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Ketamine: More than Just NMDA Blocker

*Bhargab Deka, Biswajit Dash, Alakesh Bharali
and Ashique Ahmed*

Abstract

Ketamine has been extensively used in the medical field for more than 50 years, but its exact mechanism of action remains unknown. It's used to induce dissociative anesthesia (a state of profound analgesia, amnesia with light sleep, immobility, and a sense of disassociation from one's own body and surroundings). Clinical studies on ketamine as a dissociative anesthetic, a model for psychosis, and as a rapidly acting antidepressant have sparked great interest in understanding its effects at the molecular and cellular level. It exerts uncompetitive inhibitory effects on NMDARs (N-Methyl-D-aspartate) and may preferentially affect the function of NMDARs in interneurons. The hypnotic effects of this drug are attributed to its blocking action on NMDA and HCN1 receptors; however, both positive and negative modulation of choline, amine, and opioid systems appears to occur. It is likely that ketamine's effect on chronic pain and depression far outlasts its actual levels. This could be due to the hyperglutamatergic state induced by ketamine causing a secondary increase in structural synaptic connectivity. The authors of this review have attempted to highlight the action of ketamine not only on NMDA receptors but also on a variety of biochemical processes and functions found in intercellular environments, which may explain its diverse role in many diseases.

Keywords: ketamine, NMDA, antidepressant, analgesia, anesthesia

1. Introduction

Ketamine is an anesthetic drug that has been used for around more than 50 years in the medical field. In contrast to more traditional volatile-based anesthesia, it produces a broader range of anesthetic effects, resulting in a qualitatively different type of anesthesia [1]. This state is known as "dissociative anesthesia". These include: (a) hypnosis with psychotomimetic properties at low doses, accompanied by increased sedation and unconsciousness at higher doses; (b) analgesic properties (or antinociception); (c) sympathetic stimulation; and (d) maintenance of intrapulmonary pressure and respiratory regulation. Research has found that ketamine inhibits the N-methyl-D-aspartate (NMDA) receptor in a dose-dependent manner and that this blocking of excitatory synaptic activity [2]. It is responsible for the loss of responsiveness associated with clinical ketamine anesthesia. However, later scientific research has revealed that it has a wide array of molecular effects that have a clinically beneficial effect on many illnesses, including acute and chronic pain, and recently as an antidepressant with a rapid onset [3]. It is intriguing to note that many of these therapeutically

beneficial effects appear long after the drugs are almost fully eliminated from the body. The link between drug binding and therapeutic outcomes is more intricate than previously understood.

Researchers and Clinicians are increasingly keen to understand the exact mechanism of action by which ketamine and other N-methyl-D-aspartate receptors (NMDAR) antagonists affect the brain [4]. Pioneering investigations by Krystal and colleagues in the early 1990s established that a 40-minute subanesthetic infusion of ketamine (0.5 mg/kg) produced temporary psychotic symptoms in otherwise healthy subjects. As a result of ketamine infusions, sensory illusions, persecutory ideas, and altered cognition, including difficulties with attention, word-finding, and acute learning difficulties were observed. A few hours after cessation of the infusion, these symptoms disappeared [5]. Researchers discovered that in patients with major depression, the same ketamine infusion produces a slower but still rapid antidepressant effect. In some patients, this effect began within a few hours of ketamine infusion and lasted for a week or more [6]. Additionally, it has shown antidepressant effects, including rapid improvements in suicidal thoughts in patients with treatment-resistant depression [7]. Ketamine does not bind closed NMDAR channels; instead, it requires them to open before it can cause antagonistic effects. In a similar manner to phencyclidine and MK-801, ketamine also causes an open channel block that involves binding to an electrically deep part within the channel, which stops ion flow, persisting within the channel until the channel closes. The latter attribute is responsible for an extended block relieved by channel opening [8]. In the membrane depolarization theory, the dissociation of drugs is accelerated, but an electrostatic model of voltage dependence does not fully explain the mechanism by which it decreases block. Ketamine is less effective than phencyclidine and MK-801 due to its quicker dissociation from the open channel [9]. Despite the fact that it is not selective for NMDARs, and recent research has called into question the significance of NMDAR antagonism as an antidepressant, the effects of ketamine on NMDARs appear to contribute significantly to its analgesic, anesthetic, and psychotomimetic, if not antidepressant, properties [10]. The research is yielding a plethora of innovative hypotheses about mood and psychotic illnesses, including the possible function of NMDARs in these diseases and the application of novel therapeutic approaches. In this review, we will provide a wide overview of the available data on ketamine's effects and possible repercussions [11].

