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Review

The tetrapartite synapse: a key concept in the pathophysiology of schizophrenia

Gabriele Chelini[a,b], Harry Pantazopoulos[a,b], Peter Durning[a], Sabina Berretta[a,b,c,*]

[a] Translational Neuroscience Laboratory, Mclean Hospital, 115 Mill Street, Belmont, MA, 02478 USA
[b] Dept. of Psychiatry, Harvard Medical School, 25 Shattuck St, Boston, MA, 02115 USA
[c] Program in Neuroscience, Harvard Medical School, 220 Longwood Ave., Boston, MA, 02115 USA

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ABSTRACT

Growing evidence points to synaptic pathology as a core component of the pathophysiology of schizophrenia (SZ). Significant reductions of dendritic spine density and altered expression of their structural and molecular components have been reported in several brain regions, suggesting a deficit of synaptic plasticity. Regulation of synaptic plasticity is a complex process, one that requires not only interactions between pre- and post-synaptic terminals, but also glial cells and the extracellular matrix (ECM). Together, these elements are referred to as the 'tetrapartite synapse', an emerging concept supported by accumulating evidence for a role of glial cells and the extracellular matrix in regulating structural and functional aspects of synaptic plasticity. In particular, chondroitin sulfate proteoglycans (CSPGs), one of the main components of the ECM, have been shown to be synthesized predominantly by glial cells, to form organized perisynaptic aggregates known as perineuronal nets (PNNs), and to modulate synaptic signaling and plasticity during postnatal development and adulthood. Notably, recent findings from our group and others have shown marked CSPG abnormalities in several brain regions of people with SZ. These abnormalities were found to affect specialized ECM structures, including PNNs, as well as glial cells expressing the corresponding CSPGs. The purpose of this review is to bring forth the hypothesis that synaptic pathology in SZ arises from a disruption of the interactions between elements of the tetrapartite synapse.

1. Introduction

Growing evidence points to synaptic pathology across several brain disorders, including schizophrenia (SZ), bipolar disorder, major depression, autism spectrum disorder and Alzheimer's disease. Research on the underlying mechanisms for this pathology has only very recently begun to make headway, and important questions arise with regard to the potential common denominators of synaptic pathology among these disorders, and their timeframe across lifespan. With regard to the latter, it is important to consider that synaptic remodeling occurs constantly throughout life. During postnatal development, excessive synaptic formation is followed by elimination of less active synapses, a process named synapse pruning [1,2]. During adult life, synapses are highly dynamic, with constant, experience-driven synaptic growth and elimination. It is plausible to postulate that timeframe-, mechanism- and brain region- specificity underlying synaptic pathology across a spectrum of brain disorders may at least in part contribute to their diverse clinical and pathophysiological manifestations. Within this context, we suggest that the concept of 'tetrapartite synapse' may be a useful starting point for investigating synaptic pathology. We focus on schizophrenia as a notable example.

1.1. The tetrapartite synapse

The chemical synapse has classically been considered as composed of two main elements, i.e. the presynaptic and postsynaptic elements. This concept evolved over the past two decades to include a third element, i.e. the astrocyte, as processes

Abbreviations: ADAMS, a disintegrin and matrix metalloproteases; ADAMTS, ADAMS with a thrombospondin domain; AMPAR, α amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; ATP, adenosine trisphosphate; C4, complement component 4; CS, chondroitin sulfate; CSPG, Chondroitin sulfate proteoglycan; EAAT1, excitatory amino acid transporter 1; EAAT2, excitatory amino acid transporter 2; ECM, extracellular matrix; GABA, γ-Aminobutyric acid; GAG, glycosaminoglycan chains; GWAS, genome wide association study; IHC, immunocytochemistry; LTD, long term depression; LTP, long term potentiation; MMP, matrix metalloproinase; NG2, neural/glial antigen 2; NMDA, *N*-methyl-D-aspartate; O4, O4 sulfatide; PDGFαR, platelet-derived growth factor α receptors; PNNs, perineuronal nets; PSD, postsynaptic density; SZ, schizophrenia; WFA, *Wisteria floribunda* agglutinin.
*Corresponding author at: McLean Hospital, Mailstop 149, 115 Mill Street, Belmont, MA, 02478, USA.

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from these cells envelope the synapse and play a key role in regulating its functions [3,4]. The ensemble of pre- and post-synaptic elements and astrocytes has been proposed to form a functional complex referred to as the 'tripartite synapse' [5]. Growing evidence indicates that other populations of glial cells, including NG2 glia and microglia, also play critical roles in regulating synaptic functions and plasticity. Thus, we suggest that distinct populations of glial cells with specific functions may be considered together to represent the third element of tripartite synapse. Yet more recently, the extracellular matrix (ECM) has come to the forefront of neuroscience as an active component of neural functions and, in particular, synaptic regulation. On the basis of this evidence, Dityatev et al., proposed the elegant concept of the 'tetrapartite synapse', composed of pre- and post-synaptic elements, glial processes and ECM, and elegantly documented the interactions between these components [6–8] (Fig. 1). Here, we review evidence supporting the idea that synaptic functions and plasticity result from interactions between all elements of the tetrapartite synapse, and focus on evidence that these interactions are disrupted in SZ.

