A Comprehensive Review of Ketamine Mechanism and Its Pleiotropic Effects

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Abstract

Objective: In the world of anesthetics, ketamine is unique. Over thirty years ago, the substance was first used in therapeutic practice to act as a “monooanesthetic,” causing analgesia, forgetfulness, loss of consciousness, and immobility. Ketamine is frequently found in equal amounts as the enantiomers S(-) and R(+)-ketamine in a racemic mixture. From a pharmacological perspective, glutamate, the primary excitatory neurotransmitter in the brain, is the primary target of ketamine. It is a non-competitive antagonist Working at one of the three glutamate receptors, the N-methyl d-aspartate (NMDA) receptor. Despite its side effects, ketamine has shown to be an effective treatment due to its short half-life and lack of clinically significant respiratory depression. Aim: the review sought to highlight the important neurobehavioral activity of ketamine in the light of their agonism of mu, delta, and kappa opioid receptors. Methods: That included online published materials from Google Scholar, PubMed, Medline, ResearchGate, and many other websites to gather as much as possible of information together. Conclusions: Ketamine, is a potent anesthetic and psychotropic drug. Beyond its antidepressant properties, ketamine has also been investigated for its potential in treating chronic pain, post-traumatic stress disorder (PTSD), and substance use disorders.

1. Introduction

The phenylcyclohexylamine derivative (Molecular weight. = 237.73 Da) known as (R,S)-ketamine, or simply “ketamine,” is composed of its two optical enantiomers, (S)- and (R)-ketamine (1). The ketamine molecule is chiral due to the asymmetry of the cyclohexanone ring’s second carbon (Figure 1). That’s why ketamine is commonly found in equal parts of the enantiomers S(-) and R(+)-ketamine in a racemic combination. This feature indicates a significant impact on pharmacology and its chemical characteristics, since the anesthetic potency of the S(-)-ketamine enantiomer is four times higher than that of the R(+)-ketamine isomer, and twice that of the racemic combination (2). An antiquated intravenous anesthetic substance called ketamine was first described in 1965 (3), and received clinical approval for usage in 1970 (4,5). From a pharmacological viewpoint, Ketamine primarily affects glutamate, the main excitatory neurotransmitter in the brain. It is a non-competitive antagonist that works at the N-methyl d-aspartate (NMDA) receptor, one of the three glutamate receptors. The NMDA-receptor is essential for memory and learning because of its function in synaptic plasticity. The subunits of the glutamate receptors come together to form tetrameric complexes (6), and subunits belonging to the same functional receptor class are the only way that functional receptors are generated (7). Pharmacology and structural homology have led to the classification of glutamate receptors into four separate classes: AMPA receptors (a-amino-3-hydroxy-5-methylisoxazole-4-propionic) (Glua1–Glua4), kainate receptors (GluK1–GluK5), NMDA receptors) N-methyl d-aspartate jGluN1, GluN2A–GluN2D, GluN3A, and GluN3B), and _ receptors (GluD1 andGluD2). GluA1 through GluA4 are the AMPA receptor subunits that may form homo- and heteromeric. GluK1 through GluK3 are the
kainate receptor subunits that also form homo- and heteromers; however, GluK4 and GluK5 only form functional receptors when coexpressed with GluK1 through GluK3. Both in native cells and in heterologous expression methods, the receptors GluD1 and GluD2 can create homomeric receptors but do not appear to be able to form heteromers with AMPA, kainate, and NMDA receptor subunits (8). Eighth subunits to form functional NMDA receptors, two GluN1 subunits must be assembled with two GluN2 subunits, two GluN3 subunits, or a mix of GluN2 and GluN3 subunits. Additionally, ketamine acts at additional receptor sites, but less prominently. It may enhance the effects of gamma-aminobutyric acid (GABA) synaptic inhibition and block muscarinic acetylcholine receptors (9, 10). The glycine binding sites are provided by the GluN1 and GluN3 subunits (11), which along with the GluN2 subunits provide the glutamate binding sites (12). Additionally, ketamine activates the release of dopamine (13). Since ketamine delivers all the necessary elements of surgical anesthesia, including pain reduction, immobility, forgetfulness, and loss of awareness, it was formerly thought to be the perfect and comprehensive anesthetic agent when it was first introduced for clinical use (14). However, the discovery of psychedelic side effects (delirium, euphoria, and sensory distortions) associated with this medication has restricted its therapeutic application (15). Ketamine’s appeal as a substance of abuse has mostly been due to its hallucinatory properties (16). Phencyclidine (PCP) was the source of ketamine, which was developed to reduce the drug’s propensity for misuse and severe psychotomimetic/psychodyssleptic side effects. PCP was eventually taken off the market in 1978 (2). Ketamine nonetheless continues to have dissociative effects (17), and possesses the capacity for abuse (18), yet not as much as PCP. Ketamine has shown to be a useful medication despite these negative effects because of its short half-life and absence of clinically significant respiratory depression (19). Along with its well-established anesthetic effects in adults, kids, and pregnant patients, ketamine also has antidepressant properties (20, 21). Rapid blood-brain barrier crossing is a characteristic of the lipid-soluble ketamine-free base molecule. More research is being done on and usage of ketamine in intravenous, oral, intranasal, and sublingual forms (22-26).

