The role of DHEA in the quality of life and longevity

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Abstract

The development from a hormonal memory based on the hypothalamic-pituitary-adrenal (HTPA) axis is constituted by a complex set of direct influences and feedback interactions, among the components of an adrenal neuroendocrine system that during human nurturing allows hormonal communication, integrating a newborn with his family. The brain hypothalamus functions to regulate the anterior pituitary to develop hormonal (fully emotional) communication that precedes the stage of language development. A pure emotional language constitutes an unconscious, a barrier to self-cognition on the own personality dynamics. This one could be potentiated by Doppler analysis of vector neuronal emotional childhood association to the adult stage to constitute new psyche connectomes. These ones are accessible to psychoanalytic techniques that focus on the study of the psyche, and treatment by using free association to allow healing. Dehydroepiandrosterone (DHEA), an endogenous corticoid (internally produced), is the most abundant circulating steroid in humans, which is not required as vitamins, which are only available from food. DHEA is a prohormone derived from cholesterol and pregnenolone that is a precursor of mineralcorticoids (aldosterone, etc.), glucocorticoids (cortisol, etc.) and testosterone and estradiol. Usually a clinical treatment to supplement the level of testosterone or estradiol will produce the desired immediate effect, but thereafter reduce the physiological natural production, as expression of a negative feedback. DHEA might prove to have benefits in treating people diagnosed with certain conditions, such as adrenal insufficiency and lupus. Hence, these ones will respond to a physiological regulation through the attractive sexual pathways. Adolescence increases DHEA levels declining by 75-90% by the time humans hit 75-80 years old associated with a loss of function and increased risk for disease. It impacts quality of life and longevity. DHEA has become a popular anti-aging supplement. A 12 years study of old men found that an increase of 100 μg/dL of DHEA-sulfate solution injected in blood showed a 36% reduced risk of death.

Results

The adrenal cortex is the outer region and also the largest part of an adrenal gland. It is divided into three separate zones: zona glomerulosa, zona fasciculata and zona reticularis. Each zone is responsible for producing specific hormones.

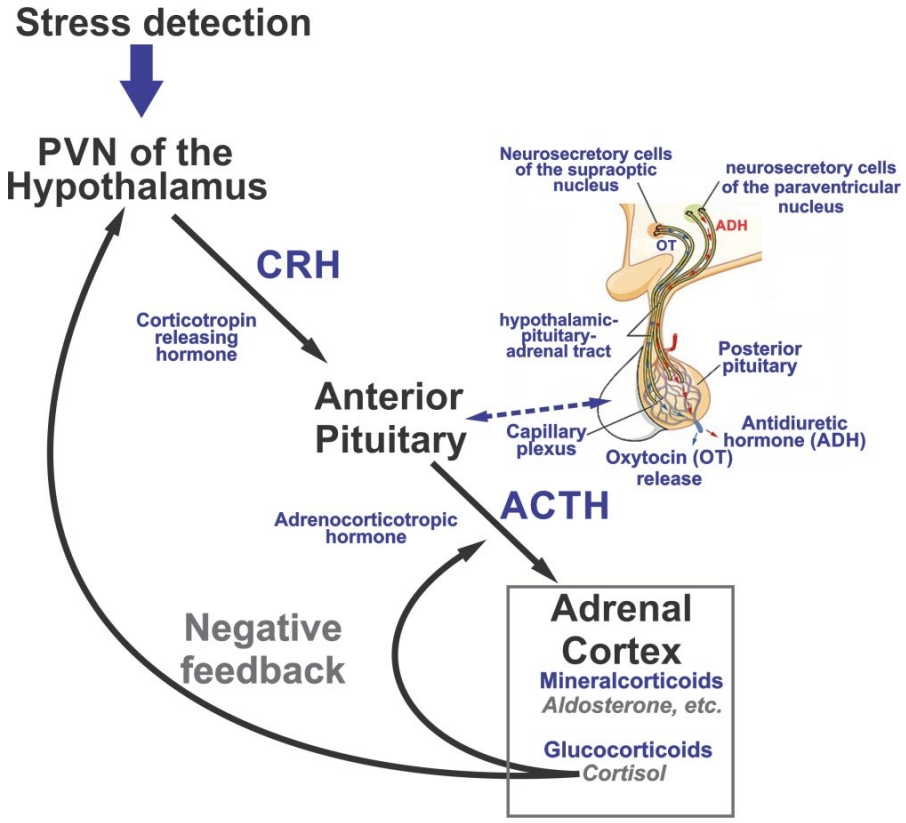

***Figure 1: HPTA axis**: PVN (paraventricular nucleus) of the hypothalamus, corticotropin-releasing hormone (CRH) with direct control of the Anterior Pituitary and negative feedback from cortisol. Anterior control of the adrenal cortex by adrenocorticotropic hormone (ACTH) and is negative feedback. Mineralocorticoids and glucocorticoids are distinguished from and sex steroids by their specific receptors, target cells, and effects. The posterior pituitary hormones are oxytocin, serotonin and antidiuretic hormone (ADH) or Vasopressin, etc.*

The adrenal cortex and adrenal medulla

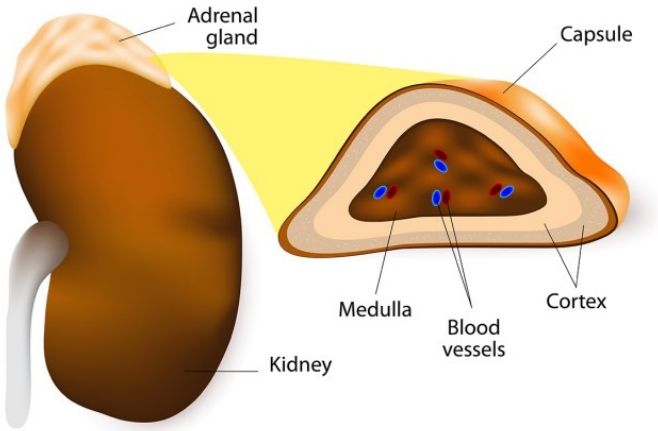

Figure 2: Adrenal gland.

The adrenal cortex and adrenal medulla are enveloped in an adipose capsule that forms a protective layer around an adrenal gland.

The role of the adrenal glands in your body is to release certain hormones directly into the bloodstream. Many of these hormones have to do with how the body responds to stress, and some are vital to existence. Both parts of the adrenal glands — the adrenal cortex and the adrenal medulla — perform distinct and separate functions.

The hypothalamic brain area, below the thalamus, links the pituitary gland for control of adrenals/suprarenal secretion of glucocorticoids and the mineralcorticoids, constituting the hypothalamic-pituitary-adrenal (HPTA) axis.

Adrenal Fatigue (or fibromyalgia) manifests from physical or psychological trauma as a clinical persistence of the adrenals fight-or-flight response.

DHEA might prove to have benefits in treating people diagnosed with certain conditions, such as adrenal insufficiency and lupus.

DHEA

Dehydroepiandrosterone sulfate or androstenolone sulfate (DHEA-S) is an endogenous androstane steroid that is produced by the adrenal cortex. It is the 3β-sulfate ester and a metabolite of DHEA and circulates in far greater relative concentrations than DHEA. The steroid is hormonally inert and is instead an important neurosteroid and neurotrophin.

DHEA is a hormone that your body naturally produces in the adrenal gland. DHEA helps produce other hormones, including testosterone and estrogen. Natural DHEA levels peak in early adulthood and then slowly fall as you age.

DHEA has been found to directly act on several neurotransmitter receptors, including acting as a positive allosteric modulator of the N-methyl-D-aspartate (NMDA) receptor, is a glutamate receptor and ion channel found in neurons, as a negative allosteric modulator of the γ-aminobutyric acid (GABA) $GABA_A$ is an ionotropic receptor and ligand-gated ion channel.

A small study suggested that taking DHEA supplements might improve skin hydration and firmness, and decrease aging spots in elderly adults.

Depression: DHEA might be more effective at treating depression than placebo, especially in people with low DHEA levels.

Osteoporosis: Study findings on the effects of DHEA supplementation in the treatment of osteoporosis are mixed. More research is needed to determine whether taking DHEA supplements improves bone density in older adults with low DHEA.

Vaginal atrophy: Limited research suggests that DHEA might improve vaginal dryness in postmenopausal women.

Research on the effects of DHEA on muscle strength and physical performance in younger adult but leads to The National Collegiate Athletic Association, banned is used among athletes.

DHEA-S originates in women almost exclusively from 95 to 100% secreted by the adrenal cortex.

In the circulation, DHEA is mainly bound to albumin, with a small amount bound to sex hormone-binding globulin (SHBG). The small remainder amount circulates unbound and free.

Approximately 50 to 70% of circulating DHEA originates from desulfation of DHEA-S in peripheral tissues. DHEA easily crosses the blood-brain-barrier (BBB) into the central nervous system.

Prior to puberty in humans, DHEA and DHEA-S levels elevate upon differentiation of the zona reticularis of the adrenal cortex. Peak levels of DHEA and DHEA-S are observed around age 20, which is followed by an age-dependent decline throughout life

eventually back to prepubertal concentrations. Plasma levels of DHEA in adult men are 10 to 25 nM, in premenopausal women are 5 to 30 nM, and in postmenopausal women are 2 to 20 nM. Conversely, DHEA-S levels are an order of magnitude higher at 1–10 μM.

DHEA increases by regular exercise. Also, calorie restriction increase endogenous DHEA and lead to suggest that it the responsible for its expectancy of increasing longevity [1].

The DHEA endogenous production prevents to be denominated as a vitamin is only needed because are exogenous product, which means that not produced by the human body. However, if this production becomes clinical low could be used as a dietary supplement. The decline levels of DHEA and DHEA-S to the lower nanomolar and micromolar ranges in men and women aged 60 to 80 years, beyond that age became undetectable.

Research has suggested that DHEA and/or DHEA-S may in fact be phylogenetically ancient "ancestral" ligands of the neurotrophin receptors from early on in the evolution of the nervous system. The findings that DHEA binds to and potently activates neurotrophin receptors may explain the positive association between decreased circulating DHEA levels with age and age-related neurodegenerative diseases [2].

DHEA is an uncompetitive inhibitor *in vivo* at high concentration of glucose-6-phosphate dehydrogenase (G6PDH) (EC 1.1.1.49) ($K_i = 17\ \mu M$) and reduce nicotinamide adenine dinucleotide phosphate (NADPH)-dependent free radical production.

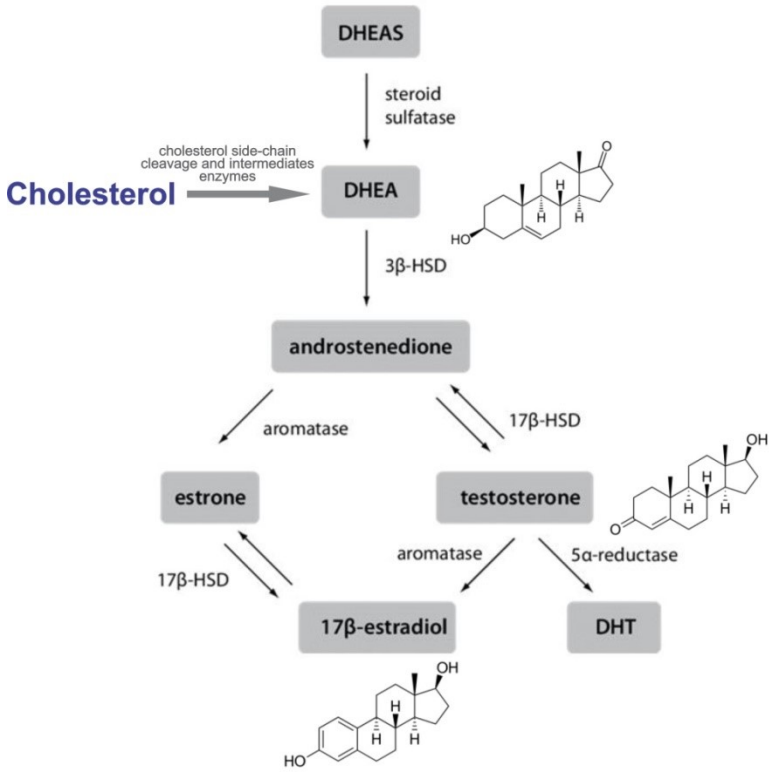

Figure 3: *DHEA* [3] *is produced mostly in the adrenal cortex, zona reticularis, controlled by adrenocorticotropic hormone (ACTH), gonads under the control of gonadotropin-releasing hormone (GnRH) and the brain, with only 10% being secreted from the gonads. All steroid hormones readily diffuse across the cell membrane and thereafter translocated into cellular nucleus. All of the different forms of estrogen are synthesized from androgens, specifically testosterone and androstenedione, by the enzyme aromatase.*

Choroid plexus epithelium

The choroid plexus epithelium (CPE) generates cerebrospinal fluid (CSF) in a mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma 0mV -60mV to hydrophobic-CSF +4mV.

CPE folds into many villi with a brush border of microvilli greatly increase the surface area around each capillary, creating frond-like processes that project into the ventricles and its role in the secretion of the cerebrospinal fluid (CSF), actively transport Na^+ ions, into the ventricles and water follows the resulting osmotic gradient.

Thus, suggests a potential of hydrophilic-plasma to hydrophobic-CSF for the choroid plexus Na^+-GABA transporter in the disposition of GABA in the brain.

Upon opening, the $GABA_A$ receptor on the postsynaptic cell is selectively permeable to chloride ions (Cl^-) and, to a lesser extent, bicarbonate ions (HCO_3^-) [4], determining the contribution of the electrogenic Na^+-HCO_3^- cotransporter NBCe2 to CSF pH regulation.

GABA subtypes have distinct brain regional and subcellular localization, age-dependent expression, and the ability to undergo plastic alterations in response to experience, including drug exposure.

If the membrane potential is higher than the equilibrium potential (also known as the reversal potential) for chloride ions, when the receptor is activated Cl^- will flow into the cell. This causes an inhibitory effect on neurotransmission by diminishing the chance of a successful action potential occurring at the postsynaptic cell. The reversal potential of the GABAA-mediated inhibitory postsynaptic potential (IPSP) in normal solution is −70 mV, contrasting the GABAB IPSP (-100 mV).

Astrocytes are cells with actin filaments for pulsatile propulsion in the cell's skeleton, bi-directional transport of ions gradient Na^+, which impulses the CSF flux into the lumen along a glial network. Luminal K^+ is required for sustained CSF secretion. At ventricular side, the turnover rate of Na^+/K^+-ATPase [5] is about 100 s^{-1}, releases the Na^+ determine a plasma membrane's permeability to specific ions and regulate the cytosolic concentration of ions and the membrane potential, carrying signals from one end of a neuron to the other. In myocytes, rapid opening of Ca^{2+} channels in the sarcoplasmic reticulum releases the Ca^{2+} that triggers muscle contraction.

Quantum mechanics microtubules nano scale (10^{-9}m) flow a parallel transportation from the exterior to the nuclei of glucose, nascent Mg^{2+}, O_2, etc., and antiparallel of dimers. The microtubule diameter allows a very small number of molecules in a minimal volume to reach a saturation state for enzyme activity. The number of random collisions concatenates Na^+/K^+ translocation by space at minimal capacitance to operate at maximal voltage.

In voltage-gated ion channels (oligomeric proteins) are gated in response to some type of cellular event, like an extracellular or intracellular small molecule produce a binding changing by allosteric transition in the protein transmembrane electrical potential (Vm) causes a charged protein domain to move relative to the membrane, opening or closing the channel.

A channel typically opens in about 1.5×10^{-3}s, operating in the nervous system for fast signal transmission, with 10^4 ions/1ms moving through a single ion channel.

The choroid plexus (CPE) generates CSF functions in the mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma to hydrophobic-CSF flow. Cl^- and HCO_3^- influx is recycled across the membrane. At ventricular side, the

Na^+/K^+-ATPase releases the Na^+. The K^+-Cl^--cotransporter (KCC4) secretes Cl^- into the lumen containing CSF. Luminal K^+ is required for sustained CSF secretion.

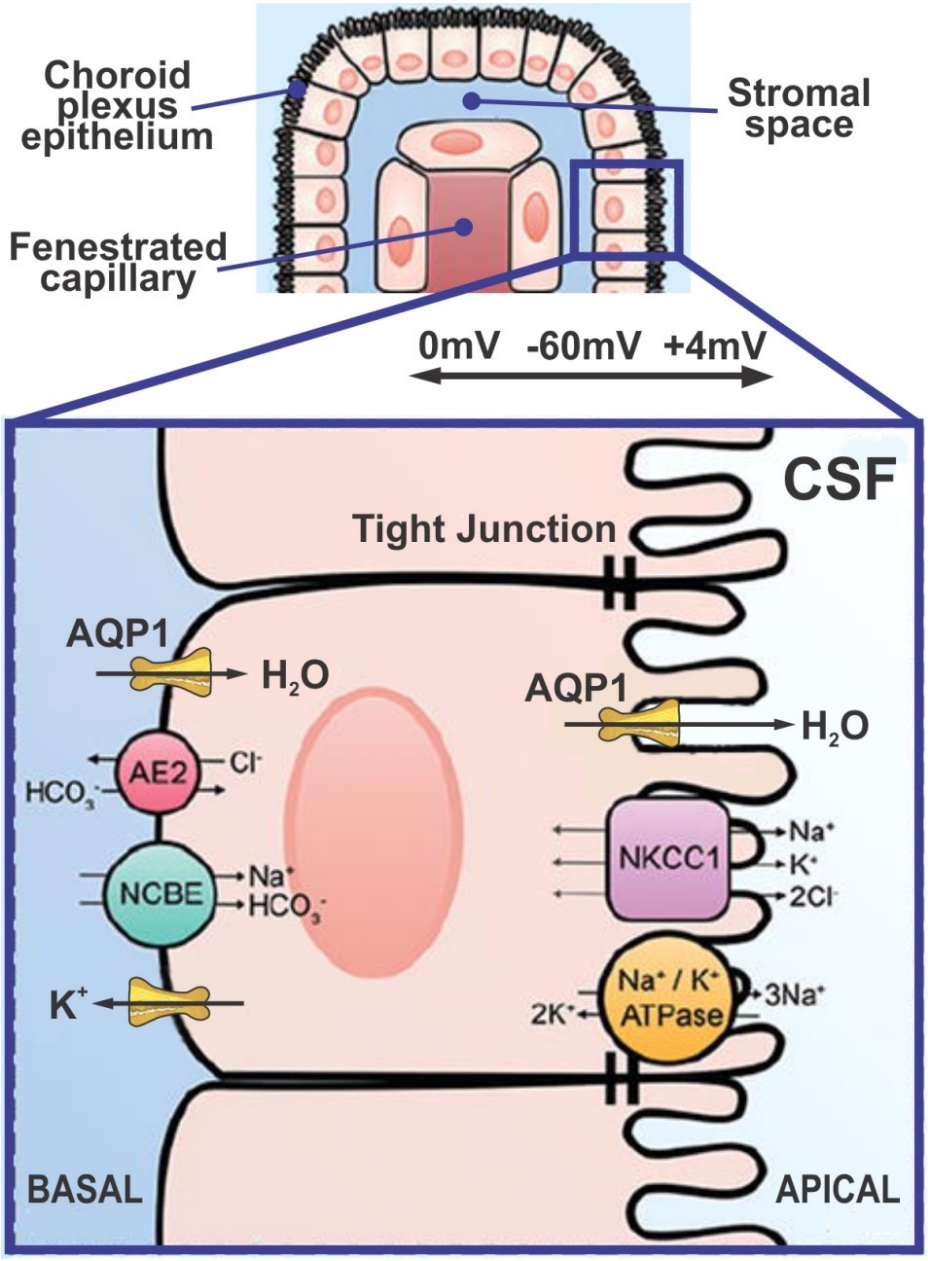

Figure 4: The choroid plexus generating from plasma the cerebrospinal fluid (CSF) functions vectorial kinetic according to a potential of hydrophilic-plasma to hydrophobic-CSF flow, conducting in a unilateral sense the flow for brain irrigation and entropy release.

