Alternatives to ketamine in depression: state-of-the-art and future perspectives

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Background

Pharmacological treatments in major depressive disorder (MDD) have historically focused on monoaminergic modulation. However, this strategy has limitations, such as a significant delay in the onset of therapeutic action and a large proportion of patients demonstrating persistent, treatment-resistant depression. There is a real need for novel rapid-acting antidepressants with alternative mechanisms of action.

The glutamate system is increasingly implicated in the pathophysiology of mood disorders and has become a new focus of investigation.[1] The *N*-methyl-D-aspartate (NMDA) receptor antagonist ketamine, a dissociative anaesthetic developed in the 1960s, produces rapid antidepressant effects (within hours of intravenous administration), even in those with treatment resistance and as such, ketamine has been hailed "the biggest breakthrough in depression research in half a century."[2] However, the use of ketamine in the treatment of MDD has raised concerns regarding perceived negative side effects and abuse potential.

Ketamine remains an off-label treatment for depression, and although larger trials are underway, other attempts are being made to develop novel agents designed to mimic ketamine's action without the dissociative and psychotomimetic effects or abuse potential. Here, we broadly discuss some of these compounds and mechanistic considerations before finally considering future avenues of research.

Alternatives to ketamine

One of the main pharmacological actions of ketamine is NMDA receptor antagonism, and it has been hypothesized that this mechanism is central to its antidepressant action. Using different approaches to modulate the NMDA receptor, including the use of lower affinity or NMDA subunit-selective receptor antagonists or by targeting NMDA allosteric sites, provides promising routes in the development of rapid-acting antidepressants without ketamine's undesirable side effects.

A single infusion of the NMDA receptor antagonist CP-101,606, specific for the NR2B subunit, has shown significant antidepressant effect in patients with treatment-resistant MDD in a double-blind, randomized controlled trial (RCT).[3] Although initial doses used in the study produced dissociative side effects similar to ketamine, subsequent dose reductions achieved antidepressant effects without dissociative reactions. In a small placebo-controlled study, daily doses of an oral formulation of MK-0657, another selective NR2B antagonist, also demonstrated significant antidepressant effects on secondary efficacy measures without dissociative side effects as early as day 5.[4]

Infusions of lanicemine (AZD6765), a low-trapping NMDA receptor antagonist, produced rapid but short-lived antidepressant effects (within 80 min, lasting less than 24 h) in a double-blind, crossover RCT of 22 participants with treatment-resistant MDD, again without psychotomimetic side effects.[5] A large multisite trial has since been unable to demonstrate longer-term clinical efficacy of repeated lanicemine infusions at 6 weeks,[6] with the high placebo response potentially limiting the ability to differentiate the drug response from placebo.

AVP-786 is an experimental compound consisting of a combination of a deuterium-modified form of dextromethorphan, an uncompetitive NMDA receptor antagonist, and quinidine, a CYP26 enzyme inhibitor that works to increase the bioavailability of dextromethorphan by inhibiting its breakdown. A clinical trial of AVP-786 as adjunctive therapy in MDD has recently been

completed with the results pending (ClinicalTrials.gov ID: NCT02153502).

Nitrous oxide is a common analgesic with a mechanism of action that includes NMDA receptor antagonism. A recent proof-of-concept trial investigating nitrous oxide for treatment-resistant depression demonstrated a significant improvement in depressive symptoms at 2 h and 24 h compared with placebo (mean 21-item Hamilton Depression Rating Scale difference at 2 h and 4 h, –4.8 points, $p = 0.002$ and −5.5 points, $p < 0.001$, respectively; comparison between nitrous oxide and placebo, $p < 0.001$).[7] Although these preliminary findings are promising, the authors noted that subsequent studies are required to determine optimal dosing strategies and the risk:benefit ratio of nitrous oxide in a larger and more diverse population of patients with treatment-resistant depression.

Memantine is a noncompetitive NMDA antagonist that lacks the unwanted side effects associated with ketamine at therapeutic doses. However, repeated attempts have failed to demonstrate a rapid antidepressant effect in individuals with major depression,[8,9] calling into question whether NMDA receptor blockade is the sole mechanism underlying ketamine's antidepressant effects. It has been shown that memantine does not inhibit the phosphorylation of eukaryotic elongation factor 2 (eEF2) or increase brain-derived neurotrophic factor (BDNF) expression and synaptic formation,[10] which are critical determinants of ketamine-mediated antidepressant efficacy, potentially explaining the difference in clinical effects of these compounds.

