Glutamate and Psychiatry: Where Are We, and What Does the Future Hold?

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Glutamate, NMDA Receptors, and the Quest for Rapid Antidepressants

The story of ketamine

Evolution of Antidepressants: 1950–1980s

Antidepressants 1990s–2015

Slow Progress in Discovering Novel Drug Targets Beyond Serotonin, Norepinephrine, and Dopamine

What are Key Unmet Needs for Antidepressants?

- Rapid onset of activity
- Prevention of relapse
- Impacts suicide risk
- Low side effect burden
- Addresses underlying pathophysiology
**Glutamate**

- Most common excitatory amino acid neurotransmitter in CNS
- Fundamental to brain bioenergetics and metabolism
- Derived from both neuronal/glial pathways as well as TCA cycle
- Distribution of glutamate in compartments
  - Neurons: 90%–95%
  - Glia: 5%–10%
  - Blood: 0.02%
  - Extracellular space: 0.0008% (1/100,000 of total)

**Tight Physiological Control of Glutamatergic Neurotransmission and Potential Therapeutic Targets**

**Enhancement of Cellular Plasticity May Be Final Common Pathway for Antidepressant Treatments**

**NMDA Antagonists Show Antidepressant-Like Activity in Preclinical Models**

**The Washington Post**

Onetime party drug hailed as miracle for treating severe depression

*By Sara Solovitch February 1, 2016*

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CNS = central nervous system; TCA = tricarboxylic acid.

Mason G. Presented at: 71st Annual Meeting of the Society of Biological Psychiatry; May 12-14, 2016: Atlanta, GA.


Ketamine: History

- Synthesized in 1962 by Calvin Stevens, a Parke-Davis chemist seeking an alternative anesthetic to PCP
- FDA approved for use in humans in 1970
- Indications
  - "...the sole anesthetic agent for diagnostic and surgical procedures that do not require skeletal muscle relaxation."
  - "...the induction of anesthesia prior to the administration of other general anesthetic agents."
  - "...to supplement low-potency agents, such as nitrous oxide."

Ketamine and NMDA Receptor

- Dissociative anesthetic
- Uncompetitive high-affinity NMDA antagonist
- Binds to PCP “angel dust” site within ion channel
- Membrane depolarization relieves Mg block, and with co-agonist binding, Ca2+ and Na+ enters cell
- 4 NR2 subunits

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**Subanesthetic Dose IV Ketamine Rapidly Efficacious in TRD**

Rapid Antidepressant Effects of IV Ketamine Compared to Psychoactive Control

- Ketamine dose = 0.5 mg/kg
- Reduction in MADRS score 24 hours after infusion was the primary outcome measure and was significantly greater for the ketamine group than for the midazolam group (P < .002).
- MADRS = Montgomery-Åsberg Depression Rating Scale
- % improvement from baseline in mean score

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Percent Improvement from Baseline in MADRS Individual Items 24 Hours after Infusion

- Ketamine (n=47)
- Midazolam (n=25)

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Summary of Acute Response Rates in Ketamine Depression Studies

Figure 1. Response Rates Following Acute Treatment With Ketamine in Major Depression

At 1 day

IV Ketamine – Efficacy in TRD

At 1 week

Change in Depression Severity after Intranasal Ketamine or Placebo

Change in Depression Severity Over 1 Week Following Intranasal Ketamine or Placebo

Repeated Ketamine Infusions Eliminates Suicidal Ideation Continuously over a 2-Week Period

Repeated Ketamine Infusions in TRD: Pilot Experience

Change in MADRS Suicide Item

Ketamine may work best for those at highest risk:

Largest differential effects of ketamine over midazolam seen in patients with highest suicidality at baseline

Ketamine = Quick Inventory of Depressive Symptomatology

Caveats

- Dissociative Side Effects
- General Side Effects
- Effects on Hemodynamics
- Abuse Liability

Effects on Positive Psychotic Symptoms

*4 key BPRS items: conceptual disorganization, hallucinatory behavior, suspiciousness, unusual thought content. Scores range from 4 to 28.
BPRS = Brief Psychiatric Rating Scale.

Dissociative Side Effects

- Dissociative properties
  - Things in slow motion
  - Things seem unreal
  - Disconnected from body
  - Sense of body changed

Pooled Analysis of Behavioral and Hemodynamic Effects of IV Ketamine in TRD


Neurocognitive Impact of Ketamine 1 Week following Treatment

Mechanisms of Action: Beyond NMDA Receptors?

Ketamine might work in depression because of activity in non-NMDA receptors

Effects of Prolonged Stress


A glutamate pathway to faster acting antidepressants?
A single dose of ketamine induced rapid activation of mTOR mediated signaling pathways


Signaling Pathways Underlying the Rapid Antidepressant Response to Ketamine


Are the Antidepressant Actions of Ketamine Independent of NMDA Receptor Activity?


