From Pathophysiology to Novel Antidepressant Drugs: Glial Contributions to the Pathology and Treatment of Mood Disorders

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Several structural and cellular changes, including marked glial anomalies, have been observed in association with major depressive disorder. Here we review these cellular alterations and highlight the importance of glial cell pathology, especially astroglial dysfunction, in the pathophysiology of neuropsychiatric disorders with a particular interest in major depressive disorder. The functional role of astrocytes in glutamate uptake and glutamate/glutamine cycling is discussed, as is the deleterious effects of chronic stress on glial cell function. Lastly, we discuss the effect of antidepressants on glial cell function and the possibility of targeting glial cells in the quest to develop novel therapeutics.

Key Words: Antidepressant, astrocytes, depression, EAAT, glia, prefrontal cortex, stress

Mounting evidence now suggests that structural as well as functional changes are present in the brains of many individuals suffering with mood disorders. Numerous studies have demonstrated significant reductions in cerebral blood flow, metabolism, and volume of limbic brain structures including hippocampus, prefrontal cortex (PFC), and amygdala in major depressive disorder (MDD) patients (1). Other studies have further identified specific cytoarchitectural abnormalities, especially reductions in glial cell number and density, in individuals afflicted with mood disorders (2). Could this evidence of glial cell pathology afford us insight into some of the pathophysiological processes contributing to mood and other psychiatric disorders and ultimately suggest new targets for drug development?

Introduction to Glial Cells

Since their discovery more than 150 years ago (3), glial cells have largely been considered relatively unimportant in brain physiology, serving primarily as the "glue" of the brain. However, relatively recent discoveries elucidating the critical role of glial cells in a host of physiological processes implicate glial cell pathology as a potential contributor to many different neuropsychiatric disorders.

Historically, glial cells have been classified into three major subgroupings, astrocytes, oligodendrocytes, and microglia. Astrocyte and oligodendrocyte lineage cells are derived from neural stem cells, whereas microglia originates from the immune system. Each of these classes of glia is now known to serve a broad range of physiological roles, ranging from regulation of brain energy supplies and amino acid neurotransmitter metabolism to driving aspects of synaptic remodeling. Disrupted function of any of these cell types is likely to alter normal brain function and possibly contribute to the development of neuropsychiatric disorders (4).

Oligodendrocytes unsheathe long axons in the central nervous system (CNS) with myelin and provide trophic support, allowing for rapid impulse propagation and the maintenance of normal axon transport and long-term survival. Recent findings suggest these cells might also play critical roles in the pathogenesis of several neuropsychiatric disorders (5). Microglia, the resident tissue macrophages in the CNS, provide immunomodulatory functions in response to injury or disease (6). More recently, it has also been appreciated that the microglia serve additional roles related to neural plasticity, including removal of apoptotic cells and inappropriate neural connections and sculpting and modifying both the developing and mature CNS (7). Other recent work has implicated microglial dysfunction in a variety of neuropsychiatric disorders (8).

Astrocytes are the most abundant form of glial cells and are commonly further divided into protoplasmic and fibrous subtypes on the basis of their presence in the gray or white brain matter respectively. However, it is now clear that there is a much greater level of heterogeneity included in this general class of astrocytes (9). The broader class of astrocytes are known to serve a large number of CNS functions, including regulating regional blood flow and energy metabolism, immune defense, amino acid neurotransmitter clearance, neurotrophin production, regulation of D-serine and glycine that serve as co-agonist in *N*-methyl-D-aspartate receptor (NMDAR) excitation, stabilization and stripping of synaptic connections, and adult neurogenesis (10,11) (Figure 1). More recently, the unique complexity of higher primate and human astrocytes has been appreciated (12), and there is increasing evidence to suggest that disruption of astroglial development or function is a potential contributor to a range of neuropsychiatric disorders (13).

Evidence of Glial Pathology Associated With Mood Disorders

Human Data

Following-up on initial neuroimaging studies showing that the volume of the subgenual part of Brodmann area 24 is reduced in familial forms of MDD and bipolar disorder (BD), Ongur *et al.* (14) used unbiased stereological techniques to demonstrate that the numbers of glia were reduced in both MDD and BD. The most prominent reductions were evident in subgroups of subjects with familial MDD or BD who exhibited marked (24% and 41%, respectively) reductions in the number of glial cells compared

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Received Dec 13, 2012; revised Mar 9, 2013; accepted Mar 13, 2013.

