Bachelor's thesis

NTNU
Norwegian University of Science and Technology

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What underlying mechanisms led the dissociative anesthetic ketamine to be clinically recognized as an antidepressant?

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Supervisor: Elisabeth Egholm Jacobsen
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Abstract

Ketamine has been used in medical practice for decades as a dissociative anesthetic. Research into its pharmacological properties began in the 2000s when it was observed that subanesthetic doses had a significant effect on patients with depressive disorders. These doses gave rapid-acting antidepressant responses and were later found to benefit individuals with treatment-resistant depression. In a recent significant development, ketamine was approved as a medication for depression in 2019.

This thesis will provide a contextual background of ketamine and its progression from its origin to its current clinical relevance as an antidepressant. The discussion will focus on the underlying mechanism responsible for the antidepressant response. Despite ongoing research, the precise processes involved when ketamine is administered at subanesthetic doses remain elusive due to the complexity of the NMDA receptors. It is suggested that ketamine modulates glutamate neurotransmission at these doses, leading to the stimulation of AMPA glutamate receptor and subsequent increase of glutamate levels. This mechanism facilitates the restoration of synaptic connectivity in brain regions dysregulated by depression disorders. However, conflicting findings and proposed alternative mechanisms indicate the presence of multiple contributors to ketamine's antidepressant effects.

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1. Introduction

1.1 Background

Forbes Health reported in 2024 that the World Health Organization has estimated that around 5% of adults suffer from depression on a global scale, but this number is only based on individuals who have received an official diagnosis.[1] Therefore, it can be suspected that the actual statistics on depression are considerably higher. The traditional antidepressants used to treat these patients are known as selective serotonin reuptake inhibitors (SSRIs) that primarily target monoamines. However, it has been observed that around one-third of these patients do not respond to the given medication and are diagnosed with treatment-resistant depression (TRD).[2] Research has suggested that the rationale behind the TRD diagnosis originates from the composition of neurotransmitters in the mammalian brain. The monoamine neurotransmitters have been found to make up for around 20 percent of the neurotransmitters in the brain, while the remaining 80 percent consist of GABA and glutamate neurotransmitters.[3]

In 2019, the pure enantiomer S-ketamine was approved as an antidepressant nasal spray, commercially available under the name “Spravato”. A chief psychiatrist at Yale Medicine has characterized the use of ketamine as an antidepressant medication as a game changer.[3] It is suggested to target patients with TRD, as it has been proposed to act on glutamatergic neurotransmissions. In addition, it has been observed to be advantageous over traditional antidepressants due to its rapid onset, with effects appearing within hours after administration, whereas SSRIs are typically observed to take effect after weeks. However, ketamine is not originally known for its antidepressant properties. Instead, it has been recognized in medical practice for over 50 years for its effectiveness as an anesthetic in emergency medicine and pain management. It gained attention for its action on N-methyl-D-aspartate (NMDA) receptors, diverging from traditional anesthetics targeting a different route leading to sedative and hypnotic properties. At high doses, ketamine produces its anesthetic properties by blocking the NMDA receptor and inhibiting it from being activated by glutamate, resulting in dissociation, and eventually inducing a state of unconsciousness. This process was considered a safer option in clinical settings, as the drug’s effect supports cardiovascular stability and the preservation of respiratory function.[2]

The paper will therefore provide a contextual background of ketamine, offering insights into how it was discovered to be a therapeutic agent for antidepressant purposes. This will lay the groundwork for discussing the uncertainties about the precise mechanism behind its antidepressant effects. The thesis question is then formulated as follows:

What is the progression of racemic ketamine from its initial synthesis as an anesthetic to its current clinical significance as an antidepressant, and what are the underlying mechanisms responsible for its antidepressant effects?

1.2 Ketamine's discovery

Ketamine was first synthesized in the laboratories of Parke-Davis and Company in Michigan, USA, during the 1950s to develop an improved anesthetic alternative to existing options.[4] The initial analgesia agent was a water- and ethanol-soluble white solid with the given trade name Sernyl, PCP [N-(1-phenyl- cyclohexyl)-piperidine], as shown in Figure 1.

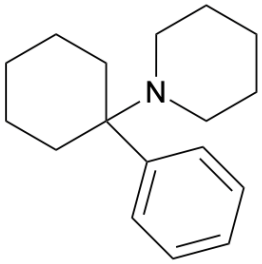

Figure 1: Phencyclidine [4].

