CNS Neuroscience & Therapeutics

REVIEW

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Ketamine Pharmacology: An Update (*Pharmacodynamics and Molecular Aspects, Recent Findings*)

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Keywords
Alzheimer's disease; Behavioural neurology; Neuropsychopharmacology; Stroke.

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Received 22 October 2012; revision 22 February 2013; accepted 23 February 2013

doi: 10.1111/cns.12099

Pr Georges Mion is the recipient of a master in anesthesiology (1993). The paper is not based on a previous communication to a society or meeting.

SUMMARY

For more than 50 years, ketamine has proven to be a safe anesthetic drug with potent analgesic properties. The active enantiomer is S(+)-ketamine. Ketamine is mostly metabolized in norketamine, an active metabolite. During "dissociative anesthesia", sensory inputs may reach cortical receiving areas, but fail to be perceived in some association areas. Ketamine also enhances the descending inhibiting serotoninergic pathway and exerts antidepressive effects. Analgesic effects persist for plasma concentrations ten times lower than hypnotic concentrations. Activation of the (N-Methyl-D-Aspartate [NMDA]) receptor plays a fundamental role in long-term potentiation but also in hyperalgesia and opioid-induced hyperalgesia. The antagonism of NMDA receptor is responsible for ketamine's more specific properties. Ketamine decreases the "wind up" phenomenon, and the antagonism is more important if the NMDA channel has been previously opened by the glutamate binding ("use dependence"). Experimentally, ketamine may promote neuronal apoptotic lesions but, in usual clinical practice, it does not induce neurotoxicity. The consequences of high doses, repeatedly administered, are not known. Cognitive disturbances are frequent in chronic users of ketamine, as well as frontal white matter abnormalities. Animal studies suggest that neurodegeneration is a potential long-term risk of anesthetics in neonatal and young pediatric patients.

Introduction

In the 1950s, Parke-Davis industries were searching, among cyclohexamine drugs, an ideal anesthetic agent with analgesic properties. CI-395 (phencyclidine or N-1-phenyl-cyclohexyl-piperidine [PCP] chlorhydrate) and CI-400 (N-ethyl-1-phenyl-cyclohexamine chlorhydrate) were initially developed [1]. If these two drugs had no respiratory or cardiovascular depressive effects, severe psychodysleptic effects were observed (vivid dreams, hallucinations, sometimes involving outer space) [2]. PCP was commercialized in the US (Sernyl®), but its abusive use as a recreational drug ("angel dust") stopped its production in 1978. Because of the severe psychodysleptic effects of cyclohexamine, further research in the 1960s ultimately led to the synthesis and development of ketamine (CI-581, 2-O-chloro-phenyl-2-methylamino-cyclohexanone, Ketalar®). First clinical studies were published in 1965 [3]. Ketamine demonstrated a lower and shorter effect than PCP, but the "psychic effects" were also less marked.

Physicochemical Characteristics

Ketamine is a hydrosoluble aryl-cyclo-alkylamine (Figure 1) with a molecular mass of 238 g/mol and a pKa 7.5. Used as a chlorhydrate in a slightly acid (pH 3.5–5.5) aqueous solution, ketamine sometimes includes benzethonium chloride or chlorobutanol as preservatives. The second carbon of the cyclohexanone radical is asymmetrical. Ketalar® is the racemic mixture (optically inactive) of 2 enantiomers of equal quantity (isomers that diverge light in opposite ways). The active enantiomer is S(+)-ketamine ("S" spatial structure, light diverged to the right), two times stronger than the racemic form, and four times than the R(−)-ketamine isomer. S(+)-Ketamine is available (Ketanesth®) in some European countries (Germany, Austria, Italy, and the Netherlands).

