Rapid Anti-Depressant Relief by Ketamine: Exploring A Complex Mechanism of Action

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Abstract: Background: Suicide rates and narcotic overdose have doubled since 2000. At least 30 percent of people with major depression are Treatment-Resistant (TR) and require novel therapeutics. Ketamine at low doses has been shown in clinical trials to induce a rapid, short-lived anti-suicide and anti-depressant effect.

Objectives: To review the potential mechanism of action of ketamines’ alleviation of depressive symptoms from both animal and available human literature.

Methods: This is a synthesis of information from papers listed in PUBMED Central. Although not exhaustive, this review highlights the most compelling work in the field related to this remarkable clinical rapid anti-depressant effect.

Results: While there have been several theories and with some scientific evidence to date, the conclusion here is that currently, an exact and acceptable mechanism of action (MOA) for ketamines’ rapid anti-depressant effect is not apparent. The MOA of this compound with psychoactive abuse potential at a higher dosage and acute antidepressant effect in the most resistant patients is unknown.

Discussion: Possible MOAs reviewed, include dopamine receptor modulation through epigenetic neuroadaptation via specific D1/D2 antagonism, D1 activation using optogenetic stimulation, and the role of D2/D3 availability in the ketamine therapeutic action.

Conclusion: Unraveling MOA could guide the development of other unique Psychoplastogens capable of rapidly promoting structural and functional neural plasticity in cases of TR Major Depressive Episodes (MDE) and unipolar Major Depression Disorder (MDD).

Keyword: Dopamine, ketamine, Mechanism of Action (MOA), rapid antidepressant effect, Treatment Resistant Depression (TRD).

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1. INTRODUCTION

Suicide rates and narcotic overdose have doubled since 2000. At least 30 percent of people with major depression are Treatment-Resistant (TR) and require novel therapeutics. Ketamine at low doses has been shown in clinical trials to induce a rapid, short-lived anti-suicide and anti-depressant effect.

1.1. Prevalence Data for Major Depressive Disorder (MDD)

The prevalence data for Major-Depressive-Episodes (MDE) are from the 2016 National Survey on Drug Use and Health (NSDUH). The study definition is: “Two weeks or longer during which there is either depressed mood or loss of interest or pleasure, and four or more symptoms that reflect changes in functioning, such as problems with energy, sleep, eating, self-image, concentration, or recurrent thoughts of death or suicide. Unlike the definition in the DSM-IV, there were no exclusions for MDE caused by medical illness, bereavement, or substance use disorders” [1].

In 2016, of more than 10 million U.S. adults aged 18 or older with a major depressive episode, 64% had at least one major depressive episode with severe impairment. This number represented 4.3% of all U.S. adults. Moreover, the combined number of deaths among Americans from suicide and unintentional overdose doubled to 110,749 in 2017 and has exceeded the number of deaths of diabetes. Indeed, this increase includes opioid overdose deaths, as well as those related to Major Depressive Disorder (MDD). It is known that chronic effects of prescribed potent analgesics impact dopamine release at the Nucleus Accumbens (NAc) by dysregulation of the glutaminergic drive at the Ventral Tegmental Area (VTA) [2, 3]. Increasing mortality rates highlight the need to investigate medications that may affect the glutaminergic system like Psychoplastogens that have rapid onset and possibly better response rates to treat resistant patients with MDE.

1.2. A Paradigm Shift in Approaches to Treating Brain Disorders

Olson, D. E. [4] in 2018 suggested that the ability to change and adapt in response to stimuli (neural plasticity) is an essential aspect of healthy brain function that might become the basis of treatment for a wide variety of brain disorders. Many neuro-psychiatric diseases, including mood, anxiety, and substance use disorders, arise from an inability to weaken the pathologic and strengthen beneficial neurological circuits, ultimately leading to maladaptive behavioral responses [3]. Therefore, compounds capable of facilitating the structural and functional reorganization of neural circuits to produce positive behavioral effects have broad therapeutic potential. Several known drugs and experimental therapeutics have been shown to promote plasticity, but most rely on indirect mechanisms and are slow acting. However, evidence suggests that in humans, ketamine increases glutamate release in the prefrontal cortex, a mechanism previously linked to schizophrenia pathophysiology and implicated in the induction of rapid antidepressant effects [4].

