REVIEW article

Ketamine a mysterious drug and its mechanism, effects, and misuse: A mini-review

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Abstract: Ketamine is a special kind of anesthetic. The drug was first used as a monoanesthesia in therapeutic therapy inducing analgesia, forgetfulness, unconsciousness, and immobility more than thirty years ago. In a racemic combination, ketamine is often present in equal proportions to the enantiomers S(-) and R(+)-ketamine. From a pharmacological standpoint, ketamine's main target is glutamate, the brain's main excitatory neurotransmitter. It is an adversary that does not compete, operating at the N-methyl-d-aspartate receptor, one of the three glutamate receptors. Because of its short half-life and lack of clinically significant respiratory depression, ketamine has proven to be a successful treatment despite its negative effects. Much is still unknown about the epidemiology of ketamine, specifically concerning the frequency of its and in what settings, and the trends over the years. The review aimed to draw focus on ketamine's significant neurobehavioral activity, mechanism of action, use, misuse, abuse, and adverse consequences.

Introduction

Ketamine, (R,S)-ketamine, is a phenylcyclohexylamine derivative (molecular weight=237.73 Dalton) that is made up of its two optical enantiomers, (S)- and (R)-ketamine [1]. The asymmetry of the second carbon in the cyclohexanone ring makes the ketamine molecule chiral. For this reason, ketamine is frequently present in racemic combinations of equal amounts of the enantiomers S(-) and R(+)-ketamine. This characteristic suggests a substantial influence on pharmacology and its chemical properties, as the anesthetic potency of the S(-)-ketamine enantiomer is twice that of the racemic combination and four times that of the R(+)-ketamine isomer [2]. From a pharmacological perspective, glutamate, the brain's primary excitatory neurotransmitter, is the primary target of ketamine. It functions as a non-competitive antagonist at one of the three glutamate receptors, the N-methyl d-aspartate (NMDA) receptor. The NMDA receptor's role in synaptic plasticity makes it crucial for memory and learning. Glutamate receptor subunits combine to create tetrameric complexes [3], and functional receptors can only be produced by subunits of the same functional receptor class [4]. Glutamate receptors have been divided into four distinct classes based on pharmacology and structural homology: kainate receptors (GluK1-GluK5), NMDA receptors (GluN1, GluN2A-GluN2D, GluN3A, and GluN3B), AMPA receptors (a-amino-3-hydroxy-5-methylisoxazole-4-propionic) (GluA1–GluA4), and - receptors (GluD1 and GluD2). The AMPA receptor subunits that can form homo- and heteromes are GluA1 through GluA4. The kainate receptor subunits GluK1 through GluK3 can also form homo- and heteromers, but only when co-expressed with GluK1 through GluK3 can GluK4 and GluK5 create functional receptors [5]. It is necessary to join two GluN1 subunits with two GluN2 subunits, two GluN3 subunits, or a combination of GluN2 and GluN3 subunits to generate functional NMDA receptors. Furthermore, ketamine has a less noticeable effect at other receptor locations. Muscarinic acetylcholine receptors may be blocked, and the effects of gamma-aminobutyric acid (GABA) synaptic inhibition may be amplified [6, 7].

Although its mode of action is complicated, ketamine mainly acts as a noncompetitive antagonist that targets the NMDA receptor (NMDAR). These days, ketamine is mostly used to induce and sustain surgical procedures. It has been used in both human and veterinary surgery due to its rapid induction and recovery. Ketamine has become the go-to option for parenteral anesthesia in pediatric patients during the last three decades [8]. Although ketamine is utilized in emergency rooms for anesthesia, it has demonstrated encouraging therapeutic promise for the treatment of other illnesses, including asthma and depression. However, because of its characteristics, unfavorable neurological and peripheral effects are typically recorded about dose and duration. Ketamine is a potent psychostimulant that has gained popularity as a recreational drug due to its rewarding and reinforcing effects, which explains the continuous rise in its non-medical use around the world [9].

