Glutamate: The Emerging Frontier of Psychopharmacology for Schizophrenia and Mood Disorders

(page 245 in syllabus)

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Individual Disclosure Statement

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Speakers Bureau: Dainippon Sumitomo, Forest, Lilly, Merck, Pamlab, Pfizer, Sepracor/Sunovion, Servier, Wyeth
Objectives

- To discuss the pathophysiology of schizophrenia and mood disorders in relation to glutamate
- To show how glutamate pharmacology is linked to new drug development
- To identify relevant compounds in the pipeline and discuss their novel mechanisms of action and potential clinical utility in schizophrenia and mood disorders
Increases dopamine, serotonin, and adrenaline. And that's just sitting still.
Glutamate Pharmacology

- Glutamate receptors
- Glutamate synthesis and metabolism
- Role of cotransmitters glycine and d-serine
Glutamate and glycine are amino acids. They are used:

- For protein synthesis
- As neurotransmitters and cotransmitters

**Glutamate** works as a neurotransmitter at 2 types of glutamate receptors:

1. Ionotropic: Those linked to ion channels (including NMDA and AMPA)
2. Metabotropic: Those linked to second messenger systems

**Glycine** works as:

1. A neurotransmitter at glycine synapses
2. A co-transmitter at the glutamate receptor NMDA
Background:
Glutamate AMPA and NMDA Receptors

AMPA and NMDA are ionotropic glutamate receptors

AMPA
1. Activated when bound by glutamate
2. Activation opens its ion channel
3. This results in neuronal depolarization

NMDA
Requires 3 steps to be activated and to open its ion channel:
1. Neuronal depolarization (AMPA activation) to release its magnesium plug
2. Glutamate binding
3. Glycine binding

This results in long-term potentiation, which is linked to regulation of learning, memory, and dopamine neurotransmission.
Glutamate Receptors

EAAT = Excitatory amino acid transporter
vGlu-T = Vesicular glutamate transporter
NMDA = N-methyl-d-aspartate

Postsynaptic metabotropic receptor
Presynaptic metabotropic receptor
NMDA receptor
AMPA receptor
Kainate receptor
Glutamate Receptors

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Presynaptic metabotropic receptor

Postsynaptic metabotropic receptor

vGlu-T

EAAT

NMDA receptor

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Glutamate Receptors

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Presynaptic metabotropic receptor
Postsynaptic metabotropic receptor
NMDA Receptors: Coincidence Detectors

- **AMPA receptor**
- **NMDA receptor**
  - **glutamate**
  - **Mg++**
  - **glycine**

NMDA Receptors: Coincidence Detectors

AMPA receptor

activated

glutamate

NMDA receptor

Mg++

glycine

NMDA Receptors: Coincidence Detectors

AMPA receptor

glutamate

activated

Na+

Ca++

glycine

Mg++

NMDA receptor

activated

Long-term potentiation

Glutamate Is Recycled and Regenerated

vGly-T = Vesicular glycine transporter
SNAT = Specific neutral amino acid transporter

SNAT
Reversed SNAT
Glial cell
Glutaminase
Glutamate
vGly-T
Glutamine
Glutamine synthetase
EAAT
Glutamate

vGly-T = Vesicular glycine transporter
SNAT = Specific neutral amino acid transporter
Glutamate and Glycine: Cotransmitters at NMDA Receptors

NMDA currents enhanced
Glutamate and Schizophrenia

- NMDA hypofunction hypothesis of schizophrenia
- Neurodevelopmentally abnormal glutamate synapses
- Hypofunctional NMDA receptors
- Overstimulation of downstream glutamate receptors
Cortical Glutamate Regulation: Normal

- Glutamate neuron
- NMDA
- GABA inter-neuron
- GABA
- Glutamate neuron
Cortical Glutamate Regulation: Normal
PCP-Ketamine: Model of Schizophrenia

