ScienceDirect®

The neurobiology of depression, ketamine and rapid-acting antidepressants: Is it glutamate inhibition or activation?

Chadi G. Abdallah [a b] 🖂, Gerard Sanacora [a c], Ronald S. Duman [a b c], John H. Krystal [a b c]

Show more ⌄

⋖ Share   🔗 Cite

Get rights and content ↗

Abstract

The discovery of the antidepressant effects of ketamine has opened a breakthrough opportunity to develop a truly novel class of safe, effective, and rapid-acting antidepressants (RAADs). In addition, the rapid and robust biological and behavioral effects of ketamine offered a unique opportunity to utilize the drug as a tool to thoroughly investigate the neurobiology of stress and depression in animals, and to develop sensitive and reproducible biomarkers in humans. The ketamine literature over the past two decades has considerably enriched our understanding of the mechanisms underlying chronic stress, depression, and RAADs. However, considering the complexity of the pharmacokinetics and in vivo pharmacodynamics of ketamine, several questions remain unanswered and, at times, even answered questions continue to be considered controversial or at least not fully understood. The current perspective paper summarizes our understanding of the neurobiology of depression, and the mechanisms of action of ketamine and other RAADs. The review focuses on the role of glutamate neurotransmission – reviewing the history of the "glutamate inhibition" and "glutamate activation" hypotheses, proposing a synaptic connectivity model of chronic stress pathology, and describing the mechanism of action of ketamine. It will also summarize the clinical efficacy findings of putative RAADs, present relevant human biomarker findings, and discuss current challenges and future directions.

Introduction

Serendipity, combined with astute clinical observations, has dominated the path to drug discovery in psychiatry (Klein, 2008). In 1951, the first antipsychotic drug was discovered unexpectedly, as chlorpromazine was being developed for potentiating anesthesia. The first tricyclic antidepressant, imipramine, was synthesized in 1899 and decades later failed as antipsychotic compound (Ban, 2006). Yet, one case report in mid-1950s showing imipramine's antidepressant effect in a female with severe depression has led to further investigation and eventual discovery of the monoaminergic class of antidepressants. Similarly, the first benzodiazepine was lingering on a laboratory shelf for years until it was accidentally discovered during a "spring-cleaning" in 1957 and subsequently demonstrated strong anxiolytic effects (Ban, 2006).

Another unanticipated observation in the 1950s was the report that the anti-tuberculosis d-cycloserine, an *N*-methyl-D-aspartate receptor (NMDAR) modulator, may possess antidepressant properties (Crane, 1959). Yet, this fortuitous observation has gained little to no attention for more than four decades, until it was discovered in the late 1990s that a single subanesthetic dose of the NMDAR antagonist ketamine induces rapid and sustained antidepressant effects in severely depressed patients (Berman et al., 2000). At the time, in the context of accumulating evidence proposing NMDAR modulation as a target for antidepressants, and relating depression to excess glutamate neurotransmission and excitotoxicity, the ketamine findings have generated considerable interest in the field to target glutamate neurotransmission for the development of novel rapid-acting antidepressants (RAADs) (Berman et al., 2000; McEwen, 1999; Skolnick et al., 1996; Zarate et al., 2006). Early attempts have primarily focused on investigating glutamate release inhibitors and NMDAR antagonists, both of which were thought to inhibit glutamate transmission and offset the depression-related excitotoxicity. Unfortunately, the glutamate release inhibition approach has had limited success in human studies over the past 2 decades, with pilot or inconsistent findings of antidepressant properties following sustained treatment and no evidence of RAAD effects (Mathew, Gueorguieva, Brandt, Fava, & Sanacora, 2017; Solmi et al., 2016). Conversely, the NMDAR antagonism approach has shown promise (Abdallah, Averill, & Krystal, 2015; Bobo et al., 2016). Yet, it is becoming increasingly apparent that the NMDAR agents with RAAD properties are putatively exerting their effects through glutamate neurotransmission activation, rather than inhibition (Aleksandrova, Wang, & Phillips, 2017; Murrough, Abdallah, & Mathew, 2017).

In this perspective paper, we will (1) review the history of the "glutamate inhibition" and "glutamate activation" hypotheses, (2) propose a synaptic connectivity model of chronic stress pathology, (3) describe the mechanism of action of ketamine, (4) summarize the clinical efficacy findings of putative RAADs, (5) present relevant human biomarker findings, and (6) discuss current challenges and future directions.

Section snippets

Glutamate inhibition or activation? A historical perspective

Early in the 1990s, a number of NMDAR antagonists have demonstrated antidepressant-like effects in rodents (Trullas & Skolnick, 1990). Follow-up studies have later shown that chronic, but not acute, administration of several traditional antidepressants (i.e., slow-acting antidepressants; SAADs) alter NMDAR binding, leading to the hypothesis that downregulation of NMDAR function

may be a common pathway across antidepressants (Skolnick et al., 1996). During the same period, gray matter structural …

Synaptic model of chronic stress pathology (CSP)

The synaptic CSP model proposes that trauma and repeated stressors lead to wide spread neuronal remodeling consistent with both reduced and increased synaptic connectivity, depending on the brain region. The chronic stress induced reduction in synaptic connectivity has been mostly studied in the prefrontal cortex (PFC) and the hippocampus. Conversely, the CSP-related increases in synaptic connectivity were most commonly shown in the nucleus accumbens (NAc) and certain nuclei within the amygdala. …

