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Review article

Ketamine and other potential glutamate antidepressants

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ABSTRACT

The need for rapid acting antidepressants is widely recognised. There has been much interest in glutamate mechanisms in major depressive disorder (MDD) as a promising target for the development of new antidepressants. A single intravenous infusion of ketamine, a N-methyl-D-aspartate (NMDA) receptor antagonist anaesthetic agent, can alleviate depressive symptoms in patients within hours of administration. The mechanism of action appears to be in part through glutamate release onto non-NMDA receptors including α-Amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) and metabotropic receptors. However these are also reported effects on 5-HT, dopamine and intracellular effects on the mammalian target of rapamycin (mTOR) pathway. The effects of SSRI (Selective Serotonin Reuptake Inhibitor) antidepressants may also involve alterations in NMDA function. The article reviews the effect of current antidepressants on NMDA and examines the efficacy and mechanism of ketamine. Response to ketamine is also discussed and comparison with other glutamate drugs including lamotrigine, amantadine, riluzole, memantine, traxoprodil, GLYX-13, MK-0657, RO4917523, AZD2066 and Coluracetam. Future studies need to link the rapid antidepressant effects seen with ketamine to inflammatory theories in MDD.

Contents

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1. Introduction

The need for rapid acting antidepressants is widely recognised. Despite the introduction of selective serotonin reuptake inhibitors (SSRI) and several other mechanisms of antidepressant action revolving around monoamine theory in the 1980s, response rates have not improved beyond approximately 60% (Mulrow et al., 2000). Naturalistic studies have observed remission of major depressive disorder (MDD) in only 28% of patients after first line treatment with citalopram in the Sequenced Treatment Alternatives to Relieve Depression (STAR*D) trial (Trivedi et al., 2006). Furthermore second and third line treatments demonstrated declining rates of remission in spite of various augmentation strategies (Nierenberg et al., 2006; Trivedi et al., 2008). This has led to interest in new targets for antidepressant action over recent years including neurokinin, corticotrophin releasing factor, intracellular signalling cascades and modulation of glucocorticoid, cytokine, opioid and cannabinoid receptors (Pacher and Kecskemeti, 2004).

Interest in the role of glutamate in depression and antidepressant effects goes back to pharmacological studies in the late 1980s. Reynolds and Miller (1988) reported that tricyclic antidepressants had zinc-like functional effects on the NMDA receptor – they occluded the ion channel associated with the NMDA glutamate receptor. Trullas and Skolnick (1990), on the basis of stress and antidepressant effects on long-term potentiation in the hippocampus, proposed and demonstrated that functional antagonists at the NMDA receptor had antidepressant-like behavioural effects in animals. Berman et al. (2000) made the seminal human observation that a single intravenous infusion of ketamine (a NMDA receptor antagonist anaesthetic agent) alleviated depressive symptoms in patients within hours of administration and peaking some days later (Berman et al., 2000; Zarate et al., 2006a). These effects were replicated by Zarate et al. (2006a) and in bipolar depressive disorder by Diazgranados et al. (2010b). These findings stimulate a number of questions about the role of glutamate in MDD; what is the effectiveness of different glutamate drugs, what is their mechanism of action and how do they affect the glutamate system in MDD?

2. Efficacy of ketamine in MDD

2.1. Methodology of studies

The clinical studies of ketamine are summarised in Table 1. Five of the studies were double-blind crossover randomised controlled trials (RCTs) (Berman et al., 2000; Zarate et al., 2006a; Diazgranados et al., 2010b; Zarate et al., 2012b, Sos et al., 2013). One trial was a double blind RCT (Murrough et al., 2013a). The remaining RCTs were not double blinded. Of the remaining trials, a single blind study observed the effect of ketamine when used as part of an anaesthetic in patients with MDD undergoing orthopaedic surgery (Kudoh et al., 2002). The remaining studies were either open label (Correll and Futter, 2006; Machado-Vieira et al., 2009b; Phelps et al., 2009; Salvadore et al., 2009; aan het Rot et al., 2010; Paslakis et al., 2010; Okamoto et al., 2010; Salvadore et al., 2010; Ibrahim et al., 2011, 2012b; Salvadore et al., 2012; Carlson et al., 2013; Duncan et al., 2013a; Murrough et al., 2013b; Rasmussen et al., 2013) or crossover studies (Paul et al., 2009; Valentine et al., 2011). Mathew et al. (2010) used open label i.v. ketamine examining the effects of lamotrigine pre-treatment and riluzole maintenance treatment. Two studies, which were open label, compared drug effects in MDD patients and healthy volunteers (Salvadore et al., 2009; Okamoto et al., 2010). Although the majority of studies included only patients with MDD, two studies were carried out in bipolar depression and another included one bipolar depressive into the trial group (Berman et al.; 2000; Diazgranados et al., 2010b; Zarate et al., 2012b).

