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

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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.

Keywords

neuron-astrocyte interaction; glutamate; tripartite synapse; neuroinflammation; psychiatric disorders

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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, 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 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; Seffek 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; b). 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 myoinositol, 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, 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 cellular mechanisms. Pathway or functional gene sets analyses of the combined effect of multiple SNPs appear a more promising direction (Ramanan et al, 2012; Goudriaan et al, 2014; Duncan et al, 2014).

In summary, postmortem, genetic and biomarkers studies have implicated astrocytes in the etiology and pathophysiology of schizophrenia. These studies have guided the development of animal models to gain a deeper understanding of the mechanisms whereby genetic mutations and/or pathology of astrocytes result in behavioral disorders consistent with schizophrenia.

3. Animal models of astrocyte dysfunction

The field of animal models of astrocyte dysfunction in schizophrenia is rapidly expanding. We will review the existing animal models by grouping them in the categories related to the major functions of astrocytes found to be abnormal in schizophrenia. We will focus on genetic models but non-genetic preparations will be reviewed as well if they employ selective manipulations of astrocytes to induce schizophrenia-like behavioral phenotypes.

3.1 Models related to structural changes

In order to model decreased density of glia in cortical regions, an astrocyte specific toxin, L-alpha-aminoadipic acid (L-AAA), was injected in the PFC of adult rats. L-AAA induced anhedonia in sucrose preference test, anxiety, and helplessness in forced swim test (FST). Importantly, these effects were not seen after ibotenate-induced neurotoxic lesion of the PFC, suggesting specificity of the affective behaviors of astrocyte ablation (Banasr et al, 2008). This toxin was also found to affect attentional set-shifting, working memory and reversal learning (Lima et al., 2014). The effects of L-AAA appear to support the role of astrocytes in behavioral disorders due to dysfunction of the medial PFC. The limitation of using this toxin for neurobehavioral analysis is a progressive neuronal loss and dendritic atrophy in the surviving neurons in L-AAA-treated animals.

A recent paper describes a new transgenic mouse model with inducible expression of tetanus neurotoxin (TeNT) in astrocytes without globally affecting neuronal functions. TeTX expression led to a robust decrease in electroencephalographic (EEG) power in the gamma frequency range without affecting neuronal synaptic activity. This reduction in cortical gamma oscillations was accompanied by a selective deficit in novel object recognition, whereas working memory and fear conditioning were unaltered. Both EEG and behavioral phenotypes appeared to be transient as they were reversed by suppression of TeNT expression with doxycycline treatment. The results provide a further support for astrocytes as essential players in the mechanisms of information processing (Lee et al, 2014).

There have been several attempts to assess behavioral effects of genetic manipulation of the major astrocytic proteins (e.g., Shibuki et al., 1996). The effects of over-expression of *S100β* on exploratory behaviors were studied in transgenic mice. A significant difference in the spatial and temporal exploratory pattern was observed between control and *S100β* mutants (Roder et al., 1996). Mutant mice with deletion of *S100β* developed normally with the

preserved cytoarchitecture of the brain but exhibited enhanced long-term potentiation (LTP) in the hippocampal CA1 region and a better performance in Morris water maze and contextual fear conditioning (Nishiyama et al., 2002). Both transgenic and knockout models have provided the initial characterization of behavioral outcomes of manipulations of the gene. However, these preparations do not mimic human SNPs and their relevance remains limited. New technologies (e.g, the CRISPR/Cas or TALERN systems) should facilitate the development of SNP-based animal models (Boch and Jens, 2011; Mali et al, 2013).

3. 2 Models related to glycogen metabolism

There is evidence of dysregulation of glucose metabolism and glycogen utilization in schizophrenia (Amar et al., 2011). Recent studies have shown that brain glycogen is contained in astrocytes that deliver energy substrates, e.g., lactate, to neurons (Gold et al., 2013). A study reports that training significantly increases levels of hippocampal astrocyte-derived extracellular lactate. Disruption of the astrocytic lactate transporters monocarboxylate transporter 4 (MCT4) or MCT1 produced amnesia and LTP impairment, which can be rescued by L-lactate but not equicaloric glucose. These data suggest that astrocyte-neuron lactate transport is critical for long-term memory (Suzuki et al., 2011). Consistently, another pharmacological study found that inhibition of astrocytic glycogenosis impaired memory and this impairment was rescued by lactate (Newman et al., 2011). Given that abnormal neuroplasticity and impaired cognitive functioning represent a major deficit of schizophrenia, new models targeting glycogen metabolism in astrocytes may help uncover new targets for therapeutic interventions to treat cognitive impairment in patients.

