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ARTICLE

Non-neuronal cells, information processing, and neuropsychiatric syndromes

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Abstract

We believe that the neurovascular unit (NVU) can be envisioned as the structural and functional assembly of the brain where cellular and the extracellular macromolecules join their properties to engender global molecular networks that enable human information processing. Furthermore, we believe that the concept of NVU may facilitate understanding of neuropsychiatric conditions.

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Introduction

Structurally, the brain cells are packed into three cellular compartments: neuronal, glial (astrocytes, oligodendroglia, and microglia), and vascular (endothelial cells and pericytes).[1,2] The extracellular space (ECS) anchors the cells together and provides a highway for non-synaptic communication, such as volume transmission (VT).[3] Studying the interactions, connectivity, and information processing among all brain cells offers the best modality of a brain-based understanding of neuropsychiatric disorders.[4]

Cellular and molecular information processing

It was hypothesised that at the brain cellular level, information processing occurs in complex cellular networks (CCN) comprised of functional and structural connectivity among various cells that communicate with or without immediate physical contact.[3] In this respect bidirectional neuronal-glial signaling has been well known and documented for some time, but more recently cross-talk between pericytes and endothelial cells was described as well as communication between endothelial cells of brain microvessels and neurons.[5]

The cellular dialogue among neurons can occur via synapse or non-synaptically by VT where signaling molecules are released into the ECS. VT was described by Luigi Agnati and Kjell Fuxe in 1986 as a communication platform among brain cells in which signaling molecules travel with the flow of cerebrospinal fluid (CSF) and/or interstitial fluid (ISF) to act upon non-synaptic receptors situated at some distance from the source of the signal.[6] The neurovascular unit (NVU) consists of cells and the ECS situated between an arterial and a venous capillary, a distance of approximately 40 μm where the synaptic and non-synaptic signaling occurs.[7]

The NVU cells consist of neurons, glia, endothelial cells, and pericytes. These structures are embedded in the ECS comprised of a solid phase, the extracellular matrix (ECM), and a liquid phase, the ISF exchanging with CSF via aquaporin 4 channels (AQP-4) found in astrocytic endfeet.[7]

In the NVU, the volume of the ECM is regulated by adhesion molecules forming a biological Velcro, and holding neighbouring cells together. ECM molecules such as hyaluronic acid, lecticans, and tenascins are enmeshed with the receptors and adhesion molecules on the cellular membranes.[7] The matrix molecules engender a labyrinth of

pores and channels that comprise the riverbed for the flow of ISF. The ECM is also home to enzymes such as matrix metalloproteinase (MMP) involved in the synaptic plasticity and the learning process.[8]

Interestingly, the ECM of the NVU is the place where the intracellular and extracellular molecular networks reach toward each other, establishing contact. The intracellular proteins comprising the cellular cytoskeleton are known to assemble with membrane adhesion molecules such as integrins which in turn bind to ECM proteins, generating global molecular networks (GMN) which criss-cross not only the NVUs, but the entire central nervous system (CNS).[6,9] The GMNs are the molecular equivalents of brain cellular networks.

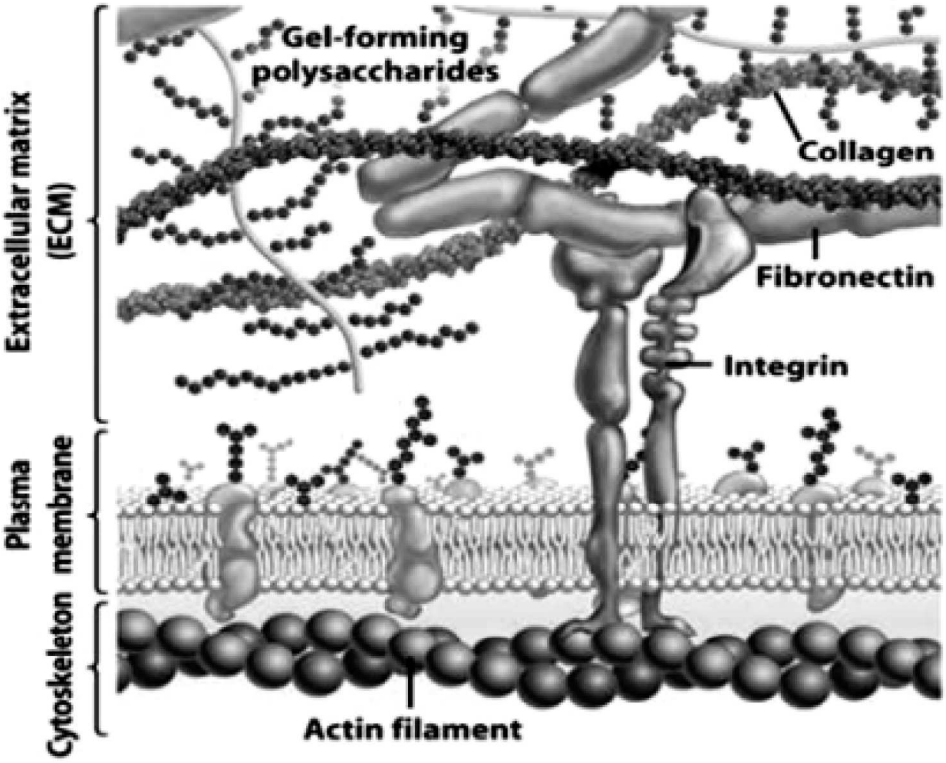

Figure. *Adhesion molecules such as integrins connect the intra and extracellular molecular networks (public domain image).*

