The imidazole ring of proline allows a polypeptide folding dynamics by H-bonds breakdown sliding for a vectorial exergonic hydrophilic to an endergonic hydrophobic configuration for Hb and active site functions

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Abstract

Prigogine proposed a coupling between larger sources of enthalpy to allow an open system to operate life. The sun flow of energy is coupled to water cluster thermogenic breakdown of H-bonds to vapor. The position of proline in a polypeptide chain allows sliding between segments, in the tertiary folding structure response to electrostatic attractions, could differentiate positive vs negative domains. Thus, bypass the microscopic reversibility principle, illustrated as a single door, vectorial kinetic only made possible by the jokingly Maxwell proposed operator demons. The physiological function of Hb oxygenation by pO_2 shows a microscopic thermogenesis biological vector, functioning by the enthalpy potential of the large mass action of surrounding air and releasing entropy. The mechanism shows the H-bonds breakdown required for changes in the structure-function levels by the proline mediated folding. The tense (T) to relax (R) forms shows vectorial microscopic dynamics, during Hb oxygenation. Thus involves a sliding by H-bonds breakdown, distancing between subunits β_2 and α_1. Thus, open a larger entrance to a fully hydrated Mg^{2+} to coordinate amphoteric and negative R groups characterizable to a hydrophilic site. The transition of R to T allows positive R groups to bind 2,3-DPG^{5-} to form deoxyHb. Thus, a microscopic smaller entrance by decreasing its opening size does not allow entrance of the fully hydrated Mg^{2+}, but allow the exit of nitric oxide (NO) and a poorly hydrated Mg^{2+}, denominated *nascent*. This one acts for competitive hydration sieving on the shells of Na^+, which in terms take water from the K^+ shell, potentiating a K^+/Na^+-translocation operating the electrogenic transmembrane potential. The deoxygenation in the reverse transition of R to T binds NO, protecting against a premature decrease of the chromosome's telomeres size by stressing factors such as depression, anxiety and physic traumatisms, over endothelial cells delaying premature senescence. The arginine metabolism produces NO, dilating blood vessels, improving the circulatory systems and the muscular recovery-development. In vascular niches, endothelial cells of blood vessels produce NO, which activates the Notch signaling pathway of neighboring cancer stem cells, thus regulating their self-replication. A diet rich in arginine by producing a high sustainable level of NO may prevent the resistance to treatment by the consolidation of large vascular masses. The H-bonds donor potential by their breakdown leads to randomness (or entropy) decreasing the kinetic energy of solvation, scaling down the polarity on the thermogenic dissipation of oxy vs deoxyHb and choroid plexus epithelium on plasma generation of cerebrospinal fluid (CSF). The enthalpy of photosynthesis-metabolism releases CO_2, whereas the water cluster mediated thermostatic function releases vapor. In both systems, the entropy release maintains a high potential of enthalpy. Hence, overcomes the thermic and electric noises by an irreversible dissipative kinetics, facilitating a clear development of a meditative level of reasoning and learning. Thus, the brain acquires an autonomous function, beyond behavioral genetic conditioning.

Introduction

The chloroplast's studies showing the vector kinetic of the ATP synthase-ATPase was in apparent contradiction with the principle of microscopic reversibility. The impossibility to differentiate between hot- and cold-molecules allowed a humorous description by Maxwell that the operators of a single door, capable of doing so, should be called *demons*.

Figuratively, the principle describes that a single microscopic door allows transit in both senses, allowing only a closed thermodynamic system, which only allows changes by mass-action equilibrium. However, an irreversible open system do have vectorial kinetic as long that enthalpy is totally dissipated.

Hence, to evade that incompatibility [1], it is possible to assume two inversely linked doors, mutually exclusive, one open to be when the other is closed. The conformational changes described are operating when one domain is hydrophilic and the other turns to become hydrophobic.

Vectorial kinetics is conferred by proline-dependent polypeptide folding dynamics. The H-bonds could be regarded as doors, when open attracts water cluster to the segment containing negative R groups capable to coordinate Mg^{2+} (first door).

This hydrophilic configuration has to be mutually exclusive by H-bonds breakdown (second door) to reconfigure a hydrophobic structure of positive R groups to attract negatively charged molecules like ADP^{3-} and AMP^{-}. However, the endergonic product: cAMP, which could not be liberated from a hydrophobic close environment, which allows water exclusion for vectorial decrease in energy of cyclization. However, Mg-cAMP is released by the large mass action of water clusters and the increase in free Mg^{2+}. Turnover requires the mass-action of water cluster for additional H-bond breakdown, reconfiguring the obligatory Mg site characterizing the hydrophilic state.

These are transitions thermodynamically coupled between an exergonic reaction couples to drive the endergonic, sliding event by the H-bonds breaking of the binding folding dissipative heat release.

The directionality would be given by mutual exclusion and this complementarity would be the conformational change of the protein, dependent on a breakdown of a small ratio of H-bonds of the total potential of the water cluster. A subsequent event depends on the exergonic uphill event of H-bond breakdown to recreate the hydrophilic domain (3th door). However, this step has the large contribution to the enthalpy of the system by a natural coupling to the high H-bond mass action of water clusters at molar level. The system operates with the remaining H-bonds within the water cluster. This is rather not detectable since at the test tube reactants and products are at μmolar level. However, the water cluster involves the solvation energy of encompassing saturation surroundings [2] [3] [4] [5].

Experimentally the solvation tendency was measured on the activity shown by the heat activated-ATPase, determined from its maximal value assayed as basal with glycerol addition at 0% only in the presence of water clusters. The curve obtained by decreasing enzyme activity to zero is reached by adding glycerol to reach 8% concentration into the mixture.

A Lineweaver plot allowed the determination of a cooperativity number of 16 that divided by two, a value for the microscopic energy of solvation. The presence of two active sites revealed that each one was structured by the binding of water at 8 solvation sites. Therefore, the basal condition showed that glycerol was a competitive antagonist to H-bond breakdown.

The number of 2-, 3- and 5-coordinated water molecules produced from broken tetrahedral structures increase upon heating [6]. Temperature and shearing can break down a large number of H-bonds within a network. At low temperatures 50% of water molecules are included within clusters.

With increasing cluster size the oxygen to oxygen distance is found to decrease, which is attributed to so-called cooperative many-body interactions: due to a change in charge distribution. The H-acceptor molecule becomes a better H-donor molecule with each expansion of the water assembly. Many isomeric forms seem to exist for the hexamer $(H_2O)_6$ from ring, book, bag, cage, to prism shape with nearly identical energy. Two cage-like isomers exist for heptamers $(H_2O)_7$ and octamers $(H_2O)_8$.

The imidazole ring of proline role in polypeptide dynamics

The H-bond dynamics on folding allows the peptide bond a resonance stabilized polar and planar structures. Two parallel β-pleated sheets with an intervening strand of α helix domains bends on the surface of globular proteins. This structure offers little steric hindrance to a modification in the direction of the polypeptide chain.

The imidazole ring, a five-membered ring of proline, allows a second residue to manifest a reverse turn.

Constructing mutual exclusion domains through H-bonds turnover allows the interaction between distant regions of a polypeptide chain. The hydrophobic effect drives protein folding in about

10^{-1} to $10^{-13}s$ to rotate around the $C-C_{\alpha}$ and $N-C_{\alpha}$ bonds of the polypeptide backbone.

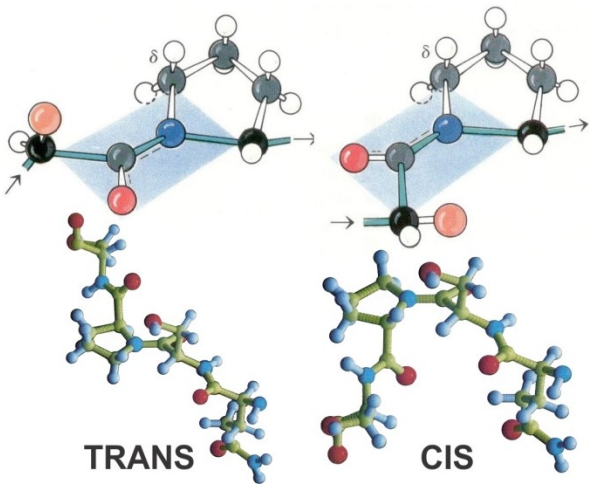

Figure 1: Dynamics of isomer cis of proline in configuration allowing sliding between two domains helix-turn-helix changing the correspondence between a hydrophobic vs hydrophilic site.

Required to bend, twists and folds the polypeptide sequence at the tertiary structure level, by producing differential configurations by hydrophilic associations of cations $(Mg^{2+}, Ca^{2+}, \text{etc.})$ and hydrophobic for anions $(2,3-DPG^{5-}, ATP^{4-}, ADP^{3-}, AMP^{2-}, cAMP^{-}, \text{etc.})$.

Hemoglobin and O_2/Mg^{2+} control of a membrane action potential

The crystallography x-ray analysis by Max Perutz [7] was able to determine the quaternary structure of oxyHb, without characterization of the Mg^{2+} role for a hydrophilic site.

The oxyHb has a topology of two hydrophilic interphase $\beta_2\alpha_1$ and $\alpha_2\beta_1$ that coordinate one Mg^{2+} each. In deoxyHb the topology is restructured by the tetramer subunits, lining positivity-charged R groups of amino acids and His β_2 143 that turns around into the central pocket to bind $2,3–DPG^{5-}$. A decrease in pH favors the protonated forms for formation of deoxyHb. Hence, the oxyHb contains two interphases to coordinate $2Mg^{2+}$ into hydrophilic domains, which are mutually exclusive with a single $2,3–DPG$-dependent domain included in the tetramer structure of deoxyHb [8] [9] [10] [11] [12] [13].

The conformational irreversible change involved two Mg^{2+} chelating dynamics interfaces in the Hb tetramer with a His R groups at the interface of $\beta_1\alpha_2$ chains of Hb, an a second symmetric chelating site at the $\beta_2\alpha_1$ interface for each Mg^{2+}. The conformational change by the release of $4O_2$ and $2Mg^{2+}$ at tissue level became irreversible because the amphoteric R group His 143 move from coordinating Mg^{2+} at oxyHb to integrate the deoxyHb to conform within the positive R groups that form a single binding center for $2,3–DPG^{5-}$ at the deoxyHb.

At the deoxyHb a vectorial by kinetic by the sieving effect at the α_1 subunit by the R group of Pro 44 sliding between β_2 His 97 and α_1 Thr 41 to block now the entrance of the larger fully hydrated Mg^{2+} into the interface of β_2 and α_1 chains, which now only allows the exit of the smaller incompletely hydrated: nascent Mg^{2+}. The neutral soluble in fat and water NO enters attracted by the positive R groups, holding $2,3–DPG^{5-}$.

The absence of guanylate cyclase activity at the human red cells shows its capability to be a carrier of cGMP by its uptake from extracellular fluids.