The goal here is to present a minireview, to bring together pertinent animal and human articles from the literature that identify possible mechanisms of action of ketamine, and to explore questions about how ketamine alleviates depressive symptoms, why the effects are both rapid and short-lived, as well as, elucidate the addictive and dissociative side-effects.

2. WHAT IS KETAMINE?

Ketamine is a synthetic anesthetic, used in low doses in Vietnam where it became established as an effective anesthetic /analgesic. Ketamine is part of a recently discovered class of fast-acting therapeutic Psychoplastogenic compounds including psychedelics that have short-lived antidepressant therapeutic effects. They are capable of rapidly promoting structural and functional neural plasticity and must be considered in cases of treatment-resistant (TR) Major Depressive Episodes (MDE).

The use of Psychoplastogenic medications in psychiatry represents a paradigm shift in approaches to treating brain disorders that emphasizes selective modulation of neural circuits and focuses less on rectifying "chemical imbalances" [4]. The effects of ketamine include neuroplasticity, the reconstruction of neural networks through neurotrophic effects. Zhang et al. [5] provided some evidence showing in rodents that subanesthetic
intravenous ketamine infusion altered neuroplasticity-related proteins in the hippocampus, amygdala, and the prefrontal cortex.

2.1. The Anti-Depressant Effects of Ketamine: Clinical Observations

Ketamine is considered a significant breakthrough in the field of treatment for refractory depression [6]. Many recent studies looked at the efficacy of ketamine for the treatment of Major Depressive Disorder (MDD) and Suicidal Ideation (SI).

In support of the anti-depressant effects of ketamine, Reed et al., [7] used functional magnetic resonance imaging (fMRI) emotion-based attentional task for a placebo-controlled, crossover study of 33 un-medicated participants with MDD and 26 healthy controls (HCs). In MDD, brain activity post-ketamine was similar to healthy controls post-placebo. These findings suggest that ketamine may act by normalizing brain function in depressed individuals.

Caddy et al. [8] reviewed the use of glutamate receptor modulators in unipolar depression. Among all glutamate receptor modulators, only ketamine (administered intravenously) proved to be more efficacious than placebo, although limitations included small sample sizes and risk of bias. There was low quality evidence that treatment with ketamine increased the likelihood of response after 24 hours (odds ratio (OR) 10.77, 95% confidence interval (CI) 2.00 to 58.00; 3 RCTs, 56 participants), 72 hours (OR 12.59, 95% CI 2.38 to 66.73; 3 RCTs, 56 participants), and one week (OR 2.58, 95% CI 1.08 to 6.16; 4 RCTs, 131 participants). The effect of ketamine was even less likely at two weeks, as data were available from only one trial (OR 0.93, 95% CI 0.31 to 2.83; 51 participants, low-quality evidence). Compared to the placebo, ketamine caused more confusion and emotional blunting [7].

Grady et al. [9] reviewed seven randomized controlled trials of ketamine usage in major depressive disorder and bipolar depression. They found that ketamine demonstrated a statistically significant improvement over placebo or midazolam in MDD and bipolar depression and suggested that ketamine may be helpful for patients that have exhausted other therapeutic options.

Ballard et al. [10] pointed out that until the glutamatergic modulator ketamine was found to elicit rapid changes in active suicide-ideation (SI), no pharmacological treatments existed. They evaluated clinical, demographic, and neurobiological factors from data pooled from five clinical ketamine trials. Treatment-resistant inpatients (n=128) with DSM-IV-TR-diagnosed MDD or bipolar depression received one sub-anesthetic (0.5mg/kg) ketamine infusion over 40 min. Growth mixture modeling generated the SI response classes used to analyze composite SI variable scores, and multinomial logistic regression was used to evaluate class membership predictors. They found that response only extends to Day 3. Plasma markers were used rather than cerebrospinal fluid (CSF) markers. The heterogenic response to ketamine of those with SI underscores its potential independence from changes in a depressed mood. Individuals reporting symptoms that suggested a longstanding history of chronic SI were less likely to respond or remit post-ketamine.

Ren et al. [11] evaluated the use of ketamine in electroconvulsive therapy ECT for depressive disorder in a systematic review and performed a meta-analysis of sixteen studies, including 928 patients. They found that at the end of six ECTs, no significant standardized mean difference (SMD) was observed in favor of the ketamine group, although depressive scores were lower in the ketamine group after 1st ECT and 3rd to 6th ECTs. They found that while ketamine used in ECT cannot reduce the depressive symptoms at the end of treatment, it could accelerate the anti-depressive effect in depressive patients receiving ECT, especially in those who used ketamine as an add-on anesthetic. However, adverse events were increased, primarily related to cardiovascular and psychiatric systems, during the whole ECT course.

