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Presynaptic Glutamatergic Dysfunction in Bipolar Disorder

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In this issue, Eastwood and Harrison (1)provide additional new data to support the key role that the glutamatergic system may play in the pathophysiology of bipolar disorder (BPD), and lend credence to the notion that this system may be a key target for developing novel drugs that are more effective for treating BPD than currently available therapeutic options.

BPD is a common, severe, and often highly disabling illness. Outcome is poor for many patients, with associated high rates of chronicity, residual symptoms, relapse, subsyndromes, cognitive and functional impairment, increased suicide risk, and psychosocial disability. In the context of the tremendous personal, familial, financial, and societal toll that BPD exerts, it is striking that only one medication–lithium–has ever been developed *specifically for the treatment of BPD*. While the pathophysiology of this devastating illness has remained poorly understood, growing evidence suggests that discrete glutamatergic system abnormalities may play an important role in the pathophysiology and treatment of BPD. This paper by Harrison and Eastwood (1) provides new data to further delineate the nature of these glutamatergic abnormalities.

Briefly, glutamate is the major excitatory neurotransmitter in the CNS (for a recent overview see (2)). Neuronal impulses trigger the release of glutamate into the synaptic cleft. Upon release, glutamate binds to and activates ionotropic and metabotropic receptors, resulting in both immediate changes in membrane potential as well as sustained alterations in synaptic connectivity. Glutamate is then cleared primarily by being transported into glial cells through excitatory amino-acid transporters (EAATs). In glial cells, glutamate is converted to glutamine by glutamine synthetase. Glutamine cycles back to presynaptic glutamatergic terminals, where it is converted back to glutamate by glutaminase. Presynaptic glutamate for neurotransmission is also supplied via the tricarboxylic acid cycle. Glutamate uptake into presynaptic vesicles for activity-dependent release occurs via the vesicular glutamate transporters (VGLUTs); three VGLUTs have been identified, two of which (VGLUT1 and VGLUT2) are primarily expressed in glutamatergic neurons. Netrin-G1 and netrin-G2, members of the netrin superfamily, bind to their receptors, NGL-1 and NGL-2, located on the postsynaptic side of the excitatory synapse (3). These receptors interact with postsynaptic density (PSD) proteins and other proteins

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including N-methyl-D-aspartate (NMDA) receptors, to regulate the development of axons, dendrites, and synapses (3).

Recent evidence from disparate sources has consistently implicated glutamatergic dysfunction in the pathophysiology of mood disorders–both major depressive disorder (MDD) and BPD (for a review see (2)). Human postmortem studies point to altered glutamatergic receptors, EAAT levels, and glial pathology in the brain tissue of individuals with BPD. Preclinical evidence, in turn, has shown that treatment with mood stabilizers modulates glutamatergic receptors in brain regions, and that the manipulation of glutamatergic receptors alters mood-associated behaviors in rodents. Eastwood and Harrison (1) build upon this work and report that mRNA levels of VGLUT1, netrin-G1d, netrin-G1f, and netrin-G2 are elevated in the anterior cingulate cortex (ACC) of individuals with BPD. Collectively, these data extend our current thinking regarding glutamatergic dysfunction in BPD to encompass the presynaptic side as well as aberrant excitatory synaptic connections in the ACC.

Eastwood and Harrison's study is particularly intriguing when considered with previous human brain imaging and postmortem findings that glutamate levels and glutamine/glutamate ratios are altered in several brain regions of individuals with BPD. Hashimoto and colleagues studied frontal cortical levels of glutamate, glutamine, glycine, D-serine, and L-serine in tissues obtained from the brain collection of the Stanley Foundation Neuropathology Consortium (SFNC) (Stanley Medical Research Institute, USA); they found that postmortem interval-corrected levels of glutamate–but not glutamine, D-serine, or L-serine–were elevated in individuals with BPD and MDD compared to controls (4). Increased glutamate levels and glutamate/glutamine ratios were also found in the dorsolateral prefrontal cortex (PFC) (Brodmann area 9) of individuals with BPD compared with controls (5). However, another study found no significant differences in parietal-cortical levels of glutamate between tissues from different diagnostic groups (6); these discrepancies suggest that the glutamatergic alterations in mood disorders might be region-specific.