2. Mechanism of action

2.1. Effects on NMDA Receptors

Ketamine has a complicated neuropharmacology, and ionotropic glutamate receptors are how its anesthetic and analgesic actions are mediated (2, 27). A variety of glutamate receptors, including alpha-aminooxy acid-5-methyl-4-isoxazole-propionic acid and kainate receptors, are categorized as either non-NMDA or NMDA receptors. The majority of NMDA receptors consist of two NR1 and two NR2 subunits, which together create an ionic channel, bound to the cytoplasmic membrane, that is specific for cations (2). Ketamine’s principal mode of action involves noncompetitive antagonistic interactions with transmembrane NMDA receptors located in the brain and spinal cord (2). In the realm of anesthesia and analgesia, ketamine is a highly specialized medication due to the antagonistic action of NMDA, which produces forgetful, psychosensory, and analgesic properties (27). Phosphorylation and the binding of glutamate and glycine to the receptor are necessary for NMDA activation (2). When the NMDA receptor is activated, calcium enters the cell, triggering the production of prostaglandins, nitric oxide (NO), and other secondary messengers inside the cell. Presynaptic glutamate is released more readily when NO is present, which is important for both nociception and neurotoxicity (2). Ketamine blocks NMDA receptors in a noncompetitive manner. It also inhibits Ca2+ influx by lowering the Ca2+ channel’s frequency and mean opening time (29). NMDA receptors have a role in both the regulation and transmission of pain. They are involved in processes underlying chronic pain, including wind-up and central sensitization (30).

2.2. Effects on Other Receptors in the Central Nervous System

Although the agonism of the mu, delta, and kappa opioid receptors contributes to some of the analgesic action of ketamine in animals, these receptors have high inhibition constants (Ki) (31-33). When it comes to opioid receptor affinity, S-ketamine is 2-3 times more potent than R-ketamine (33). Naloxone, on the other hand, had little effect on ketamine’s activity in humans, suggesting that opioid receptors play only a minimal part in the ketamine treatment of clinical pain (34). A hyperadrenergic condition is brought on by ketamine, particularly S-ketamine, which inhibits neuronal and extra-neuronal absorption of catecholamines, raising blood levels of norepinephrine (3). By using positron emission tomography on healthy volunteers, ketamine was shown to have no affinity for GABAA receptors in the human brain at subanesthetic dosages, in contrast to many other anesthetics (36). Since very high ketamine concentrations are required to activate spinal GABA receptors, at analgesic dosages of ketamine, spinal GABA receptors are not engaged in pain inhibition (37, 38). Ketamine interacts with a variety of receptors in the rat central nervous system, however its Ki values for serotonin 5-HT, dopamine D2, and NMDA receptors are low.