Sinyor et al. [12] used a case series of five inpatients admitted to a tertiary care hospital for six serial ketamine infusions to explore ketamine augmentation for MDD and SI in a real-world inpatient setting. The standard 0.5mg/kg intravenous (IV) ketamine was used for about two weeks and evaluated using suicide and depression rating scores; Scale for SI and the Montgomery-Asberg Depression Rating Scale, (MADRS) at baseline and on treatment days. They found that all patients
experienced benefit with ketamine. In terms of SI scores, they diminished by 84% from 14.0+/-.45 at baseline to 2.2+/-.2.5 at study endpoint. The MADRS scores decreased by 47% from 42.2+/-.5.3 at baseline to 22.4+/-.8.0. One patient withdrew from the study to initiate ECT, and another due to dissociative effects during the ketamine infusion. They suggest that these preliminary pilot data are promising with a more than two-fold reduction in SI following ketamine infusions and large-scale randomized controlled trials to confirm the efficacy of serial ketamine for the treatment of SI in "real-world" settings.

In a randomized, double-blind, placebo-controlled trial, Ionescu et al. [13] reported on twenty-six medicated outpatients with Severe Major Depressive Disorder (SMDD) and current, and chronic SI randomized to saline placebo or six ketamine infusions (0.5mg/kg over 45 minutes) over three weeks. Depression and SI assessments were made at baseline, 4 hours post-infusion, and during a three-month follow-up phase. During the infusion phase, there were no differences in depression severity or SI between placebo and ketamine was seen (p=0.47 and p=0.32, respectively). By the end of the infusion phase, two patients in the ketamine group and one in the placebo group met criteria for remission from depression. The three-month follow-up yielded two patients in each group who met the criteria for remission from depression. Uncontrolled outpatient medication regimens, the small sample size, and the restriction to outpatients, who may have had lower levels of SI than would be seen in emergency or inpatient settings, were limitations of this study. In this double-blind, placebo-controlled study, non-escalating repeated doses of ketamine did not outperform placebo for patients with severe TRD and current, chronic SI. The commonly used dose of 0.5mg/kg from previously published open-label data was not sufficient in this severe and chronically ill outpatient population.

3. THE MONOAMINE HYPOTHESIS OF DEPRESSION

Importantly, the impact of conventional antidepressants on clinical symptoms, are thought to be due to increasing the availability of amine neurotransmitters. The full antidepressant response takes weeks of daily administration; some patients do not respond adequately. Moreover, the lack of adequate immediate response is a crucial limitation of antidepressant therapy because this prolonged time to act results in a lack of medication compliance, difficulty switching medications, and the risk of suicide [2, 14]. These phenomena highlight an urgent need for new drugs with higher response rates and a rapid onset of action: ketamine at low doses, unlike typical antidepressants, has been shown in clinical trials to induce a rapid, although short-lived anti-suicide and anti-depressant effect.

In summary, the fMRI study found that compared to placebo, post-infusion, Ketamine normalizes brain function in depressed individuals. The studies also evaluated the efficiency of standard doses, dosing protocols, and Ketamine in combination with ECT and medication. However, the outcomes measured in the length of symptom remission are mixed. A better understanding of the mechanism of action (MOA) of Ketamine and prolonging the antidepressant effects would be worthwhile goals.

A focused review of the use of glutamate receptor modulators in unipolar depression from Caddy et al. [8] found ketamine to be effective compared to placebo at time points up to one week, with less certain effects at two weeks post-treatment.

