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Ketamine and Depression.

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Introduction

Since Domino and colleagues (1) reported the first clinical use of ketamine more than half a century ago there have been many clinical and laboratory studies to determine both mechanism(s) of action and the most appropriate clinically useful properties of this enigmatic drug. These include analgesia, favourable cardio-respiratory profile, anti-inflammatory effects and anti-cancer actions (2-4). In addition to this, anti-depressant actions of ketamine have been recognized that are of clinical applicability (5-7). In psychiatry, many clinical studies demonstrate that existing antidepressant medications show limited effectiveness and slow onset of clinical response (8). Indeed, development of new therapeutic strategies for major depression represents a major clinical need and represents an area where there is much pharmaceutical interest. Does ketamine fit the bill? In this editorial, this new facet is explored in terms of utility and mechanisms of actions.

Clinical evidence and relevance of the anti-depressant actions of ketamine

Several systematic reviews and meta-analyses of the clinical utility of ketamine for patients with major depressive disorder have been reported. Han et al (5) reported 9 studies and found that ketamine could produce rapid amelioration of major depressive disorder. Alberich et al (6) reported that bipolar depression may also be treatable with ketamine although its effective duration was short. These data were obtained from 1 clinical trial, 5 cohort studies, and 4 case reports. Moreover, Wilkinson et al (7) reported on 10 identified comparative intervention studies in which either saline or midazolam was included as a control treatment. It was concluded that ketamine rapidly (within 1 day) and significantly reduced suicidal ideation and this effect continued for up to 1 week. Although mood depression is often reported in postoperative patients, small doses of ketamine (0.5 mg/kg) at induction of anaesthesia may reduce mood depression with an increase in serum brain-derived neurotropic factor (BDNF).

This is correlated significantly with the Patient Health Questionnaire-9 depression rating scale (9). However, two Cochrane Database Systematic Reviews (10, 11) show limited evidence for ketamine's efficacy over placebo in both unipolar and bipolar depression. Grunebaum and colleagues (12) reported that ketamine could cause clinically significant reduction in suicidal ideation in depressed patients within 24 hours compared with midazolam. Gamble and colleagues (13) also reported that ketamine anaesthesia provided faster response and remission following electroconvulsive therapy (ECT) compared with propofol anaesthesia. However, a number of clinical trials (14, 15) suggest ketamine anaesthesia may not significantly improve depression after ECT. It should be noted that depression is not a simple unitary phenomenon and what is true for one condition might not be true for all. High quality randomized controlled trials (with adequate blinding) are required to determine the differential efficacy of ketamine for unipolar and bipolar depression and how to sustain any antidepressant response.

Potential mechanisms of anti-depressant actions of ketamine (Figure 1)

N-methyl-D-aspartate(NMDA) receptors mechanism

Ketamine is recognised as a non-competitive NMDA receptor antagonist and this mode of action underlies its anaesthetic properties (3). Trullas and Skolnick (16) reported that MK-801, a non-competitive NMDA receptor antagonist, produced antidepressant-like actions in a mouse model of depression. Using a chronic unpredictable stress model, Jiang and colleagues (17) found that a subanaesthetic dose of ketamine (10mg/kg ip) induced rapid antidepressant effects in adult male rats. This was based on (i) an increase in body weight, (ii) increased spontaneous locomotor activity to anxiety-eliciting situations in the open field of the elevated plus maze (iii) more entries into the open arm of the elevated plus maze, (iv) increased activity in the forced swimming test, and (v) higher sensitivity to sucrose after ketamine treatment.

Ketamine is also known to increase hippocampal BDNF protein levels, which may be important for producing a rapid onset of antidepressant action (18). The NMDA receptor hypothesis is as follows (19). Although anaesthetic doses of ketamine reduce prefrontal glutamatergic transmission, subanaesthetic doses increase glutamate cycling and as a result, extracellular glutamate increases in the prefrontal cortex (PFC). NMDA receptor blockade of γ-aminobutyric acidergic (GABAergic) interneurons inhibits their activity. In addition, ketamine inhibits presynaptic NMDA receptor followed by reduction in presynaptic HCN1 channels activity, which would lead to increasing glutamate release and subsequently postsynaptic glutamate receptor activity (20). Then, postsynaptic α-amino-2,3-dihydro-5-methyl-3-oxo-4-isoxazolepropanoic acid (AMPA) receptors are activated and extrasynaptic NMDA receptors are inhibited. A combination of AMPA receptor activation and extrasynaptic NMDA receptor inhibition facilitates postsynaptic activation of neuroplasticity-related signalling pathways involving BDNF and the mammalian target of rapamycin (mTOR). Synaptic NMDA receptor blockade by ketamine leads to suppression of eukaryotic elongation factor-2 (eEF2) kinase. Phosphorylation of eEF2 gradually decreases and BDNF translation increases. Up-regulation of BDNF translation evokes tyrosine-related kinase-B (TrkB) signalling leading to transphosphorylation and downstream activation of extracellular signalling related kinases (ERKs) and proteinkinase-B (Akt/PKB), and suppression of glycogen synthase kinase-3 (GSK-3). As a result, mTOR is activated to induce synaptogenesis (21). Yang and colleagues (22) recently suggest that the rapid antidepressant effects of ketamine may be due to blocking of NMDA receptor-dependent bursting activity in the lateral habenula neurons, “anti-reward centre” to activate downstream reward centre. These biochemical responses may mediate the rapid and long-term antidepressant effects of ketamine. Another NMDA receptors mechanism has recently been suggested by Williams et al (23). They reported that naltrexone markedly diminished ketamine-induced antidepressant effects in patients with treatment-resistant