3.3 Models related to glutamate signaling

3.3.1 Glutamate uptake—GLU uptake is one of the major functions of astrocytes and is indispensable to influence GLU synaptic transmission (Danbolt, 2001). It has been suggested that GLT-1 function could be elevated in the PFC of patients with schizophrenia (Matute et al, 2005). In order to test this hypothesis in an animal model, pre-pulse inhibition (PPI) of the acoustic startle was evaluated in rats treated with ceftriaxone, an antibiotic that selectively enhances GLT-1 expression and activity. Ceftriaxone-induced GLT-1 up-regulation was associated with reduced PPI that was reversed by dihydrokainate (DHK), a GLT-1 antagonist (Bellesi et al, 2009). Curiously, the PPI inhibitory effects of ceftriaxone were additively enhanced by a single injection of phencyclidine (PCP) (Melone et al, 2009).

3.3.2 D-serine—D-serine is a gliotransmitter that acts as a co-agonist of the NMDAR glycine site. D-serine produced by SRR that converts L-serine in D-serine (Hashimoto and Oka, 1997; Kantrowitz and Javitt, 2010; Oliet and Mothet, 2009; Snyder and Kim, 2000). Although SRR appears to be predominantly expressed by neurons (at least in the normal conditions) (Balu et al., 2013), astrocytes can also express this enzyme and play a considerable role in secretion of D-serine. ASC-1 system is proposed to shuttle D-serine from neurons to astrocytes for subsequent secretion (Wolosker, 2011). A couple of studies have manipulated activity of SRR selectively in astrocytes and evaluated the behavioral consequences. Ma and colleagues have demonstrated that SRR binds to and is stabilized by Disrupted-In-Schizophrenia-1 (DISC1), a genetic risk factor (Kamiya et al, 2012). Mutant DISC1 selectively expressed in astrocytes fails to bind to SRR, facilitating ubiquitination

and degradation of SRR and a decrease in D-serine production. Decreased production of D-serine was associated with greater responses to an NMDA antagonist, MK-801, in open field and PPI tests. The observed behavioral changes were rescued with D-serine treatment (Ma et al., 2013). Otte and associates have generated transgenic mice (SrrTg) to selectively over-express mouse SRR in astrocytes using the human GFAP promoter. As a result, these mutant mice have elevated brain levels of D-serine. Transgenic mice demonstrated decreased immobility in FST, shorter latency in novelty-suppression feeding test and blunted locomotor response to bulbectomy, suggesting diminished affective behaviors. The similar set of behavioral alterations was observed when control mice were given chronic D-serine supplementation (Otte et al., 2013). Although these studies confirmed the role of astrocytes in D-serine metabolism, given that SRR is a predominantly neuronal enzyme future models should try to alter D-serine metabolism in cell- and time-dependent manner in order to better appreciate the relative roles of astrocytes and neurons in D-serine metabolism.

3.3.3 Purines—Purines can be derived from many sources in the nervous system (Blutstein and Haydon, 2013). Adenosine triphosphate (ATP) is released in the extracellular space and metabolized to adenosine diphosphate (ADP), adenosine monophosphate (AMP) and ultimately to adenosine. Both neurons and astrocytes can release purines (Lopes et al, 2011). Adenosine is proposed to play a role of a homeostatic modulator of neural networks at different levels (receptors, bioenergetics, and epigenetics) and may be utilized to reverse the imbalance in glutamate and/or dopamine in schizophrenia (Boison et al, 2012; Hirota and Kishi, 2013).

Several publications report the behavioral effects of manipulation of adenosine signaling (Shen et al., 2012; Singer et al., 2013a; Singer et al., 2013b; Yee et al., 2007). The majority of those studies did not selectively modulate astrocytic sources of purines, making it difficult to infer cell-specific contributions to behavioral abnormalities. Recently, the behavioral effects of astrocyte-selective perturbation of adenosine's release have been published. In order to test the hypothesis that adenosine is released through soluble N-ethylmaleimide–sensitive factor attachment protein receptor (SNARE) protein-dependent mechanisms, Haydon's lab has generated a mouse model of inducible and astrocyte-selective expression of dominant-negative form of the cytosolic portion of the SNARE domain of synaptobrevin 2 (Pascual et al, 2005). Mutant mice exhibit decreased release of adenosine, leading to “attenuated the accumulation of sleep pressure” that prevents cognitive deficits associated with sleep loss. It was suggested that astrocytes modulate sleep and its cognitive consequences through A1 receptors. (Halassa et al., 2009), providing a novel pathway for treatment of affective symptoms in schizophrenia and other major psychiatric disorders (Hines et al., 2013).