Phencyclidine (PCP) was recognized as the most potent general anesthetic without significant depression in cardiovascular and respiratory function, but the drug's safety for patients was compromised by its prolonged duration of adverse side effects. The extended period, lasting up to 12 hours after a single dose, led to acute toxic psychoses characterized by delirium and hallucinations, resembling schizophrenic symptoms. These pharmacological limitations prevented its clinical relevance; however, the significance of the discovery of PCP was not lost. It laid the foundation for what we now recognize as ketamine [2-(O-chloro-phenyl-2-methyl-amino cyclohexanone], as shown in Figure 2. In 1962, Calvin Lee Stevens, Ph.D., employed at Park-Davis, developed the ketamine through synthesis of a series of phencyclidine derivatives[5].

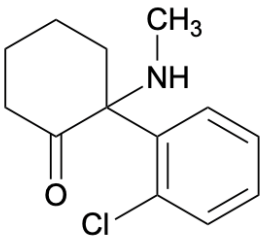

Figure 2: Ketamine.[4]

The new molecule proved to demonstrate increased patient tolerance and a substantial improvement in the duration of adverse side effects. Psychiatrist Dr. Elliot Luby suggested that ketamine exhibited similar schizophrenic symptoms as the unauthorized PCP and advocated for discontinuing the drug's development due to these effects. However, the pharmaceutical company dismissed Luby's concerns and instead used their in-house psychiatrist to conduct clinical studies on the new molecule.[5] This resulted in differing conclusions regarding the intensity of the adverse effects, arguably due to the subjective nature of pharmaceutical drug development depending on the need for medications. Interestingly, at the time, there was a high demand for a drug such as ketamine to be used as a medication for American soldiers during the Vietnam War.[4,5]

Ketamine has since been recognized in medical practice as a desirable anesthetic and later as analgesia, serving as a safer substitute for the original PCP. However, due to its adverse psychotomimetic effects, it has been classified as a "dissociative" anesthetic[6]. These effects have led to its classification as a highly abused substance. Initially listed as a Schedule III drug, its classification was elevated to Schedule II due to increased abuse. Ketamine, whether in its pure form or mixed with other drugs, is not only subject to substance abuse but also frequently used as a date rape drug. The issue persists, and whether it's known as "Ket", "Kit Kat", "Kizzo," or potentially by new terms, this remains one of the significant drawbacks of the clinically important medication.[5]

2. Theory

2.1 Original synthesis of ketamine

The synthesis initiates with the first step involving the reaction with cyclopentyl magnasiumbromide **(1)**. This compound is derived by combining cyclopentyl bromide and magnesium to react in ether. Subsequently, the resulting product is introduced into o-chlorobenzonitrile **(2)** and the reaction is stirred for 3 days. In the next step, the reaction undergoes hydrolysis by adding a mixture of crushed ice and ammonium chloride to give the solvent o-chlorophenyl cyclopentyl ketone **(3)**. The ketone undergoes bromination to form bromoketone **(4)**, which is inherently unstable, necessitating immediate utilization. In the subsequent step, the bromoketone is dissolved in liquid methylamine freebase, using benzene as a solvent. This process yields 1-hydroxy-cyclopentyl-(o-chlorophenyl)-ketone N-methylimine **(5)**. The last step involves thermal rearrangement, facilitated by the presence of methylamine dissolved in decalin. Through refluxing in decalin, the hydroxylamine is immediately converted into the liberated product 2-methylamino-2-(o-chlorophenyl)-cyclohexanone **(6)**, commercially trademarked as Ketamine. As observed in the synthesis, the name derives from the combination of a ketone with an amine.[7]

