Glutamate Modulation in Mood and Anxiety Disorders: Toward a Rational Pharmacology?

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Despite an explosion in basic neuroscience research in the past decade, there is a significant "pipeline" problem in psychopharmacology: there are few novel and innovative therapies emerging. In many psychiatric disorders, particularly mood and anxiety disorders, reiterations of drugs that block the reuptake of serotonin, norepinephrine, and dopamine have resulted in numerous "me-too" medications. Novel approaches that aim to accelerate speed of onset, enhance efficacy, and are well-tolerated are needed. This issue of CNS Spectrums contains three insightful and scholarly articles that review the functional significance of glutamate for mood and anxiety disorders with an aim toward identifying rational, biologically informed pharmacotherapies that complement existing monoaminergic drugs.

Glutamate is an excitatory amino acid neurotransmitter that mediates fast synaptic neurotransmission in widely distributed circuits throughout the central nervous system. Glutamatergic projections originating from cortical and limbic regions have been found to modulate activity of monoaminergic neurons in neural circuits relevant to emotional expression. As noted by Moghaddam and Wolff, because glutamate mediates fast synaptic neurotransmission, targeting specific glutamate receptors was not considered to be a feasible and safe option for the chronic treatment of psychiatric disorders. However, the characterization of modulatory sites on ionotropic glutamate receptors (ie, N-methyl-D-aspartate [NMDA], α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid, and kainite) and identification of allosteric modulators of G protein-coupled receptors (labeled "metabotropic") has suggested many potential targets for drug development.

Akira Kugaya, MD, PhD, and Gerard Sanacora, MD, PhD, review the complex role of glutamate in mood disorders. They propose a pathophysiological model of abnormal glutamatergic function. Their laboratory at Yale University has been at the forefront of investigation of the role of amino acid neurotransmitters in mood disorders. They have also published a series of papers describing lowered γ-aminobutyric acid (GABA) and elevated cortical glutamate concentrations, as detected by in vivo proton magnetic resonance spectroscopy. Their model hypothesizes that disrupted astrocytic function, observed in post-mortem mood disorder samples, results in decreased uptake of glutamate with a resultant elevation of extracellular glutamate levels. Disruptions in glutamate-glutamine neuronal-glial cycling is also believed to cause decreased glutamate release and decreased cortical GABA content. Moving beyond simplistic hypotheses regarding neurotransmitters being "high" or "low," they proffer a view of dynamic regional amino acid transmitter dysfunction. Studies using carbon-13-magnetic resonance spectroscopy, which can ascertain measures of glial cell metabolism, will offer much improved understanding of biological processes than steady state determinations of glutamate, glutamine, and GABA.

Until relatively recently, glutamate has received little attention in anxiety disorders. Bernadette M. Cortese, PhD, and K. Luan Phan, MD, provide an incisive review of the preclinical and (more limited) clinical literature. They present some of their own neuroimaging data in social phobia. In a sample of patients with generalized social phobia, they found a 13.2% increase in the glutamate/creatine ratio in the anterior cingulate cortex (ACC) compared with a well-matched, healthy control group. The magnitude of ACC glutamate concentrations correlated with the intensity of social anxiety symptoms, lending support for functional relevance of this overactivity. An equally significant contribution to this literature, however, is their finding that glutamate/creatine concentrations, using magnetic resonance spectroscopy, correlated with activation of rostral ACC in response to harsh, aversive faces, using functional magnetic resonance imaging. While the correlational nature of neuroimaging data makes it inherently difficult to distinguish cause from compensatory or epiphenomenal effects, investigations that attempt to relate regional
Introduction

Glutamate concentrations to functional measures of blood flow/metabolism are critical to develop working models of disorder pathophysiology.

In the final article, Charles F. Gillespie, MD, PhD, and Kerry J. Ressler, MD, PhD, present a stellar example of “bench-to-bedside” research. Davis and colleagues first demonstrated that enhancing neurotransmission at NMDA receptors with the partial NMDA agonist D-cycloserine (a drug used for many years for tuberculosis) facilitated fear extinction in rodents. As extinction learning is central to the mechanism of action of cognitive-behavioral therapies for fear disorders, this same drug was tested in humans with height phobias, in conjunction with a virtual reality exposure therapy. Remarkably, after only two doses of medication, patients showed significant reductions in fear to the specific exposure environment, an improvement which persisted 3 months following treatment. The suggestion from these translational studies was that D-cycloserine was not a direct anxiolytic; rather, it enhanced learning, and, thus, extinction. NMDA glutamate receptors mediate learning processes that occur during the acquisition of fear, and thus provide a target for therapies, particularly when coupled with exposure-based psychotherapy.

Novel glutamatergic agents, such as α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor potentiators and metabotropic glutamate receptor agonists, have received the most attention from investigators eager to uncover the next therapeutic breakthrough for mood and anxiety disorders. The D-cycloserine story is a reminder, however, that it is still possible to “teach an old dog new tricks.” One of the important discoveries of this year, reported by Rothstein and colleagues, was that the many beta-lactam antibiotics potently increased brain expression of the glutamate transporter GLT1, thereby decreasing glutamate-mediated excitotoxicity. One drug, ceftriaxone, slowed neurodegeneration in an animal model of amyotrophic lateral sclerosis. Similar to the translational perspective of the D-cycloserine work, clinical trials of ceftriaxone have begun in patients with amyotrophic lateral sclerosis.

Critical challenges ahead include identifying appropriate patient populations for glutamatergic modulation and refining methods of dynamic spectroscopy to make this a clinically useful tool. 

REFERENCES