Figure 1. The enantiomers of R(+)-ketamine and S(+)-ketamine
Additionally, cholinergic, nicotinic, and muscarinic receptors are how ketamine exerts its effects (2). The increase in mucus production and bronchial discharge following ketamine administration can be explained by the inhibitory impact on muscarinic receptors. Ketamine profoundly inhibits muscarinic signaling via m1 muscarinic receptors. This effect might explain some of the anticholinergic clinical effects of ketamine, both central (effects on memory and consciousness) as well as peripheral (prominent sympathetic tone, bronchodilation, mydriasis) (Durieux 1995; Fisher and Durieux 1996). Ketamine also affects m2 and m3 muscarinic receptors. This might contribute to amnesia and mydriasis bronchodilation, and at least partly explains the increase of bronchial and mucus secretion. (4,41). It has been suggested that physostigmine can counteract ketamine’s central anticholinergic effects and speed up a person’s recovery from ketamine anesthesia (42,43). It did not, however, lessen hallucinations or speed up recovery from ketamine anesthesia (44). Ketamine blocks voltage-operated sodium channels, emulating the effects of a local anesthetic (45) differences between ketamine and lidocaine-like local anesthetics. Although tonic block at hyperpolarized holding potentials occurs in the same concentration range for both ketamine enantiomers as for lidocaine, the difference in affinity between resting and inactivated channel states derived from the voltage shift in the availability curve was approximately 8- to 10-fold with ketamine in our study, as opposed to approximately 50-fold in the case of lidocaine (1).

3. Actions of ketamine

3.1. Ketamine and analgesic-anesthetic effects

Both humans and animals undergo dissociative general anesthesia when given ketamine (27,46). Ketamine is a great anesthetic option for people who are hemodynamically unstable since it maintains cardiac output (41). Ketamine maintains protective pharyngeal and laryngeal reflexes without suppressing breathing, which is another significant benefit over other anesthetics and opioids. This property makes ketamine a desirable field anesthetic (47). To enhance pain management in the prehospital and emergency room, low-dose ketamine has been administered in addition to intravenous opioids (48-50). Instead of administering a bolus of ketamine, a low-dose infusion lasting 10 minutes may lessen the frequency of adverse effects (49). Recurring postsurgical pain may be lessened with a multimodal analgesic approach that includes ketamine and regional anesthesia (51). It has recently been demonstrated that low-dose ketamine can reduce perioperative opioid intake by 40% without causing significant adverse effects (52). Devices that process human electroencephalography while the patient is sedated include entropy and bispectral index (BIS) devices. When administering propofol, thiopental, desflurane, isoflurane, or sevoflurane anesthesia, monitors display the content of a complicated signal as a straightforward numerical index to determine the level of hypnosis. Unfortunately, these tools are unable to provide a trustworthy estimation of ketamine-induced hypnosis (53,54). Ketamine is a great alternative to many other intravenous anesthetics for individuals who are hemodynamically unstable since it inhibits neuronal catecholamine absorption and central sympathetic stimulation to maintain cardiac output (41). Following surgical operations, between 10 and 50 percent of patients experience ongoing discomfort (55). Ketamine short-term relieves a variety of neuropathic pain syndromes, including migraine, fibromyalgia, ischemia pain, whiplash pain, and temporomandibular pain (16,56). Acute and persistent postoperative pains are treated with intravenous ketamine as an analgesic (57). The primary mechanism via which analgesic effects are conveyed in chronic pain situations is the blockage of NMDA receptors, and descending inhibition may also be enhanced (2,58,59). Patients with persistent pain have also been investigated in Randomized controlled trials with topical ketamine (60), showing that applying topical ketamine to a limb with CRPS (complex regional pain syndrome), is a form of chronic pain that usually affects an arm or a leg, decreased allodynia, one of the most uncomfortable symptoms of the condition, but did not improve pain (61).