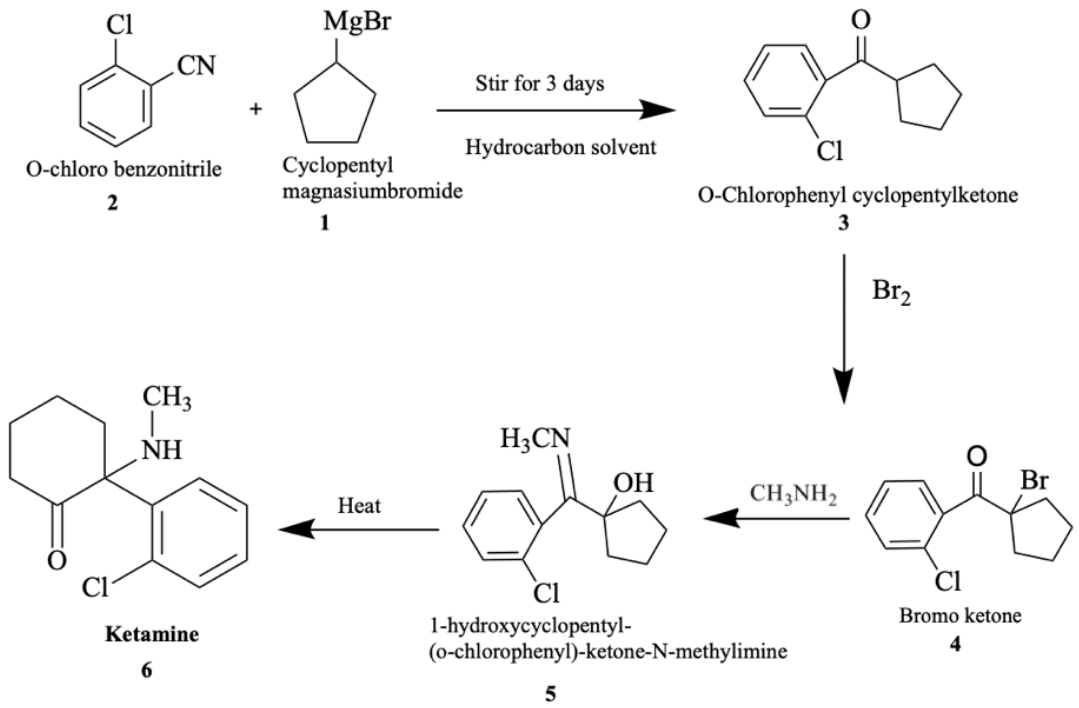

Figure 3: Synthesis for ketamine. [7]

2.2 Improvements of the original synthesis

Paul T. Anastas and John C. Warner developed the 12 main principles of green chemistry. These principles were intended to establish a framework or guidelines for implementing enhanced chemical processes to mitigate adverse environmental effects, essentially producing more with less[8]. The trajectory of ketamine's development aligns with the principles, with initiatives undertaken to improve the original synthesis. Steven's method is initially associated with drawbacks such as the use of high temperatures and inadequate yield[9]. An approach was taken to improve the yield by leveraging the stability of the imine through the utilization of the hydrochloride salt of the imine.[7] Another initiative was researched by Elhawi *et al.* where the authors employed a methodological approach aimed at improving the conditions of the thermal rearrangement step originally proposed by Calvin Stevens. They confirmed Stevens' original intermediate of the alpha-hydroxy-amine as the basis for the thermal rearrangement between the five- and six-membered ring ketones but introduced microwave energy as an alternative method. While this approach exhibited positive outcomes in terms of reaction time, the researchers did not find sufficient evidence to conclude that it significantly improved the overall yield[10]. In addition, measures have been taken to enhance the metabolic stability of ketamine, aiming to enhance its antidepressant properties using deuterated analogues. Dimitrova *et al.* highlights the work of Gant and Sarshar, who synthesized the deuterated methylamino ketamine analogue, aiming to improve its duration of action and potentially reduce the dissociative side effects.[7]

Despite the establishment of these principles already in the 1990s, the ongoing environmental concerns ensure their continued relevance. This is evidenced by a recent study undertaken in 2020, aimed at addressing the original synthesis of ketamine by removing unnecessary toxicity in the synthesis and enhancing an efficient route. They achieved this by eliminating the common use of toxic bromine and employing acidic liquid (IL), which is known to be a reusable agent, in the dehydration step. The steps can be observed in Figure 4, included to demonstrate the process comparable to the original synthesis shown in Figure 3. A detailed description can be found in the research paper by Zekri *et al*. Their study documented an increased yield from their study. Their intermediate steps demonstrate higher yields, as depicted in Figure 4, compared to the original synthesis that yields 66% and 84% for bromoketone and 1-hydroxy cyclopentyl-(o-chlorophenyl)-ketone, respectively (others not reported). Thereby, they achieved a 72.5% yield of ketamine, which the authors stated to be higher than what can be obtained in the original

synthesis[9]. These initiatives taken to further enhance the route of ketamine emphasize the significance of ketamine as a pharmaceutical drug.