The erythrocyte uptake of cAMP and cGMP allow their signaling to participate in the regulation of intracellular process, without *in situ* formation because could be delivered by blood [14].

At tissue level the erythrocyte, at low O_2 the Hb protein release of $4O_2$ jointly with the breakdown of 2 coordinated Mg^{2+} (Mn^{2+} or Zn^{2+}) atoms, involved the existent of vectorial kinetic by the movement of the pyrrole R group of Pro α 44, allowing the tertiary structure for sliding of the α_1 vs β_2 positions in amino acids polypeptide subunits.

Thus opening in the T-->R transition for uptake and coordination of Mg^{2+} and closing in the R-->T transition for releasing and preventing the coming back of Mg^{2+} the system shows vectorial kinetic. Thus, evading the principle of microscopic reversibility since the event could be characterized by over two linked conformational changes, acting synchronized in inverse relationship, one open and the other closed hereby described as mutual domain exclusion.

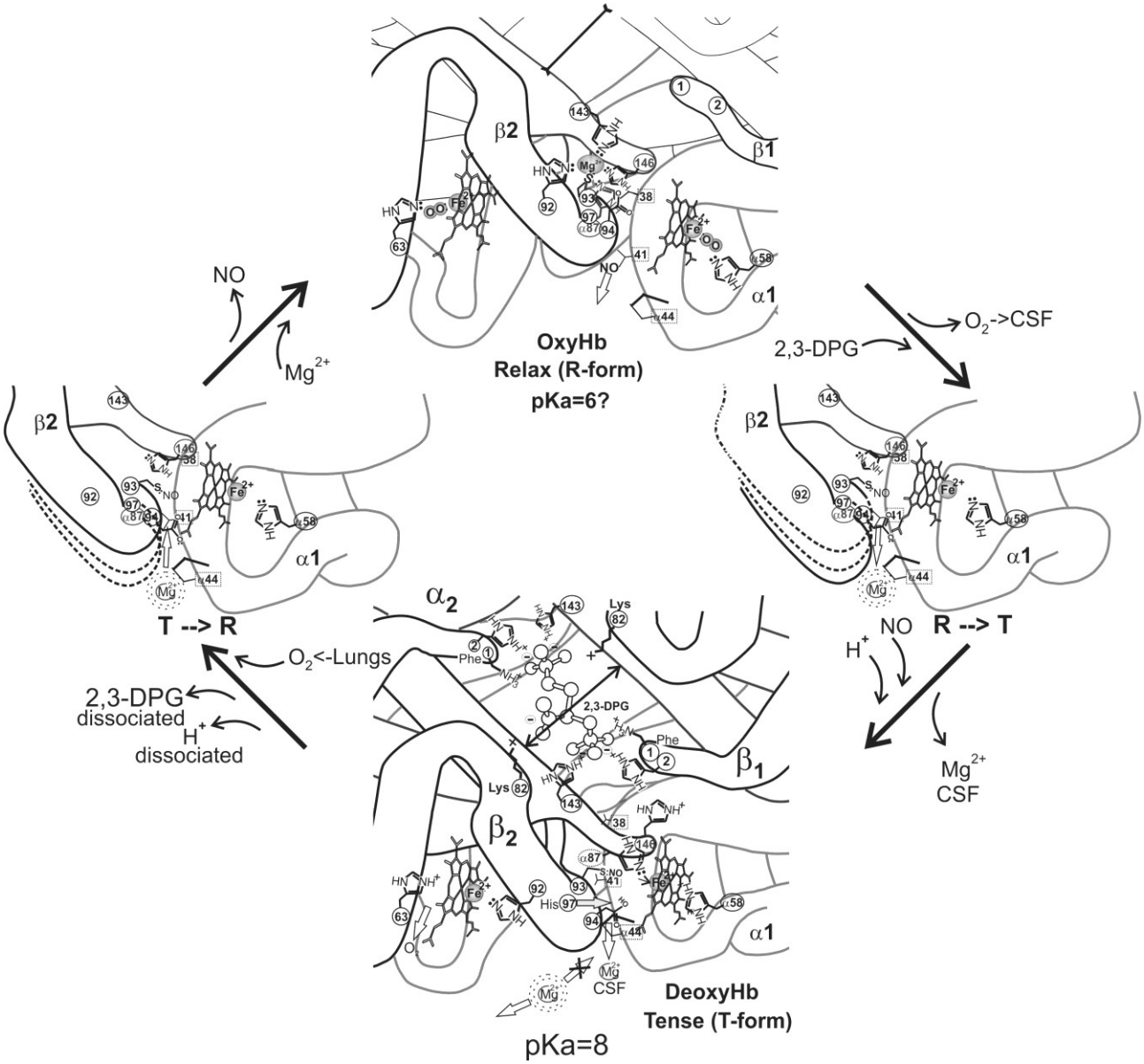

Figure 2: The four Heme oxygenation sites correspond to two dimer interfaces: $\alpha_2\beta_1$ and $\beta_2\alpha_1$. *The negative R groups force the release of NO when $2Mg^{2+}$ coordinate and $4O_2$ occupy the 4 heme to form the hydrophilic oxyHb. A relax (R) form of oxyHb has a pKa=6.2 acting as a carrier for O_2 and Mg^{2+} to be release at tissue level. The action results in the hydrophobic tense (T) form of deoxyHb pKa=8.2. The in between H-bond breakdown allows an irreversible kinetic step, between both forms of Hb, because are mutually exclusive.*

The O_2 pressure between lung and tissue level becomes the physiological/biological driving for an open system function relates to cycle of O_2, but since the turnover itself comprises conformation changes is also coupled to the H-bond breaking out, releasing energy and the large mass action of water cluster $(H_2O)_n$ to reconstruct the solvation state. The H-bonds decreases "n" and the single molecule of water formed without H-bond as vapor. Thus, both sources of energy are dissipative functions with irreversible kinetic in the absence of solar energy.

Peptide bonds are rigid and fixed in a plane in where two α-carbons, 3.6 Å apart, rotate by angles ϕ (fi) and ψ (psi). The tertiary structure in the 2α and 2β polypeptide chains of Hb bends, twists and folds over and back upon imidazole R-groups. With pKa of 6.5 that at about pH 6 shows two NH bonds that share in a resonance a positive charge. Hence, the hydrophobic state form of the protein by an O_2 induce conformational changes $\alpha_1\beta_1$ dimer to rotate 15° around of other dimer $\alpha_2\beta_2$.

The two His β_1 and β_2 143 during oxygenation are changed in relative position by the

quaternary restructuring topology and move to the interphase $\beta_2\alpha_1$ and $\alpha_2\beta_1$ to participate in the disruption of the 2,3-DPG binding site. Hence, the oxyHb contains two ions at the interphases: Mg^{2+}-dependent hydrophilic domain, which is mutually exclusive by rotating His β_2 143 into binding with 2,3-DPG. This R group, the amphoteric or zwitterionic form (can react both as an acid and as a base) changes hydrophilic state to be included in the positive R group domain of $2{,}3{-}DPG^{5-}$, within the tetramer structure of positive deoxyHb.

The two dimer interfaces: $\alpha_2\beta_1$ and $\beta_2\alpha_1$ link by two $Mg^{2+}.(H_2O)_n$ the dynamics of conformational change to an hydrophilic state of the protein, by chelating [15] the R groups His β_2 92, Cys β_2 93 and Asp β_2 94, could attract sequentially the iron in the 4 hemes by His β_2 92, moving to coordinate Mg^{2+} and coordinate to His α_1 87. The 4 irons within the 4 Hemes could move to the outside surface to interact with the distal His β 63, increasing Hb affinity for the ligands by forming an H-bond with O_2.

The publications at Rutgers [16] showed conformational allosteric changes, were kinetically depend of hydrophilic configuration to form a coordinative center for Mg^{2+} (or Zn^{2+}), operating the dynamics of R groups response to oxygenation.

The His α_1 87 moves by Mg^{2+} coordination to interact with the oxy Heme α_1.

Deoxygenation allows His β_2 143 to be released from Mg^{2+} to participate in the $2{,}3{-}DPG$ stability.

Thus, shows that the mutual exclusion between binding O_2 or $2{,}3{-}DPG$ has synchronized the motion of R groups responding to oxygenation function.

The importance of this contribution was to show protein dynamics in reference to pressure of O_2 mass action in the orientation of hydrophilic R groups (His, Cys, Asp).

The binding of $2{,}3{-}DPG$ to charged positive R groups lead to hydrophobic state of the protein, with the energy potential in the protein structure in the direction of the spontaneous exergonic dissipative state and therefore the system becomes a potential dissipative thermodynamic path, between hydrophilic oxyHb and hydrophobic deoxyHb.

The dissipative potential functions from the greater atmospheric O_2 pressure to the lower one at the tissue level, became self-organized by Mg^{2+} sequential coordinative from negative residues and the amphoteric histidine. Thus, O_2 pressure creates maximizes potential by Mg^{2+} saturation through bi-, tetra-, hexa-dentate stages, and steadily releases along the differential axis of tissue consumption of O_2 delimited by lower and lower pH (the vertical human posture favors oxygenation of its brain, over that its lower extremities, absent at the quadruple posture of other mammalian.

The model explains sigmoidal binding properties (i.e. positive cooperativity) by the progressive binding by $[Mg.(H_2O)_6]^{2+}$ from two to fourth to six coordinative states with the corresponding number of R groups.

An open system magnifies the function of the mass action of substrate concentration because the product is in a dissipative state and therefore could acquire a lower concentration than predicted from kinetic equilibrium.

Accordingly, at the brain membrane potential transmission of electric signal are potentiated well above that of thermic noises. Thus, because adrenaline could not cross the blood-brain barrier (BBB), the body became restricted to signal stress feedback, capable to turn-off the hypothalamic-pituitary-adrenal (HTPA) axis to persist in exhaustion of metabolic reserves.

This system allows the human brain to be conditioned by achievement related to the euphoric sense of an athletic successful performance, even at the cost of stressful events. The mechanism may involve the conversion of dopamine to noradrenaline (NA) by dopamine β-monooxygenase, which occurs predominantly inside neurotransmitter vesicles.

Most vertebrate species devote between 2% and 8% of basal metabolism to the brain. In primates, however, the percentage is much higher in humans it raises to 20–25%, a person uses about 320 calories only to think. Thus, this exceptional energy expenditure leads to autonomous thermogenesis, involved in the daily turnover consuming 450ml of cerebrospinal fluid (CSF), to be released as a 5% of vapor in exhaled air.

The vomeronasal organ (VNO) [17] [18] in the oral cavity contains the cell bodies of sensory neurons which have receptors that detect specific non-volatile (liquid) organic compounds which are conveyed to them from the saliva, environment, etc.