depression. Thus, they concluded that opioid system activation, particularly μ-opioid receptors must be required to produce acute antidepressant effect of ketamine. It was also reported ketamine could increase endogenous β-endorphin release (24), and it may consequently induce an increase in μ-opioid receptor activity that is potentiate by NMDA receptor antagonism to produce the antidepressant actions.

Non-NMDA receptors mechanism

1) Catecholamine turnover

Current antidepressants are SSRI (selective serotonin reuptake inhibitors), SNRI (serotonin–norepinephrine reuptake inhibitors), NaSSA (noradrenergic and specific serotonergic antidepressant) and NDRI (norepinephrine and dopamine reuptake inhibitor). Ketamine has been reported to increase monoamine releases including norepinephrine, dopamine and serotonin and also inhibits their reuptake (25). Ketamine may therefore have more conventional antidepressant actions as SNRI, NaSSA and NDRI. In addition, SSRIs may stimulate serotonin type 3 receptor (5HT3R) which is expressed with insulin-like growth factor-1 (IGF-1) in the same neurons in the hippocampal dentate gyrus. IGF-1 has been reported to have antidepressant effects. Kondo et al (26) found that 5HT3R regulates hippocampal extracellular levels of IGF-1 levels, which mediates 5HT3R-dependent hippocampal neurogenesis. As we found that the expression of IGF-1 was upregulated in response to ketamine treatment in C6 glioma cells (4), an increase in IGF-1 by ketamine may contribute to the mechanism of the antidepressant effects.

2) Anti-inflammatory actions

Recent studies strongly indicate a mutual relationship between inflammation and major depression. Indeed, inflammatory mediators may be potential markers of depression and treatment responsiveness. Several transcription factors such as NF-E2-related factor 2 (Nrf2) and nuclear factor-κB (NF-κB) have been reported to contribute to depressive disorders (2827). In addition, integrative brain analysis of rat and human prefrontal cortex transcriptomes

demonstrates that a number of convergent genes may be involved in the pathogenesis of depressive disorders as 80% of these genes relate functionally to the stress response signalling cascade involving NF-κB, activator protein 1(AP1) and ERK/MAPK, which are associated with depressive disorder, neuroplasticity and neurogenesis (28). In fact. anti-inflammatory agents such as nonsteroidal anti-inflammatory drugs (NSAIDs), statins and cytokine-inhibitors have potential antidepressant properties whilst pro-inflammatory treatment often induces psychiatric side effects such as depressive symptoms (29). In this regard, ketamine has anti-inflammatory effects, which have been confirmed in clinical settings. Dale et al (30) performed a systematic review and meta-analysis and found that intraoperative ketamine could attenuate inflammatory reactivity following surgery as postoperative plasma IL-6 was significantly lower with ketamine. It has been reported that ketamine may decrease the binding affinity of lipopolysaccharide (LPS) for LPS-binding protein and suppress phosphorylation of several protein kinases and transcription factors including NF-κB and AP-1 via TLR-mediated signal-transduction (3) in sepsis model. Thus, it is likely that ketamine can exert anti-inflammatory actions not only in systemic inflammation but also neuroinflammation including depressive disorders. However, recent clinical trial data does not support anti-inflammatory effects of ketamine as a single subanaesthetic dose (0.5mg/kg) did not prevent postoperative delirium, which may be due to neuroinflammation, in elderly patients undergoing major surgery (31). Further studies will be necessary to determine the effects of ketamine on neuroinflammation.

3) Effects of ketamine metabolite, (2R,6R)-hydroxynorketamine

Yao and colleagues (32) found that not only ketamine but also its metabolite, (2R,6R)-hydroxynorketamine could induce lasting alterations in the AMPA receptor function and synaptic plasticity at glutamatergic synapses in the brain reward circuit including the nucleus accumbens and the ventral tegmental area. In addition, these antidepressant actions are independent of NMDAR inhibition.

