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Review

Behavioral sequelae of astrocyte dysfunction: focus on animal models of schizophrenia

Meng Xia [a,e,f], Sofya Abazyan [a], Yan Jouroukhin [a], Mikhail Pletnikov [a,b,c,d,*]

[a] Department of Psychiatry and Behavioral Sciences, Johns Hopkins University School of Medicine, United States
[b] Department of Molecular and Comparative Pathobiology, Johns Hopkins University School of Medicine, United States
[c] Solomon H. Snyder Department of Neuroscience, Johns Hopkins University School of Medicine, United States
[d] Department of Molecular Microbiology and Immunology, Johns Hopkins Bloomberg School of Public Health, United States
[e] Preclinical College, Guangxi University of Chinese Medicine, Nanning, 530001 Guangxi Province, China
[f] Chinese Medicine College, Hubei University for Nationalities, ENSHI, 445000 Hubei Province, China

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ABSTRACT

Astrocytes regulate multiple processes in the brain ranging from trophic support of developing neurons to modulation of synaptic neurotransmission and neuroinflammation in adulthood. It is, therefore, understandable that pathogenesis and pathophysiology of major psychiatric disorders involve astrocyte dysfunctions. Until recently, there has been the paucity of experimental approaches to studying the roles of astrocytes in behavioral disease. A new generation of in vivo models allows us to advance our understanding of the roles of astrocytes in psychiatric disorders. This review will evaluate the recent studies that focus on the contribution of astrocyte dysfunction to behavioral alterations pertinent to schizophrenia and will propose the possible solutions of the limitations of the existing approaches.

1. Introduction

Astrocytes are in the center of integration of homeostatic information to maintain neuronal functions, to coordinate immune responses, and to modulate metabolic exchange through the blood–brain barrier (Clarke and Barres, 2013; Hamilton and Attwell, 2010; Parpura et al., 2012; Araque et al., 2014). It is therefore not surprising that alterations in astrocytic functions produce behavioral abnormalities resembling aspects of schizophrenia and other major psychiatric disorders

Although the field of behavioral effects of astrocyte pathology is still growing, new reports are being regularly published (Pannasch et al., 2014). Thus, we sought to overview the recent studies that deal with behavioral abnormalities due to selective manipulations of astrocytes relevant to schizophrenia. Another goal of this review is to analyze the field from a perspective of animal models for psychiatric disease, which has been mainly advanced for neuronal animal preparations (Kannan et al., 2013).

2. Astrocyte pathology in schizophrenia

There is considerable evidence that pathological changes in astrocytes could contribute to the pathophysiological mechanisms of schizophrenia and related conditions. Furthermore, recent genome-wide association studies (GWAS) have directly implicated the astrocytic genes and/or gene sets in the etiology of schizophrenia (Goudriaan et al., 2014). We will briefly overview what is known about the pathology of astrocytes in schizophrenia to set a stage for our analysis of relevant animal models. For more comprehensive reviews of human data, we refer the readers to the recent publications on this topic (Cotter et al., 2001; Bernstein et al., 2009, 2014; Takahashi and Sakurai, 2013).

2.1. Postmortem histological studies

The main goal of postmortem histological studies has been to determine whether the number of astrocytes is altered in the brain of patients with schizophrenia. While some authors reported no changes (Casanova et al., 1990; Arnold et al., 1996; Falkai et al., 1999; Damadzic et al., 2001), others found both increased (Schnieder and Dwork, 2011) and reduced numbers of astrocytes (Rajkowska et al., 2002; Webster et al., 2001). Cotter and colleagues suggest that inconsistent findings could be explained, at least in part, by regional alterations and/or heterogeneity of schizophrenia symptoms. For

* Corresponding author at: Johns Hopkins University School of Medicine, 600 North Wolfe Street; CMSC 8-121, Baltimore, MD 21287, United States. Tel.: +1 410 502 3760.
E-mail address: mpletnik@jhmi.edu (M. Pletnikov).