2. Ketamine and its molecular effects

2.1 Immediate effects

It is now known that ketamine directly influences a wide range of cellular processes in clinical doses. In this case, as shown in **Figure 1**, the effects include blocking NMDA channels, hyperpolarization-induced cationic currents (also known as hyperpolarization-activated cyclic nucleotide channels (HCN1)), nicotinic acetylcholine channels, delta, opioid receptor agonists and potentiators [12], the nitric oxide (NO)–cyclic guanosine-mono-phosphate (cGMP) system, non-NMDA glutamate receptors (α -amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA)), and metabotropic glutamate receptors (mGluR), decreased activity of cholinergic neurons, stimulation of aminergic neurons (dopamine and noradrenaline), L-type Ca^{2+} channels, and neurosteroids. Each of these systems is a component of the integrated nervous system, and they interact at all levels [13, 14].

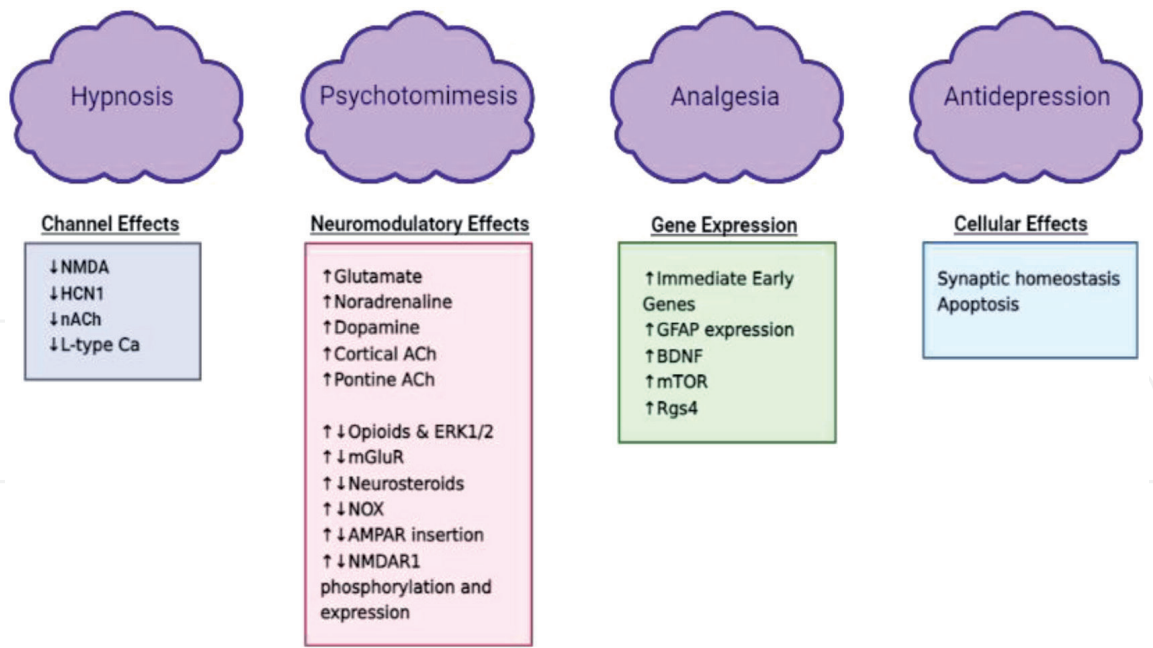


Figure 1. There are immediate effects and actions on the left, and delayed and prolonged ones on the right. [NMDA: N-methyl-d aspartate, HCN1: Hyperpolarization-activated cyclic nucleotide channels, ACh: Acetylcholine, nACh: Nicotinic acetylcholine receptors, AMPA: α-amino-3-hydroxy-5-methylisoxazole-4-propionic acid, mGluR: Metabotropic glutamate receptors, ERK1/2: Extracellular signal-regulated kinases, NOX: NADPH oxidase, BDNF: Brain-derived neurotrophic factor, mTOR: Mammalian target of rapamycin, Rgs4: Regulator of G protein signaling 4, L-type Ca²⁺: L-type calcium channels, GFAP: Glial fibrillary acidic protein].