Enantiomeric differences in the antidepressant actions of ketamine.

Clinically available ketamine used in many countries is presented as a racemic mixture containing equal amounts of two enantiomers, S(+)- and R(-)-ketamine. S(+)-ketamine has greater potency and higher clearance for anaesthesia and analgesia than R(-)-ketamine (21). S(+)-ketamine has about four and three-fold greater antagonistic potency for a NMDA (21) and μ-opioid receptors (3433), respectively. In addition, S(+)-ketamine produces better intraoperative amnesia but fewer psychotic emergence reactions and less agitation (21). There are many case reports of antidepressant effects of S(+)-ketamine (34). Repeated administration of S(+)-ketamine has been reported to be effective in both bipolar and unipolar depressed patients with pharmacotherapy, psychotherapy, and electroconvulsive therapy-resistance and/or suicidal crisis (34). However, several animal studies clearly showed that R(-)-ketamine could produce more potent, safer and longer lasting antidepressant actions (3635). How can R(-)-ketamine induce more beneficial antidepressant effects than S(+)-ketamine? The mechanism remains elusive but one possible explanation might be as follows. R(-)-ketamine significantly attenuates the reduction in dendritic spine density, BDNF TrkB signalling and synaptogenesis in the prefrontal cortex, hippocampal cornu ammonis-3 region (CA3) and dentate gyrus (35). In addition, a positron emission tomography study suggests that the psychotomimetic and hyperfrontal metabolic actions of ketamine are probably induced by S(+)-ketamine as psychotomimetic doses increase cerebral metabolic rates of glucose (CMRglu) in the frontal cortex and thalamus; equimolar doses of R(-)-ketamine decreased CMRglu with no psychotic symptoms (36).

Side-effects of ketamine

The first systematic review of the safety of ketamine in the treatment of depression after single

and repeated doses has been recently published in Lancet Psychiatry (37).

Acute adverse reactions

The most common acute psychiatric side effect was anxiety followed by agitation or irritability, euphoria or mood elevation, delusions or unusual thoughts, panic, and apathy. The most common psychotomimetic side effect reported was dissociation, followed by perceptual disturbance, odd or abnormal sensation, derealization, hallucinations, feeling strange, weird, bizarre, or unreal, and depersonalization. No long-term psychotomimetic side effects were reported. The most common cardiovascular changes were increased blood pressure and increased heart rate. The most common neurological side effects were headache and dizziness. The most frequently reported other side effects were blurred vision and nausea. However, in general, these side effects resolved shortly after dose administration.

Chronic adverse reactions

Although there are no reports regarding chronic adverse reactions of ketamine in this population, several studies have been performed for the efficacy of clinical use of ketamine for treatment of chronic pain (38-41). These reports show that the occurrence of ketamine-induced adverse reactions is limited and often well-tolerated by patients (38-41). However, Niesters et al (39) reported that repetitive or continuous administration of ketamine caused liver enzyme elevations in about 10 % of patients, which returned to the normal within 3 months of cessation. In contrast, recreational ketamine users often reveal urological toxicity, hepatotoxicity, cognitive deficits, and dependency risks. Regarding urological toxicity, cystitis and bladder dysfunction, an increase in urinary frequency, urgency, dysuria, urge incontinence, occasionally painful haematuria, and secondary renal damage have been reported. More than 20% of recreational ketamine users are estimated to have urinary tract symptoms although much higher rates were reported in studies from Spain and Hong Kong (46% and 90%, respectively) (37). These data indicate severe adverse reactions may often occur when used in uncontrolled

circumstances. In addition, as recreational ketamine users use high doses and simultaneously several illicit drugs of abuse. Moreover, contamination of ketamine with other substances may also contribute to the adverse reactions (39). It is difficult to be sure if these adverse reactions are directly caused by ketamine per se. Any long-term clinical use will require careful monitoring of patients to detail this profile.

Conclusion

In the United States most of the so-called “Ketamine Clinics” where patients with depression are treated are run by anaesthetists rather than psychiatrists (42); anaesthetists understand how to use this drug safely. We would welcome further study and use of this ‘anaesthetic’ drug in psychiatric indications.

Authors’ Contributions and Authorship

Both K.H. and D.G.L. discussed the topic together. K.H. wrote the first draft of the manuscript. D.G.L. revised it.