Ketamine blockade of NMDA receptors
PCP-Ketamine: Model of Schizophrenia

Ketamine blockade of NMDA receptors
Glutamate and the Dopamine Hypothesis of Schizophrenia

• So how does all of this relate to the dopamine hypothesis of schizophrenia?
Mesolimbic Dopamine Pathway

- Overactivation
- Normal
- Baseline
- Hypoactivation
Mesolimbic Dopamine Pathway

Positive symptoms

HIGH

Overactivation
Normal
Baseline
Hypoactivation

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Mesocortical Dopamine Pathway

- Overactivation
- Normal
- Baseline
- Hypoactivation
Mesocortical Dopamine Pathway

Negative symptoms

Cognitive symptoms

Overactivation
Normal
Baseline
Hypoactivation

LOW

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NMDA Glutamate Hypoactivity Leads to Mesolimbic Dopamine Hyperactivity and Positive Symptoms of Schizophrenia
NMDA Glutamate Hypoactivity Leads to Mesolimbic Dopamine Hypoactivity and Negative Symptoms of Schizophrenia


Overactivation
Normal
Baseline
Hypoactivation

Negative symptoms
Novel Glutamatergic Treatments for Schizophrenia: Direct Acting Glycine Site Agonists

Glutamate neuron

Direct acting glycine site agonists
- d-cycloserine
- d-serine
- Glycine

NMDA currents enhanced

Glutamate

10-123
Novel Glutamatergic Treatments for Schizophrenia: Glycine Transporter 1 Inhibitors (e.g., bitropertin RGH1678)

Glutamate neuron

Glutamate

NMDA currents not enhanced
Novel Glutamatergic Treatments for Schizophrenia:
Glycine Transporter 1 Inhibitors (e.g., bitropertin RGH1678)
Novel Glutamatergic Treatments for Positive Symptoms of Schizophrenia: Glycine Transporter 1 Inhibitors (e.g., bitropertin RGH1678)

Positive symptoms

Overactivation
Normal
Baseline
Hypoactivation

Restored NMDA receptor function
Novel Glutamatergic Treatments for Negative Symptoms of Schizophrenia: Glycine Transporter 1 Inhibitors (e.g., bitropertin RGH1678)

Increased NMDA receptor activation

Overactivation
Normal
Baseline
Hypoactivation

Negative symptoms

Glutamate and New Drugs for Schizophrenia

- Reduce overstimulation of downstream glutamate receptors
  - mGluR 2/3 presynaptic agonists
PCP-Ketamine Model of Schizophrenia

Ketamine blockade of NMDA receptors
Presynaptic mGluR 2/3: Autoreceptor Regulating Glutamate Release
Presynaptic mGluR 2/3: Autoreceptor Regulating Glutamate Release

mGluR type II/III presynaptic autoreceptor
Cortical Glutamate Regulation: mGluR 2,3 Agonist LY2140023 Reverses Symptoms of Schizophrenia
mGluR2/3 Agonist: Phase II Clinical Trial

Glutamate and Schizophrenia: Compensate for Downstream Glutamate Release Secondary to Hypofunctional NMDA Systems?

- mGluR2/3 presynaptic agonist LY2140023
- Positive proof of concept in schizophrenia
- Second study failed
- Seizures 3/600
- Third monotherapy trial in progress
- Add-on trial in progress
Glutamate, Mood Disorders, and New Drug Treatments

• Possible glutamate excess in depression
  • Unipolar, treatment resistant, bipolar, and suicidal
  • MRS scans
  • CSF studies

• Improvement by anti-glutamate treatments
  • Opposite pharmacology from schizophrenia?
  • Lamotrigine/riluzole
  • Memantine/amantadine
  • Ketamine
  • NR2B selective antagonists
Possible Sites of Action of Lamotrigine and Riluzole on Glutamate Release