Mechanism of action: Ketamine has a complex neuropharmacology, and its analgesic and anesthetic effects are mediated by ionotropic glutamate receptors [10]. Alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid and kainate receptors are among the many glutamate receptors that fall into one of two categories: NMDA or non-NMDA. Most NMDA receptors are made up of two NR1 and two NR2 subunits that work together to form a cation-specific ionic channel that is attached to the cytoplasmic membrane. The main way that ketamine works is through noncompetitive antagonistic interactions with the brain and spinal cord's transmembrane NMDA receptors [2]. Because of NMDA's antagonistic activity, which results in forgetting, psychosensory, and analgesic effects, ketamine is a very unique drug in the field of anesthesia and analgesia (**Figure 1**). NMDA activation requires phosphorylation as well as glutamate and glycine binding to the receptor [10]. Calcium enters the cell when the NMDA receptor is activated, which causes the cell to produce prostaglandins, nitric oxide (NO), and other secondary messengers. When NO is present, presynaptic glutamate is released more easily, which is crucial for both neurotoxicity and nociception [2]. NMDA receptors are noncompetitively blocked by ketamine. Decreasing the frequency and mean opening duration of the Ca^{2+} channel, also prevents Ca^{2} Influx [11]. Both the transmission and control of pain are influenced by NMDA receptors. They play a role in wind-up and central sensitization, two processes that underlie chronic pain [12].

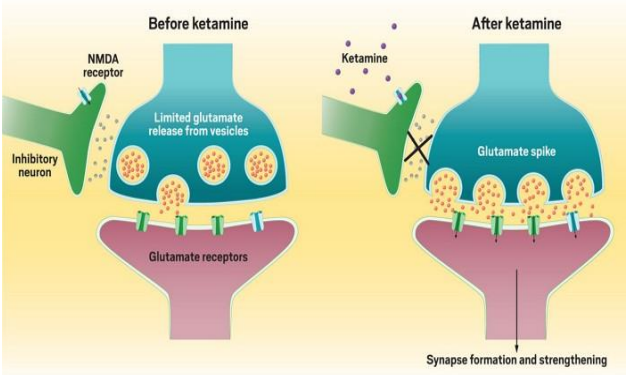

Figure 1: Ketamine possible mechanism of action on NMDA receptor [13]

Ketamine and depression: Ketamine's potential for treating major depressive disorder has been studied recently. Exciting human studies have demonstrated that ketamine has very rapid and sustained antidepressant effects when administered at subanesthetic dosages [13]. This assertion is supported by studies using animal models of forced swimming, unavoidable stress, learned helplessness, and tail suspension [14]. Ketamine's unique properties are emphasized by its quick-acting antidepressant effects. A potential antidepressant mechanism includes GSK-3 beta inactivation, prefrontal brain synaptogenesis, and rapamycin pathway activation [15]. It is unclear how NMDA receptor inhibition works. It's interesting to note that when ketamine is used with the GSK-3 receptor inhibitor lithium, its antidepressant effects are enhanced and extended [16].

When compared to S-isomer, R-ketamine exhibits more potent and long-lasting antidepressant-like effects in rats. When a group of depressed people who had not responded to medicine received an S-ketamine infusion at a dose of 0.25 mg/kg, the results were positive. Compared to racemic ketamine, S-ketamine has received less study attention as an antidepressant. Ketamine is a safe and effective anesthetic medication that can be used in combination with electroconvulsive therapy (ECT) to treat depression that is resistant to treatment. Ketamine with ECT can alleviate depression in a synergistic way [17].

Clinical uses: Ketamine is used to relieve pain in human and veterinary medicine. It is a potent analgesic that prevents spinal cord neurons from "winding up," or becoming sensitive to unpleasant stimuli. [18]. Ketamine has also been used to treat individuals with prolonged epileptic seizures in intensive care units [19]. Even at non-analgesic dosages, ketamine has been demonstrated to improve opioid analgesia in rats. The effects of subanalgesic dosages of ketamine (30 mg/kg IP) on morphine-induced analgesia (2.5, 5.0, and 7.5 mg/kg, s.c.) were investigated using the tail-flick test in rats. The findings demonstrated a dose-related increase in the duration and strength of morphine antinociception when ketamine and morphine were combined [20]. Opioids are the only analgesics used for anesthesia and post-operative pain management, although they have been demonstrated to induce tolerance and hyperalgesia. For those suffering from excruciating pain that is uncontrollable due to cancer, trauma, or neuropathy, these advantages are particularly noteworthy. The development of tolerance and dependence may result from prolonged exposure to opioids, high dosages of opioids, or both. Receptor desensitization, which involves internalization and loss of receptor function, may play a part, per fundamental research [21]. According to earlier studies, intravenous ketamine inhibits albumin extravasation in a rat model of chemical peritonitis. Ketamine has been found to partially inhibit nuclear factor-kB (NF-kB) and transcription factor activator protein-1, which regulate the production of pro-inflammatory mediators, which contributes to its immune-inhibitory effects [22]. By decreasing the levels of cyclooxygenase-2, inducible nitric oxide synthase protein, and NF-kB-binding activity, a ketamine anesthetic dosage minimized the liver damage brought on by lipopolysaccharide [23]. An unmet medical need is the development of fast-acting antidepressants for individuals with bipolar disorder or major depressive disorder who are not responding to treatment. Ketamine has demonstrated potent antidepressant and anti-suicidal effects in patients with major depressive disorder who are not improving with treatment, according to multiple lines of evidence. Because of this, it is coincidental that ketamine's antidepressant effects were found in people with mood disorders [24].