Mechanism of action of ketamine and RAADs

The discovery of the robust RAAD effects of ketamine offered a unique opportunity to better understand the neurobiology of depression and to unravel the processes involved in reversing CSP. To date, two ketamine-induced glutamate neurotransmission changes appear to be critical to its RAAD effects: (1) a transient activation of glutamate neurotransmission in the PFC (often referred to as glutamate "surge" or "burst") and (2) a sustained increase in PFC synaptic connectivity (Fig. 2). It is …

Clinical efficacy of RAADs

Following the regimen used in the first study (Berman et al., 2000), clinical trials have mostly administered 0.5 mg/kg intravenous (i.v.) ketamine infused over 40 min [reviewed in (Abdallah, Averill, & Krystal, 2015)]. To date, there is well replicated evidence showing the RAAD effects of a single ketamine infusion in MDD (McGirr et al., 2015). Concerns regarding the efficacy of the treatment blinding were partially addressed using active placebo (Murrough et al., 2013). A major limitation of …

Clinical biomarkers of RAADs

To better understand the neurobiology of depression and RAADs, numerous clinical biomarker studies over the past decade capitalized on the RAAD effects of ketamine, its potent effects on prefrontal glutamate neurotransmission, and its robust neuronal remodeling 24 h post infusion. Here, we will briefly review biomarker studies of relevance to the ketamine induced acute glutamate surge (i.e., during infusion) and sustained neuronal remodeling (i.e., 24 h post treatment).

Several lines of evidence …

Current challenges & future directions

The ketamine findings have generated considerable excitement about the promise of a truly novel class of robust and effective RAADs. This excitement was translated into a sizable investment from academia, the pharmaceutical industry, and funding agencies. Hundreds of papers over the past

decade have investigated the mechanisms of ketamine and/or its potential therapeutic utility. However, while preclinical data have extensively investigated ketamine's targets and putative mechanisms, the …

Conflict of interest statement

CGA has served as a consultant and/or on advisory boards for Genentech and Janssen, and editor of *Chronic Stress* for Sage Publications, Inc. GS reports personal consulting fees from Alkermes, Allergan, Biohaven Pharmaceuticals, Eli Lilly and Co., Genetech, Janssen Pharmaceuticals, Lundbeck Research USA, Merck & Co., Naurex, Navitor Pharmaceuticals, Noven Pharmaceuticals, Teva Pharmaceuticals Industries, Taisho Pharmaceutical Co., Takeda Pharmaceutical Co, Sage Pharmaceuticals Inc., Sevier, …

Recommended articles

References (172)

C.G. Abdallah

What's the Buzz About Hydroxynorketamine? Is It the History, the Story, the Debate, or the Promise?

Biol Psychiatry (2017)

C.G. Abdallah *et al.*

Prefrontal connectivity and glutamate transmission: Relevance to depression pathophysiology and ketamine treatment

Biological Psychiatry: Cognitive Neuroscience and Neuroimaging (2017)

C.G. Abdallah *et al.*

A pilot study of hippocampal volume and N-acetylaspartate (NAA) as response biomarkers in riluzole-treated patients with GAD

European Neuropsychopharmacology (2013)

C.G. Abdallah *et al.*

Prefrontal cortical GABA abnormalities are associated with reduced hippocampal volume in major depressive disorder

European Neuropsychopharmacology (2015)

C.G. Abdallah *et al.*

Neurobiology of posttraumatic stress disorder (PTSD): A path from novel pathophysiology to innovative therapeutics

Neuroscience Letters (2017)

A. Anticevic *et al.*

Global prefrontal and fronto-amygdala dysconnectivity in bipolar I disorder with psychosis history

Biological Psychiatry (2013)

A. Anticevic *et al.*

N-methyl-D-aspartate receptor antagonist effects on prefrontal cortical connectivity better model early than chronic schizophrenia

Biological Psychiatry (2015)

A. Anticevic *et al.*

Global resting-state functional magnetic resonance imaging analysis identifies frontal cortex, striatal, and cerebellar dysconnectivity in obsessive-compulsive disorder

Biological Psychiatry (2014)

L.A. Averill *et al.*

Glutamate dysregulation and glutamatergic therapeutics for PTSD: Evidence from human studies

Neuroscience Letters (2017)

R.M. Berman *et al.*

Antidepressant effects of ketamine in depressed patients

Biological Psychiatry (2000)

∨ | View more references

Cited by (188)

Molecular mechanisms of the rapid-acting and long-lasting antidepressant actions of (R)-ketamine

2020, Biochemical Pharmacology

Show abstract ∨

The Mesolimbic Dopamine System in Chronic Pain and Associated Affective Comorbidities

2020, Biological Psychiatry

Show abstract ∨

Effects of Psilocybin-Assisted Therapy on Major Depressive Disorder: A Randomized Clinical Trial ↗

2021, JAMA Psychiatry

[Single-nucleus transcriptomics of the prefrontal cortex in major depressive disorder implicates oligodendrocyte precursor cells and excitatory neurons ↗](#)

2020, Nature Neuroscience

[Rapid-acting antidepressant ketamine, its metabolites and other candidates: A historical overview and future perspective ↗](#)

2019, Psychiatry and Clinical Neurosciences

[The effects of ketamine on prefrontal glutamate neurotransmission in healthy and depressed subjects ↗](#)

2018, Neuropsychopharmacology

> [View all citing articles on Scopus ↗](#)

View full text

Published by Elsevier Inc.

ELSEVIER

RELX™