3.3.4 Models related to trophic factors and extracellular matrix proteins—Astrocytes secrete trophic factors and extracellular matrix (ECM) proteins (e.g., proteoglycans) to support neuronal growth and synaptic activity (Cohen-Cory et al., 2010; Faissner et al., 2010). Alterations in production of these factors could impact neurodevelopment and adult neuronal plasticity and have been implicated in schizophrenia (Autry and Monteggia, 2012; Martinotti et al., 2012; Pandya et al., 2013). Even if relevant

variants of the genes for neurotrophic factors or ECM proteins remain scarce, animal models that selectively perturb the functioning of these genes in astrocytes can still help advance our understanding of the role of these systems to schizophrenia.

Brain-derived neurotrophic factor (BDNF) is a secreted protein that, in humans, is encoded by the *BDNF* gene (Barbacid, 1995). BDNF acts on neurons, supporting their survival, proliferation and differentiation. The recent findings have suggested that astrocytes produce BDNF (Girardet et al., 2013; Sun et al., 2014). Overexpressing BDNF in astrocytes, Quesseveur and colleagues examined behavioral outcomes of the altered neurons-to-astrocytes BDNF ratio. BDNF overexpression in hippocampal astrocytes was found to produce anxiolytic and antidepressant-like activity in the novelty suppressed feeding and to increase hippocampal neurogenesis. These observations implicate hippocampal astrocytes in the synthesis of BDNF, which can act through neurogenesis-dependent and independent mechanisms to regulate different facets of anxiolytic-like responses (Quesseveur et al., 2013). Unfortunately, behavioral changes related to schizophrenia-like phenotypes have not been evaluated in this animal model. Nevertheless, the data seem to be interesting in light of affective disorders associated with schizophrenia (Yasamy et al, 1987; Bartels et al, 1988; Tandon et al, 2013).

Astrocytes express aquaporin 4, (AQP4), a water channel protein, involved in water homeostasis, edema formation and neuroinflammation that is frequently associated with blood brain barrier (BBB) dysfunction (Badaut et al., 2002; Badaut et al., 2014). AQP4 is the primary AQP in the CNS, and is primarily expressed in astrocytic endfeet at the BBB (Nagelhus and Ottersen, 2013; Scharfman and Binder, 2013). A dysfunction of AQP4 could induce pathological conditions in neuronal activity. Several genome scan studies found a suggestive linkage on 18q, where human AQP4 (18q11.2-12.1) is located nearby, although negative findings were also reported (Muratake et al, 2005; Chung and Lung, 2012; Katsel et al, 2011). Skucas et al evaluated LTP and long-term depression (LTD) in AQP4 knock-out (KO) and wild-type mice. KO mice had deficient LTP and LTD and unaffected basal transmission or short-term plasticity. Notably, it was BDNF-dependent not BDNF-independent LTP that was impaired in KO mice. LTD was also impaired in KO mice, which was rescued by a scavenger of BDNF or blockade of tropomyosin-receptor-kinase (Trk) receptors. The KO mice also had cognitive impairment as was observed in location-specific object memory test but not MWM or contextual fear conditioning. The results suggest that AQP4 channels in astrocytes may be involved in neurotrophin-dependent plasticity and some forms of learning and memory (Skucas et al., 2011).

Among astrocytes-produced factors, ephrin-A3 is the major ligand for EphA, which is a member of the Eph family of receptor tyrosine kinases that express in forebrain neurons to regulate synaptic function and plasticity (Klein, 2009; Pasquale, 2008). Notably, significant association between SNP rs9520087 of the ephrin-B2 (*EFNB2*) gene and schizophrenia was reported (Zhang et al, 2010). Further, ephrin signaling is an essential component of the Reelin pathway (Sentürk et al, 2011), and reelin signaling is involved in neuronal migration and is found to be abnormal in schizophrenia (Folsom and Fatemi, 2013). Carmona and associates report that the ephrin-A3 ligand, which is located in the perisynaptic processes of astrocytes, is essential for maintaining EphA4 activation and normal spine morphology.

Ephrin-A3-KO mice have dendritic spine irregularities similar to those observed in EphA4-KO mice. There were found no alterations in locomotor activity, sensorimotor responses, motor coordination, anxiety, or depression-related behaviors in ephrin-A3-KO mice. In order to assess hippocampus-dependent learning, cue- and context-dependent fear conditioning was used. While cue-dependent amygdala-supported conditional fear was unaffected, the freezing responses to the contextual cues were significantly reduced in KO mice, indicating impaired hippocampus-dependent contextual memory. In the object placement test, compared to WT mice, the ephrin-A3-KO mice spent more time exploring the object during the training phase but less preference for a new location of the same object during the test phase, suggesting poorer recognition of a new place. Notably, this deficit was no longer observed if the training phase was prolonged to 30 minutes. The performance of KO mice in the Barnes maze was unaltered. The findings suggest that interplay between neuronal EphA4 and glial ephrin-A3 regulates synapse morphology and hippocampal function (Carmona et al., 2009).