Water is subsequently "dragged" via osmotic forces across the epithelium and traverses the apical membrane of the choroid plexus epithelial cell through AQP1 in both the luminal and basolateral membranes.

Secretion by the aquaporin-1 (AQP1), AE2 and NCBE at a $Na^+/Cl^-/HCOO_3^-$ ratio o 18:15:3 transports ions taken up from the basolateral membrane. Na^+ into the CSF enter via NKCCl (Na^+-K^+-2Cl^--cotransporter) to keep and mediate the

bidirectional transport of ions gradients of blood vs CSF and is regulated by SPAK (Ste20/SPS1-related proline-alanine-rich protein kinase).

The brain of the newborn enjoys a hormonal system development involving about 60% of total calories ingested, which became stabilized at adult age as 25% of total body energy.

At maturity the contributions of the H-bond breakdown energy, by the enzyme state of hydration vs dehydration turnovers, adds to a thermogenic flow of energy, which requires that the brain develops an autonomous cooling system. Thus, at the blood-brain barrier 150ml CSF are maintained permanently, and 0.3-0.4 ml/min CSF are renovated constantly to generate about 500ml/daily output. The equivalence H-bond contribution is $(H_2O)_{n=3.4}$ for each water cluster kinetic configuration about 3.4×5kcal/mol=17kcal/mol.

The thermodynamics relationship between structure and function requires an astrocytes network for circulation after breakdown of H-bonds.

The water clusters exhausted at the H-bond transition of hydrated negative R groups in polypeptide dynamics of folding in oxyHb are in mutual exclusion with the dehydrated positive R groups in deoxyHb. Accordingly, the circulation sense, decreasing oxygenation, continuously depletes H-bonds energy until reaching a choroid plexus epithelium to generate CSF, but its circulation requires a liquid state. Thus, allows a non-polar kinetic tension between orbitals to conform a resonance state at the water dimer ($H_2O{\sim}OH_2$) integration.

Adrenal cortex

The adrenal cortex secretes: mineralocorticoids such as aldosterone, homeostasis mediate Na^+ vs K^+, cortisol secretion (the stress response). Androgen increases in both males and females during puberty. Androgens are synthesized in the testes, the ovaries, and the adrenal glands.

Aldosterone

The mineralcorticoids are synthesized in the zona glomerulosa of the adrenal cortex and influence salt and water balances (electrolyte balance and fluid balance). The primary mineralocorticoid is aldosterone.

The corticosteroids are synthesized from cholesterol within the zona glomerulosa and zona fasciculata of adrenal cortex. Most steroidogenic reactions are catalyzed by enzymes of the cytochrome P450 family. They are located within the mitochondria and require adrenodoxin as a cofactor (except 21-hydroxylase and 17α-hydroxylase).

Aldosterone synthesis is stimulated by several factors:

- Increase in the plasma concentration of angiotensin III, a metabolite of angiotensin II.
- Increase in plasma angiotensin II, ACTH, or potassium levels, which are present in proportion to plasma sodium deficiencies. (The increased potassium level works to regulate aldosterone synthesis by depolarizing the cells in the zona glomerulosa, which opens the voltage-dependent calcium channels.) The level of angiotensin II is regulated by angiotensin I, which is in turn regulated by renin, a hormone secreted in the kidneys.
- Serum potassium concentrations are the most potent stimulator of aldosterone secretion.
- The ACTH stimulation test, which is

sometimes used to stimulate the production of aldosterone along with cortisol to determine whether primary or secondary adrenal insufficiency is present. However, ACTH has only a minor role in regulating aldosterone production; with hypopituitarism there is no atrophy of the zona glomerulosa.

- Plasma acidosis
- The stretch receptors located in the atria of the heart. If decreased blood pressure is detected, the adrenal gland is stimulated by these stretch receptors to release aldosterone, which increases sodium reabsorption from the urine, sweat, and the gut. This causes increased osmolarity in the extracellular fluid, which will eventually return blood pressure toward normal.
- Adrenoglomerulotropin, a lipid factor, obtained from pineal extracts. It selectively stimulates secretion of aldosterone.
- The secretion of aldosterone has a diurnal rhythm.

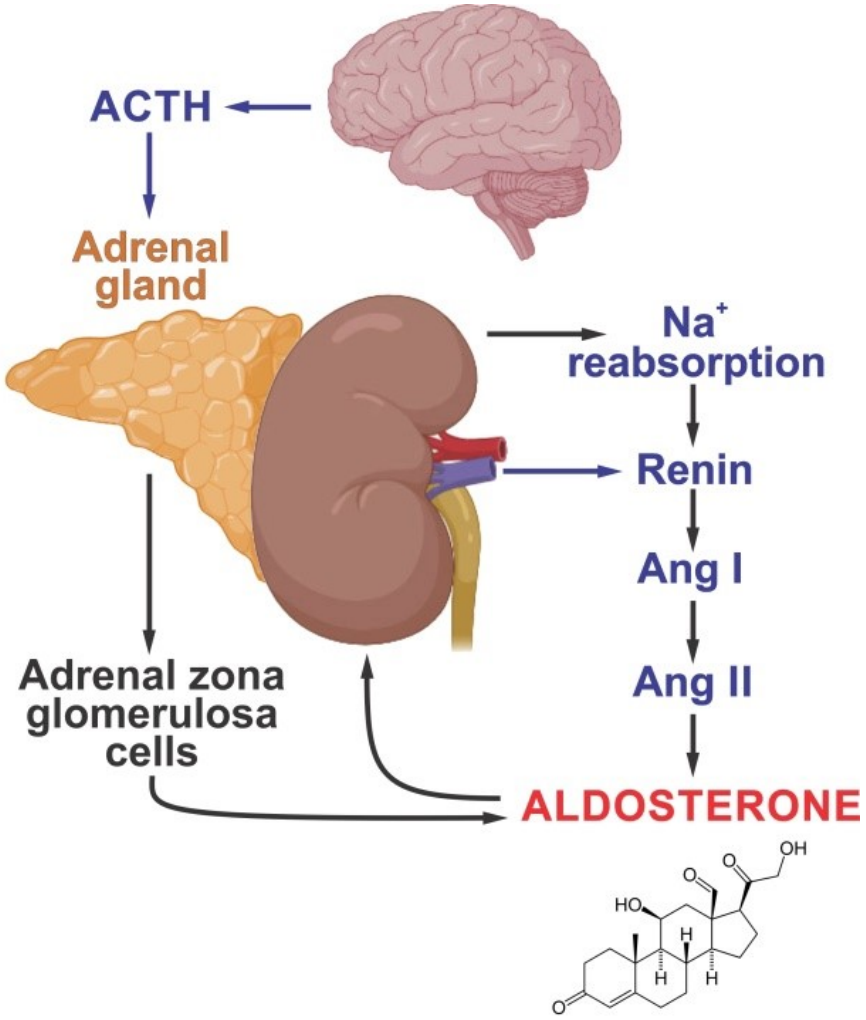

Figure 5: Aldosterone.

Aldosterone is the main mineralocorticoid steroid hormone produced by the zona glomerulosa of the adrenal cortex in the adrenal gland [6] [7]. It is essential for sodium conservation in the kidney, salivary glands, sweat glands, and

colon [8]. It plays a central role in the homeostatic regulation of blood pressure, plasma sodium (Na+), and potassium (K^+) levels. It does so, primarily by acting on the mineralocorticoid receptors in the distal tubules and collecting ducts of the nephron. It influences the reabsorption of sodium and excretion of potassium (from and into the tubular fluids, respectively) of the kidney, thereby indirectly influencing water retention or loss, blood pressure, and blood volume [9]. Dysregulated aldosterone is pathogenic and contributes to the development and progression of cardiovascular and kidney disease [10]. Aldosterone has exactly the opposite function of the atrial natriuretic hormone secreted by the heart.

Aldosterone is part of the renin–angiotensin–aldosterone system. It has a plasma half-life of less than 20 minutes. Drugs that interfere with the secretion or action of aldosterone are in use as antihypertensives, like lisinopril, which lowers blood pressure by blocking the angiotensin-converting enzyme (ACE), leading to lower aldosterone secretion. These drugs stimulate the excretion of sodium and water in urine, while they block the excretion of potassium. Water flows through an aquaporin-1 (AQP1) channel 10^9 per second (s^{-1}), with $\Delta G < 3.6$ kcal/mol activation energy, by not allowing protons flow prevent collapse of electrochemical gradients.

Sex hormones: testosterone and estrogen

Testosterone is the major androgen in male characteristic performance enhancement - pharmacological use hypogonadism, transgender men, bodybuilding, etc.

The gonads initially develop from the mesothelial layer of the peritoneum.

The embryologic development of the human sex organs are the correspondence of its primary and secondary characteristics.

The labia majora originates from the labioscrotal folds in females while it forms the scrotum in males.

The labia minora forms the ventral shaft of the penis in males.

Clitoris is a small, sensitive, erectile part of the female genitals at the anterior end of the vulva. It is the equivalent of male glans penis.

The corpus cavernous is a type of erectile tissue that merges together and protrudes to the exterior of the vulva as the glans.

The dihydrotestosterone (DHT) and androstenedione are involved in male differentiation in the utero, the vagina looking structure at the three months fetus state causes differentiation, leading of the penis, scrotum and prostate. Clinical when testosterone production is suppressed at the testicular level, sexual change could be maintained by continuous use of injectable estradiol to produce trans-sexual changes.

An anomalous family gene was detected by Harvard scientists in a large Puerto Rico's family characterized by an embryological clock dysfunction retarding DHT secretion. This one, affecting X and Y male individuals (popularly denominated for what they look like or in Spanish: *lo que se ve*, in broken language *quesevedo*). They reach the sexual differentiation stage at reaching the age of puberty, occasional after had been married.

Androgens [11] made hormones, also produced by females at lower levels: they function in libido and sexual arousal. Also, androgens are the precursors to estrogens in both men and women.

Testosterone [12] has anabolic steroid effect in males. In humans, testosterone plays a key role in the development of male reproductive tissues such as testes and prostate, as well as promoting secondary

sexual characteristics such as increased muscle and bone mass, and the growth of body hair.

Testosterone in both sexes is involved in health and well-being, where it has a significant effect on overall mood, cognition, social and sexual behavior, metabolism and energy output, the cardiovascular system, and in the prevention of osteoporosis. Insufficient levels of testosterone in men may lead to abnormalities including frailty, accumulation of adipose fat tissue within the body, anxiety and depression, sexual performance issues, and bone loss.

It is associated with increased aggression, violence, and criminal behavior, sex drive, the inclination to impress partners and other courting behaviors.

Steroid hormones that interact with vertebrate steroid hormone receptors are made by the gonads (ovaries or testes). The sex hormones include the androgens, estrogens, and progestogens. Their effects are mediated by slow genomic mechanisms through nuclear receptors as well as by fast nongenomic mechanisms through membrane-associated receptors and signaling cascades.

The androgen receptor (AR), also known as NR3C4 (nuclear receptor subfamily 3, group C, member 4), is a type of nuclear receptor that is activated by binding any of the androgenic hormones [13].

In some cell types, testosterone interacts directly with androgen receptors, whereas, in others, testosterone is converted by 5-alpha-reductase to dihydrotestosterone, an even more potent agonist for androgen receptor activation. Testosterone and dihydrotestosterone (DHT) receptors are present in the cytoplasm.

In humans the mesonephric duct (also denominated: Wolffian or Leydig's duct is a paired organ that develops in the early stages of embryonic development are located the primary androgen receptor-activating hormone.

Dihydrotestosterone is the main androgenic hormone in the urogenital sinus, urogenital tubercle, and hair follicles. Testosterone is therefore responsible primarily for the development of male primary sexual characteristics, and dihydrotestosterone, which is responsible for secondary male characteristics.

Androgens cause slow maturation of the bones, but the potent maturation effect comes from the estrogen. Steroid users of teen age may find that their growth had been stunted by androgen and/or estrogen excess. People with too little sex hormones can be short during puberty but end up taller as adults. Populations in the North of Europe, Sweden, differentiate by taller skeletons from that of the shorter ones in Sicily, Italy.

This effect has been link to the age development response to sex hormones.

The actions of estrogen [14] are mediated by the estrogen receptor (ER), a dimeric nuclear protein that binds to DNA and controls gene expression. Like other steroid hormones, estrogen enters passively into the cell where it binds to and activates the estrogen receptor. The estrogen:ER complex binds to specific DNA sequences called a hormone response element to activate the transcription of target genes (in a study using an estrogen-dependent breast cancer cell line as model, 89 such genes were identified). Since estrogen enters all cells, its actions are dependent on the presence of the ER in the cell. The ER is expressed in the ovary, uterus and breast. The metabolic effects of estrogen in postmenopausal women have been linked to the genetic polymorphism of the ER.

Estrogens are responsible for the development and regulation of the female reproductive system and secondary sex characteristics.

While estrogens are present in both men and women, they are usually present at significantly higher levels in women of reproductive age. There are three major endogenous estrogens that have estrogenic hormonal activity: estrone (E1), estradiol (E2), and estriol (E3). Estradiol, an estrane, is the most potent and prevalent. Another estrogen called estetrol (E4) is produced only during pregnancy. Once inside the cell, estrogens bind to and activate estrogen receptors (ERs) which in turn modulate the expression of many genes, involved in the development of female secondary sexual characteristics, such as breasts, and are also involved in the thickening of the endometrium and other aspects of regulating the menstrual cycle. In males, estrogen regulates certain functions of the reproductive system important to the maturation of sperm and healthy libido.

Estrogen increased fat storage or estrogenic fat in some body parts such as breasts, buttocks, and legs but decreased abdominal and visceral fat (androgenic obesity). Estradiol also regulates energy expenditure, body weight homeostasis, and seems to have much stronger anti-obesity effects than testosterone in general.

Women on average have about the same increases of muscle mass in responses to resistance training as men and far faster relative increases in strength.

Additionally, estrogens bind to and activate rapid-signaling membrane estrogen receptors (mERs), such as GPER (GPR30).

Quantitatively, estrogens circulate at lower levels than androgens in both men and women. While estrogen levels are significantly lower in males than in females, estrogens nevertheless have important physiological roles in males.

The estrogens and androgens are produced from C 19 steroid precursors through several enzymatic conversions. Testosterone can be converted to the most active ligand on the androgen receptor, DHT, or the most active ligand on the estrogen receptor.

Testosterone had to be transform by aromatase in 17β-estradiol before excretion. Physiologically this reaction characterizes human sexual interaction, in which both sexes by raising testosterone produce desire. The latter hormone unconsciously leads to aggressive playfulness. The achievement of ending of the copulation stage requires dispose-off the increment in testosterone level by increasing the rate of conversion to estrogen. The latter circulatory amount allows softening of the skin of both sexes and dissipates the behavioral aggressively that characterizes testosterone and it is usual that leads to homely peace agreement.

Cortisol

The glucocorticoids [15] [16] [17] bind to the glucocorticoid receptor play a role in the regulation of glucose metabolism is produced in the zona fasciculata of the adrenal cortex. Cortisol (hydrocortisone) is the most important human glucocorticoid, it is essential for life, and it regulates or supports a variety of important cardiovascular, metabolic, immunologic, and homeostatic functions. Various synthetic glucocorticoids are available; these are widely utilized in general medical practice and numerous specialties, either as replacement therapy in glucocorticoid deficiency or to suppress the body's immune system.

It is produced in many animals, mainly by the zona fasciculata of the adrenal cortex in the adrenal gland [18]. It is produced in other tissues in lower quantities [19]. It is released with a diurnal cycle and its release is increased in response to stress and low blood-glucose concentration. It functions to

increase blood sugar through gluconeogenesis, to suppress the immune system, and to aid in the metabolism of fat, protein, and carbohydrates [20]. It also decreases bone formation [21]. Many of these functions are carried out by cortisol binding to glucocorticoid or mineralocorticoid receptors inside the cell, which then bind to DNA to impact gene expression.

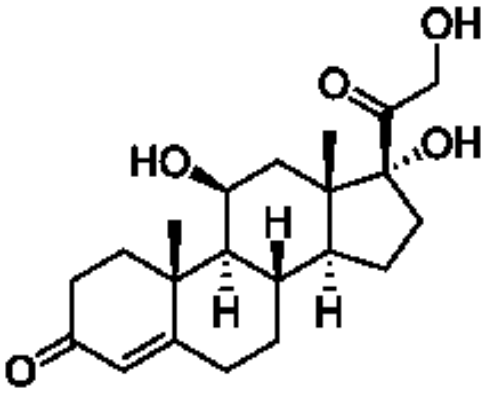

Figure 6: Cortisol is a steroid hormone, in the glucocorticoid class of hormones. *When used as a medication, it is known as hydrocortisone.*

Cortisol stimulates gluconeogenesis: the synthesis of "new" glucose from non-carbohydrate sources, which occurs mainly in the liver, but also in the kidneys and small intestine. The net effect is an increase in the concentration of glucose in the blood, further complemented by a decrease in the sensitivity of peripheral tissue to insulin, thus preventing this tissue from taking the glucose from the blood. Cortisol has a permissive effect on the actions of hormones that increase glucose production, such as glucagon and adrenaline.

