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The Neurobiology of Depression, Ketamine and Rapid-Acting Antidepressants: Is it Glutamate Inhibition or Activation?

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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 will summarize our understanding

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Conflict of Interest statement

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of the neurobiology of depression, and the mechanisms of action of ketamine and other RAADs. The review will focus 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.

Keywords

depression; chronic stress; ketamine; rapid-acting antidepressants; glutamate neurotransmission; prefrontal cortex; nucleus accumbens

1. 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.

2. 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, grey matter structural deficits were demonstrated in stress-related disorders in humans (Bremner, et al., 1995; Sheline, Wang, Gado, Csernansky, & Vannier, 1996), and were thought to parallel the dendritic atrophy observed following chronic stress in rodents (McEwen, 1999). Interestingly, inhibiting NMDARs or glutamate release blocked the effects of chronic stress on dendritic atrophy (McEwen, 1999). Together, these early data supported a model in which downregulation of excess glutamate may exert antidepressant effects, and raised the question whether the RAAD effects of ketamine are due to glutamate neurotransmission inhibition by blocking NMDARs.

In contrast to the glutamate inhibition model, it has been previously shown that subanesthetic doses of ketamine transiently activate rather than inhibit glutamate neurotransmission (Moghaddam, Adams, Verma, & Daly, 1997). Moreover, the 1990s also witnessed the rise of the neurotrophic hypothesis of depression (Duman, Heninger, & Nestler, 1997), which associated chronic stress and depression with a deficit in brain derived neurotrophic factor (BDNF) and demonstrated that traditional antidepressants increase brain BDNF expression (Nibuya, Morinobu, & Duman, 1995). Interestingly, acute glutamate neurotransmission activation – rather than inhibition – was initially associated with upregulation of BDNF and other neurotrophics (Gall & Isackson, 1989; Patterson, Grover, Schwartzkroin, & Bothwell, 1992; Zafra, Castren, Thoenen, & Lindholm, 1991). In addition, it was found that glutamate transmission activation, using α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPAR) potentiators, increases brain BDNF and exhibits RAAD properties in rodent models (Lauterborn, Lynch, Vanderklish, Arai, & Gall, 2000; X. Li, et al., 2001). Hence, by early 2000s, convergent evidence strongly supported the role of neuronal plasticity in the pathophysiology of depression and in the mechanisms of antidepressant action (D'Sa & Duman, 2002; Manji, Drevets, & Charney, 2001; McEwen, 2004). In addition, it became evident that targeting glutamate neurotransmission offers a novel approach for discovery of new antidepressants (Javitt, 2004; Krystal, et al., 2002). However, it was not fully clear whether these novel antidepressants should activate and/or

inhibit glutamate neurotransmission, with the latter possibility gaining the most attention considering the evidence available at the time.

3. 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.

In the PFC (Fig. 1), it was shown that prolonged stress precipitates neuronal synaptic hypoconnectivity, as evident by reduced dendritic length and arborization, and by reduction in synaptic density and strengths (Duman & Aghajanian, 2012). Glial cells, which play a critical role in regulating glutamate neurotransmission and preventing excitotoxicity, were also found to be deficient following chronic stress (Sanacora & Banasr, 2013). While the mechanisms underlying the CSP-related hypoconnectivity are not fully known, accumulating evidence implicates glucocorticoid signaling and dysregulation in glutamate neurotransmission (Popoli, Yan, McEwen, & Sanacora, 2012; Sanacora, Treccani, & Popoli, 2012). In particular, trauma- and stress-related dysregulation of glucocorticoid signaling and glutamate release, combined with glial deficit and reduced glutamate uptake, are believed to paradoxically maintain high levels of extracellular glutamate despite the reduction of resting prefrontal synaptic glutamate neurotransmission following chronic stress.

In this model, acute stress precipitates a prefrontal glutamate surge associated with transient (minutes-to-hours) increase in extracellular glutamate (Moghaddam, 1993), but sustained (days-to-weeks) increase in NMDARs, AMPARs, and synaptic strength (Yuen, et al., 2009; Yuen, et al., 2011). In contrast, chronic stress leads to a sustained increase in extracellular glutamate (S. X. Li, et al., 2017), combined with reduced resting prefrontal glutamate transmission (Banasr, et al., 2010), and reduction in NMDARs, AMPARs, and synaptic strength (Yuen, et al., 2012). Here, the distinction between “acute” and “chronic” stress is critical, with the timing (i.e., acute vs. chronic) pertains mostly to the length of the stress response – rather than the duration of the stressor. For example, a single severe traumatic event may induce a chronic sustained threat response. Conversely, repeated escapable and/or predictable mild stressors will result in appropriate adaptation with only acute transient stress responses.

