Al muthanna University **Pharmacy college**
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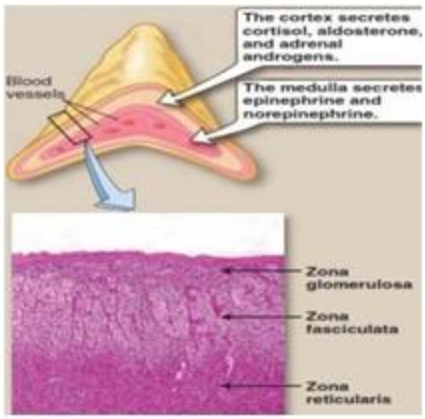
HYPOTHALAMIC–PITUITARY–ADRENAL AXIS



Adrenal gland: Stress, salt, and sex are responsibilities for this set of glands located just above each kidney. Each gland can be divided into two main sections:

A- The cortex (90% of gland weight) is further divided into the zona glomerulosa, zona fasciculata, and zona reticularis.

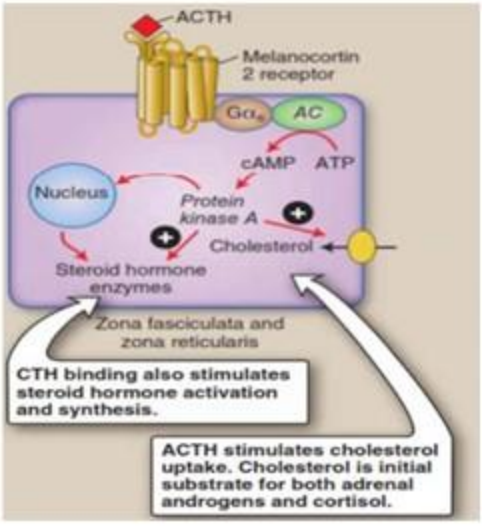
The adrenal cortex is controlled and regulated by:

1- Axis control is directed primarily at the zona fasciculata and reticularis.

2- The zona glomerulosa is regulated primarily by other hormones angiotensin II and ions K^+.

B- The medulla (10%) regulated by the sympathetic nervous system

Hypothalamus: Corticotropin-releasing hormone (CRH) is synthesized and released into hypophyseal portal circulation for carriage to the anterior pituitary. A number of higher brain centers stimulate CRH release during physical, biochemical (e.g., low blood glucose), and emotional stress. CRH release follows a circadian rhythm, peaking just before waking and then pulsing throughout the day. The paraventricular nucleus also produces antidiuretic hormone (ADH), which can further regulate CRH release and stimulate corticotropes.



Pituitary gland: CRH binds to corticotropin-releasing hormone receptor (CRH-R1), pituitary gland production adrenocorticotropic hormone (ACTH), which is released into the bloodstream. ACTH's target is the adrenal cortex.

Adrenal cortex:

Adrenocortical hormone (i.e., aldosterone, cortisol, Dehydroepiandrosterone, and androstenedione) synthesis begins with cholesterol. There are a number of common enzymes and intermediates in the synthesis of cortex hormones. The activation or

inhibition or even the presence of one enzyme but not another can preferentially shunt the production to cortisol rather than an adrenal androgen, or vice versa.

I. ALDOSTERONE

Other name mineralocorticoid because effect of aldosterone on ions (minerals), is synthesized in the zona glomerulosa, which have facilitates the final step in the conversion of cholesterol into aldosterone. Once released into the circulation, aldosterone binds with low affinity to corticosteroid-binding protein and albumin.

Function

a- increases Na and water reabsorption as well as K secretion from renal tubules.

b- Aldosterone also increases Na reabsorption by intestinal enterocytes.

c- increases the body's Na stores.

Secretion regulation

Aldosterone synthase is the gatekeeper of aldosterone production and is regulated by:

a- plasma K levels.

b- Ang-II, a hormone within the renin–angiotensin–aldosterone system, is stimulated by low circulating fluid volume, low pressure in the glomerulus, and increases in SNS activity.

c- An increase in ACTH, which is vital for regulation of other renal cortex hormones, must be present but is less of a stimulator for the final step in aldosterone synthesis.

II. Androgens

The adrenal androgens (Dehydroepiandrosterone and androstenedione). Adrenal androgens are synthesized and secreted primarily by the zona reticularis and lesser extent, by the zona fasciculata. In the blood, DHEA and androstenedione bind with low affinity to albumin and other blood globulins.