3.4 Models related to inflammatory molecules

Astrocytes coordinate immune response to invading pathogens and peripheral inflammatory factors (Ovanesov et al., 2008; Ransohoff and Brown, 2012). A growing body of evidence suggests the involvement of inflammatory processes in the pathophysiology of psychiatric disorders, and a leading role of astrocytes in mediating neuroinflammation (Meyer, 2011; Meyer et al., 2011; Muller et al., 2013; Shastri et al., 2013). Given the absence of gliosis in postmortem brain samples, it is subtle activation of astrocytes that likely plays a role in the pathophysiology of schizophrenia (Sofroniew and Vinters, 2010; Burda and Sofroniew, 2014). A number of studies have convincingly demonstrated that neuroinflammation is associated with activation of the enzyme, indoleamine 2,3-dioxygenase (IDO), resulting in increased production of KYNA (Muller et al, 2011; Schwarcz et al., 2012). KYNA is a tryptophan metabolite that is synthesized and released by astrocytes and acts as a competitive antagonist of the glycine site of NMDAR and as a noncompetitive antagonist of the α7-nicotinic acetylcholine receptor. The discovery of increased cortical KYNA levels in schizophrenia prompted the hypothesis that elevated KYNA concentration may underlie working memory impairment observed in patients (Schwarcz et al., 2001). In order to experimentally test this hypothesis, Chess et al treated rats with ip administration of kynurenine (100 mg/kg) that led to its 37-fold increase in the brain. They found that treated animals demonstrated increased errors in the radial arm maze without changes in locomotor activity or the latency to retrieve food reward (Chess et al., 2007). In a follow-up study, rats were given kynurenine on postnatal days 7-10 and were tested as adults. Kynurenine-treated animals exhibited decreased social behavior and locomotor activity; however no effects on attentional function and fear conditioning were observed (Iaccarino et al., 2013). Although the doses of kynurenine used in these studies appear very high, the results suggest a possible mechanism whereby neuroinflammation can influence cognitive function via glia-secreted molecular factors in a time-dependent manner.

Toxoplasma gondii (*T. gondii*) infection is a risk factor for schizophrenia (Yolken et al., 2009; Yolken and Torrey, 2008). *T. gondii* infection has been shown to stimulate the synthesis of KYNA, presumably in astrocytes (Schwarcz and Hunter, 2007; Notarangelo et

al, 2014). It is plausible that *T. gondii* infection could contribute to the disorder by increasing KYNA production by astrocytes. Although there have been several reports on schizophrenia-like behaviors in chronically *T. gondii*-infected rodents, the contribution of KYNA or other astrocyte-produced factors has to be yet determined given a considerable range of direct and indirect effects of the parasite on the brain (Kannan and Pletnikov. 2012).

Using an immune dysfunction model of schizophrenia, it has been found that a short-term one-week cuprizone exposure produces increased responses to methamphetamine and phencyclidine, as well as impaired working memory. The study reports that in contrast to long-term cuprizone exposures, this short-term treatment led to perturbation of astrocytes and microglia and significant up-regulation of interleukin-6 (IL-6) in GFAP+ cells consistent with some inflammatory markers observed in schizophrenia (Tezuka et al., 2013).

Expression of many pro-inflammatory factors is regulated by the transcription nuclear factor-kappa B (NF-κB) (Bales et al., 2000; Petegnief et al., 2001). There are several genetic (Liou et al, 2012; Chen at al, 2014), biomarker (Song et al, 2009) and postmortem studies (Sun et al, 2001; Roussos et al, 2013) that implicate NF-κB in schizophrenia. Brambilla and colleagues generated transgenic mice where NF-κB function was selectively suppressed in astrocytes by over-expressing a dominant-negative N-terminal truncated form of the inhibitor of nuclear factor kappa B α NF-κB (IκBα), under the control of the GFAP promoter (Brambilla et al., 2005). No differences between control and mutant mice were observed in general health measures, locomotor activity, sensorimotor function or anxiety. Female GFAP-IκBα-dn mice exhibited mild deficiency in the last stage of the non-cued version of the Barnes maze as evidenced by the greater latency to the first correct nose poke and less time spent in the quadrant of the maze previously containing the goal box. These data point to a hippocampal deficit in learning and memory in female mice. Curiously, GFAP-IκBα-dn female mice were even more impaired in the cued version of the Barnes maze, consistent with a deficit in extra-hippocampal components of learning and memory; however, one cannot completely rule out an abnormality in vision. Sex-related alterations were also observed in fear conditioning, highlighting importance of evaluating consequences of genetic manipulations in males and females. The cognitive deficits were associated with reduced LTP and lower expression of metabotropic glutamate receptor 5 and post-synaptic density protein 95 (PSD95) in female transgenic mice. Taken together, these findings indicate that astroglial NF-κB is involved in synaptic plasticity underlying learning and memory (Bracchi-Ricard et al., 2008).