2.2 Disruption of NMDA channel functions by ketamine

There is a great deal of complexity in the way in which several groups of compounds affect NMDA receptor function at the level of chemical binding, and this is explored in great detail in this review. Many compounds have been shown to influence the action of NMDA. Generally, they fall into the following categories: (a) open channel blockers (ketamine is one of the least potents), (b) competitive antagonists, and (c) allosteric modulators, (d) non-competitive antagonists [12, 15]. In all of these compounds, the relative potency of their action on the various NMDA receptor subtypes is different (commonly termed GluN1, GluN2A, GluN2B, GluN2C, and GluN2D – but also called NR1, NR2A-D) [16]. The distributions of these subtypes in the brain are markedly heterogeneous, which may explain why different NMDA blocking compounds produce different clinical effects. GluN2A is reported to be present throughout the brain, while GluN2B is present mainly in limbic systems, thalamus, and spinal cord. The thalamus and cerebellum contain GluN2C, whereas the brain stem, diencephalon, and spinal cord contain GluN2D. The off-rate of the compound is another important reason for the variation in effect. The phenomenon is known as “trapping block” [17]. High-trapping antagonists with a slow off-rate include compounds such as ketamine (86% trapping) and MK-801 (almost 100% trapping) [18]. After glutamate has dissociated from its binding site on the NMDA receptor, ketamine remains trapped in the closed ion channel, disrupting both physiological and pathological functions. Conversely, low-trapping (fast off-rate) antagonists escape the channel before it closes, preserving NMDA function at some level, and having fewer side effects. As an example, the compound memantine (50–70%) has minimal psychotomimetic or sedative effects. This is a slow-off-rate, low-affinity open-channel blocker. Thus, it blocks NMDA channels only when they are pathologically open, but not when they are temporarily open as in most physiological states [19]. In many ways, this mechanism is similar to persistent sodium channel blockers used in antiepileptic drugs. The end result is an NMDA blocker without any apparent anesthetic effects.

2.3 Ketamine possesses delayed effects

The functions of a cell go far beyond ion channels. Almost every immediate effect of ketamine disrupts subsequent and more long-lasting cellular processes, including gene expression and protein metabolism. It is not surprising since NMDA is largely responsible for calcium entry into cells, and calcium ions play a significant role in protein and mitochondrial metabolism. In subjects with mechanical injuries, it suppresses immediate early gene expression (fosB, c-jun, junD, zif/268, c-fos, junB,) [20]. A rat and mouse model of hyperalgesia have shown altered NMDA receptor1 phosphorylation and NMDA receptor1 mRNA expression [21], which has reduced the expression of the glial fibrillary acidic protein (GFAP) and also reduction in astrocytic and microglial activation [22, 23], an effect that is associated with reduced neuropathic pain. These chronic pain models represent complex patterns of nociception, but they may also encompass acute pain. A study found that ketamine can affect the number and function of synaptic connections in rat hippocampal regions by increasing brain-derived neurotrophic factor (BDNF) and mammalian target of rapamycin (mTOR) [24, 25] protein levels.

3. Psychotomimetic effects of ketamine

Aside from encouraging illegal usage, the psychotomimetic effects of ketamine can lead to distressing psychic disturbances, particularly in children, with the risk of experiencing nightmares, hallucinations, and delirium. Recent studies reveal that ketamine disrupts synaptic homeostasis - either by altering the release or uptake of neurotransmitters or by modifying neuromodulator activity. In addition, one intriguing possibility is that ketamine might inhibit NADPH oxidase (NOX2) from controlling glutamate release. There has been an association between psychosis and an excess of glutamate activity [26]. Alternatively, or perhaps simultaneously, ketamine may disrupt RGS4 (Regulator of G protein signaling 4). This particular protein regulates the G protein-coupled receptors such as opiate and muscarinic receptors [27]. Historically, ketamine's effects in increasing dopamine production [28] along with a possible decrease in acetylcholine activity [14] will be responsible for aggravating delirium.

The oral formulation of ketamine offers an effective analgesic for patients with chronic pain. In a study of 21 patients with chronic neuropathic pain in the central and peripheral nerves, the starting dose of oral ketamine was 100 mg/day, which was gradually increased by 40 mg/day every 2 days until the desired effect was achieved. Nine of the 21 patients stopped using ketamine because of unpleasant side effects, including psychotomimetic effects such as dissociative experiences, somatic sensations, sleep, and taste abnormalities [26]. During a double-blind, randomized placebo-controlled study, 73 traumatized participants with severe acute pain (expressed on a visual analog pain scale) were administered either ketamine 0.2 mg/kg or placebo (isotonic saltwater) along with morphine 0.1 mg/kg followed by 3 mg every 3 minutes [29]. There was a significant reduction in consumption of morphine with ketamine (0.20 mg/kg versus 0.15 mg/kg), even though no differences were noted in the pain scores. It showed a greater degree of adverse effects, including increased incidences of neuropsychiatric symptoms. Patients in both groups found their treatments satisfactory and no adverse reactions were requiring additional treatment [30]. Due to the short study period (30 minutes), it is possible that adverse reactions were not identified as a result of this, although a power study was not designed to explore this.

Again, in a randomized, double-blind, placebo-controlled study involving 120 people who underwent elective laparotomy, the effects of administering ketamine 0.1 mg/kg/hour along with tramadol 0.2 mg/kg/hour were evaluated. The ketamine group consumed 54% less morphine compared with the placebo group, resulting in superior analgesia. No differences were found in nausea and use of antiemetic drugs, mental performance, sleep difficulties, or non-disturbing hallucinations. However, there were three patients, receiving ketamine who opted out of the study because they experienced disconcerting hallucinations [31].

A linear relationship between plasma ketamine concentrations of 50–200 ng/ml and psychotomimetic effects was observed in a placebo-controlled experiment on 10 healthy young men. The psychedelic effects were similar to those reported in an earlier study of dimethyltryptamine, an illegal LSD-25 type of drug. Additionally, the effects were proportional to plasma concentrations rather than simply one of emergence. In clinical studies, plasma levels of 100–200 ng/ml resulted in useful analgesia. Observations of lateral nystagmus were consistent across subjects at 200 ng/ml plasma concentrations. Large doses of ketamine rapidly cause patients to become unconscious, and therefore the effects that were observed in this study are usually only evident afterward [32, 33].

Ketamine is a racemic mixture consisting of two enantiomers, R- and S-ketamine. Both of the enantiomers displays similar pharmacological effect but there is a question regarding the psychotomimetic effects of these enantiomers. Earlier research findings reported S-ketamine to be less prone to psychotomimetic side effects as compared to R-ketamine. While recent studies reported R-Ketamine to cause fewer psychotomimetic side effects. In a recent study with 11 participants, the pharmacological and psychotomimetic effect of R- and S-enantiomeric ketamine has been tested. The participants received 0.5 mg R-ketamine and then 0.15 mg S-ketamine separately for 1 week [34]. Using a nerve stimulator placed on the right central incisor tooth, these subjects were exposed to painful stimulation before and after the administration of each drug. Both drugs were equally effective in suppressing pain. The subjects reported that S-ketamine produced less pleasant psychotomimetic effects than R-ketamine. Of the 11 subjects, seven preferred R-ketamine to S-ketamine [35]. Based on these results, it is considered that ketamine may have a significant neuropsychiatric effect predominantly due to its S-enantiomer, making R-ketamine an ideal alternative. In contrast to earlier research suggesting that the most serious neuropsychiatric side effects are caused by R-ketamine, this study finds no evidence of this.

4. Hypnosis

Ketamine loses its vulnerability when the concentration is about 20 times higher (about 2000 ng/ml) than the concentration required inducing psychotropic effects. Because it has an elimination half-life of approximately 3 hours, there is a prolonged period during which drug levels are near the concentrations required to produce psychomimetic effects [36]. It should also be noted that the duration of hypnosis strictly corresponds to changes in drug concentration in the blood (and the site of action), indicating that the slow side effects in hypnosis/anesthesia do not have a significant causal effect. Ketamine is anomalous among commonly used anesthetics in that it has a strange combination of tranquilizers (such as NMDA antagonism) and stimulants (increasing amines, excess glutamate, and increasing AMPA receptor administration), as well as molecular effects. As a result, achieving complete anesthesia is difficult. Ketamine is typically used in conjunction with 2-adrenergic agonists to achieve surgical anesthesia in many animal species and veterinary

anesthesia. It causes central nervous system depression because the NMDA receptors on the dendrites of inhibitory neurons are less sensitive to the effects of ketamine than the receptors on excitatory neurons [37].

In hypnosis, other molecular effects may play significant roles in addition to NMDA blockade. Numerous sources provide evidence on this point. As a first point, the hypnotic effect is unrelated to NMDA blockade effectiveness. Numerous NMDA blocker compounds, including dizocilpine maleate (MK801) and dextrorphan, have weak hypnotic effects. This difference may be explained by ketamine having a considerably stronger effect on GluN2C receptors which would theoretically cause more thalamic hyperpolarization than drugs that are more effective on GluN2A or B receptors (such as MK801) [38]. The counterexample is memantine, which has an affinity for GluN2C receptors similar to ketamine but does not cause clinical sedation. Memantine and ketamine have a markedly different trapping blocks, which may explain this difference in results.

NMDAR knockout animals should be completely resistant to ketamine. Petrenko and colleagues discovered that knockout mice lacking the NMDA receptor GluE epsilon1 subchain are resistant to ketamine hypnosis. Furthermore, these animals cannot be sedated by anesthetics or pentobarbital, which do not directly block NMDA, implying that their excitatory effects are nonspecific. Based on their findings, the authors concluded that the decreased ketamine sensitivity of animals was due to a compensatory increase in monoaminergic tone, which would help reduce hypnotic tendencies rather than a genetic knockout of NMDA receptors [39].

Furthermore, ketamine has been shown to hypnotize by interacting with other receptor types. Its hypnotic activity was reduced by 30% in a mouse model with conditional forebrain knockout of the HCN1 channel [40, 41]. Rather, it promotes wakefulness by increasing aminergic [42] and cholinergic activity in the neocortex [43].

5. Pain

In concentrations similar to that which produces psychotomimetic effects (200 ng/ml), ketamine reduces pain scores. In addition to producing hypnotic, analeptic, and anti-nociceptive effects, it also exhibits an unusual mix of anti- and pro-nociceptive properties. It is still largely debated whether ketamine is a useful analgesic in clinical practice or not. A careful examination of its analgesic effects is required, with the analgesic effects being compared to the specific pain syndrome [42] in question [44, 45]. Notably, norketamine has been reported to have anti-analgesic effects [46], while ketamine can facilitate endogenous pain pathways under certain conditions. Because the drug's analgesic effects are often accompanied by excessive sedation or psychotomimetic effects, its widespread use is somewhat limited. In many cases, the mechanism of direct receptor-mediated analgesia is dependent on drug levels for their analgesic effect. Long post-drug analgesia has been shown to outlast the effective drug levels in chronic neuropathic pain syndromes, which indicates that downstream mechanisms are involved [46–48].

Ketamine also directly stimulates opioid mu-receptors, acting as an opioid mu-receptor agonist, and is considered to have the strongest anti-nociceptive effect [49]. It undoubtedly alters opioid receptor responsiveness [50]. A series of studies using G protein-coupled inwardly rectifying potassium channels (GIRK2s) knockout mice have provided evidence for the hypothesis that opioids and clonidine exert a significant portion of their analgesic effects via the influence of these channels. In contrast to opioids, ketamine's analgesic effects have been associated with increased dopamine activity in mice [46]. Among the patients suffering from chronic pain, ketamine probably reduces opioid tolerance more than other opioid antagonists.

