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Perspective

Novel approaches for the management of depressive disorders

Manuella P. Kaster [a], Morgana Moretti [b], Mauricio P. Cunha [a], Ana Lúcia S. Rodrigues [a,*]

[a] Department of Biochemistry, Center of Biological Sciences, Federal University of Santa Catarina, Florianópolis, SC, Brazil
[b] Department of Nutrition, Center of Health Sciences, Federal University of Santa Catarina, Florianópolis, SC, Brazil

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ABSTRACT

Major depressive disorder is a disabling psychiatric condition that causes a significant burden on individuals and society. There is still a lack of a clear understanding of the neuropathological changes associated with this illness and the efficacy of antidepressants is still far from optimal. Research into antidepressant therapies has evolved from serendipitous observation in human trials, but more than 60 years after the first monoaminergic antidepressants emerged they remain the mainstay for treating depression. However, glutamatergic modulators such as ketamine became the forefront of antidepressant exploration, especially for treatment-resistant depression and suicidal ideation. The glutamatergic hypothesis of depression is not new, however other NMDA receptor modulators do not seem to share the rapid and sustained effects of ketamine, suggesting that a unique combination of intracellular targets might be involved in its effect. Interestingly, inflammation can impact the glutamatergic system enhancing excitotoxicity and decreasing neuroplasticity. The points of convergence between the inflammatory and glutamatergic hypotheses of depression are not completely established, especially regarding the effects of fast-acting antidepressants. In this review, we discuss the most recent research surrounding glutamatergic fast-acting antidepressants, capable of modulating cellular plasticity and synaptogenesis and the potential of anti-inflammatory compounds evaluated from a different perspective. The combination of innovative ideas plus improvements on the discoveries made so far might lead to advances in antidepressant research with the promise of finding compounds that are both effective and fast-acting, even in patients who have tried other therapies with limited success.

1. Major depressive disorder (MDD) – pathophysiology and current antidepressant treatment

MDD causes profound socioeconomic burden and negative impact on functioning and quality of life of patients (Papakostas and Ionescu, 2015). Although there has been significant research directed towards understanding the biologic underpinnings of MDD, there is not a complete consensus about the neurochemical alterations present in depressive individuals. The monoamine hypothesis of depression proposes that underactivity of monoamines may underlie the pathophysiology of this disorder (Schildkraut, 1965). In addition, impairments on structural plasticity and cellular resilience associated with reduced levels of brain-derived neurotrophic factor (BDNF) have been implicated in the pathophysiology of MDD (Sen et al., 2008). Chronic antidepressant treatment increases BDNF levels, particularly in the hippocampus and prefrontal cortex, leading to stimulation of intracellular signaling pathways and consequent regulation of genes associated with neuroplasticity and cell survival (Castrén and Rantamaki, 2010).

Inflammation has also emerged as an important etiologic factor, and thus a potential pharmacological target for MDD. Pro-inflammatory cytokines are increased in depressed patients (Dowlati et al., 2009) resulting in an imbalance in critical neuroactive compounds and changes in brain structural and synaptic plasticity (Dantzer and Walker, 2014). Interestingly, antidepressant therapy may attenuate this inflammatory dysfunction in depressed individuals (Lanquillon et al., 2000). Moreover, neuroinflammation is associated with increased extracellular glutamate levels, causing neurotoxicity that contributes to depressive symptoms (Sanacora et al., 2012).

Current antidepressant treatments are limited in both efficacy and tolerability. The drawbacks include delayed therapeutic onset and side effects that reduce adhesion to treatment (Papakostas and Ionescu, 2015). Approaches targeting new pathways have been investigated and may represent a significant improvement in

* Corresponding author.
E-mail address: alsrodri@gmail.com (A.L.S. Rodrigues).

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the therapeutic armamentarium for treating MDD.

2. The search for fast-acting antidepressants: targeting the glutamatergic system

Seminal work by Trullas and Skolnick (1990) was the first reporting that NMDA receptor antagonists exhibit antidepressant properties in preclinical models. After this observation, several laboratories demonstrated that functional antagonists at multiple NMDA receptor sites including ligands at glutamate, polyamine, glycine, bivalent cations and ionophore recognition sites are efficacious in models of depression (Sanacora et al., 2012).

In the late 1990s reduction of NMDA receptor function was recognized as a long-term adaptation associated with antidepressant effects (Skolnick, 1999). A promising clinical study by Berman et al. (2000) showed that the non-competitive NMDA receptor antagonist ketamine induced a rapid and persistent antidepressant response in severe depressive patients. Evidence now indicates that ketamine inhibits NMDA receptors on GABAergic interneurons increasing glutamate release. The consequent activation of AMPA receptors causes depolarization of postsynaptic neurons, leading to voltage-dependent calcium channel activation. As a consequence, BDNF released from vesicles activates mTOR signaling. Finally, translation of synaptic proteins in prefrontal cortex, particularly those implicated in synaptogenesis, including PSD-95, synapsin and GluA1 is the final event associated with ketamine's rapid antidepressant effect (Li et al., 2010).

Although the discovery of ketamine for treating severe depressed patients has represented a significant advance in the field, its abuse liability and potential neurotoxicity upon repeated use has led to the interest in the development of safer fast-acting antidepressants (Abdallah et al., 2015). Considering that ketamine modulates the glutamatergic system, there has been increasing interest in targeting this system for the development of novel fast-acting antidepressants.

