The vomeronasal organ functions in entropy dissipation, the communication by pheromones for a feedback by the pituitary over brain plasticity and the development of the unconscious

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Abstract

A model of human brain evolution should take in account the constitutive separation of two integrated parameters: the one for neuronal synapsis and circuits, from that by a multiple wrapped-around astrocytes and their exchanges. The main function of glial cells is the absorption of the generated, thermal-like brokening of H-bonds, from polymerized water provides the activation energy, coupled for the turnover of structural changes, between hydrophobic and hydrophilic enzyme forms. Thus, increasing rotational and vibrational kinetic activity, on the separated individual molecules, but maintaining a liquid coherence, during circulation within astrocytes until the lower pressure at the vomeronasal organ (VNO) 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 ratios between metabolite concentrations and the electrogenic action potential in dissipative states, within an open system. Cell-free fetal DNA (cffDNA) from an evolutive disaggregation of the olfactory bulb, but still present as an olfactory epithelium, adapted for sex pheromones and behavioral responses stimulus on adenylate cyclase for cAMP-dependent unzipping of the cffDNA fragments. This allows into transcription sites for RNA messenger expression, as a psychosomatic molecular carrier of emotional and communication needs of a newborn. Thus, through the VNO communication with the brain acts a hypothalamic feedback of hormones (NA, cortisol, dopamine, serotonin, oxytocin, etc.), as a restriction on the randomness of brain evolution. This functions to form an unconscious level, which diversifies individual emotional characteristics, approaching a level of animic personalities, which when age allows a conscious level, could offer a differentiable response to the social influences.

Keywords: VNO, dissipation of entropy, pheromones communication, psychosomatic, hypothalamic-adenylate cyclase, cAMP unzipping cffDNA, postnatal memory, psychosexual development complexes, unconscious, autism, oxytocin, feedback on brain evolution patterns.

Introduction

The pheromone communication level from animals is as an integrative function whereas appears as an evolutionary transition stage in humans. Before the development of an active audio-visual language, the neuronal system of the newborns, allows for the memorization of experience, through the scent-smell-touch system of pheromone exchanges.

The epithelium of the oral cavity could absorb the pheromone signals that reach at the vomeronasal organ (VNO). The characterization of a noradrenaline (NA)-AC of rat brain hypothalamus [1], indicated that cAMP, could be involved in pheromone-communication. The kinetic equilibrium of the hypothalamic-adenylate cyclase (AC) [EC 4.6.1.1] produces cAMP for unzipping cell-free fetal DNA (cffDNA) of memory pathways and their transduction into messenger RNA (mRNA), of non-nuclear and non-inheritable origin, psychosomatic carrier of many emotions like fear, attachment, etc.

At the stage of nurturing, the creation of a transitory memory could not be the nuclear DNA of neurons that would be connected into mature neuronal circuits.

Thus, the newborn connects a scent-smell-touch communication functions as a psychic level. It is clear that pheromone-like chemical signals play a role in offspring identification and mother recognition and sucking pleasure.

The pheromone-dependent activation of hypothalamic-AC interacts with cffDNA, originated from the never develop olfactory bulb cells, as fragments between 50 and 200 base pairs of DNA, and released to the blood plasma, which becomes increasingly frequent in circulation with the onset of age [2]. cffDNA in the maternal blood is variable, but on average it is 10% of the fetus and the rest of the mother, 5-7 gestation weeks, but two days after delivery is no longer detectable in maternal blood [3].

The human VNO olfactory cavity connects with the brain and reveals a role for pheromone carried by air-saliva function as a primitive molecular communication of recognition and memory reflecting a previous evolutionary stage.

Oxytocin is a neuropeptide released by the posterior pituitary [4] increases trust and social bonding. It plays a role in sexual reproduction, and childbirth [5], maternal behavior, causes sexual arousal, like kissing between lovers (saliva) or breastfeed between mother and baby (milk). Oxytocin signaling through the VNO triggers a behavioral response to the presence of prey, predators, and sex pheromones.

The bonding by oxytocin [6] and other pheromones appear as smell-touch communication memory between mother and its child, for healthy nurturing and rising. Hence, the origin of complexes could be related to the Freudian psychology of psychosexual development stages: 1. the Oral, 2. the Anal, 3. the Phallic, 4. the Latent, and 5. the Genital. This relates the body region of the libido pleasure to a different erogenous zone of the infant's body. The newborn memory of care by their parents would surface as a latter age as the origin of Oedipus and Electra complexes, etc. Low levels of oxytocin, during nurturing, could become a condition leading to a disease, like autism, or repressed anguish and angry feeling.

The vomeronasal organ axis conditioning the unconscious

The scent-touch of the newborn of pheromones communication could be characterized as a molecular level origin of the memory persisting as psychosomatic complexes. The axons from neurons, called cranial nerve zero (CN 0), project to the accessory in human olfactory epithelium (not detectable as an organ *per se* as is the case of the animals developed olfactory bulb).

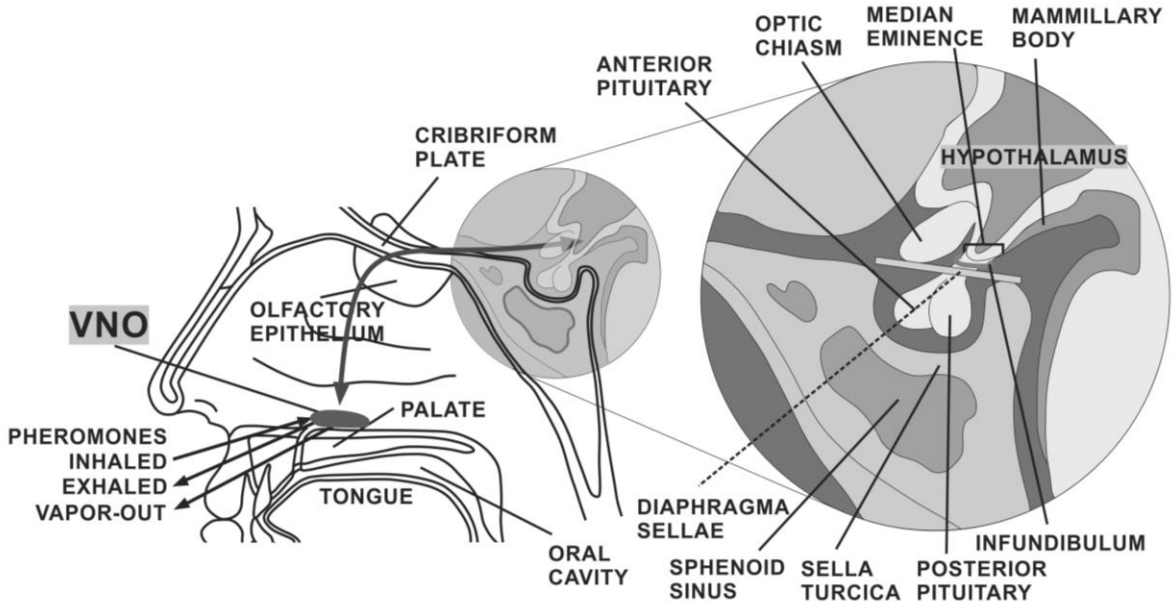


Figure 1: The vomeronasal organ (VNO) as an auxiliary olfactory (smell) sense of the paired (two slits), which is located in the soft tissue of the nasal septum at the base of the nasal cavity, located just above the roof of the mouth (the hard palate), and its epithelium functions as a sponge tissue, exchanging liquids or smells. Hypothalamic-pituitary-adrenal axis shows a bed nucleus of the stria terminalis, serving as a relay site of a major output pathway of the amygdala that responds to threat with anxiety. Oxytocin acting in the mesolimbic dopamine system promotes social approach in positive social contexts. **Hypophyseal fossa in cavity, Sella Turcica:** covered by a flat piece extension of the dura mater (diaphragma sellae), with a circular hole, allowing the vertical passage of the pituitary stalk to the hypothalamus. The latter, controls the energy balance, synthesis, release, activity of anterior pituitary (such as physical and emotional stress, coitus and suckling) and feedbacks by target glands hormones (Thyroxin, Cortisol and Gonadal steroids), through the hypophyseal portal circulation.

VNO neurons are activated by the binding of certain chemicals to their G protein-coupled receptors: they express receptors from three families, called V_1R [7] [8] [9], V_2R, and FPR [10] [11]. The mammalian species encode genes of seven-transmembrane (7TM) G-protein-coupled receptors, which function to identify odorants and pheromones [12], that are characterized by transcription and expression of the sensory neuroepithelium.

The physiological changes of the multiple equilibriums, over AC, allows a signaling predominance of Mg^{2+} over Ca^{2+} or vice versa, connecting with the Ca^{2+} inhibition of AC, allowing the concurrent activation of the α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor.

Pheromone from saliva and smell breastmilk could be uptake through the two slits of VNO, hypophyseal AC will respond forming the cAMP-Mg-cffDNA complex, at the early stages of a newborn conditioned memory of emotional bonding with her or his parents.

The structure and function of the olfactory system integrates the VNO connections with the hypothalamic AC, to facilitate pheromone uptake, memory conditioning and olfactory emotional communication.

Hypothalamic-adenylate cyclase activation and pheromone release response

Adrenergic nerve fibers make up the sympathetic nervous system which releases the neurotransmitter NA at the synapse, or junction. Alterations in the endogenous cAMP could be caused by changes in metabolic conditions, or for example, caffeine-dependent inhibition of the phosphodiesterase breakdown of cAMP, correlated to a possible effect of longevity.

The isolation from rat's brain AC and characterization for its neurotransmitter responsiveness allowed evaluation of a possible role of the enzyme in cAMP-dependent memory processes. NA activation, when Mg^{2+} is in excess of substrate, of an isolated AC from brain, was first reported for cortex and corpus striatum [13]. The enzyme relates to a network of tissues [14] supporting brain activity [15] by

their *in common* response to the modification by changes in the concentration of chelating metabolites of free ionic Mg^{2+}.

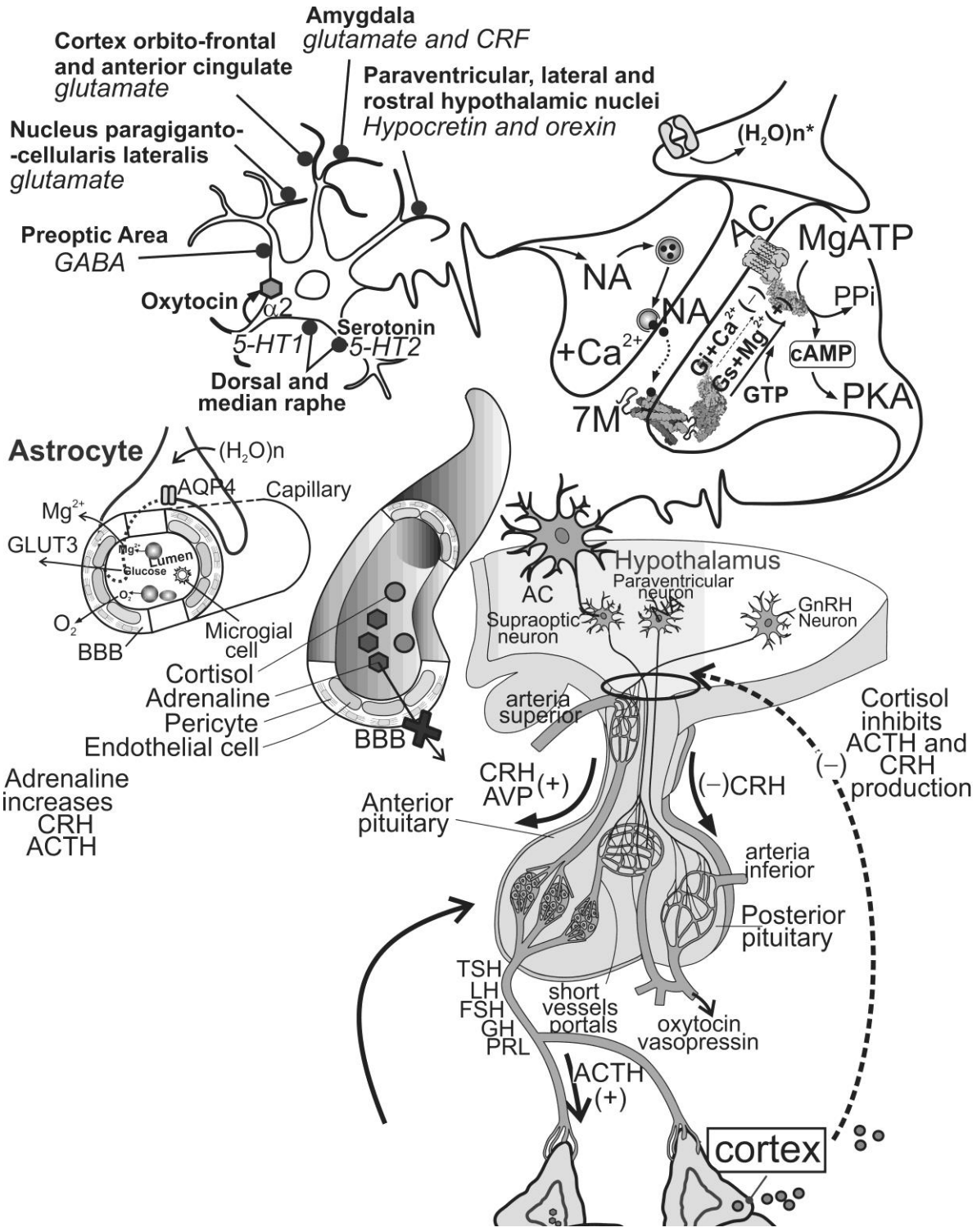


Figure 2: Ionic-metabolic integrative coupling of the pheromones-neuronal system. G-protein-coupled receptor (GPCRs) exchange its binding to GDP inactive for GTP active (GDP/GTP-exchange) for NA receptor coupling to AC. Neuron uptake and stoichiometric cycling reversing the glutamate synthase reaction supports release of glutamate (Glu), activating the postsynaptic N-methyl-D-aspartate (NMDA) receptor and ion channel protein. At the astrocyte synaptically released GLU is co-transported with Na^+ by the Na+/K+ ATPase consuming one ATP in the exchange for extracellular K^+. These various effectors are then responsible for carrying out the cAMP signaling functions that include control of metabolism, gene transcription and ion channel activity. In many cases, these functions are modulatory in that cAMP often acts to adjust the activity of other signaling pathways and thus has a central role to play in the cross-talk between signaling

pathways. This modulatory function is particularly evident in the case of Ca^{2+} signaling in both neuronal and muscle cells to control voltage-gated ion channels finely tuned to regulate many aspects of signal transduction and their dysfunction effect on several disorders [16] [17].

Cognition and Memory

The origin of cognition and memory could be attributed to the post-natal scent-smell communication memory. Degraded cell-free fetal DNA (cffDNA) fragments released to the blood plasma, could not correspond with a characteristic expression of the genetic DNA in the nuclei, which is transmissible to the progeny. The process is a compulsive memory of similar mechanistic characteristic expression, but of cognition and memory. The latter, is not transfer by hereditary mechanism, like would be the case of arachnid's spiderweb. This, will involve duplication of DNA preserved in the nuclei, from where, according to genetics should have been, a marker transmitted by successive generation. Conditioning could on the other hands implicate anticipatory memory, for appetitive which is present as a reflex. The reflex conditioning response described by Pavlov using dog's experimental studies could correspond to the mechanism that allow lecture of free DNA, which is not subject to an inherit process.

In animals, the olfactory organ integrates a memory, which allowed their offspring to reach self-care, in a short time.

In the newborn human, the residual structure from evolutional deletion of the olfactory sense allows a memory unable to coordinate muscles, but provides for pheromone-communication by the hypothalamus, which could function as a feedback on brain development, opposing the randomness of evolution itself.

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.

Oxytocin bonding process implicates memory for the nurturing infant of primordial imaging of parents, assigning pheromone signals to the care presence of Mother and Father, and given origin to complexes of Oedipus and Electra, at a later unconscious level. At adult stages an oxytocin deficiency, may result in psycho-neuronal and social dysfunctions, expressed as syndromes like a breakup of a couple, which not only could induces a mourning period, but tragically also abnormal responses of anger.

The hypothalamic-astrocytes-vomeronasal organ axis

H-bond dissipated water through the astrocytes system eventually could reach the respiratory epithelium lining of the human vomeronasal organ (VNO) [18] [19].

The evidence suggests that the increased morphological complexity of astrocytes that has occurred within primate phylogeny may increase cognitive function [20].

Astrocytes constitute 20–40% of the glial cells in the central neurons system (CNS) [21], 50:1 astrocytes per neuron are the more numerous cells of the neuronal system. A single astrocyte could contact with up to 2 million synapses [22] [23]. Astrocytes are wrapped around neurons utilizes the perivascular spaces formed by the vascular endfeet of astrocytes, around the vasculature.

The glymphatic system has a role of maintaining the homeostasis of the central nervous system (CNS), extensive contact with the cerebral capillaries that modulates the blood flow, during neuronal activatory response [24].

Radial astrocytes can be found between the grey and pia matter and communicate with cerebrospinal fluid (CSF) and help in maintaining the blood-brain barrier. They release glutamate, D-serine, GABA, and ATP to the neurons. Astrocytes express glutamate transporters, K^+ channels and water channels, allowing them to contribute to the maintenance of glutamate homeostasis, potassium homeostasis and water homeostasis, respectively [25].

The Hypothalamic-Pituitary-Adrenal Axis Control on the Psychosomatic Metabolic Network

The characterization of the noradrenaline(NA)-dependent overstimulation of the hypothalamic-pituitary adrenal axis could turn-on the fight-or-flight response. The increment of adrenaline and cortisol shift body metabolism in the direction of depleting metabolic reserves like fats and releasing amino acids from proteins to support gluconeogenesis. Adrenaline could not cross the blood-brain barrier for a negative feedback, returning to the homeostatic metabolic and functional states of brain. Adaptive brain evolution may explain the lack of adrenaline feedback as a restriction to signaling, which allows the dominance of brain over its metabolic supporting tissue network. A molecular perspective could therefore explain the advantage of assigning to the brain unchallenging control, for maximizing the organismal efforts required for survival. This brain pattern of control over metabolic supporting functions corresponds to a similar equivalent of the structuring of a psychosomatic unconscious, unable of a feedback reporting on the conscious level.

Pheromone activation of hypothalamic-adenylate cyclase and cAMP unzipping of cffDNA

This conjecture had experimental support from many laboratories and has been successfully generalized as behavior-cAMP linked models [26] [27] [28] [29] [30]. An adrenaline active site on AC is coupled to G-proteins 7TM receptors activated by a GTP cycle. Noradrenaline (NA) is released by the long axons of the locus-coeruleus into the synaptic junctions for sensorial-integrated perception. The activation of the Na+/K+-ATPase pump release nascent Mg^{2+}, by decreasing [ATP^{4-}], which has an inhibitory effect on AC. The capture by nascent Mg^{2+} of water from the hydration shells of the less strong ions decreases the sizes of Na^{+} and K^{+}, fitting both to their gates, allowing across the membrane the sieve effects, which confers specific pattern to the wavelength of the action potential.

