

Disturbance of the Glutamatergic System in Mood Disorders

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The role of glutamatergic system in the neurobiology of mood disorders draws increasing attention, as disturbance of this system is consistently implicated in mood disorders including major depressive disorder and bipolar disorder. Thus, the glutamate hypothesis of mood disorders is expected to complement and improve the prevailing monoamine hypothesis, and may indicate novel therapeutic targets. Since the contribution of astrocytes is found to be crucial not only in the modulation of the glutamatergic system but also in the maintenance of brain energy metabolism, alterations in the astrocytic function and neuroenergetic environment are suggested as the potential neurobiological underpinnings of mood disorders. In the present review, the evidence of glutamatergic abnormalities in mood disorders based on postmortem and magnetic resonance spectroscopy (MRS) studies is presented, and disrupted energy metabolism involving astrocytic dysfunction is proposed as the underlying mechanism linking altered energy metabolism, perturbations in the glutamatergic system, and pathogenesis of mood disorders.

Key words: mood disorders, major depressive disorder, bipolar disorder, glutamate, astrocytes, magnetic resonance spectroscopy

INTRODUCTION

A number of pharmacological interventions are now established

and available for the treatment of mood disorders [1]. However, there are considerable drawbacks of currently available treatment modalities, such as relatively slow therapeutic effects and limited efficacy for treatment-resistant cases [2], which impose substantial burdens on the affected individuals as well as on public health and society [3, 4]. Accordingly, there exists a compelling need for a more improved neurobiological understanding of mood disorders, which may complement the limitations of the prevailing monoamine hypothesis [5], and corresponding new treatment strategies [5]. In line with these circumstances, the glutamatergic system is receiving more attention as one of the potential targets of novel therapeutic agents for mood disorders [2, 5]. Glutamate is the major excitatory neurotransmitter in the brain, and growing

Received December 3, 2013, Revised February 24, 2014,
Accepted February 24, 2014

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evidence indicates abnormalities in the glutamatergic system of patients with mood disorders [2, 5]. Researchers are working to develop medications acting on the glutamatergic system, which may lead to a breakthrough in the pursuit of more effective measures to treat mood disorders [6].

Glutamate is a ubiquitous molecule that is engaged in the majority of the excitatory transmission in the brain, yet excessive glutamate release may cause brain damage due to excitotoxicity [7]. For the adequate neurotransmission of glutamate, not only glutamatergic neurons but also astrocytes are indispensable [8]. Indeed, astrocytes are essential in glutamatergic activities including glutamate reuptake, synthesis of glutamate precursors, and removal of excess glutamate [8, 9]. In addition, there is evidence that astrocytes play an important role in the neuroglial system which enables an efficient coupling of glutamatergic neuronal activities and task-dependent changes in brain energy utilization [10]. Thus, perturbations in astrocytic function may contribute to alterations in glutamate and energy metabolism observed in mood disorders [11]. In the present review, we will discuss the roles of the glutamatergic system, astrocytes, and brain energy metabolism in the pathogenesis of mood disorders.

ABNORMALITIES OF THE GLUTAMATERGIC SYSTEM IN MOOD DISORDERS

Glutamate is an essential and abundant amino acid with various functions in the brain, most notably as an excitatory neurotransmitter and precursor of the inhibitory neurotransmitter γ -aminobutyric acid (GABA) [5, 12]. Inappropriate regulation of glutamate is known to incur neurotoxicity and other deleterious effects on neurotransmission, neuroenergetics, and cell viability [7]. Accordingly, a considerable number of studies have been conducted to investigate the potential association between the glutamatergic system and neurological or psychiatric disorders [7].

In line with these studies, the importance of the glutamatergic system has been increasingly emphasized in the study of mood disorders [5]. As glutamate plays a crucial role in synaptic transmission and plasticity, perturbation of the glutamatergic system is considered to be at least partially involved in synaptic abnormalities found in mood disorders [5]. Indeed, several studies observed abnormalities of the glutamatergic system in depression, particularly in glutamate clearance at the synaptic space and in modulation of astrocytic energy metabolism involving glutamate [13, 14]. The fast-onset antidepressant effect of the drug tianeptine is also notable in light of the glutamate hypothesis of depression, as the medication appears to exert its influence partly through the glutamatergic system [15]. Ketamine, an N-methyl-D-aspartate

(NMDA) receptor antagonist, has also been reported to exert a rapid antidepressant effect in patients with MDD [6, 16].