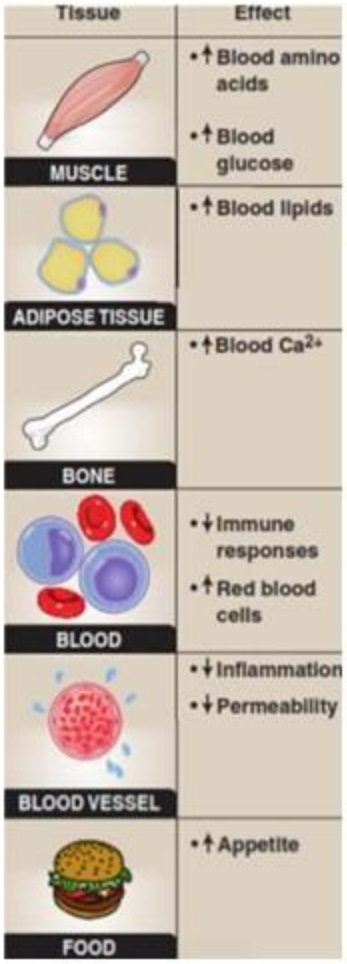
Function

DHEA and androstenedione are less potent than androgens produced by the gonads but do have functional effects on secondary sex characteristics and are involved in development during childhood and adolescence. DHEA can be converted into androstenedione, which can then be converted to more potent androgens, such as testosterone and estrogens, in peripheral tissues.

Secretion regulation

DHEA, and androstenedione are controlled by the negative feedback loops of CRH and ACTH.The input rhythms associated with growth and development during puberty and across the lifespan affect ACTH production and release.

III. Cortisol and corticosterone:



are synthesized and secreted primarily by the zona fasciculata and, lesser by the zona reticularis. In the blood, cortisol binds corticosteroid-binding protein with a high affinity.

Function

Cortisol and corticosterone prepare the body for stress. Cortisol diffuses across the cell membrane and binds to a cytosolic glucocorticoid receptor. Cortisol also binds with low affinity to mineralocorticoid receptors and, thus, induces some minor collateral aldosterone-like responses. Cortisol causes a number of physiologic effects:

1. **Metabolic:** increases plasma glucose is part of the origin of the glucocorticoid classification of cortisol, and free fatty acid concentration in order to provide energy substrates to body tissues for their response to the stressful event.

a. Increased catabolism: Cortisol increases skeletal muscle protein catabolism, liberating amino acids that are then converted to glucose via gluconeogenesis in the liver.

b. Increased lipolysis: stimulates white adipose tissue to undergo lipolysis to liberate free fatty acids and triglycerides. The fatty acids and triglycerides are then transported in the blood for use as an energy source by other tissues.

c. Increased intake: stimulates appetite. Acutely, this is beneficial to provide energy substrates to respond to the stressful event. However, if the stressful event does not involve physical work, then this increased appetite can lead to weight gain.

2. Immune: Cortisol suppresses both immune responses and inflammation.

a- The mechanisms by which this immunosuppression is accomplished are via decreased production of lymphocytes and interleukins 1 and 6 (IL-1 and IL-6) and T-cell suppression.

b- The antiinflammatory effects of cortisol are due to decreases in capillary permeability as well as reductions in both prostaglandin and leukotriene synthesis that mediate increases in local blood flow.

3. Musculoskeletal:

a- increases bone resorption and decreases Ca_2 absorption from the GI tract and reabsorption from the kidney. Chronic high levels of cortisol can lead to osteoporosis.

b- decreases collagen formation throughout the body.

c- Protein catabolism to increase plasma glucose levels can eventually lead to muscle weakness and early fatigue onset during physical activity.

4. Cardiovascular:

a- increases erythropoietin release, which stimulates red blood cell production.

b- potentiates vasoconstrictor responses by blocking local vasodilators, such as nitric oxide and prostaglandins, and through glucocorticoid receptors in vascular smooth muscle by altering Ca_2 homeostasis within these cells.

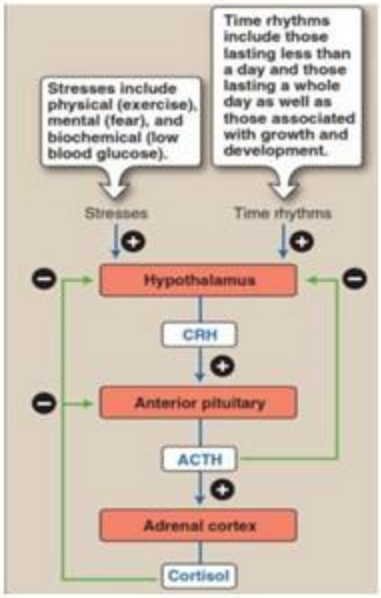
c- Glucocorticoids increase the effectiveness of catecholamine actions, such as inotropy and vasoconstriction, through the upregulation of adrenergic receptors.

Secretion Regulation:

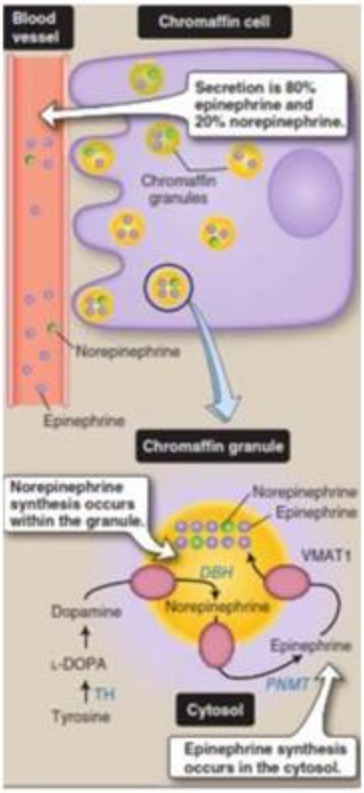
Cortisol and corticosterone release are controlled by the negative feedback loops of CRH and ACTH. Hypothalamic–Pituitary–Adrenal Axis, activated by physical, emotional, and biochemical stress stimulate the release of CRH, ACTH, and cortisol. The control of CRH is primarily for regulation of cortisol and less so for adrenal androgens or aldosterone.

IV. CATECHOLAMINES

The adrenal medulla is derived from the neural crest, this means that the medulla functions as an extension of the SNS. The medulla is composed of small clusters of chromaffin cells (medullary cells), which synthesize catecholamines from the amino acid tyrosine. Dopamine is synthesized in the cytosol, and transports it into secretion vesicles. Dopamine is then converted to norepinephrine via dopamine-hydroxylase. Unlike postganglionic adrenergic nerves of the SNS, chromaffin cells contain phenylethanolamine N methyltransferase. This enzyme is located in the cytosol and facilitates the conversion of norepinephrine to epinephrine. Therefore, norepinephrine must be transported back into the cytosol to be converted to epinephrine, which is in turn transported back into the secretion vesicle. Epinephrine and norepinephrine are then stored with chromogranin (binding protein) in preparation for vesicle exocytosis and hormonal release. Chromaffin cells secrete norepinephrine and epinephrine in an approximate 1:4 ratio into the fenestrated medullary capillary network for delivery to various body tissues.



Function: produces classic fight-or-flight responses, or the "adrenaline rush." Thus, the key actions of epinephrine and norepinephrine are similar to those of the SNS. Delivery via the circulation means that responses to hormones, although typically slower, are wider ranging because they can reach receptor populations that are not specifically located within a SNS synaptic cleft. The functional effects are related to the amount secreted and the tissue responsiveness.

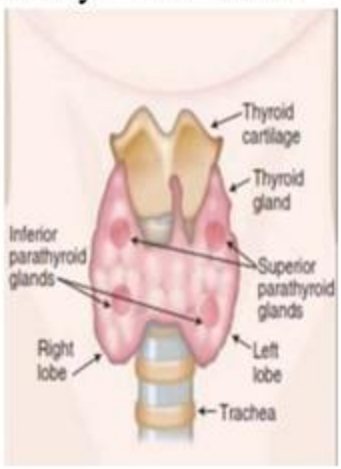


Secretion regulation

Catecholamine release is regulated by the SNS rather than the hypothalamic–pituitary–adrenal axis. Thus, secretion is increased during stresses to homeostasis; strong emotions, such as anger and fear; and exercise, membrane receptors can be internalized, thereby reducing responsiveness to subsequent catecholamine stimulation. Conversely, tissue catecholamine responses may be increased by cortisol and triiodothyronine (for example), by increased receptor synthesis or increased receptor trafficking to the cell membrane.

HYPOTHALAMIC–PITUITARY–THYROID AXIS:

The thyroid gland is located in the neck just below the larynx and is regulated by a multitiered endocrine axis involving the hypothalamus and pituitary. The active hormones of the hypothalamic–pituitary–thyroid axis are triiodothyronine (T3) and thyroxine (T4).



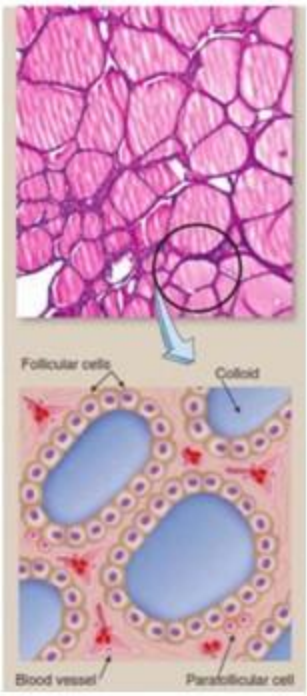
Hypothalamus: secrete thyroid-releasing hormone (TRH) and somatostatin into the hypophyseal portal circulation. Both hormones target thyrotropes in the pituitary gland.

Pituitary gland

TRH binds to thyrotrope TRH receptors. TRH receptor occupancy stimulates TSH synthesis and release from secretory granules. In contrast, somatostatin decreases TSH production and release. Neurons within hypothalamic nuclei that initiate TSH release also express TSH receptors, which provide a negative feedback pathway by which high circulating TSH levels can inhibit further release.

Thyroid gland

TSH regulates the thyroid gland, which is an assemblage of numerous, hollow spheres (follicles) filled with a protein-rich fluid matrix known as colloid. Follicles are the site of thyroid hormone and secretion. Parafollicular C cells, which synthesize calcitonin, are randomly distributed between follicles throughout the gland. The TSH receptor is a GPCR that stimulates formation when occupied.



TSH increases the

1. Follicles: Follicular epithelial cells synthesize and secrete thyroid hormones when stimulated by TSH. TSH also increases expression of cellular components needed for thyroid hormone synthesis.
2. Colloid: The oxidative chemistry involved in thyroid hormone synthesis can be very harmful to cells, so it is performed extracellularly within colloid. This is a similar concept to walling off hydrogen peroxide reactions within cytosolic peroxisomes. production of colloid.

Thyroid Hormones

The thyroid gland produces and secretes T_3 and T_4 in a ratio of 1:10. T_4 has a relatively low biologic activity. Conversion of T_4 to T_3 occurs primarily in target tissues. The thyroid hormones target virtually all cells in the body and exert their effects via cytosolic receptors that modulate gene expression.

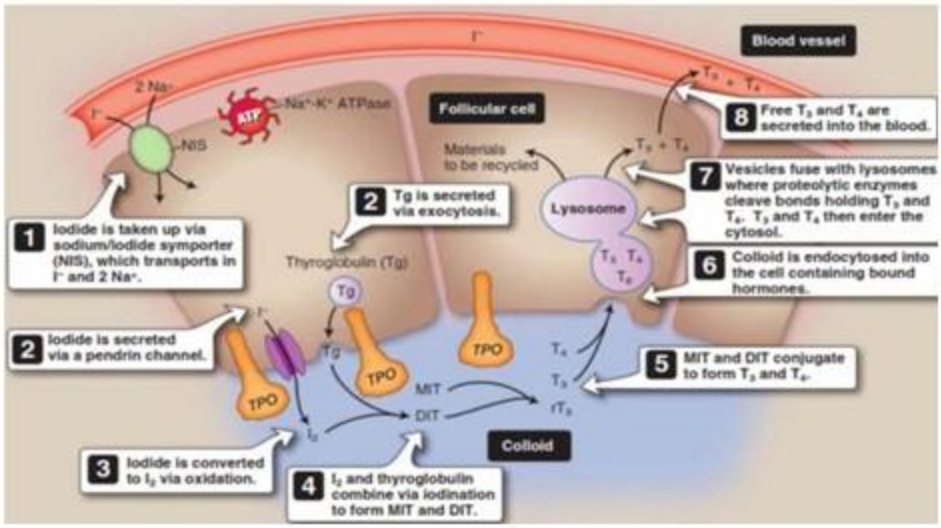
Synthesis

Thyroid hormone synthesis and secretion is a multistep process involving eight sequential steps:

