THOMAS ADEWUMI UNIVERSITY, OKO, KWARA STATE
Science | Technology | Medicine

LECTURE NOTE

ON

BCH 324

PRINCIPLES OF ENDOCRINOLOGY

PREPARED BY: L.B. BELLO
bello.lukman@tau.edu.ng

COURSE OUTLINE

- Endocrine cells and hormones
- Properties and functions of hormones
- Mechanism of hormone action
- Secretion and regulation of hormones
- Functions and metabolic disorders of hormones of pituitary, hypothalamus and thyroid glands
- Sex hormones, adrenal hormones, catecholamines and hormones of the GIT
- Biochemistry of nerve impulse transmission, neurotransmitters, endocrine integration versus neural integration

DID YOU KNOW?

- The human body secretes and circulates about 50 different types of hormones?
- The hypothalamus is responsible for hunger, mood swings, thirst, sleep, body temperature, and sex drive.
- Diabetes mellitus is caused by insufficiency or inefficiency of a hormone called insulin.

ENDOCRINE CELLS AND HORMONES

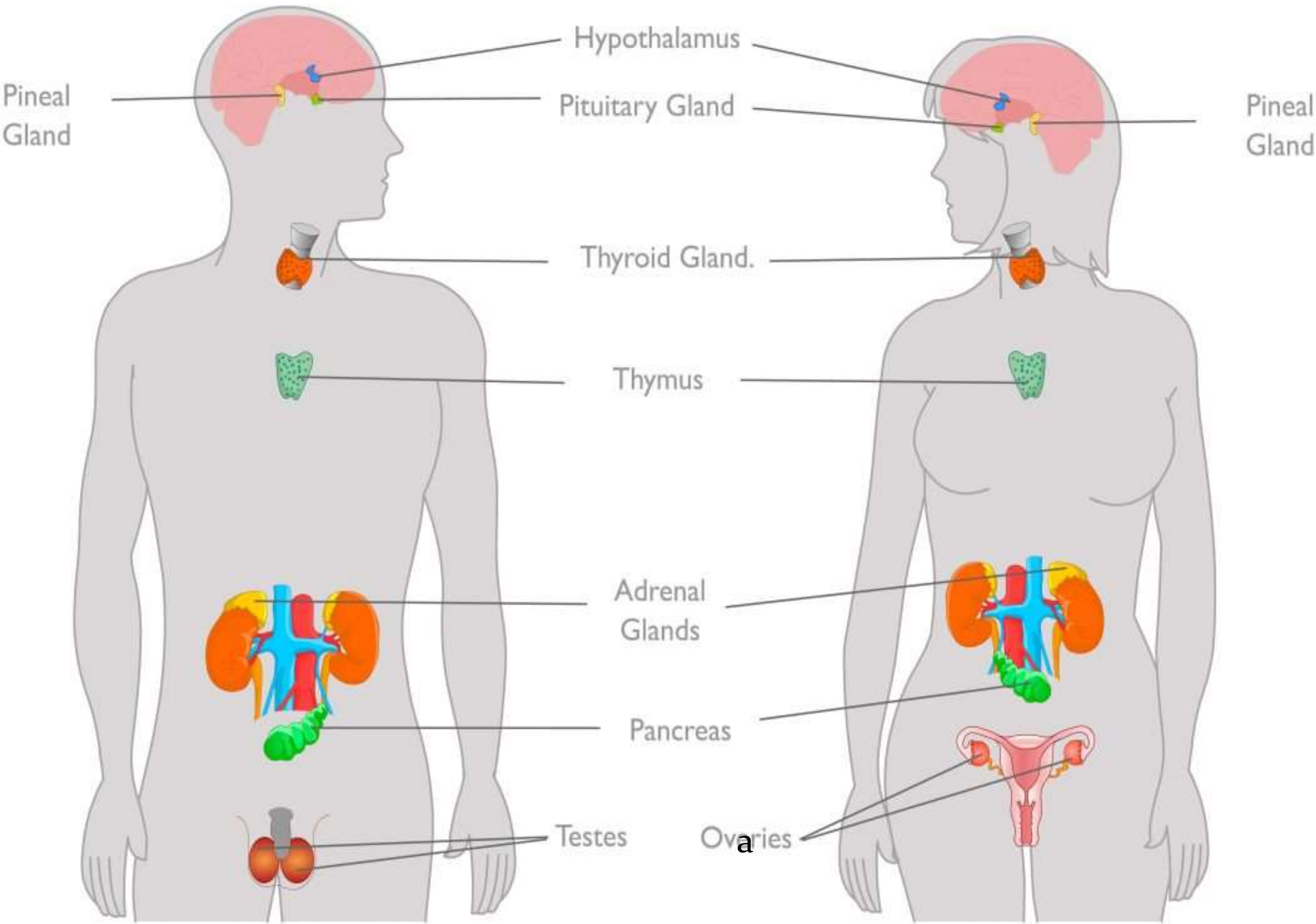
- **Endocrine cells** are the cells that make up the endocrine system, which is a control system comprising hormone-secreting glands.

- These cells typically make up larger tissues and organs (endocrine glands) that function within and outside of the endocrine system.

- **Endocrine glands** are glands of the endocrine system that secrete hormones directly into interstitial spaces where they are absorbed into the blood rather than through a duct.

- The major glands of the endocrine system include the pineal gland, pituitary gland, pancreas, ovaries, testes, thyroid gland, thymus, hypothalamus and adrenal glands.

HUMAN ENDOCRINE SYSTEM



Source: napervilleintegratedwellness.com

HORMONES

- Hormones maybe defined as chemical messengers produced in small amount by endocrine glands, secreted into the blood stream to control metabolism and biological activities in target cells or organs.

- They are regarded as the chemical messengers involved in the transmission of information from one tissue to another and from cell to cell.

- They affect distant cells by binding to specific receptor proteins in the target cell, resulting in a change in cell function.

- Hormones are required for the correct development of animals, plants and fungi.

- They may be classified in many ways based on their characteristics and functions.

CLASSIFICATION OF HORMONES BASED ON THEIR CHEMICAL NATURE

Hormones can be categorized into three groups based on their chemical nature:

1. Protein or peptide hormones e.g. insulin, glucagon, antidiuretic hormone, oxytocin.

2. Steroid hormones e.g. glucocorticoids, mineralocorticoids, sex hormones.

3. Amino acid derivatives e.g. epinephrine, norepinephrine, thyroxine (T_4), triiodothyronine (T_3).

CLASSIFICATION OF HORMONES BASED ON THEIR MECHANISM OF ACTION

Hormones are classified into two broad groups (I and II) based on the location of the receptors to which they bind and the signals used to mediate their action:

Group I hormones: These hormones bind to intracellular receptors to form receptor hormone complexes (the intracellular messengers) through which their biochemical functions are mediated.

Group I hormones are lipophilic in nature and are mostly derivatives of cholesterol (exception—T_3 and T_4). e.g. estrogens, androgens, glucocorticoids, calcitriol.

- **Group II hormones:** These hormones bind to cell surface (plasma membrane) receptors and stimulate the release of certain molecules called **second messengers**, which in turn, perform various biochemical functions.

- Thus, hormones themselves are the first messengers.

- Group II hormones are **subdivided into three** categories based on the chemical nature of the second messengers:

  (a) The second messenger is cAMP e.g. ACTH, FSH, LH, PTH, glucagon, calcitonin.

  (b) The second messenger is phosphatidylinositol/calcium e.g. TRH, GnRH, gastrin, CCK.

  (c) The second messenger is unknown e.g. growth hormone, insulin, oxytocin, prolactin.

PROPERTIES OF HORMONES

i. Hormones have low molecular weight.
ii. They are small organic molecules.
iii. They are transported in the blood stream.
iv. They are soluble in water, making it possible to be transported via blood.
v. They are non-antigenic.
vi. Their rate of diffusion is very high and are readily oxidized but their effect do not remain constant.
vii. They are effective in low concentration.
viii. They have their target sites different from where they are produced and are specific to a particular target.
ix. They are non-specific for organisms and may influence the body process of other individuals.
x. When their function is over, they are readily destroyed, excreted or inactivated.
xi. Their activities are not hereditary.

FUNCTIONS OF HORMONES

Hormones regulate and coordinate a wide range of physiological and behavioral activities such as:

i. Metabolism of food.
ii. Growth and development.
iii. Hunger and thirst.
iv. Preservation of body temperature.
v. Maintenance of homeostasis
vi. Sleep and wake cycle
vii. Mental and emotional functions.
viii. Establishing and sustaining sexual development and reproduction

MECHANISM OF HORMONE ACTION

MECHANISM OF ACTION OF GROUP I HORMONES

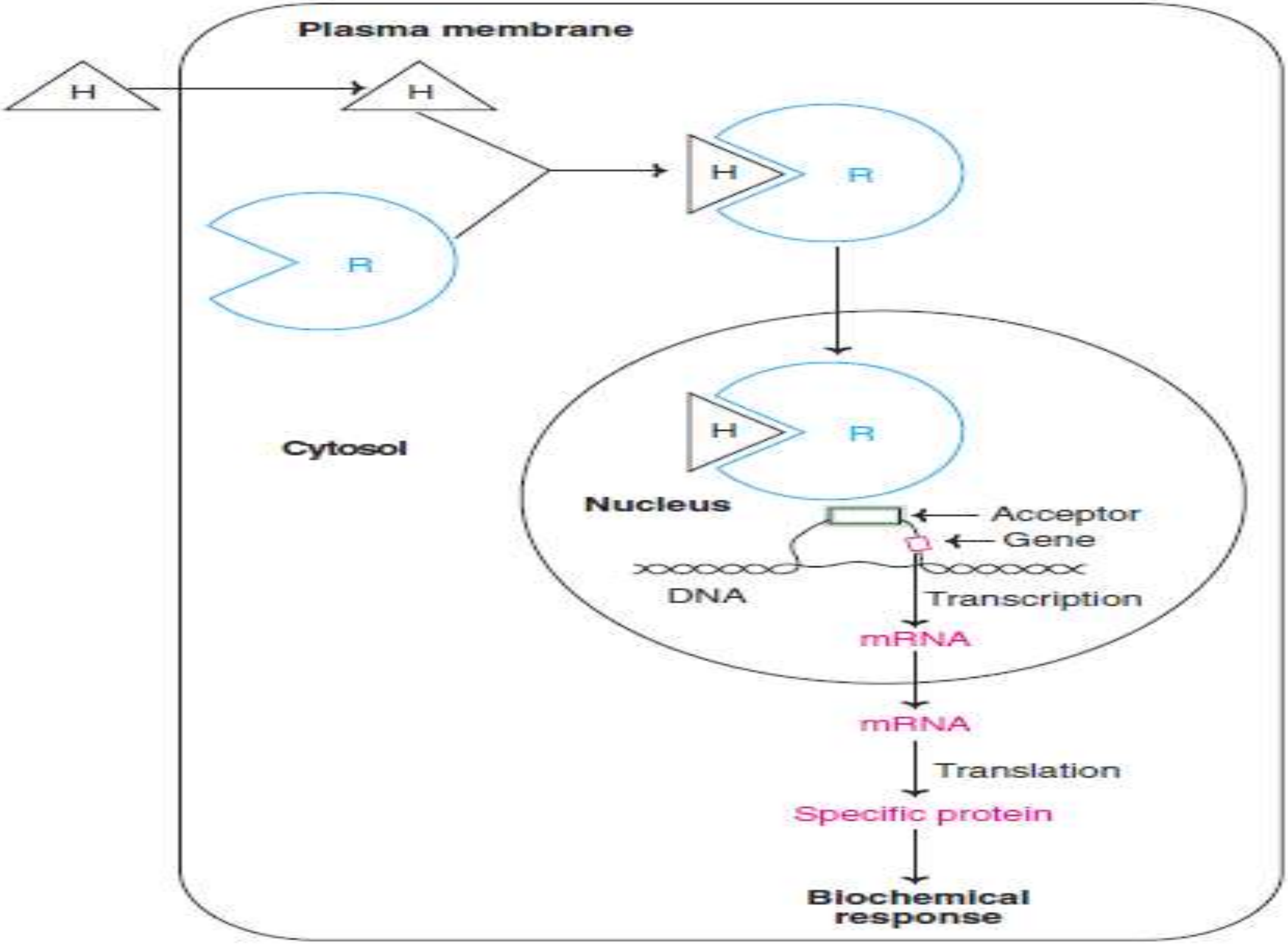
- GroupI hormones are lipophilic in nature and can easily pass across the plasma membrane.