Mechanisms: Suicide Attempts and High Suicidal Intent Associated with Increases in Inflammatory Marker Quinolinic Acid


“Kinder and Gentler” Glutamate-Based Approaches?

Survey of recent developments
Candidate Glutamatergic Modulators for Depression

- **Na Channel**
  - Riluzole
  - mGlur2/3 PAMs
  - JNJ-40411513
  - ADX41149
  - MD30336
  - mGlur2/3 NAMs
  - R0446133
  - R04461673

- **GlyT-1 Inhibitors**
  - Saracine
  - Bitopertin

- **mGluR2 PAMs**
  - AZD2066
  - STX-107
  - RO4775633
  - RO576001

- **mGluR2/3 Antagonists**
  - MGS0039
  - LY341495

- **mGluR2/3 NAMs**
  - R04499819
  - R04491533

- **mGluR5 NAMs**
  - AZD2066
  - STX-107
  - RO4917523
  - RG7090

- **EAAT2 Enhancers**
  - Ceftriaxone

- **AMPA Potentiator**
  - ORG-26576

**EAAT = excitatory amino acid transporter; NAMs = negative allosteric modulators; PAMs = positive allosteric modulators.**

**Courtesy of Carlos A. Zarate, MD.**

Investigational NMDA Receptor Antagonists for Major Depressive Disorder (2016)

<table>
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<tr>
<th>Compound</th>
<th>Pharmacology</th>
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<tr>
<td>GLYX-13</td>
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<td>Allergan</td>
<td>IV</td>
<td>Phase 3</td>
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<td>NR2B-selective antagonist</td>
<td>Cerecor</td>
<td>Oral</td>
<td>Phase 2</td>
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<tr>
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<td>Nonselective, noncompetitive</td>
<td>Janssen</td>
<td>Intranasal</td>
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<tr>
<td></td>
<td>Channel blocker</td>
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<tr>
<td>AVP-786</td>
<td>Nonselective uncompetitive</td>
<td>Avanir (Otsuka)</td>
<td>IV</td>
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<tr>
<td></td>
<td>NMDA antagonist (deuterated</td>
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<tr>
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<td>dextromethorphan + quinidine</td>
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**Early Antidepressant Effect of Memantine during Augmentation of Lamotrigine in Bipolar Depression: A Double-Blind, Randomized, Placebo-Controlled Trial**

- Study
- Odds ratio and 95% CI
- Control
- Memantine

- **Riluzole Mechanism of Action**
  - Inhibits glutamate release
  - Increases AMPA trafficking
  - Increases glutamate uptake
  - Regulates Neurotrophic factors

- **Lanicemine in TRD**
  - Lanicemine 100 mg (n = 53)
  - Lanicemine 150 mg (n = 53)
  - Placebo (n = 56)


D-Cycloserine: Enhancement of Extinction Learning

Repurposing an old drug used for treatment of tuberculosis

D-Cycloserine

- Partial agonist of NMDAR glycine site, with antagonist activity at higher doses
- Preclinical models have found that infusion of DCS in specific fear extinction circuits aids in the consolidation of extinction learning
- Since 2004, numerous clinical studies (anxiety disorders, OCD, addictions, schizophrenia, anorexia nervosa), with administration of DCS before exposure/CBT
- Goal: enhance the consolidation of therapeutic learning of CBT


D-Cycloserine (1 g/day) Augmentation in TRD

- Response over Time
- Serum glycine elevations have been associated with SSRI non-response
- Effect size largest in patients with highest serum glycine levels (≥ 300 μM)
- Favorable tolerability
- Previous trial of 250 mg/day was negative; thus, higher doses might be necessary to induce NMDAR antagonist effect


Conclusions

- Glutamate is the main excitatory amino acid neurotransmitter in the CNS
- A major function of its receptors is the modulation of synaptic plasticity, critical for memory, learning, and potentially for antidepressant response
- The initial promise of ketamine for depression has sparked interest in the role of specific glutamate receptors such as NMDA and AMPA
- Recent evidence supports the role of non-NMDA receptor activity in the cascade of events involved in rapid antidepressant activity
Practical Take-Aways

- While ketamine is increasingly administered off-label in specialized clinics, there is a lack of long-term data to guide clinicians beyond the acute phase.

- Given the potential hemodynamic risks of ketamine, monitoring by an ACLS-trained clinician is prudent.

- Glutamate modulators such as memantine and riluzole may have limited or no significant benefit for depression.

- D-cycloserine (high dose) has promising results for TRD, while a low dose may enhance extinction in fear-based disorders.