3.2. Ketamine and Neurobehavioral effects

Hallucinations, euphoria, lack of judgment, forgetfulness, anxiety-related behaviors, and other behavioral abnormalities are all seen by recreational ketamine users (62). Ketamine neurotoxicity is accompanied by neuropsychiatric symptoms, which include a significant alteration in psychological health and cognitive performance (18). These brain abnormalities result from impacts on the hippocampus and cerebral cortex’s dense population of glutamate NMDA receptors, as well as on the striatum and cortex’s transmission of modulatory monoamines including dopamine (DA) and serotonin (5-HT) (63). Acute ketamine use lessens feelings of discomfort, depersonalization, and loss of sensation of surroundings. Addicts who experience disorientation, transient paralysis, difficulty moving, clouded vision, and difficulty speaking exacerbate this (15,64). Long-term recreational ketamine use is associated with impairments to working and episodic memory, semantic processing, and persistent neuropsychiatric symptoms, which are typically defined as symptoms resembling schizophrenia (18). In reality, long-term ketamine exposure permanently inhibits NMDA receptors, which results in cell death in the developing brain through a mechanism involving the up-regulation of NMDA receptor subunits as a compensatory response. The activation of the nuclear factor kappa B (NF-κB) signaling pathway, a rise in oxidative stress, and a hazardous build-up of intracellular calcium might be linked to this up-regulation and render neurons more susceptible even after ketamine cessation (65).

3.3. Ketamine and cognitive dysfunction

Long-term potentiation, a kind of synaptic plasticity essential to learning and memory, is believed to be mediated by the NMDA receptor. Since this NMDA receptor is where ketamine primarily acts, there has been a good amount of
Research done on the effects of ketamine usage on cognition. Humans who take a single dosage of ketamine experience significant, dose-dependent deficits in working and episodic memory, which have a significant negative influence on their capacity to operate (66). In mice, a daily injection of 5 mg/kg has been reported to result in reduced fear memory, which is the reduction of fear in a fear conditioning paradigm, but not after two weeks (67). All things considered, ketamine usage for recreational or occasional purposes does not seem to be linked to long-term cognitive damage (68).

The strongest evidence suggests that regular ketamine users have severe deficits in short- and long-term memory (66). Since much research has been cross-sectional, causality cannot be addressed. In a long-term research, however, regular ketamine use resulted in deficits in spatial working memory and visual recognition that were linked with variations in ketamine usage over 12 months (69).

3.4. Ketamine and depression
Recent research has examined the potential of ketamine in the management of major depressive disorder. Exciting research in humans shows that when given at subanesthetic levels, ketamine provides very quick and long-lasting antidepressant benefits (70). Research employing animal models of forced swimming, inescapable stress, learned helplessness, and tail suspension supports this claim (71). The effectiveness of current antidepressants is limited, and their onset is somewhat sluggish (72). The fast-acting antidepressant effects of ketamine highlight the unusual characteristics of this anesthetic. GSK-3 beta inactivation, prefrontal cortex synaptogenesis, and activation of the rapamycin pathway are components of a putative antidepressant mechanism (72). The function of inhibition of NMDA receptors is unclear (73). It’s interesting to note that ketamine’s antidepressant effects are prolonged and amplified when paired with the GSK-3 receptor inhibitor lithium (74). R-ketamine has stronger and more durable antidepressant-like effects in rats when compared to S-isomer (75). Using an S-ketamine infusion at a dose of 0.25 mg/kg, a group of individuals with depression who had not responded to medication had encouraging outcomes (73). S-ketamine is currently less well-researched as an antidepressant than racemic ketamine. When used in conjunction with electroconvulsive therapy (ECT) to treat therapy-resistant depression, ketamine is a safe and efficient anesthetic drug. ECT and ketamine can work synergistically to reduce depression (76).