- They act through the intracellular receptors located either in the cytosol or the nucleus.

- The hormone-receptor complex binds to specific regions on the DNA called hormone responsive element (HRE) and causes increased expression of specific genes as illustrated below.

- It is believed that the interaction of hormone-receptor complex with HRE promotes initiation and, to a lesser extent, elongation and termination of RNA synthesis (transcription).

- The ultimate outcome is the production of specific proteins (translation) in response to hormonal action.



Mechanism of action of group I hormones

(H–Hormone; R–Receptor; HR–Hormone-receptor complex)

MECHANISM OF ACTION OF GROUP II HORMONES

- These hormones are considered as the first messengers.
- They exert their action through mediatory molecules, collectively called second messengers.
- A typical example of a second messenger is cAMP.

SECRETION AND REGULATION OF HORMONES

- The rate of hormone synthesis and secretion is often regulated by a homeostatic negative feedback control mechanism.

- Such a mechanism depends on factors that influence the metabolism and excretion of hormones.

- Thus, higher hormone concentration alone cannot trigger the negative feedback mechanism.

- Negative feedback must be triggered by overproduction of an "effect" of the hormone.

- For instance, blood glucose levels are maintained at a constant level in the body by a negative feedback mechanism.

- When the blood glucose level is too high, the pancreas secretes insulin and when the level is too low, the pancreas then secretes glucagon.

- Hormone secretion can be stimulated and inhibited by:

1. Other hormones (stimulating- or releasing -hormones).
2. Plasma concentrations of ions or nutrients, as well as binding globulins.
3. Neurons and mental activity
4. Environmental changes, e.g., of light or temperature

- One special group of hormones is the tropic hormones that stimulate the hormone production of other endocrine glands.

- For example, thyroid-stimulating hormone (TSH) causes growth and increased activity of another endocrine gland, the thyroid, which increases output of thyroid hormones.

- To release active hormones quickly into the circulation, hormone biosynthetic cells may produce and store biologically inactive hormones in the form of pre- or pro-hormones.

- These can then be quickly converted into their active hormone form in response to a particular stimulus.

- **Eicosanoids** are considered to act as local hormones because they possess specific effects on target cells close to their site of formation.

- They also have a rapid degradation cycle, making sure they do not reach distant sites within the body.

FUNCTIONS AND METABOLIC DISORDERS OF HORMONES OF PITUITARY, HYPOTHALAMUS AND THYROID GLANDS

ANTERIOR PITUITARY HORMONES

- The anterior pituitary or adenohypophysis is regarded as the ***master endocrine organ***, as it produces several hormones that influence, either directly or indirectly, a variety of biochemical processes in the body.

- The hormones of adenohypophysis are broadly classified into three categories:

  i. **The growth hormone-prolactin group** e.g. growth hormone (GH), prolactin (PRL) and chorionic somatomammotropin (CS; placental lactogen).

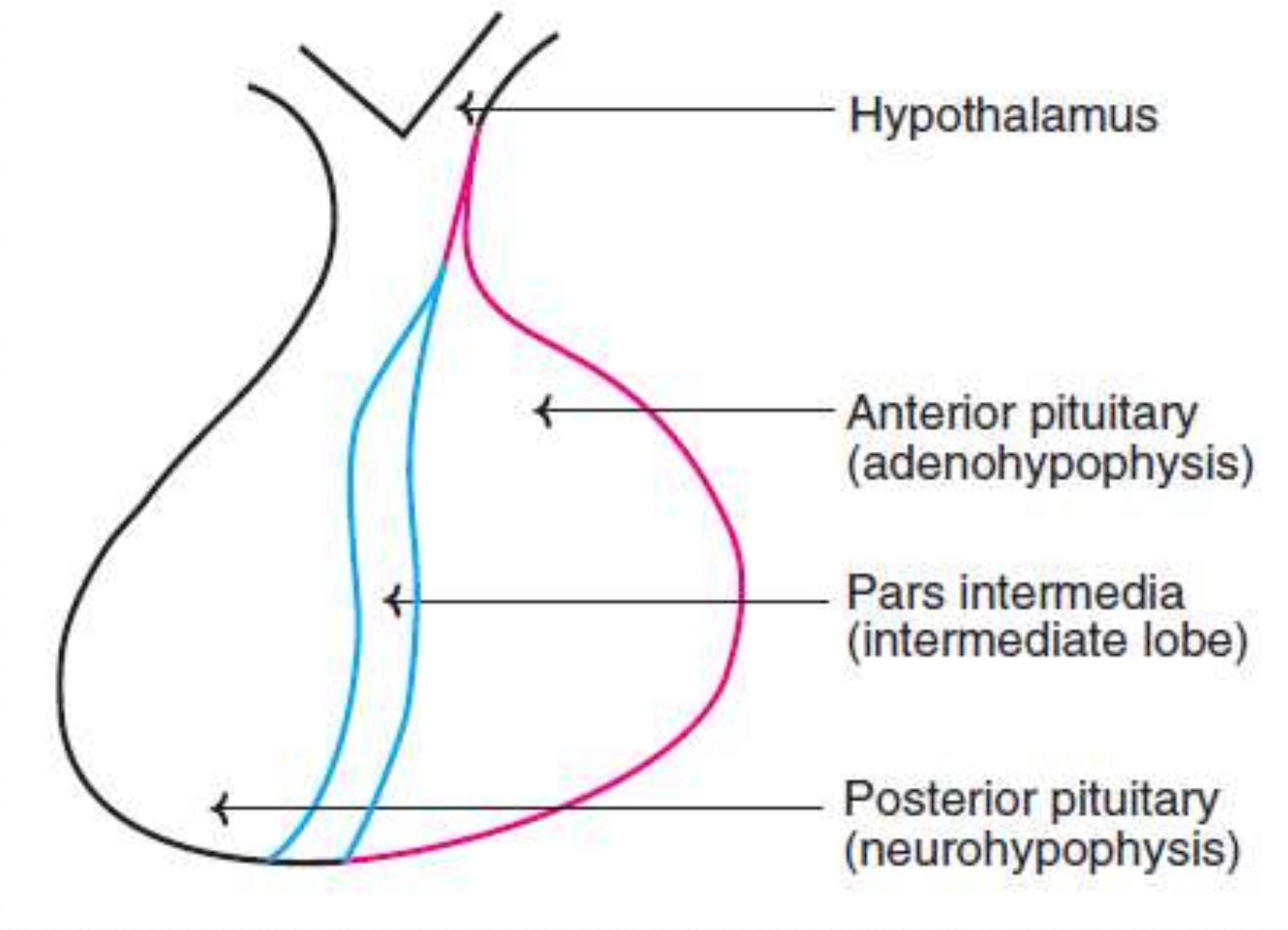
  ii. **The glycoprotein hormones** e.g. thyroid stimulating hormone (TSH), follicle stimulating hormone (FSH), luteinizing hormone (LH) and human chorionic gonadotropin (hCG).

- The last three hormones are collectively referred to as **gonadotropins** due to their involvement in the function of gonads.

- The hormone hCG is produced by human placenta and not by pituitary.

iii. **The pro-opiomelanocortin peptide family** e.g. adrenocorticotropic hormone (ACTH), lipotropin (LPH) and melanocyte stimulating hormone (MSH) and several (about 24) neuromodulators such as endorphins and enkephalins.

The name **pro-opiomelano-cortin** is derived since it is a ***pro***hormone to ***opio***ids, ***melano***cyte-stimulating hormone and ***corti***cotropi***n***.



A diagrammatic view of the pituitary gland

Source: Satyanarayana and Chakrapani, 2013

FUNCTIONS OF GROWTH HORMONE (GH)

- **Effects on growth:** Growth hormone is essential for growth, and its growth-related effects are mediated through insulin-like growth factor I (IGF-I) which is also known as ***somatomedin C*** (formerly sulfation factor), produced by the liver.

- **Effects on protein metabolism:** Growth hormone has an anabolic effect on protein metabolism.

- It promotes the uptake of amino acids into the tissues and increases protein synthesis.

- The overall effect of Growth hormone is a positive nitrogen balance that leads to increase in body weight.

- **Effects on carbohydrate metabolism:** Growth hormone is antagonistic to insulin and causes hyperglycemia.

- It increases gluconeogenesis, decreases glucose utilization, impairs glycolysis and reduces the tissue uptake of glucose.

- **Effects on lipid metabolism:** Growth hormone promotes lipolysis in the adipose tissue and increases the circulatory levels of free fatty acids and their oxidation.

- It also increases ketogenesis, particularly in diabetes.

- **Effects on mineral metabolism:** Growth hormone promotes bone mineralization and its growth, as clearly observed in the growing children.

DISORDERS OF GROWTH HORMONE (GH)

- **Deficiency of GH:** Impairment in the secretion of growth hormone in growing age causes dwarfism.

- The other deficiency metabolic effects are not that serious in nature.

- **Overproduction of GH:** Excessive production of GH causes **gigantism** in children and **acromegaly** in adults.

- This usually occurs in the acidophil tumor of pituitary gland.

- Gigantism is characterized by increased growth of long bones and this is observed before the epiphyseal plates close.

- Acromegaly occurs after epiphyseal closure and is characterized by increase in the size of hands, facial changes (enlarged nose, protruding jaw), excessive hair, thickening of skin etc.

FUNCTIONS OF PROLACTIN (PRL)

- Prolactin (PRL) is also called lactogenic hormone, luteotropic hormone, mammotropin or luteotropin.

- Prolactin is primarily concerned with the initiation and maintenance of lactation in mammals.

- PRL increases the levels of several enzymes involved in carbohydrate and lipid metabolism.

- PRL promotes HMP shunt, increases lipid biosynthesis and stimulates lactose production in mammary glands.