Cytokines are polypeptides that mediate the communication between cells during inflammation (Heinrich et al., 2003). Interleukin-6 (IL-6), identified as B-cell differentiation factor (Hirano et al., 1985), is a major cytokine involved in interplay between the immune system and brain (Deverman and Patterson, 2009). IL-6 has been implicated in stress response, synaptic plasticity, learning, sleep and neurodevelopment (Bauer et al., 2007; Deverman and Patterson, 2009). Altered levels of IL-6 have been found in patients with schizophrenia (Smith et al., 2007).

Several studies assessed the behavioral changes in conventional *il-6 KO* mice and reported inconsistent results (Quintana et al., 2013). To overcome the limitations of that KO model,

floxed mouse lines were generated to study the role of IL-6 in a cell-specific manner. Floxed mice either for IL-6 or its receptor were crossed with GFAP-Cre mice to delete either gene in astrocytes. The data indicate the astrocyte IL-6 system mediates locomotor activity, anxiety and exploratory behaviors. The authors conclude that both similar and distinct phenotypes were observed in *il-6* vs. *il6r* conditional KO models. Notably, some alterations in conditional KO models were totally unexpected from previous results with conventional *il-6* KO model (Quintana et al., 2013). These findings implicate astrocytic IL-6 in normal brain physiology and behavior.

Heme oxygenases 1(HO-1) expression found to be elevated in schizophrenia can be induced by oxidative and inflammatory stimuli (Prabakaran et al., 2004). Selective overexpression of HO-1 in astrocytes in transgenic mice results in oxidative stress, lower neuronal reelin content, elevated dopamine and serotonin concentrations in the basal ganglia; reduced D1 receptor binding in the nucleus accumbens and altered hippocampal cytoarchitectonics. These pathological signs were associated with increased locomotor activity and decreased PPI, without affecting anxiety or motor balance in transgenic mice. The data shed light on the possible role of glial HO-1 in the development of monoaminergic circuitry and suggest that abnormal expression of HO-1 in astrocytes can be responsible for schizophrenia-like phenotypes in transgenic mice (Song et al., 2012).

3. 5 Models for emerging astrocytic targets

Cannabinoid receptors (i.e., CB1) are expressed on glia cells and regulate both development and adult functions of glia cells (Navarrete and Araque, 2008; Stella, 2010). Importantly, CB1 receptors are the targets of marihuana, abuse of which during adolescence has been linked to the increased risk for schizophrenia and/or cognitive impairment (Arseneault et al., 2004; Burns, 2013; Stone, 1973; van Os and Murray, 2008). That's why recent studies of the role of CB1 receptors on astrocytes in adverse effects of marihuana on learning and memory have drawn much attention.

Acute exposure to Δ(9)-tetrahydrocannabinol (Δ(9)THC) was reported to affect spatial working memory and LTD at hippocampal CA3-CA1 synapses, and these effects were completely blocked in mice lacking CB1 receptors in astroglial but not in glutamatergic or GABAergic neurons (Han et al., 2012). A different group extended this finding by demonstrating that that synaptic and cognitive impairments produced by repeated THC injections were dependent on the activation of cyclooxygenase-2 (COX-2), an inducible enzyme that converts arachidonic acid to prostanoids in the brain. Importantly, the study presents the pharmacological and genetic findings that COX-2 induction is also mediated via CB1 receptor-coupled G protein βγ subunits. These studies have directly implicated astrocytic CB1 receptors in cognitive functions in the brain (Chen et al., 2013). Future research should address time-dependent aspects of CB1 involvement in neuron-astrocyte interplay in cognition and evaluate if genetic risk factors expressed by astrocytes could potentiate adverse effects of adolescent exposure to marihuana. In addition, since marihuana exposure has been associated with neuroinflammation and ensuing behavioral and cognitive deficits, this putative link needs to be explored in greater details as it could offer a new

avenue for treating marihuana abuse-related cognitive impairments (James et al, 2013; Burns, 2013).

The animal models reviewed here have provided important insights in how astrocyte dysfunction could contribute to behavioral responses relevant to schizophrenia. Table 1 summarizes the strengths and weaknesses of each animal model reviewed. Figure 1 depicts the astrocytic functions found to be abnormal in schizophrenia and animal models that recapitulate aspects of pathological changes in patients.