Most studies used ketamine 0.5 mg/kg by intravenous infusion over 40 minutes but some used lower dosages (Correll and Futter, 2006; Sos et al., 2013). Higher doses of 1.0 mg/kg and 1.5 mg/kg have been used as anaesthetic during ECT and preoperatively prior to orthopaedic surgery (Kudoh et al., 2002; Goforth and Holsinger, 2007). A problem common to all studies ia that the immediate subjective effects of ketamine reveal the treatment condition so the use of saline placebo infusions does not maintain the blind. One study used midazolam as an active placebo with no saline control group (Murrough et al., 2013a). A number of trials allowed the use of concomitant medications including other antidepressants (Kudoh et al., 2002; Stefanczyk-Sapieha et al., 2008; Diazgranados et al., 2010v; Irwin and Iglewicz, 2010; Rasmussen et al., 2013). A number of studies had MDD patients with comorbid anxiety disorders (Salvadore et al., 2009; Salvadore et al., 2010; Valentine et al., 2011).

The majority of studies used reduction in the Montgomery Asberg Depression Rating Scale (MADRS) or Hamilton Depression Rating Scale (HAM-D) as primary outcome measures except one (Messer et al., 2010). However these scales may have limited validity when used more frequently than weekly. Some studies included measures of psychotomimetic effects (Phelps et al., 2009; Diazgranados et al., 2010b; Ibrahim et al., 2011, 2012b; Zarate et al., 2012b; Carlson et al., 2013; Murrough et al., 2013a, 2013b, Lapidus et al., 2014).

The main problems with the studies are that they employed small sample sizes – most less that 20 participants in the active treatment groups. The samples in seven of the studies had statistically significant differences in patient characteristics between controls and depressives. They included differences in baseline MADRS scores, age, number and severity of episodes (Phelps et al., 2009; Salvadore et al., 2009; Diazgranados et al., 2010b; Mathew et al., 2010; Valentine et al., 2011; Sos et al., 2013). The time points at which MADRS was measured limited understanding the time of the peak effect of ketamine. Additionally, data were read from graphical data in the papers which may have led to errors.

2.2. Response to ketamine infusion

All the studies agree that the antidepressant effect of ketamine begins within 24 hours of a single intravenous infusion and can last up to 14 days. However, there is some variability in the response. The peak reduction on HAM-D scores varied from 15% (Abdallah et al., 2012) to 86% (Denk et al., 2011). Similar changes were seen in the Beck Depression Inventory (BDI) and MADRS scores. The response rates following ketamine infusion range from 20% (Rasmussen et al., 2013) to 90% (aan het Rot et al., 2010). In bipolar depression peak reduction in mood rating scales was noted as early as 40 minutes after start of infusion (Diazgranados et al., 2010a; Zarate et al., 2012b). The antidepressant effect noted in the bipolar depression study (Diazgranados et al., 2010a) occurred earlier but was less sustained than noted by Zarate et al. (2006a) in MDD. Furthermore, lower response rates were noted in bipolar depression than in MDD at the end of day 1 (42% in bipolar depression vs. 71% in MDD) in the ketamine group (Diazgranados et al., 2010a, Zarate et al., 2006a).

Eight studies examined whether repeated doses of ketamine cause a more sustained effect than single dosage (Correll and Futter, 2006; Stefanczyk-Sapieha et al., 2008; Liebrenz et al., 2009; aan het Rot et al., 2010; Messer et al., 2010; Murrough et al., 2013b; Rasmussen et al., 2013; Szymkowicz et al., 2013). aan het Rot et al. (2010) demonstrated relapse in depressive symptoms could be delayed by up to 19 days after the final i.v. ketamine infusion when repeated infusions of ketamine were used. However, patients had