Glutamate neuron

Lamotrigine
Riluzole

Riluzole
Lamotrigine
Ketamine

- NMDA blocker
- Like phencyclidine, induces schizophrenia-like symptoms in normal volunteers and exacerbates them in patients
- Short-term, low-dose IV ketamine does not induce full range of psychotic symptoms in experimental setting
Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor

PCP site (in the ion channel)
Site of Action of Ketamine: Binds to Open Channel at PCP Site to Block NMDA Receptor
PCP-Ketamine: Model of Schizophrenia or Novel Antidepressant?
PCP-Ketamine: Model of Schizophrenia or Novel Antidepressant?
New Approaches to Resistant Depression

Published online 7 August 2006 | Nature | doi:10.1038/news060807-1

Club drug finds use as antidepressant

• Psychedelic ketamine hits the blues surprisingly fast
• Pills popped in a nightclub are potential therapeutics too
• The "club drug" ketamine may be the fastest-acting antidepressant ever tested, researchers report today
• A team based at the U.S. National Institute of Mental Health in Bethesda, Maryland, studied ketamine in 17 people with major depression. All the subjects had failed to respond to treatment with standard antidepressant drugs or more drastic methods, such as electroshock therapy. But 71% felt better the day after taking ketamine, and 35% still felt better a week later. None improved when dosed with a placebo
Antidepressant Effect of Ketamine Within Hours in Patients With Treatment-Resistant Depression

HDRS: Hamilton Depression Rating Scale
Zarate CA Jr et al. Arch Gen Psychiatry 2006;63:856-64.

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Ketamine Rapidly Increases the Density and Function of the Dendritic Spines of Layer V Pyramidal Neurons in the Prefrontal Cortex

The bottom slide shows regeneration of synaptic connections in group receiving ketamine compared to control group (Courtesy of Yale University)
Fast Action of Ketamine

AMP, {alpha}-amino-3-hydroxy-5-methyl-4-isoxazole-propionate; 4E-BP1, eukaryotic initiation factor 4E binding protein 1; ERK, extracellular signal-regulated kinase; GluR1, AMPA receptor subunit 1; mTOR, mammalian target of rapamycin; NMDA, N-methyl-D-aspartate; p70S6K, p70S6 kinase.

In rats, a single dose of ketamine activates the mTOR pathway in the prefrontal cortex, increasing the expression of synaptic proteins and the density of dendritic spines and inducing an antidepressant response within a day.

Forced Swim Test

- Behavioral paradigm in which rats or mice are forced to swim in an environment from which there is no escape (a narrow water-filled cylinder). After an initial period of vigorous activity, during which the rodent attempts to escape, there is a period of relative immobility, with the subject making only minimal efforts to stay afloat.
- Acute antidepressant treatment reduces the time spent immobile.
- The forced swim test is highly predictive of antidepressant activity. It is generally considered the gold standard for screening of putative antidepressants.
The NMDA Receptor Has Subtypes Including NR2A and NR2B
NR2B Selective NMDA Antagonists

- **Taxoprodil**
  - CP101,606
  - Positive proof of concept
  - Pfizer

- **AstraZeneca compound**
  - In Phase II

- **EVT101/103**
  - In Phase II
  - Evotec/Roche

- **Radiprodil**
  - RGH 896
  - Gedeon Richter
  - Phase II

- **MK 0657**
  - Merck/NIMH
  - Phase II
NR2B Selective NMDA Antagonists: Some Key Questions

• Why would a mechanism associated with a human model of schizophrenia cause improvement in depression?

• "Rebooting" the system?

• One dose? Sustaining the effect over time?

• Treatment-resistant depression?

• Consequence of downstream actions: Although this blocks glutamate at one receptor, the release of glutamate results in stimulation of all the other glutamate receptor subtypes

• Which is the desired action?
Summary

• The pathophysiology of schizophrenia and mood disorders is linked to glutamate

• New drugs for schizophrenia target hypothetically hypoactive NMDA receptor functioning

• New drugs for mood disorders target hypothetically overactive glutamate functioning