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Waterworld: a hydro-molecular hypothesis of neurocomputation

Abstract

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 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 properties including, linking together, electronic conductance and generation of allosteric or vibration "bar codes" which may enable information processing. 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 biomolecular networks are physiologically turned "on" during wakefulness and "off" during sleep by the extracellular water, accounting for different neurocomputation modes in the two circadian states.

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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, triage data by decision-making, and epigenetically silence or activate genes in adaptive manner.[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 known 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] Furthermore, 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 scaffolding proteins, while outside (via transmembrane proteins) with the biomolecules of the extracellular matrix (Figure 1). It has been hypothesized that these links engender global molecular assemblies with possible roles in not only in wakefulness and sleep, but also in generation of novel ideas or artistic forms.[13]

Over the past decade nanoneuroscience has attempted to shed light on the molecular substrates of cognitive processes by studying the dendritic spines' proteins in the excitatory brain neurons. These endeavors demonstrate 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 receptors into heteroreceptor complexes.[3,19-22]

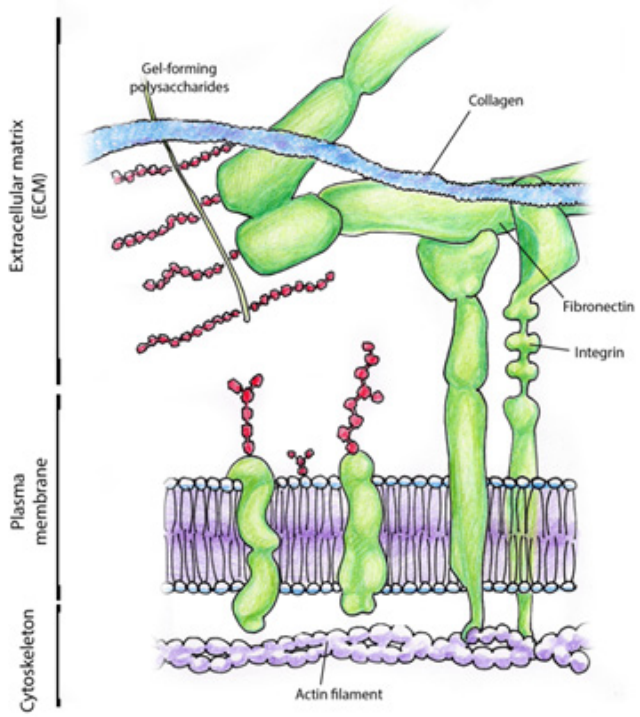

Figure 1 Integrin molecules link the intracellular and extracellular molecular networks into global molecular networks (GMNs). Both, sleep-induced volume changes and folding/unfolding of the integrin molecule may disrupt this link, turning "off" information processing in the GMNs.

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/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), enmeshing the entire CNS as global molecular networks (GMN).[17-23] 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 various neural groups dispersed throughout the CNS into processing in unison 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 a meaningful perception. 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 syndromes present 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 these conditions are Alzheimer's, Huntington's, Parkinson's, prion disease, and Frontotemporal dementia.[26-29] In addition, proteomic alterations were demonstrated other disorders associated with altered level of consciousness 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 new science of proteomics allows analysis of body-wide protein populations. Over the past decade proteomic databases have been developed, providing insight into physiological and pathological role of proteins.[34,35] It has been well established that when a new protein is produced it is biologically inactive. In order to perform its job in the cellular machinery adequately 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 proper folding of proteins as it forms hydrogen bonds with the amino acid chains, engendering unique funnel-shaped systems indispensable for proper folding. In the presence of water protein folding occurs adequately and instantly, while in the absence of hydration, proteins become stuck into incorrect shapes, with resultant proteinopathies.[37-39] Folding and molecular dynamics enables proteins to function as "switches" connecting and disconnecting molecular networks. For example, Figure 1 demonstrates how by altering its length, the integrin molecule may connect and disconnect the flow of information 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 contents, disabling secondary processes. It is well known today that water comprises 80% of the brain volume and its circulation between the intra and extracellular compartment 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 convexity of cell membranes which is held together by the Velcro-like force 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 due to a temporary water-induced disruption of information processing in 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 are activated like a screen saver by the absent activity in GMNs.The hydro-molecular hypothesis suggests therefore that water is not a passive support system, but it controls brain information processing via GMNs. We are of the opinion that water accomplishes this control biochemically through protein folding and changes in conformational dynamics. Our hypothesis is complementary to Moore's hemo-neural model, but we opine that not the whole blood, but its water component participates in information processing.[42]

Interestingly, several proteinopathies are associated with over-expression of AQP-4 proteins.[43] They include epilepsy.[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, but growing field of study. Aside from protein folding and conformational dynamics, water was shown to be a key catalyst, mediating protein-ligand and protein-protein interactions.[49] Water entry into the ECS matrix during sleep may relax the biomolecular links, decreasing molecular crowding and loosening the matrix. A loose, watery ECS matrix may disrupt the adhesion molecules, turning "off" the information flow in GMNs.[50] Interestingly, it was demonstrated that inhibition of matrix metaloproteinase-9 (MMP-9) attenuates brain edema. In addition, β1-integrin was shown to alter the expression of AQP-4 proteins.[51,52] With the same token, integrins were demonstrated to play a major role in epilepsy, Alzheimer's disease, and schizophrenia.[53]

Conclusion

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 swells the volume and loosens the matrix, severing the link between intra and extracellular molecular networks, temporarily turning "off" the information flow in GMNs. Inactivity in the GMNs enables dream-like primary processes, to substitute rational information processing. The opposite may occur

during wakefulness: the lower water volume tightens the matrix, reestablishing the link between intra and extracellular molecular networks, which like the movement of a computer mouse, awakens GMNs to rational neurocomputation. The same mechanism may be at play in psychotic neurocomputation 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.

Acknowledgments

None.

Conflicts of interest

None.

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