In the NAc, a number of chronic stress paradigms were found to increase synaptic connectivity, as evident by increased dendritic length and arborization, as well as increased synaptic density and strength (Campioni, Xu, & McGehee, 2009; Christoffel, et al., 2011; Christoffel, et al., 2012; Coplan, et al., 2018; Muhammad, Carroll, & Kolb, 2012; Warren, et al., 2014). While the prefrontal hypoconnectivity was associated with glutamate dysregulation and excitotoxicity, the stress-induced NAc synaptic hyperconnectivity is related to monoamine dysregulation. In particular, chronic stress leads to phasic activation of the dopaminergic neurons from the ventral tegmental area (Chaudhury, et al., 2013), which

precipitates the co-release of dopamine and BDNF in the NAc (Walsh, et al., 2014). Subsequently, the BDNF upregulation and the induction of its high affinity receptor TrkB lead to the CSP-related NAc neuronal hypertrophy (Wook Koo, et al., 2016).

In preclinical studies, depressive-like behaviors were directly associated with these synaptic alterations in the PFC and NAc (Duman, Aghajanian, Sanacora, & Krystal, 2016; Krishnan & Nestler, 2008; Russo & Nestler, 2013). Reversal of the synaptic impairment induces antidepressant effects. Moreover, both SAADs and RAADs are known to increase PFC, but reduce NAc, synaptic connectivity (Hare, Ghosal, & Duman, 2017; Melo, et al., 2015; Yao, Skiteva, Zhang, Svenningsson, & Chergui, 2017). Notably, the CSP-related microstructural synaptic alterations are evident at the macrostructural level as assessed by magnetic resonance imaging (MRI) (Kassem, et al., 2013). Thus, providing support for the synaptic CSP model, human MRI studies have shown increased NAc, but reduced hippocampal and PFC volumes in major depression (C. G. Abdallah, A. Jackowski, et al., 2017; Kempton, et al., 2011). Here, it is important to highlight that the PFC and hippocampal gray matter deficits were absent in several human depression studies. These gray matter deficits are most evident in patients with amino acid neurotransmitters (i.e., glutamate & GABA) reduction and in individuals who are treatment resistant to SAADs, which are primarily monoaminergic drugs [reviewed in (C. G. Abdallah, A. Jackowski, et al., 2017; Abdallah, Jackowski, et al., 2015)]. Therefore, it was proposed that the synaptic PFC/hippocampus hypoconnectivity and NAc hyperconnectivity reflect two pathways that may independently precipitate clinical depression (C. G. Abdallah, A. Jackowski, et al., 2017). In this Dual Pathology model, patients with underlying amino acid-based pathology (ABP), leading to excitotoxicity and synaptic loss, would show PFC/hippocampus gray matter deficit, present with amino acid impairment, and be treatment resistant to monoaminergic antidepressants. Conversely, patients with monoamine-based pathology (MBP), leading to localized increase in BDNF and synaptic gain, would show NAc gray matter hypertrophy, lack of amino acid impairment, and effectively respond to monoaminergic antidepressants (C. G. Abdallah, A. Jackowski, et al., 2017).

Finally, although the synaptic CSP model has been typically studied and interpreted within the context of major depression, CSP appears to be a common pathway across numerous psychiatric disorders (Adams, et al., 2018; Daskalakis & Binder, 2015; Goddard, 2017; Kwako & Koob, 2017; L. Y. Maeng & Milad, 2017; Patriquin & Mathew, 2017; Prescot, et al., 2018). Hence, the evidence of synaptic loss and dysconnectivity is not limited to major depression, but rather common to several stress-related disorders – e.g., posttraumatic stress disorder (PTSD), generalized anxiety disorder (GAD), obsessive compulsive disorder (OCD), and bipolar depression (Abdallah, et al., 2013; C. G. Abdallah, K. M. Wrocklage, et al., 2017; Akiki, et al., 2017; Anticevic, et al., 2013; Anticevic, et al., 2014; Averill, Abdallah, et al., 2017; Haukvik, et al., 2015; Kwon, et al., 2003; Pietrzak, et al., 2015; Wrocklage, et al., 2017). In addition, antidepressants – known to reverse the CSP in animals – have shown efficacy in alleviating symptoms of PTSD, GAD, OCD, bipolar depression, and other disorders with a considerable chronic stress component. Here, we note that synaptic dysconnectivity could be a predisposing factor, an outcome, or a perpetuator of the psychopathology (Averill, Purohit, et al., 2017; Matosin, Cruceanu, & Binder, 2017; Sheth, McGlade, & Yurgelun-Todd, 2017; Syed & Nemeroff, 2017). Furthermore, while synaptic

loss appears to be common across stress-related disorders, the location and pattern of the synaptic dysconnectivity, combined with individual characteristics (e.g., genes & environment), may be the mechanism through which CSP is associated with distinct clinical presentations and psychopathologies (Abdallah, Southwick, & Krystal, 2017; Averill, Purohit, et al., 2017; Krystal, et al., 2017). Together, the presented synaptic model proposes that CSP is common across many psychiatric disorders and that targeting synaptic connectivity may be a convergent pathway across antidepressants.