4. PHARMACOGENETICS OF KETAMINE

Clinical evidence about the metabolism of ketamine to norketamine was used by Li et al. [15] to explore the pharmacogenetics of ketamine. He found that the presence of the CYP2B6*6 allele variant of the CYP2B6 genotype might explain the 60-80 percent inter-individual variability of plasma ketamine concentrations. In chronic pain patients, the CYP2B6*6 allele associated with a substantial decrease in steady-state ketamine plasma clearance that resulted in higher plasma concentrations and may result in higher ketamine adverse effects. Other influences on ketamine plasma concentrations include age and other challenging to quantify influences, such as pro-inflammatory effects and opioid-induced hyperalgesia. Age-related change, possibly due to decreased blood flow to the liver, might account for 20 to 30 percent of the differences in ketamine plasma clearance.
Moaddel et al. [6] explored the plasma to profile ketamine and placebo in a crossover trial of treatment-resistant major depressive disorder (n=29) healthy control subjects (HCs) (n=25). They found that ketamine treatment resulted in a general increase in circulating sphingomyelins levels, without a correlation to response to ketamine. However, in the kynurenine and the arginine pathways at four hours post-infusion, more pronounced effects were observed. Circulating kynurenine levels decreased, and the bioavailability of arginine increased in responders to ketamine treatment. Arginine is an α-amino acid that is used in the biosynthesis of proteins and is the precursor for the biosynthesis of nitric oxide (NO), suggesting NO as a possible mechanism for response to ketamine.

5. UNDERSTANDING THE NEGATIVE EFFECTS KETAMINE: STILL A MYSTERY

David Olsen [4] pointed out that the risks associated with using these drugs that are capable of profoundly impacting the neuronal structure are unknown. The promotion of neuronal growth during development could interfere with the normal processes which refine neural circuits. Equally, the effects psychoplastogens will have on the aging brain like mTOR activation, are unclear. Excessive mTOR activation is associated with some diseases, including autism spectrum disorder and Alzheimer’s disease.

The therapeutic benefit of ketamine, while useful for those with TRD, has thus far been short-lived. The neurotoxic effects and the potential for abuse suggest that the use of ketamine in a clinical setting warrants further investigation. Development of new and improved drugs or protocols that retain the antidepressant effects and avoid issues like the mechanism-related dissociative side-effects of ketamine (or esketamine), and explore the route of administration are needed [16, 17].

Moreton et al. investigated the abuse potential of ketamine in rhesus monkeys. They worked with self-administration behavior daily for 2-hours. That the data showed that ketamine maintains self-administration behavior like that of some other drugs and conventional reinforcers [18]. The dissociation and delirium effects of ketamine have led to recreational abuse, which puts users at risk of environmental harms like nonconsensual sexual intercourse. Chronic ketamine use may lead to memory impairment of and persistent dissociative, depressive, and delusional thinking. Also, lower urinary tract infections, including cystitis and gastric and hepatic pathology; abnormal liver function tests, choledochal cysts, and dilations of the common bile duct, have been reported [19].

6. THE SEARCH FOR THE MECHANISM OF ACTION OF KETAMINE: WHY IS THE ANTIDEPRESSANT ACTIVITY SO SHORT LIVED?

Chronic depression causes atrophy of the neurons in the Prefrontal Cortex (PFC), a region of the brain that controls anxiety and regulates mood. The branches and spines shrivel up and disconnect from other neurons. One hypothesis about why ketamine is useful is that it can rapidly regrow the arbors and spines of these critical neurons.

Studies from Olson’s group [4] at UC Davis of neurons grown in dishes, and experiments using rodents and fruit flies, demonstrated that several psychoplastogens, like psychedelics and ketamine, activate the mammalian target of rapamycin (mTOR); a protein an essential in cell growth that encourages neuronal proliferation of more branches and spines [4]. Importantly, this does not explain why the antidepressant effect is so transient when the growth of PFC atrophic neurons is induced by ketamine [20]? Also, Grady et al. [9] suggested that ketamine exerts its antidepressant properties through N-methyl-D-aspartate (NMDA) receptor antagonism.

Witkin et al., reviewed the literature in 2018 [20] found that a documented extracellular glutamate efflux is induced by these drugs, and hypothesized that the triggering mechanism is excitatory neurotransmission produced by α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor amplification.

Further, Lur et al. [21] found that four hours after ketamine treatment, glutamatergic synapses themselves are not significantly affected. However, they reported that the loss of Regulator of G-protein Signaling (RGS4) activity might be due to the disruption of synaptic modulation through a very complicated neuromodulatory mechanism. It is known that under control conditions, α2 adren-
ergic receptors and type B \(\gamma\)-aminobutyric acid \(\text{(GABAB)}\) receptors selectively inhibit \(\alpha\)-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid \(\text{(AMPA)}\) -type glutamate receptors \(\text{(AMPARe)}\) and NMDARs, respectively. If the GABA inhibitory activity is interrupted by ketamine through the above mechanism, would this dis-inhibition drive dopaminergic release at the VTA-NAc? The difficulty is to understand why following ketamine infusion and reduction in RGS4 activity, via the mechanism observed by Lur et al. [21], the resultant disinhibition of glutamnergic transmission induced anti-depressant response in TRD is short-lived.