- Prolactin promotes the growth of corpus luteum (hence also known as luteotropic hormone) and stimulates the production of progesterone.

FUNCTIONS OF THYROID STIMULATING HORMONE (TSH)

- TSH binds with plasma membrane receptors and stimulates adenylate cyclase with a consequent increase in cAMP level.

- Through the mediation of cAMP, TSH exerts the following effects:

  i. Promotes the uptake of iodide (iodide pump) from the circulation by thyroid gland.

  ii. Enhances the conversion of iodide (I^-) to active iodide (I^+), a process known as ***organification***.

  iii. Increases the proteolysis of thyroglobulin to release T_3 and T_4 into the circulation.

- TSH increases the synthesis of proteins, nucleic acids and phospholipids in thyroid gland.

FUNCTIONS OF FOLLICLE-STIMULATING HORMONE (FSH)

In females,

- FSH stimulates follicular growth,
- increases the weight of the ovaries, and
- enhances the production of estrogens.

In males,

- FSH stimulates testosterone production,
- required for spermatogenesis, and
- also promotes growth of seminiferous tubules.

Functions of Luteinizing Hormone (LH) and Human Chorionic Gonadotropin (hCG)

- Luteinizing hormone stimulates the production of progesterone from corpus luteum cells in females and testosterone from Leydig cells in males.

- LH and FSH are collectively responsible for the development and maintenance of secondary sexual characters in males.

- The levels of hCG in plasma and urine increase almost immediately after the implantation of fertilized ovum.

- The detection of hCG in urine is conveniently used for the early detection (within a week after missing the menstrual cycle) of pregnancy.

FUNCTIONS AND DISORDERS OF ADRENOCORTICOTROPIC HORMONE (ACTH)

- ACTH promotes the conversion of cholesterol to pregnenolone in the adrenal cortex.
- It enhances RNA and protein synthesis and thus promotes adrenocortical growth.
- ACTH increases lipolysis by activating lipase of adipose tissue.
- **Overproduction of ACTH:** Cushing's syndrome is caused by an excessive production of ACTH, which may be due to a tumor.
- This syndrome is characterized by hyperpigmentation and increased production of adrenocorticosteroids.
- The associated symptoms include negative nitrogen balance, impaired glucose tolerance, hypertension, edema, muscle atrophy etc.

FUNCTIONS OF β-LIPOTROPIN (β-LPH)

- β-LPH is found only in the pituitary and not in other tissues since it is rapidly degraded.
- The biochemical functions of β-LPH, as such, are limited.
- However, β-LPH promotes lipolysis and increases the mobilization of fatty acids.
- The most important function of β-LPH is its precursor role for the formation of β-endorphin and enkephalins.
- Endorphins and enkephalins are the natural analgesics that control pain and emotions.
- They were discovered after an unexpected finding of opiate receptors in the human brain.

- Endorphins and enkephalins are peptide neurotransmitters that produce opiate-like effects on the central nervous system.

- Hence, they are also known as ***opioid-peptides***.

- They bind to the same receptors as the morphine opiates and are believed to control the endogenous pain perception.

- Endorphins and enkephalins are more potent (20-30 times) than morphine in their function as analgesics.

- It is believed that the pain relief through acupuncture and placebos is mediated through opioid peptides.

FUNCTIONS OF MELANOCYTE-STIMULATING HORMONE (MSH)

- The functions of MSH have been clearly established in some animals.

- MSH promotes the synthesis of skin pigment melanin (melanogenesis) and disperses melanin granules that ultimately leads to darkening of the skin.

- In humans, MSH does not appear to play any role in melanin synthesis.

POSTERIOR PITUITARY HORMONES

- Two hormones namely **oxytocin** and **antidiuretic hormone** (ADH, vasopressin) are produced by the posterior pituitary gland (neurohypophysis).
- These hormones are nonapeptides (containing 9 amino acids).
- The release of oxytocin from the posterior pituitary gland is caused by the neural impulses of nipple stimulation.
- The other stimuli responsible for oxytocin release include vaginal and uterine distention.
- The release of ADH is mostly controlled by osmoreceptors (of hypothalamus) and baroreceptors (of heart).
- Any increase in the osmolarity of plasma stimulates ADH secretion.

FUNCTIONS OF OXYTOCIN

- **Effect on uterus:** Oxytocin causes the contraction of pregnant uterus (smooth muscles) and induces labour.

- **Effect on milk ejection:** In mammals, oxytocin causes contraction of myoepithelial cells (look like smooth muscle cells) of breast.

- This stimulates the squeezing effect, causing milk ejection from the breast.

- **Effect on steroids synthesis:** Oxytocin synthesized in the ovary appears to inhibit the synthesis of steroids.

FUNCTIONS AND DISORDERS OF ANTIDIURETIC HORMONE (ADH)

- ADH is primarily concerned with the regulation of water balance in the body.
- It stimulates the kidneys to retain water and, thus, increases blood pressure.
- In the absence of ADH, the urine outputwould be around 20 L/day.
- ADH acts on the distal convoluted tubules of kidneys and causes water reabsorption with a result that the urine output is around 0.5-1.5 l/day.
- **Diabetes insipidus:** This disorder is characterized by the excretion of large volumes of dilute urine (polyuria).
- It may be due to insufficient levels of ADH or a defect in the receptors of target cells.

HYPOTHALAMIC HORMONES

- The hypothalamus is a specialized center in the brain that functions as a ***master coordinator*** of hormonal action.

- In response to the stimuli of the central nervous system, hypothalamus liberates certain releasing factors or hormones.

- These factors stimulate or inhibit the release of the corresponding tropic hormones from the anterior pituitary.

- Tropic hormones stimulate the target endocrine tissues to secrete the hormones they synthesize.

- The hypothalamus produces at least six releasing factors or hormones.

FUNCTIONS OF THE HYPOTHALAMIC HORMONES

1. **Thyrotropin-releasing hormone (TRH):** It is a tripeptide consisting of glutamate derivative (pyroglutamate), histidine and proline.

   TRH stimulates anterior pituitary to release thyroid stimulating hormone (TSH or thyrotropin), which in turn, stimulates the release of thyroid hormones (T_3 and T_4).

2. **Corticotropin-releasing hormone (CRH):** It stimulates anterior pituitary to release adrenocorticotropic hormone (ACTH), which in turn, acts on adrenal cortex to liberate adrenocorticosteroids.

   CRH contains 41 amino Acids.

3. **Gonadotropin-releasing hormone (GnRH):** It is a decapeptide, and it stimulates anterior pituitary to release gonadotropins, namely luteinizing hormone (LH) and follicle stimulating hormone (FSH).

4. **Growth hormone-releasing hormone (GRH):** It has 44 amino acids, and it stimulates the release of growth hormone (GH or somatotropin), which promotes growth.

5. **Growth hormone release-inhibiting hormone (GRIH):** It contains 14 amino acids, and is also known as somatostatin.

   GRIH inhibits the release of growth hormone from the anterior pituitary.

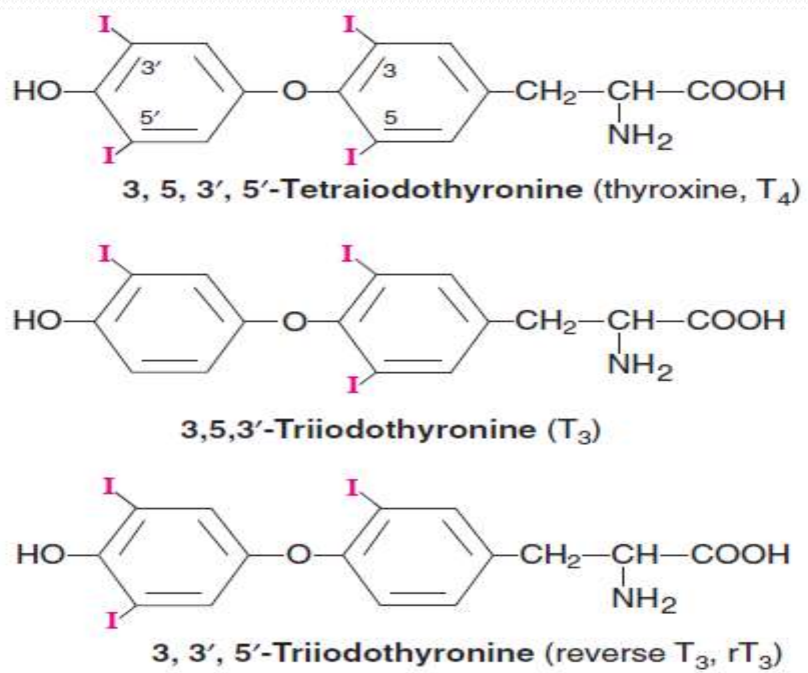
6. **Prolactin release-inhibiting hormone (PRIH):** It is believed to be a dopamine and/or a small peptide that inhibits the release of prolactin (PRL) from anterior pituitary.

THYROID HORMONES

- Thyroid hormones are hormones produced by the thyroid gland.

- The thyroid gland produces two principal hormones—thyroxine (T_4; 3,5,3',5'-tetraiodothyronine) and 3,5,3'-triiodothyronine (T_3)—which regulate the metabolic rate of the body.

- It also secretes calcitonin, a hormone concerned with calcium homeostasis.



Structures of thyroid hormones

Functions of Thyroid Hormones

- Thyroid hormones increase basal metabolic rate (i.e. basal metabolism).
- They regulate protein synthesis.
- They promote carbohydrate metabolism.
- They enhance the utilization of lipids.
- They maintain water and electrolyte balance.

DISORDERS OF THYROID FUNCTION

- The thyroid gland is the most susceptible endocrine gland for hypo- or hyperfunction.

- There are three known abnormalities associated with thyroid functions:

1. Goiter: It refers to any abnormal increase in the size of the thyroid gland.

Enlargement of the thyroid gland is mostly to compensate the decreased synthesis of thyroid hormones and is associated with elevated TSH.

Goiter is primarily due to a failure in the autoregulation of T_3 and T_4 synthesis, which may be caused by deficiency or excess of iodide.

- **Goitrogenic substances (goitrogens):** These are the substances that interfere with the production of thyroid hormones.

- These include thiocyanates, nitrates and perchlorates and the drugs such as thiourea, thiouracil, thiocarbamide etc.

- Certain plant foods—cabbage, cauliflower and turnip—contain goitrogenic factors (mostly thiocyanates).

- **Simple endemic goiter:** This is due to iodine deficiency in the diet.

- It is mostly found in the geographical regions away from sea coast where the water and soil are low in iodine content.

- Consumption of iodized salt is advocated to overcome the problem of endemic goiter.

- In certain cases, administration of thyroid hormone is also employed.

2. Hyperthyroidism: This is also known as thyrotoxicosis and is associated with overproduction of thyroid hormones.

Hyperthyroidism is characterized by increased metabolic rate (higher BMR), nervousness, irritability, anxiety, rapid heart rate, loss of weight despite increased appetite, weakness, diarrhea, sweating, sensitivity to heat and often protrusion of eyeballs (exopthalmos).