Hb transport of nitric oxide

The enzyme nitric oxide (NO) synthase catalyzes from arginine the products citrulline and NO. This one is a strongly reactive radical by having an unpaired electron, solubility in water and lipids, which allows crossing biological membranes. Endothelial cells at the blood vessels surround smooth muscles, which do not have sarcomeres (involuntary non-striated muscle). Muscarinic receptors to acetyl choline (ACh) distend muscle. The endothelial release of Ca^{2+} binds to calmodulin activating the enzymes hemoxygenase: HO-1 (spleen and liver) for NO and HO-2 (brain) for CO from Heme group of Hb, and a third system CSE producing H_2S.

Nitric oxide synthases (NOSs) synthesize the metastable free radical NO. Three isoforms are known for the NOS enzyme: endothelial (eNOS), neuronal (nNOS), and inducible (iNOS) - each with separate functions.

NO and CO integrate to activate the cellular smooth muscle activating guanylate cyclase (sGC), generating from GTP the product cGMP. The latter by bridging actin and myosin relaxing muscle and H_2S, activating the K^+ discharge through the K^+ channel, and dilatation of blood vessels.

At low concentrations of the 3 gases contribute to control blood pressure, favor the release of other transmitters and hormones, protecting cells from the oxidative stress. At the brain stimulates learning and cognition. NO differentiates from other transmitters usually enclosed in vesicles and liberated at synapsis like acetylcholine, dopamine and glutamate. NO could diffuse to a distance of $300\mu m$, reaching simultaneously 2×10^6 synapses. Thus, activates in a retrogression manner, the presynaptic neuron. Thus, the process could prolong for many hours the liberation of neurotransmitters by the neurons to potentiate a learning state.

The broad spectrum of NO release of other transmitters in the nervous system, dilates blood vessels in the cardiocirculatory system, protects against oxidizing agents in somatic cells, participates in learning and memory processes in the brain, in the lungs relaxes the respiratory muscles and relaxes the digestive tract and produces erections.

The NO protector effect is expressed along the body and it is considered aggressive at large concentration, it has an odd electron that makes it very reactive and volatile.

The macrophages of the immunity system and the astrocytes microglia, producing myelin at the brain axons has been endowed with a toxic barrier indistinctly acting against all microorganisms, parasites and tumor cells. Hence, is a nonspecific inborn, constitutive and protective defense that could be increased by diet, including arginine.

Consequently, adds to the specific antigenic action by the reaction produces by microorganisms generating disease, which leads the immunity system to produce the corresponding recognizing anti-bodies, which can be reinforced by vaccines.

The NO could react with peroxide water (H_2O_2) to produce peroxynitrite $(ONOO^-)$.

NO in excess could damage cells and at the neuromuscular synapsis activates cAMP production, potentiating the cAMP response element binding protein (CREB). Also, inhibits the cAMP destruction by phosphodiesterase prolonging its time action, favoring a neuronal circuit plasticity state.

Dietary nitrate as source of NO green, leafy vegetables is concentrated by about 10-fold in saliva and reduced to nitrite in the surface of the tongue by a biofilm of anaerobic bacteria [19]. In the stomach reacts reducing metabolite as vitamin C to produce a high concentration of NO. Thus, allows sterilization of swallowed food and to maintain a gastric mucosal flow into blood [20].

NO is an obligate intermediate in the denitrification pathway and it is converted to nitrous oxide by the activity of NO reductase (NRs). NRs are molybdoenzymes that reduce nitrate (NO_3^-) to nitrite (NO_2^-) in both mammals and plants.

In mammals, the salival microbes take part in the generation of the NO_2^- from NO_3^-, which further produces NO in the presence of nitrite reductases (NiRs) [21].

NO diffusion tubes could be used as a spray in absence of consumers to fumigate food locals, modifying air conditioning could add protecting ventilation, airplane, etc.

Physiological NO production by adding to diet of arginine, presently used as a dietary supplement by bodybuilders because can potentiate the physiological role of NO, dilating blood vessels, improving circulatory systems and muscular

development, potentially can improve sports performance and muscle recovery.

Arginine role in aging

At the end of the eukaryotic chromosome, long repetitive DNA strands (telomeres) are configured. Aging produces its shortening, which is correlated with chronic pain and phobic anxiety.

Telomeres shortening in atherogenesis leads to investigate telomerase, a RNA-directed DNA polymerase, which extends the telomeres of eukaryotic chromosomes.

Nitric oxide (NO) is a reactive free radical that regulates transcription of genes involved in development, metabolism and differentiation. Is has been shown that NO activates telomerase and may have in endothelial cells a delay of senescence [22] [23].

Endothelial cells (ECs) undergo a limited number of cell divisions, stop dividing, and reach a replicative senescence by acting as a molecular clock. By the reactivation of telomerase, a cellular reverse transcriptase could prevent telomere shortening [24].

The endothelial isoform of the nitric oxide synthase (eNOS) [25] effect on downstream signaling of the catalytic subunit of human telomerase reverse transcriptase (hTERT, for understanding the pathogenesis and searching for therapeutic approaches) and ERs, counteract the process of endothelial cell aging [26] [27].

The telomeric repeat-binding factor 2 (TRF2) is a protein that is present at telomeres but its function, throughout the cell cycle, has been studied for possible regulatory effect by arginine methylation.

It is suggested that a restriction of senescence progress could be approach, by incubation procedures for Hb, to be used as a carrier of NO. Consequently, adapts the NO saturation of Hb for its *in situ* release to endothelial cells. Thus, allows the gas exchanges, required for vasodilation of blood vessels, in cardiovascular physiology. Exercise improves endothelial function with produce NO, which keeps blood vessels healthy.

Nascent Mg^{2+} compete by attracting water from the shells of Na^{+}/K^{+} allow sizing translocation at the ions gates that support the membrane potential

The erythrocyte as a carrier of the kosmotropic Mg^{2+} could function signaling for the capture of water from the hydration shells of Na^{+} and K^{+}, fitting both into their gates, allowing across the membrane the sieve effects, which confers specific pattern of an action potential, contained in neuronal junction's vesicles to activate the NA activated-adenylate cyclase (AC) located in the locus-coeruleus.

This sieve effect potentiates the K^{+}/Na^{+}-translocation operating the membrane potential. Mg^{2+} activates the Na^{+}/K^{+} ATPase pump opening the gates for Na^{+} in and K^{+} out.

In response to a nervous impulse, their hydric and dipolar states can change by dynamics of the H-bonds could manifest discrete states of molecular vibration, at $36.6℃$. The brain maintains a steady state in which small changes that last between 200 and 2000 ns do not alter the frequency. Quantum mechanics describes them as wave, phonon. This could be cycled as a vectorial function of hydric-ionic translocation, participating into the active site for enzyme state turnover. The energetic contribution of the H-bond breakdown its value is about: -5kcal/mol utilized to configure a conformational change by mutual exclusion.

Ca^{2+} [28] released activates the glutamate neurotransmission [29]. Serotonin (5-hydroxytryptamine, 5-HT) produced in Raphe nuclei located in the brainstem, could induced Ca^{2+} increase and reduced the cAMP increase [30], indicating cross-talk between the 5-HT-sensitive Ca^{2+} and cAMP pathways. Ionic equilibrium controlling Ca^{2+} effects for a simultaneous dead-end by CaATP [31] [32] inhibition of adenylate cyclase (AC) and mutual exclusion activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor, first glutamate receptor ion channel domain.

Turnover, with release of Mg^{2+} from the enzyme 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.

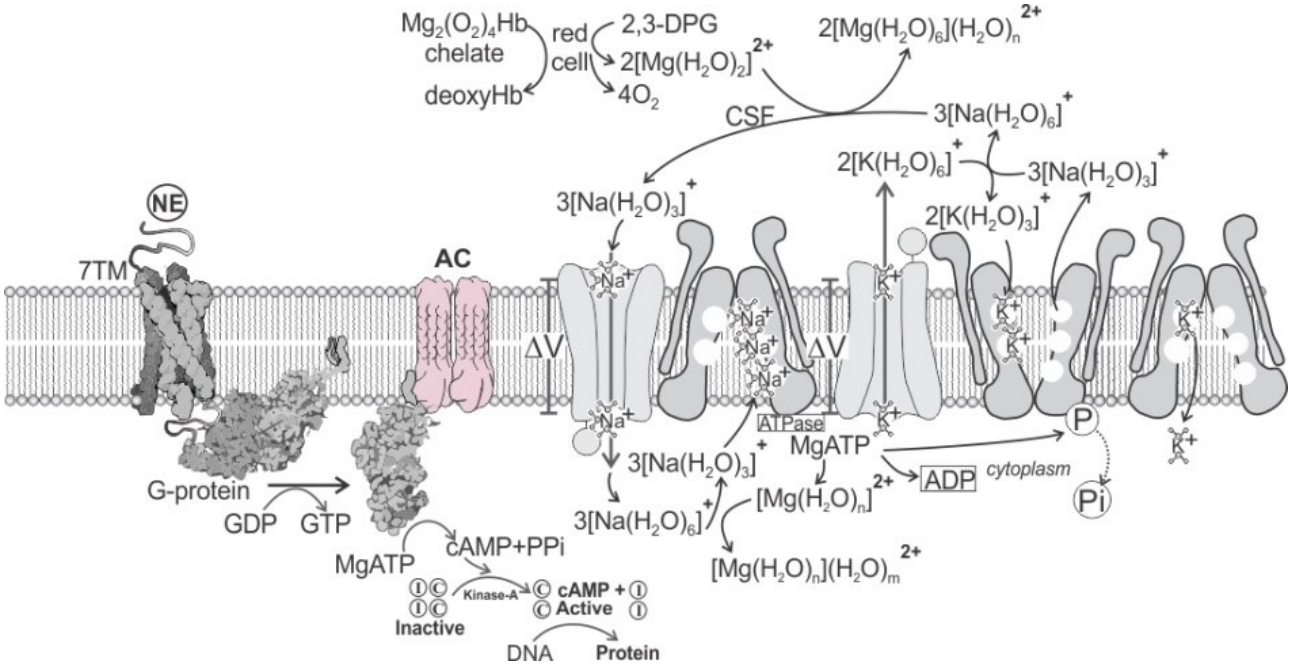

Figure 3: The mutual exclusion between oxyHb vs deoxyHb *allows Hb to be a carrier of O_2 plus the hydration shell of nascent Mg^{2+} released to activate the tissues demands for electrogenic action potential. The nascent Mg^{2+} tends to subtract water from the hydration spheres of other ions, to complete their own. The incomplete octahedral geometry of the second hydric layers of kosmotropic: $(12H_2O).[(6H_2O).Mg^{2+}]$ allows subtracting H_2O from the hexagonal geometry in the first hydric layer of $[(6H_2O).Na^+]$ to configure an $[(3H_2O).Na^+]$ a smaller size, which allows access to the its outside channel to transverse into membrane inside to subtract H_2O from the inside $[(6H_2O).K^+]$, allowing its translocation to the outside. Thus, activating the Mg^{2+} required Na^+/K^+-ATPase.*

Change conformation turnover of protein is supported by the activation energy of broken H-bonds, from polymeric water in cerebrospinal fluid (CSF), conversion into waste water. Astrocytes [33] could maintain the H-bond wasted state of water in a liquid phase until their release as vapor to the outside of the system, which is equivalent to entropy dissipation.

