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Role of glutamate receptors and glial cells in the pathophysiology of treatment-resistant depression

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ABSTRACT

Treatment-resistant depression (TRD) causes substantial socioeconomic burden. Although a consensus on the definition of TRD has not yet been reached, it is certain that classic monoaminergic antidepressants are ineffective for TRD. One decade ago, many researchers found ketamine, an N-methyl-D-aspartate receptor (NMDAR) antagonist, to be an alternative to classic monoaminergic antidepressants. The major mechanisms of action of ketamine rapidly induce synaptogenesis in the brain-derived neurotrophic factor (BDNF) pathway. Although excessive glutamatergic neurotransmission and consequent excitotoxicity were considered a major cause of TRD, recent evidence suggests that the extrasynaptic glutamatergic receptor signal pathway mainly contributes to the detrimental effects of TRD. Glial cells such as microglia and astrocytes, early life adversity, and glucocorticoid receptor dysfunction participate in complex cross-talk. An appropriate reuptake of glutamate at the astrocyte is crucial for preventing 'spillover' of synaptic glutamate and binding to the extrasynaptic NMDA receptor. Excessive microglial activation and the inflammatory process cause astrocyte glutamatergic dysfunction, which in turn activates microglial function. Early life adversity and glucocorticoid receptor dysfunction result in vulnerability to stress in adulthood. A maladaptive response to stress leads to increased glutamatergic release and pro-inflammatory cytokines, which then activate microglia. However, since the role of inflammatory mediators such as pro-inflammatory cytokines is not specific for depression, more disease-specific mechanisms should be identified. Last, although much research has focused on ketamine as an alternative antidepressant for TRD, its long-lasting effectiveness and adverse events have not been rigorously demonstrated. Additionally, evidence suggests that substantial brain abnormalities develop in ketamine abusers. Thus, more investigations for ketamine and other novel glutamatergic agents are needed.

1. Background

1.1. Definition

The pharmacological treatment for major depressive disorder (MDD) is not very effective in real-world clinical practice compared to randomized clinical trials. For instance, in four successive treatment trials within 14 months, remission rates were 36.8%, 30.6%, 13.7%, and 13.0% in each step in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Rush et al., 2006). In the STAR*D trial, the cumulative remission rate was only 67%.

Given the low remission rates, the concept of treatment-resistant depression (TRD) is important to understand in the treatment of MDD in clinical practice. Whereas there has been no consensus on the definition of TRD, five different methods have been suggested for staging treatment-resistance in the treatment of depression (Ruhe et al., 2012). Each staging method has its own criteria for treatment duration, classes and number of antidepressant trials, severity of depression, and application of electroconvulsive therapy (ECT). Although there is a lack of consensus regarding the criteria of TRD, generally failure to respond

Abbreviations: TRD, Treatment-resistant depression; NMDAR, N-methyl-D-aspartate receptor; BDNF, brain-derived neurotrophic factor; MDD, major depressive disorder; STAR*D, Sequenced Treatment Alternatives to Relieve Depression; ECT, electroconvulsive therapy; MRI, magnetic resonance imaging; DMN, default mode network; PCC, posterior cingulate cortex; PFC, prefrontal cortex; DBS, deep brain stimulation; ELA, early life adversity; HPA, hypothalamus–pituitary–adrenal; CYP, cytochrome P450; GSRD, European Group for the Study of Resistant Depression; TPH2, tryptophan hydroxylase-2; COMT, catechol-O-methyltransferase; 5HTTLPR, serotonin-transporter-linked polymorphic region; GENDEP, Genome-Based Therapeutic Drugs for Depression, selective serotonin reuptake inhibitors SSRI, SSRI; MARS, Munich Antidepressant Response Signature; AMPAR, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptors; mTOR, mammalian target of rapamycin; 4E-BP1, 4E binding protein 1; ERK, extracellular signal-regulated kinase; NBQX, 2,3-dihydroxy-6-nitro-7-ulfamoyl-benzo[f]quinoxaline-2,3-dione; Ark, adhesion related kinase; eEF2, eukaryotic elongation factor 2; MADRS, Montgomery–Åsberg Depression Rating Scale; mGlu, metabotropic glutamate receptors; EAAT, excitatory amino acid transporters; CREB, cyclic adenosine monophosphate response element-binding protein; TNF-α, tumor necrosis factor-α; IL-1β, interleukin-1β; CA1, cornu ammonis 1; NAAG, N-acetylaspartylglutamate; LPS, lipopolysaccharides; MAPK, mitogen-activated protein kinase; IDO, indoleamine-pyrrole 2,3-dioxygenase; IFN-α, interferon- α; GFAP, glial fibrillary acidic protein; CBT, cognitive behavioral therapy; VNS, vagus nerve stimulation; AAP, atypical antipsychotics; RCT, randomized controlled trial; PGC-1α1, peroxisome proliferator-activated receptor gamma coactivator 1-alpha 1.