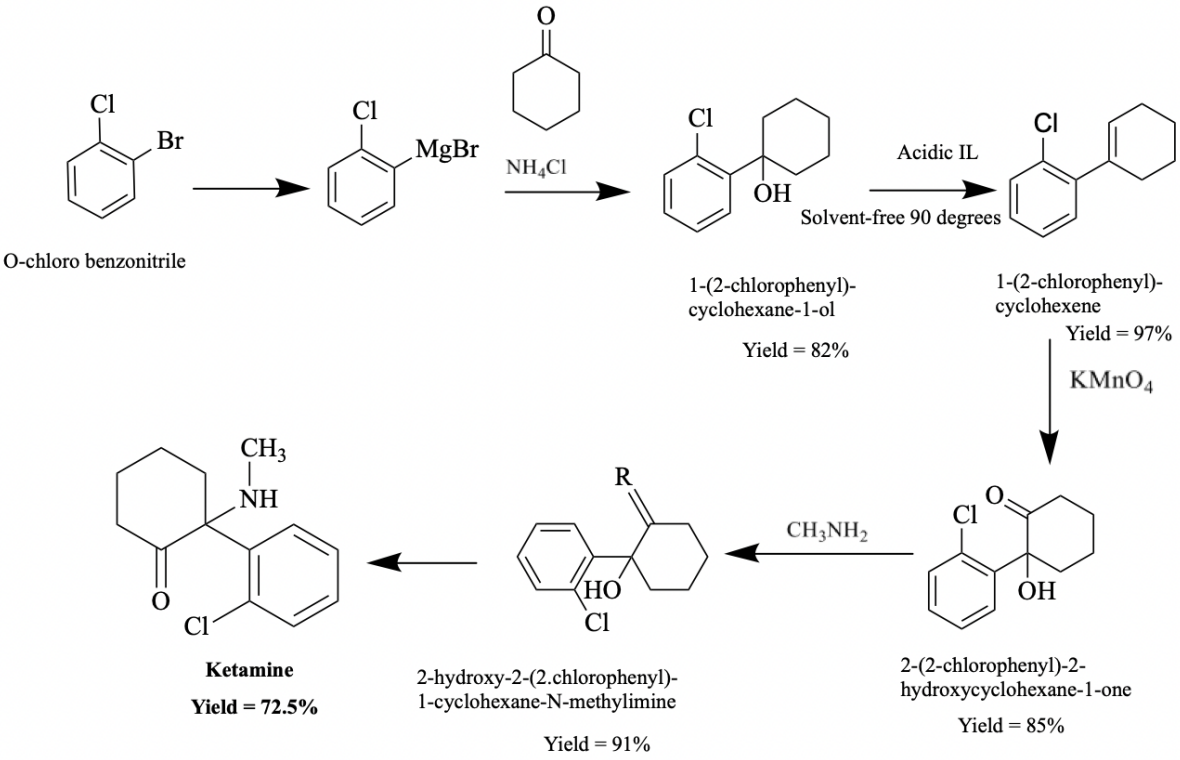

Figure 4:Enhanced synthesis route for ketamine by Zekri et. al.[9].

2.3 NMDA receptor

Already from the 1980s, studies showed that ketamine's anesthetic and analgesic effects arise from its interaction with the N-methyl-D-aspartate (NMDA) receptors[4]. By blocking these receptors, ketamine inhibits the channel's activity, leading to suppression of excitatory synaptic activity, which in turn results in the loss of responsiveness[6]. The analgesic effect functions, for instance, through ketamine's selective inhibition of spinal NMDA receptors, thereby reducing nociceptive hypersensitivity and alleviating various types of pain[12].

In Figure 5, a simplified representation of the NMDA receptor is illustrated, adapted from a schematic image provided by Aboghazel *et al.*[13] The NMDA receptor is a subtype of the glutamate receptor channels and operates as an ionotropic receptor. Activation of NMDA receptors is mediated by the excitatory amino acid glutamate, and the mediation means that for the NMDA receptors to open and allow ions to pass through (activation of the channels), glutamate must bind to it. When a drug such as ketamine is introduced, it functions as a

noncompetitive NMDA antagonist, meaning it does not compete with glutamate for its binding site. Instead, it binds to a specific receptor within the NMDA channel, known as the phencyclidine receptor, and thus requires the channels to be open to antagonize them. When ketamine is attached, it inhibits glutamate's ability to activate the channel. In addition, as the site of attachment is deep within the ion channel, it allows for the possibility that ketamine remains even when the channel closes, resulting in ketamine being "trapped." This has led to the effects of ketamine remaining in the body after the actual drug has been excreted from the body.[6]

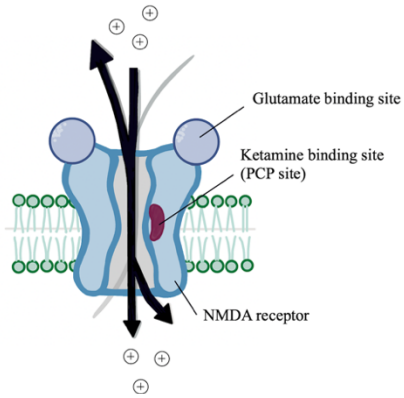

Figure 5: Simplified representation of NMDA receptor.[13]

As research progresses, the essential role of NMDA receptors in synaptic plasticity and synapse formation becomes increasingly evident. Synaptic plasticity is essential for the brain's ability to modify the strength of connections between neurons, and synapse formation, which causes our memory, learning, and formation of neural networks during development, are both intricately linked to the function of NMDA receptors. However, an over-activity of the NMDA receptors can produce pathological states such as psychiatric disorders and neuropathic pain syndromes[11]. This understanding has initiated research into the glutamatergic activity associated with NMDA receptors and furthered the understanding of the pathophysiology of hyperalgesia (increased sensitivity to pain), schizophrenia, and mental functioning. Eventually, further research was initiated to investigate ketamine's role as an NMDA antagonist in doses that did not induce unconsciousness.[4]

2.4 Characteristics of ketamine

Ketamine is produced as a racemate whereby there is an almost equal amount of the two enantiomers.[14] In Figure 6, the chemical structure of ketamine depicts both enantiomers, particularly, (S)- and (R) ketamine stereoisomers as depicted by Jelen *et al.* The chiral forms are shown as non-superimposable mirror images, much like the distinction between our right and left hands. This arises from the fact that they have the same number and type of atom groups but differ in their spatial arrangements[15].