1. Iodide uptake (also called I trapping): from the vasculature by follicular cells I is transported across the basolateral membrane from blood by a Na-I cotransporter (or, sodium/iodide symporter [NIS]), powered by the Na gradient established by the basolateral Na-K ATPase.
2. Apical secretion: I^- is then transported across the apical membrane primarily by a specialized Cl-I cotransporter known as a pendrin channel, when this channel is defective, such as in Pendred syndrome, the patient presents with low circulating thyroid hormones. Thyroglobulin is synthesized in the follicular cells and is exocytosed across the apical membrane into the colloid.
3. Oxidation: The thyroglobulin-laden secretory vesicles express thyroid peroxidase (TPO), a heme-containing enzyme, on their inner surfaces. When the vesicles fuse with the apical membrane, TPO is presented to the colloid lumen and immediately catalyzes

an oxidation reaction in which iodide is combined with H_2O_2 to form iodine (I_2) and H_2O.

4. Iodination: TPO also facilitates iodination (or organification) of thyroglobulin tyrosine residues to form monoiodotyrosine (MIT) and diiodotyrosine (DIT).



5. Conjugation: MIT and DIT combine to form T_3 and reverse T_3 (rT_3), whereas two DIT residues combine to form T_4. The hormones remain attached to thyroglobulin until internalized by the follicular cells.

6. Endocytosis: The iodinated and conjugated thyroglobulin is then endocytosed back into follicular cells, initiated by megalin receptors. TSH regulates megalin receptor expression and, thereby, indirectly controls the amount of colloid endocytosed.

7. Proteolysis: The endocytosed vesicle containing colloid then fuses with a lysosome, and the iodine-containing molecules are cleaved from thyroglobulin. T3 and T4 are released into the follicular cytosol near the basolateral membrane, and the remaining molecules and colloid material are recycled.

8. Secretion: The final step is secretion of T3 and T4 from the follicular cell into the blood. Cytosolic thyroid hormones diffuse through the basolateral cell membrane to the interstitial space, where they enter the capillary network and blood vessels of the highly vascularized thyroid gland.

Transport and regulation Approximately 99% of the T3 and T4 released into the circulation binds to thyroid hormone-binding globulin and, to a lesser degree, albumin and transthyretin. Binding increases the half-life to as long. Both free (unbound) T3 and T4 participate in negative feedback control at the level of the hypothalamus and thyrotropes. In addition, thyroid hormones also increase somatostatin, which further decreases TSH release from thyrotropes.

Function: Effects T4 and T3 diffuse across the target cell membrane, and T4 is converted to T3 by 5- deiodinase. T3 then binds to a nuclear thyroid receptor, that complexes with a retinoid X receptor (RXR). This receptor complex then binds to the

thyroid-response element of DNA, through both the addition of a coactivator and release of a corepressor, begins transcription. Proteins synthesized mediate a wide range of cellular responses, including:

1. Growth and development: of nervous tissue and bone are dependent on thyroid axis hormone synthesis and release. In nervous tissue, T3 and T4 which development of stretch reflexes. In bone, thyroid hormone increases ossification and linear growth in children and adolescents. Thyroid hormone deficiencies can, thus, result in mental impairments and short stature in children.

2. Macronutrient metabolism: alter the rate of metabolism and also affect energy substrates by:

1- increase both the breakdown of glycogen (glycogenolysis) and the formation of glucose (gluconeogenesis).

2- increase the formation of lipids (lipogenesis) followed by promoting lipolytic enzymes, break down the stored lipids into free fatty acids to be used as an energy substrate. Having a low thyroid axis hormone level has the opposite effect on the breakdown of carbohydrates, proteins, and lipids.

3. Basal metabolic rate: thyroid hormone induces expression of the "always-on" induces expression of the "always-on" pump uses more energy and produces more heat. The opposite occurs if pump expression is reduced by hypothyroid conditions

4. Thyroid hormone and catecholamine synergy: When T3 and T4 and norepinephrine (from the sympathetic nervous system) are released in concert (e.g., during severe cold stress), the physiological functions of both are heightened. Thyroid hormones also upregulate adrenergic receptors, which potentiates these synergistic effects.