4. 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 believed that acute administration of subanesthetic doses of ketamine induces a transient surge in prefrontal glutamate neurotransmission, which in turn induces a number of intracellular processes ultimately leading to sustained increase in prefrontal synaptic connectivity within 24h of treatment (Abdallah, et al., 2016; Duman, et al., 2016).

Transient PFC glutamate neurotransmission activation leads to activity-dependent release of BNDF, activates the mechanistic target of rapamycin complex 1 (mTORC1) signaling, and increases protein synthesis and synaptic strength (Lepack, Bang, Lee, Dwyer, & Duman, 2016; Lepack, Fuchikami, Dwyer, Banasr, & Duman, 2015; Liu, et al., 2012). The preclinical evidence of ketamine-induced glutamate release has long been demonstrated using microdialysis (Moghaddam, et al., 1997) and, more recently, evidence of transient glutamate transmission activation was demonstrated using *ex vivo* carbon-13 magnetic resonance spectroscopy (^{13}C MRS) (Chowdhury, et al., 2012; Chowdhury, et al., 2016; Rothman, De Feyter, de Graaf, Mason, & Behar, 2011). Here, it is important to distinguish between presynaptic glutamate release and postsynaptic activation. The latter – i.e., postsynaptic glutamate activation – is required for the induction of BDNF and its high affinity receptor TrkB, the increase in synaptic strength, and the RAAD effects. Hence, mechanisms independent of evoked presynaptic release of glutamate have been proposed for ketamine (Autry, et al., 2011; Miller, Moran, & Hall, 2016) and agents directly targeting postsynaptic glutamate activation may possess RAAD properties (e.g., AMPAR potentiators or NMDAR partial agonists; Fig. 2).

The role of the transient postsynaptic glutamate activation in the RAAD effects of ketamine has been abundantly shown in preclinical studies. First line of evidence stems from a consistent observation that the inhibition of postsynaptic glutamate activation – using AMPAR antagonists – blocks the synaptic remodeling and the RAAD effects of ketamine (N. Li, et al., 2010; S. Maeng, et al., 2008). Here, we note that even selective AMPAR antagonists will presumably block overall postsynaptic glutamate activation through inhibition of both AMPAR and NMDAR, considering that AMPAR activation leading to membrane depolarization is required for NMDAR signaling. In this context, most of the

evidence relating AMPAR blockade to the inhibition of RAADs would be considered an indication of the need for postsynaptic glutamate activation rather than specific AMPAR activation. For example, NMDAR potentiators – without AMPAR modulating properties – may possess RAAD effects by inducing transient postsynaptic glutamate activity (e.g., NMDAR partial agonists). Furthermore, the RAAD effects of these NMDAR potentiators will still be blocked by pretreatment with AMPAR antagonists, because the latter also inhibits NMDAR signaling. Another line of evidence underscoring the role of transient glutamate activation is that postsynaptic depolarization and activation of L-type voltage-dependent calcium channels (VDCC) are necessary for the synaptic changes and the RAAD effects of ketamine (Jourdi, et al., 2009; Lepack, et al., 2015) and other RAADs (Ghosal, et al., 2018).

While the mechanisms through which ketamine induces a transient postsynaptic glutamate activation are not fully known, a leading hypothesis is that subanesthetic doses of ketamine preferentially inhibits NMDARs on a subpopulation of interneurons precipitating pyramidal neurons disinhibition and paradoxical surge in glutamate release (Homayoun & Moghaddam, 2007). However, alternative hypotheses have also been proposed. One study hypothesized that blockade of at rest NMDAR signaling – i.e., without evoked glutamate release – would be sufficient to increase eukaryotic elongation factor 2 (eEF2) signaling and BDNF translation, leading to increased protein synthesis and synaptic connectivity (Autry, et al., 2011). Yet, using AMPAR modulation, the same study has also demonstrated that postsynaptic glutamate activation is necessary for the RAAD effects of ketamine (Autry, et al., 2011). A main metabolite of ketamine is (2S,6S;2R,6R)-hydroxynorketamine (HNK). Following injection, ketamine rapidly reaches the brain within 1 minute and it maintains a brain/plasma concentration ratio equal 6.5 for 10 minutes (Cohen, Chan, Way, & Trevor, 1973). In rodents, the plasma concentrations of ketamine and norketamine, both potent NMDAR antagonists, peak at 10 minutes post-injection and decrease exponentially thereafter, while the HNK concentration peaks at 30 minutes (Can, et al., 2016; Moaddel, et al., 2015; Paul, et al., 2014). Recently, it was found that HNK possesses RAAD properties without blockade of NMDARs (Zanos, et al., 2016). However, the same study has also demonstrated that postsynaptic glutamate activation is necessary for the RAAD effects of ketamine (Zanos, et al., 2016), and preliminary evidence has since shown that (2R,6R)-HNK also induces a glutamate release surge (Pham, et al., 2017; Schwarcz, Wu, Zanos, & Gould, 2017). Together, the data highlights the ability of ketamine to induce a surge in glutamate transmission and that the transient postsynaptic activation is responsible for its RAAD effects (Fig. 2).