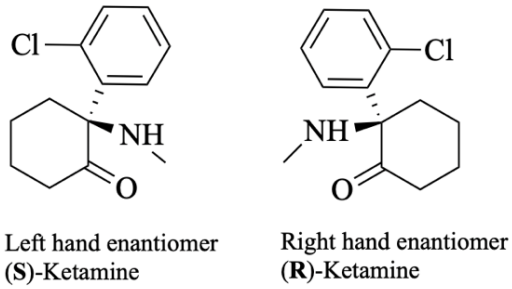

Figure 6: Chemical structure of ketamine enantiomers.[14]

The compound's chiral form influences its interactions within the body, leading to selectivity in its interactions with specific targets. For example, one enantiomer may exhibit different pharmacological activity, absorption, protein binding, and metabolism than the other.[14] The R-enantiomer of the drug may not have the same actions as the (S)-enantiomer upon first entering the body; one enantiomer may produce therapeutic effects while the other may result in side effects. Thalidomide is an example of such a drug, where (S)-thalidomide caused birth defects, while the (R)-enantiomer held the therapeutic effect.[16]

Ketamine, as mentioned is classified as a "dissociative" anesthetic and induces observed side effects such as feeling strange, bizarre, and dissociated from the environment.[20] However, unlike thalidomide, ketamine does not distinctly differentiate between its enantiomers upon entering the body. Both enantiomers of ketamine have been identified as antagonists at the phencyclidine site on the NMDA receptors.[6] However, the (S)-enantiomer exhibits a two to threefold higher affinity to NMDA receptors. The increased potency means that only around half the dose is required to achieve the same therapeutic effect, resulting in faster recovery time and possibly reduced side effects.[14] Therefore, the (S)-ketamine in its pure enantiomer form has been used for years in analgesia and anesthesia. Although the dissociative side effects are reduced, they are still present as it is the interaction with the NMDA receptor that causes both

the therapeutic and adverse side effects.[6] Direct comparative studies of the enantiomers have shown inconsistency, and the specific distinction besides the potency is not fully understood.[15] While the pure enantiomer S-ketamine has been approved as an antidepressant nasal spray, there is still limited understanding of the effects of the separate enantiomers. Therefore, the discussion focuses on the mechanistic actions of racemic ketamine.

3. Discussion

The understanding of the mechanistic actions of ketamine as a noncompetitive NMDA antagonist has contributed to the advancement in research questioning the drug's clinical value as an antidepressant. The following section will then delve into various research discussing the underlying mechanisms responsible for its antidepressant effects.

Researchers have considered whether the dissociative side effects of ketamine have had an impact on mental functioning, particularly since these effects share similarities with the symptoms of schizophrenia. This initiated research to understand the nature of these effects, leading to experimental testing of various doses of ketamine that did not induce anesthesia, as such doses would result in unconsciousness. These doses are known as subanesthetic doses. In a 1995 study by Lahti *et al.* involving nine schizophrenic patients, four intravenous injections were administrated. Three of these were subanesthetic doses of ketamine at 0.1, 0.3, and 0.5 mg/kg, and one placebo solution. It was observed that ketamine increased psychotic symptoms in these individuals, and the effect was dependent on the dosage.[17] In 2000, Berman *et al.* conducted a placebo-controlled, double-blinded study examining the effects of subanesthetic doses of ketamine on depressed patients. They administrated intravenous subanesthetic dosage at 0.5 mg/kg to these patients and revealed it had a significant improvement in their symptoms within 72 hours.[18] The immediate antidepressant effects were regarded as clinically beneficial compared to traditional antidepressants, given that the therapeutic onset of the latter may require several weeks.[19]