Brain imaging studies similarly extend our understanding of how glutamatergic system dysfunction may be implicated in mood disorders, particularly in mood state- and treatment-dependent ways. One study found no significant changes in ACC or parieto-occipital cortex levels of glutamate in acutely manic BPD patients, despite the fact that glutamine/glutamate ratios were significantly higher in individuals with BPD due to higher glutamine levels (although the glutamine elevations themselves were not statistically significant) (7). In contrast, another study found that Glx (glutamate plus glutamine) levels were elevated in the grey matter of the cingulate gyrus in medication-free BPD patients presenting predominantly in depressed or mixed-mood states (8). Consistent with these findings, significant increases in glutamate, but not glutamine, were found in the ACC/medial PFC of patients with bipolar depression (9). The same investigators also reported no significant alterations of left dorsolateral PFC glutamate levels in medication-free BPD patients experiencing a variety of mood states (10). Hippocampal glutamate levels were recently found to be elevated in stably remitted BPD-I patients receiving chronic lithium maintenance therapy for an average of 10 years (11).

The study by Eastwood and Harrison (1) is notable particularly because it intended to address this issue of whether glutamate levels change in ACC/middle PFC regions in ways that correspond with altered glutamatergic neurotransmission. Their thoughtfully-constructed study found that VGLUT1 mRNA levels were significantly elevated in individuals with BPD compared to those with schizophrenia or controls. These results suggest that more glutamate can be packaged in the vesicles for activity-dependent release. In addition, the study further demonstrated significant increases in mRNA levels of netrin-G2, netrin-G1d, and netrin-G1f in the brains of individuals with BPD, suggesting more active excitatory synapse formation in

the region. Taken together, the findings support hyper-glutamatergic neurotransmission in the ACC associated with BPD.

Obviously, the major weakness associated with this postmortem study is the lack of critical protein data to support the functional significance of these altered mRNA levels; as a result, the possibility that the mRNA increases are compensatory changes for protein losses cannot be ruled out. Furthermore, although the study attempted to control for the impact of postmortem interval delay, pH, agonal state, antemortem medication, substance use, and other comorbidities, their potential effects cannot be completely excluded. Nevertheless, existing data from a variety of studies do strongly support the role of VGLUT1 in mood regulation in general. For instance, treatment with a variety of antidepressants as well as electroconvulsive shock (ECS) significantly increased mRNA levels of VGLUT1, but not VGLUT2 or VGLUT3 in frontal, orbital, cingulate, and parietal cortices, as well as hippocampal regions; these VGLUT1 mRNA changes correlated with increased protein levels (12). Another study found that treatment with antidepressants, lithium, and the atypical antipsychotic clozapine increased mRNA levels of VGLUT1, but not VGLUT2, in the cer ebral cortex and hippocampus; these increases were also associated with elevated protein levels (13).

The role of VGLUT1 in MDD and in the action of antidepressant agents is further corroborated by animal behavior data. VGLUT1 heterozygous knockout mice (which express half the amount of VGLUT1) showed increased immobility duration in the forced swim test, more anxious-like displays in the light-dark exploration test, and long-term memory impairments in the novel object recognition test (12). These mutant mice also have higher neuronal synthesis of glutamate and less consumption of sucrose solution (intended as a measure of anhedonia) (12), suggesting that VGLUT1 may be associated with depression-like behavioral abnormalities.

Given the putative importance of these findings, future human postmortem brain studies, though understandably difficult to conduct, should address whether mRNA and protein alterations of the genes reported in this article by Eastwood and Harrison are linked to mood states (depression and mania) or whether they persist throughout the illness–perhaps as markers for, or contributors to, vulnerability to mood swings.

The present study indicates that mRNA alterations of VGLUT1 and netrin-G in BPD are brain region-specific, and that mRNA levels of VGLUT1 are increased in the ACC of individuals with BPD. Notably, a recent study found decreased mRNA levels of VGLUT1 in the entorhinal cortex of individuals with BPD and MDD (14). The current study (1) similarly showed increased mRNA levels of netrin-G2, netrin-G1d, and netrin-G1f in the ACC of individuals with BPD. An earlier study by the same authors showed that netrin-G1c expression was decreased in the temporal cortex in BPD and that the expression of netrin-G2 was decreased in CA3 and CA4 of hippocampus in BPD (15).

It is worth noting that, to date, much of the research regarding how complex synaptic glutamatergic dysfunction contributes to BPD has focused on the critical roles that modifying levels of synaptic AMPA and NMDA receptors–in particular by receptor subunit trafficking, insertion, and internalization–plays in regulating various forms of synaptic and behavioral plasticity associated with BPD. The mood stabilizers lithium and valproate have been found to reduce synaptic/surface expression of GluR1 and GluR2, while anticonvulsants with an antidepressant profile enhanced expression (16). A number of studies suggest that regulating postsynaptic AMPA/NMDA throughput may play a critical role in depressed states and antidepressant treatment (2,17). Taken together, the predominant focus of this research has been on regulating postsynaptic AMPA/NMDA function to develop novel therapeutics.

