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Review article

New targets for rapid antidepressant action

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ABSTRACT

Current therapeutic options for major depressive disorder (MDD) and bipolar disorder (BD) are associated with a lag of onset that can prolong distress and impairment for patients, and their antidepressant efficacy is often limited. All currently approved antidepressant medications for MDD act primarily through monoaminergic mechanisms. Glutamate is the major excitatory neurotransmitter in the central nervous system, and glutamate and its cognate receptors are implicated in the pathophysiology of MDD, and in the development of novel therapeutics for this disorder. The rapid and robust antidepressant effects of the *N*-methyl-D-aspartate (NMDA) antagonist ketamine were first observed in 2000. Since then, other NMDA receptor antagonists have been studied in MDD. Most have demonstrated relatively modest antidepressant effects compared to ketamine, but some have shown more favorable characteristics. This article reviews the clinical evidence supporting the use of novel glutamate receptor modulators with direct affinity for cognate receptors: (1) non-competitive NMDA receptor antagonists (ketamine, memantine, dextromethorphan, AZD6765); (2) subunit (GluN2B)-specific NMDA receptor antagonists (CP-101,606/traxoprodil, MK-0657); (3) NMDA receptor glycine-site partial agonists (GLYX-13); and (4) metabotropic glutamate receptor (mGluR) modulators (AZD2066, RO4917523/basimglurant). We also briefly discuss several other theoretical glutamate receptor targets with preclinical antidepressant-like efficacy that have yet to be studied clinically; these include α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid (AMPA) agonists and mGluR2/3 negative allosteric modulators. The review also discusses other promising, non-glutamatergic targets for potential rapid antidepressant effects, including the cholinergic system (scopolamine), the opioid system (ALKS-5461), corticotropin releasing factor (CRF) receptor antagonists (CP-316,311), and others.
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Abbreviations: ACC, anterior cingulate cortex; ACPC, 1-aminocyclopropanecarboxylic acid; AKT/PKB, protein kinase B; AMPA, α-amino-3-hydroxyl-5-methyl-4-isoxazolepropionic acid; Arc, activity-regulated cytoskeleton-associated protein; BD, bipolar disorder; BDI, Beck Depression Inventory; BDNF, brain-derived neurotrophic factor; CNS, central nervous system; CREB, , cyclic adenosine monophosphate response element-binding protein; CRF, corticotropin releasing factor; DBS, deep brain stimulation; dlPFC, dorsolateral prefrontal cortex; EEG, electroencephalography; e-EF2, eukaryotic elongation factor 2; ERK, extracellular signal-related kinase; fMRI, functional magnetic resonance imaging; GABA, gamma aminobutyric acid; GluA1, AMPA receptor subunit 1; GSK-3B, glycogen synthase kinase 3B; HAM-D, Hamilton Depression Rating Scale; HDAC, histone deacetylase; HNK, hydroxynorketamine; HPA, hypothalamic pituitary adrenal; IRS, insulin receptor substrate; LAC, L-acetylcarnitine; MADRS, Montgomery Asberg Depression Rating Scale; MDD, major depressive disorder; mGluR, metabotropic glutamate receptor; MRS, magnetic resonance spectroscopy; mTOR, mammalian target of rapamycin; NK1, neurokinin 1; NMDA, *N*-methyl-D-aspartate; PCP, phencyclidine; PET, positron emission tomography; PFC, prefrontal cortex; PI3K, phosphoinositide-3 kinase; PSD95, postsynaptic density protein 95; RDoC, research domain criteria; SMD, standardized mean difference; SNRI, serotonin–noradrenaline reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor; TCA, tricyclic antidepressant; TrkB, tropomyosin receptor kinase B; VOCC, voltage-operated calcium channels.

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1. Introduction

Depression directly affects the brain and periphery and is associated with diverse other medical comorbidities due its systemic deleterious effects. The "monoamine hypothesis" of depression – which was developed after observing the pharmacological effects of early drugs for depression – is no longer the only model capable of explaining the mechanism of action of antidepressants or for studying the underlying pathophysiology of depressive episodes in mood disorders.

Currently available conventional antidepressants unfortunately have low rates of treatment response; while one-third of patients with depression will respond to their first antidepressant, approximately two-thirds will respond only after trying several classes of antidepressants (Trivedi et al., 2006). Furthermore, therapeutic approaches must be considered not only in the context of treating acute episodes, but for relapse prevention as well as intervention in the early phases of illness. With regard to conventional antidepressants, few targets besides the monoamines and the hypothalamic pituitary adrenal (HPA) stress axis have been identified as key candidates; nevertheless, the interaction between organs, proteins, hormones, and several comorbid diseases remains complex, and results of studies investigating these targets are preliminary. Thus, there is a strong need to identify and rapidly test novel antidepressants with different biological targets beyond the classic monoaminergic receptors and their downstream targets; these agents would also be expected to act faster in a larger percentage of individuals. However, in recent years the pharmaceutical industry has been investing less in psychiatry and mood disorders as a therapeutic area. This review discusses some of the striking recent advances in the development of novel, rapid-acting antidepressants as well as the potential issues and pitfalls related to research in this field. We also present an overview of the most promising targets and approaches as well as ideas for next steps for drug development.

2. Rapid onset of antidepressant action

As noted above, currently available monoaminergic antidepressants are associated with a delayed onset of action of several weeks, a latency period that significantly increases risk of suicide and self-harm and is a key public health issue in psychiatric practice (Machado-Vieira et al., 2009c). This concept of a latency period before achieving antidepressant efficacy is widely accepted despite the fact that very few trials have evaluated efficacy outcomes on a daily basis during the first week of treatment with conventional antidepressants. High rate of placebo response has also been problematic when evaluating new antidepressants. As a result, much remains unknown about the actual timing of antidepressant efficacy (that is, early improvement) for any class of standard antidepressants (Katz et al., 2004; Machado-Vieira et al., 2010); most of these data come from post-hoc analyses.

Nevertheless, several clinical studies suggest that rapid antidepressant effects are achievable in humans. This lends an additional urgency to the development of new treatments for depression that target alternative neurobiological systems, particularly for those subgroups of patients who do not respond to any currently available pharmacological agents. New therapeutics could significantly lower morbidity and mortality for both major depressive disorder (MDD) and bipolar disorder (BD) and commensurately minimize or prevent disruption to personal, family, and occupational life and functioning as well as lower risk of suicide. In addition, the neurobiological impact of cumulative exposure to depression would be minimized, which might result in less chronicity and fewer recurrences. It should also be noted that new insights into the potential association between early improvement and long-term outcomes would be helpful tools in clinical practice; knowledge gleaned from such studies could be used in the context of personalized medicine. Indeed, identifying new targets for rapid antidepressant efficacy seems to be a relevant approach not only in treatment-resistant cases but also for the initial treatment of patients who respond well to conventional monoaminergic antidepressants and are, as a result, expected to wait several weeks for therapeutic effects to manifest. Nevertheless, developing agents that exert rapid antidepressant effects remains difficult. Perhaps the most significant challenge is dealing with the gap between rapid antidepressant response, long-term treatment, and maintenance therapy after response and remission.

In the context of developing novel therapeutic targets for depression, glutamate and other ionic channel receptors seem to induce faster biological effects at intracellular downstream targets and currently represent the most promising targets for drug development. Rapid improvement is a key paradigm for achieving fast relief of symptoms and, in some cases, preventing new episodes when prodromal symptoms are observed; this paradigm is similar to that seen for other medical illnesses such as asthma, migraine, and atrial fibrillation. Below, we discuss the concept of rapid antidepressant action and present findings and perspectives