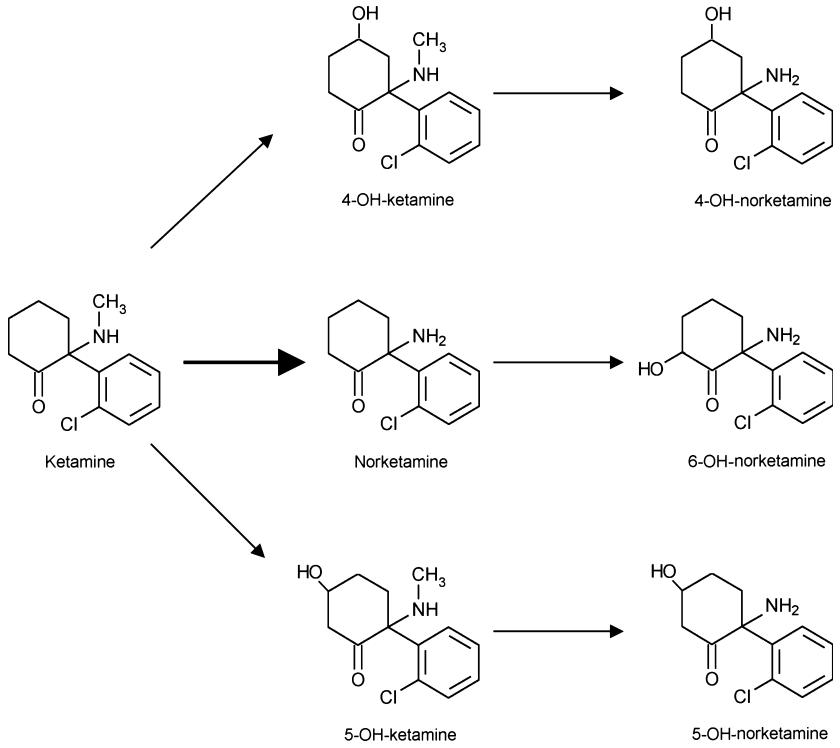

Figure 1 Metabolism. Ketamine is metabolized mainly to norketamine (80%), itself secondarily transformed into hydroxy-norketamine (15%), mainly 6-hydroxy-norketamine. Accessory pathway passes directly through the transformation of ketamine in hydroxy-ketamine (5%).

Pharmacokinetics

Ketamine Metabolism

Ketamine metabolism is characterized by a low binding to plasma proteins, about 10–30% [4]. Because of a liposolubility five times higher than thiopental, ketamine has an extensive distribution. Central compartment volume is about 70 l, and the distribution volume at steady state is around 200 l [5], or 2.3 l/kg [6]. Because of an oxidation by a microsomal enzyme system (N-demethylation), ketamine is mostly metabolized in norketamine (80%), an active metabolite that is itself principally hydroxylized in 6-hydroxy-norketamine (15%), finally excreted in bile and urine after glucuronoconjugation. Three other less important metabolites are also formed (Figure 1). Another way directly transforms ketamine into hydroxy-ketamine (5%) [7]. This metabolism does not simply involve the liver [8], particularly in animals: the kidneys, the intestine, and the lungs are the site of significant metabolism [9]. R(−)-ketamine can be transformed in S(+)-norketamine but it seems there is, *in vivo*, no connection between enantiomers. Ketamine elimination clearance is high (1000–1600 ml/min or 12–20 ml/min/kg), equal to liver blood flow, and then dependent on this flow [5]. Ketamine elimination half-life is 2–3 h. Its pharmacokinetics can be described as a tree compartment model [10]. Its clearance may be 20% higher in women than in men [11].

Cytochromes, belonging to the cytochromes P450 system and responsible for ketamine metabolism, are not totally identified [12], but in humans, several microsomal enzymes are responsible for norketamine demethylation. Ketamine has an inhibiting action on some cytochromes belonging to P450 complex, and this could partly explain the tachyphylaxis observed during the repeated use of the molecule [13].

S(+) isomer demethylation is superior to that of R(−) isomer, which explains a 22% higher clearance compared to R(−)ketamine [14]. S(+) isomer distribution volume is also higher [15]. Racemic mixture pharmacokinetics is less favorable than that of S(+)-ketamine [16], because R(−) isomer otherwise inhibits S(+) isomer demethylation [17] to a proportion of 30% [18]. This interaction seems to exist in both ways; S(+) isomer also inhibits R(−) metabolism, probably by the same enzyme competition. However, differences in enantiomers are essentially pharmacodynamic, because their cerebral and blood concentrations are similar [19]. For an i.v. perfusion (50 mg/min), racemic and S(+)-ketamine induce narcosis in 3 ± 1 min [20] for a duration of 6 ± 2 min, but S(+)-ketamine has a better pharmacokinetics than the racemic mixture, with a shorter emergence phase [15].

Norketamine Pharmacokinetics

Norketamine appears in blood 2–3 min after a ketamine i.v. bolus administration and reaches a peak about 30 min later. Norketamine is an analgesic molecule, whose power is about 20–30% compared with ketamine [21]. Its pharmacokinetics is not well known, but time plasma concentration analysis after a unique ketamine administration demonstrates a slow elimination: norketamine persists more than 5 h after administration [21]. Ketamine elimination half-time is inferior to that of norketamine [22], which strongly participates in the pharmacological effects observed in the elimination phase, particularly the analgesic effect. Because of norketamine accumulation, the need for keta-

mine, when administered in continuous perfusion, decreases over time [23].

Kinetics and Metabolism's Modification Due to Other Drugs

Enzyme inducers, such as rifampicin, increase metabolism and clearance [7], not only for ketamine (13%), but essentially for norketamine (200%). Enzyme inhibitors, such as clarithromycin, have the opposite effect. Benzodiazepines seem capable of inhibiting ketamine N-demethylation.

Administration Routes

By i.v. route, the study of the transfer to the action site demonstrates that ketamine reaches its receptors very quickly with a transfer half-life of less than 1 min. Ketamine can also be administered through intramuscular (i.m), intrarectal, oral, or intranasal routes. Ketamine i.m. administration has a high bioavailability (93%), with a plasma peak obtained in 5 min. Per os, its bioavailability is limited (20%) because of the hepatic metabolism [24]. Concentration peak occurs in 20–30 min [18]. Intrarectal and intranasal ketamine bioavailabilities are, respectively, about 25 and 50% [21]. After a unique epidural dose, ketamine rapidly goes to the systemic circulation [25]: this can explain the high frequency of psychodysleptic effects observed after intrathecal or epidural injection [26].

Relationship with Renal and Liver Functions

The influence of kidney function on ketamine pharmacokinetics and on its active metabolite is low. For patients with kidney dysfunction, ketamine concentrations (obtained after the same dose) are 20% higher than for patients with normal kidney function: at a steady state, this corresponds to a moderate decrease in clearance. Only dehydronorketamine concentrations are statistically higher in patients with kidney dysfunction. Experimentally, ketamine has very little influence on the arterial or portal liver blood flow [27].

Pharmacokinetics in Children

Intramuscular absorption is faster in children than in adults. This phenomenon could be linked to muscle weakness in children and to differences in regional flows. Distribution volume is slightly lower (1.9 l/kg) but plasma clearance is more important (16.8 ml/kg/min) than in adults. Elimination half-life is also shorter in children: 100 min [6]. After an identical dose expressed in mg/kg, norketamine plasma concentrations are higher in children. However, in children from 4 to 10 years old and after an i.v. 2 mg/kg or i.m. 6 mg/kg injection, ketamine plasma concentrations are similar to those observed in adults. On the other hand, in the first 3 months of life, ketamine plasma clearance is shorter, probably due to a diminution of liver transformation and of kidney excretion. In this case, there is an increase in the elimination half-life in newborns and infants. Distribution volume seems to be comparable to older children.

Pharmacodynamics

Neurophysiological Effects

Clinical Aspects, Site of Action, and Modification of EEG

Ketamine provides a totally different state of anesthesia compared with other anesthetic drugs (barbiturates, propofol, benzodiazepines, halogenated volatile anesthetics, etc.), the so-called "dissociative anesthesia" [2]. This is a cataleptic state in which the eyes stay open, with a typical nystagmus and conservation of laryngeal, corneal, and papillary reflexes. Some muscle hypertonia and motions are also observed. The anesthesia depth is compatible with the performance of a surgical procedure, with the absence of motor reaction orientated toward the nociceptive stimulus [28].

