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Original Research Paper

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WATERWORLD: A HYDRO-MOLECULAR HYPOTHESIS OF NEUROCOMPUTATION

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Proteins are the building blocks of life which are encoded in the genome and regulated by the environment via epigenomic modulation. These biomolecules possess Transformers-like abilities to instantly change shape, assemble and disassemble, birthing compounds with different biological functions. Proteins also present with origami-like capabilities of folding along specific lines, engendering functional or prion-like pathological entities. These properties enable a multitude of physiological processes in the living world, ranging from endocrine control and immunity to memory and self-awareness. Furthermore, biomolecules are endowed with other equally amazing qualities including, linking to each other in Lego-like fashion, electronic conductance and generation of allosteric or vibration "bar codes" which may enable long term potentiation and memory. In addition, proteins may facilitate synchronization of neuronal firing rates among anatomically distant areas of the CNS, a phenomenon believed necessary for consciousness. In this article we hypothesize that global molecular networks are physiologically turned "on" during wakefulness and "off" during sleep by the extracellular space water, accounting for the difference in neurocomputation modes during the two circadian states.

Can Proteins "think"?

The brain processes information differently during sleep, psychosis or wakefulness. Freud noted this discrepancy and believed that the unconscious id "thinks" in a dream-like, irrational manner, which he named primary processes, while the conscious ego operates via reason, or secondary processes (1). The molecular underpinnings of these two modes of neurocomputation may be distinguished at the biomolecular level as information processing in local vs. global molecular networks (GMNs) (2-3). Novel biophysical studies demonstrate that in regards to computation, biomolecules rival modern electronics as they are endowed with transistor-like abilities to transduce information from the environment to the cell nucleus and back, to triage data by decision-making, and to adaptively silence or activate genes (4). Biomolecules were shown to process information by their ability to access logic gates, the elementary building blocks of digital circuits. In addition, these molecules are endowed with Transformers-like abilities to adaptively change shape in response electronic signals or electromagnetic fields (5-9). For example, the calcium-calmodulin-dependent kinase III, a component of neuronal microtubules, is believed to store long term memory by reorganizing its spatial structure in response to synaptic activity (10). With the same token, actin regulatory protein N-WASP was documented to spatially reassemble in order to access the logic gate AND (11). Moreover, proteins are endowed with Lego-like abilities to link with each other, engendering large intra and extracellular biomolecular networks with hypothesized roles in neurocomputation (12). For example, actin filaments are known to connect inside the cell with the scaffolding proteins, while outside (via transmembrane proteins) with the biomolecules of the extracellular matrix (Fig. 1). It is believed that these links engender brain-wide molecular assemblies with role in sleep physiology and also in the creative abilities of the mind, such as intuition and generation of novel ideas or artistic forms (13). Over the past decade nanoneuroscience has clarified the molecular substrates of cognitive processes by studying the role of dendritic spines' proteins within the CNS excitatory neurotransmission. These studies revealed that spine biomolecules may play a crucial role in associative memory as they endow neural circuits with Boolean logic (14-17). In addition, the population of biomolecules in each spine was found to assume unique spatial characteristics, different from other synapses, suggesting a role in higher forms of personalized mentation (18). Furthermore, spines' transmembrane proteins, (such as densin, integrin, neuroligin and cadherin) were shown to bridge the synaptic gap, linking the scaffolding proteins of the presynaptic neuron with the proteins of the postsynaptic density. It was hypothesized that neuronal firing induces protein vibrations or allosteric changes in the postsynaptic density, engendering memory "bar-codes", via rearrangement of postsynaptic receptors into heteroreceptor complexes (3)(19-22).

Can Proteins Engender Consciousness?

At the present time the brain can be studied at two levels of resolution: cellular and molecular. Cells are known for their assembly into neuronal, glial or neuronal-glial networks and for their ability to communicate by extracellular vesicles or electrical and chemical signaling. On the other hand, biomolecules were shown to communicate and form molecular networks which are fitted inside the cellular networks, like Matryoshka dolls. Interestingly, the cellular and molecular networks are physiologically complementary but follow different sets of rules in regards to cellular membranes. Biomolecules do not respect cell boundaries, their networks do not terminate at the cell edges, but cross into the extracellular space (ECS), and synaptic gap, enmeshing the entire CNS as global molecular networks (GMN)(23)(17)(21).