Brain metabolism releases CO_2 and H-bonds breakdown thermogenesis are carried by air and CSF respectively to dissipate entropy and maximize the enthalpy potential through an open system function

The myelin is a lipoprotein material that constitutes complexes of phospholipid bilayers. It is found in the nervous system of all vertebrates, forming a thick layer around the axons of neurons that allows the transmission of nerve impulses between different parts of the body thanks to its insulating power.

The glycation process requires the N-Acetyl-D-glucosamine (2-Acetamido-2-deoxy-D-glucose, D-GlcNAc) [34].

The process consists of adding a single N-acetylglucosamine sugar to the serine or threonine of a protein. This is a mean of either activation of enzymes and transcription factors or deactivation by a removal process.

In many animals, the olfactory bulb [35] integrates motor function, which allowed their offspring to reach self-care, in a short time.

After normal myelination in the utero, myelination of the neonatal brain is far from complete. In the column of Burdach, the first myelination is seen as early as the 4 months of gestation, but increases rapidly during 24th week.

Humans are born with an unmyelinated central nervous system (CNS), which reach maturity in the child 2 years old child.

In the human atrophy of the olfactory bulb leads the loss of newborn baby brain motor projections and under develop vision.

The lack of response of the sympathetic motor system, to a signaling by the hypothalamospinal tract, could not become consolidated until the infant [36] learn to walk.

Myelin sheath wraps appears in the CNS in spinal cord, brain and optic nerve. At the peripheral nervous system (PNS), by the cytoplasm extension of Schwann glial cells, wraps the oligodendrocyte along neuronal axons.

The function of segmentation by Ranvier nodes in between myelin sheets is to provide localization of voltage gating Na^+-channels, to allow jumps of action potential. Thus, accelerates its transmission along fine-tune circuits, differentiated by the structural connectivity.

Myelin reduces the accumulation of charges or capacitance of the axonal membrane at the Ranvier nodes (1 micron unmyelinated section). In this the action potential "jumps" following a nodes sequence. At the axon terminal the action potential releases the neurotransmitter at the synapses.

Insulating by myelin results in normal operations of walking and the sensory system: hearing, seeing and skin sensitivity.

Increasing myelination of the motor system allows lifting the head, roll over, reach out and crawl, and eventually walk and running. Learning motor skills require practice, connecting the sensory feedback by the spinal cord brain connection.

The myelin structural plasticity role in cognition could restructure important brain connections, by the myelination of axons.

Process improves by about 300% the velocity of the action potential transmission. Also by myelin isolation of an action potential pathway could prevent the interference between neuronal circuits, a *noise* equivalence, which facilitates learning and use of interneuron signaling or language.

O-GlcNAcylation decline in the human brain by aging is associated with cognitive decline. When O-GlcNAcylation was increased in the hippocampus of aged mice, spatial learning and memory improved [37].

Synapsis plasticity

The learning mechanisms of *Caenorhabditis elegans* (302 neurons) are simple. It detects and memorizes an enormous diversity of stimuli: smells, tastes, temperature, tactile sensations, and oxygen concentration.

Its sensor cells connect with the interneurons responsible for processing received information and sending a response to the command neurons.

The neurons activated by a stimulus release glutamate to the synapses, from a smaller number of receptors, promoting the entry of calcium into the neurons, which entails the fixation of memories. But their structure is very similar to mammals, and they function in learning, although they have originated in remote periods of evolution.

Among the transcription factors, the cAMP response element binding protein (CREB) stands out. In humans, the CREB protein promotes the formation of lasting memories, since it facilitates the production of proteins that modify synapses [38].

Genetic vs environmental experiential learning along the nurturing context of emotional intelligence development

Genes account for between approximately 50% and 70% of the variation in cognition at the population level.

A connectome is a comprehensive map of neural connections in the brain, and may be thought of as its "wiring diagram". An organism's nervous system is made up of neurons which communicate through synapses. A connectome is constructed by tracing the neuron in a nervous system and mapping where neurons are connected through synapses.

During childhood, cognitive abilities dramatically improve to make us who we are: persons capable of multiple academic, social, and professional activities [39].

Intelligence quotient (IQ) differences between individuals have been shown to have a large hereditary component. However, it does not mean at groups-level exist evidence for a genetic component between racial groups.

The results suggest a synchrony between gender-related differences in the brain network and behavior [40].

During nurturing conectomas for sex differentiation had been characterized in men by prefrontal to visual cortex and by transversal connectivity in woman.

Stronger structural connectivity in motor, sensory, and executive functions matched higher spatial and motor skills in men. In the latter there is an increase of neural connectivity within one hemisphere of the brain. Thus, suggesting that men's brains are structured to facilitate connectivity and coordination between perception and action.

In women, there are stronger neural connections between both cerebral hemispheres, which would facilitate communication between the analytical mind and intuition. In women, the subnets associated with social cognition, attention and memory showed greater connectivity, which was consistent with higher cognitive-social and memory skills in women than in men.

No differences have been found in the size of the corpus callosum or in the white matter, which allows the two sides of the brain to communicate with each other.

Studies of human patterns resulting from interaction of mother-infant separation, as related with decreased glucocorticoid receptor gene methylation of post-traumatic from early life stress.

In the newborn human, the residual structure from evolutional deletion of the olfactory sense allows a memory unable to coordinate muscles most likely the sympathetic motor pathway has yet to be integrated. This process requires a long period of parental care, before reaching the brain structure of neuronal circuits, capable to support muscular interaction and development through a cognitive visual-hearing language.

The locus coeruleus contains about 6×10^4 noradrenaline-adenylate-cyclase (NA-AC) neurons characterized by their very long axons reaching almost every region. Thus, inputs from saliva at the 7TM receptors of AC, located at the rostral-oral-cavity reach [41] the hypothalamic-pituitary-adrenal (HTPA) axis controls on the psychosomatic metabolic network. The increment of adrenaline secretion [42] [43], but without entering the cerebrospinal fluid (CSF) [44], shifts body metabolism in the direction of depleting metabolic reserves like fats and cortisol, releasing amino acids from some brain proteins by gluconeogenesis control. This mechanism is based in the absence of negative feedback by adrenaline. The latter could not cross the blood-brain barrier (BBB) and therefore have only an incomplete control over the inhibitory signaling, allowing to stop adrenal secretion.

A metabolic perspective could explain the function and structure thermodynamics advantage of assigning to the brain, unchallenging nutritional control of body metabolism for maximizing its own development.

Thus, a brain pattern of emotional-hormonal control, over metabolic supporting functions, may participate on the psychosomatic bases of the unconscious [45]. Thus, emotional rewards are granted for human competitions adding a selective control response to the primitive animal fight-or-flight conditioning.

Hormonal glands secretion at the arterioles irrigating the oral cavity could represent a near autonomous hormonal signaling control of behavior, through the emotional responses of the oral-cavity-NA-AC-Hypothalamic (OC-NA-AC-HT) axis.

Moreover, the sensorial 7TM hormonal receptor structure of NA activated AC at the locus coeruleus from distant regions, could integrate the five senses (sound, smells, touch, visual and gustatory regions) into simultaneous multiple perception associated to emotional events.

The auditory cortex processes ear signals. The neuronal network responses for attention, only when the dorsolateral prefrontal cortex and a part of the parietal cortex are simultaneously activated, resulting in acoustic signals is more discernible because of human ability to integrate the visual perception of lips movement.

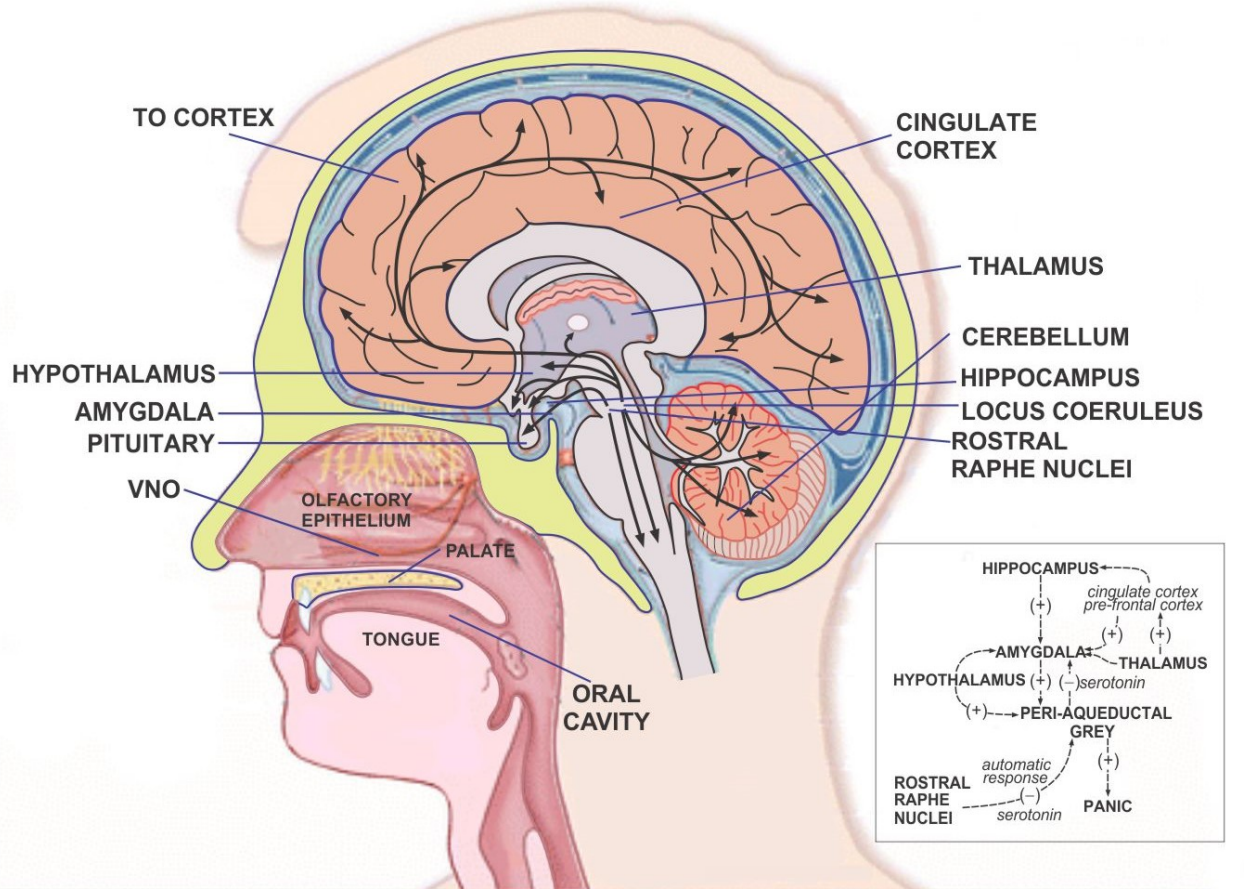

Figure 4: Emotional cognitive connection at the oral-cavity-hypothalamic-NA-AC-brain axis. *The hypothalamus (bidirectional) receives projections from sympathetic motor system (carried by the hypothalamospinal tract and they activate the sympathetic motor pathway), from the medial forebrain bundle carried by the mammillothalamic tract. Thus, notable inputs are from the nucleus of the ventrolateral medulla and locus coeruleus.*

The stimulation the frontal cortex communication tie with the deep brain at the limbic centers related to emotions, memory and learning of the hyperactive depressed patients were calm down. Thus, shows that reason and emotion are link by a crossing turnover. The oral-cavity-hypothalamic-brain axis appears to provide an alternative therapeutic medication to the brain implantation of electrodes. It is suggested a treatment localized at vomeronasal organ (VNO) and/or the surrounding palate areas with stimulatory procedures either: electric discharge or pharmacological access to hormones like oxytocin, dopamine, NA, etc.