A research paper from 2020 by Ballard *et al*. introduces a discussion on antidepressant responses influenced by its dissociative side effects, referencing a study conducted by Luckenbaugh *et al.* in 2014, which revealed a correlation between dissociative side effects and antidepressant response. This study revealed a correlation between the two, with statistically

significant results on both day 1 and day 7. Another study cited by Ballard et al. supported these findings and observed significant results at higher levels of ketamine (0.5 and 1.0mg/kg). Interestingly, doses higher than 0.6 mg/kg are not suggested to exhibit higher antidepressant efficacy, a conclusion reinforced by the findings in this study. The paper then questions the sensitivity of the method used to measure dissociative effects and whether it accurately captures them.[20] In addition, reported side effects in patient observations in clinical trials occur immediately after administration but dissipate within hours. In contrast, the antidepressant effects have been observed to last up to a week or more post-treatment suggesting a separation between the two effects.[19] Interestingly, a study aimed to assess if individuals could notice whether they received ketamine due to its dissociative side effects, potentially biasing the results. Therefore, their placebo alternative was midazolam, known as a psychoactive placebo. Both the treatment and placebo groups would then experience dissociative effects to reduce the risk of this bias. However, even in this study, it was reported that individuals who received ketamine had a 64% higher antidepressant response compared to the 28% observed by those receiving midazolam.[21]

Furthermore, it can be argued that the mechanism that contributes to the antidepressant response leans more toward the glutamate hypothesis as the underlying mechanism. Research has identified that the underlying pathology of depression is associated with the intrinsic circuitry of the cortex and limbic system, which are regions in the brain linked to cognitive and emotional behaviors. In these regions, the neurons that are primarily released are glutamate and GABA instead of monoamines (such as serotonin, noradrenaline, and dopamine) which the traditional antidepressants tend to target.[22] It is documented that when external factors influence the glutamate transmissions in the limbic areas of the brain have been shown to impact structural changes, such as a reduction in synapses, which is one of the alterations observed when individuals undergo depression.[23] Therefore, research has indicated that modulating glutamate levels in different synaptic areas of the brain can be beneficial when finding medication for depressed patients. One research discussed the concerns related to the dynamic properties of glutamate synapses. If they become overactive, they can undergo neurotoxicity. Therefore, the author suggests that treatments should avoid using direct agonists, as they may result in sustained receptor activation, potentially leading to overaction. Instead, the modulation of glutamate neurotransmissions should involve altering receptor function only when they are activated by the natural neurotransmission to reduce this risk. Therefore, arguably ketamine is deemed a beneficial therapeutic drug because it acts as a non-competitive antagonist by binding

at the PCP site, requiring the natural glutamate neurotransmitter to bind to it before activation occurs.[24]

On the one hand, research suggests that ketamine's antidepressant properties stem from its indirect modulation of NMDA receptors on GABAergic interneurons. This leads to increased glutamate levels, subsequently enhancing the stimulation of AMPA glutamate receptors. This activation triggers a cascade of events that cumulate in increased dendritic spine formation and restoration of synaptic connectivity. This interaction has been explored in animal studies.[22] A study involving 21 human participants supports the antidepressant response associated with increased glutamate release. These participants underwent two carbon-13 magnetic resonance spectroscopy scans, revealing observed glutamate release in the prefrontal cortex induced by ketamine, which stimulated the cortical rate of conversion of C-glutamate to 13-C glutamine. Interestingly, they also indicated that the glutamate surge induced the psychomimetic side effects but did not provide evidence for these effects influencing the antidepressant response. [25] Another study revealed that ketamine decreases signals on excitatory (pyramidal) neurons in this area. This, in turn, increases glutamatergic neurotransmission.[26] These studies converge on the release of glutamate surge as the underlying mechanism, but the precise series of processes is still under discussion due to the complexity of the NMDA receptors.

On the other hand, Lazarevic et al. question the method used to observe an increase in glutamate levels, suggesting it may be dependent on the research technique employed. They argue that the use of carbon-13 magnetic resonance spectroscopy and NMR spectroscopy may have influenced these findings. In their 2021 study, they proposed a contrary perspective, asserting that the infusion of ketamine results in suppressed glutamate levels. Interestingly, they employed different methods than those listed above to obtain their results. The authors found that when the drug was administrated locally to the ventral and dorsal subiculum and prelimbic prefrontal cortex, areas associated with depression, it resulted in a reduction in glutamate levels. They further investigated the mechanisms behind this effect and revealed the involvement of adenosine A1 receptor mediates the effect, counteracting ketamine's effect on glutamate release and presynaptic activity.[27]

Nonetheless, it is alternatively suggested that the underlying mechanism of ketamine is its interaction by targeting monoamines, the same targets as SSRIs. One study found that ketamine administration in nonhuman primates significantly increased the binding of 5-HT_{1B} receptors,

which are linked to serotonin, in certain brain regions. They examined the antidepressant response by pretreating with an AMPA receptor antagonist before ketamine, infusion, considering the central role of AMPA receptors in ketamine's mechanistic action for its antidepressant response. When the drug aimed at blocking the AMPA receptor activation was administered, it was observed that the increase in serotonin activity caused by ketamine was prevented. However, while this does not provide conclusive evidence of ketamine's targeting of monoamines influencing the antidepressant response, it does suggest a potential link. Therefore, the role of monoamines cannot be entirely discounted when trying to understand ketamine's underlying mechanism.[21] In addition, researchers have also suggested that ketamine acts on other targets, but these have not received the same attention and therefore have not been brought into the discussion.