Thus, the suggestion has been that ketamine’s short-acting anti-depressant effect may in part be due to GABAergic activity. While a thorough search in the literature reveals several theories with some evidence, the foremost studies seem contradictory. Boczek et al. [22] reported that following a 5-day infusion of subanesthetic doses to rats; post-mortem analysis revealed diminished GAD67 expression in the cortex of the cerebellum (by \(~60\%) and in the hippocampus (by \(~40\%) that correlated with lowered protein level in these areas. The expression of GAD65 isoform decreased by \(~45\% in the striatum, but a pronounced \(~90\% increase was observed in the hippocampus. Consecutively, reduction in glutamate decarboxylase activity and GABA concentration was detected in cortex, cerebellum, and striatum, but not in the hippocampus. Ketamine administration decreased GABA transaminase protein in cortex and striatum (by \(~50\% and 30\%, respectively), which was reflected in the diminished activity of the enzyme. They also observed synaptic GABA release to be reduced by \(~30\% from striatal terminals. In terms of the inhibitory role of reducing glutamnergic drive, lowered GABA activity could help explain the subsequent increase of NAc dopamine release and ketamine’s anti-depressant effects.

Magnetic resonance spectroscopy data, recently supported evidence available since 1980, suggesting that central nervous system GABA concentrations in major depressive disorder \(\text{(MDD)}\) patients are reduced, leading to the assumption that the underlying etiology MDD’s maybe an overall reduction in GABA-mediated inhibitory neurotransmission. Along these lines, albeit not in agreement, Fuchs et al. [23] found that loss of inhibitory synaptic input resulted in increased excitability of SST+ interneurons \(\text{(somatostatin-positive GABAergic interneurons)}\). Increased frequency of spontaneous inhibitory postsynaptic currents pyramidal cell targets of SST+ neurons was observed. Enhanced GABAergic inhibitory synaptic inputs from SST+ interneurons to pyramidal cells resulting in chronic reductions in the synaptic excitation-inhibition-ratio and represents a novel strategy for antidepressant therapies that reproduces behavioral and biochemical endpoints of rapidly acting antidepressants like ketamine. New theories suggest that higher brain concentrations of glutamate \(\text{(excitatory)}\) and lower GABAergic interneuron input \(\text{(inhibitory)}\) promote depression. In terms of understanding related mechanisms of antidepressant effects, the conclusion that increasing glutamnergic drive by reducing inhibitory control through GABA induces depression, in fact, using this logic, the opposite would be expected. Pehren and Sanchez [24] strongly argue that the considerable gaps in comprehension of the relationship between MMD and GABA physiology, must be corrected with new data from well-controlled empirical studies. The conclusion, of their review, suggests that the hypothesis that MDD is caused by reduced GABA neurotransmission is too simplistic and a more nuanced and complex model of the role of inhibitory neurotransmission in MDD is needed.

Although these newer views of the causes of MDD seem counterintuitive, they are not. The idea that sustained GABAergic transmission results in disinhibition of GABAergic interneurons that increase frequency of spontaneous inhibitory postsynaptic currents resulting in chronic reductions in the synaptic excitation-inhibition-ratio, reduces depression supporting the earlier view of the monoamine hypothesis of depression; that reduced dopamine at brain reward sites is described as the primary cause of depressive symptoms [25, 26]. The sustainability of the antidepressant effect of ketamine may reside in the sustainability of the GABAergic transmission via ketamine infusion.

Beluion & Grace [25] suggest that anhedonia is an essential aspect of depression, and while dopaminergic activity is complicated, its dysregulation leads to MDD. They point out that dopaminergic activity is complicated, its dysregulation leads to MDD. They point out that dopaminergic
activity is under the regulation of multiple brain structures, such as the ventral subiculum of the hippocampus and the basolateral amygdala. However, whereas basic and clinical studies demonstrate deficits of the dopaminergic system in depression, to further understand not only specific therapeutic targets of ketamine, the origin of these deficits may lie in dysregulation of its regulatory afferent circuits. The newer view involving disinhibition of somatostatin-positive GABAergic interneurons that results in an anxiolytic and antidepressant-like brain state represents a new opportunity to target GABAergic interneurons for the treatment of TRD that could increase the effect duration while maintaining the rapid effect of treatment.