0006-3223/$36.00
http://dx.doi.org/10.1016/j.biopsych.2013.03.032

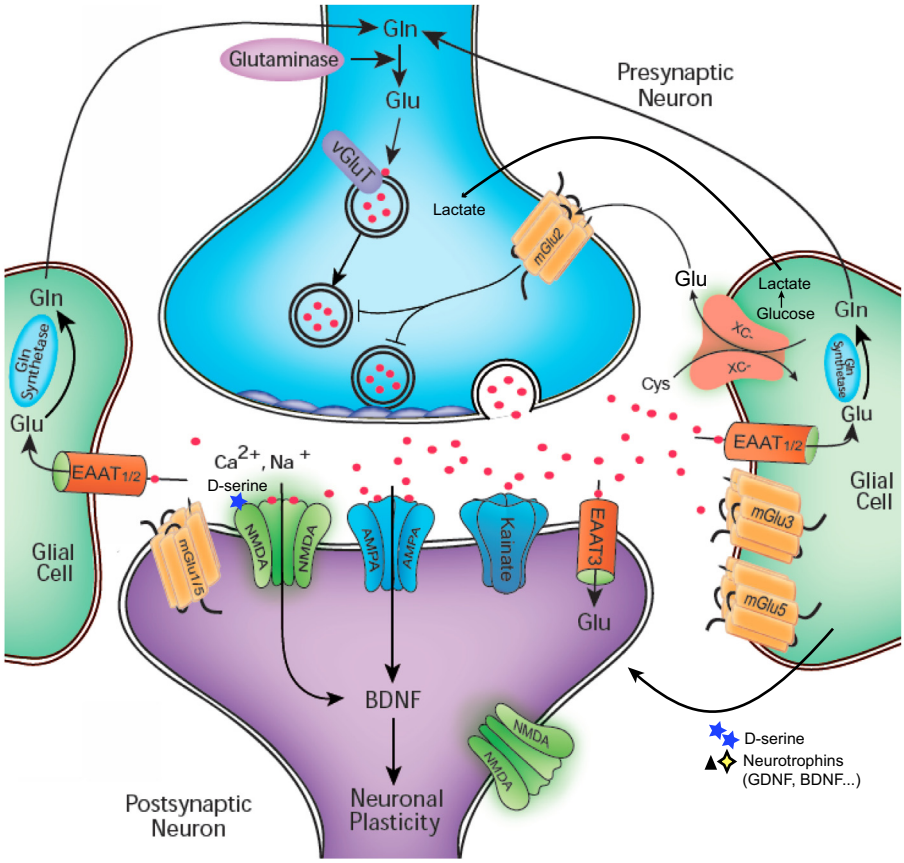

Figure 1. Neuron-glial interactions within the tripartite synapse. Glutamate (Glu) is released from vesicles within presynaptic neurons on excitation. Once released, the Glu can activate a variety of ionotropic and metabotropic receptors on postsynaptic and presynaptic neurons as well as glial cells. Some additional Glu is released into the extracellular space through the cystine (Cys)/Glu transporter (xc-) on glial cells. Glutamate is cleared from the extracellular space via high-affinity excitatory amino acid transporters (EAATs), which are located primarily on neighboring glial cells ($EAAT_{1/2}$) and, to some extent, on neurons (EAAT 3). In glial cells, Glu is converted into glutamine (Gln) by Gln synthetase. Glutamine is then transported back into the glutamatergic neuron, where it is hydrolyzed into Glu by glutaminase. Glial cells also provide metabolic and energy support to neurons through a supply of lactate. Additionally, Serine racemase, the D-serine-synthesizing enzyme, is expressed by astrocytes. On release, D-serine serves as a co-agonist at *N*-methyl-D-aspartate (NMDA) receptors. Astroyctes serve additional critical physiological roles through the synthesis and release of several neurotrophic factors including glial-derived neurotrophic factor (GDNF) and brain-derived neurotrophic factor (BDNF). AMPA, alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid; Ca^{2+}, calcium ion; mGlu, metabotropic glutamate; Na^{+}, sodium ion; vGluT, vesicular glutamate transporter.

with control subjects. Similar reductions in Brodmann area 24 glial cell density were also reported by Cotter *et al.* (15) and most recently by Gittins and Harrison (16). Early observations of prominent glial density reductions in the orbitofrontal region and both supra- and infragranular layers of dorsolateral prefrontal cortex (DLPFC) in depressed subjects were also reported by Rajkowska *et al.* (17). Later studies continued to show reductions in glial cell number and density in the dorsolateral frontal cortical regions (18–20) as well as the subgenual cingulate cortex gray matter (21) and the amygdala (22,23). Although several studies provide evidence that the reduced glial cell numbers and density are not unique to mood disorders but also common to schizophrenia, other studies have failed to find differences between mood disorder and control cases. Table S1 in Supplement 1 provides a more comprehensive outline of the postmortem studies examining glial cell pathology in several brain regions associated with mood disorders.

Additional studies have provided information suggesting selective pathologies in subpopulations of glial cells. A few analyses have found evidence of significant oligodendrocyte pathology in mood disorders. A recent review by Edgar and Sibille (24) specifically discusses the potential role impaired oligodendrocyte structure and function might play in neural circuitry and how this potentially contributes to mood regulation in human psychiatric disorders. Evidence of microgliosis has also been observed in the DLPFC, anterior cingulate cortex, and thalamus of suicide patients (25), suggesting that there might be abnormalities of microglial function associated with MDD. A recent review thoroughly discusses these findings and the potential role of activated microglia in the pathophysiology of mood and other neuropsychiatric disorders (26).

Other studies suggest astrocyte pathology is a prominent feature of mood disorders, and this will serve as the primary focus for the remainder of this review. Glial fibrillary acidic protein (GFAP) is an intermediate filament protein that is expressed by several cell types in the body. In the CNS, it has traditionally been considered a marker of astrocytes that can be induced by degeneration, damage, or aging. However, it is now known that the expression of GFAP is in fact much more complicated, with various isoforms of GFAP expressed in different cell types and unique subsets of astrocytes (9). With these caveats in mind, several studies have identified reduced levels of GFAP expression in postmortem brain tissue from regions of the hippocampus (27), PFC (28–30), anterior cingulate (16), amygdala (31), and even