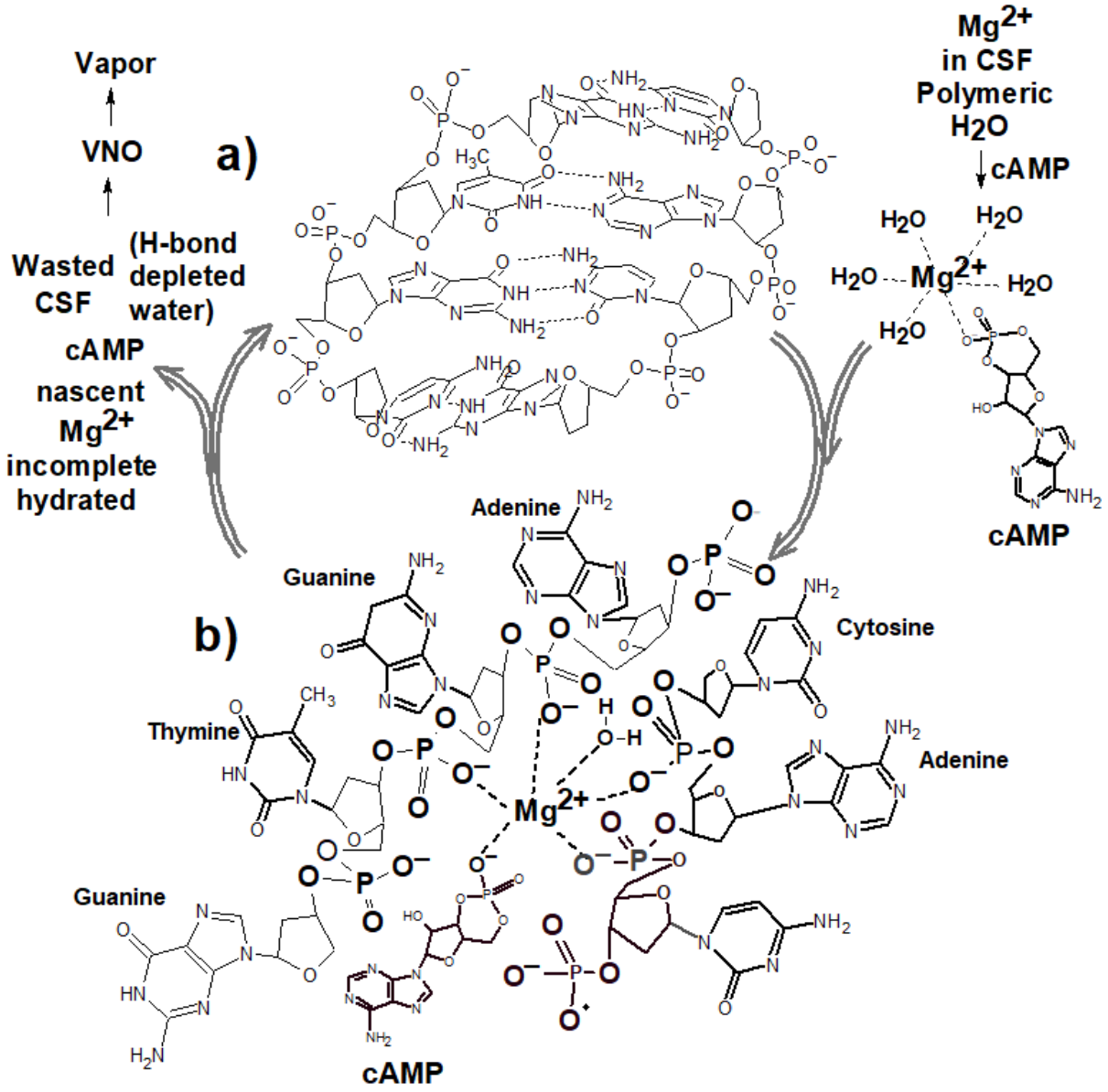


Figure 3. Physiological mechanism for chemical cAMP fitting into the double strands unzipping structure of cffDNA. **a)** Base sequence of the two chains attracted to match in a double stranded binary rotational symmetry of DNA. **b) cAMP unzipping mechanism opens the double-stranded DNA structure** positioning to the outside purines and pyrimidines bases. Mg-cAMP binds to the pentahydrated Mg^{2+} ion to coordinate to both chains through the negatively oxygen of phosphate groups, on both of the backbone, connecting the repeated pattern of sugars and on that of cAMP [6, 14]. The DNA expression occurs by the transcription function. The triplet pairing rule for synthetizing mRNA and recognize their tRNAs partners are based upon each of the three bases pairing with its appropriate partner.

The non-physiological treatment technic of heating DNA at 65^0C allows the strands separation and transcription that has been used experimentally.

The cAMP-Mg-DNA acts as a physiological process because can achieve a local opening of the double-stranded by the insertion of 3'-5'cyclicAMP through the cyclic configuration of its phosphoryl group 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 figure 3 shows that the phosphoryl groups of the opening in the DNA are now facing with their charged oxygen (O^-) to the inside to bind coordinately to Mg^{2+} [31].

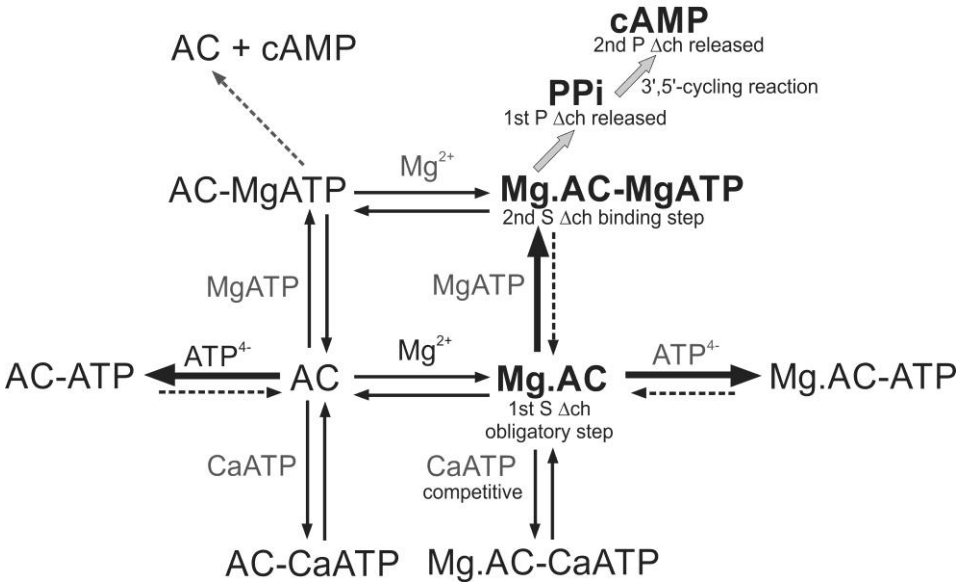
The catabolite activator protein (CAP) functions by binding in the presence of the allosteric promoters and enhances the ability of RNA polymerase holoenzyme (RNAP) to bind and initiate transcription [32].

The activation of Mg^{2+} stimulated adenylate cyclase results in cAMP production, which in cerebrospinal fluid (CSF) unzipping of the cell-free DNA (cfDNA) and cell-free fetal DNA

(cffDNA), for mRNA production in the glial cells of cortical, hippocampal, and spinal cord, responding to oxytocin, which a AC activation at the hypothalamus results in the development of postnatal long-term memory.
The cffDNA is from the fetal vestige cells originated from a never configured olfactory bulb.
The cfDNA circulating in the maternal blood originates from cells shed from placental trophoblasts microparticles [33], disappears after two hours from delivery. Prenatal diagnosis targets on the cffDNA analysis show correspondence with the gene responsible for the sex-determining region Y protein (SRY) on the Y chromosome and the DYS14 sequence [34] [35].

Ionic equilibrium controlling Ca^{2+} effects for a simultaneous CaATP inhibition of adenylate cyclase and activation of the AMPA receptor

Drummond et al., 1971, Johnson and Sutherland, 1973, show that the responsiveness of AC to stimulation by adrenaline of fat-cell-AC or noradrenaline(NA)-brain-AC or basal hypothalamic-AC [36] is controlled by obligatory ions Mg^{2+} requirement exceeding participation in substrate formation. cAMP and Ca^{2+} signaling determine amplitude, phase and period of circadian rhythms [37]. Kinetic characterization of the hypothalamic adenylate cyclase response to Ca^{2+} releases to 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 [38].
The responsiveness of AC to stimulation by hormones or neurotransmitters is controlled by an obligatory Mg^{2+} requirement that exceeds the one participating in substrate formation [39].
The finding that CF_1-ATPase requires Mg^{2+} for binding to the membrane and reconstitution of allotopic properties [40] suggests a similar obligatory participation of Mg^{2+} in the formation of a hormone receptor-Mg^{2+}-AC complex [41]. Thus, the RARE BiBi mechanism predicts that hormones will increase $h(MgCl_2)$ from basal =2.6 to 4, because ATP^{4-} and AC are competitive ligands of Mg^{2+} to form an AC-Mg^{2+} and Mg^{2+}-AC-MgATP complex. An NA additional AC saturation parameter adds to a higher *n* value. The experiment described here has been restricted to characterize the basal kinetics of the enzyme only, without hormone interaction with the hormone receptor an Mg^{2+}-dependent integration with the membrane, to avoid a higher equilibria complexity.



Scheme 1. RARE BiBi (2 substrates and 2 products) ordered binding (macro mechanism) of adenylate cyclase including ATP^{4-} and CaATP as dead-end inhibitions. Applying the initial rate studies for Mg^{2+} could be assumed to be equally valid for Mn^{2+}. S_1=Mg^{2+}, S_2=MgATP; P_1=PPi (pyrophosphate); P_2=cAMP (3',5'-cyclic adenosine monophosphate); E=AC; Δch=conformational change.

The RARE BiBi mechanism shows a second-order dependence on substrate concentration: Mg^{2+} has to bind first to activate the binding site for MgATP.
Thereafter a 3',5'-cyclic is formed, to produce cAMP and PPi are released. The sequential steps forming by conformational changes of obligatory binding sites for S_1, allowing S_2 binding, and specific conformational changes for 1st product, the release of PPi before cycling, and after release of 2nd product, cAMP.
The scheme 1 represents the molecular kinetics synchronization that prevents microscopic reversibility, because could not be conceptually assimilated as a single door, which could only allow transit in both senses. The scheme illustrate as a similitude to the entrance and exit points of a submarine tower: two hatches 1st, open and 2nd closed, enter and 1st closed and 2nd open. Thus, microscopic irreversibility results from the enzymes turnover between their hydrophilic and hydrophobic forms. Change of protein conformation turnover is supported by the activation energy of broken H-bonds, from polymeric water in cerebrospinal fluid (CSF), conversion into waste water, a depleted of coordinative bonds between molecules. Astrocytes could maintain the waste state of water in a liquid state until their release as vapor to the outside of the system, equivalent to entropy dissipation.
AC shows a RARE BiBi mechanism with death-end inhibitors of the active site: ATP^{4-} and Ca-ATP. Alternatively, a decrease in chelating metabolites (ATP^{4-}) decreases CaATP, strongly activating AC-mediated and cAMP-dependent activation of pathways for memory affirmation. Turnover, with release of Mg^{2+} from the E as a nascent ion Mg^{2+} acquires a stronger intrinsic charge.
The effects of divalent metals and/or ATP^{4-} (in excess of their participation in complex formation) were determined from the corresponding apparent affinity values and the following kinetic constants were obtained: Mg^{2+} (Mg_T) can easily displace Ca^{2+} from ATP. The equilibrium favors that Mg^{2+} can easily displace Ca^{2+} from ATP, and reduce the concentration of CaATP. Since Ka (MgATP)=$-20\times10^3M^{-1}$, $K_i(ATP^{4-})$=0.27mM, Ka(CaATP)= $-9\times10^3M^{-1}$, K_i(CaATP)=0.015mM. ATP^{4-} and CaATP were shown to compete for the active site of the enzyme.

Coupling of H-bonds consumption for proteins/enzymes turnover

The cerebrospinal fluid (CSF) expended H-bond water is in liquid state at 36.6°C because the H-bond between molecules has been broken, allowing a transition state in which the internal (intrinsic) structure of the water molecule itself has absorbed vibrational and rotational kinetic energy, allowing an aggregate state, until the space allows the translational energy that characterizes the vapor state. In physics the phenomenon is described as a transition state of second order that became independent of the microscopic structure. In a laboratory is well known that the distilled and condensed water is highly active (energy excess on the individual molecules) and has to be stationed for 24hs, before the fitting of water molecules allows their full H-bonding state.
The blood-brain capillaries release metabolites to the CSF interphase with glial cells, and the latter the toxic products and the depleted H-bonds from water released by protein turnover from hydrated to hydrophobic forms, into the CSF interphase with the venous system.
Astrocytes through rapid circulation function as a radiator could prevent that the brain to absorb the entropy of the 30% the total calories ingested by the individuals, through the process transferring the energy excess of exhausted H-bond CSF, by moistening the VNO sponge-like epithelium tissue and allow a low pressure transformation of a liquid into a vapor phase.
Approaching a mirror to the mouth, a condensation test for vital signs, allows detection of a 5% vapor present in breath, to become evident. The thermodynamics turnover for an out of the system release of waste water, maintains a dissipative state characteristic of open systems. Thus, prevents a reversal of the metabolic flow and therefore conserve the energy capable to support the hydration shell turnover of ions and proteins, which maintains the cell membrane action potential.

Thermodynamic of cerebrospinal fluid (CSF) daily turnover

Thermodynamically a donor solvation media, like CSF could be calculated on the bases of a turnover value of 500ml CSF, which could be expressed as 27.77 H_2O mol, considering an average value of 2.3 mol H-bond per mol H_2O and -2.6kcal per mol H-bond.

$$Energy = 27.77\ mol\ H_2O \frac{2.3\ mol\ H\text{-}bond}{1\ mol\ H_2O} \frac{-2.6kcal}{mol\ H\text{-}bond} = -166kcal$$

Outside the body exhausted H-bond water regenerates by cooling into cluster water because is a favorable thermodynamic process.

The epithelial membranes with an outside and inside confers the properties of open systems, because the depleted H-bonds from water in CSF does not have the tendency to aggregate, but by entering in the spongy tissue of VNO it rapidly became separated in individual molecules and evaporate.

Thus, exhaled air in adults of about 6 liters per minute has a 5% vapor contribution from the VNO conductance process of depleted H-bonds from water in CSF.

cAMP Mg-dependent zipping-out of DNA results in an cAMP- Mg^{2+}-DNA complex open up for regulation of gene expression, during memory dependent plasticity, and eventually, a memory circuit could be formed to operate for long-term memory. Erythrocytes are a carrier of cGMP to complete the cAMP signaling [42].

The hydration shell of *nascent* Mg^{2+} allows capture molecules of water from the hydration sphere of Na^+ and this one in term replaces this loss from capture of H_2O from the hydration sphere of K^+. The sequence allows the sieve effects, required to activate the electrogenic pump and the potential of neuronal membrane.

Since the physiological mechanism could be bypass by heating DNA at 65^{o}C, which non-physiologically unzips DNA, not much progress has preceded this report on the complementary structure of the cAMP-Mg-DNA complex for unzipping of the double helix, ignoring that there is a need to relate the well-known effect of cAMP of memory affirmation pathways for structuring neuronal circuits.

Mg^{2+} has been shown required for specific binding of the double-stranded DNA containing the consensus CRE sequence.

The product of AC activation is cAMP which correlates with the central role of the enzyme subtract. Thus, the reactions of cAMP with Mg^{2+} and water result in unzipping DNA through the formation of Mg^{2+}-cAMP-DNA complex. The cAMP-response-element-binding (CREB) was proposed in 1987 as a cAMP-responsive transcription factor regulating the somatostatin gene [43].

NA (noradrenaline) released by the long axons of the corpus coerellus into the synaptic junctions, also contributes to additional up-regulation of AC, increasing cAMP beyond basal values.

Thus, the up-regulation of AC by Mg^{2+} is turning off by Ca^{+2}. The stressors trigger the Mg^{2+} response and subsequently by an excess of free Mg^{2+} over subtract activates AC unchaining the fight or flight response.

The regenerative capacity of cAMP could be used for treatment in Alzheimer's disease could be selected in order to reach specific brain areas. It could be assumed that dysfunctions of the vomeronasal pathway during nurturing could lead to autism.

Excitotoxicity due to excessive glutamate release and impaired uptake occurs as part of the ischemic cascade and is associated with stroke [44], autism, [45], some forms of intellectual disability, and diseases such as amyotrophic lateral sclerosis, lathyrism, and Alzheimer's disease [46]. In contrast, decreased glutamate release is observed under conditions of classical phenylketonuria [47] leading to developmental disruption of glutamate receptor expression [48].

Discussion

Pheromones integration for DNA unzipping and hypothalamic feedback

Oxytocin produced by the hypothalamus, stored and secreted by the posterior pituitary gland acts as a neurohypophysial/neuromodulator of intimacy, sex and reproduction. It is released in large amounts

after distension of the cervix and uterus during labor, facilitating birth, maternal bonding, and, after stimulation of the nipples, lactation [49].
The Locus Coereleus neurons by the effect of NA acting on the brain led to the recognition of the molecular equivalent for the psychosomatic axis and its impact on many social problems.
A mechanism separating emotional-long-term (LTM) from short-term memories (STM) also called working memory may not require totally independent pathways. Both could operate from CREB mediate process of accumulation of transduced information into peptides. The latter, could be selectively encoded within the membrane. Natural selection may adjudicate lasting neuronal patterns, out of nurturing experiences, along the life learning period, which characterizes each animal species. This could be exampled by nurturing, sex, etc., could activate CREB-dependent induce genes involved in the oxytocin peptide synthesis. Working memory could be expressed because emotional conditions lead to stimulate constitutive gene expression of oxytocin recognition receptors. Oxytocin could be measured in saliva samples. At the spines and/or dendrites, the binding of Mg^{2+} stimulates the oxytocin-occupied receptor for a rapid release of the pheromone response.
Social olfactory deficits in mice without the oxytocin gene [50] [51] are rescued with injection of oxytocin into rat olfactory bulbs. Oxytocin-mRNA has been shown to be highly expressed in human paraventricular nucleus of the hypothalamus, the lateral hypothalamic area, and the supraoptic nucleus [52].
Increased mRNA in the human olfactory epithelium region may be vestigial, as olfaction is not as important for human conspecific identification, compared to most other mammals due to species specialization.
Oxytocin's feedback secretion is controlled by Ca^{2+} release expected to be a potential therapeutic resource for the social core symptoms of autism spectrum disorder (ASD), since this neuropeptide can modulate human social behavior and cognition [53]. Oxytocin interacts with the neural pathways responding to motivationally relevant stimuli and dopamine system [54], craving for oxytocin induces aggressive response to abandonment like gender violence [6].
Dopamine's feedback is a self-reward for many risks deports, conditioning the unconscious and conscious level, which is essential to voluntary motion and cognition, improving outcomes in newborn infants with a suspected lack of oxygen during birth, also regulates motivation and the reward system, related to love through desire.
The oxytocin signaling as a feedback system operates synergistically with the dopaminergic and muscarinic acetylcholine, signaling systems to exert its complex effects on cognition and memory.
A daily photic signaling to the hypothalamic suprachiasmatic nucleus (SCN) became the central oscillator for the appropriate phasing of the various biological rhythms.

H-bonds thermodynamics contribution to dissipative states of the open system

The Prigogine model for decreasing entropy was applied to a model of mutual inclusion, during transition of the Oxy- to Deoxy- forms of Hb. Thus, conformational dynamics for its hydro- to dehydro- forms, could release O_2 and Mg^{2+} for a flow of matter and energy, during the function of the brain's blood-astrocyte-neuronal system.
The kinetics of brain adenylate cyclase (AC) have a high basal activity that analyzed by a RARE BiBi mechanism (scheme 1) shows an obligatory excess of Mg^{2+} (S_1), over Mg-ATP (S_2) prior to the binding of S_2, indicating that Mg^{2+} is required to configure a site for MgATP binding.
Turnover of the enzyme release Mg^{2+} from the E as a nascent ion (n-Mg^{2+}), which shows a stronger intrinsic charge. Microscopic reversibility is restricted by coupling the cerebrospinal fluid (CSF), containing polymerized water loss of H-bonds that eventually are released as vapor, as an entropy decrease mechanism.
A GTP cycle is coupled to noradrenaline (NA) active site. Adrenaline is not present in brain; it has separated functions like an increased heart rate and preparing the body for stress [1]. NA is released by the long axons of the $8.6x10^4$ neurons of the locus coeruleus into the synaptic junctions activating AC for sensorial-integrated perception areas for an all-inclusive memory function. Because of the blood-brain barrier (BBB), noradrenaline play separated roles for brain AC that adrenaline for the body AC (figure 2).

The lack of adrenaline access by the BBB prevents a negative feedback for metabolic homeostatic control of the hypothalamic–pituitary–adrenal (HTPA) axis. Thus, allowing persistence of stress-stimulus, acting on the hypothalamus. This increases the release of orexins A and B. Orexin-A is capable to stimulate the adrenocortical cells to secrete cortisol (figure 2). This one leads to a constant increase in cortisol, and thus becoming the main stress-hormone.
The activation of the Na^{+}/K^{+}-ATPase pump, by decreasing ATP^{4-}, release the ion Mg^{2+} with an activatory effect on AC (scheme 1).
Mg-cAMP and Mg-cGMP (carried by erythrocytes) controls the physiological gene expression. These are expected to contribute to the understanding of plasticity, and its relationship to the response to learning, by creating neuronal circuits, which characterize memory. Stress mediated by increasing adrenaline secretion, usually shows a pattern of hyperfunction follow by hypofunction, which when the stressed organ is brain, it could be associated with a symptomatology of persistent anxiety followed by depression [1].
Under prolonged stress, the synthesis of new AC, may not match the rate of NA-dependent AC inactivatory decrease. The viability of functional synapses may be controlled by the speed of synthesis of the proteins, which make-up the hormonal receptor sites and/or AC-itself, versus the rate of inactivation or destruction of AC. This generalized molecular modeling for the brain evolution of psychosomatic diseases could be tested, with regard to more specific physiological conditions and permit prognosis of dysfunction, allowing preventing treatments. Already medical applications have been developed, based in the use of beta-blocker drugs help to prevent heart organic damage, by stressful condition and could attenuate traumatic memory events.

Conclusions

The VNO relates the olfactory cavity to inhale and exhale pheromones, which act at the accessory olfactory epithelium cells and their projecting axons to perceive scents, absorption of saliva, sweat, mother' milk smell, sexual hormones, etc., as signals to the hypothalamic-amygdala-pituitary-adrenal axis. Also the system responds as a relay site for oxytocin released in the posterior pituitary in the period after childbirth for the anxiety response to threat stress.
The human newborn from the evolutive disintegration of the mammal olfactory bulb, have acquired the cells for an olfactory epithelium, and from the destruction of these cells nuclei, their cffDNA. Hence, the human brain has evolved from a mammal smell-olfactory-memory organ, which allows in the short time a capability for continuous coordination and muscle control. In humans a pheromone-communication level remains for a long nurturing time until could be replaced by a new audio-visual recall memory, at the conscious level. This one contains memory from the previous evolutive stage as vestiges into a subconscious level, which structure psychosomatic complexes.
A restriction on the randomness of evolution could result, from sensorial signaling response to pheromone communication by the G-protein 7TM receptors, activating hypothalamic AC. The cAMP produced could form cAMP-Mg-cffDNA complex transcribed in the messenger RNA, modulating brain plasticity by acting as a feedback on brain evolution, capable to overcome either the randomness, or inherited patterns, but adapting the developing neuronal circuit network for a greater cognitive capacity.
Brain evolution has been conditioned and circumscribed by transition stage parameters, adjusted by nurturing to energy (nutritional contents) and emotional exchanges, to develop the psychosomatic complexes, like a child's desire for parental care for the opposite-sex parent time.
The VNO operates as a radiator mechanism, dissipating heat captured by the brokening of H-bonds between molecules of circulating in the astrocytes of water in cerebrospinal fluid (CSF), as a second order transition state, during which is independent of acquiring the microscopic structure stable vapor phase until released as a 5% vapor of exhaled air and preventing an entropy increase.
This thermodynamics approach allows the evolutive increase in efficiency of the 1.6 kg brain to process a 30% of total body ingested calories, disposing of expended CSF-water (poor H-bonds content) by the astrocytes, maintaining a liquid state at 36.6 ^{0}C.
Mass-action effects by Ca^{2+} inhibit AC and activate calcium permeable AMPARs receptor, during the brain state of sleeping. This state of synchrony contributes circuits in a labile state for memory

formation. An abnormal synchrony expression during sleep-wake [14] has been implicated in drug addiction and memory disorders.
A lower caloric diet (or starvation) lowers ATP^{4-} and CaATP both dead end inhibitor activating AC, which raises cAMP as a molecular signal driving adaptive evolution and conferring longevity to man and animals.
A technic of assay of cAMP levels could provide a test to manifest organic dysfunctions. Assay of oxytocin could be a test for diagnosis of autism and psychosomatic dysfunctions, which could result from a detached care of newborns, during the breastfeeding period. Moreover, to create a proper commercial mother's milk substitute, may require the addition of pheromones that may contribute to potentiate a desirable ulterior behavior.

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