The role of transient postsynaptic glutamate activation is not limited to the neurobiology of ketamine. In fact, the mechanisms of several other RAADs have been related to transient glutamate activation. Scopolamine, a muscarinic cholinergic receptor (M-AChR) antagonist, was shown to increase glutamate release and postsynaptic activation, leading to increased PFC BDNF and synaptic connectivity, and to RAAD effects. The molecular and behavioral effects of scopolamine are blocked by inhibiting postsynaptic glutamate activation (Chowdhury, et al., 2016; Ghosal, et al., 2018; Voleti, et al., 2013; Wohleb, et al., 2016). Similarly, rapastinel (also known as GLYX-13) – a drug with presumable NMDAR partial agonist properties – was shown to increase PFC BDNF and synaptic connectivity, and to

exert RAAD effects, all of which were dependent on postsynaptic glutamate activation as evident by manipulation of AMPAR and VDCC (Lepack, et al., 2016; Liu, et al., 2017). The transient glutamate activation was also related to many other putative RAADs, including the selective NMDAR subtype 2B (GluN2B) antagonists Ro 25-6981 and traxoprodil (also known as CP-101,606), the mGluR2/3 antagonist LY341495, and the AMPAR potentiator LY392098 [*Positive allosteric modulators (PAM) or ampakines*] (Chowdhury, et al., 2016; Karasawa, Shimazaki, Kawashima, & Chaki, 2005; X. Li, et al., 2001; Tang, et al., 2018). Here, it is important to note that the reviewed literature is specific to transient glutamate effects, and may not necessarily translate to the effects of sustained increase in glutamate activation. Indeed, comparable to CSP, it is a concern that frequent daily administration of ketamine or chronic activation of glutamate may lead to excitotoxicity and synaptic dysconnectivity. Consistent with this concern, extensive preclinical literature relates repeated ketamine administration to neurotoxicity and behavioral abnormalities [e.g., (Schobel, et al., 2013)]. Similarly, the substance abuse literature of daily use of ketamine underscores its detrimental effects on cognition and mood (Morgan, Curran, & Independent Scientific Committee on, 2012). Future studies should investigate whether infrequent glutamate activation, such as twice per week administration of ketamine, would provide optimal balance for maintaining the beneficial synaptic connectivity changes.

While there is evidence to support the SAAD properties of glutamate release inhibitors [e.g., lamotrigine (Solmi, et al., 2016)], these medications do not typically induce RAAD effects. Moreover, the ultimate effects of the chronic administration of these glutamate modulators may still be increasing glutamate neurotransmission and BDNF, and subsequent normalization of synaptic connectivity. For example, chronic treatment with the glutamate release inhibitor lamotrigine was shown to reverse the pathology of chronic stress and to increase prefrontal and hippocampal BDNF (N. Li, et al., 2011). In addition, chronic riluzole treatment – an agent believed to inhibit the calcium-dependent glutamate release and increase astrocytic glutamate re-uptake – was shown to reverse CSP and increase overall PFC glutamate neurotransmission activation, rather than decreasing it (Banasr, et al., 2010; Chowdhury, et al., 2008). Finally, in contrast to synaptic NMDARs where activation would lead to increased synaptic formation and strength (i.e., synaptogenesis), the activation of extrasynaptic NMDARs is thought to promote synaptic death (Hardingham & Bading, 2010). Extrasynaptic NMDARs are activated by excessive extracellular levels of glutamate, which causes overstimulation of NMDARs. This leads to an increased calcium influx, activates toxic metabolic processes and triggers cell death (Deutschenbaur, et al., 2016; Paoletti, Bellone, & Zhou, 2013). Therefore, selective blockade of extrasynaptic NMDARs may induce synaptogenesis and exert antidepressant effects. A recent study has shown that targeting the extrasynaptic NMDARs would exert RAAD effects in rodents (S. X. Li, et al., 2017). Another study has shown that ketamine blockade of the lateral habenula bursting activities precipitates RAAD effects (Yang, et al., 2018). However, a major limitation of these studies is that the behavioral effects were tested immediately after ketamine administration, rather than 24h later to confirm the presence of RAAD effects in the absence of ketamine intoxication (S. X. Li, et al., 2017; Yang, et al., 2018). Additionally, the selective NMDAR modulation approaches used may have inadvertently induced a paradoxical glutamate surge in the PFC, similar to the *in vivo* effects of ketamine and many

other NMDAR modulators. Future studies would be necessary to demonstrate the RAAD effects at 24h post administration, and to determine whether selective blockade of extrasynaptic NMDAR signaling is sufficient to exert RAAD effects without the need for postsynaptic glutamate neurotransmission activation.