Thalamus prevents sensorial signaling to reach the cerebral cortex.

Synaptic strengthening is promoted by oxytocin and dopamine for maternal cognitive memory [46].

Oxytocin release into nucleus accumbens shell is also activated by vaginocervical and lactation stimulation.

The paraventricular hypothalamic area is the source of oxytocin input into nucleus accumbens shell, which is signal by dopamine for reward-seeking behaviors.

Adrenaline, oxytocin and dopamine rewards link the emotional responses, coupling with the cognitive reasoning pathways originated at the amygdala and the hippocampus.

Periodic breaks and breathing times at work do the brain good. An important control center (the prefrontal cortex) sends signals to deeper and older brain regions: the hippocampus and the amygdala, decreasing stress. This interaction favors the transmission of social information, and the development of selective recognition.

Function magnetic resonance image (fMRI) studies, with participants, evaluated for the neuronal activity of the hippocampus. The results showed an inverse relation, differentiating between the task measurements for predictability vs memory functionality. Thus, indicating that both processes compete for use of shared, limiting neurological

requirements. However, these could be not only structural, but functional like metabolic ones, thermogenic dissipation, etc. Hence, responding to homeostatic controls.

The human brain could be characterized by reflexive behavior of self-language interactions rather than genetically triggered reflexes, which appears to be hormonal configured, generating an emotional intelligence.

Thus, lead to infer that opens a learning period through emotional communication, which allows humans to develop an emotional brain and emotional intelligence. This event has evolved out of genetic restriction, but responds to a pathway introducing self-rewards feedbacks like achievement. Thus, could emanate from competition that human evolution consolidates behavioral coupled to reasoning as an expectation response for emotional reward.

Plasma-CSF

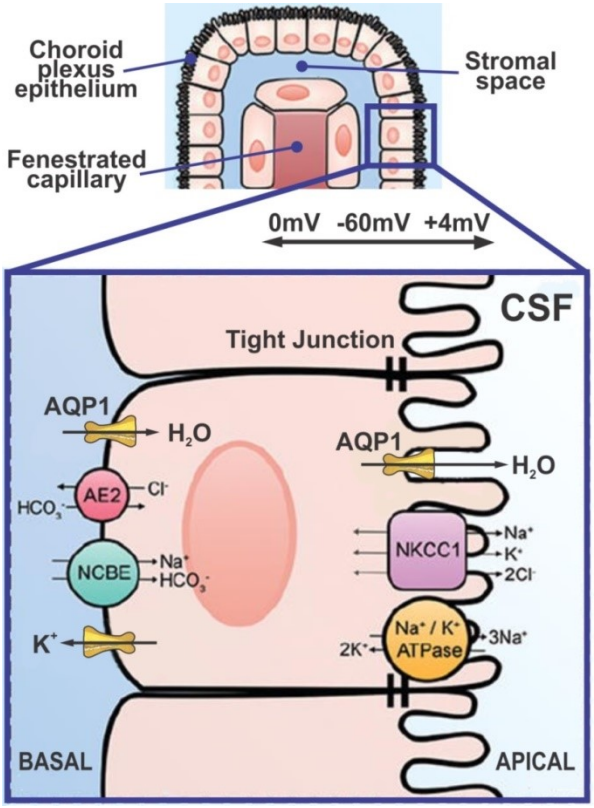

Figure 5: The choroid plexus epithelium (CPE) generates cerebrospinal fluid (CSF) functions in the mutual exclusive vectorial kinetic according to a potential of hydrophilic-plasma to hydrophobic-CSF flow. *Cl^- and HCO_3^- influx is recycled across the membrane. At ventricular side, the Na^+/K^+-ATPase releases the Na^+. The K^+-Cl^- cotransporter (KCC4) secretes Cl^- into the lumen containing CSF. Luminal K^+ is required for sustained CSF secretion. Secretion by the AQP1, AE2 and NCBE at a $Na^+/Cl^-/HCO_3^-$ ratio of 18:15:3 transports ions taken up from the basolateral membrane. Na^+ into the CSF enter via NKCC1 (Na^+-K^+-2 Cl^- 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). Net ion movement from the blood to the CSF creates a small osmolarity between both compartments [47], retaining in plasma polypeptides.*

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.

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

At maturity the contributions of the H-bond energy, by the enzyme 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 (150ml CSF) barrier 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 configuration about 3.4x5kcal/mol=17kcal/mol.

The thermodynamics relationship between structure and function requires an astrocytes network [48] [49] for circulation after breakdown of H-bonds.

Astrocytes are cells with actin filaments in the cell's skeleton, which impulses the CSF flux along the glial network for pulsatile propulsion and the support of the metabolic needs of the neurons. Also its handedness transport entropy and potentiate learning. Smaller entropy magnifies the enthalpy potential.

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 strain between orbitals to conform a resonance state at the water dimer $(H_2O{\sim}OH_2)$ integration.

The adenylate cyclase vectorial system

The RARE BiBi mechanism shows a second-order dependence on substrate concentration: Mg^{2+} shows an obligatory step to bind first to activate a site, allowing a binding site for MgATP. Hence, the noradrenaline (NA) activated of the hypothalamic tissue is controlled by obligatory ions Mg^{2+} exceeding the substrate concentration. The cAMP and calmodulin release of Ca^{2+} determine signaling of the amplitude, phase and period of circadian rhythms [50]. ATP^{4-} and chelating metabolites decreases CaATP, strongly activating adenylate cyclase (AC) to increment the cAMP-dependent activation of pathways for memory affirmation.

The feedback inhibitory response to Ca^{2+} occurs after cAMP product has been synthetized in condition needing to the expulsion of water from the hydrophobic enclosure. The rupture of this enclosure by the mass action of water cluster will liberate cAMP. This leads to vectorial kinetic because prevent the reentrance of cAMP into a kinetic equilibrium, because the active site has collapsed. Restructuration requires the hydrophilic obligatory step. Thus, turnover requires various folding steps, all irreversible by consuming H-bonds. Each kinetic step configures the reorganization of new folding structures because the hydrophilic sequence is always exergonic and involves the MgATP cleavage to generate pyrophosphate and AMP^{-} by about -8kcal/mol. The AMP cycling to generate cAMP is endergonic by about +10kcal/mol. The hydrophilic step evidently could not contribute that enthalpy, but the folding conformation of a hydrophobic cavity involves the H-bond breakdown and expulsion of water. Moreover, in order to release cAMP is needed the mass action of water cluster. The polypeptide changes in folding sum-up to several doors, mutually exclusive, because the sense changes add up as an opening step in the exergonic direction, only after H-bond has been expended to randomness, preventing a return.

NA (noradrenaline) release by the long axons of the corpus coerellus into the synaptic junctions also contributes to up-regulation of adenylate cyclase (AC) by Mg^{2+} and is turning off by Ca^{2+}.

As open system the accumulated mass action of substrate over dissipative product allows to a human brain to maximize neuronal transmission at a much clear potential overcoming the kinetic energy at a homeostatic temperature.

Adrenaline is coupled to the active site in transfer to AC that is coupled to 7TM G protein receptors [51] activated by a GTP cycle [52] [53]. NA is released by the long axons of neurons [54] of the locus-coeruleus into the synaptic junctions for sensorial-integrated perception between many brain areas. The activation of the Na^{+}/K^{+}-ATPase pump [55] release nascent Mg^{2+}, by decreasing $[ATP^{4-}]$, which has an inhibitory effect on AC.

Mg-cAMP turn-on/off of switch for CREB function

Mg-cAMP binds to coordinate to both DNA chains by coordination to the negatively oxygen of phosphate groups, on both backbones, connecting the repeated pattern of sugars and on that of cAMP.

The phosphoryl groups of the open DNA structure are now facing with their charged oxygen (O^{-}) to the inside to bind coordinately to Mg^{2+} [56].

The cAMP-Mg-DNA complex acts as a physiological process. The insertion of 3'-5'cyclicAMP of phosphoryl groups by coordination of Mg^{2+} to the negative charged oxygen, to face the hexahydrated Mg^{2+} and allowing the DNA chains to rotate for the purine and pyrimidine groups to face outwards.

The catabolite activator protein (CAP) functions by binding in the presence of the allosteric promoters and enhances the ability of RNA polymerase holoenzyme (RNAP) to bind and initiate transcription [57]. The cAMP induced Mg^{2+}-dependent open DNA configuration could represent in working memory, the role of a short-term memory intermediate stage.

In molecular biology, extracellular signal-regulated kinases (ERKs) or classical MAP kinases are widely expressed protein kinase intracellular

signaling molecules that are involved in functions including the regulation of meiosis, mitosis, and postmitotic functions in differentiated cells. Many different stimuli, including growth factors, cytokines, virus infection, ligands for heterotrimeric G protein-coupled receptors, transforming agents, and carcinogens, activate the ERK pathway. The term, "extracellular signal-regulated kinases", is sometimes used as a synonym for mitogen-activated protein kinase (MAPK), but has more recently been adopted for a specific subset of the mammalian MAPK family.

In the MAPK/ERK pathway, Ras activates c-Raf, followed by mitogen-activated protein kinase kinase (abbreviated as MKK, MEK, or MAP2K) and then MAPK1/2.

Anti-inflammatory and analgesic effects of Traditional Chinese Medicine Qianghuo Shengshi decoction (QSD) may be achieved by regulating the MAPKs protein and further regulating the expression of the cAMP response element binding protein (CREB) [58]. The level of intracellular cAMP and the protein level of p-CREB, p-AKT, p-PDK1 and PKA protein were up-regulated after the treatment of SNH compared with OGD/R modeling [59].