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to more than two classes of antidepressants with adequate dosage and for an adequate duration is defined as TRD (McIntyre et al., 2014).

1.2. Socioeconomic burden

TRD is one of the common mental health problems in primary care. Although the prevalence of TRD has been thought to range from 10 to 30% (Keller, 2005), it is estimated that more cases of TRD are likely encountered in real-world primary clinical practice. For instance, it has been reported that 55% of depressed patients who take an adequate dose of antidepressants over 6 weeks have TRD (Thomas et al., 2013).

TRD is substantially important in its close relationship with poor clinical prognosis and high socioeconomic burden. Generally, patients with TRD experience a greater number of depressive episodes and comorbid disorders (Olchanski et al., 2013). TRD patients are at high mortality risk after acute coronary syndrome (Carney and Freedland, 2009). Those unsatisfactory treatment responses worsen the quality of life and psychosocial functioning of such patients (Mrazek et al., 2014).

TRD also causes a substantially higher socioeconomic burden compared to treatment-responsive depression. Several studies have consistently reported that TRD disproportionately contributes to the socioeconomic burden compared to non-TRD. A recent systematic review has suggested that TRD results in $9529 higher total costs than treatment-responsive depression (Mrazek et al., 2014). A claim data study has shown that the median cost of TRD is $56,433, which is significantly higher than the $29,063 of non-TRD (Olchanski et al., 2013). In that study, classification of TRD substantially increased health care expenditures among patients with MDD after adjusting for other influential factors such as age, sex, and number of comorbid disorders.

2. Pathophysiology

As the definition of the TRD suggests, failure of monoaminergic antidepressant treatment is the key pharmacological feature of TRD. Although many monoaminergic antidepressants have been developed based on the serotonergic deficiency hypothesis (Wong et al., 2005), time lag until response and overall low response rates to the first prescription of antidepressants suggest that there are other complex neuromolecular mechanisms underlying depression. Currently, various factors such as neuronal, glial, and synaptic dysfunctions explain the pathophysiological mechanisms of depression and pharmacological approaches (Duman and Aghajanian, 2012). In this review, we aimed to broaden the scope of the pathophysiology of TRD by including a discussion of its interactions with stress, glucocorticoids, glutamatergic neurotransmission, and glial cells.