There is a functional and electrophysiological dissociation between thalamo-neocortical and limbic systems: sensory inputs may reach cortical receiving areas, but fail to be observed in some of the association areas [2].

Thanks to modern functional magnetic resonance imaging, it has been shown in humans that ketamine plasma concentrations of 200 ng/ml, which reduce pain scores, concomitantly decrease insular cortex and thalamus activities, usually activated by a nociceptive stimulation [29]. Sprenger et al. investigated the effects of subanesthetic IV S(+)-ketamine doses (0.05–0.15 mg/kg/h) on the perception of painful heat stimuli in healthy volunteers. During placebo administration, a typical pain activation network (thalamus, insula, cingulate, and prefrontal cortex) was found, whereas decreased pain perception with ketamine was associated with a dose-dependent reduction of pain-induced cerebral activation. Analysis of the dose-dependent ketamine effects on pain processing showed a decreasing activation of the secondary somatosensory cortex (S2), insula, and anterior cingulate cortex, which has been linked to the affective pain component that underlines the potency of ketamine in modulating affective pain processing [30]. Honey et al. [31] showed that, even when overt behavior is unimpaired, ketamine has an impact on episodic memory task performance.

Although supraspinal action is preponderant [32], the spinal action is significant [33]. Ketamine blocks afferent signals from the spino-reticular pathways without modifying the conduction of the spino-thalamic one. The medial reticular formation, relay of the pain perception emotional side, is selectively depressed, as well as medial thalamic nuclei [28]. It has been demonstrated in cats that ketamine stops the signal from the reticularis formation, considered as an important relay in the nociceptive transmission between the spine and the supraspinal level [34]. Contrary to other anesthetic drugs, ketamine enhances the descending inhibiting serotoninergic pathway [35,36].

Ketamine modifies electroencephalogram (EEG) differently from other anesthetic drugs. The most typical EEG aspect is the diminution of alpha rhythm amplitude (even its abolition) without modification of its frequency [37] and the appearance of theta waves, without a measurable relationship with the depth of narcosis [38]. Moreover, ketamine does not decrease the amplitude of mid-latency auditory evoked potentials [39] or somatosensory evoked potentials [40]. Finally, S(+)-ketamine also provides a

diminution of alpha rhythm amplitude [41], but R(−)-ketamine has no action on EEG. Ketamine does not decrease the bispectral index (BIS) [42] and can even increase it [43]. This effect is dose dependent: in a randomized controlled study, 0.5 mg/kg significantly increased the BIS (from 40 to 63) of patients undergoing general anesthesia with propofol and fentanyl, while 0.2 mg/kg did not increase it [44].

Doses and Concentration-Effect Relationship

Ketamine alters memorization for a concentration of 70 ng/ml and provokes a lateral nystagmus for about 200 ng/ml [45]. ED_{50} for narcosis (absence of verbal response) is 0.4–0.7 mg/kg. ED_{50} and ED_{95} for anesthesia (absence of response to the nociceptive stimulus) are, respectively, 0.6 and 1.3 mg/kg [46,47]. These ED correspond to an efficient concentration of about 10 μM [48]. The ketamine analgesic effect persists for steady-state plasma concentrations superior to 100–160 ng/ml [49] (about 0.5 μM). After a peripheric neurological lesion, ketamine-efficient analgesic concentrations to reduce hyperalgesia and allodynia are at least superior to 100 ng/ml [50]. After oral administration, ketamine-efficient analgesic concentrations are lower (40 ng/ml), because of the more important action of norketamine [51].