Adverse effect of ketamine: When taken in small dosages and over brief periods, ketamine is generally regarded as being rather safe and does not cause significant negative effects. However, up to 40% of patients receiving continuous subcutaneous ketamine infusion may experience adverse effects. Dizziness, impaired vision, changed hearing, hypertension, nausea and vomiting, vivid nightmares, and hallucinations are some of these possible side effects [25]. Ketamine may generate an excessive glutamate release and consequent cortical excitability, which can result in psychotic behavior and cognitive impairments, because of its NMDA receptor-blocking activity [26]. Ketamine's initial effects, which are mostly linked to aberrant activation of the prefrontal cortex and limbic structure, can cause both positive and negative symptoms resembling schizophrenia in a dose-dependent way. Due to the brain's vulnerability to ketamine's apoptogenic effects, a 5-hour exposure may be enough to elicit a notable neuroapoptotic response in both foetal and neonatal development. A ketamine-related NMDA receptor blockade triggers a neuroapoptotic cascade that includes caspase-3 activation, cytochrome c efflux to the outer surface of the mitochondria, and translocation of bcl-2-like protein 4 (Bax) to mitochondrial membranes [27]. Repeated ketamine dosages can cause major toxicity and long-term health issues. Ketamine is eliminated through the urine tract, which can cause symptoms like urgency, increased frequency, dysuria, haematuria, and cystitis. For ketamine users, ulcerative cystitis caused by ketamine can have serious and even permanent consequences. These adverse effects are observed in clinical practice in ketamine abusers, and their frequency can be decreased by lowering the dosage [28, 29]. Despite relaxing the bronchial smooth muscle, ketamine may produce airway obstruction in 10.0%-20.0% of pediatric

children because it increases salivation, which increases the likelihood of laryngospasm [30]. Long-term ketamine usage can cause significant sympathetic denervation, fibrosis, and ventricular myocardial apoptosis, all of which can lead to cardiac arrhythmia [31].

Ketamine metabolism: Ketamine metabolism is typified by a low (10.0%-30.0%) binding to plasma proteins [32]. Ketamine is generally broken down into norketamine (**Figure 2**) (80.0%), an active metabolite that is mostly hydroxylated into 6-hydroxy-norketamine (15.0%), and then eliminated in bile and urine following glucurono-conjugation due to oxidation by a microsomal enzyme system (N-demethylation). Additionally, three other, less significant metabolites are produced. Ketamine can also be directly converted into hydroxy-ketamine (5%) in another manner [33]. This metabolism is not limited to the liver [34], especially in animals, where major metabolism occurs in the kidneys, intestines, and lungs [35]. Although R(~)-ketamine may be converted to S(+)-norketamine, it appears that the enantiomers are unrelated in vivo. The hepatic blood flow is equal to the high ketamine elimination clearance (1000-1600 ml/min or 12-20 ml/min/kg), which is thus reliant on this flow. The half-life of ketamine elimination is 2-3 hours. One way to characterize its pharmacokinetics is as a tree compartment model [36].