There are also some studies disregarding the effect of ketamine-inducing antidepressant response altogether. An anesthesiologist, Theresa Lii, argues that the alleviation of depression symptoms in patients may be attributed to the holistic process they undergo during treatment. She argues that it is the combination of individuals seeking help and enduring the treatment process, along with the one-on-one interactions with doctors and psychiatrists, that plays a significant role in their improvement.[28] She supports this claim with findings from a study she co-authored in 2023, involving 40 participants with moderate-to-severe depression. The study employed a randomized and placebo-controlled trial design, where half of the participants received a single dose of intravenous ketamine (0.5 mg/kg diluted into 40 ml of normal saline), while the other half received a normal saline placebo solution. Both groups received the infusion over 40 minutes. The study found no significant short-term antidepressant efficacy of the ketamine infusion compared to the placebo. Interestingly, 36.8% of the participants correctly guessed their treatment assignment. [29] It could be argued that this may be because the saline placebo solution may not induce dissociative effects.

However, there appears to be a growing consensus suggesting that ketamine indeed has an effect. Even when different techniques, the results vary, but they consistently show an antidepressant response. Studies generally tend to use the administration method of infusing ketamine via a pump over a period of 40 minutes and effects are often observed within 24 hours. One study used a different method where 20 patients received subanesthetic doses of ketamine (0.5 mg/kg of body weight) administered six times over a two-week period. It was administered intravenously as a bolus injection, with each injection lasting no longer than two minutes.

Effects were observed within one hour of administration, notably after the first dose.[30] In addition, research investigating the discrepancies between the drug's short half-life and its lasting antidepressant effects indicates that ketamine demonstrates an effect. It has been suggested that these sustained effects stem from ketamine's noncompetitive antagonism, where the drug binds to the phencyclidine site deep within the channel. Since the channel must be open for ketamine to antagonize it, there is a possibility of ketamine getting "trapped" in the channel, remaining until the channel opens again. This mechanism explains observations where ketamine, despite its relatively short half-life of around 3 hours, continues to exert antidepressant effects for up to 3 to 14 days. Ma, Chen, et al. recent findings support this research wherein they find that in mice the trapping effect of ketamine was shown to drive the sustained effects of the antidepressant effects.[31]

Lastly, the challenges inherent in determining the mechanistic actions of the drug may also be derived from the limited understanding of the underlying pathophysiology of depression.[19] A study found that the long-lasting effects of ketamine are effective for unipolar depression, but for bipolar depression, its efficacy diminishes after 3 or 4 days. This adds complexity, as it indicates that patients with different depressive disorders experience varying responses after being administrated a similar subanesthetic dosage and administration technique of ketamine.[14] Therefore, one may argue that there is a need for a deeper understanding of the intrinsic nature of depressive disorders before systematically determining the underlying mechanisms responsible for ketamine's antidepressant responses.

4. Conclusion

In conclusion, since its discovery in the laboratories of Parke-Davis, ketamine has been recognized as an important anesthetic with advantages over other alternatives due to its lesser impact on cardiovascular and respiratory function. It was also termed as a safer alternative than PCP, but still carries the adverse side effects of dissociation. In the 1980s, it was discovered that ketamine's anesthetic properties stem from its actions on the NMDA, which blocks the activation of glutamate and inhibits the channels activity leading to a state of unconsciousness.

In 2000, Berman *et al.* published an article where they found that administering subanesthetic doses of 0.5 mg/kg resulted in significant antidepressant responses in depressed patients. Additionally, a rapid onset of action was observed, which was advantageous compared to the

prolonged onset associated with the traditional alternatives. Their findings expanded the understanding of ketamine beyond its traditional use as an anesthetic, suggesting its potential as an antidepressant medication. This led to ongoing research about the underlying mechanistic action of ketamine responsible for these effects. From the discussion, it is evident that researchers are delving into the glutamate hypothesis, given the growing understanding of the neurotransmitter's role in the brain's signaling network. It is suggested that ketamine modulates glutamatergic neurotransmission by acting as a noncompetitive NMDA antagonist. Through this process, ketamine exerts therapeutic effects in areas that may have been dysregulated by the depressive disorder, and the modulation of glutamate levels impacts structural changes in these areas, restoring synaptic connectivity. However, researchers also propose alternative perspectives where ketamine's action involves other targets, such as monoamines, and there is disagreement in the literature on the precise effect of the modulation of glutamate neurotransmission. Therefore, the precise mechanisms remain elusive based on current research, and it can be argued that this complexity arises from possible multiple involved actions.