Ras is typically activated by growth hormones through receptor tyrosine kinases and GRB2/SOS, but may also receive other signals. ERKs are known to activate many transcription factors, such as ELK1 and some downstream protein kinases.

The protein kinase Hippo signaling pathway [60] that controls organ size in animals through the regulation of cell proliferation and apoptosis.

The figure shows that 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 [61]. Thus, producing neurotrophins and nerve growth factor, related of inducible gene expression [62]. The D1-like dopamine (DA) receptors act signaling activatory stage to intracellular pathways. Activation of MAP kinases in neuronal and endocrine cells is critical for cell differentiation and function. This action requires guanine nucleotide exchange factor (GEF)-mediated activation of downstream a host of Ras family small GTPases, which lead to Ras-Raf-MEK-ERK (MAPK/ERK), is a chain of proteins within cell [63] [64] that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.

DHEA is an endogenous steroid hormone precursor the human levels declines by aging. It is one of the most abundant circulating steroids in humans. DHEA is produced in the adrenal glands, the gonads, and the brain [65]. It functions as a metabolic intermediate in the biosynthesis of the androgen and estrogen sex steroids both in the gonads and has a variety of biological effects, binding to nuclear and cell surface receptors acting as a neurosteroid and modulator of neurotrophic factor receptors. It is essential for the biosynthesis of the glucocorticoids such as antiglucocorticoid (cortisol) effects and for its actions on both androgen and estrogen receptors, may function as a therapeutic of high levels of inflammatory diseases, or where adrenal production is altered, or addition as a supplement in the diet for ancient peoples.

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, and with multiple aspects of immune function and supportive of immunocompetence [66].

An emotional functioning brain develops under nurturing by reward hormonal conditioning by dopamine could be expected from the cAMP release by AC hormonal stimulation. The cAMP response element binding (CREB) protein became phosphorylated via G protein coupled receptors (GPCR) by dopamine signaling. The release of stimulated a brain growth factor (BDNF) a neurotrophin during neuron development became involved in synaptic plasticity. Dysregulation of GPCR signaling has been reported as involved in early stress models, leading to aberrant emotionality.

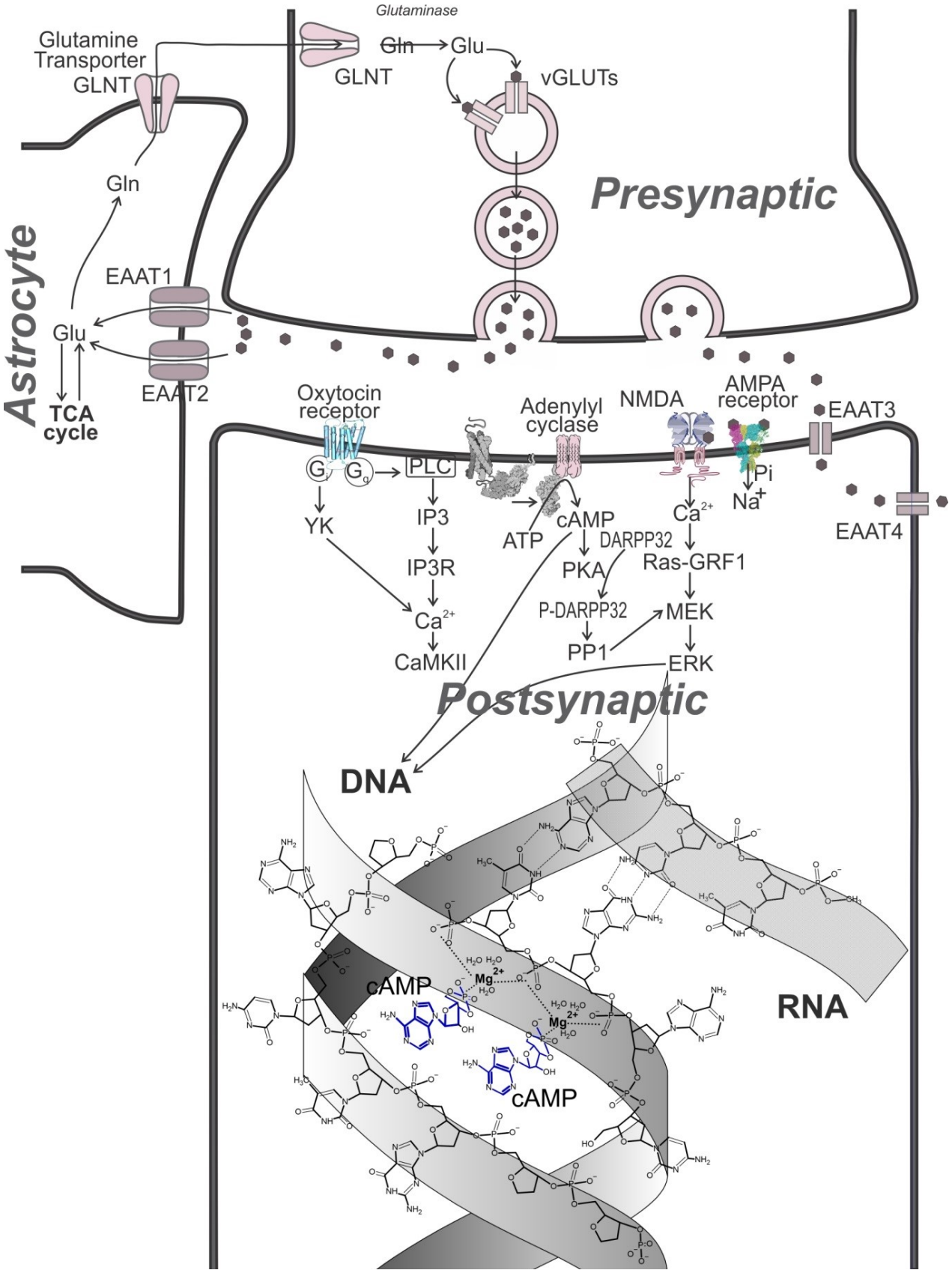

Figure 6: Crystallographic data has been used to illustrate a structure of the CREB B-ZIP protein domain, in which a hexahydrated Mg^{2+} ion binds with additional cAMP binding opens the double-stranded DNA containing the consensus CRE sequence (5'-TGACGTCA-3'). *This ZIP domain could acquire the double-stranded separation because the phosphoryl group of the nucleotide of the chain would rotate to face the hexahydrated Mg^{2+}. Each one of the purine groups would be facing outwards and allow the binding of the cAMP through its negative charged oxygen in the cyclic configuration of its phosphoryl group.*

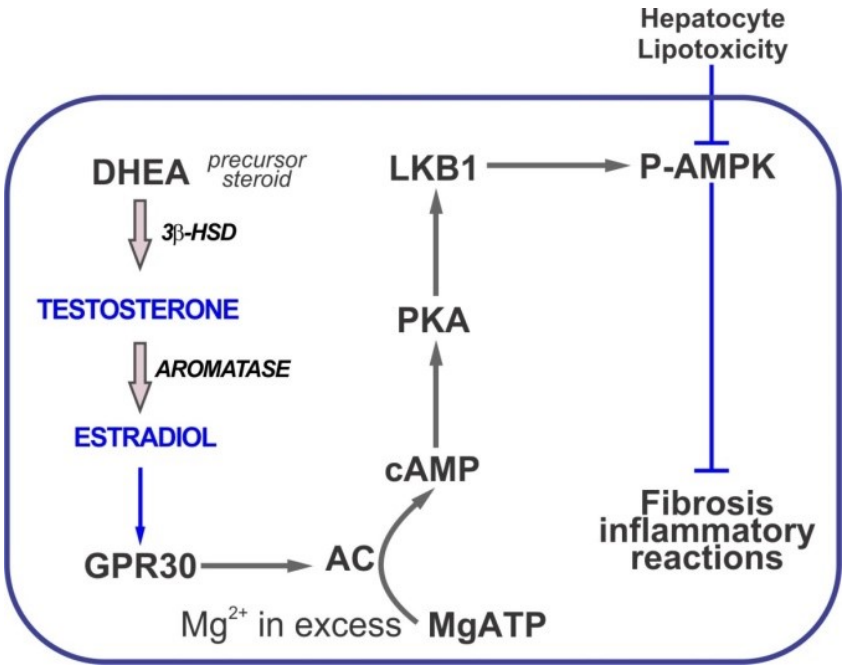

Figure 7: Dehydroepiandrosterone (DHEA) is the most abundant circulating steroid with immune and metabolic regulatory properties, and its level markedly declines with increasing age in humans. G protein-coupled estrogen receptor (GPR30), protein kinase A (PKA), the LKB1-AMPK pathway: metabolism and growth control in tumor suppression, 5' AMP-activated protein kinase or AMPK.

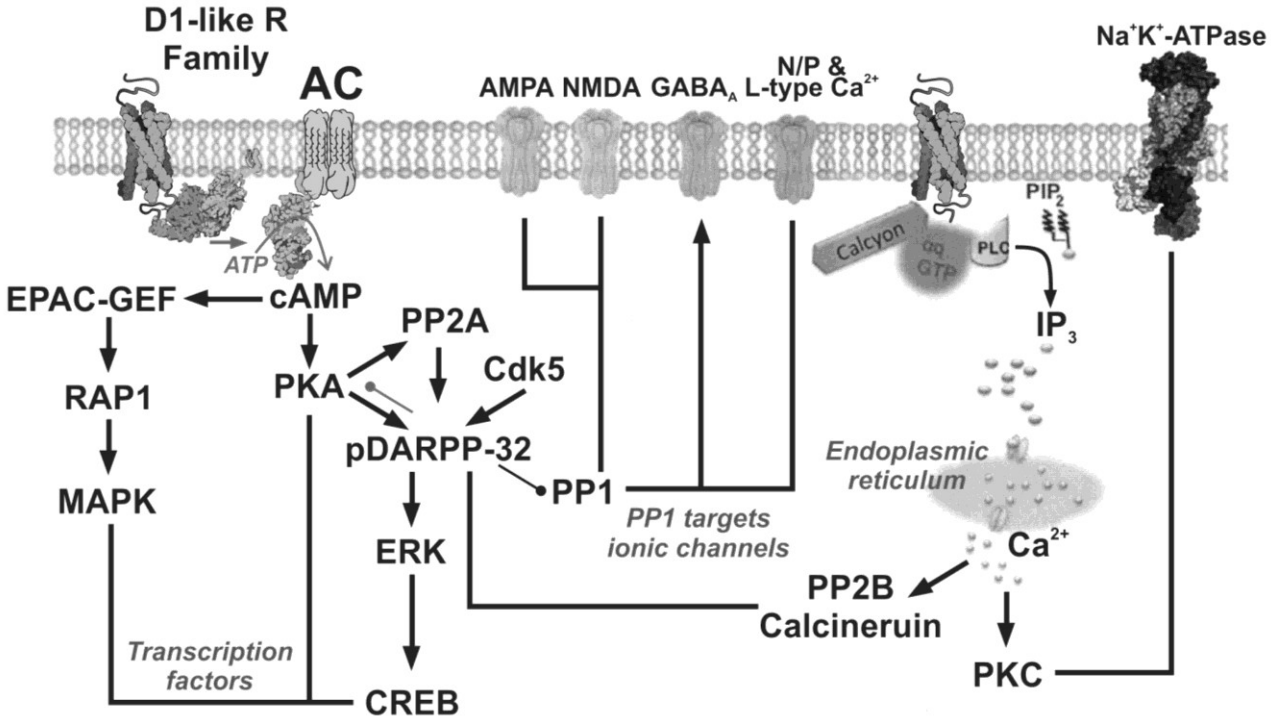

Figure 8: Producing neurotrophins and nerve growth factor, related of inducible gene expression. The D1-like dopamine (DA) receptors act signaling activatory stage to intracellular pathways. *Activation of MAP kinases in neuronal and endocrine cells is critical for cell differentiation and function. This action requires guanine nucleotide exchange factor (GEF)-mediated activation of downstream a host of Ras family small GTPases, which lead to Ras-Raf-MEK-ERK (MAPK/ERK), is a chain of proteins within cell that communicates a signal from a receptor on the surface of the cell to the DNA in the nucleus of the cell.*

CREB 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).

