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Review article

Mechanisms of action and clinical efficacy of NMDA receptor modulators in mood disorders

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ABSTRACT

Although the biogenic amine models have provided meaningful links between clinical phenomena and pharmacological management of mood disorders (MDs), the onset of action of current treatments is slow and a proportion of individuals fail to adequately respond. A growing number of investigations have focused on the glutamatergic system as a viable target. Herein we review the putative role of *N*-methyl-D-aspartate (NMDA) signaling in the pathophysiology of MDs. Prompting this focus are several lines of evidence: 1) altered glutamate and NMDA receptor (NMDAR) expression and functioning; 2) antidepressant effects of NMDAR signaling blockers; 3) interaction between conventional therapeutic regimens and NMDAR signaling modulators; 4) biochemical evidence of interaction between monoaminergic system and NMDAR signaling; 5) interaction between neurotrophic factors and NMDAR signaling in mood regulation; 6) cross-talk between NMDAR signaling and inflammatory processes; and 7) antidepressant effects of a number of NMDA modulators in recent clinical trials. Altogether, these studies establish a warrant for the refinement of novel compounds that target glutamatergic mechanisms for the treatment of MDs.

1. Introduction

Mood disorders (MDs) such as major depressive disorder (MDD) and bipolar disorder (BP) comprise chronic and debilitating psychiatric disorders that affect over 350 million persons worldwide (Brundtland, 2001; Merikangas et al., 2011). Characteristic of MDs is a constellation of disturbances that involve adverse thought processes, working memory impairments, and psychosomatic symptoms (e.g., changes in body weight, sleep routines, and energy levels) (Jick et al., 2004). Along with the tremendous human toll of MDs are significant socio-economic burdens (Murray and Lopez, 1997; Kessler et al., 2005; Lepine and Briley, 2011). The World Health Organization estimates that MDs will become the second leading cause of disability and death by the year 2020 (Brundtland, 2001). Despite their devastating impact, the heterogeneous mechanisms that underlie MDs have yet to be elucidated fully (Baumann et al., 1999).

Early pharmacological exploration of MDs began following the serendipitous discovery that reserpine, a drug used for the treatment of hypertensive vascular disease, precipitated depression in a few patients, symptoms that reversed following termination of treatment, rest, or electric shock therapy (Muller et al., 1955). Further experimental analysis revealed that reserpine inhibited vesicular monoamine transporters and depleted central monoamine levels [i.e., serotonin (5-HT) and catecholamines], a fact that implicated serotonin and norepinephrine (NE) in MD pathobiology (Shore et al., 1955, 1957; Weiner et al., 1972). Later it was shown that administration of monoamine oxidase inhibitors (MAOIs) and tricyclic antidepressants altered monoamine neurotransmitter levels and relieved depressive symptoms.

Abbreviations: AR, adrenergic receptor; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AMPAR, AMPA receptor; BDNF, brain-derived neurotrophic factor; BP, bipolar disorder; CAMK, Ca^{2+}/calmodulin-dependent protein kinase; CREB, cAMP response element-binding protein; eEF2, eukaryotic elongation factor 2; ERK, extracellular signal-regulated kinase; GABA, gamma-amino butyric acid; IL, interleukin; IFN, interferon; LTP, long-term potentiation; MDD, major depressive disorder; MAOIs, monoamine oxidase inhibitors; MDs, mood disorders; NE, norepinephrine; NF-κB, nuclear factor-κ; NMDA, *N*-methyl-D-aspartate; NMDARs, NMDA receptors; NT, neurotrophins; PKA, protein kinase A; PkC, protein kinase C; SSRI, selective serotonin reuptake inhibitors; 5-HT, 5-Hydroxytryptophan; TARPS, transmembrane AMPA receptor regulatory proteins; TNF, tumor necrosis factor; Trk, tropomyosin receptor kinase

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Altogether, these findings prompted the hypothesis that monoamine depletion contributed to MD pathology (Bunney and Davis, 1965; Schildkraut, 1995; Delgado, 2000; Hirschfeld, 2000), a notion referred to as the monoamine hypothesis.