GMNs may set the stage for discerning the neural correlates of consciousness and solve the "binding problem" on which neuroscience has stumbled since its inception. How does the brain synchronize multiple neural groups dispersed throughout the CNS into processing in unison the information related to an object? Moreover, how are the end-products of these computational units integrated into a whole? When watching a bird, for example the brain receives input from different sensory modalities (color, movement, shape, sound) located at various sites throughout the CNS, yet the bird is perceived as a whole rather than a list of its qualities (22). As they crisscross the entire CNS, GMNs are the ideal candidates for "binding" the processing units and their end-products into meaningful perceptions. Furthermore, GMNs may clarify the concept of qualia, as they could link multitudes of subjective and objective experiences into unique holistic perceptions (24-25).

Interestingly, several altered-level-of-consciousness (ALC) syndromes are known as proteinopathies, diseases of maladaptive protein structures. These conditions include neurodegenerative disorders caused by excessive accumulation of misfolded proteins within the brain parenchyma. The best known among them are Alzheimer's, Huntington's, Parkinson's, prion disease, and Frontotemporal dementia (26-29). In addition, proteomic alterations were demonstrated in other ALC disorders which at present are not

designated as proteinopathies, including schizophrenia (30-31), delirium (32) and traumatic brain injury (33).

As a result of technological advances such as mass spectrometry, the novel science of proteomics developed over the past decade, generating databases of body-wide protein populations which provide insight into the physiological and pathological role of proteins (34-35). In this regard, it has been established that when a new protein is produced it is biologically inactive. In order to perform its job in the cellular machinery it needs to fold along specific axes like paper in the ancient Japanese art of origami (36). It was recently demonstrated that water plays a crucial role in the correct folding of proteins as it forms hydrogen bonds with the amino acid chains, engendering unique funnel-shaped energy systems necessary for instant folding. In the absence of hydration, this process is significantly slower and frequently proteins become "stuck" into incorrect shapes, resulting in proteinopathies (37-39).

Folding and molecular dynamics enable proteins to function as "switches" connecting and disconnecting molecular networks. For example, Figure 1 demonstrates that by altering its length, the integrin molecule may connect and disconnect the flow of information in GMNs at the level of ECS matrix protein fibronectin.

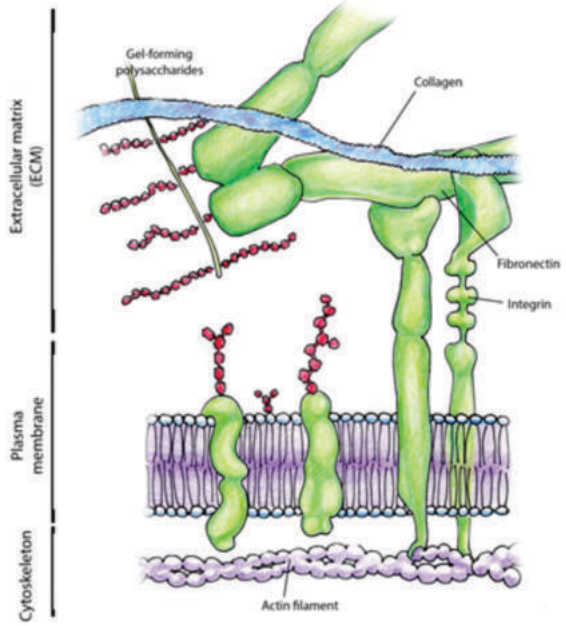

Fig.1 Integrin molecule links the intracellular actin and the extracellular fibronectin proteins, connecting the intra and extracellular molecular networks into global molecular networks (GMNs). Both, sleep-induced volume changes and folding/unfolding of the integrin molecule may disrupt this link, turning "off" information flow in GMNs.