2.1. Neuroanatomical pathophysiology

2.1.1. Functional imaging study

Functional magnetic resonance imaging (MRI) studies have mainly focused on abnormalities in the default mode network (DMN) in TRD. The DMN consists of midline structures, including the anterior cingulate, cuneus, precuneus, posterior cingulate, and medial prefrontal cortex, and shows increased activity during the resting state in MDD (Marchetti et al., 2012). Although hyperactivity in the DMN is a characteristic finding of MDD (Mulders et al., 2015), such dysregulation is typically more pronounced in TRD. A recent systematic review has suggested that abnormalities in the DMN might be more distinct in TRD than in non-TRD MDD (de Kwaasteniet et al., 2015). Another study has shown that differences in the activation of DMN are also greater in TRD compared to healthy controls than in the activation differences between treatment-responsive depression and healthy controls (Guo et al., 2013). In that study, TRD showed distinctive decreased cerebellum–cerebellar functional connectivity, although the neuroanatomical mechanisms of the decreased functional connectivity were not fully explained. However, some studies have reported inconsistent results regarding the possible role of DMN in treatment response among patients with MDD. For example, a study based on late-life depression has shown that differences in the functional connectivity of the posterior cingulate cortex (PCC) and the prefrontal cortex (PFC) between patients and healthy controls were diminished after antidepressant treatment, whereas differences in the PCC-striatum functional connectivity were maintained (Andreescu et al., 2013). In that study, it was suggested that the diminished differences in the anterior structure of the DMN could be used as a possible marker of treatment response. However, another study has reported that abnormal functional connectivity was maintained after treatment, suggesting that the anterior DMN region might be a trait-marker that could be detected in the asymptomatic or early phase of MDD (Li et al., 2013a). TRD has also shown increased functional connectivity from the right middle temporal gyrus to the medial frontal gyrus, angular gyrus, precuneus, superior frontal gyrus, and rectus (Ma et al., 2012). Patients with TRD have shown high regional homogeneity in the right middle temporal gyrus and right insula, whereas they showed low regional homogeneity in the left precuneus and inferior frontal gyrus compared to non-refractory MDD patients (Wu et al., 2011).

In a positron emission tomography study with deep brain stimulation (DBS), responders to DBS had increased metabolism in the PFC compared to non-responders (Mayberg et al., 2005). Another study has reported that TRD had higher metabolism in the amygdala and uncus than non-TRD patients and healthy controls (Martinot et al., 2011).

2.1.2. Structural imaging study

Few studies have focused on the differences in brain structure between TRD and non-TRD. Shah et al. (1998) have reported that patients with TRD had decreased gray matter volume in the left superior temporal and left lateral inferior frontal gyrus and increased right cuneus and right precuneus gray matter volume (Shah et al., 1998). The same research group has suggested that TRD had smaller right PFC volume than healthy controls. The TRD group had less right caudate tissue than the recovered patients group (Shah et al., 2002). In one study, both right and left hippocampal volumes in the TRD were smaller than those in the treatment-resistant schizophrenia group, as well as in the healthy controls (Maller et al., 2012). However, results of human brain imaging studies have not been consistent based on sex and clinical symptoms. It has been reported that females with TRD have smaller entorhinal cortices than healthy females, whereas there are no differences in the entorhinal cortex in males (Furtado et al., 2008). It has also been reported that there are no significant differences in cortical thickness or hippocampal volume between those with TRD and healthy controls (Phillips et al., 2015). There are several possible reasons for the inconsistent results in hippocampal volumes in TRD. The non-significant differences in hippocampal volume might be due to compensating outgrowth of glial cells. One study has shown that the degree of synaptic loss caused by corticosterone exceeds the overall hippocampal volume reduction (Tata et al., 2006), suggesting that glial compensating mechanisms occur in the hippocampus. However, such an idea cannot fully explain the loss of glial cells, which inevitably leads to volumetric reduction in the hippocampus in TRD. Another possible reason is related to confounding factors such as medication, sex, and early life adversity (ELA). Indeed, when adjusting for confounding factors, some of the findings of increased cortical regions have been shown to be related to antidepressants (Zhao et al., 2014).

On the other hand, hippocampal volume is associated with chronic stress and a dysregulated hypothalamus–pituitary–adrenal (HPA) axis. It is well-known that excessive cortisol and glucocorticoid receptor dysfunction are some of the main neurobiological alterations of MDD (Spijker and van Rossum, 2009). The close relation between stress and