Accordingly, therapeutic agents for MDs were derived to increase monoamine transmission acutely, either by inhibiting neuronal reuptake or by inhibiting degradation in the synaptic cleft. While this strategy has demonstrated some utility in alleviating symptoms, their slow pace of action (3–5 weeks), extensive side-effects, and poor response in a significant proportion of persons treated (65–75%) remain significant limitations (Manji et al., 2001; Oswald et al., 1972; Paul and Skolnick, 2003; Trivedi, 2006). Moreover, the fact that monoamine depletion fails to produce depressive symptoms in healthy individuals (Salomon et al., 1997) or worsen depressive symptoms in persons with MDD (Delgado et al., 1994; Berman et al., 2002) suggests that additional mechanisms and systems are involved in the pathophysiology of MDs.

Currently, glutamate and glutamate-mediated activation of *N*-methyl-D-aspartate receptors (NMDARs) and associated subcellular calcium-dependent pathways are considered as viable therapeutic targets for several neuropsychiatric disorders. Supporting this notion is evidence that brain regions implicated in MD pathobiology are modulated by monoamine projections from midbrain and brainstem nuclei (serotonin from the dorsal raphe located in the periaqueductal grey area, and NE from the locus coeruleus). Furthermore, disruptions in these systems parallel NMDAR dysfunction (Auer et al., 2000; Michael et al., 2003; Mitani et al., 2006; Hashimoto et al., 2007; Frye et al., 2007; Walter et al., 2009; Finlay et al., 2015). Glutamatergic abnormalities occur in the blood (Altamura et al., 1993; Mitani et al., 2006) and cerebrospinal fluid (Frye et al., 2007) of persons with MDs. While a number of confounding factors in postmortem studies make it more difficult to interpret the results (Hashimoto et al., 2007), important information has been gained through these studies. Significant alterations have been reported in postmortem brain samples in both glutamate and NMDAR expression in patients with MDs (Choudary et al., 2005; Beneyto et al., 2007; Beneyto and Meador-Woodruff, 2008; Feyissa et al., 2009; Hashimoto, 2010; Sanacora and Banasr, 2013; Bernstein et al., 2015). For instance, a number of studies have shown increased brain glutamate levels in both MDD and BP (Hashimoto et al., 2007; Lan et al., 2009; Sanacora et al., 2012). As for the NMDARs, while decreased hippocampal *NR1* and *NR2A* gene expression has been detected in both MDD and BP (Scarr et al., 2003; McCullumsmith and Sanacora, 2015) no alterations in NR1 activity have been found in either condition (Thompson et al., 2003; Toro and Deakin, 2005). A number of preclinical studies have demonstrated that several NMDAR antagonists exert antidepressant effects (Trullas and Skolnick, 1990; Paul and Skolnick, 2003) that appear to utilize mechanisms other than monoamine reuptake inhibitors. That is, NMDAR antagonists rapidly induce spine formation and, by corollary, may reverse the synaptic disconnection in the cortico-limbic circuit that is impaired in MDs (Hornung, 2003; Waselus et al., 2011; Duman, 2014). Evidence of these rapid effects creates an imperative to pursue novel treatments for MDs that target alternate neurobiological points of vulnerability and protection, particularly for patient groups that fail to respond to extant therapies.

Awareness of the latter prompted us to focus on putative interactions between NMDAR signaling and neurobiological pathways (e.g., biogenic amines, trophic factors, and inflammation) that affect neuroplasticity by serving as a point of vulnerability or protection. Then we emphasize specific agents (ketamine, memantine, dextromethorphan, and MK-0657/RDPC) targeting the glutamatergic system that have demonstrated some efficacy in the treatment of MDs.