Several findings from postmortem studies, which may provide important histological and molecular information for the neurobiological understanding of psychiatric disorders [17], are also in accordance with the evidence of glutamate abnormalities in mood disorders. For instance, an elevated level of glutamate was identified in the postmortem frontal cortex of patients with MDD or BD [18], while dysregulated expression of glutamate-related genes was observed in the hippocampus of patients with depression [19]. Also, the level of glutathione, which functions as a physiologic reservoir of neuronal glutamate, was reduced in the postmortem prefrontal cortex [20]. There also have been reports of altered binding properties of the NMDA receptor in the brain of suicide victims [21], decreased expression of the NMDA receptor subunits in the prefrontal cortex of patients with MDD [22], and abnormalities in the levels of excitatory amino acid transporters (EAATs) in the postmortem prefrontal cortex of patients with bipolar disorder (BD) [23]. However, the inherent shortcomings of postmortem studies, including the extremely limited repository of available brain tissues which often results in underpowered studies with small sample sizes [24] and the confounding effects of varying durations of premortem agonal period or postmortem interval and terminal stress level, suggest that *in-vivo* approaches are warranted to obtain a more complete picture of the living brain.

In contrast to the postmortem approach, magnetic resonance spectroscopy (MRS) provides a non-invasive method which allows *in-vivo* study of the biochemical environment in the brain [25]. Since glutamate and glutamine share a highly similar structure and thereby have overlapping chemical shifts, MRS studies conducted at field strength lower than 3.0 tesla generally assess the combined signal that mainly comes from the two metabolites, which is referred to as "Glx" [26]. In the following sections, we will summarize the glutamate- or Glx-related outcomes from MRS studies in MDD and BD.

Glx in Major Depressive Disorder

The existing MRS literature consistently indicates reductions in the Glx level of several brain regions in MDD [25]. For example, in a study which assessed the levels of various brain metabolites in the anterior cingulate cortex (ACC) and parietal white matter, the level of Glx was significantly lower in patients with MDD [27]. In the same study, when only severely depressed patients were considered, the levels of glutamate alone as well as Glx were reduced [27]. Another study found a decreased ACC Glx level in MDD, which was later restored to the normal level in the MDD

group effectively treated with electroconvulsive therapy (ECT) but not in the untreated MDD group [28]. It was also reported by a different study that the Glx level was reduced in the dorsolateral prefrontal cortex (PFC) of patients with treatment-resistant MDD, and that the difference in the Glx level between the patient and control groups disappeared after successful treatment of MDD with ECT [29]. MDD-associated reductions in the Glx level were also observed in the dorsomedial/dorsal anterolateral PFC and ventromedial PFC, in a study that controlled the possible influence of medication by implementing a minimum medication-free period of four weeks as a selection criterion [30]. In addition, even in a study which used a minimum medication-free period of eight weeks, the hippocampal Glx level was significantly lower in the MDD group [31].

Interestingly, there exist a number of studies which reported normal or elevated Glx levels in remitted MDD [32, 33]. In association with the reports of normalized Glx level after successful ECT for MDD, these results suggest that Glx, which declines along with the depressive state, may be restored or compensated [28, 29, 32]. Also, an MRS study conducted in the melancholic subtype of depression reported that the level of glutamate in the occipital lobe was actually increased [34]. Meanwhile, there are a few studies that did not observe Glx reductions in MDD [35, 36], although they appear to have limited implications. A study reported an elevated Glx level in elderly patients with MDD, but the increase was not statistically significant and the outcome may not be generalized to non-elderly populations [35]. In another study that focused on the ACC and occipital cortex, MDD-related differences in Glx were found to be not significant, even though a decreasing trend in the ACC Glx level was observed [36]. As suggested by these studies, it is possible that the direction and magnitude of changes in the level of glutamate may differ in different brain regions, but the converging evidence generally suggests that meaningful alterations in glutamate level do occur in MDD [5].