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example, schizophrenia patients with affective symptoms seem to exhibit more profound abnormalities (Cotter et al., 2001). Similarly, the increased density of S100β+ astrocytes was found in patients with paranoid but not residual schizophrenia (Steiner et al., 2008). In their review, Schnieder and Dwork also point to the limitations related to small samples, erroneous designs, and methodological biases (Schnieder and Dwork, 2011). Given considerable diversity of brain astrocytes (Clarke and Barres, 2013), a use of multiple markers for assessing the number of astrocytes could provide new and sometimes unexpected results. Notably, one study reports the altered number of chondroitin sulfate proteoglycan (CSPG) positive glial cells in the amygdala and entorhinal cortex without significant changes in the number of GFAP+ astrocytes (Pantazopoulos et al., 2010). Another approach includes an analysis of morphologically different astrocytes, e.g., fibrillary vs. gemistocytic (Williams et al., 2014) or an assessment of intracellular organelles, e.g., mitochondria (Uranova et al., 1996). With the advance of molecular tools, examination of subtle changes has become increasingly popular and may point to a more promising direction that would be consistent with mild pathology of astrocytes hardly detectable by histological methods.

2.2. Genes and proteins expression studies

There are several reports about altered expression of astrocytic genes in schizophrenia (Bernstein et al., 2014). Similar to postmortem studies, expression of glial fibrillary acidic protein (GFAP) at both mRNA or protein level has been extensively evaluated and the findings are also controversial. In addition to the absence of changes (Karson et al., 1993), both up-regulation (Webster et al., 2005; Bruneau et al., 2005; Fatemi et al., 2004) and down-regulation (Barley et al., 2009; Feresten et al., 2013; Catts et al., 2014) of GFAP levels have been observed.

Besides GFAP, altered expression of the factors involved in glutamate (GLU) metabolism (e.g., glial glutamate transporter (GLT-1), glutamine synthetase, glutaminase and serine racemase) was found (Matute et al., 2005; Burbaeva et al., 2003, 2007; Bruneau et al., 2005; Toro et al., 2006; Steffek et al., 2006, 2008). In addition, up-regulation of an inducible isoform of heme oxygenase (HMOX1), that is restricted to glial cells and oxidizes cellular heme to biliverdin, carbon monoxide (CO), and free ferrous iron (Schipper, 2004), was found in the prefrontal cortex (PFC) of patients with schizophrenia (Prabakaran et al., 2004).

In order to examine regional expression of the astrocytic markers, Katsel and associates (Katsel et al., 2011) used laser capture microdissection to study three distinct partitions of the anterior cingulate gyrus (layers I–III, IV–VI, and the underlying white matter) in the brains of 18 well-characterized persons with schizophrenia and 21 unaffected controls. While the expression of the astrocyte markers selected was not altered in the superficial layers or the underlying white matter of the cingulate cortex of subjects with schizophrenia, the expression of diodinase type II, aquaporin-4, S100β, glutaminase, excitatory amino-acid transporter 2 (EAAT2), and thrombospondin was significantly reduced in the deep layers of the anterior cingulate gyrus. These results suggest that a subset of astrocytes localized to specific cortical layers can be affected in schizophrenia. In addition to sub-regional differences, the inconsistent results may be due to variable aetiopathology, illness stage, or history of treatment (Catts et al., 2014).