2. Glutamatergic system and NMDAR signaling

Glutamate is the principal excitatory neurotransmitter in the brain of mammals (Niciu et al., 2012), and binding sites for glutamate are abundantly localized in brain regions implicated in MD pathology. Upon release, glutamate can bind to NMDARs, tetrameric structures composed of 7 subunits including an obligatory GluN1 subunit along with various combinations of GluN2 and GluN3 subunits that differ according to anatomical distribution, developmental profile, and functional activity (Hynd et al., 2004; Benarroch, 2011). In addition to those for glutamate, there are multiple binding sites on NMDARs for glycine (D-serine), Mg^{2+}, and other polyamines.

Increasingly, it is thought that synaptic and extrasynaptic NMDARs play a vital role in the antidepressant efficacy of NMDA antagonists (Hardingham and Bading, 2010). The NMDA channel contains a Mg^{2+} plug that prevents ions from freely flowing through their channels under resting conditions. Yet adjacent α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors can depolarize the cell membrane and expel the Mg^{2+} plug from the channel when given a sufficient stimulus. This allows NMDARs to become responsive to glycine and glutamate binding and undergo a conformational change to permit the nonselective influx of Na^{+} and Ca^{2+} ions. Entering Ca^{2+} ions then act as secondary messengers to elicit several intracellular signaling cascades, including those that regulate monoaminergic activity, neurotrophin expression, dendritic development and neuronal growth, long-term potentiation (LTP), and cell–cell interactions (Johnson and Taniuchi, 1987; Chiu et al., 1999; Mothet et al., 2000; Ghasemi and Schachter, 2011; Ghasemi et al., 2014; Sanacora et al., 2008). However, excess glutamate levels disrupt glial transport of glutamate from the synapse, impair synaptic transmission and plasticity, and, ultimately, are excitotoxic to affected neurons, a mechanism putatively implicated in MD pathobiology (Bliss and Collingridge, 1993; Cacabelos et al., 1999; Cull-Candy and Leszkiewicz, 2004; Lau and Zukin, 2007; Hardingham and Bading, 2010). These processes make it seem plausible that the neuronal atrophy and disconnection in MD-related circuits co-occur with imbalances in synaptic and extrasynaptic NMDAR signaling caused by synapse loss, altered Ca^{2+} transduction signals from the synapse to the nucleus, or redistributions of NMDARs from synaptic to extrasynaptic sites. By corollary, the antagonistic signaling of synaptic and extrasynaptic NMDARs provides a novel method of approaching neuroprotective therapies. Below, we review the pathophysiologic aspects of NMDAR signaling in MDs in relation to neurotransmitter systems.

3. Modulators of NMDAR function

Several molecules and brain circuits impose significant modulatory influence on NMDARs. Here we assess the nature and mechanisms of action of a few pharmacologically relevant modulators in MDs.

3.1. Serotonergic system

In the late 1960s, the indoleamine hypothesis of MDs was proposed (Coppen et al., 1965; Lapin and Oxenkrug, 1969), wherein vulnerability to either depression or mania was related to low 5-HT-ergic system activity as a result of diminished 5-HT release, fewer 5-HT receptors, or impaired 5-HT receptor-mediated signal transduction. Prange et al. later formulated a permissive role for 5-HT where a central neurotransmission deficit contributed to the manic and depressive phases of BP (Prange et al., 1974). Accordingly, a number of antidepressants currently available in the market are designed to increase serotonergic transmission by inhibiting neuronal reuptake (e.g., selective serotonin reuptake inhibitors [SSRIs]) or inhibiting its degradation (e.g., MAOIs). More recently, the focus has been on understanding the relationship between 5-HT and NMDAR signaling.

The first evidence of interactions between 5-HT and NMDARs was published in 1982 by Reisine et al. (Reisine et al., 1982). Using cats implanted with push-pull cannulae, these investigators demonstrated that administration of L-glutamic acid into either the caudate nucleus or