4. Future directions

The field of behavioral models of astrocytes dysfunction is constantly expanding. As it continues to make inroads, it needs to be cognizant of the pitfalls that other behavioral models have been plagued with. Refining methodological designs and implementing new technological tools will be important to overcome the limitations of the existing preparations.

4.1. Design issues

One obvious but often-neglected way of addressing variability among different studies is to utilize standard measures and approaches of behavioral neuroscience, including the same protocols for the same behavioral tests, strains of mice, and even the equipment whenever possible. Another issue is lack of systematic analyses of sex-dependent effects. Future research in behavioral models of astrocyte dysfunction should attempt to better characterize sex-specific abnormalities resulting from the astrocytic effects on the gonads or from modulatory actions of sex hormones on astrocytes themselves. This line of research may help uncover the mechanisms of gender differences in psychiatric disorders and could help identify risk/protective factors.

As with any behavioral studies, an ever-present issue is underpowered statistical analyses. Reporting “mild but significant alterations” may be misleading if the effect size is not presented. As numbers of animals is limited by cost-prohibitive housing, it is still important effect sizes and confidence intervals be reported together with significance.

Major mental disorders are disorders of brain development (Insel, 2011; Jaaro-Peled et al., 2009). Astrocyte models with manipulation in astrocytic genes at different stages of neurodevelopment (including postnatal period) are likely to be most relevant to psychiatric disorders. Thus, developmental aspects should become a focus of the future studies, including models allowing for studying time-dependent effects (Pletnikov, 2009).

4.2. Technological advances

Simple knockout and transgenic models are artificial systems inconsistent with the molecular pathology of schizophrenia or related diseases. New models with mutations in regulatory elements of risk genes with subtle and time-dependent expression or “humanized” models would seem to better approximate the genetic complexity of mental illnesses (Papaleo et al., 2012). Additionally, given heterogeneity of astrocytes in the brain, circuitry-specific and astrocyte type-specific manipulations will be needed. This approach

may prove to be particularly important for a better understanding of circuitry-specific pathology observed in schizophrenia (Arnsten 2011; Lewis, 2012). For example, increases in Ca^{2+} are induced in cortical astrocytes by GLU and norepinephrine, while hippocampal astrocytes show calcium responses to ATP, GABA, acetylcholine, and endocannabinoids (Oberheim et al, 2012), suggesting that various neurotransmitter systems will be differentially affected be the same pathology of astrocytes in the cortex vs. hippocampus. In addition, different developmental and regional profiles of expression of GLAST and GLT-1 in the brain (cortex vs. cerebellum) might contribute to differential vulnerability to environmental stressors implicated in schizophrenia.

A recent analysis of genome-wide association studies (GWAS) database of glial gene sets has provided a list of promising astrocytic candidates for the future studies (Goudriaan et al., 2013). In this context, it would be also helpful to expand the use of non-rodent genetic models to identify the common molecular processes of neuron-glia interaction across species (e.g., worms, fruit flies, zebrafish) (Freeman and Rowitch, 2013; Han et al., 2013).

Our understanding of neuron-astrocyte interaction in health and disease is unlikely to be facilitated without tools that allow us to monitor and manipulate astrocytes in behaving animals. Recent studies utilizing optogenetics and two-photon microscopy in combination with behavioral tests have demonstrated the possibility of developing and characterizing such models (Sasaki et al., 2012; Paukert et al, 2014).

There is a growing acceptance of significance of gene-environment models for schizophrenia (Kannan et al., 2013). Until recently, most gene-environment studies have focused on neuronal functions of genetic risk factors. Given the leading role of astrocytes in mediating adverse effects of environmental stressors, it is tempting to predict that future models will include glial cell-specific genes to help sort out their contribution to abnormal brain and behavior development.

Although studying complex neuron-glia communication *in vitro* will always be limited, cell models offer an excellent tool for identifying the disease-related molecular pathways in a cell-specific manner (Jiang et al, 2010; Lavoie et al., 2011). Future studies are anticipated to utilize astrocytes differentiated from induced pluripotent stem cells derived from patients. This line of investigation will likely inform our knowledge of disease-specific abnormalities in gene expression, molecular signatures and, hopefully, novel treatments (McCarroll and Hyman, 2013).

In conclusion, animal models of astrocyte dysfunction in schizophrenia have already improved our understanding of how astrocytes regulate brain circuitries to influence behavior and will continue to provide new insights into the etiological complexity and heterogeneity of schizophrenia.