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.

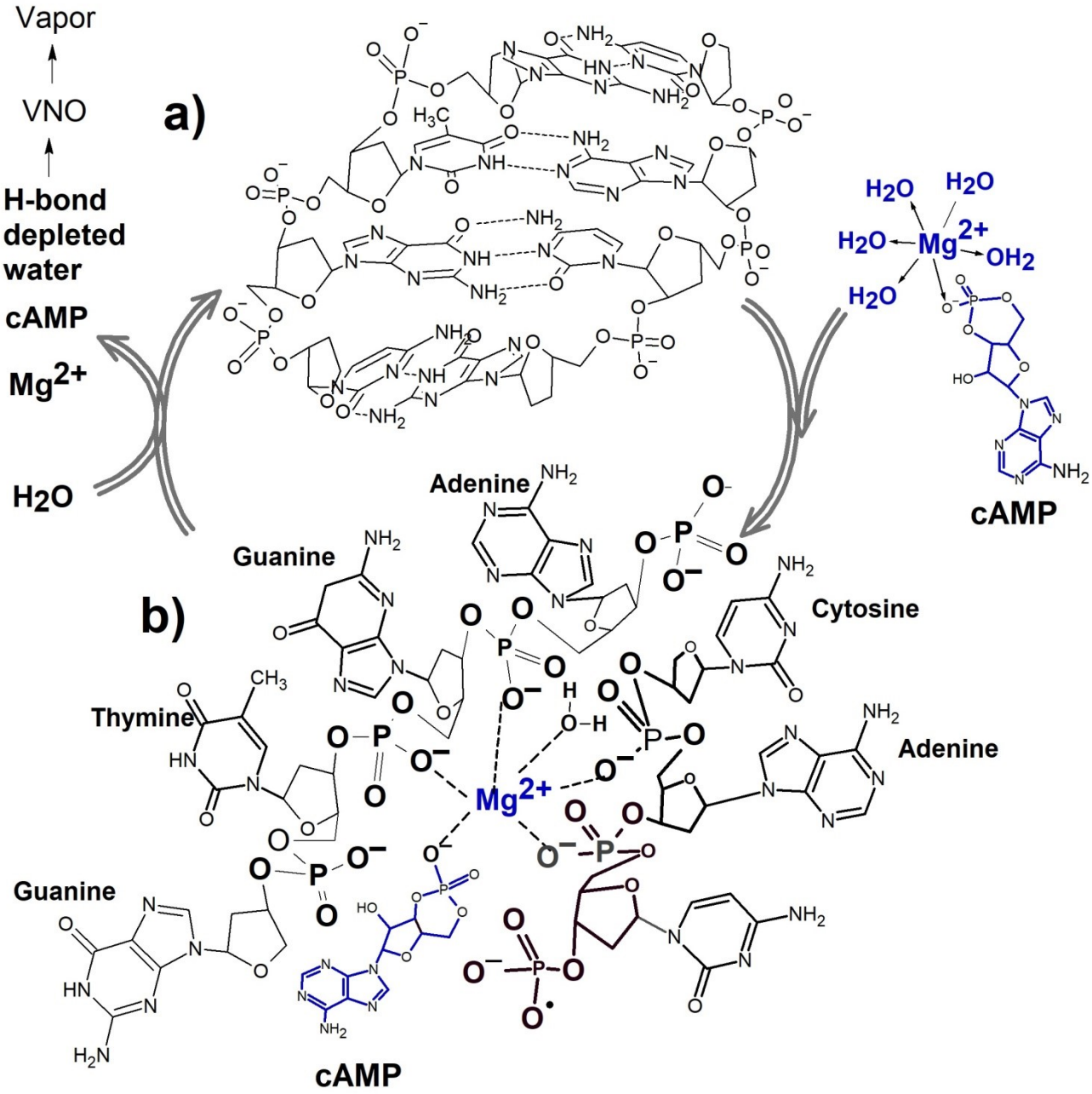

Figure 9: Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA or the transitory structure of cffDNA. *The non-physiological treatment technic of heating DNA at* 65°C *allows the strands separation and transcription used experimentally. a) Base sequence of the two chains attracted to match in a double stranded binary rotational symmetry of DNA. b) cAMP unzipping mechanism opens the double-stranded DNA structure positioning the outside purines and pyrimidines bases to transcription mechanism leading to protein synthesis.*

Physiological mechanism for cAMP fitting into the double strands unzipping of nuclear DNA or the transitory structure of cffDNA. The non-physiological treatment technic of heating DNA at $65℃$ allows the strands separation and transcription used experimentally. a) Base sequence of the two chains attracted to match in a double stranded binary rotational symmetry of DNA. b) cAMP unzipping mechanism opens the double-stranded DNA structure positioning the outside purines and pyrimidines bases to transcription mechanism leading to protein synthesis.

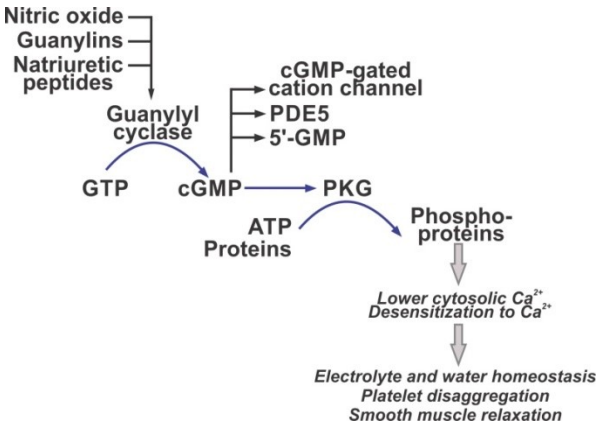

Figure 10: Cyclic GMP (cGMP) produced by guanylyl cyclases the erythrocyte transport cGMP by its uptake from extracellular fluid, without having in situ them enzyme. *Phosphodiesterases-5 (PDE5) breakdown cGMP in smooth muscle cells, platelets, gastrointestinal epithelial cells, and Purkinje cells. Also binds to cGMP to cGMP-dependent protein kinase (PKG), cGMP-gated cation channels, and allosteric sites on PDE5. Cyclic GMP binding to PKG activates the phosphotransferase to phosphorylate cellular proteins involved in Ca^{2+} homeostasis, lowering and desensitization the effects of Ca^{2+}. This effect causes relaxation of smooth muscle, decreased platelet aggregation, and altered transport of electrolytes and water in the gastrointestinal tract. PDE5 is phosphorylated in intact cells in response to stimuli that elevate cGMP, but does not response to elevation of cAMP.*

The water pair hydrophobic structure

The interaction of 2s and 2p orbitals allows a tetrahedral of 104.5° angles from two H atoms of positive charge, potential energy barrier to rotation of one of the water molecules with respect to the other.

A $O-H$ results from the 1s orbit bond strain with O to form a sp orbital. The H-bond of two water molecules, the partially positive hydrogen atom δ^+ attracts the partially 2 δ^- negative charge of one O to the other. The result in a dipole-dipole attraction mediated by the in between H-bonded distance $H-O-H--(OH_2)$ 0.177nm the polarity strength in water 104kcal/mol. The same H covalently to oxygen atom distance of 0.1nm is about 110kcal/mol. An $N-H$ and $C=O--H-N$ as between complementary pairs cytosine attracted to guanine separated by 0.27 to 0.3nm spontaneously attracted to form $H--O$ or $N--O$ by the unshared N or O electrons pairs. The water molecules detached from these intramolecular bonds within a protein become H-bonded between them, in bulk water. The dipolar state can induce transitive dipoles in other close molecules. Liquid state of water clusters show a half-life $10^{-8}s$ to $10^{-11}s$. The average number is $(H_2O)_{n=3.4}$. From liquid state (0.54kcal/g) a large number of H-bonds have to be broken to become vapor.

However, heat homeostasis at cerebrospinal fluid (CSF) hydrophobic medium at the pressure present in astrocytes, is able to maintain the release of single molecule of water by H-bonds breakdown and the hydric affinity disappears and allow a little polar state to manifest aggregated by non-polar interactions of $H_2O::OH_2$, indicating energy configuration: $(H_2O{\sim}OH_2)$, between both oxygen atoms. Thus, circulates within the astrocytes network in a metastable state of high oscillatory tension between the oxygen orbitals, between surrounding hydrogen atoms tending to maintain covalent stability. Water dimer is the most widely examined water cluster. The turnaround angle differentiates six different isomers of water dimers. Hereby, RP isomers are illustrated in figure, the potential planar resonance states, orbital-5 $E_{orb} = -15.15eV$ and orbital-9 $E_{orb} = -8.90eV$, with oscillatory potential $\Delta E = -6.25eV$.

Thus, determines several possible states of coherence. Hence, kinetic energy accumulates by resonance amplification. However, in the CSF the absence of O_2 and N_2 allows coherence and their presence in the air induce a randomness decoherence, into the oral cavity, generates the exhaled vapor to the outside, decreasing entropy of

the organism and allows brain to operate electrical impulses by the enthalpy potential of dissipative entropy, approaching the kinetic irreversibility of an open-system.

Ion pairs can form in the hydrophobic interiors of globular proteins. The free energy of solvation of an ion is so large (about 60kcal/mol) that an isolated charged residue is never found in the hydrophobic interior of a globular protein.