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Figure Legends

Figure 1. Potential mechanism(s) of anti-depressant effects of ketamine

→ & ⇨: rapid anti-depressant actions, ⇢: delayed anti-depressant actions, ↓: inhibition or decrease, ↑: activation or increase, N-methyl-D-asparate: NMDA, hyperpolarization-activated cyclic nucleotide-gated channel 1: HCN1, gamma-aminobutyric acidergic: GABAergic, brain-derived neurotropic factor: BDNF, eukaryotic elongation factor-2: eEF2, tyrosine-related kinase-B: TrkB, extracellular signaling related kinase: ERK, proteinkinase-B: Akt/PKB, glycogen synthase kinase-3: GSK-3, rapamycin: mTOR, SSRI: selective serotonin reuptake inhibitors, SNRI: serotonin–norepinephrine reuptake inhibitors, NaSSA: noradrenergic and specific serotonergic antidepressant, NDRI: norepinephrine and dopamine reuptake inhibitor, Toll-like receptor: TLR, tumour necrosis factor-α(TNF-α), interleukin: IL, lipopolysaccharide: LPS, nuclear factor-κB: NF-κB, activator protein-1: AP-1, PFC: prefrontal cortex, IGF-1: insulin-like growth factor.

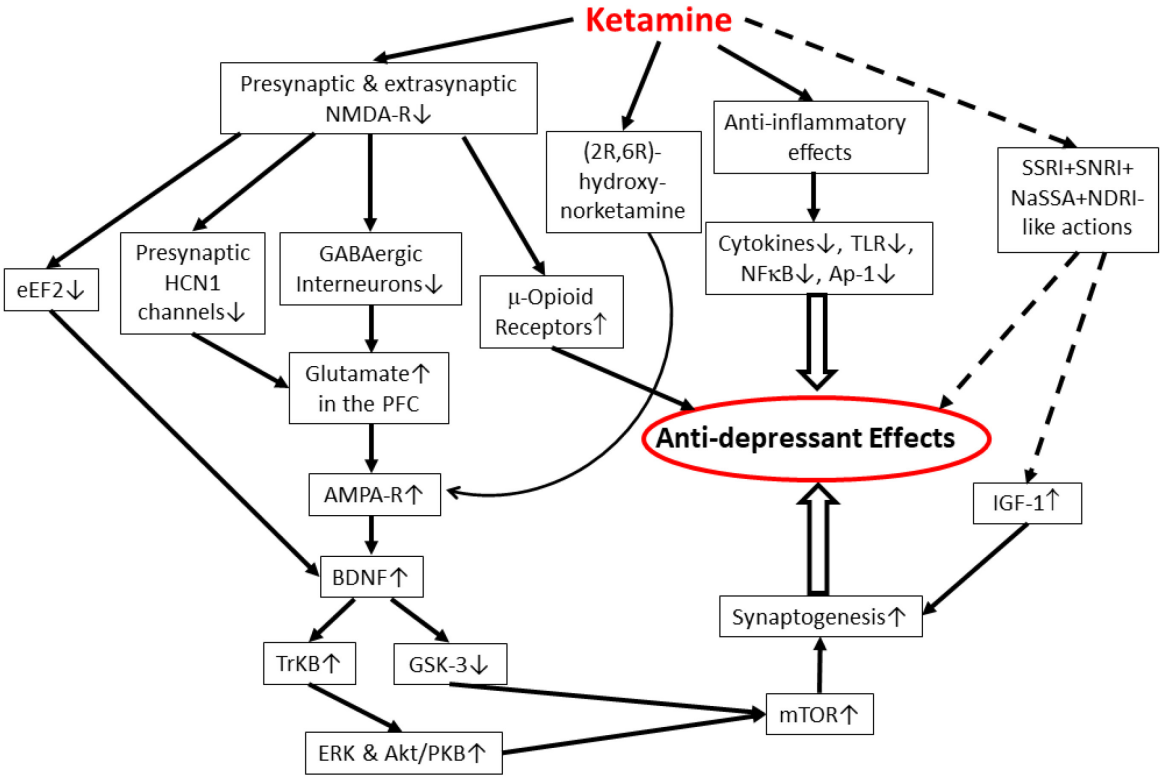
Ketamine
Presynaptic & extrasynaptic NMDA-R↓
(2R,6R)-hydroxy-norketamine
Anti-inflammatory effects
SSRI+SNRI+ NaSSA+NDRI-like actions
eEF2↓
Presynaptic HCN1 channels↓
GABAergic Interneurons↓
μ-Opioid Receptors↑
Cytokines↓, TLR↓, NFκB↓, Ap-1↓
Glutamate↑ in the PFC
Anti-depressant Effects
AMPA-R↑
IGF-1↑
BDNF↑
Synaptogenesis↑
TrKB↑
GSK-3↓
mTOR↑
ERK & Akt/PKB↑

Figure 1.