Psychodysleptic Effects

Psychodysleptic effects (also called psychedelic effects) are phenomena appearing during the "awakening phase" or "emergence phase" and are disturbances of the visual and auditive perceptions, mood, body image, and time. These disturbances may result in an impression of unreality, of floating, or depersonalization, conscious dreams, or hallucinations. During the awakening phase after anesthesia, concentrations are 600–1100 ng/ml. These effects can occur as early as 50 ng/ml. In healthy volunteers (concentrations between 50 and 200 ng/ml), a linear dose-effect relationship was demonstrated with progressive effects related to ketamine concentration [45]. More severe effects (anxiety and paranoid feelings) appear around 500 ng/ml [52]. "Emergence phenomena" is not really an adequate description: hallucinations and psychodysleptic effects can also occur during the induction of a sedation using subanesthetic dose. High doses or a too fast i.v. administration of low doses (from 5 to 10 mg) can lead to acute delirium [53]. These effects are less pronounced with the dextrogyre isomer [54].

Psychosis, Ketamine, and Antidepressive Effect

In a double-blind study in fifteen healthy subjects, a continuous subanesthetic S-ketamine infusion was administered while cortical activation was measured using functional magnetic resonance imaging. While being scanned, subjects performed an overt word generation task. Ketamine administration elicited difficulties in abstract thinking, lack of spontaneity, and flow of conversation as well as formal thought disorder. A score for formal thought disorder positively correlated to activation measures encompassing the left superior temporal gyrus, the right middle and inferior frontal gyrus, and the precuneus. Difficulty in abstract thinking was correlated with pronounced activations in prefrontal as well as in anterior cingulate regions, whereas hyperactivations in the left superior temporal gyrus were found in association with a lack of spontaneity and flow of conversation. In the absence of behavioral impairments during verbal fluency, NMDAR blockade evoked psychopathological symptoms and cortical activations in regions previously reported in schizophrenia patients [55].

Ketamine-induced psychic disorders in healthy volunteers and in schizophrenia have showed some similarities [56] and have led to pharmacological research.

Ketamine could allow the identification of a biophysical or biochemical process implicated in psychosis or the evaluation of the antipsychotic efficiency of a molecule susceptible to inhibit ketamine effects in healthy volunteers [57]. On a neurophysiological basis, prefrontal cortex [58] and locus ceruleus [59] activation has been demonstrated. From a pharmacological point of view, there is an alteration [60], also a possible hypofunction [61] of NMDA receptors, with a hyperglutamatergic state [62].

NMDA receptor is implicated in depression state, which is strongly related to the glutamatergic system as recently demonstrated [63]. Studies clearly showed ketamine antidepressive properties [64–66], with a rapid resolution of suicidal ideation, even during bipolar disorder [64,67]. Small ketamine doses also improve the postoperative mood of depressed patients [68], and this antidepressive effect has been suspected of participating in the antalgic effect in chronic pain [69].

Mechanisms of Action

Ketamine neuropharmacology is complex. Ketamine essentially acts on glutamate binding sites, NMDA (N-Methyl-D-Aspartate), and non-NMDA receptors [70]. The antagonism of NMDA receptor is responsible for the specific ketamine properties (amnesic and psychosensory effects, analgesia, and neuroprotection). There are also other glutamate-independent mechanisms.

Glutamate-Independent Mechanisms

Ketamine interacts with many binding sites such as opioid, monoaminergic, cholinergic, nicotinic, and muscarinic receptors.

γ-Amino-butyrique acid (GABA) is the most prevalent inhibiting neurotransmitter, responsible for an increase of chlorine conductance. Like other anesthetic agents, ketamine potentializes the GABA inhibition (GABA-A complex) [71] but this interaction does not really account for the analgesic effects. A ketamine agonism on spinal GABA receptors, which plays a role in spinal analgesia, is established, but only for high concentrations (more than 500 μM) that are much more higher than those obtained in human practice [72].

Ketamine binds to mu, delta, and kappa opioid receptors. The affinity of S(+)-ketamine for opioid receptors is two to three times higher than that of the R(−)isomer, but this interaction is not really responsible for its analgesic effect: in humans, this analgesic effect is not antagonized by naloxone [73]. However, some psychic effects may involve kappa opioid receptors [73].

The action on the monoaminergic system is clearly essential. With the stimulation of noradrenergic neurons and the inhibition of catecholamines uptake, ketamine provokes a hyperadrenergic state (release of norepinephrine, dopamine, and serotonin).

Inhibition of norepinephrine uptake is stereo specific: R(−) isomer only inhibits its neuronal uptake, while S(+) isomer also inhibits extra-neuronal uptake. There is a prolonged synaptic action, leading to an increased transfer of norepinephrine in the circulation [70]. Alpha-2 agonists are able to decrease this hyperadrenergic state, but also psychic phenomena induced by ketamine [74]. Because of its interfaction with the serotonin transporter [75], ketamine also inhibits dopamine and serotonin uptake [76]. Moreover, ketamine emetic properties are inhibited by ondansetron, which suggests a serotoninergic mechanism. These interactions involving noradrenergic neurons are partially implicated in the hypnotic, psychic, and analgesic effects of the molecule.

In the hippocampus and in the striatum, cholinergic neurons control the liberation of acetylcholine. In prefrontal cortex, these cholinergic neurons could be activated by nicotinic and muscarinic receptors. Ketamine has a direct inhibiting effect on these receptors, which plays an important role in the occurrence of psychic phenomena. Thus, an anticholinesterasic agent, physostigmine, is able to reverse the central anticholinergic effects and also antagonize ketamine hypnotic effects [77]. In this way, Balmer and Wyte have demonstrated, while injecting a ketamine perfusion (50 μg/kg/min) and physostigmine (0.5 mg) afterward, that the latter molecule antagonized ketamine sedative and hypnotic effects but respected its analgesic effects [78]. Ketamine could also facilitate acetylcholine liberation in the hippocampus, because of a dopamine increase. However, at clinical efficient concentrations, ketamine could, in some models, inhibit acetylcholine liberation initiated by NMDA receptors [70]. Ketamine, for clinical efficient concentrations (2.8 $\pm$ 0.6 mM), inhibits nicotinic receptors [79]. It has an antagonist activity on muscarinic receptors [80], S(+)ketamine affinity being two times greater than that of the R(−) enantiomer.

Some ketamine effects involve the purinergic system, like toxic effects on the urinary tract [81].

Ketamine also has other effects because of its interactions with sodium channels (local anesthetic properties), L-type calcium channels, and potassium channels.

Some psychodysleptic effects, which can be antagonized by nimodipine, could be initiated by L-type calcium channels [82]. The inhibition of sodium currents in the cardiac parasympathic neurons in nucleus ambiguus would be another explanation for the tachycardia induced by ketamine [83]. An antagonism on sodium channels is linked to local anesthetic properties [84]. Ketamine is similar to lidocaïne in terms of pKa and molecular weight. It may bind to the same site inside the sodium channels as local anesthetics [85] and is efficient as a local analgesic agent used in topical application [86]. Ketamine inhibits neuron potassium channels [87]: this mechanism could explain a part of (S)+isomer neuroprotective properties [88].

Glutamate-Dependant Mechanisms

NMDA Receptor

The NMDA receptor, blocked by ketamine for concentrations between 2 and 50 μM, is responsible for ketamine's most important pharmacological properties. Glutamate is the most prevalent amino acid in the central nervous system (CNS), involving glutaminergic synapses. Its liberation activates several pre- and postsynaptic receptors located on ion channels. Ionotropic glutamate receptors are usually classified as NMDA (specifically activated by N-methyl-D-aspartate) and non-NMDA [89] (such as AMPA [alpha-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid] and KA [kainate]) receptors. NMDA receptors are present on nearly all the cells of the CNS, particularly in the structures implicated in nociception, such as primary afferents or spinal dorsal horn. When glutamate is released in the synaptic cleft, there is an activation of the postsynaptic ionotropic receptors, which leads to the opening of ion channels, and is then responsible for a membrane depolarization [90]. Permeable to sodium–potassium exchanges, the NMDA receptor is especially remarkable for its calcic conductance. Some have a presynaptic location. Like the AMPA receptor, the NMDA receptor is a heteromeric multimer. The most likely structure is tetrameric, the basic structure being constituted by two subunits (dimers of dimers). Most of the NMDA receptors of the CNS are constituted by two NR1 subunits and by two NR2 subunits. They are anchored in the plasmic membrane (Figure 3A) through the PSD-95 protein (postsynaptic density 95). The subunits, which share common sequences with those of the AMPA and kainate receptors, are of three types: NR1, NR2, and NR3, also called GluN1, GluN2, and GluN3. These subunits possess four hydrophobic segments (M1 to M4) in their central region, with an arrangement in three transmembrane domains (M1, M3, and M4). The M2 segment that faces the cytoplasm represents the ionic channel of the receptor (Figure 2). Two wide domains are extracellular: the NTD N-terminal extremity (N-terminal domain) and the ABD domain (agonist-binding domain), which allows, on NR2, the glutamate binding and, on NR1, glycine binding. These two domains, NTD and ABD, have a spatial clam structure (Figure 2).