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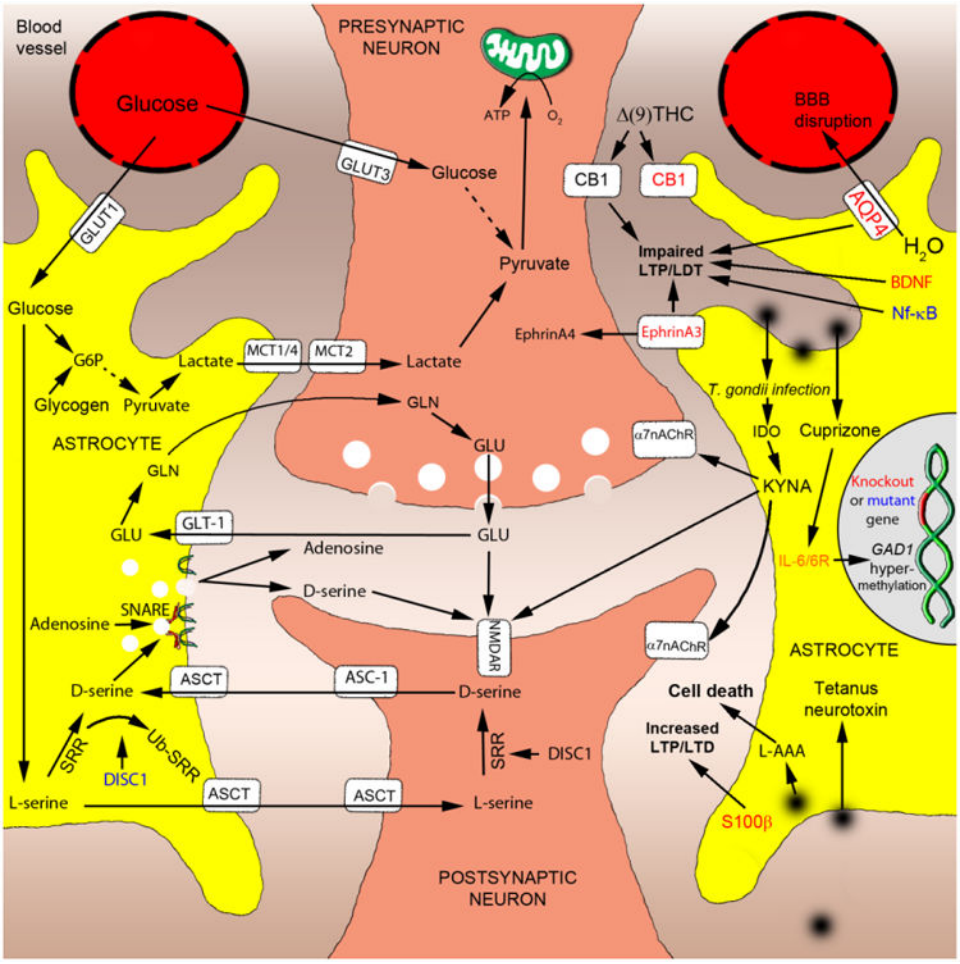

Figure 1. Functions found abnormal in schizophrenia and recapitulated in animal models

Pathways related to **glutamate signaling and glucose metabolism (**the left-hand side; top-down):

- Conditional knockout of monocarboxylate transporter 1 or 4 (MCT1/4) alters a release of lactate from astrocytes and impairs long-term potentiation (LTP);
- Over-expression of glial glutamate transporter 1 (GLT-1) or serine racemase (SRR) increases glutamate uptake or levels of D-serine, respectively;
- Over-expression of dominant-negative soluble N-ethylmaleimide-sensitive factor attachment protein receptor (SNARE) domain selectively blocks a release of adenosine, leading to suppression of synaptic transmission;
- Over-expression of mutant Disrupted-In-Schizophrenia-1 (DISC1) facilitates ubiquitination of SRR, resulting in decreased production of D-serine and associated schizophrenia-like behaviors.

Pathways related to **trophic support, inflammation and emerging targets** (the upper right-hand side):

- Knockout of aquaporin 4 (AQP4), brain-derived neurotrophic factor (BDNF) or EphrinA3 impaired LTP and/or long-term depression (LDT);
- Astrocytic (cannabinoid receptor type 1) CB1 receptors are indispensable for the detrimental effects of Δ(9)-tetrahydrocannabinol (Δ(9)-THC) on learning and memory;
- *T.gondii* infection- or direct administration-produced increase in levels of kynurenic acid (KYNA) results in antagonism at NMDA and α7 nicotinic acetylcholine receptors (α7nACR) and associated cognitive impairment;
- Administration of cuprizone or conditional knockout of interleukin-6 or IL-6 receptor (IL-6/IL-6R) result in abnormal methylation of the *GAD1* gene (Kundakovic et al, 2009; Lee et al, 2011);
- Over-expression of dominant-negative nuclear factor-kappa B (NF-κB) affects LTP in transgenic mice.