The Hydro-molecular Hypothesis

C.G. Jung believed that water symbolized the unconscious mind, the realm of primary processes, which Freud named id. Jung envisioned psychosis as flooding of the conscious mind with unconscious content, disabling secondary processes. It is well known today that water comprises 80% of the brain volume and its circulation between the intra and extracellular compartments is crucial for the CNS homeostasis. It is also well established that water can move passively by diffusion and convection, or actively, against the gradient, via aquaporin-4 proteins (AQP-4)(40).

It was recently demonstrated that during sleep water fills the ECS of the brain, augmenting its volume by up to 60%, while during wakefulness, water shifts away, probably into the astrocytes via AQP-4 water receptors (41). The ECS is an area demarcated by the convexities of cell membranes which is held together by the Velcro-like forces of adhesion molecules. These biomolecules link the intracellular and extracellular matrix proteins, assuring uninterrupted flow of information in GMNs. Water entry into this space during sleep and volume augmentation along with conformational changes of matrix proteins may overcome the grip of adhesion molecules, interrupting the continuity and flow of information in the GMNs.

The hydro-molecular hypothesis proposes that the circadian changes in neurocomputation are caused by a temporary water-induced disruption of information flow in the GMNs at the level of the ECS matrix proteins. In other words, rational neurocomputation by secondary processes requires an uninterrupted flow of information in GMNs; disrupting this flow triggers primary processes, which like a screen saver activates by the absence of activity in GMNs.

The hydro-molecular hypothesis suggests therefore that water is not a passive support system, but controls brain information processing via GMNs. We are of the opinion that water accomplishes this control through protein folding and changes in conformational dynamics. Our hypothesis is complementary to Moore's hemo-neural model however we opine that not the whole blood, but its water fraction participates in information processing (42). Interestingly, several proteinopathies associated with ALC syndromes are also characterized by over-expression of AQP-4 proteins. They include epilepsy (43-44), traumatic brain injury (45), Alzheimer's disease (46), neuromyelitis optica (47) and schizophrenia (48).

The role of water as an integral component of biomolecules is a new and growing field of study which has revealed that aside from protein folding and conformational dynamics, water is a key catalyst for protein-ligand and protein-protein interactions as it can facilitate or inhibit biomolecular links (49). Entry of water into the ECS matrix during sleep may relax biomolecular grips, loosening the matrix. A loose, watery ECS matrix may alter the folding of adhesion molecules, thus turning "off" the information flow in GMNs (50). Interestingly, it was demonstrated that two matrix proteins, associated with ALC syndromes, matrix metaloproteinase-9 (MMP-9) and □1-integrin alter the expression of AQP-4 proteins and are pharmacological targets for brain edema (51-52). In addition, these two proteins were demonstrated to play a major role in epilepsy, Alzheimer's disease, and schizophrenia (53-54).

CONCLUSIONS

Proteins are endowed with properties as amazing as life itself. Aside from their function as body building blocks, they may facilitate cognition, memory and consciousness. Their assembly into brain-wide networks may represent the "missing link" on how the brain integrates the work of geographically distant computational units to synthesize a holistic gnosis. We emphasize that proteins do not function in isolation, but in solution: water is the forgotten building block of life which may modulate information processing via GMNs. Our hydro-molecular hypothesis suggests that the overabundance of water in the ECS during sleep loosens the matrix and alters the folding of matrix proteins, severing the link between intra and extracellular molecular networks, thus temporarily turning "off" the information flow in GMNs. GMNs inactivity activates dream-like primary processes which substitute rational neurocomputation. The opposite may occur during wakefulness: the lower water volume tightens the matrix, restoring previous configuration of proteins which, like the movement of a computer mouse, awakens GMNs information flow, reestablishing rational neurocomputation.

The same mechanism may be at play in psychotic information processing as the pathways of sleep and psychosis intersect. Psychosis may be a molecular failure to activate GMNs during wakefulness, if so, the matrix proteins and AQP-4 water receptors may represent novel molecular targets for antipsychotic drugs.

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