Furthermore, researchers suggested that the dissociative effect mediates the antidepressant response; however, with the recent research, it seems unlikely to be the sole determinant of the effect. While some researchers disregard its antidepressant properties altogether, the majority of research shows significant results in the treatment of depression. Future research should perhaps expand to further understand the pathophysiology of depression. This may lead to a deeper comprehension of systematic approaches to determine the underlying mechanism responsible for ketamine's action when administrated in subanesthetic doses. Such knowledge is important to ensure that patients receive the accurate dosage and methods required to effectively alleviate their depressive symptoms.

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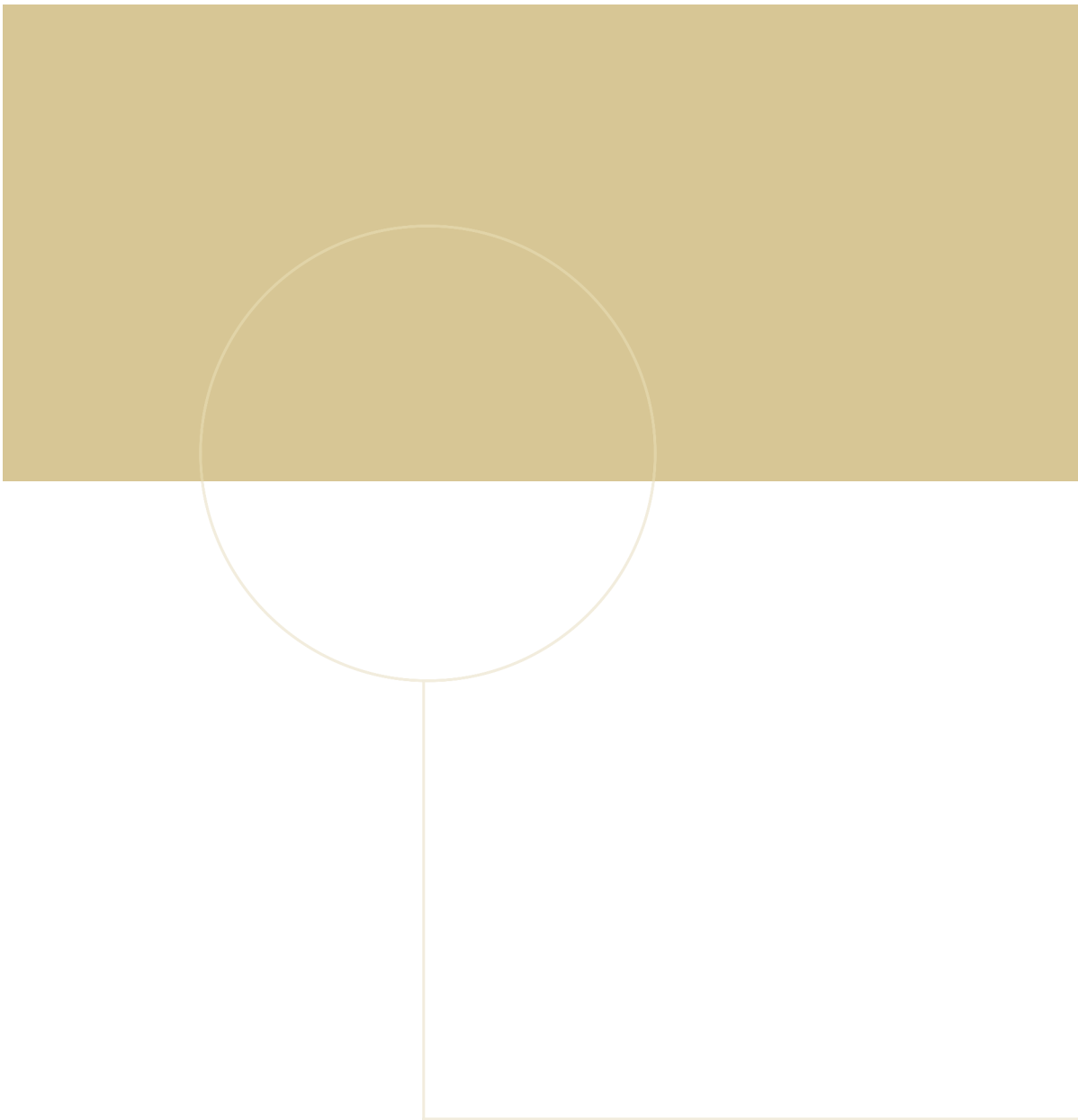

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