1.1.1. The tetrapartite synapse: pre- and post-synaptic elements

The brain possesses the extraordinary ability to continuously reshape itself throughout the entire lifespan. This property, defined as plasticity, is based on the highly dynamic properties of synaptic contacts, i.e. the ability to generate new synapses, eliminate them, and alter the electrophysiological, molecular and structural properties of existing ones in response to experience. The mechanisms underlying synaptic plasticity have been the object of intense work and exciting discoveries over the past few decades, focused initially on the interplay between the presynaptic and postsynaptic elements. For example, the discovery that trains of presynaptic action potentials induce a long–lasting increase in synaptic strength during long term potentiation (LTP) generated intense debate over whether the predominant underlying changes may be related to postsynaptic modification in α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors (AMPARs) or altered presynaptic transmitter release [9,10]. Ensuing work demonstrated that these mechanisms include a series of steps, from receptor phosphorylation, to protein synthesis and, eventually, structural changes including growth of new dendritic spines and increased size of pre-existing spines, mediated by changes dendritic spine molecular cytoskeleton, including long-lasting increases in F-actin content within spines and condensation of the post-synaptic density (PSD), a dense aggregate of scaffolding proteins implicated in structural maintenance and signal transduction [11–13]. Similarly, long-term depression (LTD) of synaptic strength results in spine shrinkage and elimination [14–17]. A review of current knowledge on the role of pre- and post-synaptic elements in plasticity is beyond the scope of this manuscript; arguably plastic modifications of these elements may be considered to be the final result of complex, experience-driven mechanisms, and the underlying substrate of learning and memory.

1.1.2. The tetrapartite synapse: role of glial cells

1.1.2.1. Astrocytes. Astrocytic processes envelop the pre- and post-synaptic elements and closely approach the synaptic cleft, thus representing a key component of the synapse [3,18] (Fig. 1). Their robust expression of the high-affinity glutamate transporters EAAT1–EAAT2 allows them to rapidly re-uptake excess of glutamate released from the presynaptic terminals, thus restricting excitatory transmission [19]. In turn, astrocytes actively contribute to synaptic transmission and plasticity. Although electrically silent, they respond to presynaptic activation with G-protein-mediated Ca2 signals, triggering the release of 'gliotransmitters', including glutamate, ATP, and GABA, which modulate local synaptic transmission [20–25]. Astrocyte-derived glutamate facilitates NMDA receptor activation on the postsynaptic sites, enhancing the probability of triggering LTP [26]. Moreover, stimuli inducing synaptic LTP rapidly induce structural remodeling of astrocytic processes enwrapping synapses, resulting in changes in their ability to modulate synaptic transmission [27]. Together, these considerations compellingly point to astrocytes as key active mediators of synaptic plasticity.

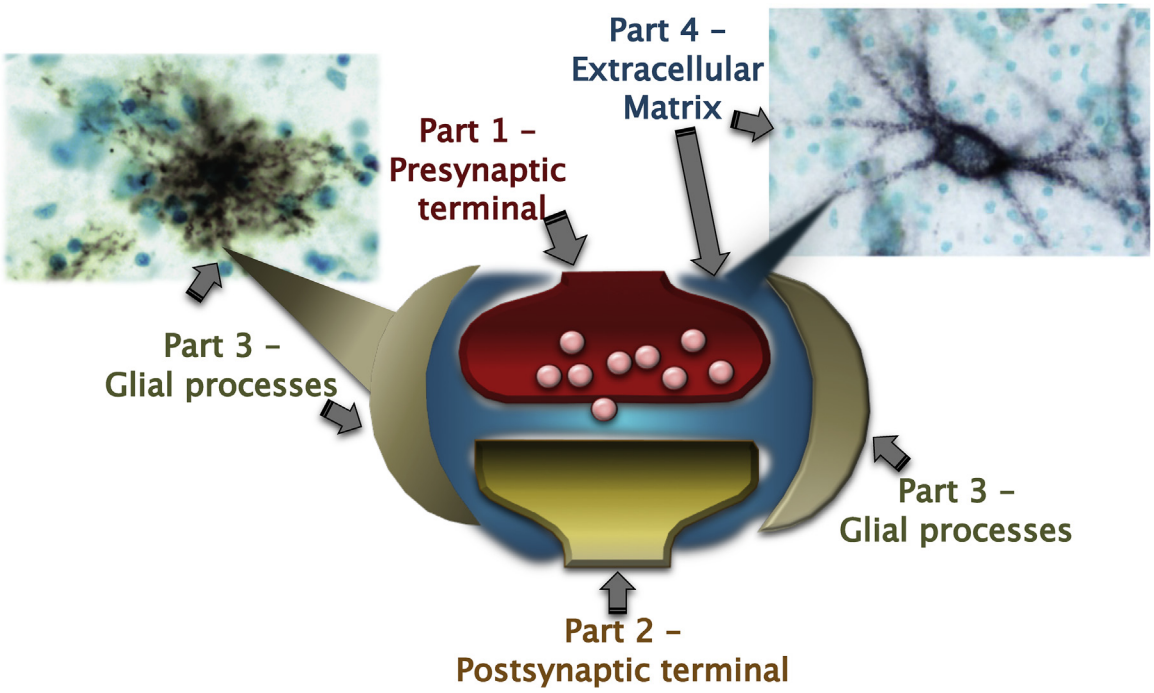

Fig. 1. Diagramatic representation of the tetrapartite synapse. Elements composing it are the pre- and post-synaptic terminals, astrocytic processes surrounding them and perisynaptic extracellular matrix condensations interposed between these elements.

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