Adhesion molecules, such as integrins are crucial components of GMNs because of their molecular dynamic property that allows them to shrink and elongate, turning on and off the contact between intra and extracellular networks. Integrins are composed of three domains: an intracellular one in touch with the cytoskeleton, a trans-membrane and an extracellular domain that interacts with the ECM macromolecules.[10,11] When a ligand binds to the cytoplasmic domain, it causes elongation of the extracellular subunit of the integrin molecule establishing contact with the ECM macromolecules (the switch is in "ON" position). Conversely, when a ligand binds to the extracellular subunit, the integrin shortens, thus turning "OFF" the cytoskeleton-ECM contact.[12-15]

In addition to changing shape, the conformational dynamic of adhesion molecules endows them with electronic conductance and access to logic gates, the building blocks of computation.[16-19] A growing number of biophysical studies demonstrated that cytoskeletal macromolecules such as actin filaments and microtubules conduct electronic signals and respond to electromagnetic fields by structural organisation.[10,14] Indeed, it was recently demonstrated that individual proteins can perform logic operations.[11,20-22] For example, performance of the logic gate AND by the actin regulatory protein, neuronal Wiskott-Aldrich syndrome (N-WASP), was described.[23] Moreover, synthetic proteins based upon naturally existing proteins have been shown to perform a number of different logic operations.[19,20] Dendritic spines' proteins were hypothesised to endow neuronal networks with Boolean logic.[24]

The pathology of the NVU, CCNs, and GMNs

There is growing evidence that disruption in the NVU environment impairs information processing in both CCNs

and GMNs, leading to neuropsychiatric pathology. These pathological changes include organic brain syndromes, neuropsychiatric and functional syndromes.

Organic brain syndromes

There are data demonstrating that psychosis due to lupus, Sjogren syndrome, and substance abuse involves the cerebral microvasculature,[25] suggesting faulty information processing in non-neuronal cells of the NVU. A strong comorbidity was described between neuropsychiatric conditions such as mood disorders, psychosis, and dementia with primary genetic vasculopathies such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), suggesting non-neuronal aetiology of these symptoms.[26]

Neuropsychiatric syndromes

In Alzheimer's disease (AD), a loss of cholinergic innervations to brain capillaries and apposed astrocytic endfeet was described, suggesting a NVU, rather than neuronal pathology.[26] Glial and microvascular changes were documented by numerous AD studies; involvement of retinal microvessels was suggested as a biomarker for AD.[27-29] Elevation of S100B has been demonstrated in various neuropsychiatric conditions with cognitive impairment such as delirium.[30,31] ECM metalloproteinases - 9 (MMP-9) were implicated in post-surgery delirium,[31] suggesting that information integration may be dependent on the proper function of integrins in the ECM of the NVU.

Functional syndromes

Microvascular abnormalities were documented in elderly with major depressive disorder, suggesting involvement of non-neuronal cells.[32] In schizophrenia, retinal microvascular abnormalities were described, raising the possibility of vascular involvement in this disorder.[33] Postmortem laser microdissection studies in patients with schizophrenia demonstrated impairments in NVU-mediated energy supply.[34] Inflammatory or immunologic processes involving non-neuronal cells, such as microglia, astrocytes, and endothelial cells were demonstrated in both psychosis and depression.[35,36] Decreased blood flow was documented in patients with major depressive disorder, especially in the frontal cortex, cingulate gyrus, basal ganglia, and temporal cortex, possibly as a result of faulty haemo-neural signaling in the NVU.[36] Non-neuronal pathology such as reduced capillary diameters in the anterior cingulate cortex (ACC) was documented in elderly with unipolar or bipolar depression.[36,37] Astrocytic involvement reflected in the elevation of astrocytic marker S100B was documented in depression, with subsequent decrease after treatment with selective serotonin reuptake inhibitors (SSRIs), suggesting that other cells, rather than neurons alone, may be involved in the pathogenesis of major depressive disorder.[38] Other non-neuronal macromolecules such as connexins were involved in emotional and motivational processing.[39] For example, connexin30 and connexin43 (expressed primarily by astrocytic endfeet) are known to modulate NVU energy supply and to be altered in major depressive disorder.[40,41] Connexin43 blocker carbenoxolone elicits depressive-like behaviours[40] in laboratory animals, also rats subjected to chronic unpredictable stress (CUS), were found to exhibit decreased expression of connexin43 in the prefrontal cortex.[42]

Conclusions

All cellular compartments of the brain along with the ECS seem to be involved in human information processing. Synaptic and volume transmission, neuronal and non-neuronal cells may integrate information and confer meaning to sensory input. Understanding cooperation between cellular and molecular networks in the brain may shed light on pervasive, mass-sustained brain functions such as awareness, attention, cognition, mood, appetite, and circadian rhythm which may rely on information processing by GMNs.

The NVU seen as a basic cellular assembly of information processing, uniting function and structure, may be similar to basic units of other organs, such as lung's alveolus or the kidney's nephron, and may contribute a model by which the complexity of the human brain can be grasped with somewhat more ease. With the same token neuropsychiatric disorders may be better discerned on the grounds of a basic unit whose function involves information processing, integration, and energy supply.

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