2.3. Peripheral biomarkers

Astrocytes secrete soluble factors some of which have been evaluated as possible diagnostic and prognostic biomarkers for schizophrenia (Bernstein et al., 2009, 2014). A number of studies have reported increased serum and cerebrospinal fluid (CSF) levels of S100β in patients compared to control subjects (Pedersen et al., 2008; O'Connell et al., 2013; Qi et al., 2009). The association with schizophrenia has been found to be particularly strong in patients with negative symptoms (Rothermundt et al., 2004a, 2004b). When two markers of astroglial activation (myo-inositol and S100β) were assessed by ^{1}H-MRS or quantitative immunoassay, respectively, patients with increased S100β levels also had elevated concentrations of myo-inositol, suggesting a general dysfunction of glial cells not restricted to the specific astrocytic protein (i.e., S100β) (Rothermundt et al., 2007). A recent meta-analysis has revealed elevated serum S100β in schizophrenia without any effects of antipsychotics and has proposed that this increase is related to active secretion of the protein by astrocytes in combination with blood–brain barrier dysfunction in schizophrenia (Schroeter et al., 2009). However, there have been negative studies as well (Uzbay et al, 2013; van der Leeuw et al., 2013). Steiner and colleagues have proposed that up-regulation of S100β in schizophrenia may be a result of alterations in glucose metabolism (Steiner et al., 2010). Besides astrocytes, adipocytes may contribute to serum levels of S100β, supporting the hypothesis that lifestyle choices and the illness itself may also be responsible for changing S100β levels (O'Connell et al, 2013). In this context, S100β should be considered as a "CRP-like" marker of general pathological changes (Sen and Belli, 2007). Similar to S100β, elevated CSF levels of neopterin thought to be secreted by astrocytes were found in patients with schizophrenia (Bechter et al., 2010).

Several studies have reported increased levels of kynurenic acid (KYNA) in CSF of schizophrenia patients (Schwarcz et al., 2001; Wonodi and Schwarcz, 2010; Linderholm et al., 2012; Steiner et al., 2012). In the brain, KYNA is produced by astrocytes and acts as an antagonist at N-Methyl-D-aspartate (NMDA) and α7 nicotinic acetylcholine receptors, providing the biological rationale for using this biomarker for diagnostic purposes and as a target of potential intervention (Bernstein et al., 2009; Schwarcz et al., 2012). Although the exact mechanisms of elevated KYNA levels in schizophrenia remain to be elucidated, both inflammation and genetic variants in the enzymes of the kynurenine pathway (e.g., kynurenine 3-monooxygenase) could be responsible for elevated levels of KYNA (Aoyama et al., 2006; Kapoor et al., 2006; Wonodi et al., 2011; Holtze et al., 2012). Decreased concentrations of a co-agonist of NMDA receptors, D-serine, were detected in the plasma and CSF of patients with schizophrenia. It has been proposed that lower levels of D-serine may be related to its decreased synthesis or enhanced degradation due to genetic variants of serine racemase (SRR) and/or D-amino acid oxidase, respectively (Morita et al., 2007; Caldinelli et al., 2013). Overall, it appears that there are several promising peripheral biomarkers that could be useful in the research and clinical settings but their specificity and reliability still need to be clearly demonstrated.

2.4. Astrocytic genes and schizophrenia

It remains unclear whether astrocyte pathology results from primary genetic mutations in astrocytes or neuronal injury triggers activation of astrocytes and their dysfunctions observed in patients. Genetic association studies based on single nucleotide polymorphisms (SNPs) have been instrumental in identifying potential causative genetic variants (Goudriaan et al., 2014). Most recent publications focus on genes predominantly expressed in neurons. Few papers have reported association of astrocytic genes with schizophrenia. Schizophrenia-associated SNPs have been studied for the *S100β* gene (Bernstein et al., 2009, 2014; Liu et al., 2005; Hohoff et al., 2010; Zhai et al., 2011); thrombospondin 1 (*THBS1*), an astrocyte secreted glycoprotein that promotes synaptogenesis (Park et al., 2012); *EAAT2*, expression of which is decreased in the parahippocampal region and the dorsolateral prefrontal cortex (PFC) in schizophrenia (Shan et al., 2013; Spangaro et al., 2012); *SRR* (Morita et al., 2007); and the gene for the astrocytic enzyme that is involved in synthesis of glutathione, a key factor to guard the brain against oxidative stress (Tosic et al., 2006). However, single SNP associations provide limited insights in underlying molecular or