The Role Of Glutamate In Mood Disorders & Schizophrenia

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Today’s Speakers

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Dr. Murrough is an Associate Professor of Psychiatry and Neuroscience and Director of the Depression and Anxiety Center for Discovery and Treatment at the Icahn School of Medicine at Mount Sinai. He received his medical degree from Tufts University School of Medicine in Boston. Dr. Murrough completed his residency training in psychiatry at Mount Sinai and a research fellowship in experimental therapeutics and clinical neuroscience in mood disorders at Mount Sinai. He obtained a PhD in clinical research methodology and biostatistics from Mount Sinai. Dr. Murrough conducts clinical and translational research aimed at understanding the biological basis of mood and anxiety disorders.

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Dr. Rowland is an Associate Professor in the Maryland Psychiatric Research Center (MPRC), Department of Psychiatry at the University of Maryland, School of Medicine. She is the Director of the Chemical Imaging Core, housed within the Neuroimaging Research Program at the MPRC and the co-director of the MPRC postdoctoral training program. Dr. Rowland received her PhD in experimental psychology (behavioral neuroscience) from the University of New Mexico. Her research focuses on proton magnetic resonance spectroscopy studies of glutamatergic and GABAergic function and bioenergetic alterations in schizophrenia and related disorders.
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Objectives

Provide an overview of glutamate, glutamate receptors, and the glutamatergic system

Review the potential role of glutamate in the pathophysiology of depression and schizophrenia

Discuss potential implications for glutamatergic pharmacotherapy in depression and schizophrenia
Introduction To Glutamate
Glutamate

Glutamate is the most abundant excitatory neurotransmitter. It sits at the crossroads between multiple metabolic pathways (e.g., precursor to GABA) and can be harmful in both excessive or scarce amounts. ≥1 type of glutamate receptor is expressed by most, if not all, cells in the CNS.

CNS, central nervous system  GABA, gamma-aminobutyric acid; Gin, glutamine.
### Overview Of Glutamate Receptors

<table>
<thead>
<tr>
<th>Ionotropic Glutamate Receptors(^1,)(^2)</th>
<th>Metabotropic Glutamate Receptors(^1)</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Ligand-gated ion channels</td>
<td>• Seven transmembrane GPCRs</td>
</tr>
<tr>
<td>• Involved in excitatory neurotransmission</td>
<td>• 12 members encoded by 8 genes</td>
</tr>
<tr>
<td>• Usually postsynaptic</td>
<td>• Modulate intracellular signaling</td>
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<tr>
<td>• Families named for their selective agonists</td>
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**Ionotropic Glutamate Receptors**

- AMPA
- Kainate
- NMDA

**Metabotropic Glutamate Receptors**

- Group I: mGluR1 & 5
- Group II: mGluR2 & 3
- Group III: mGluR4, 6, 7, 8

**AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; Ca, calcium; Glu, glutamate; GPCR, G-protein coupled receptor; K, potassium; mGluR, metabotropic glutamate receptors; Na, sodium; NMDA, N-methyl-D-aspartate.**

The Glutamate Synapse\textsuperscript{1,2}

AMP, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; EAAT, excitatory amino acid transporter; mGluR, metabotropic glutamate receptor; NMDA, N-methyl-D-aspartate.

\textsuperscript{1} Murrough JW et al. Nat Rev Drug Disc. 2017;16:472-486
Measurement Of Glutamate In Vivo: Proton Magnetic Resonance Spectroscopy (\(^1\)H-MRS)

- **Description**
  - Noninvasive imaging method that provides information about cellular activity and endogenous metabolite changes\(^1\)
  - Used in combination with MRI, which provides spatial/anatomical information\(^1\)

- **Use**
  - Has been used to demonstrate changes in concentrations of Glu and Gln in schizophrenia and mood disorders\(^2\)
  - Holds promise for identifying biomarkers that can\(^3\):
    - Serve as treatment targets
    - Predict disease onset
    - Predict illness exacerbation

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Sample \(^1\)H-MRS Spectrum

Potential Benefits\(^2\):
- High signal-to-noise ratio
- No exogenous material infusion required

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Gln, glutamine; Glu, glutamate; MRI, magnetic resonance imaging.
Glutamate In Mood Disorders
Prevailing Theory: The Monoaminergic Hypothesis Of Depression

• The monoaminergic hypothesis of depression posits that the pathophysiologic cause for the disease is a deficiency of monoamine* neurotransmitters\(^1\)
  – Monoamines were first implicated in depression when it was found that patients taking monamine-depleting antihypertensives developed depression\(^2\)
  – A role for monoamines in depression was further supported by the discovery of the first antidepressants, the TCAs and the MAOIs\(^2\)

Pharmacotherapy for Depression
Many antidepressants act on the monoaminergic system\(^2\)

*The monoamine neurotransmitters include dopamine, norepinephrine, and serotonin.

MAOI, monoamine oxidase inhibitor; SNRI, serotonin-norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant.

The Potential Role Of Glutamate In Mood Disorders

Several lines of evidence implicate the glutamate system in mood disorders:

### Indirect evidence
- A loss of glia in the prefrontal cortex of patients with mood disorders has been reported; glia play an important role in regulation of glutamate signaling
- Mood stabilizers used in the treatment of bipolar disorder have been found to modulate glutamatergic neurotransmission and have been suggested to be neuroprotective against glutamate excitotoxicity

### Alterations in glutamate levels
- Comprehensive meta-analyses have identified consistent elevation of glutamate and glutamine in several brain regions in patients with bipolar disorder compared to healthy controls; these findings persisted across bipolar mood states, including euthymia
- Glutamate levels have been shown to be elevated in the plasma, CSF, and brains of people with depression
- MDD is associated with reduced glutamate and glutamine levels in the PFC and elevated glutamate levels in the occipital cortex

### Alterations in genetics/gene expression
- Glutamate-related gene variants have been associated with depression in a small number of studies
- A series of postmortem studies has reported alterations in NMDAR subunit expression in patients with MDD or bipolar disorder and in patients who died by suicide

*Either ECT or ECT + antidepressant medication.