Pathways related to **structural changes (**the bottom right-hand side):

- Administration of the astrocyte specific toxin, L-alpha-aminoadipic acid (L-AAA), produces a loss of astrocytes and impaired working memory;
- Inducible, transient and astrocyte-restricted expression of tetanus neurotoxin leads to altered gamma oscillations and impaired novel object recognition;
- Over-expression or knockout of S100β affects LTP and exploratory behaviors.

Abbreviations: Glucose transporter 1 (GLUT1) and 3 (GLUT3), Glycine (GLN), Glucose 6-phosphate (G6P), monocarboxylate transporter 2 (MCT2), alanine-serine-cysteine transporter (ASCT) and alanine-serine-cysteine transporter 1 (ASC-1); indoleamine 2,3-dioxygenase (IDO), blood–brain barrier (BBB)

Table 1

Summary of animal models related to astrocyte dysfunctions in schizophrenia

Gene or factor	Animal model	Phenotypes	Mechanisms	Strengths	Caveats	Citations
Models related to structural changes						
L-α-aminoadipate L-AA	Injection into mPFC in rats	Abnormal set-shifting, working memory and reversal learning; anhedonia	Loss of astrocytes and a progressive loss of neurons	Cell selectivity Clinical relevance	Limited etiological value	Banasr, 2008 Lima, 2014
TeNT model	Expression of tetanus neurotoxin	Deficit in novel object recognition test	Decreased EEG power in the gamma frequency	Cell selectivity Inducible system	Limited etiological value	Lee, 2014
S100β	Tg model	Abnormal exploration	No studied	Cell selectivity	No time or region specificity	Roder, 1996.
S100β	KO model	Better MWM and contextual conditioning	Increased LTP in the CA1 area	Cell selectivity	No time or region specificity	Nishiyama, 2002
Models related to glycogen metabolism						
MCT4	Conditional KO model	Impaired learning	L-lactate transport	Cell selectivity	No time or region specificity	Suzuki, 2011 Newman, 2011
Models related to glutamate signaling						
GLT-1 up-regulation	Injection of centriaxone	Impaired PPI Increased responses to PCP	Induced up-regulation of GLT-1 in the brain	Cell selectivity Clinical relevance	Limited etiological relevance	Bellesi, 2009 Melone, 2009
Mutant DISC1	Inducible Tg model	Increased response to amphetamine rescued by D-serine	Decreased D-serine production	Time- and cell-specific	Over-expression No regional specificity	Ma, 2013
Serine racemase, SRR	Tg model	Decreased depression and anxiety	Elevated D-serine levels	Cell selectivity	Over-expression No regional specificity	Otte, 2013
Mutant SNARE	Inducible Tg model	Abnormal sleep Cognitive deficits Anti-depressant effects	Decreased ATP/adenosinerelease	Time- and cell-specificity	Over-expression No regional specificity	Halassa, 2009 Hines, 2013
Models related to trophic support and ECM proteins						
BDNF	Viral vector expression	Anxiolytic and antidepressant-like activity	Increased hippocampal neurogenesis	Cell specific factor	Non-germline model	Quesseveur, 2013
AQP4	KO mice	Cognitive deficits	Impaired LTP and LTD	Cell specific factor	No time or region specificity	Skucas, 2004
Ephrin-A3	KO mice	Deficient memory	Spines deficit	Cell specific factor	No time or region specificity	Carmona, 2009
Models related to inflammatory molecules						

Gene or factor	Animal model	Phenotypes	Mechanisms	Strengths	Caveats	Citations
Kynurenic acids	Injection of kynurenine in rats	Poor learning Decreased social behavior	Effects on GLU and/or Ach receptors	Clinical relevance Specific targets	No regional specificity	Chess, 2007 Iaccarino, 2013
Cuprizone	1-week diet with 0.2% cuprizone	Increased responses to MA and PCP Impaired working memory	Perturbation of astrocytes and microglia	Some clinical relevance	Limited etiological value	Tezuka T, 2013
NF-κB	Tg model	Poor learning and memory in females	Deficient LTP Altered levels of mGluR5 and PSD95	Cell specific model	No time or region specificity	Brambilla, 2005 Bracchi-Ricard, 2008
IL-6 and IL-6R	Conditional KO model	Altered activity and exploration	Not studied	Cell specific deletion	No time or region specificity	Quintana, 2013
Heme Oxygenases HO-1	Tg model	Increased activity Decreased PPI	Oxidative stress	Cell specific model	No time or Region specificity	Song, 2012
Models related to emerging targets						
CB1 receptors	THC treatments	Impaired learning and memory	CB1 receptors,COX2 signaling	Cell specificity, Identified pathway	Limited relevance to human conditions	Han, 2012 Chen, 2013