Our research group has particular interest in antidepressant effects afforded by some endogenous compounds that target the glutamatergic system. Several compounds capable of modulating glutamatergic neurotransmission exhibit antidepressant effects in animal models, such as zinc (Manosso et al., 2015), magnesium (Cardoso et al., 2009), agmatine (Neis et al., 2015), ascorbic acid (Moretti et al., 2011), creatine (Cunha et al., 2015a) and guanosine (Bettio et al., 2012). We showed that ascorbic acid, creatine and guanosine exert antidepressant-like effects by inhibiting NMDA receptors and activating mTOR signaling (Bettio et al., 2012, Cunha et al., 2015a,b, Moretti et al., 2014). The hippocampal phosphorylation of p70S6K, a downstream target to mTOR, and increased levels of PSD-95 were already observed 1 hour after a single administration of ascorbic acid or creatine in mice (Cunha et al., 2015b, Moretti et al., 2014). Moreover, the mTOR inhibitor rapamycin abolished the antidepressant-like effect of ascorbic acid, creatine and guanosine in the tail suspension test (Bettio et al., 2012, Cunha et al., 2015b, Moretti et al., 2014), suggesting that mTOR activation may be a key event underlying the antidepressant effects of these compounds.

Although there is limited clinical evidence indicating the beneficial effects of these compounds for MDD, zinc supplementation was effective in combination with conventional antidepressants (Lai et al., 2012). Regarding magnesium, although it still remains to be established if its administration elicits ketamine-like effects in behavioral paradigms, it is reported that ketamine increases brain magnesium levels (Murck, 2013). A randomized clinical trial showed that magnesium was as effective as imipramine for treating MDD in diabetics (Barragán-Rodríguez et al., 2008). The antidepressant effect of agmatine was documented in a small number of subjects (Shopsin, 2013) and ascorbic acid was effective as adjuvant agent for MDD in pediatric patients (Amr et al., 2013). Antidepressant effects of creatine supplementation were also reported in depressive patients (Allen, 2012). However, there are no clinical studies evaluating the mood effects of guanosine.

The antidepressant effects of other NMDA receptor antagonists and glutamate-modulators such as MK-801, AP-7, RO25-6981, amantadine, memantine, CP-101,606 (traxoprodil) and riluzole were extensively studied in preclinical models (Dutta et al., 2015). Most of these agents fail to afford rapid and sustained antidepressant effects (Dutta et al., 2015; Preskorn et al., 2008; Zarate et al., 2004). Some promising results were observed with the low-trapping NMDA channel blocker AZD6765, which elicits rapid, but not sustained, antidepressant effects in treatment-resistant MDD patients (Zarate et al., 2013). However, the intracellular pathways involved in its effect are not established. Also, antidepressant-like effect of the NMDA receptor glycine-site partial agonist GLYX-13 requires AMPA receptor and mTOR activation, similar to ketamine (Lu et al., 2014). The antidepressant potential of GLYX-13 was confirmed in a clinical trial, and a fast (2 h) and sustained remission of depressive symptoms was observed without dissociative effects (Moskal et al., 2014; Preskorn et al., 2015). CP-101,606, a selective NR2B receptor antagonist, produced symptoms' remission by day 5 in depressed patients unresponsive to paroxetine (Preskorn et al., 2008). However, the intracellular pathways associated with this effect need to be elucidated in preclinical studies.

Metabotropic glutamate receptor modulators and AMPA receptor potentiators also represent interesting targets in the search for novel fast-acting antidepressant compounds. The blockade of presynaptic mGluR2/3 receptors regulates glutamate release and produces rapid behavioral responses that require activation of either AMPA receptors or mTOR signaling (Dwyer et al., 2012). Specifically, LY341495, an mGlu2/3 receptor antagonist, reduced the time required for antidepressants to exert their effects by a mechanism dependent on stimulation and expression of AMPA receptors in prefrontal cortex (Matrisciano et al., 2005). Moreover, preclinical studies have shown that AMPA potentiators LY392098 and LY451616 exhibit antidepressant effects associated with hippocampal increases on BDNF and progenitor cell proliferation. Also, the AMPAkine Ampalex elicited a rapid antidepressant effect when compare to fluoxetine (Knapp et al., 2002). Sleep deprivation, which is capable of producing rapid antidepressant effects, has similar effects on AMPA-mediated plasticity, suggesting that rapid enhancement of synaptic plasticity might represent the final target for symptoms remission (Faraguna et al., 2008).

Despite similar properties of these compounds at NMDA neurotransmission, their inability to replicate the fast, robust and sustained antidepressant effect of ketamine may be due to doses, pharmacokinetic differences, and activation of different intracellular signaling pathways.

3. Anti-inflammatory agents for the management of MDD

Depressive symptoms are commonly observed in patients with inflammatory conditions (e.g. aging and obesity), inflammatory diseases (e.g. atherosclerosis, congestive heart failure and rheumatoid arthritis), and in patients undergoing cytokine immunotherapy (Capuron and Dantzer, 2003). The presence of asthma and arthritis was significantly higher in depressed individuals (odds ratio (OR)=1.53, 95% CI, 1.03–2.28; OR=1.95, 95% CI, 1.17–3.25, respectively). Heart attack and stroke were more prevalent in depressed patients when compared to controls (OR=3.76, 95% CI, 1.95–7.27; OR=2.83, 95% CI, 1.59–5.06, respectively) (Kim et al., 2015). Diabetes mellitus is also more prevalent in the depressed group (OR=1.65, 95% CI, 0.93–2.92) and a meta-