Hyperthyroidism is caused by **Grave's disease** (particularly in the developed countries) or due to increased intake of thyroid hormones.

Grave's disease is due to elevated thyroid stimulating IgG also known as long acting thyroid stimulator (LATS) which activates TSH and, thereby, increases thyroid hormonal production.

Thyrotoxicosis is diagnosed by scanning and/or estimation of T_3, T_4 (both elevated) and TSH (decreased) in plasma.

The treatment includes administration of antithyroid drugs, and in severe cases, thyroid gland is surgically removed.

3. Hypothyroidism: This is due to an impairment in the function of thyroid gland that often causes decreased circulatory levels of T_3 and T_4.

Disorders of pituitary or hypothalamus also contribute to hypothyroidism, and women are more susceptible than men.

Hypothyroidism is characterized by reduced BMR, slow heart rate, weight gain, sluggish behaviour, constipation, sensitivity to cold, dry skin etc.

Hypothyroidism in children is associated with physical and mental retardation, collectively known as cretinism.

Hypothyroidism in adult causes myxoedema, characterized by bagginess under the eyes, puffiness of face, slowness in physical and mental activities.

Thyroid hormonal administration is employed to treat hypothyroidism.

Sex Hormones, Adrenal Hormones, Catecholamines and Hormones of the GIT

SEX HORMONES

- Sex hormones are synthesized by the gonads (testes in males, ovaries in females), and are responsible for growth, development, maintenance and regulation of the reproductive system.

- They are also essentially required for the development of germ cells.

- Sex hormones are categorized into three groups:

1. **Androgens** or male sex hormones, which are C-19 steroids.

2. **Estrogens** or female sex hormones, which are C-18 steroids.

3. **Progesterone**, which is a C-21 steroid produced during the luteal phase of menstrual cycle and also during pregnancy.

ANDROGENS

- Androgens or male sex hormones are produced by the Leydig cells of the testes, and to a minor extent, by the adrenal glands in both sexes.

- The ovaries also produce small amounts of androgens.

- **Cholesterol** is the precursor for the synthesis of androgens.

- It is first converted to **pregnenolone** which then forms **androstenedione** by two pathways, either through **progesterone** or through **17-hydroxypregnenolone**.

- **Testosterone** is produced from **androstenedione**.

- The production of androgens is under the control of LH and FSH.

- Active form of androgen : The primary product of the testes is testosterone.

- However, the active hormone in many tissues is not testosterone but its metabolite **dihydrotestosterone** (DHT).

- Testosterone, on reduction by the enzyme 5 α-reductase, forms DHT.

- This conversion mostly occurs in the peripheral tissues.

- Some researchers/authors consider testosterone as a prohormone and dihydrotestosterone, the more potent form, as the hormone.

FUNCTIONS OF ANDROGENS

1. **Sex-related physiological functions:** Androgens, primarily DHT and testosterone, influence:

- Growth, development and maintenance of male reproductive organs.
- Sexual differentiation and secondary sexual characteristics.
- Spermatogenesis.
- Male pattern of aggressive behavior.

2. **Biochemical functions:** Androgens are anabolic in nature, and many specific biochemical effects of androgens that ultimately influence the physiological functions stated above have been identified.

- **Effects on protein metabolism:** Androgens promote RNA synthesis (transcription) and protein synthesis (translation), and they also cause positive nitrogen balance and increase muscle mass.

- **Effects on carbohydrate and fat metabolisms:** Androgens increase glycolysis fatty acid synthesis and citric acid cycle.

- **Effects on mineral metabolism:** Androgens promote mineral deposition and bone growth before the closure of epiphyseal cartilage.

ESTROGENS

- Estrogens are predominantly ovarian hormones, synthesized by the follicles and corpus luteum of ovary.

- These hormones are responsible for maintenance of menstrual cycle and reproductive process in women.

- Estrogen synthesis occurs from the precursor cholesterol, and they are produced by aromatization (formation of aromatic ring) of androgens.

- The ovary produces estradiol (E_2) and estrone (E_1) while the placenta synthesizes these two steroid hormones and estriol (E_3).

- The synthesis of estrogens is under the control of LH and FSH.

FUNCTIONS OF ESTROGENS

1. **Sex-related physiological functions:** Estrogens are primarily concerned with:

- Growth, development and maintenance of female reproductive organs.

- Maintenance of menstrual cycles.

- Development of female sexual characteristics.

2. **Biochemical functions:** Estrogens are involved in many metabolic functions:

- **Lipogenic effect:** Estrogens increase lipogenesis in adipose tissue, and for this reason, women have relatively more fat (about 5%) than men.

- **Hypocholesterolemic effect:** Estrogens lower the plasma total cholesterol.

  The LDL fraction of lipoproteins is decreased while the HDL fraction is increased.

  This explains the low incidence of atherosclerosis and coronary heart diseases in the women during reproductive age.

- **Anabolic effect:** Estrogens in general promote transcription and translation.

  The synthesis of many proteins in liver is elevated e.g. transferrin, ceruloplasmin.

- **Effect on bone growth:** Estrogens like androgens promote calcification and bone growth.

  It is believed that decalcification of bone in the postmenopausal women leading to osteoporosis is due to lack of estrogens.

- **Effect on transhydrogenase:** Transhydrogenase is an enzyme activated by estrogen.

  It is capable of transferring reducing equivalents from NADPH to NAD^+.

  The NADH so formed can be oxidized.

  It is explained that in the women after menopause, due to deficiency of estrogens, the transhydrogenase activity is low.

  This results in the diversion of NADPH towards lipogenesis—causing obesity.

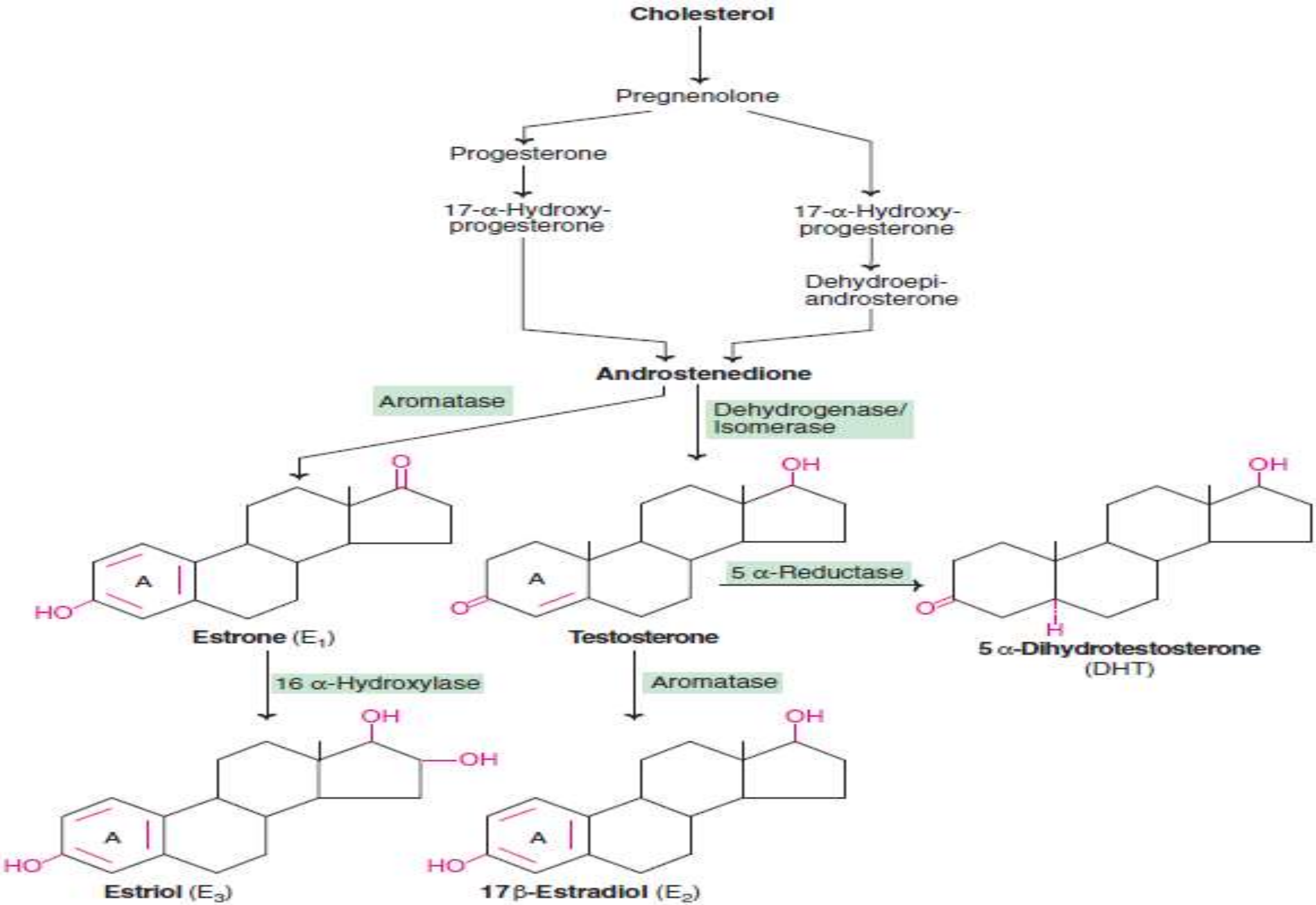
PROGESTERONE

- Progesterone is synthesized and secreted by corpus luteum and placenta.
- As such, progesterone is an intermediate in the formation of steroid hormones from cholesterol.
- Luteinizing hormone (LH) controls the production of progesterone.

Functions of progesterone

1. Progesterone is essentially required for the implantation of fertilized ovum and maintenance of pregnancy.
2. It promotes the growth of glandular tissue in uterus and mammary gland.
3. Progesterone increases the body temperature by 0.5–1.5 F°.

The exact mechanism of this thermogenic effect is not clearly known, but the measurement of temperature is used as an indicator for ovulation.



Biosynthesis of steroid sex hormones from cholesterol

Source: Satyanarayana and Chakrapani, 2013

ASSIGNMENT

Write on the following:

- Menstrual cycle
- Menopause
- Dopamine and Parkinson’s disease
- APUD cells

ADRENAL HORMONES

- The adrenal glands are two small organs (each weighing about 10g), located above the kidneys.

- Each adrenal consists of two distinct tissues—an outer cortex (with 3 zones) and inner medulla.

- As many as 50 steroid hormones (namely adrenocorticosteroids), produced by **adrenal cortex**, have been identified.

- However, only a few of them possess biological activity.

- **Adrenocorticosteroids** are classified into three groups according to their dominant biological action.

- However, there is some overlap in their functions.

1. Glucocorticoids: These are 21-carbon steroids, produced mostly by zona fasciculata.

- They affect glucose (hence the name), amino acid and fat metabolism in a manner that is opposite to the action of insulin.

- Cortisol (also known as hydrocortisone) is the most important glucocorticoid in humans.

- Corticosterone is predominantly found in rats.

2. Mineralocorticoids: These are also 21-carbon containing steroids produced by zona glomerulosa.

- They regulate water and electrolyte balance.

- **Aldosterone** is the most prominent mineralocorticoid.