5. 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 minutes [reviewed in (Abdallah, Averill, et al., 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 the single infusion treatment is that patients often relapse within 1–2 weeks. However, repeated administration of ketamine (e.g., twice per week) appears to maintain the RAAD effects (Singh, Fedgchin, Daly, De Boer, et al., 2016). While the need for intravenous administration could be a limiting factor, pilot evidence suggests that intranasal (i.n.) administration of ketamine may exert RAAD effects (Canuso, et al., 2018; Daly, et al., 2017; Lapidus, et al., 2014). The psychotomimetic effects of ketamine could be considered a limitation, although these adverse events are transient (1–2h) and typically well tolerated. The main remaining limitations of ketamine treatment are its addiction liability and the scarcity of data regarding the safety of chronic treatment (Kokkinou, Ashok, & Howes, 2018; Sanacora, Frye, et al., 2017). The latter is particularly important considering the association of heavy daily use of ketamine with ulcerative cystitis, hepatotoxicity, and neurotoxicity (Cottrell, et al., 2008; Morgan, et al., 2012; Noppers, et al., 2011; Shahani, Streutker, Dickson, & Stewart, 2007).

Other putative RAADs with published clinical trials in MDD include: (1) Scopolamine (3 i.v. infusions separated by 3–4 days) has shown efficacy compared to placebo in small clinical trials (Drevets, Zarate, & Furey, 2013); (2) Traxoprodil showed efficacy at day 5 following single infusion in a proof of concept study (S. H. Preskorn, et al., 2008), yet its development was stopped due to incidence of QT prolongation (Machado-Vieira, Henter, & Zarate, 2017); (3) Esketamine, the S enantiomer of ketamine, appears to have RAAD properties following i.v. or i.n. administration in early studies (Canuso, et al., 2018; Daly, et al., 2017; Singh, Fedgchin, Daly, Xi, et al., 2016); (4) Low doses of d-cycloserine, with NMDAR partial agonist effects, were reported to exert RAAD effects in retrospective investigations (Kim, Kushner, Yoon, Anker, & Grant, 2016); (5) Rapastinel (i.v.) has shown efficacy in a proof of concept study (S. Preskorn, et al., 2015); (6) Lanicemine, a low-trapping NMDAR antagonist, has shown efficacy in one phase II study but failed in a second larger clinical trial that may have been complicated by high placebo response rates (Sanacora, Johnson, et al., 2017; Sanacora, et al., 2013; Zarate, et al., 2013). Together, these clinical trials provide a clear evidence on the prospect of RAADs. However, additional confirmatory clinical trials are still needed to determine the efficacy of these putative RAADs.

As described earlier, the synaptic CSP model would predict that ketamine may have therapeutic effects in many psychiatric disorders with considerable chronic stress

component. In fact, pilot trials to date support this hypothesis. Accumulating evidence suggests that ketamine may have independent rapid anti-suicidal effects in depressed patients (Canuso, et al., 2018; Grunebaum, et al., 2017; Wilkinson, et al., 2018). Moreover, pilot evidence suggests potential therapeutic effects of ketamine in treating bipolar depression, PTSD, OCD, GAD, social anxiety disorder (SAD), and substance/alcohol use disorders [(Albott, et al., 2018; Diazgranados, et al., 2010; Feder, et al., 2014; Glue, et al., 2017; Ivan Ezquerra-Romano, Lawn, Krupitsky, & Morgan, 2018; Rodriguez, et al., 2013; Taylor, et al., 2018; Zarate, et al., 2012), but also see (Bloch, et al., 2012)]

6. 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 24h 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., 24h post treatment).

Several lines of evidence have supported the presence of a ketamine induced prefrontal glutamate surge in humans and have associated this surge with the psychotomimetic effects of the drug. Early studies have shown that glutamate release inhibitors would reduce the psychotomimetic effects of ketamine. Later neuroimaging studies have either shown ketamine induced increases in PFC glucose metabolism or blood flow, PFC blood oxygen level dependent (BOLD) signal, or PFC total glutamate level (Anand, et al., 2000; Breier, Malhotra, Pinals, Weisenfeld, & Pickar, 1997; Deakin, et al., 2008; Javitt, et al., 2017; Krystal, et al., 2005; Krystal, et al., 2010; Milak, et al., 2016; Rowland, et al., 2005; Stone, et al., 2012; Vollenweider, Leenders, Oye, Hell, & Angst, 1997; Vollenweider, Leenders, Scharfetter, et al., 1997). While collectively these studies provide convincing evidence of an acute glutamate surge, most of these studies were in healthy subjects which limits their ability to associate this surge to the RAAD effects. Another main limitation is that these approaches do not distinguish between presynaptic glutamate release and postsynaptic activation. As reviewed earlier, the postsynaptic glutamate activation appears to be the critical process for the RAAD effects. Moreover, recent data using *ex vivo* (in rats) and *in vivo* (in humans) ^{13}C MRS suggests that the psychotomimetic effects of ketamine may be due to the decoupling between presynaptic glutamate release and postsynaptic activation (i.e., disruption in communication fidelity across synapses), as evident by increased glutamate cycling combined with inefficient increase in neuroenergetics that are primarily due to postsynaptic activation (i.e., reduction of energy per cycle) [(Chowdhury, et al., 2016) & (Abdallah et al. under review)]. If these pilot data were confirmed in future human studies, it will offer a mechanism through which novel drugs may induce RAAD effects without psychotomimetic symptoms, provided that these new agents equally increase presynaptic release and postsynaptic activation.

Further supporting the presence of ketamine induced glutamate surge, recent studies have shown alterations in the binding of metabotropic glutamate receptors subtype 5 (mGluR5) during infusion of ketamine in healthy and depressed subjects (Davis, Holmes, Pietrzak, &

Esterlis, 2017; DeLorenzo, et al., 2015; Esterlis, et al., 2017). Yet, perhaps the most studied approach has been the use of resting state functional MRI. In particular, PFC global brain connectivity (GBC) reduction has been observed in several psychiatric disorders with a strong chronic stress component (Anticevic, et al., 2013; Anticevic, et al., 2015; Anticevic, et al., 2014; Cole, Anticevic, Repovs, & Barch, 2011). This observation has led to the hypothesis that GBC may reflect an underlying CSP of reduced PFC synaptic connectivity. Supporting this hypothesis, several studies have demonstrated reduced PFC global connectivity in MDD (C. G. Abdallah, C. L. Averill, et al., 2017; C. G. Abdallah, L. A. Averill, et al., 2017; Murrough, et al., 2016; Scheinost, et al., 2017; Wang, et al., 2014). In addition, human mechanistic studies have provided evidence directly linking glutamate neurotransmission to PFC GBC (C. G. Abdallah, C. L. Averill, et al., 2017). Moreover, subanesthetic doses of ketamine have been shown to increase PFC GBC during infusion in healthy individuals, which parallel the hypothesized glutamate surge (C. G. Abdallah, C. L. Averill, et al., 2017; Anticevic, et al., 2015; Driesen, McCarthy, Bhagwagar, Bloch, Calhoun, D'Souza, Gueorguieva, He, Ramachandran, et al., 2013; Driesen, McCarthy, Bhagwagar, Bloch, Calhoun, D'Souza, Gueorguieva, He, Leung, et al., 2013). Consistent with the role of PFC synaptic connectivity in the mechanisms of RAADs, ketamine was found to rapidly normalize PFC GBC abnormalities in MDD patients within 24h of treatment. These PFC GBC increases were also associated with treatment response (C. G. Abdallah, L. A. Averill, et al., 2017). More recently, in a randomize placebo controlled design, it was shown that ketamine increases PFC GBC in MDD during infusion and at 24h post-treatment. In addition, the amount of PFC GBC increases during ketamine infusion predicted treatment response at 24h post-treatment (C.G. Abdallah, et al., 2017). Finally, similar to the preclinical data of ketamine induced increases in hippocampal synaptic connectivity along with reduction in NAc synaptic connectivity (Melo, et al., 2015; Reus, et al., 2013; Yao, et al., 2017), recent pilot human evidence using structural MRI have shown that ketamine significantly increases hippocampal and reduces NAc volumes in MDD patients within 24h of treatment, particularly in individuals who responded to treatment (C. G. Abdallah, A. Jackowski, et al., 2017).

7. 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 clinical mechanistic evidence remains lagging.

In particular, to date, we do not have a well-established reproducible biomarker of target engagement (i.e., transient postsynaptic glutamate activation) or target validation (i.e., sustained synaptic remodeling) for the development of RAADs. This issue may have been less problematic for the development of monoaminergic drugs. Following the identification of the *in vitro* pharmacodynamics of tricyclic antidepressants, the field over the next half a century successfully produced several SAADs, which primarily shared the common *in vitro*

detectable pharmacodynamics of serotonin re-uptake inhibition (SRI). In addition, SRI largely has (1) linear dose response, (2) broad therapeutic window, and (3) relatively stable *in vivo* pharmacodynamics across administration regimens. In contrast, the development of RAADs has proven more complex; at least two NMDAR antagonists (memantine & CERC-301) and two ampakines (S47445 & ORG 26576) failed in clinical trials and other similar agents have shown promise only in preclinical studies or proof of concept trials. Several challenges may have contributed to the complexity of developing RAADs: (1) While it is evident that blocking NMDAR may induce RAAD effects, only focusing on the *in vitro* NMDAR antagonism properties appears to have low predictability for the development of new RAADs. (2) Determining the *in vivo* effects of novel RAAD agents on transient glutamate neurotransmission and sustained synaptic connectivity is critical. However, at this stage, this is only possible in animal studies. The presence of an inverted U-shaped relationship between dose and response further complicates the translatability of preclinical findings. Together, these challenges underscore the need for robust and reproducible biomarkers of prefrontal glutamate activation and synaptic connectivity in humans *in vivo*. The successful development of these biomarkers would be essential to optimize administration regimens of new RAAD compounds prior to testing them in large expensive trials. Capitalizing on the extensive preclinical and clinical ketamine data, and the swiftness and robustness of its synaptic remodeling and behavioral (psychotomimetic and antidepressant) effects, future studies have a unique opportunity to use ketamine as a tool to establish these synaptic biomarkers that are not only relevant to depression, but also to normal brain function and most neuropsychiatric disorders.