CSF, cerebral spinal fluid; ECT, electroconvulsive therapy; MDD, major depressive disorder; NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor; PFC, prefrontal cortex.

Glutamate In Depression
Complex Mechanisms

Cell growth & neuroprotection

Moderate levels of NMDAR activation promote neuroprotective signaling pathways

Timing

NMDA receptor signaling

Environment

Duration

Location

Excitotoxicity & cell death

Misappropriated NMDAR signaling has deleterious effects, with overactivation contributing to excitotoxicity and synaptic loss

Promote growth & neuroplasticity

Goal of NMDAR modulators

Inhibit negative consequences of overactivation

NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor.
Discussion
Effects Of NMDAR Antagonism On Brain Function In Depression

Caudate Response to Positive Emotional Stimuli

Healthy controls

Patients with TRD

24 hours after treatment with an NMDAR antagonist

Antidepressant response correlated with increases in connectivity of the caudate

PFC Functional Connectivity

Healthy controls

Patients with depression

Connectivity was inversely correlated with symptom severity

24 hours after treatment with an NMDAR antagonist

Connectivity was partially normalized 24 hours after treatment

*Not a quantitative representation of the data.

NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor; PFC, prefrontal cortex; TRD, treatment-resistant depression.

Glutamate In Schizophrenia
Prevailing Theory: The Dopamine Hypothesis Of Schizophrenia

Multiple lines of research support a role for dopamine dysfunction in schizophrenia:

• Compounds that increase extracellular concentrations of dopamine can induce schizophrenia-like “positive” symptoms
• In the 1970s, the clinical effectiveness of antipsychotic drugs was found to be related to their affinity for dopamine receptor binding
• Elevated dopamine synthesis capacity has been consistently detected in patients who had acute psychosis at the time of investigation

However, dopamine dysfunction may not explain all aspects of the illness:

• Dopamine-targeting antipsychotics have only modest effects on the cognitive impairments and negative symptoms of the illness
• Elevated dopamine synthesis capacity is less consistently detected in studies of patients with chronic illness
• Patients with treatment-resistant schizophrenia may have a “non-dopaminergic” subtype of schizophrenia

Current Pharmacotherapy For Schizophrenia

• Dopamine receptor D2 is regarded as the primary target associated with therapeutic antipsychotic effects\(^1\)
  
  • In most patients, clinical response to antipsychotics is strongly correlated with dopamine receptor D2 occupancy\(^2\)

• Antipsychotics have a number of off-target effects, and emerging data indicates a potential clinical benefit for some of these actions\(^1\):

  - Serotonin receptor modulation
  - NMDA receptor modulation
  - Other receptor modulation

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EPS, extrapyramidal side effects; 5-HT, serotonin; NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor.

The Potential Role Of Glutamate In Schizophrenia

Several lines of evidence suggest a role for the glutamate system in schizophrenia:

**Indirect evidence**
- The current prevailing glutamate hypothesis is for the primary involvement of NMDA receptor dysfunction in schizophrenia
  - This hypothesis initially arose from observations that non-competitive NMDA receptor antagonists led to schizophrenia-like symptoms, including both positive and negative symptom domains

**Alterations in glutamate levels**
- A large study found that patients with chronic schizophrenia had an elevated glutamine:glutamate ratio (Gln/Glu) in the anterior cingulate cortex, with a correlation reported between frontal Gln/Glu and positive psychotic symptoms

**Alterations in genetics/gene expression**
- Reduced NMDAR1 subunit density has been observed in the superior frontal cortex and superior temporal cortex in postmortem samples from patients with schizophrenia
- It has been proposed that the abnormality in schizophrenia may be aberrant glutamate receptor localization

NMDA, N-methyl-D-aspartate; NMDAR, NMDA receptor.
Glutamate In Treatment-Resistant Schizophrenia

- ~1/3 of patients with schizophrenia are treatment resistant*
- Patients with TRS show no clinical response to antipsychotics, even when dopamine receptor D2 occupancy is above the therapeutic threshold
- A systematic review of 19 studies that compared treatment-resistant and treatment-responsive patients with schizophrenia suggested:

*Defined by two failed antipsychotic trials. †Some conflicting reports exist in the literature.

ACC, anterior cingulate cortex; TRS, treatment-resistant schizophrenia.

Explaining Schizophrenia: Potential Roles For Both Dopamine & Glutamate

- Glutamate abnormalities may be present only in a subset of patients with the illness and/or only at a particular phase of illness.

- Evidence for presynaptic dopamine dysfunction is compelling and most clearly linked to psychotic symptoms in schizophrenia; evidence for involvement in negative and cognitive symptoms is less clear.

- Glutamate models involving NMDA receptor blockade appear to be better able to account for the negative and cognitive symptoms of schizophrenia.

- A combination of both NMDA hypofunction and presynaptic dopamine dysfunction may, therefore, provide the best explanation of all clinical aspects of schizophrenia.

NMDA, N-methyl-D-aspartate.
Discussion
Questions
Closing

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<tr>
<td>Benefits &amp; Challenges of Smartphone Use in Mental Health</td>
<td>• Steven Stoner, PharmD, BCPP</td>
<td>May 1, 2019</td>
<td>12:00 PM ET</td>
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<td></td>
<td>• Britton Arey, MD, MBA</td>
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