3. Androgens and estrogens: The innermost adrenal cortex zona reticularis produces small quantities of androgens (19-carbon) and estrogens (18-carbon).

- These hormones affecting sexual development and functions are mostly produced by gonads.

- **Dehydroepiandrosterone**, a precursor for androgens, is synthesized in the adrenal cortex.

SYNTHESIS OF ADRENOCORTICOSTEROIDS

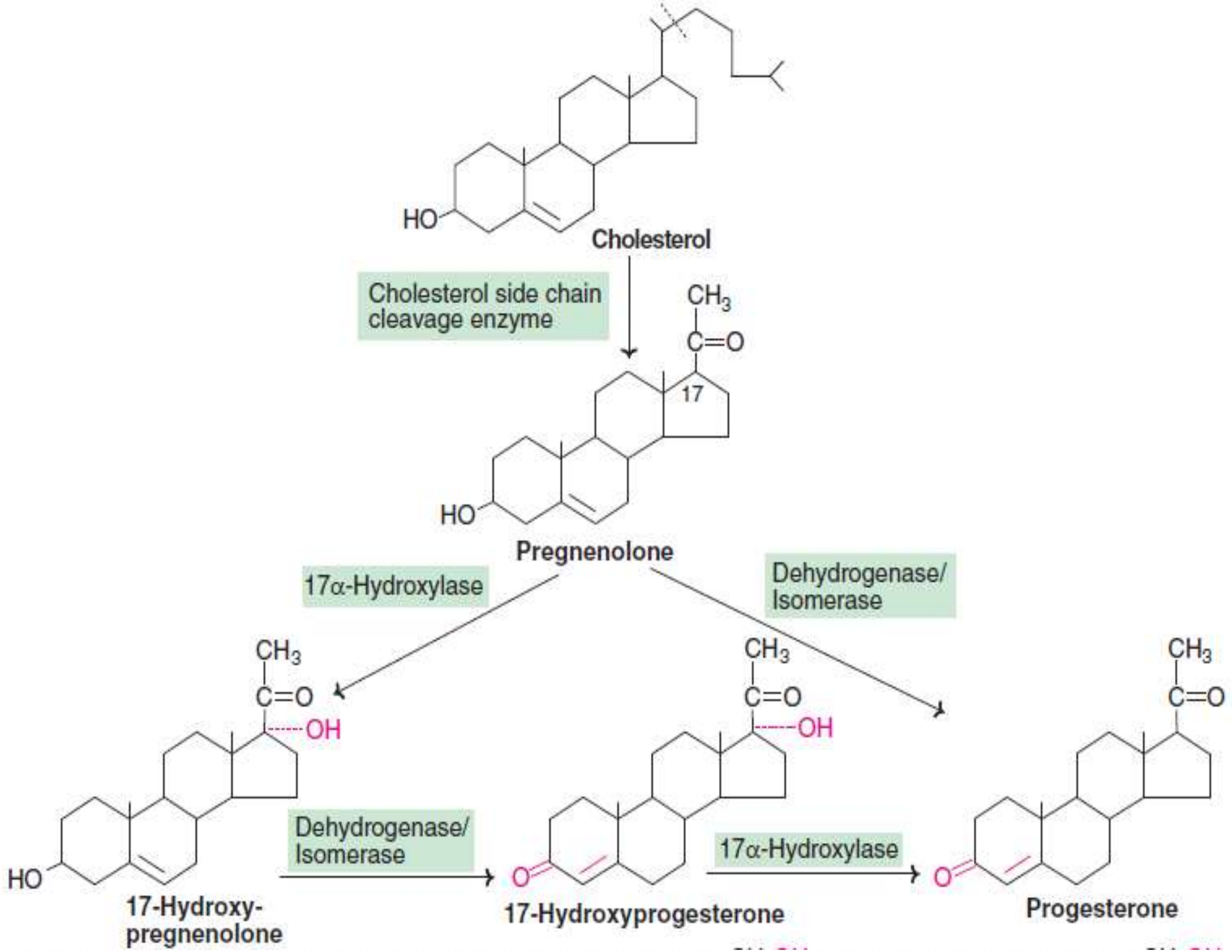
- Cholesterol undergoes cleavage with an elimination of a 6-carbon fragment to form pregnenolone.

- ***Pregnenolone is the common precursor for the synthesis of all steroid hormones***.

- Conversion of cholesterol to pregnenolone is catalysed by cytochrome P_{450} side chain cleavage enzyme.

- This reaction is promoted by ACTH.

- The enzymes hydroxylases, dehydrogenases/isomerases and lyases, which are associated with mitochondria or endoplasmic reticulum, are responsible for the synthesis of steroid hormones.



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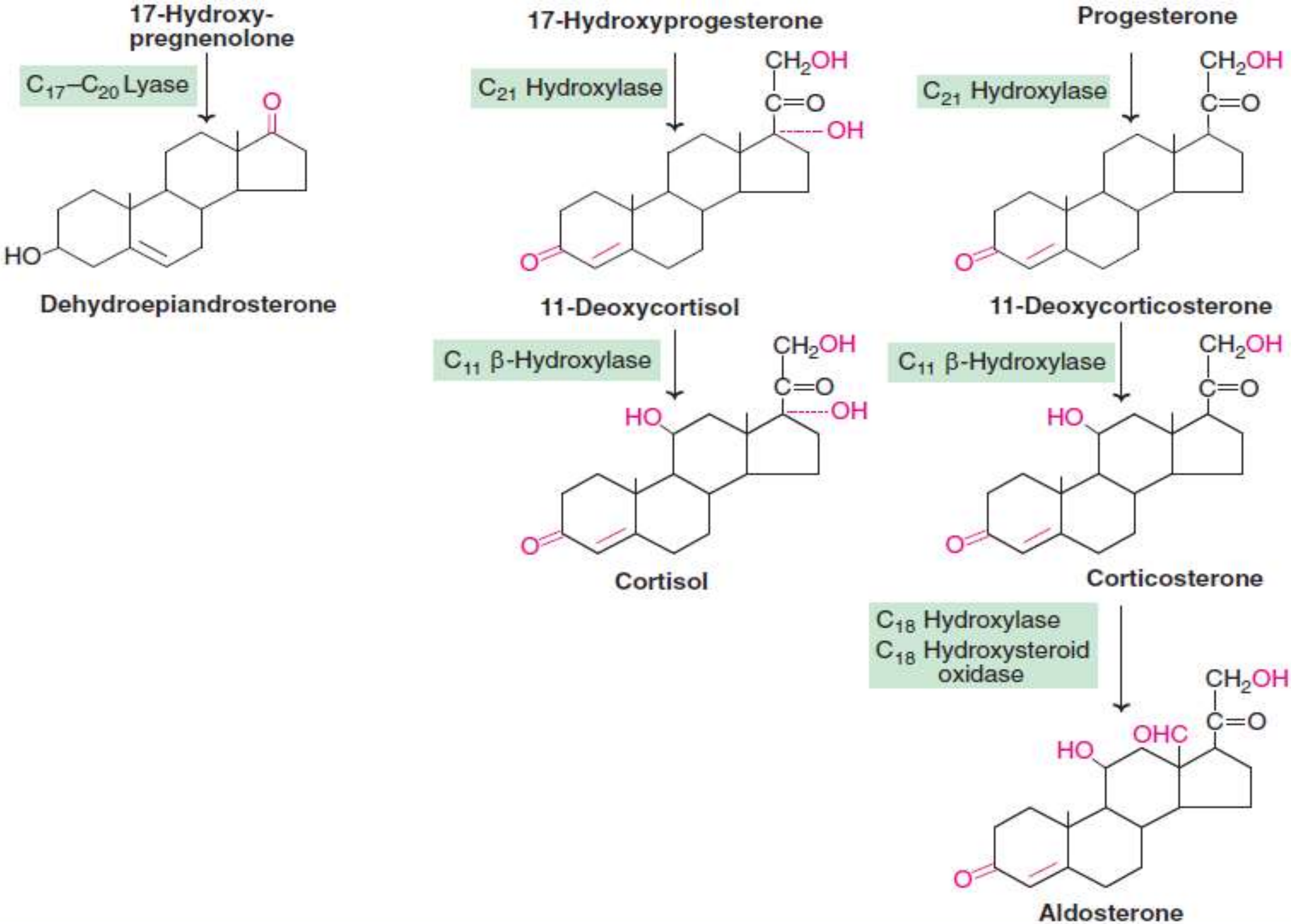


Biosynthesis of major adrenocorticosteroids

Source: Satyanarayana and Chakrapani, 2013

FUNCTIONS OF ADRENOCORTICOSTEROIDS

1. **Glucocorticoid hormones:** The important glucocorticoids are cortisol, cortisone and corticosterone, and they bring about several biochemical functions in the body.

a). **Effects on carbohydrate metabolism:** Glucocorticoids promote the synthesis of glucose (gluconeogenesis).

This is brought about by increasing the substrates (particularly amino acids) and enhancing the synthesis of phosphoenolpyruvate carboxykinase, the rate limiting enzyme in gluconeogenesis.

The overall influence of glucocorticoids on carbohydrate metabolism is to increase blood glucose concentration.

The biological actions of glucocorticoids generally oppose that of insulin.

b). Effects on lipid metabolism: Glucocorticoids increase the circulating free fatty acids.

This is caused by two mechanisms:

i. Increased breakdown of storage triacylglycerol (lipolysis) in adipose tissue.

ii. Reduced utilization of plasma free fatty acids for the synthesis of triacylglycerols.

c). Effects on protein and nucleic acid metabolism: Glucocortiocoids exhibit both catabolic and anabolic effects on protein and nucleic acid metabolism.

They promote transcription (RNA synthesis) and protein biosynthesis in liver.

These anabolic effects of glucocorticoids are caused by the stimulation of specific genes.

Glucocorticoids (particularly at high concentration) cause catabolic effects in extrahepatic tissues (e.g. muscle, adipose tissue, bone etc.).

This results in enhanced degradation of proteins.

d). Effects on water and electrolyte metabolism: The influence of glucocorticoids on water metabolism is mediated through antidiuretic hormone (ADH).

Deficiency of glucocorticoids causes increased production of ADH.

ADH decreases glomerular filtration rate causing water retention in the body.

e). Effects on the immune system: Glucocorticoids (particularly cortisol), in high doses, suppress the host immune response.

The steroid hormones act at different levels—damaging lymphocytes, impairment of antibody synthesis, suppression of inflammatory response etc.

f). Other physiological effects of glucocorticoids: Glucocorticoids are involved in several physiological functions.

i. Stimulate the fight and flight response (to face sudden emergencies) of catecholamines.

ii. Increase the production of gastric HCl and pepsinogen.

iii. Inhibit the bone formation, hence the subjects are at a risk for osteoporosis.

2. **Mineralocorticoid hormones:** The most active and potent mineralocorticoid is aldosterone.

It promotes Na^+ reabsorption at the distal convoluted tubules of kidney.

Na^+ retention is accompanied by corresponding excretion of K^+, H^+ and NH_4^+ ions.

Regulation of aldosterone synthesis: The production of aldosterone is regulated by different mechanisms, which include reninangiotensin, potassium, sodium and ACTH.

MECHANISM OF ACTION OF ADRENOCORTICOSTEROIDS

- Glucocorticoids bind to specific receptors on the target cells and bring about the action.

- These hormones mostly act at the transcription level and control the protein synthesis.

- Aldosterone acts like other steroid hormones.

- It binds with specific receptors on the target tissue and promotes transcription and translation.

METABOLISM OF ADRENOCORTICOSTEROIDS

- The steroid hormones are metabolized in the liver and excreted in urine as conjugates of glucuronides or sulfates.

- The urine contains mainly two steroids (17-hydroxysteroids and 17-ketosteroids) derived from the metabolism of glucocorticoids and mineralocorticoids.

- Androgens synthesized by gonads also contribute to the formation of 17-ketosteroids.

- Urinary 17-ketosteroids estimated in the laboratory are expressed in terms of dehydroepiandrosterone and their normal excretion is in the range of 0.2–2.0 mg/day.

ABNORMALITIES OF ADRENOCORTICAL FUNCTION

- **Addison's disease:** Impairment in adrenocortical function results in Addison's disease.

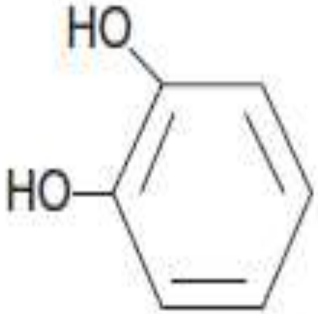
- This disorder is characterized by decreased blood glucose level (hypoglycemia), loss of weight, loss of appetite (anorexia), muscle weakness, impaired cardiac function, low blood pressure, decreased Na^+ and increased K^+ level in serum, increased susceptibility to stress etc.

- **Cushing's syndrome:** Hyperfunction of adrenal cortex may be due to long term pharmacological use of steroids or tumor of adrenal cortex or tumor of pituitary.

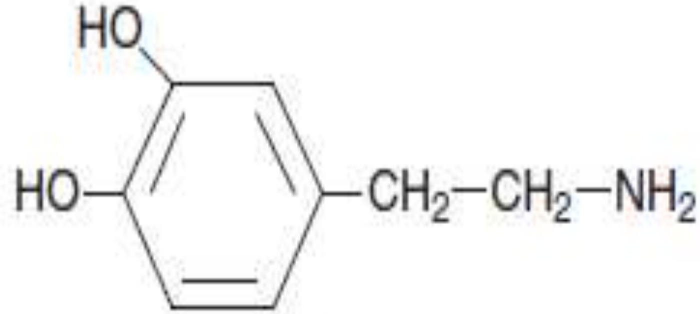
- Cushing's syndrome is characterized by hyperglycemia (due to increased gluconeogenesis), fatigue, muscle wasting, edema, osteoporosis, negative nitrogen balance, hypertension, moon-face etc.

CATECHOLAMINES

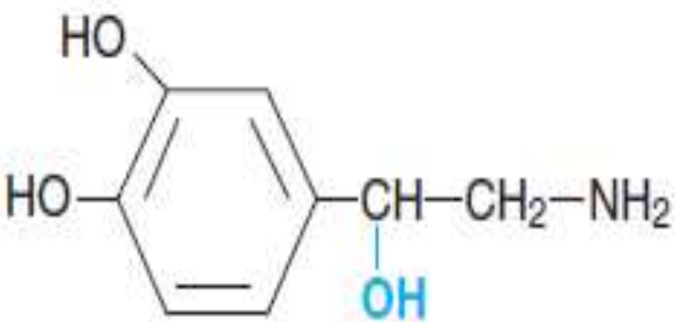
- The arenal medulla is an extension of sympathetic nervous system.
- It produces two important hormones: epinephrine (formerly adrenaline) and norepinephrine (formerly noradrenaline).
- Both these hormones are **catecholamines** since they are amine derivatives of catechol nucleus (dihydroxylated phenyl ring).
- Epinephrine is a methyl derivative of norepinephrine.
- Dopamine is another catecholamine, produced as an intermediate during the synthesis of epinephrine.
- Norepinephrine and dopamine are important neurotransmitters in the brain and autonomic nervous system.



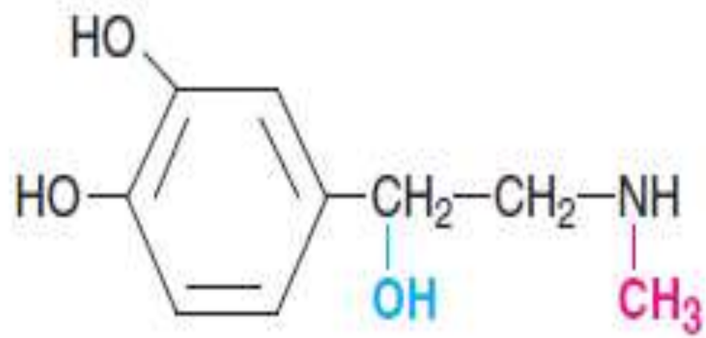
Catechol



Dopamine



Norepinephrine



Epinephrine

CATECHOLAMINES

SYNTHESIS OF CATECHOLAMINES

- The amino acid tyrosine is the precursor for the synthesis of catecholamines.

- Catecholamines are produced in response to fight, fright and flight, which include emergencies like shock, cold, fatigue, emotional conditions like anger etc.

- The name catechol refers to the ***dihydroxylated phenyl ring***.

- The amine derivatives of catechol are called catecholamines.

- Tyrosine is the precursor for the synthesis of catecholamines, namely dopamine, norepinephrine (noradrenaline) and epinephrine (adrenaline).

- The conversion of tyrosine to catecholamines occurs in adrenal medulla and central nervous system through the following reactions.

- Tyrosine is hydroxylated to 3,4-dihydroxyphenylalanine (DOPA) by **tyrosine hydroxylase**.

- This enzyme catalyzes the rate limiting reaction and requires tetrahydrobiopterin as coenzyme (like phenylalanine hydroxylase).

- In contrast to this enzyme, tyrosinase present in melanocytes converts tyrosine to DOPA.

- Hence, two different enzyme systems exist to convert tyrosine to DOPA.

- DOPA undergoes PLP-dependent decarboxylation to give dopamine, which in turn, is hydroxylated to produce norepinephrine.

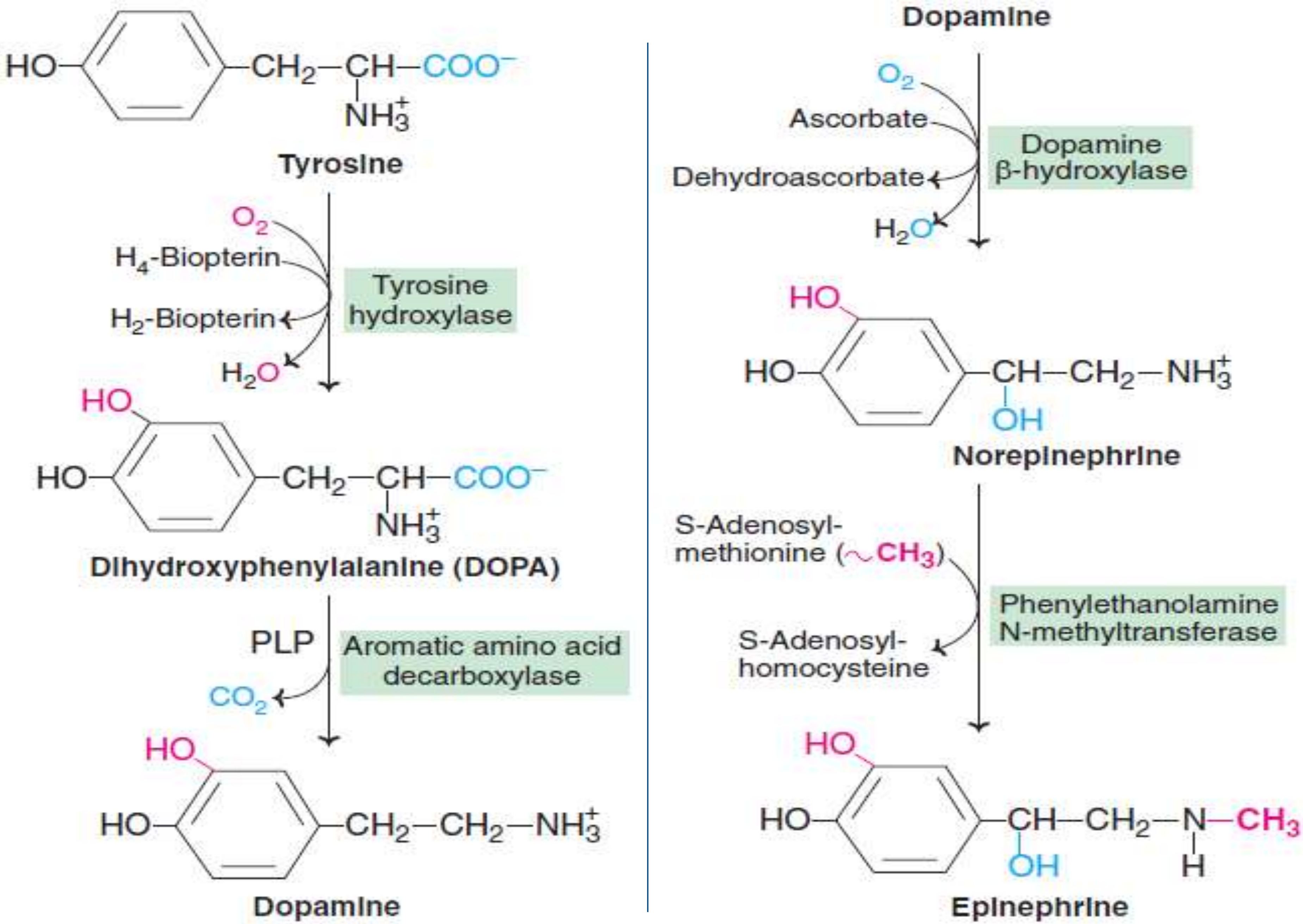
- Methylation of norepinephrine by S-adenosylmethionine gives epinephrine.

- The difference between epinephrine and norepinephrine is only a methyl group (remember that norepinephrine has no methyl group).

- There exists tissue specificity in the formation of catecholamines.

- In adrenal medulla, synthesis of the hormones, norepinephrine and epinephrine is prominent.

- Norepinephrine is produced in certain areas of the brain while dopamine is predominantly synthesized in substantia nigra and coeruleus of brain.



SYNTHESIS OF CATECHOLAMINES

FUNCTIONS OF CATECHOLAMINES

- Catecholamines cause diversified biochemical effects on the body.

- The ultimate goal of their action is to mobilize energy resources and prepare the individuals to meet emergencies (e.g. shock, cold, low blood glucose etc.).

1. **Effects on carbohydrate metabolism:** Epinephrine and norepinephrine in general increase glycogenolysis, gluconeogenesis and decrease glycogenesis.

   The overall effect of catecholamines is to elevate blood glucose levels and make it available for the brain and other tissues to meet the emergencies.

2. **Effects on lipid metabolism:** Both epinephrine and norepinephrine enhance the breakdown of triacylglycerols (lipolysis) in adipose tissue.

This causes increase in the free fatty acids in the circulation, which are effectively utilized by the heart and muscle as fuel source.

The metabolic effects of catecholamines are mostly related to the increase in adenylate cyclase activity causing elevation in cyclic AMP levels.

3. **Effects on physiological functions:** In general, catecholamines (most predominantly epinephrine) increase cardiac output, blood pressure and oxygen consumption.

They cause smooth muscle relaxation in bronchi, gastrointestinal tract and the blood vessels supplying skeletal muscle.

On the other hand, catecholamines stimulate smooth muscle contraction of the blood vessels supplying skin and kidney.

Platelet aggregation is inhibited by catecholamines.

METABOLISM OF CATECHOLAMINES

- Catecholamines are rapidly inactivated and metabolized.

- The enzymes catechol-O methyltransferase (COMT) and monoamine oxidase (MAO), found in many tissues act on catecholamines.

- The metabolic products metanephrine and vanillylmandelic acid (VMA) are excreted in urine.

ABNORMALITIES OF CATECHOLAMINE PRODUCTION

- **Pheochromocytomas** are the tumors of adrenal medulla.

- The diagnosis of pheochromocytoma is possible only when there is an excessive production of epinephrine and norepinephrine that causes severe hypertension.

- In individuals affected by this disorder, the ratio of norepinephrine to epinephrine is increased.

- The measurement of urinary VMA (normal <8 mg/day) is helpful in the diagnosis of pheochromocytomas.

HORMONES OF THE GIT

- Digestion and absorption of nutrients is regulated by the autonomic nervous system in association with peptide hormones of the gastrointestinal tract (GIT) or gut.

- The specialized cells lining the GIT are responsible for the production of GIT hormones.

- Hence, GIT may be considered as the largest mass of cells that secrete hormones.

- A large number of GIT hormones have been identified.

- However, only four GIT hormones have been well characterized.

- The uncharacterized hormones are often known as ***candidate hormones***.

CLASSIFICATION OF GIT HORMONES

- GIT hormones show certain structural relations and may be considered under two families:

i. **Gastrin family:** Some of the C-terminal amino acids are identical.

This family includes gastrin and cholecystokinin (CCK).

ii **Secretin family:** Secretin, gastric inhibitory peptide (GIP) and glucagon are structurally related, hence may be considered under this family.

GASTRIN

- Gastrin is a hormone that contains 17 amino acids, and is produced by gastric mucosa.
- It stimulates the secretion of gastric HCl and pepsinogen (proenzyme of pepsin).
- The release of gastrin is stimulated by vagus nerve of the stomach and partially digested proteins.
- HCl and certain other hormones inhibit gastrin release.

SECRETIN

- Secretin is a 27-amino acid-containing polypeptide, which resembles glucagon in many ways.

- Secretin is synthesized by the mucosa of the upper small intestine.

- It is released in response to the presence of HCl in chyme in the duodenum which is passed on from the stomach.

- Secretin stimulates pancreatic cells to produce bicarbonate (HCO_3^-) in order to neutralize HCl.

CHOLECYSTOKININ (CCK)

- CCK contains 33 amino acids and is produced by the upper part of small intestine.
- The secretion of CCK is stimulated by the products of protein and lipid digestion, namely peptides, amino acids, mono or diacylglycerols, fatty acids and glycerol.
- Cholecystokinin stimulates the contraction of gall bladder and increases the flow of bile into duodenum.
- It also promotes the secretion of digestive enzymes and HCO_3 from pancreas.

GASTRIC INHIBITORY PEPTIDE (GIP)

- GIP contains 43 amino acids and is produced by duodenal mucosa.

- The release of GIP is stimulated by the presence of glucose in the gut.

- The most important function of GIP is to stimulate the release of insulin from pancreas.

- This is evident from the fact that the plasma insulin level is elevated much before the increase in blood glucose.

- GIP also inhibits gastric HCl secretion, gastric motility and its emptying.

MECHANISM OF ACTION OF GIT HORMONES

- Many of the GIT hormones have receptor sites specific for their action.

- At least two distinct mechanisms have been identified through which these hormones act.

1. Production of cAMP through the activation of adenylate cyclase e.g. secretin, VIP etc.

2. Stimulation of intracellular Ca^{2+} usually mediated through the metabolism of phosphatidylinositol e.g. gastrin , CCK.

Both these mechanisms ultimately influence the enzyme secretions/other biological effects.

BIOCHEMISTRY OF NERVE IMPULSE TRANSMISSION, NEUROTRANSMITTERS, ENDOCRINE INTEGRATION VERSUS NEURAL INTEGRATION

Nerve Impulse

- A **nerve impulse**, also called **action potential**, is an electrical charge that travels along the membrane of a neuron.

- It can be generated when a neuron's membrane potential is changed by chemical signals from a nearby cell.

- The cell membrane potential changes quickly from negative to positive as sodium ions flow into the cell through ion channels, while potassium ions flow out of the cell.

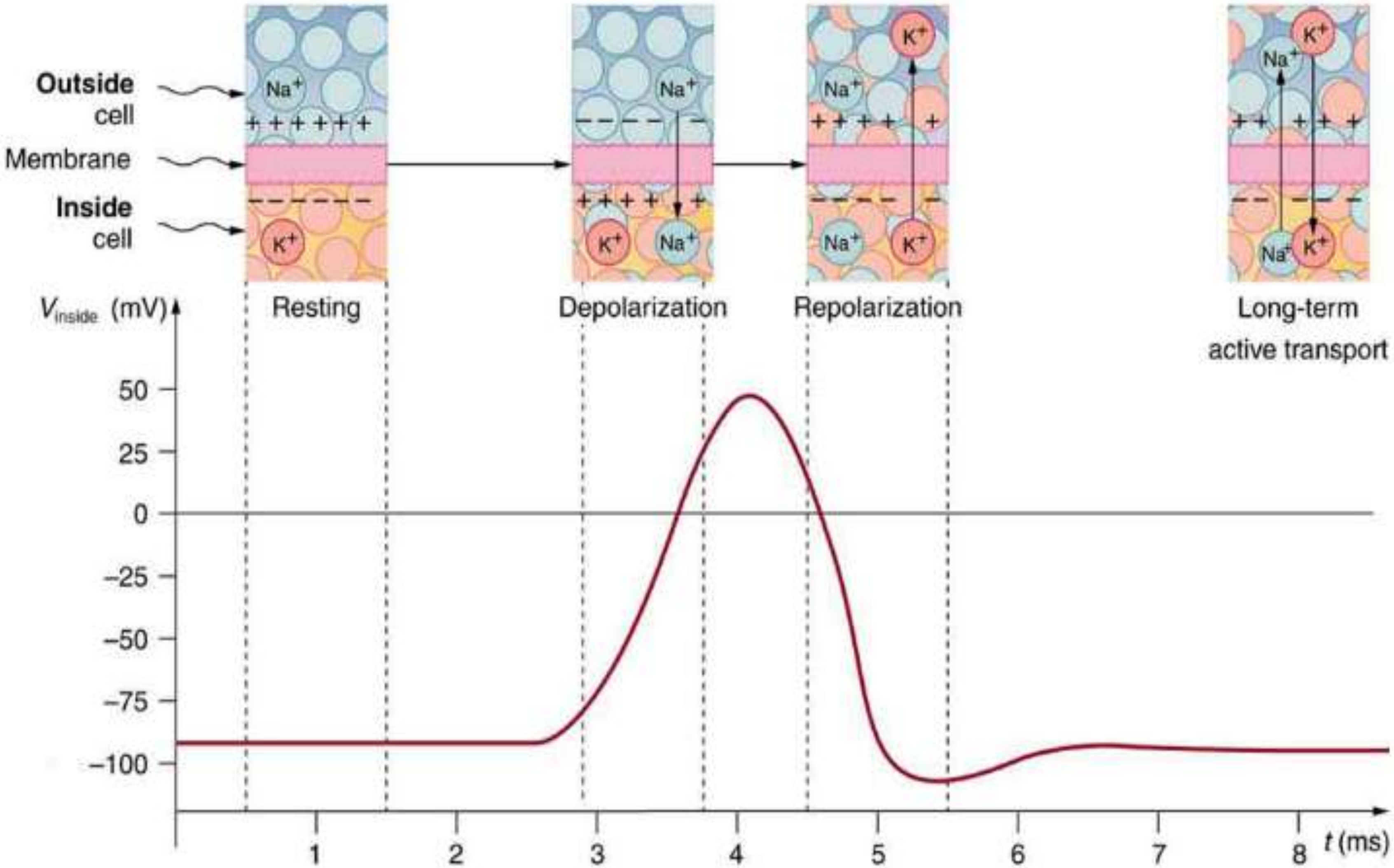
- The sodium-potassium pump is a mechanism of active transport that moves sodium ions out of cells and potassium ions into cells.

- The pump moves both ions from areas of lower to higher concentration, using energy (ATP) and carrier proteins in the cell membrane.

- Sodium is the principal ion in the fluid outside of cells, and potassium is the principal ion in the fluid inside of cells.

- These differences in concentration create an electrical gradient across the cell membrane, called ***resting potential***.

- Tightly controlling membrane resting potential is critical for the transmission of nerve impulses.



AN ACTION POTENTIAL (NERVE IMPULSE)

MECHANISM OF NERVE IMPULSE GENERATION

- The change in membrane potential results in the cell becoming depolarized.

- The membrane potential has to reach a certain level of ***depolarization***, called the ***threshold***, otherwise, an action potential will not start.

- This threshold potential varies but is generally about 15 millivolts (mV) more positive than the cell's resting membrane potential.

- If a membrane depolarization does not reach the threshold level, an action potential will not happen.

- Hence, a neuron must reach a certain threshold in order to begin the depolarization step of reaching the action potential.

- The first channels to open are the sodium ion channels, which allow sodium ions to enter the cell.

- The resulting increase in positive charge inside the cell (up to about +40 mV) starts the action potential – this is called the ***depolarization of the membrane***.

- Potassium ion channels then open, allowing potassium ions to flow out of the cell, which ends the action potential.

- The inside of the membrane becomes negative again – this is called ***repolarization of the membrane***.