Cortisol promotes gluconeogenesis in the liver and glycogenesis: cortisol is thus better thought of as stimulating glucose/glycogen turnover in the liver [22]. This is in contrast to cortisol effect in the skeletal muscle where glycogenolysis is promoted indirectly through catecholamines [23]. Cortisol and catecholamines work synergistically to promote the breakdown of muscle glycogen into glucose for use in the muscle tissue.

Cortisol is responsible for the release of amino acids from muscle (catabolism), providing substrates for gluconeogenesis. This increases the availability of glucose in the blood, thereby increasing its ability to be used as a source of energy for the body. Hence, cortisol plays a crucial role in regulating glucose metabolism with complex and diverse roles [24].

Elevated levels of cortisol, if prolonged, can lead to proteolysis (breakdown of proteins) and muscle wasting [25]. The reason for proteolysis is to provide the relevant tissue with a feedstock for gluconeogenesis. The effects of cortisol on lipid metabolism are more complicated since lipogenesis is observed in patients with chronic, raised circulating glucocorticoid levels, although an acute increase in circulating cortisol promotes lipolysis [26]. The raised blood glucose concentration through the action of cortisol will stimulate insulin release. Insulin [27] [28] stimulates lipogenesis, so this is an indirect consequence of the raised cortisol concentration in the blood but it will only occur over a longer time scale.

Cortisol prevents the release of

substances in the body that cause inflammation. It is used to treat conditions resulting from over activity of the B-cell-mediated antibody response.

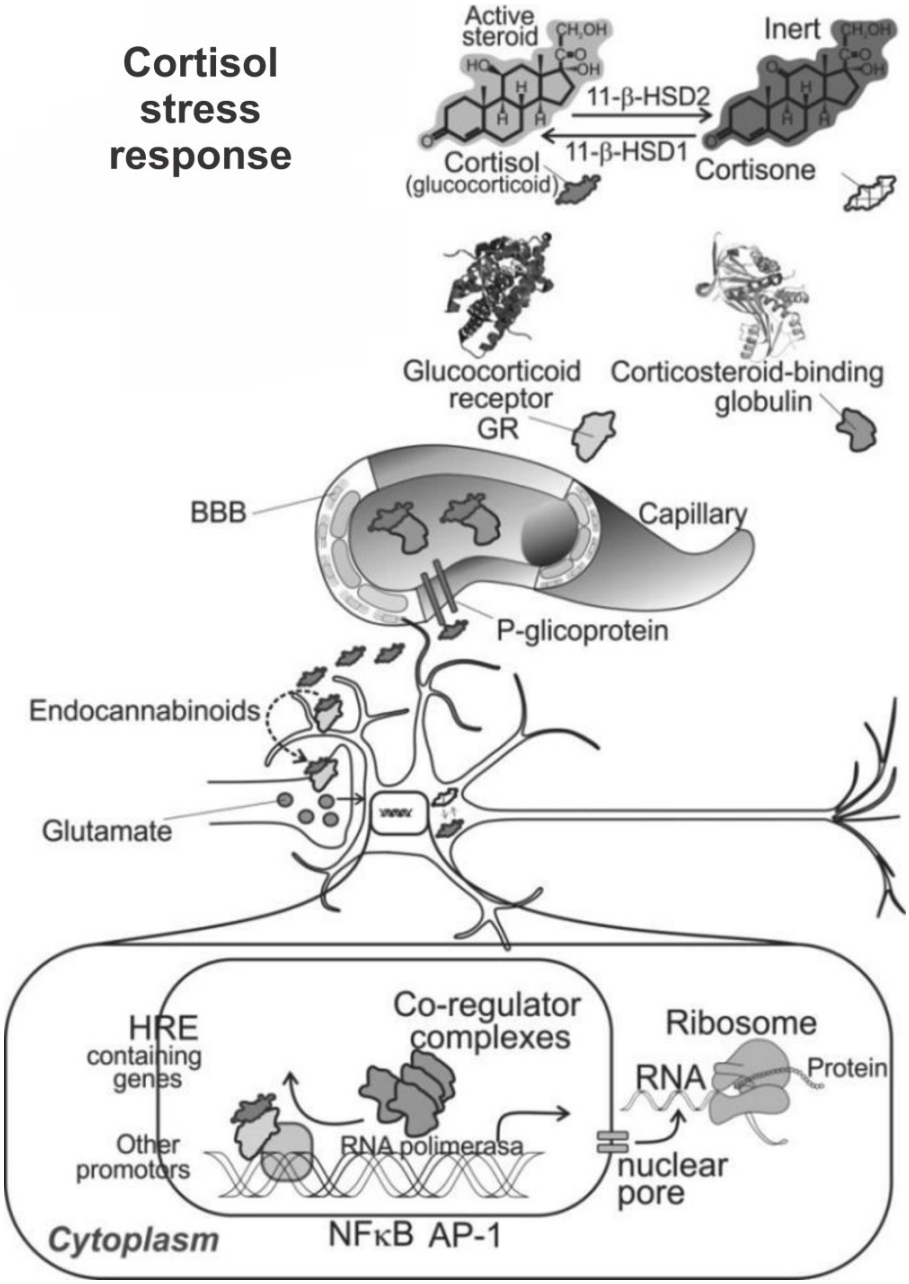

Figure 7: The adrenal medulla modulates cellular functions. *It is stimulates directly by preganglionic fibers and indirectly by the paraventricular neurons to produce adrenaline, also denominated epinephrine trophic. From the capillary the neurotransmitter glutamate acts trans-synaptically. In the neuron cortisol (glucocorticoid) by dehydrogenation is converted into cortisone. The genomic mechanism involves the Glucocorticoids receptor (GR) for cortisol/corticosterone with glucocorticoid activity and some mineralocorticoid activity. BBB is blood-brain barrier.*

Cortisol inhibits production of interleukin 12 (IL-12), interferon gamma (IFN-gamma), IFN-alpha, and tumor necrosis factor alpha (TNF-alpha) by antigen-presenting cells (APCs) and T helper cells (Th1 cells), but upregulates interleukin 4, interleukin 10, and interleukin 13 by Th2 cells. This results in a shift toward a Th2

immune response rather than general immunosuppression. The activation of the stress system (and resulting increase in cortisol and Th2 shift) seen during an infection is believed to be a protective mechanism which prevents an over-activation of the inflammatory response.

The brain hypothalamic posterior pituitary secretion of oxytocin and serotonin

The hypothalamus [29] through a stalk that contains blood vessels and nerve cells is connected to posterior pituitary to store and releases two hormones: oxytocin and antidiuretic hormone (ADH, or vasopressin).

Bonding hormone oxytocin (OT) is a peptide hormone and neuropeptide normally produced in the hypothalamus and released by the posterior pituitary.

OT is primarily synthesized in magnocellular neurons of the paraventricular (PVN) and supraoptic nuclei (SON) of the hypothalamus. The bulk of the peptide is transported to the posterior pituitary where it is released to regulate parturition and lactation.

Present in animals since early stages of evolution, in humans it plays roles in behavior that include social bonding, reproduction, childbirth, and the period after childbirth.

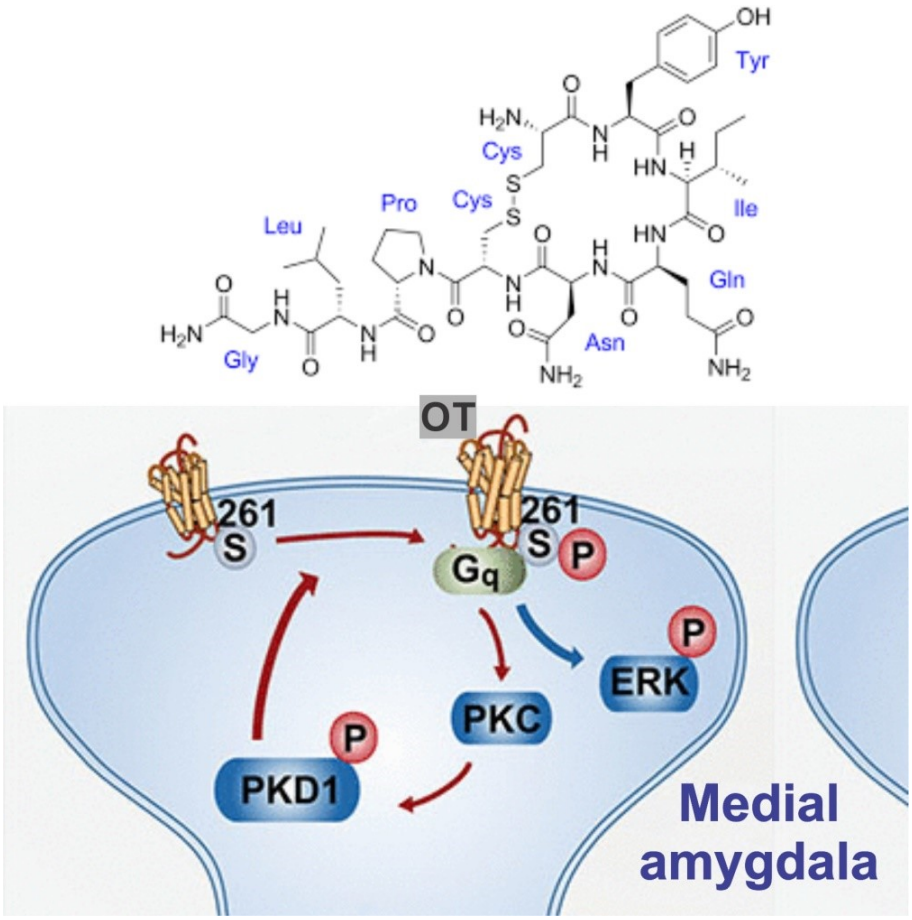

Figure 8: oxytocin social behaviors modulation. Protein kinase C (PKC), protein kinase D1 (PKD1), extracellular signal–related kinase (ERK) phosphoryl group (P) [30].

Brain circuits have been studied in long-term social recognition memory (LTSM) in mice. A DG-CA2/CA3 axis of oxytocin receptor (OTR)-expressing cells in the

hippocampus (HPC) has been described in discrimination of social stimuli: phosphorylation-dependent of $pSer^{261}$ positive feedback loop of the OTR and protein kinase D1 (PKD1), promoted downstream OTR signaling in cultured cells, and its effects on the medial amygdala (MeA)-mediated LTSM consolidation: $OTR \overset{PKD1}{\Longleftrightarrow} pSer^{261} - OTR$. Different neuronal activity of MeA is induced by the social interaction. Interruption of the latter indicated impaired recognition of familiar cage mates.

Neuronal Ca^{2+} signaling and behavior analyses revealed that rats expressing a mutated form of OTR that cannot be phosphorylated at this residue (OXTR S261A) in the MeA exhibited impaired LTSM.

Oxytocin is released into the bloodstream as a hormone in response to sexual activity and during labor. It is available in pharmaceutical form. In either form, oxytocin stimulates uterine contractions to speed up the process of childbirth. In its natural form, it also plays a role in maternal bonding and milk production. Production and secretion of oxytocin is controlled by a positive feedback mechanism, where its initial release stimulates production and release of further oxytocin [31].

When oxytocin is released during a contraction of the uterus at the start of childbirth, this stimulates production and release of more oxytocin and an increase in the intensity and frequency of contractions. This process compounds in intensity and frequency and continues until the triggering activity ceases. A similar process takes place during lactation and during sexual activity.

Serotonin role

Serotonin (hydroxytryptamine: 5-HT) [32] is a monoamine neurotransmitter derived from the amino acid tryptophan, is metabolized mainly to 5-hydroxyindoleacetic acid. Several classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin-noradrenaline reuptake inhibitors (SNRIs), interfere with the normal reabsorption of serotonin after it is done with the transmission of the signal, therefore augmenting the neurotransmitter levels in the synapses.

Approximately 90% of the serotonin the human body produces is in the gastrointestinal tract enterochromaffin cells, where it regulates intestinal movements.

Serotonin is produced in the central nervous system (CNS), specifically in the brainstem's raphe nuclei, the skin's Merkel cells, pulmonary neuroendocrine cells and the tongue's taste receptor cells. It is stored in blood platelets and is released during agitation and vasoconstriction, where it then acts as an agonist to other platelets. About 8% is found in platelets and 1–2% in the CNS [33].

The serotonin is secreted luminally and basolaterally, which leads to increased serotonin uptake by circulating platelets and activation after stimulation, which gives increased stimulation of myenteric neurons and gastrointestinal motility. The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions, including the regulation of mood, appetite, and sleep.

Serotonin secreted from the enterochromaffin cells eventually finds its way out of tissues into the blood. There, it is actively taken up by blood platelets, which store it. When the platelets bind to a clot, they release serotonin, where it can serve as a vasoconstrictor or a vasodilator while regulating hemostasis and blood clotting. In high concentrations, serotonin acts as a vasoconstrictor by contracting endothelial

smooth muscle directly or by potentiating the effects of other vasoconstrictors (angiotensin II and norepinephrine). Serotonin has a vasoconstrictive property, such as atherosclerosis or chronic hypertension. In normal physiologic states, vasodilation occurs through the serotonin mediated release of nitric oxide from endothelial cells, and the inhibition of release of norepinephrine from adrenergic nerves. Serotonin is also a growth factor for some types of cells, which may give it a role in wound healing. There are various serotonin receptors.

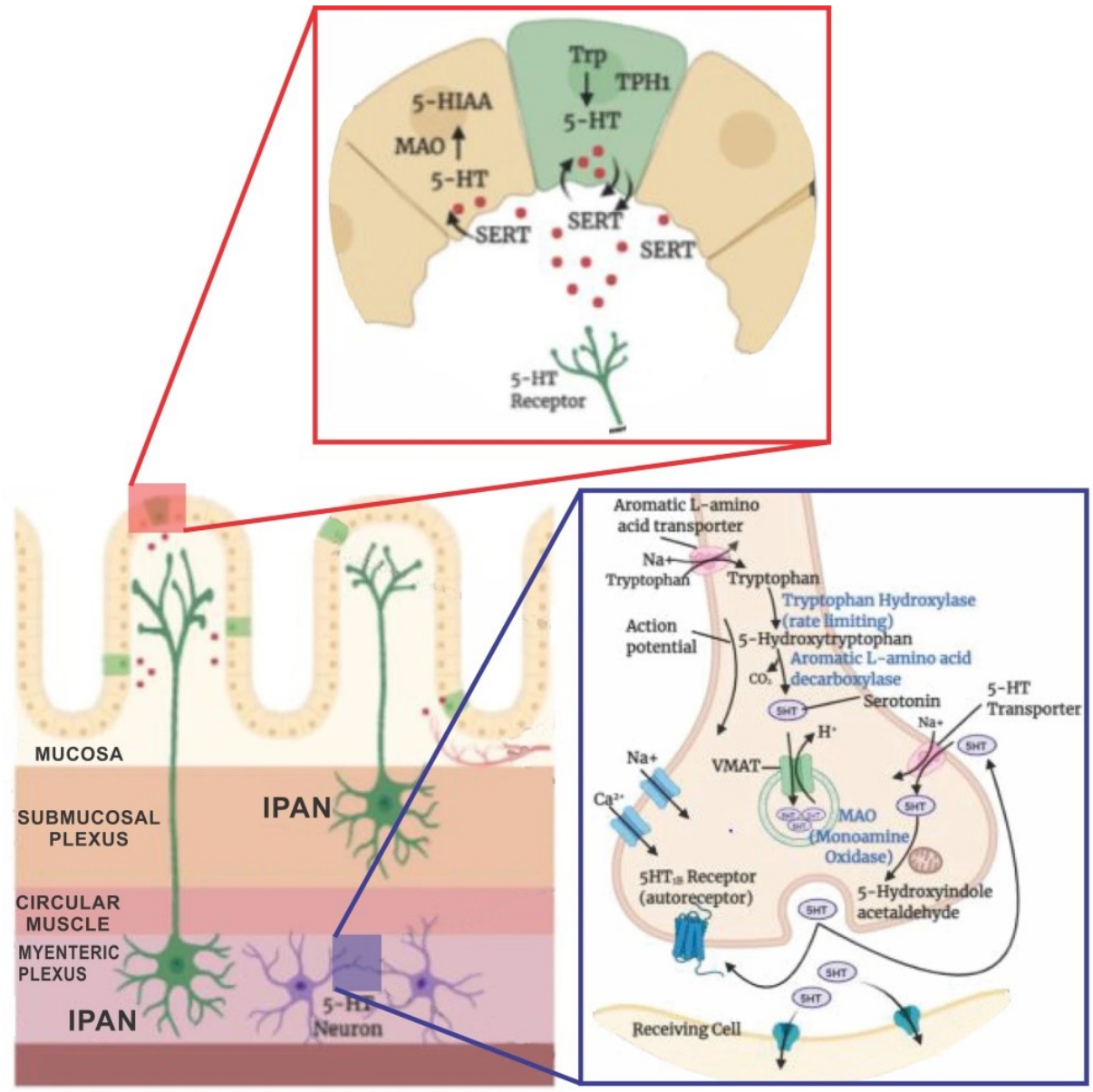

Figure 9: Serotonin (5-HT) is a monoamine neurotransmitter. *Its biological function is complex and multifaceted, modulating mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction.*

Vasopressin

Vasopressin is called antidiuretic hormone (ADH) a peptide prohormone in neurons in the hypothalamus [34] and is converted to arginine vasopressin (AVP). It

then travels down the axon terminating in the posterior pituitary, and is released from vesicles into the circulation in response to extracellular fluid hypertonicity (hyperosmolality).