A recent study by Gupta and colleagues showed that ketamine has anti-desensitization effects in vitro, acting by reducing ERK1/2 phosphorylation and reverses opioid receptor desensitization [51].

A potential mechanism through which ketamine augments endogenous anti-nociceptive systems might be its stimulation of aminergic pathways (serotonin and noradrenergic) and inhibition of its reuptake [52]. The analgesic effects of Ketamine may also be related to its inhibition of nitric oxide synthase [53], although the relative importance of these mechanisms has not been determined to date.

5.1 Control of chronic pain

Ketamine can have long- and short-term effects on chronic neuropathic pain. Low-dose analgesics (250 mg/kg) can reduce ongoing pain, allodynia, and hyperalgesia symptoms quickly (within 5 minutes) and transiently (within 2 to 3 hours) [54]. The latter could be explained by an NMDA-mediated “wind-up” reduction [55]. Nonetheless, these effects do not follow a consistent pattern from one person to the next. Even within the same subject group, there is the possibility of temporary (<2 hours), long-lasting (6–24 hours), and no analgesic effects [48]. Ketamine has even been shown to reduce chronic postsurgical pain for up to 180 days after a single infusion around the time of surgery [56].

In clinical studies, ketamine was found to be capable of producing long-lasting analgesic effects. According to the literature, some of these indicators may contradict clinical observations. In this case, ketamine’s antidepressant effect may explain why the drug has a preemptive effect on neuropathic pain that lasts long after the drug is no longer present [57, 58]. Although the cause of the causal link between depression and chronic pain is more often unknown, pain and depression are closely tied. Furthermore, its ability to inhibit gradual pathophysiological changes may help to prevent the development of chronic pain by inducing signaling cascades [59]. According to the previous section, ketamine affects several gene expression pathways that may affect the etiology of chronic pain, including the expression of NMDA receptors and astrocytic activity. This drug’s effects would last much longer than its detectable presence.

6. Antidepressant effects of ketamine

Recent studies have shown that ketamine can be a powerful antidepressant that works quickly. This time-of-onset, however, lasts for about a week, and the antidepressant effect lasts about 2 hours. This is indicative of ketamine-induced signaling cascades that happen long after the substance has been eliminated [60]. By reviewing all the putative mechanisms, Duman and colleagues suggest [4] that ketamine at low doses increases glutamate neurotransmission by both increasing glutamate release and increasing insertion of the AMPA receptors into synaptic vesicles. This leads to increased BDNF release and thus activation of ERK signaling, which then stimulates mammalian targets of rapamycin (mTOR). A protein translation kinase stimulates synaptic protein synthesis (GluR1) and increases synaptic density and insertion through a complex signal pathway. Furthermore, it increases structural connectivity between neurons, slowing down the aging process.

7. Conclusion

Ketamine affects a range of neuronal processes within cells, including the well-known NMDA receptor blockade. According to the results, blockage of NMDA

and HCN1 channels likely causes hypnotic effects to occur. On the other hand, the antidepressant-induced long-term effects are likely a result of its post-therapeutic effect. Ketamine's analgesic effects appear to be mediated by both short- and long-term changes in cellular function. Analgesic effects are probably mediated primarily through opioid system activation and the antinociceptive effects of the amine, whereas neuropathic pain is suppressed through receptor-mediated mechanisms and sustained cell signaling pathways.

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Author details

Bhargab Deka^{1*}, Biswajit Dash², Alakesh Bharali³ and Ashique Ahmed⁴

1 Department of Pharmacology, Pratiksha Institute of Pharmaceutical Science, Guwahati, Assam, India

2 Department of Pharmaceutical Chemistry, NEPEDS College of Pharmaceutical Sciences, Guwahati, Assam, India

3 Department of Pharmaceutics, Girijananda Chowdhury Institute of Pharmaceutical Sciences, Guwahati, Assam, India

4 Department of Pharmacology, NEPEDS College of Pharmaceutical Sciences, Guwahati, Assam, India

*Address all correspondence to: bhargavdeka98@gmail.com

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