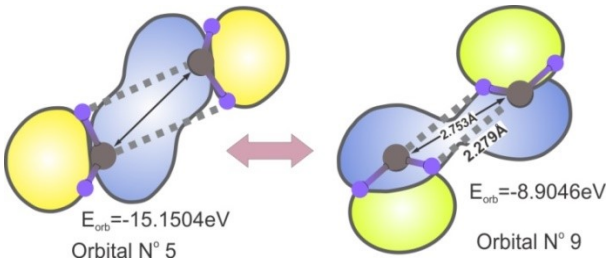

Figure 11: Two oppositely charged ions, however, can form an ion pair. *The free energy change for transfer of two oppositely charged residues from water to the monopolar interior of a protein is about -1kcal/mol. When the ion pair forms, the water molecules in the solvation sphere of each ion are released to the bulk. Each ion therefore loses its free energy of solvation, driving their force for ion-pair formation the increase in the entropy of water clusters, during formation of the ion pair.*

The microwave regions of the electromagnetic spectrum are radio waves, based in hydrogen level 1s orbital that has in energy difference of polarization change spin flip, dividing in two the energy barriers or electron density on the orbital motion. Pauli exclusion to energy density level allows movement only between tunneling is exchanges in the two pair of the H-bond donating and accepting water monomers $(H_2O{\sim}OH_2)$.

A more rigorous statement is that, concerning the exchange of two identical particles, the total (many-particle) wave function is antisymmetric for fermions, and symmetric for bosons.

This means that if the space and spin coordinates of two identical particles are interchanged, and then the total wave function changes its sign for fermions.

In the dimers has been determined to begin to flip of the acceptor monomer followed by 180º rotation about oxygen-oxygen bond. The interchange orbital exclusion could be assimilated to the Pauli's exclusion resulting between energy level (barriers).

The vibrational position results from intrinsic magnetic dipole movements as carried to the hydrogen spin. These jump interactions increase in energy parallel and decrease with anti-parallel (spin flip). The frequency (ν) of the quantum relationship $E = h\nu$ detectable by this transition $\lambda = \frac{hc}{E}$.

A water dimer is capable to expand Doppler shifts and became a much broader H spectrum when cooling CSF.

In dimers when the position of the 4H became parallel (relative positions for H-bonds with differential frequency emission). The magnetic movements are antiparallel (spin flip) create harmonics in resonances kinetic energy trapped within the dimer structure. In this which of the wave function of electron and proton overlap because de e^- encompasses partially the proton location. The structure could expand the energy contend by vibration absorbing kinetic energy, trapping in resonance maintaining coherence under limit of pressure (microtubules) and temperature.

The dimers exhibit three distinct low barriers to kinetic pressures over orbital displacement. This resistance results in vibrational states, stabilized by resonance.

Analysis of H atomic closeness distance for electron and proton leads to a Pauli's resistance to configure the same quantum state and explain a vibrational state shared at H atoms, forced to partially share microscopic space at differential time to elude the exclusion. Since the magnetic dipoles unstable state represents the possibility to emit tiny current loops, structuring the high energy reached by the dipoles, within water pairs.

Discussion

Prigogine modeled life as an open system capable of decreasing entropy. However, his cosmological model was not dissipative but based on a tendency for mass action equilibrium between enthalpy and entropy.

Common knowledge describes a thermodynamics system as open to the sun and integrated to life dependent of H_2O [67]. The confluence of requirements should be evident in terms that the sun evaporates water clusters: $(H_2O)_n$ by separating the molecules integrated in the complex and day-cycle allows the cooling for

the vapor condensing as rain and return to the water cluster state.

The state of coordinative linked H-bonds became a reactant with negative and amphoteric His R groups to coordinate Me^{2+}, associated to a domain configuring a hydrophilic state to a protein. Mutual exclusion by H-bonds breakdown leads to a reconfiguration. The presence of the proline in the polypeptide chains allows folding and displacement to create a competitive for amphoteric R groups and complemented by positive R groups domain to create attraction for negative molecules, like $2{,}3\text{–}DPG^{5-}$, ADP^{3-}, etc., which configures a hydrophobic or less polar state. Turnover from hydrophilic to hydrophobic state is a repetitive circular sense.

Thus, increasing rotational and vibrational kinetic activity, on the separated individual H_2O molecules, but maintaining a liquid coherence, during circulation within astrocytes until the lower pressure at the vomeronasal organ (VNO) [68] allows phase conversion to vapor, equivalent to entropy dissipation. The summation of the energy generated by metabolites and H-bond consumption allows the brain thermodynamics to support high ratios between metabolite concentrations and the electrogenic action potential in the dissipative states, within an open system.

The dissipative thermogenic H-bonds breakdown within water cluster configures a randomness increment when coupled to the proline-dependent folding of a polypeptide, but under experimental conditions the potential of an irreversible process would be undetectable because the protein concentrations could be μM whereas the mass-action of environmental water cluster would be several millions higher.

Conclusion

Maxwell predicted from a simplistic thermodynamics response to the randomness of heat distribution, the absence of vectorial kinetics. However, a role of structure and function become evident by the findings on the function of CF_1-ATPase-Synthase, when characterized by resolution-reconstitution and its purification. Thus, develops a prediction for the structural pathway for thermogenic flow from water clusters into its singular molecules, in the vapor state and its entropy exit. Thus, the opening and closing of doors is inalterable by a microscopic memory of the primary amino acid sequence of a polypeptide, and its differentiable domains in response to electrostatic and hydrophobic attractions. However, when the proline-dependent folding became coupled to water clusters functioning by H-bonds breakdown, mediates changes in the folding tertiary structure to respond to the dynamics of segment inter-sliding. These ones determine vectorial kinetics by approaching or distancing functional configurations, mediating the microscopic sequence of events within an active site. Moreover, the H-bonds twists reconfigurations, never reach energy equilibrium, because is irreversible by a dissipative exit from the system by a heat randomness of vapor.

The Pauli principle exclusion does not allow two fermions to occupy the same quantum state. Thus, within an atom, the electrons first lodge into an unoccupied lower orbital, then-on the empty levels up to threshold denominated Fermi distance. Under BCS (Bardeen-Cooper- Schrieffer) model, a within superconductor the electrons could not be treated as individually repulsive particles. Thus, each pair of particles does not behave like fermions, but as bosons, another relation between energy and matter, in which pairs of electrons could agglomerate as a Bose-Einstein condensate. The BCS derivative theories assume that in the boson state interactions could be related to the electron spins. The electron is not limited to orbiting a proton because it also turns around its axis. Accordingly, the movement of atoms became differentiable from classical physics description as solid, liquid and gasses. Furthermore, rotational movement could take only one sense and therefore automatically allows bypassing the microscopic reversibility principle by allowing vectorial dissipative potentials rather than tendency to only relate to mass-action equilibrium.

Moreover, the rotation sense only limits one possible sense, but creates two complementary states denominated up and down. The latter, predicts water pairs by opposite alignment of spins, which could integrate shared orbitals.

Bosons have yet to be accepted for the emergence of entanglement. However, this matter to energy relationship predicts coherence-decoherence states over the whole cosmos. But, if

so, the matter could be related to every characteristic of the cosmological level.

A cosmological dissipative system is far from equilibrium associated with the dissipative Planck bosons energy [69] based in quantum mechanics as inwardly open thermodynamics. This model meets the challenge implicated by primordial gravitational waves, which has only one turn around sense or vectorial dimensioning of a self-contained universe.

The flow of enthalpy into the system would be well above the generated entropy, which will exit as vapor or singular dissociated molecules. Therefore for all purposes the sliding turnover of the tertiary structure could maintain structure-functional changes, without truly affecting total free energy (ΔG). The conditions reflect the energy state of the polypeptide to have the dynamic of an open molecular thermodynamic state because it operates by the enthalpy input of a flow of H-bond breakdown, vectorial directed to the outside of the system.

Also may describe microscopic levels of entanglement linkage between quantic energy. This one allows superposition and uncertainty under a discontinuous spatial microscopic structure of energy. This becomes permissible if delocalization results from a shorter time-causality than the one required for encompassing a time coincidence of microscopic events.

A variable span of time parameter fluctuation, which delocalizes or not, the relationship between energy and space would lead to uncertainty.

Unstable coincidence within available energy flowing into available space could develop from the Pauli's principle of classic physics if could be integrated with a quantum mechanics treatment.

Let's consider that this means that orbitals trajectories intertwine by compression at temperatures compatible with life. This condition allows evaluation of the kinetic energy absorbed to form dimers ($H_2O{\sim}OH_2$) from H-bond depleted ones and circulates in liquid state, before that released as vapor.

Analysis of closeness H atomic distance for electron and proton leads to a Pauli's resistance to configure the same quantum state and explain a vibrational state shared at H atoms level, forced to partially share space at differential time eluding the exclusion. Since the magnetic dipoles overlap, represents the possibility to emit tiny current loops, structuring the high energy reached by the dipoles, within water pairs.

The conclusion is that the resonance between two isomers of the dimer orbitals keeps energy into the opposition between compressions and distensions by quantum mechanism, preserving vectorial kinetics.

The results should be lacking H-bonds dissipated from water clusters: $(H_2O)_n$, gain in the degree of randomness and the system as a whole pulled by opening the organismal system thanks to entropy release.

The kinetics energy solvation provides a polarity scale for unidirectional unitary sense of the circulatory flow for the thermogenic transitions for dissipation into the exit of organismal entropy.

Thermodynamically the complete process is a cyclic one. A turnover from solar thermogenesis, generating vapor, the kinetic equivalent of entropy (S), which is dissipated by cooling and generates enthalpy (H), an Gibbs free energy: $\Delta G = \Delta H - T\Delta S$. Hence, ΔG would be potentiated by dissipative entropy, which results in an open system out of the equilibrium.

Structure and function thermodynamics show that chemical transitions are coupled by mass-action, leading to equilibrium in a closed system. A symmetry breaking has to appear to prevent coupling between two differential forms of energy. Thus, chemical affinity could not couple with the randomness of the dissipative vector potential of heat. The heat expulsion-out of the system, or entropy, prevents integrative events.

The dead-end kinetic inhibition of adenylate cyclase activity [70] [71] [72], which involves H-bond breakdown of intermediates, does not manifest a singular characteristic of a direct irreversibility, but rather the incompatibility of dead-end inhibition with the obligatory step because the active site could not respond to a bidirectional transit at the same time.

The turn-on, or turn-off, involves the continuous reconstruction of the active site itself, an obligatory step, or specific path for turnover, in addition to the reactions intermediates to form cAMP. Turnover involves a Mg^{2+} activatory site before binding the substrate Mg-ATP. The integration with the coupling of Ca^{2+}, generating the dead-end inhibition could not occur simultaneously. The integration does require a

microscopic time vector to operate under differentiated microscopic spatial relationships and requires additional inputs of enthalpy.

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