The glycine-binding site has been a promising target for NMDA receptor modulation. D-cycloserine (DCS) is an antituberculosis medication and a partial agonist at the glycine-binding site that at higher doses acts as a functional NMDA receptor antagonist. It was first reported to show antidepressant effects as early as the 1950s[11] and more recently, a 6-week augmentation trial of gradually titrated high-dose (1000 mg/day) DCS in treatment-resistant patients reported significant antidepressant effects compared with placebo, was well tolerated and had no psychotomimetic effects.[12] Rapastinel (GLYX-13) also acts as a partial agonist at the glycine-binding site and in a double-blind RCT of patients with treatment-resistant depression a single infusion of 5 mg/kg or 10 mg/kg, significantly reduced depressive symptoms within 2 h and was maintained for 7 days.[13] Importantly, rapastinel did not elicit psychotomimetic or other significant side effects. NRX-1074, an orally active and higher potency analogue of rapastinel, is soon anticipated to proceed to phase II testing.

A final NMDA receptor modulator is 4-chlorokynurenine (4-Cl-KYNA) (AV-101), which acts as a potent and selective antagonist at the glycine-binding site. Although results from human studies are also pending (ClinicalTrials.gov ID: NCT02484456), preclinical studies suggest rapid and dose-dependent antidepressant effects in several rodent models including the forced swim and tail suspension test, similar to ketamine.[14] The authors reported that 4-Cl-KYNA is not associated with the rewarding and psychotomimetic effects of ketamine, and did not induce locomotor sensitization or stereotypic behaviours.

Mechanistic considerations

In addition to its NMDA receptor antagonist effects, ketamine has actions at a large number of other brain receptors and it has been suggested that its antidepressant effects may occur through actions at non-NMDA receptor sites.

Ketamine is available as a mixture of (R)- and (S)-enantiomers. Studies in depression have mainly focused on this racemic mixture, but it has been hypothesized that the (S)-enantiomer may have greater efficacy due to its higher affinity for NMDA receptors.[15] An intranasal formulation (esketamine) is being trialled in treatment-resistant depression (ClinicalTrials.gov ID: NCT02782104). However, in contrast to this hypothesis, preclinical work from Fukomoto and colleagues suggested that the (R)-enantiomer may be more efficacious as an antidepressant, with a longer duration of action.[16]

A recent paper reported that the metabolism of ketamine to (2S,6S;2R,6R)- hydroxynorketamine (HNK), is required for its antidepressant effects.[17] Interestingly, administration of the (R)-enantiomer (2R,6R)-HNK was associated with greater antidepressant actions and also lacked ketamine-related side effects in a rodent model. These effects were independent of any action on NMDA receptors but instead required α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor activation. Interesting to note, the antidepressant effects of rapastinel and 4-Cl-KYNA are also prevented

by pretreatment with an AMPA receptor antagonist.[14,18]

The findings that the rapid antidepressant actions of ketamine and its metabolite HNK require AMPA receptor activation challenge the view that these effects are caused by NMDA receptor antagonism alone. Instead, NMDA receptor antagonism may indirectly activate AMPA receptors and the actions of ketamine and HNK may converge downstream, along associated intracellular cascades, potentially at the level of eEF2 and BDNF signalling.[17,19]

One final consideration is that of ketamine's dissociative 'side effects'. Although the compounds discussed in this paper were designed to avoid such effects, it has been put forward that the dissociative experience mediates ketamine's antidepressant effect, predicting a more robust and sustained response.[20] The mechanisms behind this are still unclear but suggest we should not necessarily rush to label this as an altogether unwanted effect.

Future directions

It remains to be established whether HNK is entirely responsible for ketamine's therapeutic effects but its discovery nonetheless emphasizes the potential of AMPA receptor modulation as a target for antidepressant medications and is an area which certainly warrants further investigation. There have already been promising initial results examining the safety and preliminary efficacy for ORG-26576, a positive allosteric modulator of the AMPA receptor in the treatment of depression,[21] and results from additional clinical trials investigating AMPA receptor modulation are awaited.

Further work to identify the precise molecular mechanisms underlying both ketamine's antidepressant effects and potentially unwanted side effects will be of particular importance in the continued development of alternative antidepressants. Specifically, separating any differences in mechanisms and efficacy of both (S)- and (R)-enantiomers in humans is a key area of future investigation.

Conclusion

In the search for ketamine alternatives in depression, the NMDA receptor has been seen as a promising target with a number of compounds acting as NMDA receptor modulators showing encouraging results. However, it remains uncertain as to whether NMDA receptor engagement is required or in fact sufficient for ketamine and its alternatives to provide a therapeutic effect. As the molecular mechanisms underlying ketamine's effects are further unravelled other targets including AMPA receptor potentiation have been identified and are a new focus of investigation.

In the pursuit of alternatives, we must not forget ketamine itself, which remains a novel antidepressant with effects in patients otherwise resistant to treatment, and with a remarkably rapid speed of onset. As larger clinical trials are completed exploring long-term risks and issues relating to maintenance of response, we may well question whether there really is a need to improve on ketamine?

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