Another opportunity for future studies is that both the chronic stress related synaptic hypoconnectivity and the ketamine induced synaptic hyperconnectivity are reversible within 2 weeks of the intervention, raising mechanistic questions about this individualized homeostatic stable equilibrium of overall synaptic strength. Future studies can capitalize on this notable reversibility to determine the mechanisms underlying this putative homeostatic stable equilibrium of synaptic strength within the context of chronic stress and ketamine treatment. Successful unraveling of these mechanisms may provide information that goes beyond the progress and treatment of depression, and begins to examine the etiology and perhaps cure of depression.

In summary, elegant ketamine studies over the past decade have significantly improved our understanding of the pathophysiology of chronic stress and depression, while unraveling several mechanisms through which transient prefrontal glutamate activation produces rapid restoration of synaptic connectivity along with RAAD effects. Although there is evidence associating glutamate inhibition with antidepressant properties, these data have been primarily limited to SAAD effects. So, is it glutamate inhibition or activation? Within the PFC, chronic stress and depression seem to be associated with high extrasynaptic glutamate level, but overall reduced glutamate neurotransmission as evident by reduction in synaptic connectivity, glutamate cycling, and neuroenergetics. As for the neurobiology of ketamine and other RAADs, it is increasingly evident that transient PFC glutamate postsynaptic activation is a primary underlying mechanism. Yet, it remains to be seen in future studies whether selective inhibition of extrasynaptic NMDARs would be sufficient to induce sustained synaptic remodeling and robust RAAD effects.

Abbreviations

^{13}C MRS	carbon-13 magnetic resonance spectroscopy
ABP	aminoacid-based pathology
AMPAR	α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor
BDNF	brain derived neurotrophic factor
BOLD	blood oxygen level dependent
CSP	chronic stress pathology
GAD	generalized anxiety disorder
GBC	global brain connectivity
GluR2B	N-methyl-D-aspartate receptor subtype 2B
HNK	hydroxynorketamine
i.n.	intranasal
i.v.	intravenous
M-AChR	muscarinic cholinergic receptor
MBP	monoamine-based pathology
mGluR5	metabotropic glutamate receptor subtype 5
MRI	magnetic resonance imaging
mTROC1	mechanistic target of rapamycin complex 1
NAc	nucleus accumbens
NMDAR	N-methyl-D-aspartate receptor
OCD	obsessive compulsive disorder
PFC	prefrontal cortex
PTSD	posttraumatic stress disorder
RAAD	rapid-acting antidepressant
SAAD	slow-acting antidepressant
SAD	social anxiety disorder
SRI	serotonin re-uptake inhibition
VDCC	L-type voltage-dependent calcium channels

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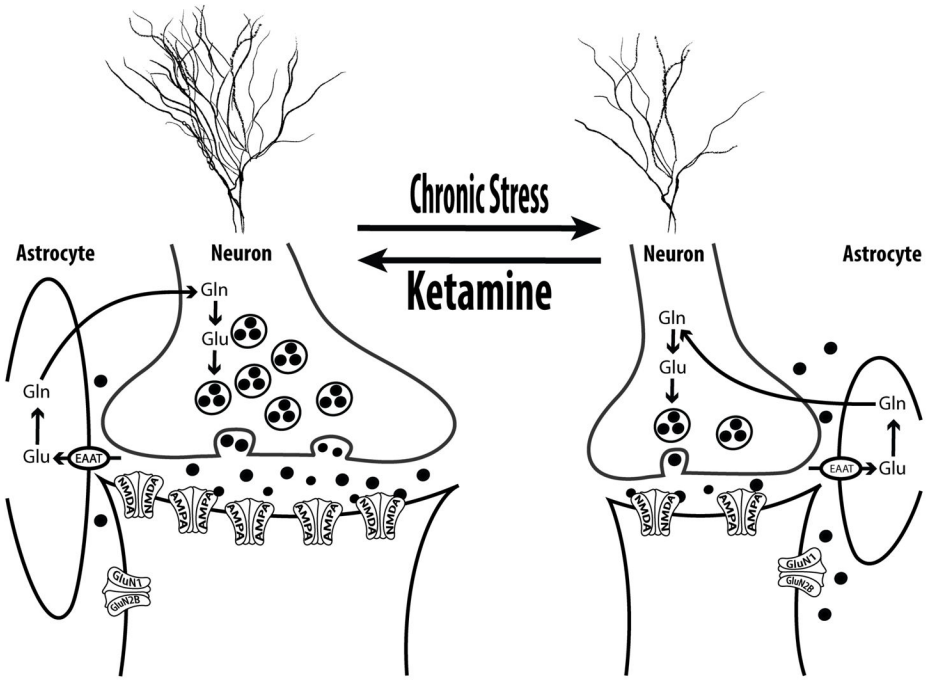