The rationale related to Glutamate/GABA excitatory /inhibitory ratios and ketamine’s antidepressant short-term effects, is presented in a brief snapshot of the currently available data which seems prudent, but additional research is required to help dissect the complex nature of this important interaction. The older view of neurochemical correlates of depressive symptoms was tied to serotonergic and dopaminergic balance and not GABA or glutamate [27], however, more recently, others [28, 29] based on analyses of depressed patients have found new evidence of reduced expression of plasma membrane glutamate transporters, and elevated brain concentrations of glutamate [30]. Therefore, in several studies, MDD is associated with attenuated GABAergic activity including reduced GABA concentrations [31-36]; decreased expression of GABA type A receptors (GABAARs) [37]; lower expression of glutamic -acid decarboxylase [38, 39]; and dysfunction of GABA type interneurons [40-42]. Moreover, chronic and high stress lead to impaired inhibition of neural pathways by chloride reversal potential of neurons, rendering GABA ineffective as an inhibitory neurotransmitter. This effect is found in the paraventricular nucleus of the hypothalamus that modulates the stress axis, as well as the hippocampus [43-45]. Importantly, cellular vulnerability to stress is augmented in a subclass of GABAergic interneurons that express the neuropeptide somatostatin (SST) [46]. In response to stress, the excitatory/inhibitory imbalances overcome by reciprocal positive reinforcement, and this mechanism has been implicated in MDD.

Recently, Liston and associates [47] reported in Science (2019) that they might have found a biological reason for neuronal changes underlying depression-related behaviors in mice. NIH researchers used high-resolution images of dendritic spines in the prefrontal cortex, before, and after mice experienced stress, to explore mechanisms underlying the transition from active depression to remission in humans. The researchers found the decreased formation of, dendritic spines, (protrusions that receive input from other neurons) in their prefrontal cortex, and increased behaviors related to depression in the stressed mice compared to non stressed mice.

Reduced resting-state functional connectivity (rsFC) and replicated studies link the emergence of depressive behaviors in mice with dendritic spine loss. Striatal dopamine deficits predicted reduced striatal functional-connectivity in major depression, as seen in concurrent 11C-raclopride positron emission tomography and fMRI investigation. Hamilton et al. [48] and Liston’s group [45] found that treatment with ketamine quickly restored functional connectivity and of neuronal assembly eliminating depression based behaviors in mice. Mice exposed to stress showed a reversal of behaviors related to depression twenty-four hours after receiving one dose of ketamine. Also, dendritic-spine formation increased compared to stressed mice that had not received ketamine. While this work could help explain the neuronal reversal of stress-induced dendritic changes in mice, and in humans, reduced rsFC has also been linked to low dopamine function, and as such depressive symptoms, the concern here is that linking human depression to mice may be problematic and must await further human-based testing.

It is current thinking that normalization of the GABA/Glutamate ratio should be the preferred therapeutic target supported by a series of studies involving anti-depressant and electroconvulsive therapy of depressed patients [49-52]. Also, Shen et al. [49] reported that reduced function of GABAARs (GABAAR γ2+/− mice) results in anxious-depressive-like phenotypes of mice that are normalized by chronic treatment with antidepressant drugs, such as the tricyclic desipramine. Remarkably, Ren et al. [53] showed that ketamine, normalizes the depressive-like phenotypes of
GABAAR γ2+/− mice, by potentiating the medial PFC inhibitory synapses. Currently, it appears that ketamine’s rapid, but short-lived anti-depressant effect, may be due to a number of complex mechanisms including 1) promoting the formation and function of synapses [53, 54]; 2) triggering a cascade of phosphorylation events 3) activating target of rapamycin (mTOR) 4) activation of p70S6K (S6K); 5) inhibition of factor 3 kinase (eEF2K); 6) attenuation of inhibitory phosphorylation of the single eEF2K target, eEF2; 7) augmented activity of eEF2 and increased mRNA translation elongation [55, 56] and 8) possible increased dendritic mRNA translation elongation [57-74].