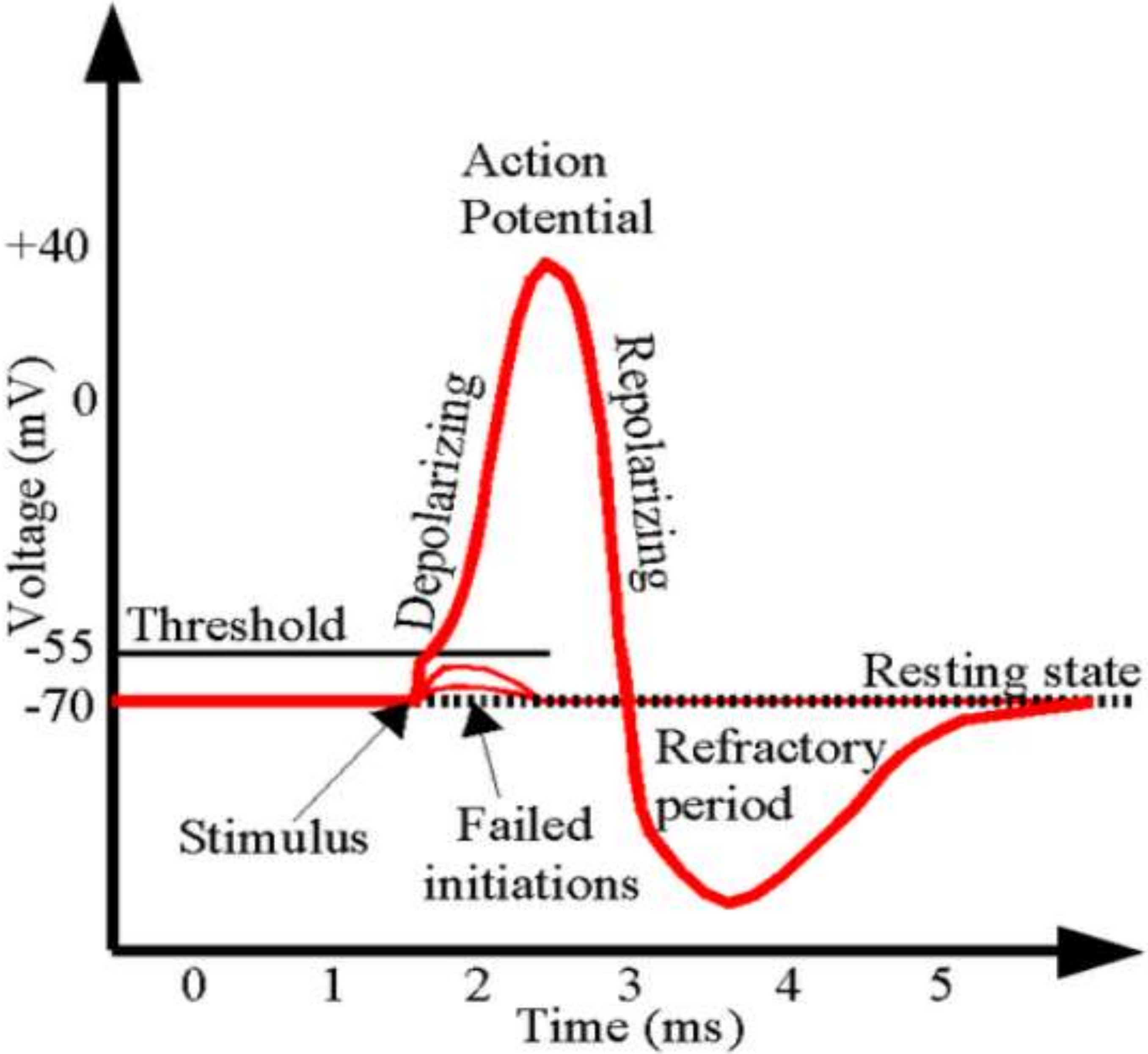
- Both of the ion channels then close, and the sodium-potassium pump restores the resting potential of -70 mV.

- The action potential will move down the axon toward the synapse like a wave would move along the surface of water.

- The figure below shows the change in potential of the axon membrane during an action potential.

- The nerve goes through a brief refractory period before reaching resting potential.

- During the refractory period, another action potential cannot be generated.



AN ACTION POTENTIAL GRAPH OF MEMBRANE POTENTIAL OVER TIME

Nerve Impulse Transmission

- The transmission of a nerve impulse to another cell occurs at the ***synapse***.

- A synapse is a place where an axon terminal meets another cell.

- The cell that sends the nerve impulse is called the ***presynaptic cell***, and the cell that receives the nerve impulse is called the ***postsynaptic cell***.

- Some synapses are purely ***electrical*** and make direct electrical connections between neurons.

- However, most synapses are ***chemical*** synapses.

- The transmission of nerve impulses across chemical synapses is more complex.

- At a chemical synapse, both the presynaptic and postsynaptic areas of the cells are full of the molecular machinery that is involved in the transmission of nerve impulses.

- The presynaptic area contains many tiny spherical vessels called ***synaptic vesicles*** that are packed with chemicals called ***neurotransmitters***.

- When an action potential reaches the axon terminal of the presynaptic cell, it opens channels that allow calcium to enter the terminal.

- Calcium causes synaptic vesicles to fuse with the membrane, releasing their contents into the narrow space between the presynaptic and postsynaptic membranes.

- This area is called the ***synaptic cleft***.

- The neurotransmitter molecules travel across the synaptic cleft and bind to receptors, which are proteins that are embedded in the membrane of the postsynaptic cell.

- The effect of a neurotransmitter on a postsynaptic cell depends mainly on the type of receptors that it activates, making it possible for a particular neurotransmitter to have different effects on various target cells.

- A neurotransmitter might excite one set of target cells, inhibit others, and have complex modulatory effects on others, depending on the type of receptors.

- However, some neurotransmitters have relatively consistent effects on other cells.

NEUROTRANSMITTERS

- A neurotransmitter is a signaling chemical molecule secreted by a neuron to affect another cell across a synapse.

- The cell receiving the signal, or target cell, may be another neuron, but could also be a gland or muscle cell.

- Neurotransmitters are released from synaptic vesicles into the synaptic cleft where they are able to interact with neurotransmitter receptors on the target cell.

- Neurotransmitters attach themselves to receptor molecules on the membrane of the synapse's target cell (or cells), and thereby alter the electrical or chemical properties of the receptor molecules.

- The neurotransmitter's effect on the target cell is determined by the receptor it binds to.

- Neurotransmitters are essential to the function of complex neural systems.

- Many neurotransmitters are synthesized from simple and plentiful precursors such as amino acids, which are readily available and often require a small number of biosynthetic steps for conversion.

- The exact number of unique neurotransmitters in humans is unknown, but more than 100 have been identified.

- Common neurotransmitters include glutamate, GABA, acetylcholine, glycine and norepinephrine etc.

- The two neurotransmitters that are most widely found in the vertebrate brain are glutamate and gamma-aminobutyric acid (GABA).

- The great majority of psychoactive drugs exert their effects by altering specific neurotransmitter systems.

- Some of these drugs include cannabinoids, nicotine, heroin, cocaine, alcohol, fluoxetine, chlorpromazine.

TYPES OF NEUROTRANSMITTERS

- **Amino acids:** glutamate, aspartate, D-serine, gamma-aminobutyric acid (GABA), and glycine.

- **Gasotransmitters:** nitric oxide (NO), carbon monoxide (CO), and hydrogen sulfide (H_2S).

- **Monoamines:**
  - **catecholamines:** dopamine, norepinephrine (noradrenaline), and epinephrine (adrenaline).
  - **indolamines:** serotonin (5-HT, SER), and melatonin.
  - **histamine**

- **Trace amines:** phenethylamine, N-methylphenethylamine, tyramine, 3-iodothyronamine, octopamine, tryptamine, etc.

- **Peptides:** oxytocin, somatostatin, substance P, and opioid peptides.

- **Purines:** adenosine triphosphate (ATP), and adenosine.

- **Others:** acetylcholine (ACh), anandamide, etc.

FUNCTIONS OF NEUROTRANSMITTERS

- **Glutamate:** exerts excitatory effects on target neurons.

  Excessive glutamate release can overstimulate the brain and lead to excitotoxicity causing cell death resulting in seizures or strokes.

  Excitotoxicity has been implicated in certain chronic diseases including ischemic stroke, epilepsy, amyotrophic lateral sclerosis, Alzheimer's disease, Huntington disease, and Parkinson's disease.

- **GABA:** exerts inhibitory effects on synapses in virtually every part of the brain.

  Many sedative/tranquilizing drugs act by enhancing the effects of GABA.

- **Acetylcholine:** it activates skeletal muscles in the somatic nervous system and may either excite or inhibit internal organs in the autonomic system.

  It is distinguished as the transmitter at the neuromuscular junction connecting motor nerves to muscles.

- **Dopamine:** regulates motor behavior, pleasures related to motivation and also emotional arousal.

  It plays a critical role in the reward system.

  Parkinson's disease has been linked to low levels of dopamine and schizophrenia has been linked to high levels of dopamine.

- **Serotonin:** regulates appetite, sleep, memory and learning, temperature, mood, behaviour, muscle contraction, and function of the cardiovascular system and endocrine system.

- **Norepinephrine:** stimulates the release of the stress hormone epinephrine (i.e. adrenaline) from the adrenal glands.

- **Epinephrine:** plays a role in the fight-or-flight response, and has vasoconstrictive effects, which promote increased heart rate, blood pressure, energy mobilization.

ENDOCRINE INTEGRATION VERSUS NEURAL INTEGRATION

- There exist an integration between the nervous system and the endocrine system, a process known as **neuroendocrine integration**.
- Neuroendocrine cells are cells that receive neuronal input (through neurotransmitters), and as a consequence of this input, release messenger molecules (hormones) into the blood.
- An example of a neuroendocrine cell is a cell of the adrenal medulla (innermost part of the adrenal gland), which releases adrenaline to the blood.
- The adrenal medullary cells are controlled by the sympathetic division of the autonomic nervous system.
- These cells are modified postganglionic neurons.

- Autonomic nerve fibers lead directly to them from the central nervous system.

- The adrenal medullary hormones are kept in vesicles much in the same way neurotransmitters are kept in neuronal vesicles.

- The hormonal effects can last up to ten times longer than those of neurotransmitters.

- Sympathetic nerve fiber impulses stimulate the release of adrenal medullary hormones.

- In this way the sympathetic division of the autonomic nervous system and the medullary secretions function together.

- The major center of neuroendocrine integration in the body is found in the hypothalamus and the pituitary gland.

- The hypothalamic neurosecretory cells release factors to the blood.

- Some of these factors (releasing hormones), released at the hypothalamic median eminence, control the secretion of pituitary hormones, while others (the hormones oxytocin and vasopressin) are released directly into the blood.

- APUD cells are considered part of the neuroendocrine system, and share many properties with neuroendocrine cells.

APUD CELLS

- APUD cells (DNES cells) constitute a group of apparently unrelated endocrine cells, which were named by the scientist A.G.E. Pearse, who developed the APUD concept in the 1960s.

- These cells share the common function of secreting a low molecular weight polypeptide hormone.

- There are several different types which secrete the hormones secretin, cholecystokinin and several others.

- The name is derived from an acronym, referring to the following:

Amine **P**recursor **U**ptake – for high uptake of amine precursors including 5-hydroxytryptophan (5-HTP) and dihydroxyphenylalanine (DOPA).

Decarboxylase – for high content of the enzyme amino acid decarboxylase (for conversion of precursors to amines).

Cells in APUD System

1. Adenohypophysis
2. Neurons of Hypothalamus
3. Chief Cells of Parathyroid
4. Adrenal Medullary Cells
5. Glomus cells in Carotid Body
6. Melanocytes of Skin
7. Cells of Pineal Gland
8. Renin producing cells in the kidney

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