Chapter 17
Involvement of Glial Cells in the Pathophysiology and Treatment of Depression

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ABSTRACT

Depression is a complex neuropsychiatric illness affecting millions worldwide. Furthermore, its exact cause remains uncertain. Theories include the monoamine hypothesis, changes in hormonal systems, inflammation, immune alterations, neurogenesis issues, and environmental factors. Recent research has highlighted the role of glial cells, particularly microglia and astrocytes, in depression. This chapter explores the implications of glial cells in depression, shedding light on their involvement in neuroinflammation, synaptic plasticity, and the regulation of mood-related circuits. An intricate interplay between glial cells, proinflammatory cytokines, and neuronal processes appears to underlie the etiology and progression of depression. Understanding the dynamic interactions between glial cells and neurons in the context of depression offers promising avenues for novel therapeutic interventions targeting this debilitating disorder's neuroinflammatory components.

INTRODUCTION

Depression is a potentially life-threatening disorder that affects hundreds of millions of people all over the world. It can occur at any age from childhood to late life and is a tremendous cost to society as this disorder causes severe distress and disruption of life and, if left untreated, can be fatal (Brigitta, 2002). The exact mechanisms of depression are not fully understood. The first major depression hypothesis was formulated about 30 years ago, and the main symptoms of the disease are due to monoaminergic systems dysfunction; norepinephrine (NE), serotonin (5-hydroxytryptamine; 5-HT), and/or dopamine (DA). It

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is highly established that the monoaminergic system regulates mood, attention, motivation, and fatigue. Hence, it is clearly that its dysfunction can lead to many behavioral symptoms such as psychomotor agitation or retardation (Brigitta, 2002). Indeed, the abnormal functional and behavioral effects of depression or mania can result from alterations in neurotransmitter synthesis, storage, or release, as well as from disturbed sensitivity of their receptors or intracellular messenger functions (Brigitta, 2002). Along with this, there is evidence that other systems are involved in triggering depressive episodes, such as the neuroendocrine axis (corticotropic axis), peptidergic (substance P), and hormonal (melatonin) systems. All these systems share the common property of affecting cell proliferation in specific cerebral regions such as the hippocampus which is one of the regions of the brain where neural progenitor cells continue to divide and give rise to new neurons in adult animals and it is involved in memory and learning function.

Meanwhile, the focus of research has shifted from monoamines toward other molecular mechanisms, and some factors other than monoamine deficiency systems must be taken into account when describing the neurobiological basis of major depression (Czéh & Lucassen, 2007). Recently, it has been hypothesized that neurotrophic dysregulation (Duman & Li, 2012) and glial cells degeneration or dysfunction, particularly astrocytes contributes to the pathogenesis of depression (Śmiałowska et al., 2013). This chapter will describe the involvement of glial cells in the pathogenesis and treatment of depression.

GLIAL CELLS DYSFUNCTION IN DEPRESSION

Glial cells are composed of distinct populations of oligodendrocytes (OLs), microglia, and astrocytes. It is known that glia (predominantly astrocytes) are thought to support neurons trophically, regulate neuronal metabolism, form synapses, and participate in neurotransmission in addition to their traditional functions in myelin formation, inflammatory processes, and neuronal migration (radial glia).

Recently, depression (Ménard et al., 2016) and neurodegenerative disorders (Capani et al., 2016; Maragakis & Rothstein, 2006), have been linked to the degradation or malfunction of glial cells, particularly astrocytes. Indeed, postmortem studies of depressed suicides show hypertrophy of astrocytes in the white matter (WM) of the anterior cingulate cortex (Torres-Platas et al., 2011), and decreased packing density or number of glial cell populations in frontolimbic brain regions (Rajkowska & A Stockmeier, 2013). It is important to note that a recent immunohistochemistry study of glial fibrillary acidic protein (GFAP) suggested that astrocytes are responsible for the overall glial pathology in Major depressive disorder (MDD) (Miguel-Hidalgo et al., 2000). There is a statically significant correlation between age and GFAP immunoreactivity among subjects with MDD. Hence, a significant reduction in the population of reactive astroglia is found in a small subgroup of young subjects with MDD, as compared to young control subjects and older subjects with MDD. Indeed, most of the participants in this subgroup of younger adults with MDD committed suicide. According to recent research, the levels of the protein GFAP are also lower in these young adults with MDD when compared to age-matched control subjects, and GFAP levels are positively correlated with both the age at death and the age of depression onset (Miguel-Hidalgo et al., 2000).

On the other hand, OLs may contribute to the cellular pathology of depression. In fact, OLs exhibit ultrastructural abnormalities and a decrease in their density and immunoreactivity in both the dorsolateral prefrontal and anterior frontal cortex in patients with MDD (Orlovskaya et al., 2000; Uranova et al., 2001). Additionally, changes in glial size and shape as well as decrease in glial density have been linked to depression-related monoamine and glutamate system dysfunction. For instance, almost all