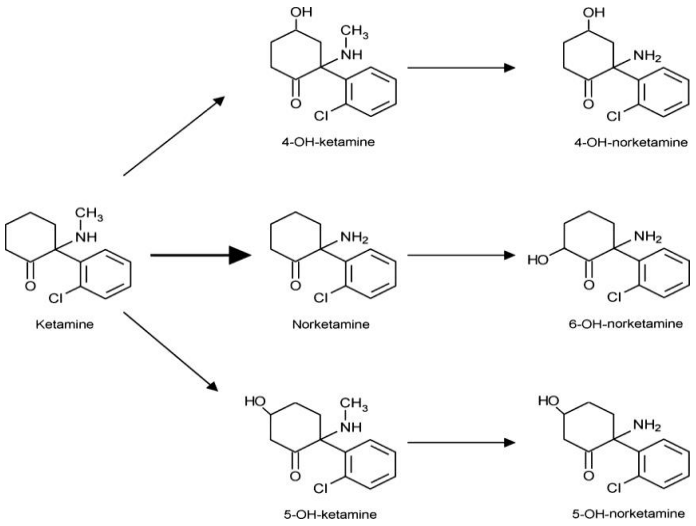

Figure 2: Metabolites from ketamine metabolism [2]

The greater demethylation of the S(+) isomer over the R(−) isomer accounts for a 22.0% increase in clearance when compared to R(~)ketamine [37]. Additionally, the S(+) isomer distribution volume is larger [38]. The pharmacokinetics of racemic mixtures are less advantageous than those of S(+)-ketamine [39]. This relationship appears to be reciprocal; the S(+) isomer suppresses R(−) metabolism as well, most likely due to the same enzyme competition. However, because of their comparable blood and brain concentrations, enantiomer differences are basically negligible [40].

Abuse of ketamine: Abuse of ketamine was first documented in the late 1960s. Abuse in North America was widely reported in the 1970s and 1980s, and it later extended to Europe and Asia. Ketamine was widely used as a recreational drug at nightclubs and raves in Europe and the US by the mid-1990s. China and Hong Kong have experienced rampant ketamine usage in the past ten years [41]. Although it is also available in liquid and tablet form, ketamine is most frequently used as a powder to be inhaled through the nose. Ketamine is primarily referred to as special vitamin K, super-K, and K. The feeling of melting into the environment, visual hallucinations, out-of-body experiences, and laughs" are the most alluring features of ketamine misuse [42]. Ketamine causes a heightened state of dissociation known as a K-hole when taken in high dosages. Users frequently experience severe dissociation in this condition, in which their perceptions completely disconnect from reality as they normally do [43]. A few common side effects exert by ketamine such as hives, hypotension, nausea, seizures, diplopia, amnesia, anxiety, and rash.

A 2009 survey found that 1285 people had taken ketamine in the year prior, indicating non-medical patterns of ketamine usage. One-third of respondents said they used less than 0.125 g, another third said they used 0.25-0.5 g, and the other third said they used more than 1.0 g in a single session when questioned about the usual doses used in a session. Furthermore, 5.0% admitted to frequently consuming more than 3.0 g in a single session. Ketamine use lasted an average of 3.5 days in a row, with 11.0% reporting at least seven days in a row [44]. Ketamine frequently co-occurs with other drugs. Alcohol, cocaine, and MDMA were all concurrently used by patients with acute ketamine poisoning, according to another study from a Hong Kong emergency room [45]. Disturbances in memory, attention, and cognition, as well as altered color perception, can result from brain changes. Abuse of ketamine is most frequently associated with kidney and gastrointestinal issues [46]. According to one retrospective study, upper gastrointestinal symptoms such as stomach pain are common among ketamine abusers. Since ketamine's NMDA receptor inhibition relaxes smooth muscles, biliary anomalies maybe the source of the pain. Liver damage is another frequent gastrointestinal issue [47, 48].

Conclusion: Ketamine is a non-competitive NMDA receptor blocker that is frequently used as a sedative and analgesic in human and veterinary medicine under very strict guidelines. This is an excellent illustration of how a medication that is currently on the market and has a reasonably stable and proven therapeutic use can be modified for a variety of purposes. The pathological condition determines the therapy option, which works well for conditions like depression, bipolar disorder, epilepsy, asthma, and alcohol and heroin addiction. However, ketamine is frequently taken illegally as a recreational drug, mostly by young adults, because of its distinct dissociative effects. To make ketamine an efficient remedy and lessen side consequences, further research is required to examine the adverse effects brought on by ketamine use.

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