Glx in Bipolar Disorder

Unlike the case of MDD, the level of Glx is generally reported to be elevated in BD [25, 37]. In the acute manic state of BD, an increased Glx level in the left dorsolateral PFC was found [38]. Furthermore, elevated Glx levels were also observed in the cingulate gyrus of the patients with BD, not only in the manic state but also in the mixed or depressed states [39]. Based on the concurrent increases in Glx and lactate, the researchers of the study proposed that disturbance in the brain energy metabolism, in particular the change in the energy redox state from oxidative phosphorylation to glycolysis, might explain the changed Glx level [39]. Findings from studies that used phosphorus MRS,

which showed pH level decreases in conjunction with lactate level increases, corroborate the shift toward glycolysis in brain energy metabolism [40].

According to a study which distinguished the melancholic and non-melancholic subtypes of BD depression, Glx was more heightened in the BD group in comparison with the control group, and the increase in Glx was more pronounced in the melancholic BD subgroup [41]. In addition, after treatment with lamotrigine, an anti-glutamatergic mood stabilizer, the treatment group that had undergone remission showed a significant reduction in Glx, compared to the non-remission group [41]. In a study which included patients with rapid cycling (RC) bipolar II disorder, those with non-RC BD, and healthy controls, the Glx level in the left dorsolateral PFC turned out to be significantly higher in the RC group in all mood states [42]. Although the study was conducted in a small population at a preliminary scale, the fact that the RC subtype is considered as a severe BD subtype [43] implicates the possibility that the elevated Glx level may be an important factor in the manifestation of characteristic symptoms of BD.

There exists a report suggesting that a substantial number of patients with postpartum depression should be diagnosed to have BD [44]. It is thus notable that the level of glutamate, which is generally increased in BD, was reported to be increased in the medial PFC of patients with postpartum depression [45]. As changes in female hormones are known to be associated with fluctuations in the glutamate level in the medial PFC [46], it can be hypothesized that the hormonal changes that occur during the postpartum period may induce disturbance in the glutamatergic system, which would in turn lead to the pathogenesis of postpartum depression [45]. It is intriguing that the increasing tendency of glutamate level in postpartum depression is more comparable to the glutamatergic change in BD than to the change in MDD. Continued research would be necessary to further elucidate the pathophysiology of postpartum depression and its possible association with that of BD.

In sum, the general tendencies of decreased Glx level in MDD and increased Glx level in BD are considered to be significant, even when the effect of brain regional differences in the level of glutamate is taken into account [25, 37].

THE ROLE OF ASTROCYTES IN MOOD DISORDERS

Astrocytes are deeply involved not only in glutamate metabolism but also in neuronal energy supply [10, 47]. Indeed, astrocytes uptake glutamate released to the synaptic cleft and synthesize glutamine from glutamate, while they deliver energy sources including glucose and lactate based on neuronal energy

requirements [8-10]. Thus, there exists a tight coupling between the glutamatergic system and brain energy metabolism via astrocytic functions.

It is thus of particular interest that astrocytic abnormalities are continuously implicated in human and animal studies of mood disorders, although changes in other kinds of glial cells have also been noticed [48-50]. Animal models of mood disorders have revealed several changes in astrocytes, which are manifested by phenomena such as altered expression or immunoreactivity of glial fibrillary acid protein (GFAP), which is a common marker of astrogliosis [51] and astrocytic glutamate transporters [48]. Evidence from human postmortem studies also indicates glial abnormalities including reductions in astrocytic densities or decreased GFAP levels [52]. For instance, a study which used postmortem amygdala sample showed that the density of GFAP-immunoreactive astrocytes was significantly lower in MDD samples than in BD, schizophrenia, or control samples [53]. A series of *in vivo* human studies conducted by a research group suggest that reduced density of reactive astrocytes is associated with MDD in an age-dependent manner, as age was positively correlated with GFAP immunoreactivity or level [54, 55]. These studies imply a meaningful relationship between mood disorders and reduced astrocytic density or GFAP levels, especially in younger patients with MDD [54, 55].