3.5. Ketamine and oxidative stress
The pathophysiology of several illnesses, particularly neurological and mental disorders, is significantly influenced by reactive oxygen species (ROS) (77). Excessive ROS concentrations can cause damage to cells and DNA, as well as oxidative stress, which, depending on the intensity and length of exposure, can trigger systems for either cell survival or death (78). The signs of oxidative stress include a rise in oxidative protein damage, DNA (and frequently RNA) base oxidation products, and lipid peroxidation end products (79). This significant occurrence has been linked to the etiology of several CNS diseases, including Parkinson’s, Alzheimer’s, and neurodegenerative illnesses (80). In actuality, ketamine’s continual blocking of NMDA receptors results in cell death in the developing brain through a process involving the compensatory up-regulation of NMDA receptor subunits. This over-expression may be linked to hazardous intracellular calcium build-up, elevated oxidative stress, and activation of the nuclear factor kappa B (NF-kB) signaling pathway, which increases neuronal susceptibility even following ketamine cessation (65). Research has shown that subanesthetic ketamine dosages of 4 and 10 mg/kg raise TBARS (thiobarbituric acid reactive substances), a sign of elevated lipid peroxidation (81,82). Subchronic ketamine injection in mice resulted in increased oxidative stress and nicotinamide adenine dinucleotide phosphate (NADPH) oxidase activity in the thalamus, hippocampus, and PFC. This loss of parvalbumin interneurons is comparable to that seen in schizophrenia (83).

3.6. Ketamine and neurogenesis
Humans can experience both positive and negative symptoms of schizophrenia when using ketamine, a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist and derivative of phencyclidine hydrochloride. These symptoms include delusions, illusions, blunted emotional responses, emotional detachment, and psychomotor retardation (84,85). Levels of glutamate in the synaptic cleft are elevated by ketamine exposure, both acute and long-term. Neurodegeneration and psychosis are caused by this impact, which causes an excessive amount of calcium ions (Ca+2) to enter cells. This sets off a series of cytoplasmic and nuclear processes. The complex process of neurogenesis involves the migration of developing neurons (86) differentiation of neurons or astrocytic cells, and proliferation of neural stem cells (NSCs). NSCs partially develop into neurons or astrocytes while retaining the capacity to divide. NSCs are found in the hilus/subgranular zone (SGZ) of the hippocampus DG. In the granule cell layer (GCL), a portion of the freshly formed granule neurons may migrate and integrate into the hippocampus circuit (granule neurons–CA3–CA1 loop) (87). The brain growth spurt (BGS), which occurs in rodents from the end of pregnancy to the first two to three weeks after birth, is a critical period for the developing central nervous system (CNS). In humans, the corresponding period starts in the last trimester of pregnancy and lasts for two years after birth (88). During this time, the brain is quite malleable; significant neurogenesis happens quickly, establishing the basis for the brain’s normal shape and function. Apart from the subventricular zone (SVZ), the hippocampal dentate gyrus (DG) is one of just two limited locations where regeneration takes place throughout development and persists into adulthood at a slower pace (87,89). External stimuli like stress, hyperoxia, and hypoxia-ischemia may affect postnatal neurogenesis in the DG (90,91). Studying how anesthetics affect postnatal neurogenesis in the DG has been more common in recent years (92-94).
4. Clinical uses and future perspectives