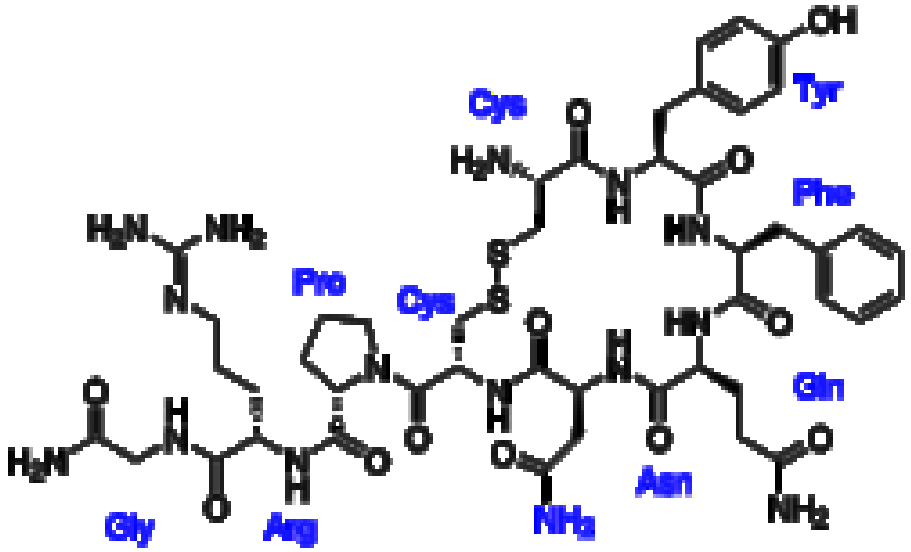

Figure 10: Vasopressin regulates the tonicity of body fluids. *It is released from the posterior pituitary in response to hypertonicity and causes the kidneys to reabsorb solute-free water and return it to the circulation from the tubules of the nephron, thus returning the tonicity of the body fluids toward normal.*

AVP may be released directly into the brain from the hypothalamus, and may play an important role in social behavior, sexual motivation and pair bonding, and maternal including the responses to the psychosomatic-metabolic axis and stress [35].

The adrenal medulla

The adrenal medulla is the inner part of the adrenal gland [36]. It is located at the center of the gland, being surrounded by the adrenal cortex. It is the innermost part of the adrenal gland, consisting of chromaffin cells that secrete catecholamines, including epinephrine (adrenaline) [37], norepinephrine (noradrenaline, NA) [38] and a small amount of dopamine, in response to stimulation by sympathetic preganglionic neurons.

The adrenal medulla is located inside the adrenal cortex in the center of an adrenal gland. It produces "stress hormones," including adrenaline.

Chromaffin cells are derived from the embryonic neural crest, and are modified postganglionic sympathetic neurons [39]. They are modified postganglionic sympathetic neurons of the autonomic nervous system that have lost their axons and dendrites, receiving innervation from corresponding preganglionic fibers.

Adrenaline is produced in the medulla in the adrenal glands as well as some of the central nervous system neurons. Within a couple of minutes during a stressful situation, adrenaline is quickly released into the blood, sending impulses to organs to create a specific response.

The cells form clusters around fenestrated capillaries where they release norepinephrine and epinephrine into the blood.

As a cluster of neuron cell bodies, the adrenal medulla is considered a modified ganglion of the sympathetic nervous system.

The adrenal medulla consists of

irregularly shaped cells grouped around blood vessels. These cells are intimately connected with the sympathetic division of the autonomic nervous system (ANS). These adrenal medullary cells are modified postganglionic neurons, and preganglionic autonomic nerve fibers lead to them directly from the central nervous system. The adrenal medulla affects energy availability, heart rate, and basal metabolic rate. The adrenal medulla may receive input from higher-order cognitive centers in the prefrontal cortex as well as the sensory and motor cortices, providing credence to the idea that there are psychosomatic illnesses.

The adrenal medulla is the principal site of the conversion of the amino acid tyrosine into the catecholamines; epinephrine, norepinephrine, and dopamine.

Because the ANS, specifically the sympathetic division, exerts direct control over the chromaffin cells, the hormone release can occur rather quickly. In response to stressors, such as exercise or imminent danger, medullary cells release the catecholamines adrenaline and noradrenaline into the blood. Adrenaline composes about 85% of the released catecholamines, and noradrenaline the other 15%.

Notable effects of adrenaline and noradrenaline include increased heart rate and blood pressure, blood vessel constriction in the skin and gastrointestinal tract, smooth muscle (bronchiole and capillary) dilation, and increased metabolism, all of which are characteristic of the fight-or-flight response. Release of catecholamines is stimulated by nerve impulses, and receptors for catecholamines are widely distributed throughout the body.

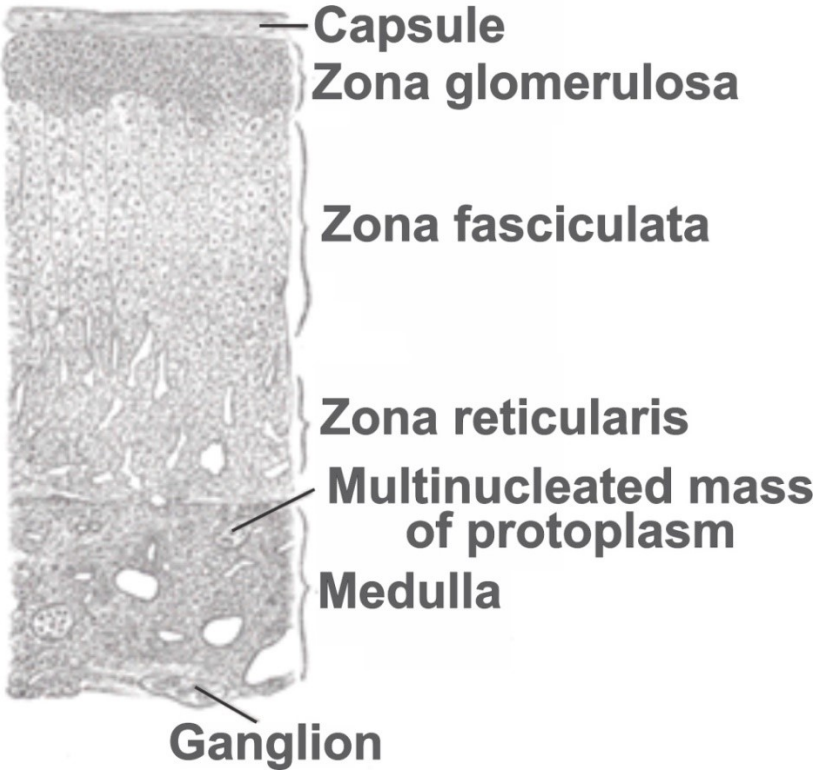

Figure 11: Layers of adrenal cortex. The adrenal cortex makes up 80% of the mass. *The cells are in the trabeculae that surround the blood sinusoids. They have a centrally located spherical nucleus, in cytoplasm there is a highly developed smooth endoplasmic reticulum, tubular mitochondria and fat droplets. The steroid area does not store their products, as they are fat-soluble and freely pass through the membrane. The adrenal cortex consists of three layers: zona glomerulosa (15%), zona fasciculata (50%), zona reticularis (7%).*

Zona glomerulosa

Aldosterone is largely responsible for the long-term regulation of blood pressure. Aldosterone effects are on the distal convoluted tubule and collecting duct of the kidney where it causes increased reabsorption of sodium and increased excretion of both potassium (by principal cells) and hydrogen ions (by intercalated cells of the collecting duct). Sodium retention is also a response of the distal colon, and sweat glands to aldosterone receptor stimulation. Although sustained production of aldosterone requires persistent calcium entry through low-voltage activated Ca^{2+} channels, isolated zona glomerulosa cells are considered non-excitable, with recorded membrane voltages that are too hyperpolarized to permit Ca^{2+} channels entry [40].

The secretion of aldosterone is also stimulated by adrenocorticotropic hormone (ACTH) [41].

The cells of the zona glomerulosa do not express 11β-hydroxylase and 17α-hydroxylase. This is the reason zona glomerulosa cannot synthesize cortisol, corticosterone or sex hormones (androgens). The expression of neuron-specific proteins in the zona glomerulosa cells of human adrenocortical tissues [42] [43] [44] it was suggested that the expression of proteins like the neuronal cell adhesion molecule (NCAM) in the cells of the zona glomerulosa reflects its regenerative function.

Zona fasciculata

Situated between the glomerulosa and reticularis, the cells of the zona fasciculata synthesize and secrete glucocorticoids (such as 11-deoxycorticosterone, corticosterone, and cortisol), as well as small amounts of adrenal androgens and estrogens. The zona fasciculata has more 3β-hydroxysteroid dehydrogenase activity than the zona reticularis. Therefore, the zona fasciculata makes more 11-deoxycorticosterone, corticosterone, and cortisol [45]. The major hormone that stimulates cortisol secretion in humans is the ACTH that is released from the anterior pituitary. It has been shown that the steroidogenic capacity of the zona fasciculata increases during illness in infants.

Zona reticularis production of DHEA-S and their secretion stimulated by ACTH

The inner most cortical layer, the zona reticularis produces adrenal androgens, as well as small amounts of estrogens and some glucocorticoids [46]. The zona reticularis has more of the cofactors required for the 17,20-lyase activity of 17α-hydroxylase than zona fasciculata. Therefore, the zona reticularis makes more androgens, mainly dehydroepiandrosterone (DHEA), DHEA sulfate (DHEA-S), and androstenedione (the precursor to testosterone) in humans. The secretion of DHEAS is also stimulated by ACTH [47].

Adrenaline released or administered soon after a given training task modulates memory processes. Since epinephrine does not readily cross the blood-brain barrier, studies have suggested that some of the central effects of epinephrine might be mediated by peripheral release of glucose.

Blood-brain barrier

Within physiological autoregulatory limits, catecholamines do not cross the intact blood-brain barrier (BBB), thereby limiting their direct cerebrovascular effects.

The crosstalk between physical exercise and BBB permeability shows the influence

of physical activity affecting permeability as it reinforces antioxidative capacity, reduces oxidative stress and has anti-inflammatory effects.

It improves endothelial function and might increase the density of brain capillaries. Thus, physical training can be emphasized as a component of prevention programs developed for patients to minimize the risk of the onset of neuro-inflammatory diseases as well as an augmentation of existing treatment [48].

The concentration of tritium-labeled adrenaline was determined in various areas of cat brain after intravenous infusion. It did not exceed that expected from the blood content of the tissue except in the hypothalamus, where small but significant amounts of H3-adrenaline were found. [49]

Dopamine

Dopamine (DA, a contraction of 3,4-dihydroxyphenethylamine) is a neuromodulatory molecule that plays several important roles in cells. It is an organic chemical of the catecholamine and phenethylamine families. Dopamine constitutes about 80% of the catecholamine content in the brain. It is an amine synthesized by removing a carboxyl group from a molecule of its precursor chemical, L-DOPA, which is synthesized in the brain and kidneys.

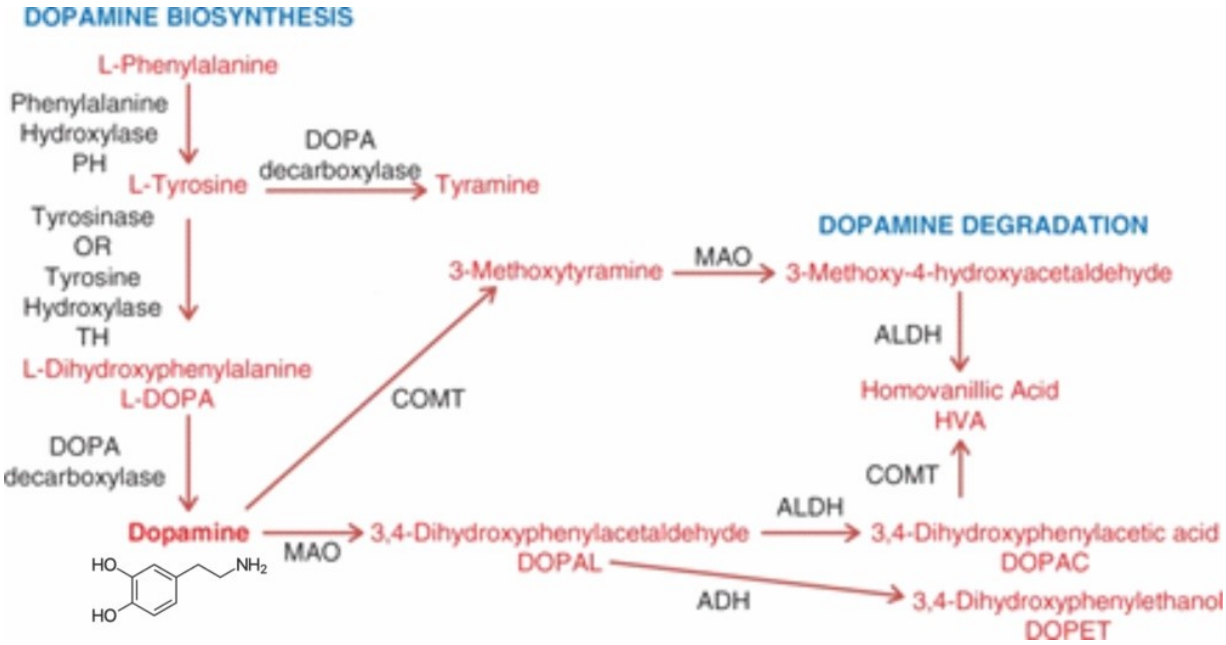

Figure 12: Dopamine is synthesized from phenylalanine or tyrosine via sequential reactions catalyzed mainly by phenylalanine hydroxylase (PH), tyrosine hydroxylase (TH), and DOPA decarboxylase. It can also be synthesized from tyramine.

In the brain, dopamine functions as a neurotransmitter, a chemical released by neurons (nerve cells) to send signals to other nerve cells. Neurotransmitters are synthesized in specific regions of the brain, but affect many regions systemically. The brain includes several distinct dopamine pathways, one of which plays a major role in the motivational component of reward-motivated behavior. The anticipation of most types of rewards increases the level of dopamine in the brain. Many addictive drugs

increase dopamine release or block its reuptake into neurons following its release. Brain dopamine pathways are involved in motor control and in controlling the release of various hormones, which is neuromodulatory.

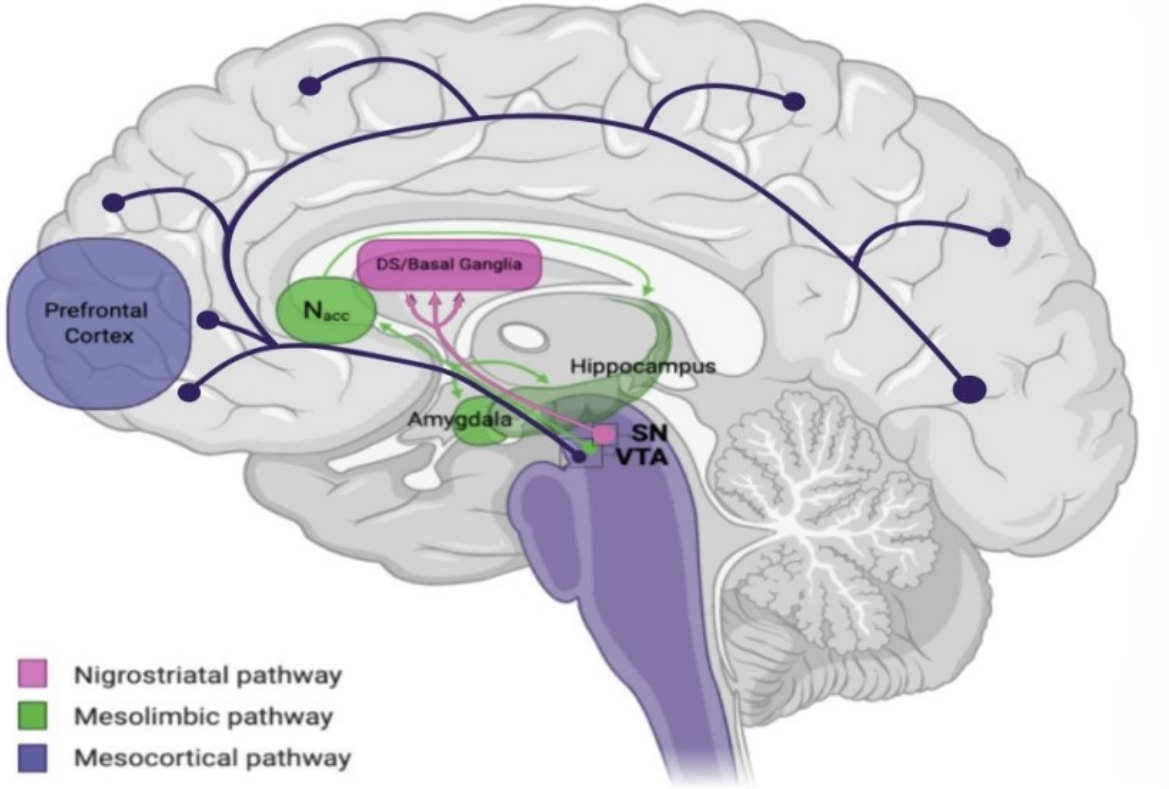

Figure 13: Dopaminergic pathways Nigrostriatal, Mesolimbic and Mesocortical pathways. *This shows ventral tegmental area (VTA), medial forebrain bundle and anterior limb of internal capsule, where nucleus accumbens (N_{acc}), hippocampus (Hippoc), amygdala (Amygd), dorsolateral prefrontal cortex (dl-PFC), Medial orbitofrontal-PFC (Of-PFC), Lateral Of-PFC.*

Serotonin

Serotonin [50] (or 5-hydroxytryptamine (5-HT)) is a monoamine neurotransmitter. Its biological function is complex and multifaceted, modulating mood, cognition, reward, learning, memory, and numerous physiological processes such as vomiting and vasoconstriction.

Serotonin is produced in the central nervous system (CNS), specifically in the brainstem's raphe nuclei, the skin's Merkel cells, pulmonary neuroendocrine cells and the tongue's taste receptor cells.

Biochemically, the indoleamine molecule derives from the amino acid tryptophan. Serotonin is metabolized mainly to 5-hydroxyindoleacetic acid, chiefly by the liver.

Approximately 90% of the serotonin the human body produces is in the gastrointestinal tract's enterochromaffin cells, where it regulates intestinal movements.

Additionally, it is stored in blood platelets and is released during agitation and vasoconstriction, where it then acts as an agonist to other platelets. About 8% is found in platelets and 1–2% in the CNS. The serotonin is secreted luminally and basolaterally, which leads to increased serotonin uptake by circulating platelets and activation after stimulation, which gives

increased stimulation of myenteric neurons and gastrointestinal motility.

The vasoconstrictive property is mostly seen in pathologic states affecting the endothelium, such as atherosclerosis or chronic hypertension.

In normal physiologic states, vasodilation occurs through the serotonin-mediated release of nitric oxide from endothelial cells.

Serotonin is a growth factor for some types of cells, which may give it a role in wound healing. There are various serotonin receptors.

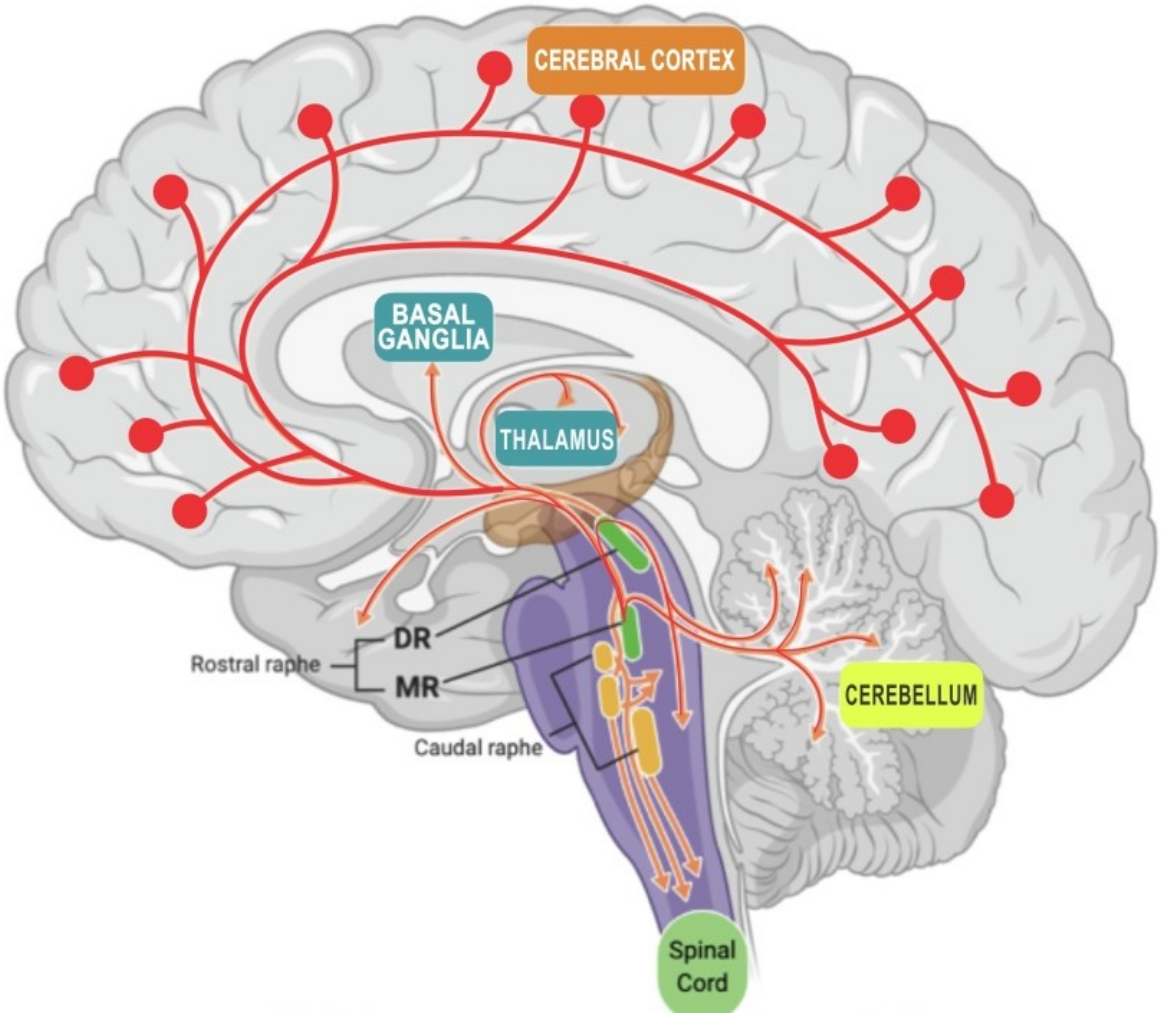

Figure 14: Serotonin shows dorsal raphe (DR) in midbrain and medial raphe (MR) in pons connects superior cerebellar peduncle and middle cerebellar peduncle located in cerebellum, connecting lobule V, VI, VIIa and VIIb, respectively. *The caudal serotonergic nuclei heavily innervate the spinal cord, medulla and cerebellum. In general, manipulation of the caudal nuclei that results in decreased activity decreases movement, while manipulations to increase activity cause an increase in motor activity.*

In brain, a serotonin pathway identifies aggregate projections from neurons which synthesize and communicate the monoamine neurotransmitter serotonin. These pathways are relevant to different psychiatric and neurological disorders.

The remainder is synthesized in serotonergic neurons of the CNS, where it has various functions, including the regulation of mood, appetite, and sleep.

The serotonin acts by inhibition of release of NA from adrenergic nerves.

Several classes of antidepressants, such as selective serotonin reuptake inhibitors (SSRIs) and serotonin–norepinephrine reuptake inhibitors (SNRIs), interfere with the normal reabsorption of serotonin after it is done with the transmission of the signal, therefore augmenting the neurotransmitter levels in the synapses.

Serotonin is also implicated in sensory processing, as sensory stimulation causes an increase in extracellular serotonin in the neocortex. Serotonin pathways are thought to modulate eating, both the amount as well as the motor processes associated with eating. The serotonergic projections into the hypothalamus could signal an increase in serotonergic thought to generally decrease food consumption.

Serotonin pathways projecting into the limbic forebrain are also involved in emotional processing, with decreased serotonergic activity resulting in decreased cognition and an emotional bias towards negative stimuli. The function of serotonin in mood is more nuanced, with some evidence pointing towards increased levels leading to depression, fatigue and sickness behavior; and other evidence arguing the opposite.

Noradrenaline

Noradrenaline [51] (or Norepinephrine) (NA) is a catecholamine and a phenethylamine. Its structure differs from that of epinephrine only in that epinephrine has a methyl group attached to its nitrogen, whereas the methyl group is replaced by a hydrogen atom in norepinephrine. Norepinephrine consists of a catechol moiety (a benzene ring with two adjoining hydroxyl groups in the meta-para position), and an ethylamine side chain consisting of a hydroxyl group bonded in the benzylic position

NA is the neurotransmitter of sympathetic postganglionic fibers and of central pathways that originate in the locus coeruleus and project to the cerebral cortex, cerebellum, spinal cord, and other regions.

In the body, the general function of NA is to mobilize the brain and body for action. NA release is lowest during sleep, rises during wakefulness, and reaches much higher levels during situations of stress or danger, in the so-called fight-or-flight response. In the rest of the body, NA increases heart rate and blood pressure, triggers the release of glucose from energy stores, increases blood flow to skeletal muscle, reduces blood flow to the gastrointestinal system, and inhibits voiding of the bladder and gastrointestinal motility.

Outside the brain, NA is used as a neurotransmitter by sympathetic ganglia located near the spinal cord or in the abdomen, as well as Merkel cells located in the skin. It is also released directly into the bloodstream by the adrenal glands. Regardless of how and where it is released, norepinephrine acts on target cells by binding to and activating adrenergic receptors located on the cell surface.

NA itself is widely used as an injectable drug for the treatment of critically low blood pressure. Stimulants often increase, enhance, or otherwise act as agonists of norepinephrine. Drugs such as cocaine and methylphenidate act as reuptake inhibitors of norepinephrine, as do some antidepressants, such as those in the Serotonin–norepinephrine reuptake inhibitors (SNRI) class.

In mammals, NA is rapidly degraded to various metabolites. The initial step in the breakdown can be catalyzed by either of the enzymes monoamine oxidase (mainly monoamine oxidase A) or Catechol-O-

methyltransferase (COMT). From there, the breakdown can proceed by a variety of pathways. The principal end products are either Vanillylmandelic acid or a conjugated form of 3-Methoxy-4-hydroxyphenylglycol (MHPG), both of which are thought to be biologically inactive and are excreted in the urine.

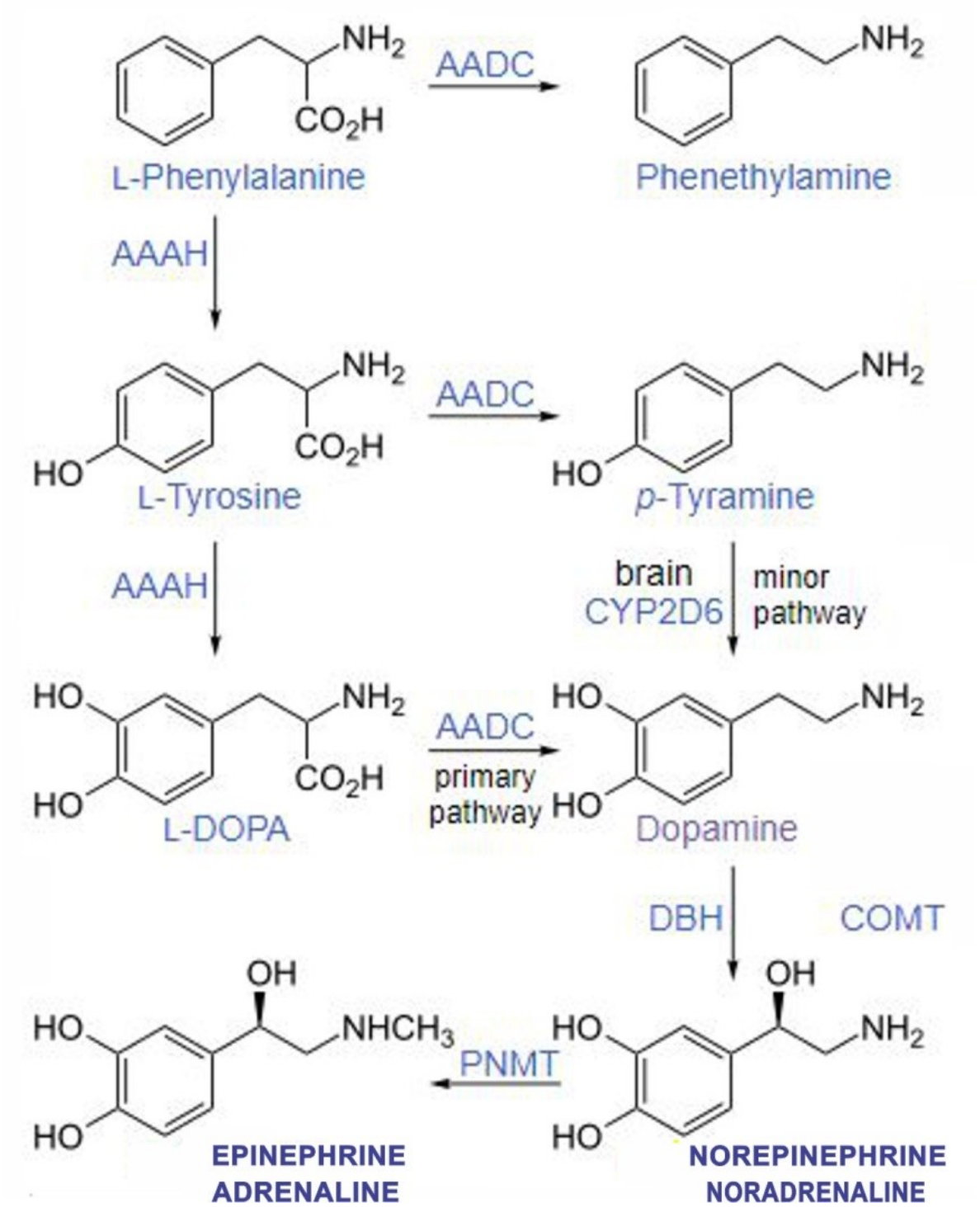

Figure 15: The metabolic pathway is: Phenylalanine → Tyrosine → L-DOPA → Dopamine → NA. *The direct precursor of norepinephrine is dopamine, which is synthesized indirectly from the essential amino acid phenylalanine or the non-essential amino acid tyrosine. These amino acids are found in nearly every protein and, as such, are provided by ingestion of protein-containing food, with tyrosine being the most common.*

Norepinephrine as neurotransmitter

In the brain, norepinephrine increases arousal and alertness, promotes vigilance, enhances formation and retrieval of memory, and focuses attention; it also increases restlessness and anxiety. NA is produced in nuclei that are small yet exert powerful effects on other brain areas. The most important of these nuclei is the locus coeruleus, located in the pons.

Many important psychiatric drugs exert strong effects on noradrenaline systems in the brain, resulting in side-effects that may be helpful or harmful.

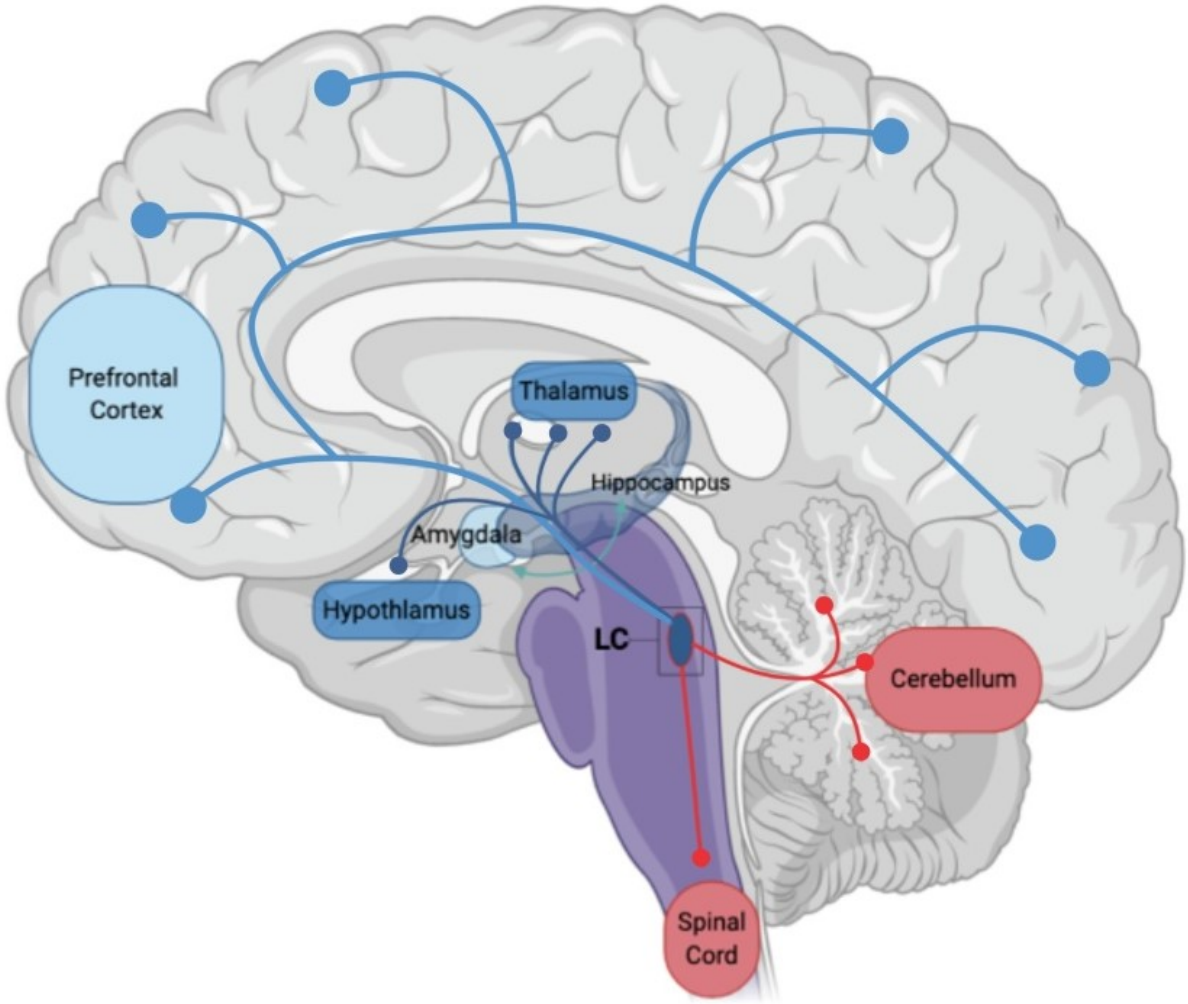

Figure 16: Locus coeruleus (LC) in the basal forebrain connects with medial forebrain bundle and anterior limb of internal capsule in prefrontal cortex (PFC) with dl-PFC, medial Of-PFC and lateral Of-PFC.

Adenylyl cyclase

Molecular cloning genetic studies of the three major components of beta adrenergic receptor (AR)-Gs-adenylyl cyclase (AC) signaling pathway: G protein-coupled receptor kinases identify for AC the corresponding cDNA [52].

AC was successfully solubilized with nonionic detergents and partially purified, and its molecular mass (>100 kD) was calculated on the basis of its hydrodynamic properties. Biochemical characterization of the enzyme obtained from various tissues

demonstrated that there were two distinct subtypes: calmodulin-sensitive and -insensitive isoforms [53].

A molecule consisting of a module of six transmembrane spans linked to a large cytoplasmic domain that was tandemly repeated. The amino acid sequence within the transmembrane domains (M1 and M2) did not show sequence homology to any other proteins. The sequences within the two cytoplasmic domains (C1a and C2a) showed significant homology to each other, are considered to be catalytic domains.

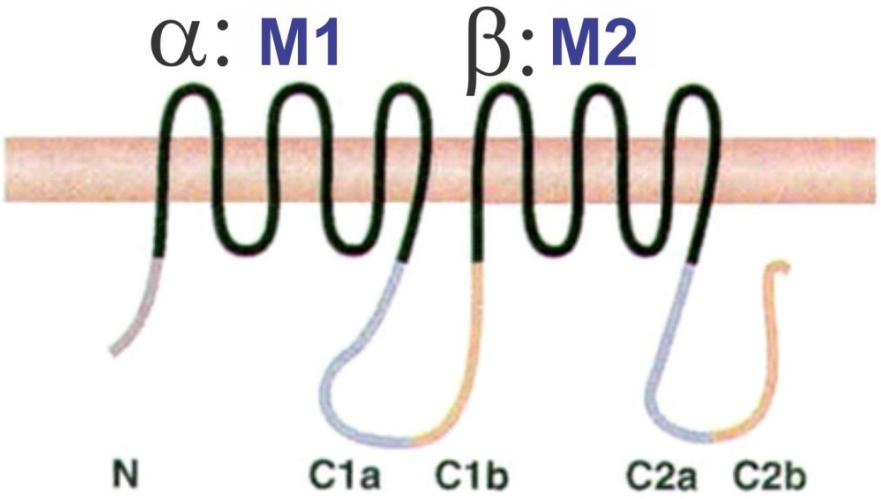

Figure 17: The entire molecule is subdivided into seven domains: N indicates the N-terminal cytoplasmic domain; M1, *the first six transmembrane-spanning domain; C1a, the first cytoplasmic catalytic domain; C1b, the first cytoplasmic linker domain; M2, the second six transmembrane-spanning domain; C2a, the second cytoplasmic catalytic domain; and C2b, the second cytoplasmic noncatalytic domain. Alpha represents the front half of the molecule; beta, the back half. C1a directly contacts C2a and that the peptide, by way of competition, blocks the interaction and thereby inhibits catalytic activity* [54].

Structure of AC membrane-delimited nears the $G_{\beta\gamma}$ subunits protein for rapid amplification of the agonist-triggered signal. AC isoform isolated from the brain as type I is calmodulin sensitive and expressed only in the brain. More generalized elevations of intracellular calcium produced by calcium ionophores do not necessarily inhibit cAMP production in these same cells; this suggests that calcium-sensitive AC isoforms may be functionally co-localized with certain calcium entry channels [55]. cAMP-triggered mechanisms can directly gate the strength and duration of the calcium signal.

cAMP and calcium concentrations may oscillate, providing both temporal and spatial information to the cell. The dynamic interplay between these two second messenger pathways has been demonstrated [56].

The voltage-sensing activity in the transmembrane regions has implicate for excitable cells such as neurons and cardiocytes

The two cytoplasmic domains of AC likely interact to initiate efficient catalytic activity. Catalytic activity is rescued when the two halves are coexpressed. The distribution of the various isoforms within the brain is heterogeneous, suggesting that each isoform is involved in a distinct aspect of neuronal signaling. The type V isoform is restricted to the striatum, implicating its involvement in motor regulation. The AC gene family expanded by chromosomal duplication rather than by gene duplication [57].

For guanylyl cyclase, it has been demonstrated that the two subunits, alpha and beta, which are distinct gene products, must be coexpressed to catalyze cGMP synthesis [58].

Potential regulators vary from simple cation concentration [59] to various kinases [60] [61]. The pattern of regulation may differ, even for the same isoform, when expressed in different cell types, between splice variants of AC isoforms or in response to various regulatory components. A striking finding that underscores the diversity in the regulation of AC isoforms is their response to various G-protein subunits: the same G-protein subunit may stimulate certain AC isoforms, inhibit other isoforms, and have no effect on the remaining isoforms. $G_{\beta\gamma}$ inhibits type I adenylyl cyclase while it stimulates type II AC [62].

Purified membrane preparations were isolated from three areas: hypothalamus, cortex and striatum from Female Sprague-Dawley rats.

Regulation of brain adenylate cyclase by ionic equilibria and integrator of signal transduction

The cAMP-synthesizing activity was identified within the membrane fraction of cells more than three decades ago [63].

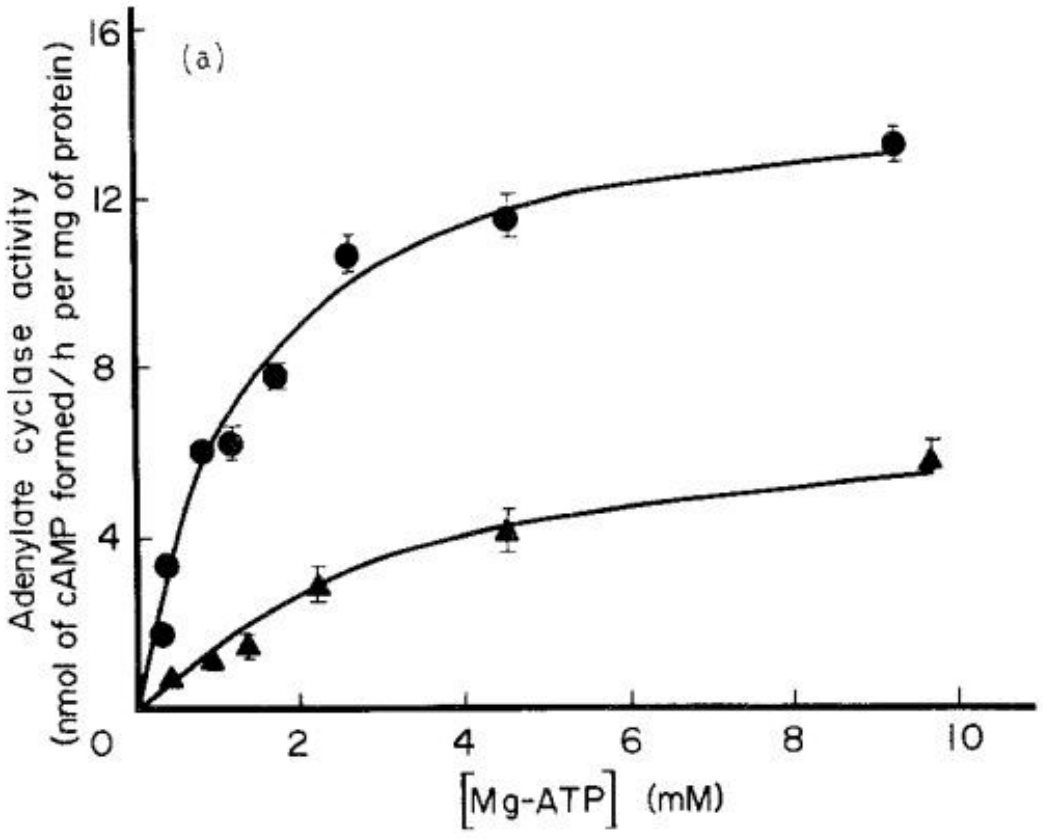

Figure 18: Effect of CaATP on the substrate saturation curve of hypothalamic adenylate cyclase. *Portions of a particulate membrane preparation containing 3.3 μg of protein increasing equimolar $MgCl_2$ and ATP (0-10 mM) concentrations (●): basal; (▲), in the presence of 0.5 mM CaATP* [64].

The addition of several concentrations of $MgC1_2$ to the $CaC1_2$ saturation curves did not change Ki(Ca^{2+}) but resulted in a Mg^{2+}-dependent decrease in the negative cooperativity for Ca^{2+}. Analysis of these curves showed that the effect of equilibrium

concentrations of Mg^{2+}, MgATP, and ATP^{4-} on the percentage of the relative saturation of the active site and Mg^{2+}-modulated site remained constant within the range 10^{-7} to 10^{-3} M $CaCl_2$. Accordingly, the negative cooperativity shown by the enzyme in response to $CaC1_2$ can only be explained by Ca^{2+} reducing the inhibitory effect of CaATP.

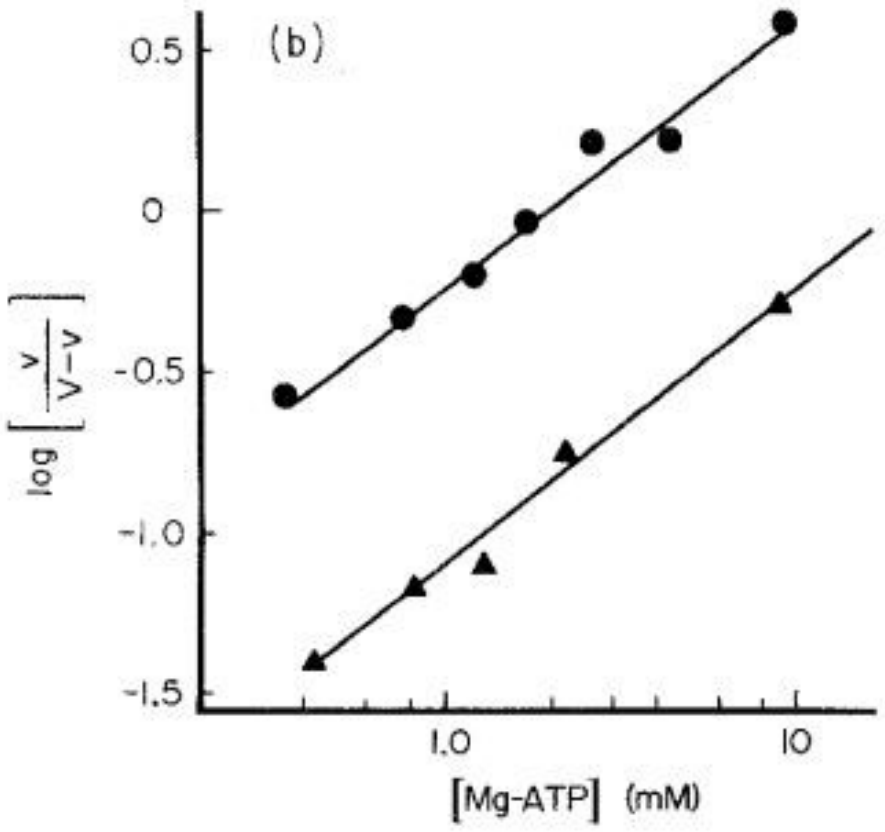

Figure 19: Hill plot effect of CaATP. *The control curve shows an h value of 1.1, which was decreased by CaATP to 0.9. The Lineweaver-Burk plot shows competitive inhibition between CaATP and substrate. CaATP increases Kmapp for the substrate from 2 mM to 20 mM MgATP. From the latter, a value of 0.06 mM was calculated for Mg^{2+} and ATP^{4-}-independent Ki(CaATP). The quantity Ki(CaATP) is an apparent Ki. These studies show that the $CaC1_2$ saturation curves, at added 1mM MgATP, yield a value of 0.016 mM $K_{i_{app}}(Ca^{2+})$ and 0.6 apparent h(Ca^{2+}).*

The inhibitory effects of Ca^{2+} may be attributed to Ca^{2+} displacing Mg^{2+} from a Mg-E-MgATP quaternary complex to form a Ca.E-MgATP quaternary complex of considerably lower activity [65].

The results demonstrate that ionic equilibria regulate the activity of membrane located AC. The ion Mg^{2+} activates AC and 7-transmembrane (7TM) receptor AC for hormones.

Thyrotropin-releasing hormone (TRH) receptor regulates the Ca^{2+} function of cells in the anterior pituitary and the central and peripheral nervous systems.

The number of ions signaling in excitable cells for a physiological membrane potential change is negligible with regard to concentrations of Na^+, K^+, and Cl^- in cells and extracellular fluid. The 10^{-7} M intracellular [Ca^{2+}] made significant a low inward flow of [Ca^{2+}].

Hence, the signaling by

phosphodiesterase breakdown of cAMP and the adenylyl cyclase generating cAMP allows crosstalk between both systems by temporal and spatial changes in [Ca^{2+}] because produce transient and localized changes in [cAMP] that controls A-kinase anchoring proteins (AKAPs).

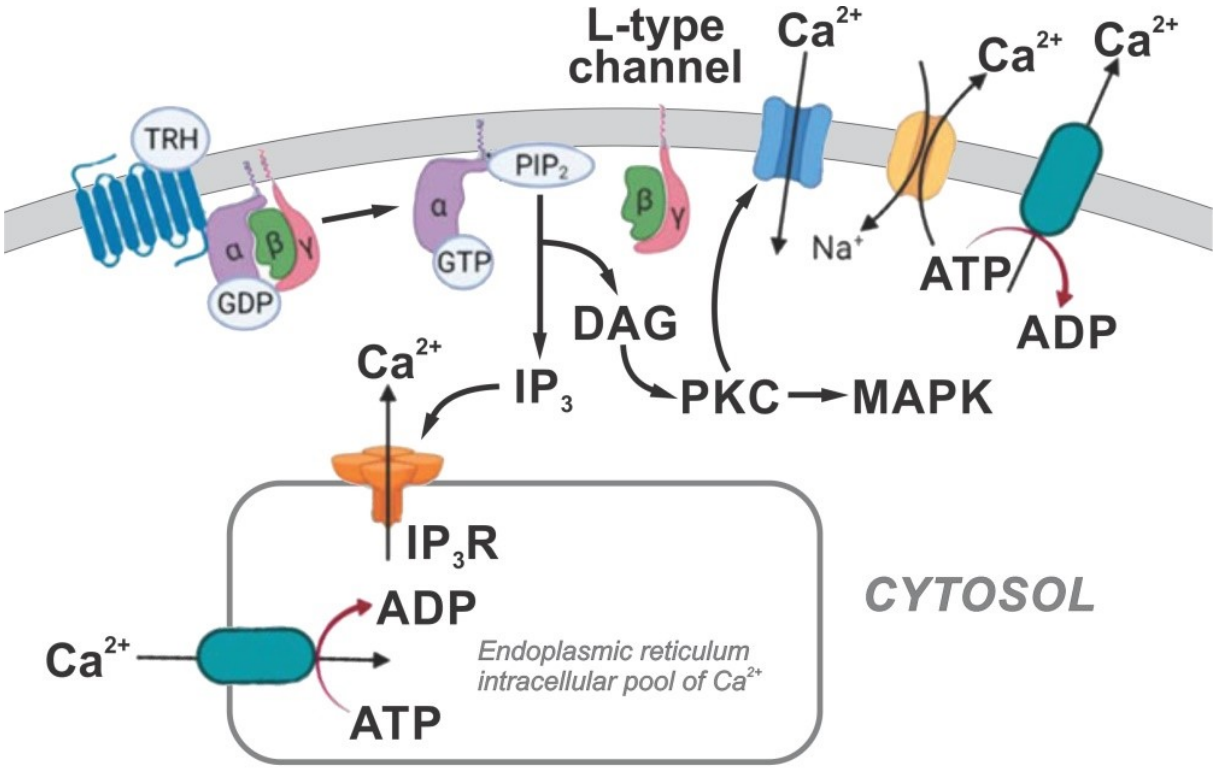

Figure 20: The G protein coupled TRH-R activates the cleavage of PIP_2 into IP_3 and DAG. IP_3 then triggers calcium release from intracellular stores. *After that, calcium pumps drive Ca^{2+} away from the cytosol. Plasma membrane-bound calcium channels are responsible for the second phase of calcium release from the extracellular space. Na^+/Ca^{2+} exchanger removes calcium from cells.*

Membrane-bound vectorial enzymes structure the brain's open system potentiating enthalpy by entropy's dissipation

In neurons, Ca^{2+} influx through L-type voltage-gated Ca^{2+} channels (LTCC) couples electrical activity to changes in DNA transcription [66].

Disruption of AKAP-PKA anchoring promoted redistribution of the kinase out of dendritic spines, profound decreases in L-type voltage-gated Ca^{2+} channels (LTCC) phosphorylation and Ca^{2+} influx, and impaired nuclear factor of activated T-cells (NFAT) movement signaling to the neuronal nucleus and activation of transcription.

Enthalpy of H-bond breakdown for dynamics of proteins and DNA from hydrophilic to hydrophobic generates entropy as dimers and the system becomes open when coupled to donor water cluster mass action for a vectorial irreversible turnover [67] [68].

The dimers flow in hydrophobic conducts until dissipated out at the oral cavity into vapor state, rising into the atmosphere and manifests water polarity for spontaneous aggregation and eventually rain as water clusters.

The RARE BiBi mechanism [69] shows a second-order dependence on substrate

concentration: Mg^{2+} has to bind first to activate the binding site for MgATP. Hence, the noradrenaline (NA) activated of the hypothalamic tissue is controlled by obligatory ions Mg^{2+} exceeding the substrate concentration. cAMP and calmodulin release of Ca^{2+} determine signaling of the amplitude, phase and period of circadian rhythms. ATP^{4-} and chelating metabolites decreases CaATP, strongly activating an Mg^{2+} in excess of substrate for adenylate cyclase (AC) activation. Effect increases the cAMP-dependent activation of CREB pathways for memory affirmation.

Ca^{2+} releases activate the glutamate neurotransmission. Serotonin (5-hydroxytryptamine, 5-HT) produced in Raphe nuclei located in the brainstem, could induced Ca^{2+} increase and reduced the cAMP increase, indicating cross-talk between the 5-HT-sensitive Ca^{2+} and cAMP pathways. Ionic equilibrium controlling Ca^{2+} effects for a simultaneous dead-end CaATP inhibition of AC. Thus, function for mutual exclusion activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, is an ionotropic transmembrane receptor for glutamate (iGluR) that mediates fast synaptic transmission in the central nervous system (CNS)

Turnover, with release of Mg^{2+} from the E as a nascent ion Mg^{2+} acquires a stronger intrinsic charge.

The molecular kinetics synchronization that prevents microscopic reversibility, because could not be conceptually assimilated to the principle of microscopic reversibility requiring a single door, which could allow transit in both senses.

Mutual exclusion between hydrophilic and hydrophobic domains allows vectorial kinetics, which bypasses microscopic reversibility, due to the enzymes turnover has only one sense the hydrophilic changing conformation to the hydrophobic one.

Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA

Base pairing in the double helix. Illustration of how bases are assembled to form DNA, a double helix with two "backbones" made of the deoxyribose and phosphate groups. The four bases form stable hydrogen bonds with one partner such that A pairs only with T and G pairs with C.

The spacing between neighboring base pairs is roughly 0.34 nm.

The binding of base pairs in DNA that holds the double helix together is based on every adenine forming two hydrogen bonds with thymidine and every cytosine forming three hydrogen bonds with guanine. The binding of transcription factors to DNA is often based on formation of H-bonds reflecting a nucleic acid-protein form of hydrogen bonding.

The nonphysiological treatment technic of heating DNA at 65°C allows the strands separation and transcription used experimentally.

The 65°C lab technic used incidence over the off-rate for transcription factor unbinding and thus the dissociation constant.

The physiological function allows an on-rate for CREB insertion of cAMP depending of H-bond breakdown of DNA and after transcription process ending and H-bond reconstruction of the double helix H-bonds from water cluster to reach off-rate. The H-bond expenditure will correspond to the turnover of H-bond. However, because the bonds are reconstituted from the active to the steady-state consume the H-bonds from

55.5M water cluster $(H_2O)n$ and the molarity decrease on the products n-1 could not be even detected at concentration at micromolar range.

Hence, because experimental difficulty to measure decreases of the active form molarity of water cluster by residual decreases mixing water cluster as a [substrate] and [product], enormous difference in concentrations could not be detected the change in concentration or measured $\Delta G=1.4\log([P]/[S])$.

The turnover process involving the CREB unzipping of DNA

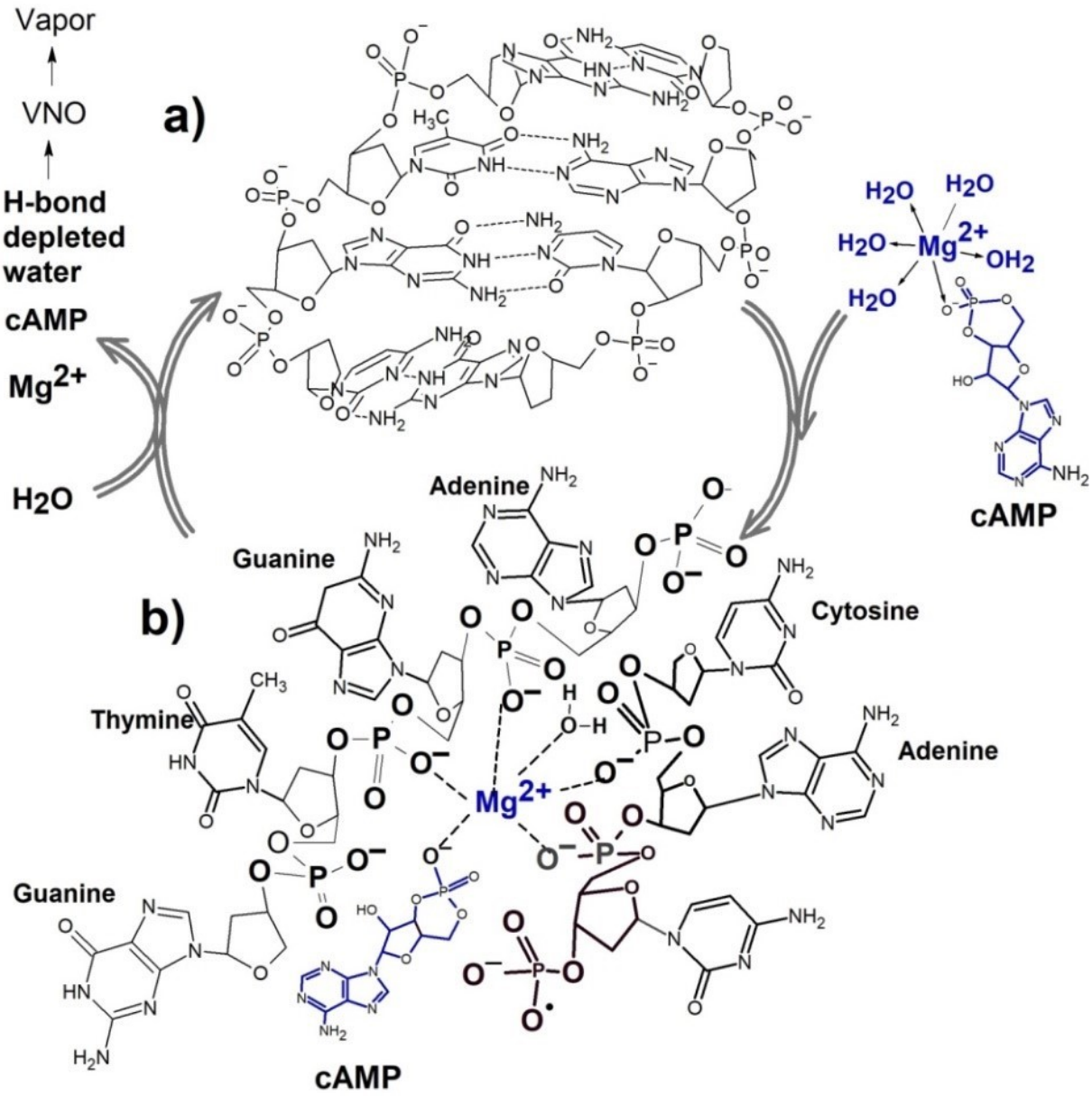

Figure 21: Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA*. The non-physiological treatment technic of heating DNA at allows the strands separation and transcription used experimentally.* ***a) Base sequence of the two chains*** *attracted by H-bonds to match in a double stranded binary rotational symmetry of DNA.* ***b) cAMP unzipping mechanism opens the double-stranded*** *DNA structure by H-bond breakdown, positioning the outside purines and pyrimidines bases to the transcription mechanism leading to protein synthesis.*

Mg-cAMP inserted in domain of DNA allows a switch-on by Mg^{2+} and –off by Ca^{2+}. A dynamic mechanism to activate gene expression in CREB by inducible gene response to dopamine phosphorylation via G protein coupled receptor. Thus, acting to synthetize brain derived growth factor, a regulator during neuronal development and synaptic plasticity.

The cAMP in the CREB [70] regulates transcription of genes: c-fos, BDNF, tyrosine hydroxylase, numerous neuropeptides (such as somatostatin, enkephalin,

VGF, corticotropin-releasing hormone), and genes involved in the mammalian circadian clock (PER1, PER2).

Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA or the transitory structure of cffDNA. [71].

At present, research on aging biology has focused on elucidating the biochemical and genetic pathways that contribute to aging over time. Several aging mechanisms have been identified; the thereafter discussed: the telomere shortening, genomic instability and cellular senescence.

The evaluation of telomerase to reverse activity and increase longevity

The molecular composition of the human telomerase complex was determined by Scott Cohen and his team at the Children's Medical Research Institute (Sydney Australia) and consists of two molecules each of human telomerase reverse transcriptase (TERT), telomerase RNA (TR or TERC), and dyskerin (DKC1). The genes of telomerase subunits, which include TERT, TERC, DKC1 and TEP1, are located on different chromosomes [72] [73].

Telomerase, also called terminal transferase is a ribonucleoprotein that adds a species-dependent telomere repeat sequence to the 3' end of telomeres. A telomere is a region of repetitive sequences at each end of the chromosomes of most eukaryotes. Telomeres protect the end of the chromosome from DNA damage or from fusion with neighbouring chromosomes. The fruit fly Drosophila melanogaster lacks telomerase, but instead uses retrotransposons to maintain telomeres.

Telomerase is the enzyme responsible for maintenance of the length of telomeres by addition of guanine-rich repetitive sequences. Telomerase activity is exhibited in gametes and stem and tumor cells. In human somatic cells proliferation potential is strictly limited and senescence follows approximately 50-70 cell divisions. In most tumor cells, on the contrary, replication potential is unlimited. The key role in this process of the system of the telomere length maintenance with involvement of telomerase is still poorly studied. No doubt, DNA polymerase is not capable to completely copy DNA at the very ends of chromosomes; therefore, approximately 50 nucleotides are lost during each cell cycle, which results in gradual telomere length shortening. Short telomeres cause senescence, following crisis, and cell death. In tumor cells the system of telomere length maintenance is activated.

Besides catalytic telomere elongation, independent telomerase functions can be also involved in cell cycle regulation. Inhibition of the telomerase catalytic function and resulting cessation of telomere length maintenance will help in restriction of tumor cell replication potential.

On the other hand, formation of temporarily active enzyme via its intracellular activation or due to stimulation of expression of telomerase components will result in telomerase activation and telomere

elongation that can be used for correction of degenerative changes.

Problems of telomerase activity measurement and modulation by enzyme inhibitors or activators are considered as well [74].

The human TERT gene (hTERT) is translated into a protein of 1132 amino acids. TERT polypeptide folds with (and carries) TERC, a non-coding RNA (451 nucleotides long). TERT has a 'mitten' structure that allows it to wrap around the chromosome to add single-stranded telomere repeats.

TERT is a reverse transcriptase, which is a class of enzymes that creates single-stranded DNA using single-stranded RNA as a template.

The protein consists of four conserved domains (RNA-Binding Domain (TRBD), fingers, palm and thumb), organized into a "right hand" ring configuration that shares common features with retroviral reverse transcriptases, viral RNA replicases and bacteriophage B-family DNA polymerases.

TERT proteins from many eukaryotes have been sequenced.

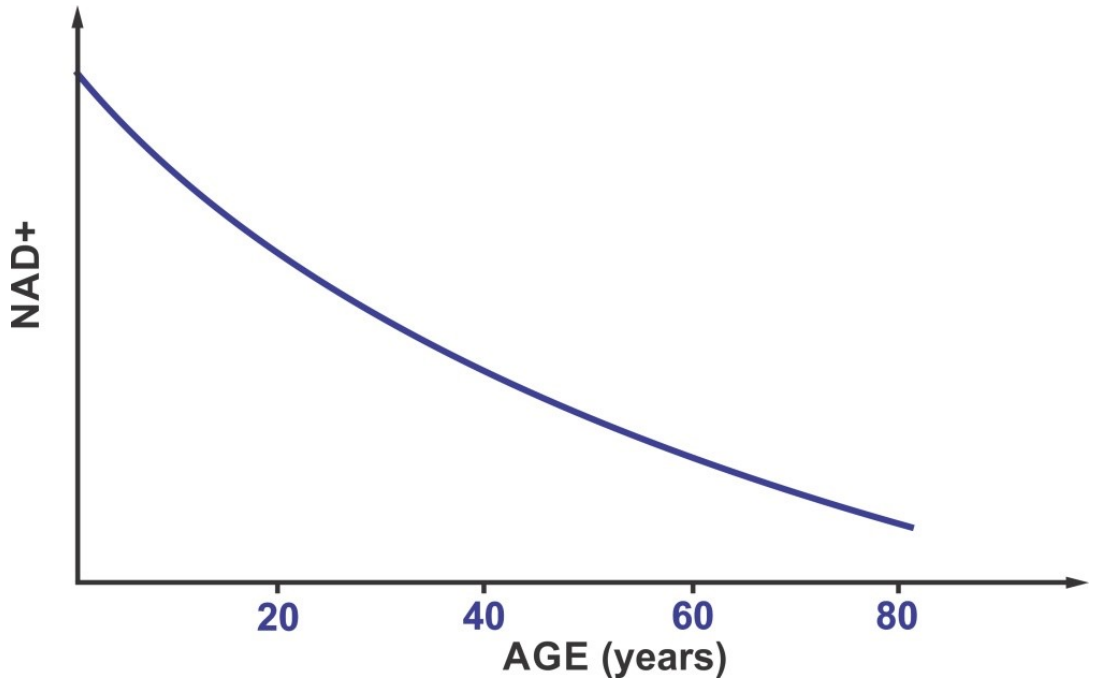

Figure 22: NAD+ levels decrease by 50% every 20 years, being at low levels from 40 years on.

As cells age, they lose their functionality, a process known as senescence, aging cells begin to release, with greater intensity, different proinflammatory substances.

The restitution of NAD+ levels for their overall metabolic impact may be involved in longevity.

Over time, the efficiency of our immune system decreases. This added to the accumulation of cell damage, in this way, increases systemic inflammation, facilitating the appearance of age -related diseases such as cognitive deterioration, type II diabetes, cardiovascular diseases and others.

Framingham Pharma, a laboratory seeking nutritional formulas, has patented in Argentina with the name Telomerina, without enzyme contain, but with other components like d-ribose and nicotinamide, clinically validated to increase NAD+ levels.

The nuclear genome decays as organism age. Numerous studies demonstrate that the burden of several classes of DNA lesions is greater in older mammals than in young mammals. More challenging is proving this is a cause rather than a consequence of aging. The DNA damage theory of aging, which argues that genomic instability plays a causal role in aging, has recently gained momentum. Support for this theory stems partly from progeroid syndromes in which inherited defects in DNA repair increase the burden of DNA damage leading to accelerated aging of one or more organs. Additionally, growing evidence shows that DNA damage accrual triggers cellular senescence and metabolic changes that promote a decline in tissue function and increased susceptibility to age-related diseases. Here, we examine multiple lines of evidence correlating nuclear DNA damage with aging. We then consider how, mechanistically, nuclear genotoxic stress could promote aging. We conclude that the evidence, in toto, supports a role for DNA damage as a nidus of aging [75].

Genomic instability role on longevity

Genomic instability is a characteristic of most cancer cells. It is an increased tendency of genome alteration during cell division. Cancer frequently results from damage to multiple genes controlling cell division and tumor suppressors

CRISPR-Cas9 (Clustered Regularly Interspaced Short Palindromic Repeats) [76] is a revolutionary gene editing technology that allows for precise and targeted modifications to an organism's DNA. The CRISPR-Cas9 system is used to create a double-stranded break (DSB) at the target DNA site specified by the gRNA. The Cas9 enzyme cleaves both strands of the DNA at the target site, which triggers the cell's natural repair machinery [77].

Transomic provides easy access to this technology through a comprehensive offering of lentiviral vector backbones and expert cloning services. One of the critical components of the CRISPR gene editing process is gRNA design. Transomic Technologies utilizes the CRoatan algorithm developed at Cold Spring Harbor Laboratories which selects gRNAs for optimal specificity, efficiency and target DNA accessibility. Additionally, the breadth of our available vectors provides maximum flexibility to allow for single and dual guide configurations as well as all-in-one vectors comprised of both gRNA and Cas9 expression cassettes.

Transomic also specializes in CRISPR-Cas9 systems that can be used for gene activation CRISPRa (dCas9-VPR) and gene interference CRISPRi (dCAS-KRAB) that do not create DNA breaks, but rather use a catalytically inactive Cas9 to target trans-activators or repressors to specific regions of a gene's promoter [78].

RNA interference (RNAi) is the silencing or knockdown of a gene's expression by specific inactivation of the corresponding mRNA using double-stranded RNA (dsRNA). Transomic Technologies provides a comprehensive array of tools that enable highly efficient gene knockdown at the transcript level.

The short hairpin RNA (shRNA) expression vectors utilize a uniquely optimized miR30 scaffold, which maximizes shRNA processing and improves the stability and specificity of the expressed shRNAs.

UltramiR systems utilize RNA polymerase II promoters that promote high expression of long RNAs which allow for multi-cistronic expression cassettes that can include shRNAs and additional reporter

genes. Our shRNA designs are created using the shERWOOD algorithm, which was developed with collaborators from Cold Spring Harbor Laboratory and predict shRNA's for maximum potency and can predict rare shRNA designs that are efficient at single copy representation in the genome.

The use of lentiviral vectors to deliver and express shRNAs offers a variety of advantages including stable integration, long-term/permanent expression of the shRNA, and highly efficient and uniform vector delivery (compared to plasmid transfection). We also offer Tet-Inducible shRNA systems to allow complete control over the expression profile and temporal kinetics of shRNA expression.

Transomic's shRNA designs and vectors can also be used to target long non-coding RNAs (lncRNAs) that do not encode for a gene but are involved in key cellular process such as transcriptional regulation, post-transcriptional regulation (e.g. splicing and translation), epigenetic regulation, and nucleation of protein complexes.

Transomic provides several valuable genomic resources to the scientific community. One of these resources is the Mammalian Gene Collection (MGC). The NIH chose Transomic as the official archive site for the collection, and as such, we offer these high-quality, full-length cDNA clones at a budget friendly price and with a rapid turnaround time. Use our gene search tool to search through the thousands of human and mouse cDNA clones to find your gene of interest.

It is recommended that All Transomic lentiviral vectors are 3rd generation transfer plasmids and have been optimized for efficient 3rd generation lentiviral packaging. The use of a 3rd generation packaging system significantly reduces the likelihood of generating replication-competent lentivirus and thus results in improved safety over earlier packaging systems.

All expression vectors have been made self-inactivating (SIN) via a deletion in 3' LTR (ΔU3). This deletion is transferred into the 5'LTR after one round of reverse transcription and abolishes transcription of the full-length virus after it has incorporated into a host cell.

A 3rd generation transfer plasmid can be used with a 2nd generation packaging system, but a 2nd generation transfer plasmid cannot be used with a 3rd generation packaging system.

H-bond breakdown energy

Change conformation turnover of protein is supported by the activation energy of broken H-bonds, from water in CSF, conversion into waste water. Astrocytes could maintain the H-bond wasted state of water in a liquid phase as dimers until their release as vapor to the outside of the system, which is equivalent to entropy dissipation.

H-bonds are ubiquitous the formation of the alpha-helix and beta-sheet secondary structures in proteins. H-bonds are often central to the function of catalytic active sites in enzymes.

Because of the high frequency of H-bonding in the energy economy of cells, it is natural to ask how much free energy is associated with the formation of these bonds. Indeed, the energy scale of these bonds, slightly larger than the scale of thermal energies, are central to permitting the transient associations so typical of macromolecular interactions and that would be completely forbidden if these bonds were based upon covalent interactions instead. Though the length of H-bonds is quite constant at ≈0.3 nm (BNID 108091), their energies defy simple and definitive characterization. This provides a challenging and interesting twist on this most basic of

biological interactions. One of the ways to come to terms with the nuance in the free energy of H-bonding is to appreciate that the members of a H-bond can interact with their environment in many different ways. If an H-bond is broken, the two members will form alternative H-bonds with the surrounding solvent – water. But this raises the following question: if the dissolution of an H-bond results in the formation of other H-bonds what is the source of any associated free energy change? In fact, such bonding rearrangements alter the level of order in the solvent and thus the entropy can be the dominant free energy contribution.

Now, many things change, but at least one H-bond that should be present is no longer there in the case of CG base pair by incorrect CT base pair. The Boltzmann distribution tells us how to evaluate the relative probability of different events as $p(1)/p(2)=\exp(-\Delta E/kBT)$, where ΔE is the energy difference between those two states. If $\Delta E \approx -6$ kJ/mol (=-2.3 kBT), a lower end value for hydrogen bond energies, this implies a 10-fold difference in the two probabilities resulting is much higher and requires the energy driven mechanism of kinetic proofreading.

The strong dependence on conformation indicates that slight change in the angle or distance between the relevant atoms and the energy will change drastically.

The neuron-astrocyte cooperative metabolism

The DHEA action on the blood-brain-barrier conversion of blood into cerebrospinal fluid (CSF) one of the participants on the control of the ion channels found in neurons.

A potential of hydrophilic-plasma to hydrophobic-CSF for the choroid plexus Na^+- γ- aminobutyric acid (GABA) transporter in a negative allosteric modulation, is an ionotropic receptor of the ligand-gated ion channel.

All levels of the central nervous system (CNS) are innervated by LC-noradrenaline (NA) axons with providing NA innervation at the isocortex, allocortex and cerebellar cortex, and additionally, caudally innervate the medulla and spinal cord. A single NA-neuron through its branching could spread with terminals over most of the entire cerebral cortex.

Divergence of axon collaterals occurs implicating non-synaptic effects by diffusion on neighboring cells, acting as a neuromodulator within circumscribe microenvironments but widespread allowing NA to reach many brain regions.

The central NA system paracrine effects appear to be related to the marked divergence sustained by the morphology of the axon terminals. The collaterals possess varicosities or boutons, and spikes across the axon release NA from multiple serial sites, in addition to the one present at the fibre endings.

The varicosities along LC-NA axons possess 0.5 μm beaded varicosities that differentiate from the larger diameter 1 to 3 μm medullary A1 and A2.

Cocaine and some antidepressants interfere with the reuptake process of norepinephrine. This prolongs its synaptic effects.

α1 antagonists leave the presynaptic α2 receptor intact and functioning. This will reduce the total norepinephrine released which will prevent the tachycardia.

At low doses, dopamine can act on β1 receptors; at higher doses on α1 receptors. It also causes the release of norepinephrine from the nerve terminals, which will also stimulate β1 and α1 receptors. This will ultimately act to increase renal blood flow,

increase cardiac output, and increase total peripheral resistance.

Acetylcholine release onto preganglionic fibers causes depolarization, calcium influx, and secretion of epinephrine. Glucocorticoid levels (elevated in prolonged stress) will induce the activity of PNMT (phenylethanolamine N-methyl transferase), resulting in increased synthesis of adrenaline.

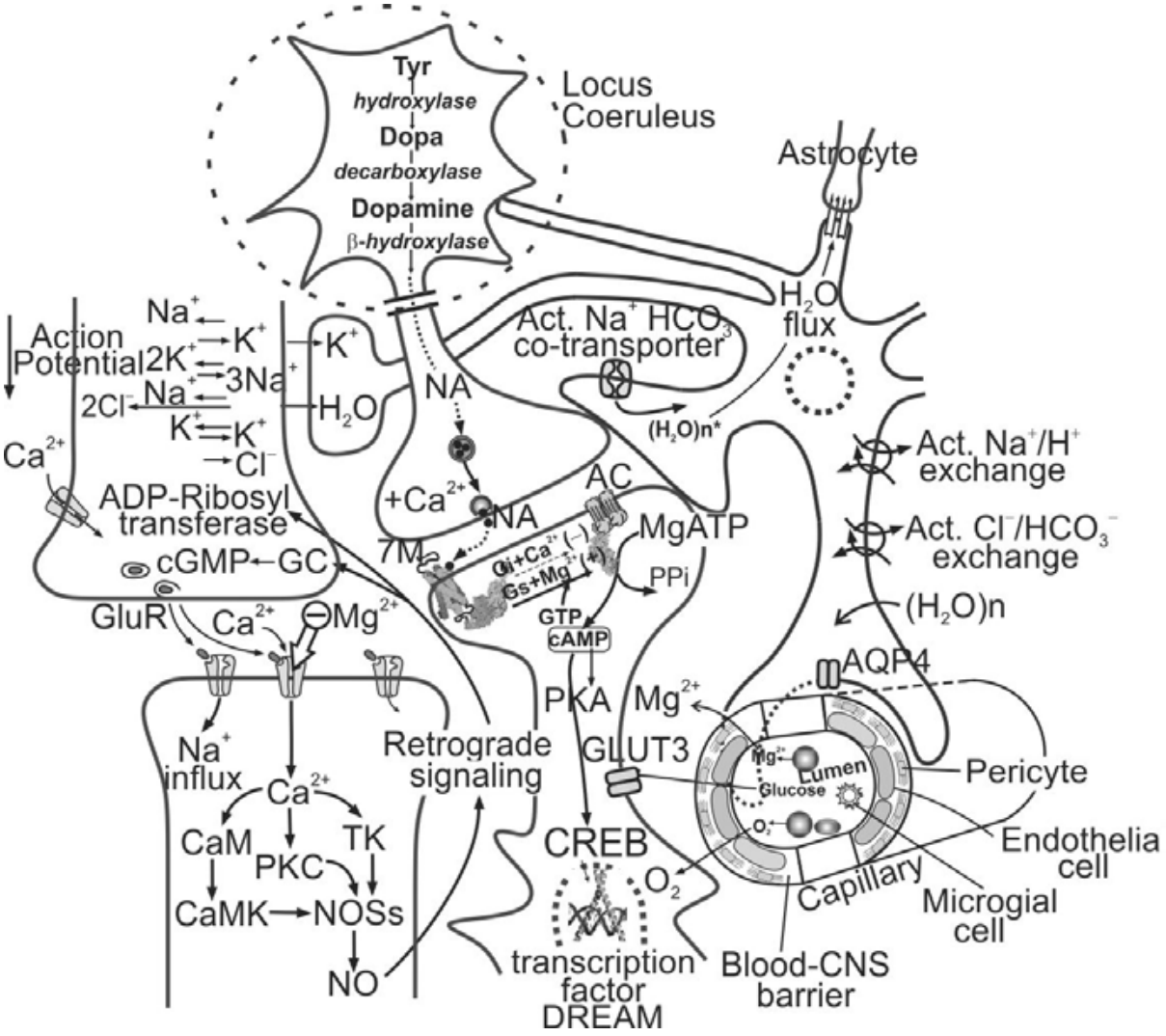

Figure 23: *Locus coeruleus axons presynaptically release noradrenaline (NA) for activation of a postsynaptic adenylyl cyclase. G-protein stimulated by a-receptor (Gas) in a Mg^{2+}-mediated coupling stimulate the postsynaptic NA-AC. The G-protein in Ca^{2+}-mediated coupling with the a-receptor inhibit (Gai) the postsynaptic basal AC. Glutamate receptors (NMDA) are inhibited by Mg^{2+}, the ion activating AC. Calmodulin (CaM), protein kinase C (PKC), tyrosine kinase (TK), nitric oxide (NO), nitric oxide synthase (NOSs), cyclic GMP (cGMP), guanylyl cyclase (GC), cyclic adenosine monophosphate (cAMP) response element-binding (CREB), glucose transporter-3 (GLUT3), NA receptors with Ca^{2+} + heterotrimeric-G-protein-a-inhibitory (Gai) result in decrease of cAMP. Mg^{2+} + heterotrimeric-G-protein-a-stimulatory (Gas) increases cAMP production [79]. Mg^{2+} may bind to the transcription factor DREAM (calsenilin/KChIP3) and alter transcription.*

The α and β antagonists are used to block to catecholamine excessive effects on the receptors in preparation for surgery.

The NA axon activity could spread to

glial (astrocyte) and the microglial release of specific cytokines and affecting permeability of the capillary, including modulation of the Mg2+ and O2, releases across the blood-brain barrier [80].

Increment of Ca^{2+} in cerebrospinal fluid (CSF) at the synaptic level could activate the glutamatergic neuron, and inhibits the noradrenergic neurons allowing the formation of the G-protein-α-inhibitory subunit complex (Gαi-receptor). The effect inhibiting AC could decrease the generation of cyclic adenosine monophosphate (cAMP) bellow basal levels.

Catecholamines are degraded by MAO (monoamineoxidase) and COMT (catecholamine-O-methyltransferase). The resulting metabolite is 3-methoxy-4-hydroxy-mandelic acid (aka VMA).

The cAMP increment by AC could initiate a voltage-gated nerve impulse because the tendency of a more reactive charge expressed by the Mg^{2+} partially deprived of hydric shell to displace Na^{+} from the outside into the inside of the membrane pore/channels. Neurotransmitters glutamate and ATP are agonists of receptor-operated channels (ROCs) present in the plasma membrane for uptake of external Ca^{2+}. The latter, as an intracellular second messenger role involves sensors that act through effectors Ca^{2+}-sensitive K^{+} channels, Ca^{2+}-sensitive Cl-channels (CLCAs). The buffer parvalbumin (PV) do not respond to a rapid Ca^{2+} signals onset, but soaks up Ca^{2+} for relaxation.

The increased volume of mitochondria couples to modulate the PV ability to remove Ca^{2+} during the recovery/reuptake phase.

Downstream regulatory element antagonist modulator (DREAM [81] like calsenilin and KChIP3 [82]) is structure of 29-kDa EF-hand Ca2+-binding protein functions as a transcriptional repressor by controlling prodynorphin expression and regulates pain-transmission. It translocates into the nucleus during calcium signaling for c-fos genes and blocks transcription by binding to downstream regulatory element (DRE) [83]. The cAMP has effect on gene expression in the nucleus of the cell and in the processes of growth and development. Cerebrum cells, lack of storage pathways are nutritionally dependent of a continuous uptake of glucose and oxygenation to support aerobic glycolysis.

Under starvation ketone bodies can only partially substitute for glucose. The need for signal transduction between tissues involved, required for matching the rates of O_2 and glucose consumption. This capability allows cerebral areas to increase by 10 times the rate of aerobic glycolysis without overcoming the homeostatic controls of glucose level in blood.

Conclusions

The endergonic transition states of the enzyme adenylate cyclase (AC) involves a number and strength of R groups on the enzyme within the membrane from its hydrophilic stage with an active site, requiring first to coordinate Mg^{2+} to produce AMP.

Conformational change occurs through reconfiguration of H-bond breakdown and their replacement from water cluster.

The new configuration allows release of nascent Mg^{2+} to coordination by Ca^{2+} and enzyme bending to form a new active site and induces a hydrophobic state required to extract water from AMP to cycle to cAMP.

The cAMP Response Element-Binding (CREB) by binding Mg-cAMP by H-bond breakdown could activate by inserting Mg-cAMP into DNA separating the two strands to produce a triple helix oriented to the outside and responding to RNA synthetase

for transcription into mRNA. The open DNA by coupling to the H-bond donor activity of the water cluster will return to the initial state to complete turnover.

The enthalpy (ΔH) flow at the brain is mainly glucose and the metabolic work generate (ΔG), will tend to a rather constant support of neuronal function, assuming 100%. The metabolism of glucose by neurons generated heat corresponds to the increasing temperature (T). The system has to be open for outflow of heat or ΔT will increase beyond homeostatic tendency, requiring 36.6℃ leading to develop an open system, excluding endogenous heat or lowering internal entropy by exclusion to the outside. This imposed intermediated circulatory stages through hydrophobic glial cells to allow the unstable dimers (H_2O~OH_2) [84] [85] to locate heat into a molecular resonance stage until reaching the outside of the system.

$$\Delta G = \Delta H - T\Delta S \quad \therefore \quad \frac{\Delta G}{\Delta S} = \frac{\Delta H}{\Delta S} - T \quad \therefore \quad \frac{100\%}{\Delta S} = \frac{\Delta H\ potential}{\Delta S} - T$$

A thermodynamics treatment of a system requires the initial and the final states. Applied to the Universe, the initial is a Big-Bang, an enthalpy flow, time parameterized by a primordial sound. The final state the assumed totally dispersed Universe in emptiness.

The Universe density and temperature through expansion relate a potential in which the tendency of entropy to accumulate inwardly that creates voids in expansion with inward vector of decreasing temperature.

Hence, expansion operates as opposed to global gravity as required by physical equations. The result is that within the Universe the balance of forces shifts from a close to an open structure with tendency to decrease the operational gravity force. Thus, accordingly the distancing tendency appears or manifests a dark energy and dark matter in the balances between the source of gravity (stars and black holes), nullifying the global curvature.

Conceptually allows that the exerted energy at the active potential level parameterized as H-bond breakdown manifested for its consumption from 55M of water cluster, assuming products of 50μM dimers $\Delta G = -1.4 \times \log\left(\frac{[P]}{[S]}\right) \quad \therefore \frac{50\mu M}{55.5\times10^6\mu M} \approx 10^{-6} \therefore$ 8kcal/mol.

Hence, 3-8kcal/mol of dimes has been obtained depending on the method because of the very difficult assay to measure the small concentration of product: dimers H_2O~OH_2 (or $(H_2O)_2$) in the large water cluster concentration.

The experimentally measured dissociation energy (including nuclear quantum effects) of $(H_2O)_2$ and $(D_2O)_2$ are 3.16 ± 0.03 kcal/mol [86] and 3.56 ± 0.03 kcal/mol [87], respectively. The O-O distance of the vibrational ground-state is experimentally measured at ca. 2.98 Å. The H-bond is almost linear, but the angle with the plane of the acceptor molecule is about 57°. The vibrational ground-state is known as the linear water dimer.

The dimer state of water retains the energy produced, which is not kinetically a collision by temperature because could be characterized as a resonance state that becomes manifest after flow by a glial system conduction to the vomeronasal organ (VNO) [88]. The operative system allows that only at the VNO the dimers structure resolve the resonance in vapor to be excluded to outside of the system.

Hence, solves as a dissipative of the accumulated entropy, cooling the brain to the homeostatic temperature 36.5–37.5℃.

Thus, in the absence of significant changes of temperature modulates the enthalpy potential flow as a function of entropy dissipation. Thus, operative by vapor water exclusion prevents any tendency for reversal reaction.

Therefore, conserves a vectorial state for a flow of enthalpy. The system allows the brain to function metabolically separated by the body adrenaline and many other hormones control of the adenylate cyclases system [89] [90] oriented to release metabolites into the blood supply available to brain.

Hence, allowing a separated NA control to the brain-AC (NA-AC). Thus, hypothalamic-NA-AC has the control of the HTPA axis of the body metabolic supplies. Hormonal preventing negative feedback by the body to oppose the brain left unrestricted access to the body metabolic reserve. Hence, the auto-regulation of the brain itself is dependent of CSF flow connected to the VNO as a final excretory organ.

The blueshift propagation allows inter-neuronal firing over distant brain areas to incorporate the functional firing of selected specific participants in the emergence of the sequence of events that configure the operative interaction between neuronal membrane micro scale and the nano scale of microtubule structures. The latter has the quantum function of antenna emission of radio microwaves that could synchronize the sequence at the molecular level of enzymes, ions and neurotransmitters for the electric potential required for firing.

These compartments form stable a plus to a minus end polarity oriented away or toward the neuronal soma. The CSF flow produces a redshift signal synchronizing events, which allows retraction of dendrites to non-firing positions between the neurons. Synchronization by antenna function of 21 cm line of H in CSF configures a signal to sequence for molecular events responding to nascent Mg^{2+} to generate Na^{+}/K^{+} translocation and activation of Na^{+}/K^{+}-ATPase, allowing to progress along the membrane of the voltage involved in the action potential for firing.

Dopamine, oxytocin, etc., at the child nurturing hormonal language allow synaptic plasticity to learn from observing lip and muscular movement of adult speaking to learn the use of sounds to confer meaning and cognition to communicate by adult language.

The Doppler shift [91] [92] could tune in with the spin-flip of electrons of a 21 cm line of hydrogen, operating as an antenna for the neuronal membrane action potential state of firing for vectorial networking. Thus, synchronizing the electric potential by a sequence of interneuronal crosstalk could avoid electromagnetic neuronal noises. At the nerve terminal, neurotransmitters are present within 35-50 nm synaptic vesicles that release neurotransmitters that dock and fuse at the base of specialized 10–15 nm cup-shaped lipoproteins. These porosomes range from 15 nm in neurons, astrocytes to 100–180 nm in endocrine and exocrine cells. In striatal neurons adenylyl cyclase (AC) coupled via 7TM receptors via stimulatory or inhibitory receptors (Rs and Ri) on G protein phosphorylation. A dopamine-(DA)-dependent cAMP/PKA interactions with acetylcholine and adenosine signals for DA transients to carry reward-related signals in learning reinforcement. The enthalpies of AC-H-bonds breakdown of intermediates coordinated by Mg^{2+} and bending and sliding when calmodulin release of Ca^{2+} to coordinative into hydrophobic box, and release of dimers in the up-hill thermodynamics cycling AMP into cAMP, creating molecular transitions capable to participate in meaningful encoding signals coordinative stages. The Mg-cAMP response

element binding (CREB) protein by insertion for DNA H-bond breakdown unzipping into three strands and transcription cycle turnover by coupling to H-bond donor water cluster..

Integration of vasopressin on the adrenergic response of the hypothalamic-pituitary-adrenal (HPTA) axis: the adrenergic tissue system. The hypothalamus through the magnocellular axons directly controls the posterior pituitary releasing oxytocin and vasopressin (ADH). The antidiuretic hormone regulates plasma osmolality and volume, and became in neurotransmitter participating on the control adrenocorticotrophic hormone release (ACTH). Pancreatic insulin and vasopressin provide coordinated parameters for the circadian rhythm

This neuro-system at the lactation nurturing stage of the human newborn is evolutionary linked to the genetic regression of the olfactory bulb into an olfactory epithelium. The consequences involve a motor disability restriction compared with four legged mammals and develop of a vomeronasal organ (VNO), which increases the human brain open system self-performance in entropy dissipation. As a consequence potentiates self-performance of the metabolic control as a perceptual of total body calories consumption.

The child's brain creates more than 1 million fresh neural connections (synapses) every second more than at any other time in life and functional speed by undergoing axon myelination.

The child's brain doubles in size in the first year and continue to grow by age 3 to about 80% of adult size.

At age 2 or 3, the brain has up to twice as many synapses.

Thereafter age 3, these brain connections slowly began to be reduced through a process called pruning and by age 5, finished 90% of total reached in adulthood.

The early human brain not yet completed is unable to be fully capable of voice control and has to develop a learning process from preceding stages of hormonal memory. Therefore, we proposed that latter on humans have incomplete access to this stage and therefore, to recognize the patterns evolved in Family containment and complexes, like the Oedipus (male child for mother) and Electra (female child for father), could be made to surfaces by psychoanalytic technics, exploring the unconscious.

The Doppler Effect at the circulatory system of blood or CSF synchronizes the transport of glucose, neurotransmitter and ions, required for enthalpy input in the structures of AC and DNA to generate the energy associated by H-bond breakdown to change their structure and affinities.

Turn-on by ionic Mg^{2+} and -off by Ca^{2+} the noradrenergic system has a pulsatile function. This could be differentially and complementary timed for the glutamatergic system turn-on by Ca2+ and inhibited by ionic Mg^{2+}. The stress related to the increment of the cortisol released hormone (CRH) could be observed in Alzheimer and acute depression.

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