Based on these findings, it has been proposed that the interplay of stress-induced changes, glial dysfunction and disturbed glutamatergic system may be deeply involved in the pathogenesis of depression [52]. As stress may incur an excess of glucocorticoids or reductions in neutrophin levels which are thought to be associated with decreased astrocytic density and impaired astrocytic function, it may in turn lead to disruption of glutamatergic system and subsequent neurotoxicity [48, 52, 56]. Furthermore, it has been suggested that antidepressants may at least partially exert their effects via directly affecting astrocytes, as these drugs have been shown to influence several factors including the number of astrocytes, GFAP expression, and astrocytic signaling pathways [57]. Accordingly, further research to elucidate the association between astrocytes and the pathogenesis of mood disorders as well as the pharmacodynamics of antidepressants may contribute to the development of novel therapeutic targets.

DEPRESSION IN DIABETES MELLITUS: IN ASSOCIATION WITH GLUTAMATERGIC ABNORMALITIES

Extensive clinical evidence indicates that depression is a common comorbidity of diabetes mellitus (DM), a disorder of dysregulated glycemic control [58]. According to a meta-

analysis, having DM was observed to increase by twice the odds of comorbid depression [58]. There have been attempts from different approaches to investigate the underpinnings of the association between depression and DM, which is suggested to be bidirectional and complex [59]. For the influence of depression on DM, depressive symptoms are reported to exacerbate DM by hindering self-care and management in patients with DM [60].

For the influence of DM on depression, psychosocial factors did not significantly predict the incidence of depression in DM [61], whereas biochemical factors, notably glutamate abnormalities, are shown to be implicated in DM-related depression [62, 63]. In a rat model of streptozotocin-induced diabetes, DM was shown to deter glutamate oxidation and glutamine synthesis in the retina [64]. Also, in the identical model, an elevated level of glutamate was observed in the retina of diabetic rats [65]. A human MRS study reported a higher prefrontal Glx level in patients with type 1 DM [62], whereas the levels of glutamate and glutamine in the subcortical brain regions were found to be significantly lower in patients with type 2 DM and MDD than in those with DM alone [63]. As indicated by the evidence suggesting glutamatergic abnormalities in DM-related depression, medications acting on the glutamatergic system may prove to be effective in the treatment of depressive symptoms in DM [62].

In consideration of the importance of astrocytes in the regulation of the glutamatergic system, it may be of particular interest that DM appears to be associated with changes in the number or function of astrocytes. A number of studies showed DM-induced reductions in GFAP levels in streptozotocin-induced DM, which are suggested to be due to hyperglycemia [66, 67]. Also, in diabetic rats, ischemia resulted in rapid astrocytic death as well as increased synthesis of inducible nitric oxide synthase, which would lead to an increase in the level of nitric oxide [68]. Although it has been proposed that reactive astrocytes may have protective effects against central nervous system injury, this result suggests that diabetic hyperglycemia may induce prolonged or excess response of reactive astrocytes and astrocytic death [68]. Another rat study showed that the level of astrocytic GFAP was reduced while glutamate uptake was increased in streptozotocin-induced DM, and these DM-related effects were suppressed by insulin treatment [69]. As these studies consistently indicate astrocytic alterations in DM, future investigations on whether there is an association between DM-induced depressive symptoms and changes in the number and function of astrocytes.

CONCLUSION

As discussed in earlier sections, the evidence of glutamate

disturbance in mood disorders has been established by a considerable amount of research [5, 70]. Because the glutamatergic system plays many important roles in neurotransmission and neuroenergetic metabolism, the glutamate hypothesis of mood disorders may have important implications, which may be useful to overcome the shortcomings of the monoamine hypothesis as well as to identify novel therapeutic targets. As the importance of the glutamatergic system is more highlighted, the role of astrocytes, which is suggested to be impaired in mood disorders, is also being emphasized [49]. For a better understanding of the neurobiology of mood disorders, further research to elucidate the complex relationships between perturbations in the glutamatergic system, astrocytic dysfunction, and altered brain energy metabolism should be conducted.

ACKNOWLEDGEMENTS

The present work was supported in part by grants A112009 (JEK) and A121080 (IKL) from the Korean Ministry of Health and Welfare; and the Global Top 5 program, Ewha Womans University (IKL).

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