While the mechanism and functional implications of brain regional differential expressions of VGLUT1 and netrin-Gs to BPD remain to be elucidated, Eastwood and Harrison's findings (1) are an important contribution to research in this area and, ultimately, to the possibility that such presynaptic glutamatergic deficits can be treated, and quality of life improved for the millions of individuals who suffer from these devastating disorders.

References

1. Eastwood SL, Harrison PJ. Markers of glutamate synaptic transmission and plasticity are increased in the anterior cingulate cortex in bipolar disorder. Biol Psychiatry. (in press).
2. Sanacora G, Zarate CA, Krystal JH, Manji HK. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat Rev Drug Discov 2008;7:426–437. [PubMed: 18425072]
3. Kwon SK, Woo J, Kim SY, Kim H, Kim E. Trans-synaptic adhesions between netrin-G ligand-3 (NGL-3) and receptor tyrosine phosphatases lar, PTP{delta}, and PTP{sigma} via specific domains regulate excitatory synapse formation. J Biol Chem.
4. Hashimoto K, Sawa A, Iyo M. Increased levels of glutamate in brains from patients with mood disorders. Biol Psychiatry 2007;62:1310–1316. [PubMed: 17574216]
5. Lan MJ, McLoughlin GA, Griffin JL, Tsang TM, Huang JT, Yuan P, et al. Metabonomic analysis identifies molecular changes associated with the pathophysiology and drug treatment of bipolar disorder. Mol Psychiatry 2009;14:269–279. [PubMed: 18256615]
6. Bendikov I, Nadri C, Amar S, Panizzutti R, De Miranda J, Wolosker H, et al. A CSF and postmortem brain study of D-serine metabolic parameters in schizophrenia. Schizophr Res 2007;90:41–51. [PubMed: 17156977]
7. Ongur D, Jensen JE, Prescot AP, Stork C, Lundy M, Cohen BM, et al. Abnormal glutamatergic neurotransmission and neuronal-glial interactions in acute mania. Biol Psychiatry 2008;64:718–726. [PubMed: 18602089]
8. Dager SR, Friedman SD, Parow A, Demopulos C, Stoll AL, Lyoo IK, et al. Brain metabolic alterations in medication-free patients with bipolar disorder. Arch Gen Psychiatry 2004;61:450–458. [PubMed: 15123489]
9. Frye MA, Watzl J, Banakar S, O'Neill J, Mintz J, Davanzo P, et al. Increased anterior cingulate/medial prefrontal cortical glutamate and creatine in bipolar depression. Neuropsychopharmacology 2007;32:2490–2499. [PubMed: 17429412]
10. Frey BN, Stanley JA, Nery FG, Monkul ES, Nicoletti MA, Chen HH, et al. Abnormal cellular energy and phospholipid metabolism in the left dorsolateral prefrontal cortex of medication-free individuals with bipolar disorder: an in vivo 1H MRS study. Bipolar Disord 2007;1(9 Suppl):119–127. [PubMed: 17543030]
11. Colla M, Schubert F, Bubner M, Heidenreich JO, Bajbouj M, Seifert F, et al. Glutamate as a spectroscopic marker of hippocampal structural plasticity is elevated in long-term euthymic bipolar patients on chronic lithium therapy and correlates inversely with diurnal cortisol. Mol Psychiatry 2009;14:696–704. 647. [PubMed: 18347601]
12. Garcia-Garcia AL, Elizalde N, Matrov D, Harro J, Wojcik SM, Venzala E, et al. Increased vulnerability to depressive-like behavior of mice with decreased expression of VGLUT1. Biol Psychiatry 2009;66:275–282. [PubMed: 19409534]
13. Moutsimilli L, Farley S, Dumas S, El Mestikawy S, Giros B, Tzavara ET. Selective cortical VGLUT1 increase as a marker for antidepressant activity. Neuropharmacology 2005;49:890–900. [PubMed: 16111724]
14. Uezato A, Meador-Woodruff JH, McCullumsmith RE. Vesicular glutamate transporter mRNA expression in the medial temporal lobe in major depressive disorder, bipolar disorder, and schizophrenia. Bipolar Disord 2009;11:711–725. [PubMed: 19839996]
15. Eastwood SL, Harrison PJ. Decreased mRNA expression of netrin-G1 and netrin-G2 in the temporal lobe in schizophrenia and bipolar disorder. Neuropsychopharmacology 2008;33:933–945. [PubMed: 17507910]

16. Du J, Creson TK, Wu LJ, Ren M, Gray NA, Falke C, et al. The role of hippocampal GluR1 and GluR2 receptors in manic-like behavior. J Neurosci 2008;28:68–79. [PubMed: 18171924]

17. Schloesser RJ, Huang J, Klein PS, Manji HK. Cellular plasticity cascades in the pathophysiology and treatment of bipolar disorder. Neuropsychopharmacology 2008;33:110–113. [PubMed: 17912251]