Figure 1. Chronic Stress Pathology (CSP) in the Prefrontal Cortex (PFC)

The synaptic CSP model proposes that synaptic dysconnectivity may be a common pathological pathway across psychiatric disorders with chronic stress component – as a predisposition, a trigger, or an outcome. In the PFC, chronic stress is believed to induce glial deficit, leading to reduced glutamate reuptake capacity and increased extrasynaptic glutamate levels and excitotoxicity. Subsequently, neuronal atrophy develops, resulting in overall reduction in glutamate neurotransmission, which reflects reduced dendritic length and branching, and reduction of spines and synapses density. In the remaining PFC synapses, the neurotransmission strength is also affected by reduced postsynaptic glutamate N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor (AMPA) receptors. Ketamine reverses this PFC CSP within 24h of injection. It is thought that ketamine induces a transient (minutes-to-hours) postsynaptic glutamate activation, which leads to upregulation of neurotrophic signaling, increased protein synthesis, and sustained (days-to-weeks) restoration of synaptic connectivity. Abbreviations: EAAT = excitatory aminoacid transporter; Gln = glutamine; GluN1 = NMDA subtype 1; GluN2B = NMDA subtype 2B; Glu = glutamate. The figure was adapted with permission from the Emerge Research Program (emerge.care).

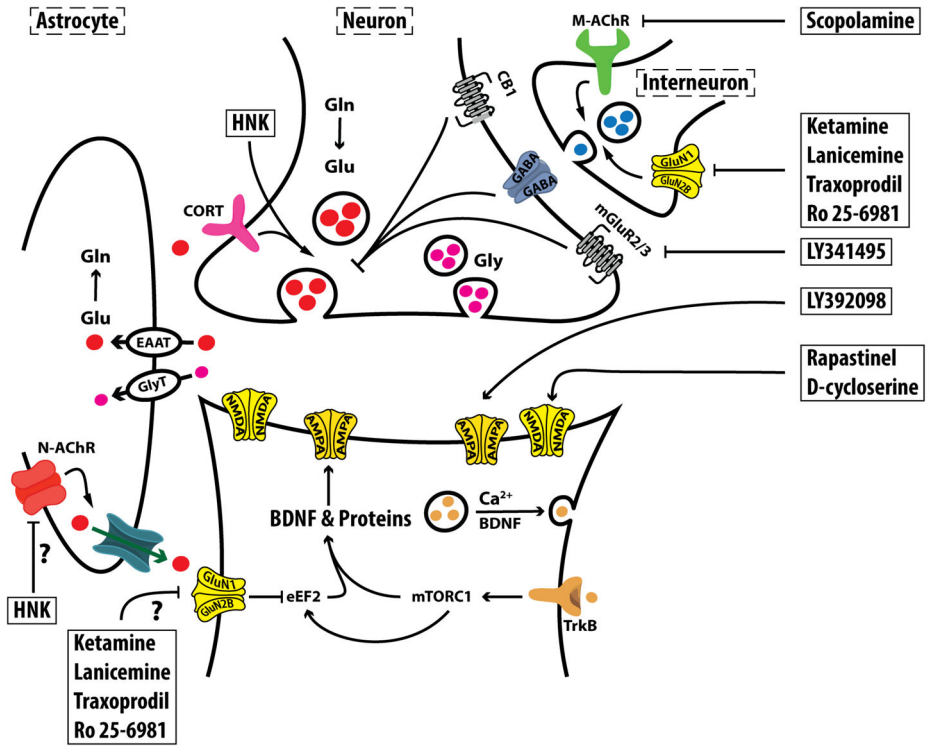

Figure 2. Molecular Targets of Rapid-acting Antidepressants (RAADs)

It is believed that RAADs exert their effects by inducing a transient (minutes-to-hours) postsynaptic glutamate activation, which ultimately leads to sustained (days-to-weeks) increase in synaptic formation and strength in the prefrontal cortex. It remains to be determined in future studies whether inhibition of extrasynaptic N-methyl-D-aspartate (NMDA) receptors would be sufficient to exert RAAD effects. The figure depicts the potential targets of agents suspected to have RAAD properties. Abbreviations: AMPA = α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid receptor; BDNF = brain derived neurotrophic factor; CB1 = cannabinoid receptor; EAAT = excitatory aminoacid transporter; eEF2 = eukaryotic elongation factor 2; Gln = glutamine; GluN1 = NMDA subtype 1; GluN2B = NMDA subtype 2B; Glu = glutamate; Gly = Glycine; GlyT = Glycine transporter; HNK = hydroxynorketamine; M-AChR = muscarinic acetylcholine receptor; mGluR2/3 = metabotropic glutamate receptor subtype 2 and 3; mTORC1 = mechanistic target of rapamycin complex 1; N-AChR = nicotinic AChR; TrkB = tyrosine kinase B receptor. The figure was adapted with permission from the Emerge Research Program (emerge.care).