It is noteworthy that defects in GABAergic synaptic transmission significantly improve the antidepressant response to ketamine. However, as suggested by others [75], none of these data demonstrate a causative relationship between enhanced GABAergic synaptic transmission and effective antidepressant therapies.

However, Newport et al. [76] conducted a systematic review and meta-analysis of ketamine and other NMDA receptor antagonists for the treatment of major depression. They searched MEDLINE, PsycINFO, and other databases for placebo-controlled, double-blind, randomized clinical trials of NMDA antagonists in the treatment of depression. Importantly, in terms of NMDA antagonists, the rates of treatment response and transient remission of symptoms, as well as changes in the frequency and severity of dissociative psychotomimetic effects, and depression symptom severity were subsequently measured. From seven trials of n=147 ketamine-treated participants, they found that ketamine produced a rapid, yet transient, antidepressant effect accompanied by brief psychotomimetic and dissociative effects. From five trials of total n=89, Ketamine augmentation of electroconvulsive therapy (ECT) significantly reduced depressive symptoms following initial treatment, but not after the ECT course. Other NMDA antagonists failed to demonstrate efficacy consistently. However, two partial agonists at the NMDA co-agonist site, rapastinel and d-cycloserine, significantly reduced depressive symptoms without psychotomimetic or dissociative effects [76]. This positive effect of partial agonism of NMDA makes sense is supported by older theories of depression linked to dopamine function.

The failure of other NMDA antagonists suggests that any future advances will depend on improving understanding of ketamine’s mechanism of action [3]. Krystal’s group recently showed in a small case series of five patients, that Ketamine’s antidepressant effect was not attenuated with naltrexone pre-treatment. The lack of effect attenuation is noteworthy because it argues against other work suggesting that ketamine’s antidepressant effect in MDD is due to opioid receptor stimulation as well as increased Global Brain Connectivity in the lateral PFC, caudate, and insula [77]. Possibly, blocking NMDA receptors could induce a reduction in glutaminergic drive at the VTA, causing a reduced Dopamine (DA) release at NAc. Indeed, NMDA antagonism does not lead to proper dopamine function and therefore should not lead to antidepressant activity. Therefore, agonism of NMDA does perhaps make more sense.

6.1. What About Dopamine?

Kokkinou et al. [78] proposed a mechanism of action for ketamine in influencing dopamine’s change from baseline. Accordingly, Ketamine blocks NMDA receptors on GABAergic interneurons disinhibiting glutamate neurons projecting to dopamine neurons in the midbrain, augmenting glutamate release resulting in enhanced dopamine neuronal firing and as such increasing dopamine levels in the striatum and cortex of rodents. A meta-analysis involving 40 original peer-reviewed studies provided evidence for the role of dopamine in ketamine’s antidepressant effects. Even in several rodent investigations, acute ketamine administration significantly enhanced dopamine levels in the cortex, striatum, and the NAc. Compared to controls, ketamine induced a 62-180% increase in dopamine neuron population firing. With chronic ketamine administration, they found cortical dopamine release to be from 88-180%. Of interest is the fact that sub-anesthetic doses of Ketamine in healthy humans acutely produces symptoms similar to schizophrenia [79] and low-level schizophrenic symptoms are seen in ketamine abusers [80].

Moreover, ketamine exacerbates psychotic symptoms in patients with known schizophrenia.
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Fig. (1). Illustrates dopamine receptor modulation through epigenetic neuroadaptation via D1/D2 antagonism, also, D2/D3 availability in the ketamine therapeutic action has a notable role in the ketamine mechanism. Depression results from attenuation of dopamine at the reward sites, but ketamine increases dopamine activity at the reward site. Also, ketamine induces a lowering of the availability of D2/D3 receptors by actually augmenting DA neuronal release at the Ventral Tegmental Area (VTA) - N. Accumbens (VTA-NAc). This effect of Ketamine provides at least one antidepressant mechanism. Also, the α2 adrenergic receptors, and type B γ-aminobutyric acid (GABAB) receptors selectively inhibit α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) -type glutamate receptors (AMPARs) and NMDARs. Thus, respectively if the GABA inhibitory activity is interrupted, this disinhibition drives dopaminergic release at the VTA-NAc, which in the end increases the activity of the reward cycle and decreases depression.