Ketamine use is rising in several therapeutic contexts (27,57), and the emergence of S-ketamine might offer some advantages compared to the racemate (2,95). In veterinary and human medicine, ketamine is also used to treat pain. It's a strong analgesic that keeps spinal cord neurons from sensitizing to painful stimuli, or ‘winding up.’ (96). Additionally, ketamine has been utilized in intensive care to treat patients who have had protracted epileptic seizures (97). Research on further possible medicinal applications of ketamine is underway (98), especially in depression that is resistant to therapy (99), as well as in alcohol and heroin addiction (100). Additionally, single-dose experimental investigations investigating the ‘ketamine model’ of psychosis have been conducted (101,102). In rats, ketamine has been shown to enhance opioid analgesia even at non-analgesic dosages. Rats' tail-flick test was used to examine the effects of subanalgetic doses of ketamine (30 mg/kg IP) on morphine-induced analgesia (2.5, 5.0, and 7.5 mg/kg, SC). The results showed that ketamine and morphine together increased the duration and intensity of morphine antinociception in a dose-related manner (103). Despite being the only analgesics used during anesthesia and for controlling pain after surgery, opioids have been shown of cause tolerance and hyperalgesia (104). These benefits are especially significant for people with acute pain that is unmanageable because of cancer, trauma, or neuropathy. Long-term exposure to opioids, large doses of opioids, or both can lead to tolerance and dependency. According to basic studies, there may be a role for receptor desensitization, which includes loss of receptor function and internalization (104, 105). Previous reports indicated that intravenous ketamine (106), in a rat model of chemical peritonitis prevents albumin extravasation. Nuclear factor-kB (NF-kB) and transcription factor activator protein-1, which control the synthesis of proinflammatory mediators, have been discovered to be partially inhibited by ketamine, contributing to its immunoinhibitory effects (107). In septic rats, a subanaesthetic dosage of ketamine resulted in a dose-dependent decrease in mortality along with a notable drop in the production of interleukin (IL)-6 and tumor necrosis factor-α(108). A ketamine anesthetic dosage reduced the amount of cyclooxygenase-2, inducible nitric oxide synthase protein, and NF-kB-binding activity, which in turn lessened the liver damage caused by lipopolysaccharide (109). Given that memories are believed to be stored by hippocampal synaptic alteration, the long-term potential is regarded as one of the primary biological processes involved in learning and memory (110). Numerous tumor cells, including gliomas, colorectal and stomach cancers, oral squamous cell carcinomas, prostate cancers, melanomas, and osteosarcomas, have been shown to contain glutamate receptor subunits (111). Furthermore, glutamate and its receptors could control the formation of tumors since glutamate receptor antagonists prevent cell division (112). Ketamine has neuroprotective potential because stimulation of NMDA receptors causes cerebral ischemia damage. Findings from experiments indicate that ketamine may have neuroprotective properties. Ketamine reduced the amount of hemorrhagic necrosis in head trauma rats, attenuated damage in the caudoputamen of hypoxic rats with chronic cerebral hyperperfusion, and improved neuronal outcome from incomplete cerebral ischaemia in rats through a mechanism linked to a decrease in plasma catecholamine levels (113). Ketamine has been shown in several studies to reduce postoperative delirium and cognitive impairment in patients after heart surgery, suggesting that it may potentially have neuroprotective effects (114). An unmet medical need is the creation of fast-acting antidepressants for MDD or bipolar depression patients who are resistant to therapy. In individuals with MDD or BD who are not responding to therapy, ketamine has been shown to have strong antidepressant and antisuicidal benefits by several lines of evidence. Therefore, it is serendipitous in the realm of mood disorders that ketamine’s antidepressant benefits were discovered in these individuals (115). Treatment-resistant depression was approved by the US FDA on March 5, 2019, for (S)-ketamine nasal spray (Spravato).Beginning in early 2019, phase 1 research was conducted on (R)-ketamine and (2R,6R)-HNK. A direct comparison of (R)-ketamine, (S)-ketamine, and (2R,6R)-HNK in depression patients would thus be highly intriguing. Old medication repurposing is evolving into a more appealing strategy due to the high attrition rates, significant expenses, and the sluggish creation of innovative medications (116).

5. Conclusions

In this review, we have highlighted a few areas of current research that are particularly interesting: the drug's distinct anesthetic profile; its analgesic effects at different doses and its capacity to prevent pathological pain; its capacity to imitate important symptoms of schizophrenia; its capacity to produce immediate and sustained antidepressant effects; its capacity to elicit mystical or spiritual feelings and insight; and its euphoric and rewarding effects. Additional therapeutic uses, such as treating resistant depression, may be possible, according to more recent study.

6. References


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كلمات المفتاحية: