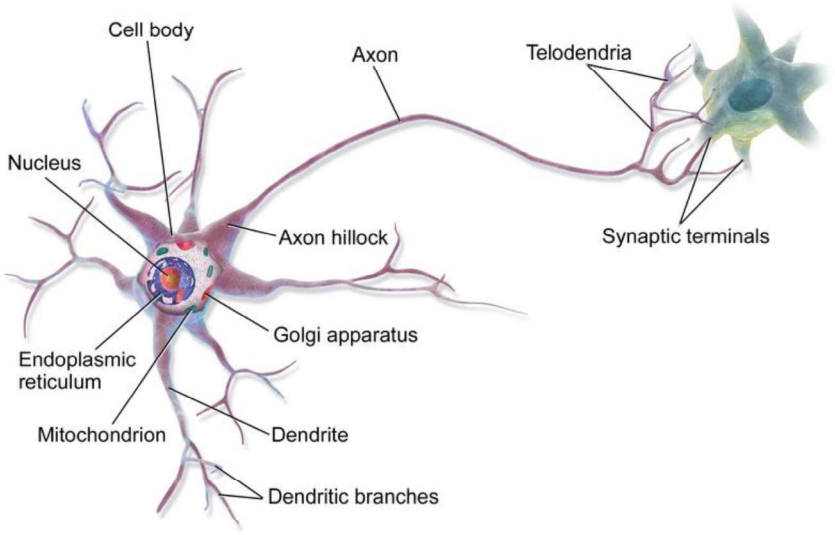


Figure 28 Diagram showing the basic structure of a neuron, including a synapse

Glial Cells - Astrocytess are star-shaped gilal cells within the brain and spinal cord, depending on the method used they make up between 20 and 40% of all glial cells (Fig 30). They have numerous functions, including:

- Providing metabolic support – The brain has a constant requirement for nutrients such glucose but they are unable to store or produce glycogen themselves. This is overcome by the fact that astrocytes **store glycogen** which can be broken down to glucose to provide fuel for neurons. Astrocytes can also store lactate which is useful as a fuel during periods of high energy consumption or ischaemia.
- Regulating the extracellular ionic environment – High-level of ions such as potassium can result in spontaneous depolarisation of the neuron. Astrocytes, thus, remove excess **potassium** ions from the extracellular space.
- Neurotransmitter uptake – Astrocytes contain specific transporters for several neurotransmitters such as **glutamate.** Rapid removal of neurotransmitters from the extracellular space is required for normal function of neurons.

- Modulating synaptic transmission – In some regions of the brain, for example the hippocampus, astrocytes release ATP in order to increase production of **adenosine,** which in turn inhibits synaptic transmission
- Promotion of myelination by oligodendrocytes

Oligodendrocytes - These cells are responsible for insulating the axons in the central nervous system. They carry out this function by producing a **myelin** sheath which wraps around a part of the axon (Fig 29).

A single oligodendrocyte has the capacity to myelinate up to **50 axonal segments.** They are equivalent to the Schwann cells in the peripheral nervous system.

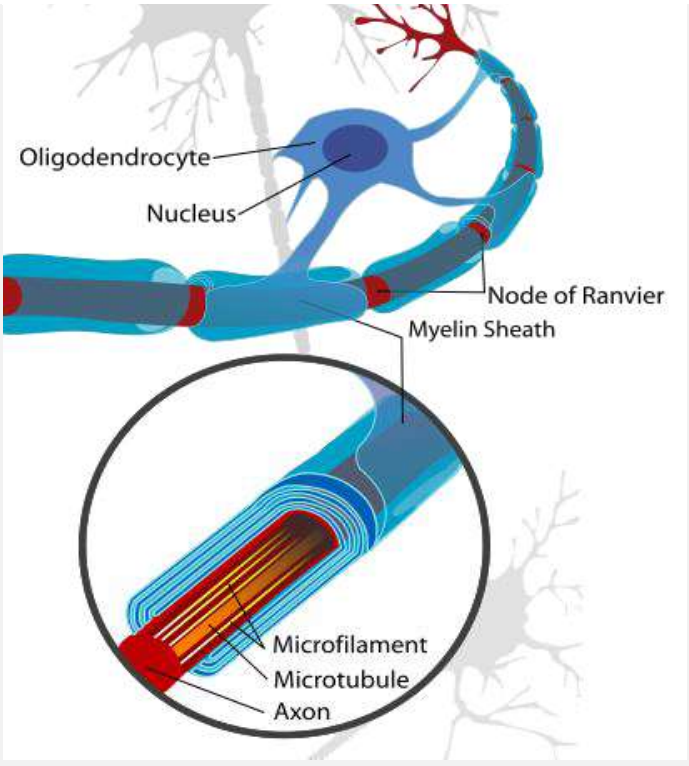


Figure 29 Diagram showing the axon of a neuron in relation to the associated oligodendrocyte and myelin sheath

Microglia - Microglial cells make up between 10 and 15% of cells within the brain and are of a **mesodermal** origin unlike the other glial cells which are of ectodermal origin.

These cells are the phagocytic and immunocompetent cells of the nervous system. They are activated in response to tissue damage and have the capability to recognise foreign antigens and initiate **phagocytosis** to remove foreign material. If needed, microglia are also able to function as antigen presenting cells.

Ependymal cells – The ependyma is the thin lining of the ventricular system of the brain and spinal cord. This lining is made up of ependymal cells, the basal membranes of which are attached to astrocytes. The main function of these cells is the production of **cerebrospinal fluid** (CSF) as a part of the choroid plexus.

Their apical surfaces are covered with cilia and microvilli, which allow for the circulation and absorption of CSF respectively.

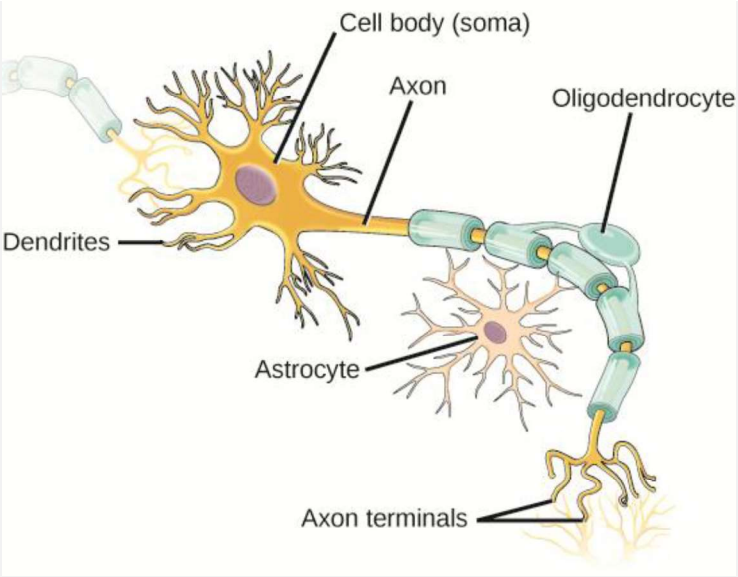


Figure 30 Diagram showing some of the glial cells in relation to a neuron

5.6 NEUROTRANSMITTERS

Neurotransmitters are substances which neurons use to communicate with one another and with their target tissues in the process of synaptic transmission (neurotransmission).

Neurotransmitters are synthetized in and released from nerve endings into the synaptic cleft. From there, neurotransmitters bind to receptor proteins in the cellular membrane of the target tissue. The target tissue gets excited, inhibited, or functionally modified in some other way.

There are more than 40 neurotransmitters in the human nervous system; some of the most important are acetylcholine, norepinephrine, dopamine, gamma-aminobutyric acid (GABA), glutamate, serotonin, and histamine.

Excitatory neurotransmitters	Glutamate (Glu) Acetylcholine (ACh) Histamine Dopamine (DA) Norepinephrine (NE); also known as noradrenaline (NAd) Epinephrine (Epi); also known as adrenaline (Ad)
Inhibitory neurotransmitters	*gamma*-Aminobutyric acid (GABA) Serotonin (5-HT) Dopamine (DA)
Neuromodulators	Dopamine (DA) Serotonin (5-HT) Acetylcholine (ACh) Histamine Norepinephrine (NE)
Neurohormones	Releasing hormones from hypothalamus Oxytocin (Oxt)

	Vasopressin; also known as antidiuretic hormone (ADH)

5.6.1 Mechanism of neurotransmission

Neurons communicate with their target tissues at synapses (Fig 31) into which they release chemical substances called neurotransmitters (ligands). As this communication is mediated with chemical substances, the process is called chemical neurotransmission and happens within chemical synapses.

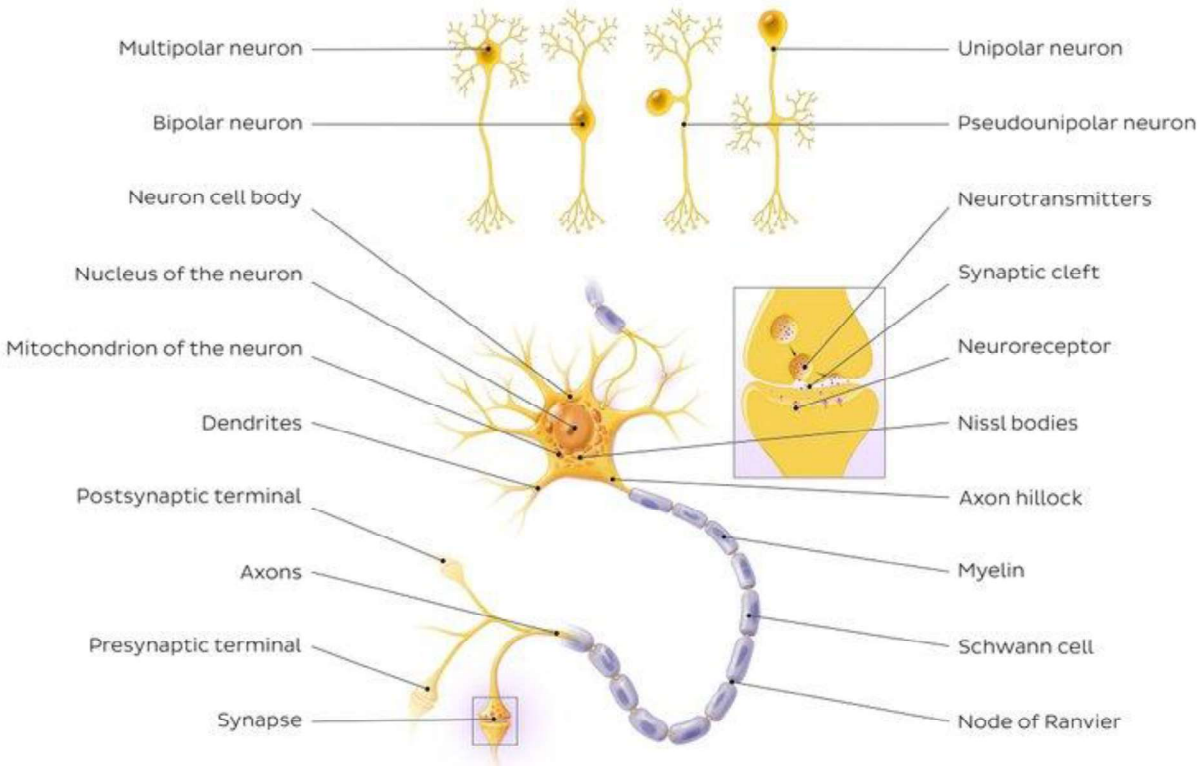


Figure 31 Synapse

Each synapse consists of the:

- Presynaptic membrane – membrane of the terminal bouton (axon ending) of the presynaptic nerve fiber
- Postsynaptic membrane – membrane of the target cell
- Synaptic cleft – a gap between the presynaptic and postsynaptic membranes

Inside the terminal bouton of the presynaptic nerve fiber, numerous vesicles that contain neurotransmitters are produced and stored. When the presynaptic membrane is depolarized by an action potential, calcium voltage-gated channels open (found in the membranes of the terminal buttons). This leads to an influx of calcium ions into the terminal bouton, which changes the state of certain membrane proteins in the presynaptic membrane, and results in exocytosis of neurotransmitters from the terminal bouton into the synaptic cleft.

After crossing the synaptic cleft, neurotransmitters bind to their receptors on the postsynaptic membrane. Once the neurotransmitter binds to its receptor, the ligand-gated channels of the postsynaptic membrane either open or close. These ligand-gated channels are ion channels, and their opening or closing alters the permeability of the postsynaptic membrane to calcium, sodium, potassium, and chloride ions. This leads to a stimulatory or inhibitory response.

If a neurotransmitter stimulates the target cell to an action, then it is an excitatory neurotransmitter acting in an excitatory synapse. On the other hand, if it inhibits the target cell, it is an inhibitory neurotransmitter acting in an inhibitory synapse. So, the type of the synapse and the response of the target tissue depends on the type of neurotransmitter. Excitatory neurotransmitters cause depolarization of the postsynaptic cells and generate an action potential; for example acetylcholine stimulates muscle contraction. Inhibitory synapses cause hyperpolarization of the target cells, leading them farther from the action potential threshold, thus inhibiting their action; for example GABA inhibits involuntary movements.

The neurotransmitter released into the synaptic cleft acts for a very short duration, only minutes or even seconds. It is either destroyed by enzymes, such as acetylcholine esterase, or is reabsorbed into the terminal button of the presynaptic neuron by reuptake mechanisms and then recycled. The best-known neurotransmitters responsible for such fast, but short-lived excitatory action are acetylcholine, norepinephrine, and epinephrine while GABA is the major inhibitory neurotransmitter.

Repeated synaptic activities can have long-lasting effects on the receptor neuron, including structural changes such as the formation of new synapses, alterations in the dendritic tree, or growth of axons. An example of this is the learning process – the more you study and repeat, the more synapses are created in your brain and enable you to retrieve that information when needed.

Besides neurotransmitters, there are other synapse-associated chemical substances called the neuromediators (neuromodulators). Neuromodulation differs to neurotransmission by how long the substance acts on the synapse. Neuromodulators aren't reabsorbed as quickly by presynaptic neurons or broken down by enzymes. Instead, they spend a significant amount of time in cerebrospinal fluid, influencing (modulating) the activity of several other neurons in the brain. The best known neuromodulators are also neurotransmitters, such as dopamine, serotonin, acetylcholine, histamine, and norepinephrine.

5.6.2 Classification

Neurotransmitters can be classified as either excitatory or inhibitory (Fig 32).

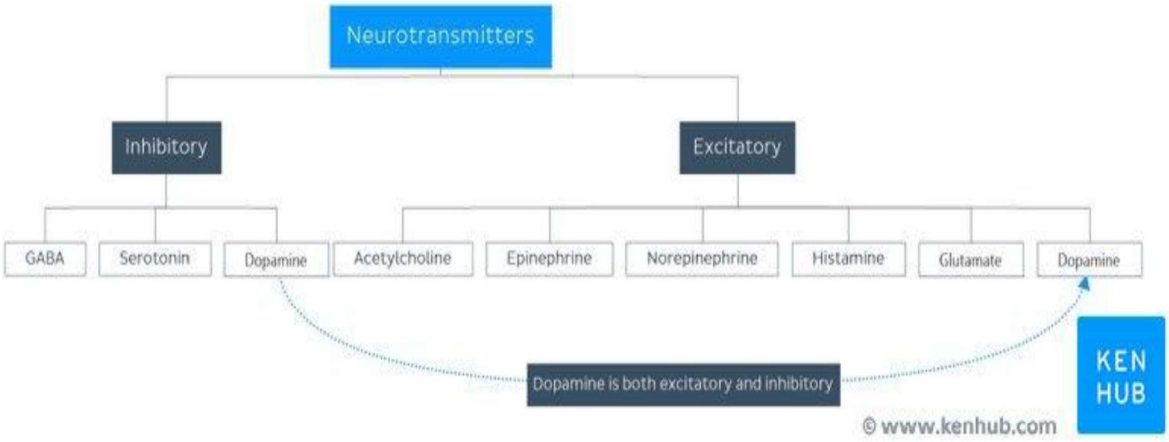


Figure 32 Neurotransmittors

Excitatory neurotransmitters function to activate receptors on the postsynaptic membrane and enhance the effects of the action potential, while inhibitory neurotransmitters function to prevent an action potential. In addition to the above classification, neurotransmitters can also be classified based on their chemical structure:

- Amino acids – GABA, glutamate
- Monoamines – serotonin, histamine
- Catecholamines (subcategory of monoamines) – dopamine, norepinephrine, epinephrine

The following are the most clearly understood and most common types of neurotransmitters.

5.6.3 Acetylcholine

Acetylcholine (ACh) is an excitatory neurotransmitter secreted by motor neurons that innervate muscle cells, basal ganglia, preganglionic neurons of the autonomic nervous system, and postganglionic neurons of the parasympathetic and sympathetic nervous systems.

Type	Excitatory in all cases except in the heart (inhibitory)
Released from	Motor neurons, basal ganglia, preganglionic neurons of the autonomic nervous system, postganglionic neurons of the parasympathetic nervous system, and postganglionic neurons of the sympathetic nervous system that innervate the sweat glands
Functions	Regulates the sleep cycle, essential for muscle functioning

Its main function is to stimulate muscle contraction. However, the only exception to this, where acetylcholine is an inhibitory neurotransmitter, is at the parasympathetic endings of the vagus nerve. These inhibit the heart muscle through the cardiac plexus.

It is also found in sensory neurons and in the autonomic nervous system, and has a part in scheduling the "dream state" while an individual is fast asleep. Acetylcholine plays a vital role in the normal functioning of muscles. For example, poisonous plants like curare and hemlock cause paralysis of muscles by blocking the acetylcholine receptor sites of myocytes (muscle cells). The well-known poison botulin works by preventing vesicles in the terminal bouton from releasing acetylcholine, thus leading to paralysis of the effector muscle.

5.6.4 Norepinephrine

Norepinephrine (NE), also known as noradrenaline (NAd), is an excitatory neurotransmitter produced by the brainstem, hypothalamus, and adrenal glands and released into the bloodstream. In the brain it increases the level of alertness and wakefulness.

Type	Excitatory
Released from	Brainstem, hypothalamus, and adrenal glands
Functions	Increases the level of alertness and wakefulness, stimulates various processes of the body

In the body, it is secreted by most postganglionic sympathetic nerves. It acts to stimulate the processes in the body. For example, it is very important in the endogenous production of epinephrine. Norepinephrine has been implicated in mood disorders such as depression and anxiety, in which case its concentration in the body is abnormally low. Alternatively, an abnormally high concentration of it may lead to an impaired sleep cycle.

5.6.5 Epinephrine

Also known as adrenaline (Ad), epinephrine (Epi) is an excitatory neurotransmitter produced by the chromaffin cells of the adrenal gland. It prepares the body for the fight-or-flight response. That means that when a person is highly stimulated (fear, anger etc.), extra amounts of epinephrine are released into the bloodstream.

Type	Excitatory
Released	Chromaffin cells of the medulla of adrenal gland

from	
Functions	The fight-or-flight response (increased heart rate, blood pressure, and glucose production)

This release of epinephrine increases heart rate, blood pressure, and glucose production from the liver (glycogenolysis). In this way, the nervous and endocrine systems prepare the body for dangerous and extreme situations by increasing nutrient supply to key tissues.

5.6.6 Dopamine

Dopamine (DA) is a neurotransmitter secreted by the neurons of the substantia nigra. It is considered a special type of neurotransmitter because its effects are both excitatory and inhibitory. Which effect depends on the type of receptor that dopamine binds to.

Type	Both excitatory and inhibitory
Released from	Substantia nigra
Functions	Inhibits unnecessary movements, inhibits the release of prolactin, and stimulates the secretion of growth hormone

As a part of the extrapyramidal motor system which involves the basal ganglia, dopamine is important for movement coordination by inhibiting unnecessary movements. In the pituitary gland, it inhibits the release of prolactin, and stimulates the secretion of growth hormone.

Dopamine deficiency related to the destruction of the substantia nigra leads to Parkinson's disease. Increased activity of dopaminergic neurons contributes to the pathophysiology of psychotic disorders and schizophrenia. Drug and alcohol abuse can temporarily increase dopamine levels in the blood, leading to confusion and the inability to focus. However, an appropriate secretion of dopamine in the bloodstream plays a role in the motivation or desire to complete a task.

5.6.7 GABA

gamma-Aminobutyric acid (GABA) is the most powerful inhibitory neurotransmitter produced by the neurons of the spinal cord, cerebellum, basal ganglia, and many areas of the cerebral cortex. It is derived from glutamate.

Type	Inhibitory
Released from	Neurons of the spinal cord, cerebellum, basal ganglia, and many areas of the cerebral cortex
Functions	Reduces neuronal excitability throughout the nervous system

Functions of GABA are closely related to mood and emotions. It is an inhibitory neurotransmitter that acts as a brake to excitatory neurotransmitters; thus when it is abnormally low this can lead to anxiety. It is widely distributed in the brain and plays a principal role in reducing neuronal excitability throughout the nervous system.

5.6.8 Glutamate

Glutamate (Glu) is the most powerful excitatory neurotransmitter of the central nervous system which ensures homeostasis with the effects of GABA. It is secreted by neurons of the many of the sensory pathways entering the central nervous system, as well as the cerebral cortex.

Type	Excitatory
Released from	Sensory neurons and cerebral cortex
Functions	Regulates central nervous system excitability, learning process, memory

Glutamate is the most common neurotransmitter in the central nervous system; it takes part in the regulation of general excitability of the central nervous system, learning processes, and memory. Thus, inappropriate glutamate neurotransmission contributes to developing epilepsy and cognitive and affective disorders.

5.6 9 Serotonin

Serotonin (5-hydroxytryptamine, 5-HT) is an inhibitory neurotransmitter that has been found to be intimately involved in emotion and mood. It is secreted by the neurons of the brainstem and by neurons that innervate the gastrointestinal tract (enteric nervous system). In addition, serotonin is found in platelets (thrombocytes) which release it during coagulation (hemostasis).

Type	Inhibitory

Released from	Neurons of the brainstem and gastrointestinal tract, thrombocytes
Functions	Regulates body temperature, perception of pain, emotions, and sleep cycle

In participates in regulation of body temperature, perception of pain, emotions, and sleep cycle. An insufficient secretion of serotonin may result in decreased immune system function, as well as a range of emotional disorders like depression, anger control problems, obsessive-compulsive disorder, and even suicidal tendencies.

5.6 10 Histamine

Histamine is an excitatory neurotransmitter produced by neurons of the hypothalamus, cells of the stomach mucosa, mast cells, and basophils in the blood. In the central nervous system, it is important for wakefulness, blood pressure, pain, and sexual behavior. In the stomach, it increases the acidity.

Type	Excitatory
Released from	Hypothalamus, cells of the stomach mucosa, mast cells, and basophils in the blood
Functions	Regulates wakefulness, blood pressure, pain, and sexual behavior; increases the acidity of the stomach; mediates inflammatory reactions

It is involved primarily in the inflammatory response, as well as a range of other functions such as vasodilation and regulation of the immune response to foreign bodies. For example, when allergens

are introduced into the bloodstream, histamine assists in the fight against these microorganisms causing itching of the skin or irritations of the throat, nose, and or lungs.

5.7 DISORDERS ASSOCIATED WITH NEUROTRANSMITTERS

5.7.1 Alzheimer's disease

Alzheimer's disease is a neurodegenerative disorder characterized by learning and memory impairments. It is associated with a lack of acetylcholine in certain regions of the brain.

5.7.2 Depression

Depression is believed to be caused by a depletion of norepinephrine, serotonin, and dopamine in the central nervous system. Hence, pharmacological treatment of depression aims at increasing the concentrations of these neurotransmitters in the central nervous system.

5.7.2 Schizophrenia

Schizophrenia, which is a severe mental illness, has been shown to involve excessive amounts of dopamine in the frontal lobes, which leads to psychotic episodes in these patients. The drugs that block dopamine are used to help schizophrenic conditions.

5.7.3 Parkinson's disease

The destruction of the substantia nigra leads to the destruction of the only central nervous system source of dopamine. Dopamine depletion leads to uncontrollable muscle tremors seen in patients suffering from Parkinson's disease.

5.7.4 Epilepsy

Some epileptic conditions are caused by the lack of inhibitory neurotransmitters, such as GABA, or by the increase of excitatory neurotransmitters, such is glutamate. Depending on the cause of the seizures, the treatment is aimed to either increase GABA or decrease glutamate.

5.7.5 Huntington's disease

Besides epilepsy, a chronic reduction of GABA in the brain can lead to Huntington's disease. Even though this is an inherited disease related to abnormality in DNA, one of the products of such disordered DNA is the reduced ability of the neurons to take up GABA. There is no cure for Huntington's disease, but we still can treat symptoms by pharmacologically increasing the amount of inhibitory neurotransmitters.

5.7.6 Myasthenia gravis

Myasthenia gravis is a rare chronic autoimmune disease characterized by the impairment of synaptic transmission of acetylcholine at neuromuscular junctions, leading to fatigue and muscular weakness without atrophy.

Most often, myasthenia gravis results from circulating antibodies that block acetylcholine receptors at the postsynaptic neuromuscular junction. This inhibits the excitatory effects of acetylcholine on nicotinic receptors at neuromuscular junctions. In a much rarer form, muscle weakness may result from a genetic defect in parts of the neuromuscular junction which is inherited, as opposed to developing through passive transmission from the mother's immune system at birth or through autoimmunity later in life.

5.8 Action of anesthetics, analgesics, hallucinogens, depressants, stimulants and toxins on the nervous system

Physicians have long recognized that different types of drugs affect people differently. Nonetheless, drugs may be categorized or classified according to certain shared symptomatologies or effects. The DRE categorization process is premised on these long-standing, medically accepted facts. DREs classify drugs in one of seven categories: central nervous system (CNS) depressants, CNS stimulants, hallucinogens, dissociative anesthetics, narcotic analgesics, inhalants, and cannabis. Drugs from each of these categories can affect a person's central nervous system and impair a person's normal faculties, including a person's ability to safely operate a motor vehicle.

5.8.1 Central Nervous System (CNS) Depressants

CNS depressants slow down the operations of the brain and the body. Examples of CNS depressants include alcohol, barbiturates, anti-anxiety tranquilizers (e.g., Valium, Librium, Xanax, Prozac, and Thorazine), GHB (gamma hydroxybutyrate), Rohypnol, and many other anti-depressants (e.g., Zoloft, Paxil).

5.8.2 CNS Stimulants

CNS stimulants accelerate the heart rate and elevate the blood pressure and "speed-up," or over-stimulate, the body. Examples of CNS stimulants include cocaine, "crack" cocaine, amphetamines, and methamphetamine ("crank") (Fig 33).

5.8.3 Hallucinogens

Hallucinogens cause the user to perceive things differently than they actually are. Examples include LSD, peyote, psilocybin and MDMA (Ecstasy).

5.8.4 Dissociative Anesthetics

Dissociative anesthetics include drugs that inhibit pain by cutting off or dissociating the brain's perception of the pain. PCP, its analogs, and dextromethoraphan are examples of dissociative anesthetics.

5.8.5 Narcotic Analgesics

Narcotic analgesics relieve pain, induce euphoria, and create mood changes in the user. Examples of narcotic analgesics include opium, codeine, heroin, demerol, darvon, morphine, methadone, Vicodin, and oxycontin.

5.8.6 Inhalants

Inhalants include a wide variety of breathable substances that produce mind-altering results and effects. Examples of inhalants include Toluene, plastic cement, paint, gasoline, paint thinners, hair sprays, and various anesthetic gases.

5.8.7 Cannabis

Cannabis is the scientific name for marijuana. The active ingredient in cannabis is delta-9 tetrahydrocannabinol, or THC. This category includes cannabinoids and synthetics like Dronabinol.

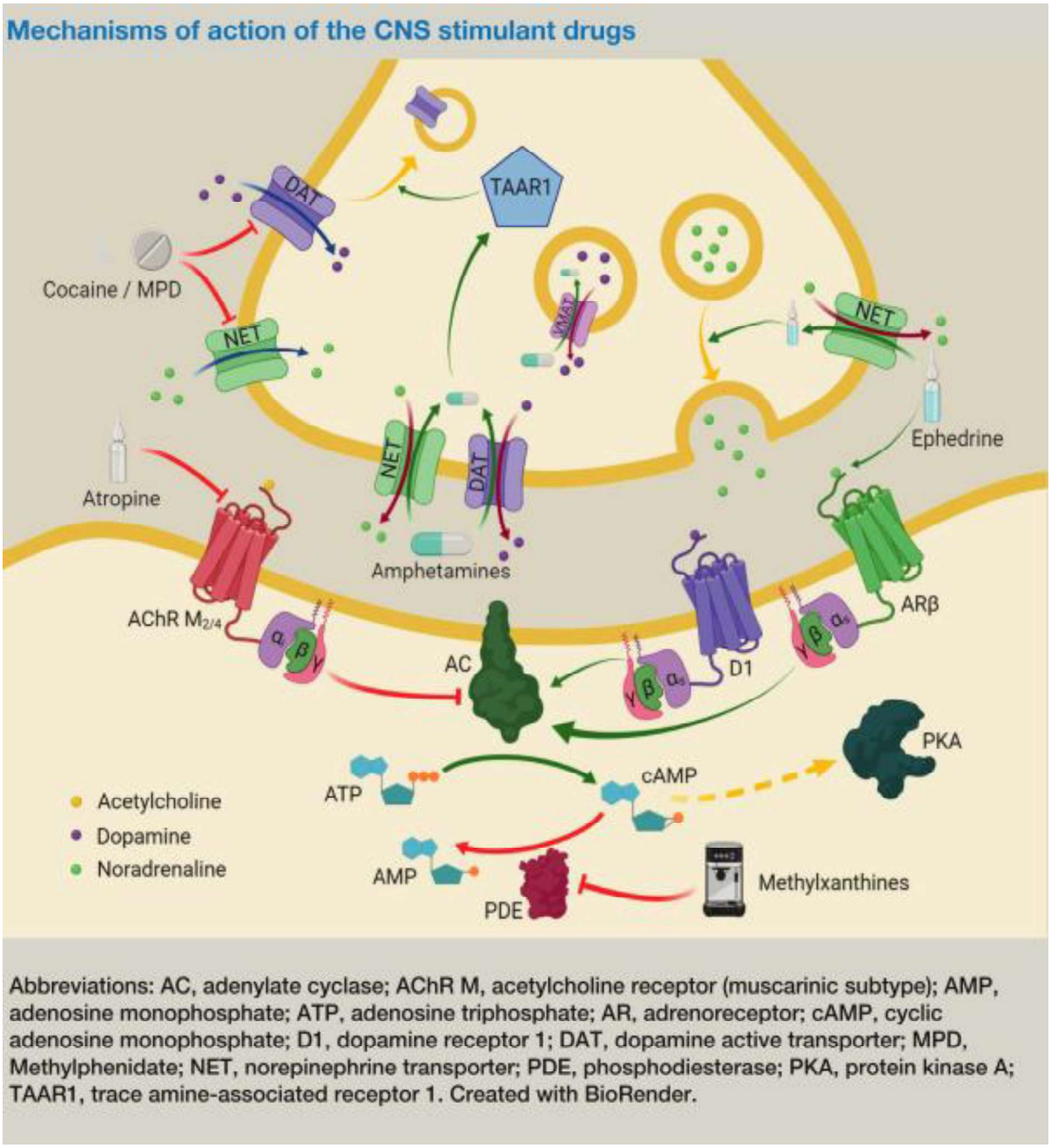


Figure 33 Mechanism of stimulant