[81]. To reiterate, Peciña et al. [27] reported that compared to controls, patients with depression had greater D2/3 receptor availability in several striatal regions, such as bilateral ventral pallidum/nucleus accumbens (vPAL/NAc), and the right ventral caudate and putamen. Moreover, the depressed group, D2/3 receptor availability in the caudal portion of the ventral striatum vPAL NAc correlated with higher anxiety symptoms. However, D2/3 receptor availability in the rostral area of the ventral striatum correlated negatively with the severity of motivational anhedonia. Importantly, MDD non-remitters showed greater baseline anxiety, greater D2/3 availability in the vPAL/NAc, and greater placebo-induced DA release in the bilateral NAc. Higher availability D2/3 receptors in the ventral striatum of patients with MDD seems to be associated with lack of response to antidepressants and comorbid anxiety symptoms, an important consideration of the antidepressant effect of ketamine in TRD. It is noteworthy that higher D2/D3 receptor availability means lower dopamine release and as such a hyperdopaminergic exists causing MDD symptoms.

The work of Hare et al. [82] offers further support for the role of dopaminergic function in ketamine’s anti-depressant effect. Using optogenetic stimulation of medial prefrontal cortex DRD1 neurons similar to ketamine stimulation induces a rapid anti-depressant effect. However, unlike ketamine, this anti-depressant effect was long-lasting. Also, disruption of DRD1 neuronal firing blocked the rapid antidepressant effects of ketamine. These results suggest that downstream- anti-depressant effects of ketamine, independent of mechanism [83-95] seem to involve dopaminergic activity (Fig. 1).
Dopamine involvement in proposed mechanisms of ketamine action and its role as an anti-depressant. Fig. (1).

7. SUMMARY

Ketamine, a known Psychoplastogens capable of rapidly promoting structural and functional neural plasticity, is effective in TRD with a short-term effect [19, 96-99]. Recent studies in humans have suggested both an important role for endogenous opioids and opioid-like effects in ketamine’s anti-depressant effect [100-102]. However, with thousands of studies published on this topic, the exact mechanism of ketamine as a rapid anti-depressant remains unknown.

It is noteworthy that ketamine’s proposed antagonistic activity of NMDA receptors as a way of explaining ketamine’s anti-depressant effect, seems counter-intuitive, and as such, we have argued this proposed mechanism, as evidenced from the work of Newport [76]. Additionally, the role of ketamine’s opioid receptor stimulant effects has also been adequately refuted [101]. It has not clearly been shown that the rapid effect of ketamine is due to enhanced dopaminergic function, which seems most likely in the face of a large body of literature, including studies on genetics related to depression and dopaminergic function [103-105]. However, its role as anti-depressant may be revealed by using newer techniques like optogenetics [82]. One important caveat is the suggestion that dopamine plays a significant role in ketamine’s antidepressant effect requiring more in-depth human rather than animal studies.

CONCLUSION

The clinical findings presented here, concern prolonging ketamine’s effects and require additional investigation. Scientific and clinical colleagues are urged to perform more extensive controlled experiments in humans to test these thought-provoking new theories. While in terms of ketamine’s effects on neural circuits, especially in animals, advances have been made in terms of explaining potential mechanisms concerned with the known rapid anti-depressant effects requiring caution until human data is executed. To date, there are 26 articles listed in PUBMED (3-22-19) using the search terms ketamine, depression, and fMRI in humans. However, currently, no definitive conclusions can be extracted from these sophisticated studies and future human studies will be required to determine ketamine’s neurochemical mechanism [102] and to avoid the addictive and dissociative side-effects. Development of new and improved drugs that retain the rapid antidepressant effects but are devoid of the issues associated with ketamine itself relies on understanding the MOA and development of new methods of drug delivery.

CONSENT FOR PUBLICATION

Not applicable.

FUNDING

KB is the recipients of R41 MD012318/NIMHD NIH HHS/United States.

CONFLICT OF INTEREST

Kalypso Wellness Centers of San Antonio, Texas, has developed several ketamine related protocols currently commercialized, and the following individuals have stock in the company: BC, CC, SW, and EC. TP is a consultant, and MM is a consultant paid by Kalypso. There are no other conflicts of interest for KB, DB, LL, BB, MSG.

ACKNOWLEDGEMENTS

The authors appreciate the staff of Geneus Health LLC., especially Justin Jones and Erin Gallagher, and Jessica -Valdez Ponce.

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[PMID: 26395901]

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