Agonists and competitive antagonists bind in the slot of this structure [91]. Seven subcategories of NR1 subunit exist (h–g). The NR2 subunits, incorporated into NR1/NR2 heteromeric complex, seem to play an important role in pathological processes associated with abnormal NMDA channel function [91], including

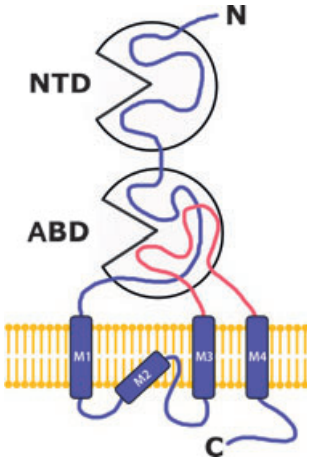

Figure 2 Structure of the four subunits of the NMDA receptor. NTD, N-terminal domain, ABD, agonist-binding domain. The M2 segment faces the cytoplasm and would be the receptor ion channel.

schizophrenia. Four subtypes, designated by the letters from A through D, determine the type of receptor. A and B types are the most common. NR2A subtype is ubiquitous. The NR2B subtype is particularly located in the limbic system, the place for emotions and memory. It is found in the anterior part of the brain, particularly the cingulate cortex, but also in the hippocampus, the amygdala, and the olfactory bulb. NR2B type also participates in the transmission of pain messages to the thalamus, spinal cord, and extrasynaptic locations, for example, at the level of primary afferents. Spinal cord is also rich in NR2D type and cerebellum in NR2C type. NR2 subunit plays a fundamental role in the spontaneous opening probability (independent of ligands) of the channel. The N-terminal domains of the NR2A and NR2B subunit control the opening of the channel. This extracellular portion controls the sensitivity of the receptor to its endogenous inhibitors (especially zinc and protons) and has the property of binding allosteric inhibitors [91].

The activation of NMDA receptors is rather complex, involving multiple agonists interacting in cooperation and regulatory mechanisms, which, on the contrary, favor the closed state of the channel. NMDA receptors have a binding site for glutamate, which is located on the ABD area of the NR2 unit (Figure 3A). This is the site that is selectively activated by N-methyl-D-aspartate. Receptor activation requires the simultaneous binding of one glycine molecule at a separate site in the ABD area on NR1 unit. Glutamate and glycine are thus described as "coagonists" of the system (Figure 3A).

Magnesium Channel Block

The main regulatory mechanism that opposes the opening of the channel is the voltage-dependent magnesium block of the NMDA receptor [92]. At the resting membrane potential (approximately 70 mV), extracellular Mg^{2+} blocks the receptor-associated channel, even if the coagonists (glutamate and glycine) are bound to their respective sites. The binding site of Mg^{2+} is located quite low in the intracellular channel side (Figure 3B). The dissociation constant of magnesium is an exponential function of membrane voltage. In the case of neuronal depolarization, the negative electrostatic forces that fasten ion Mg^{2+} at the NR2 subunit collapse, and the cation is released. This ejection of the plug allows, under the action of the coagonists, a calcium influx linked to the importance of the depolarization (Figure 3C). Although magnesium administered alone does not seem to reduce postoperative pain, these phenomena could explain lesser amounts of propofol required for narcosis and some antihyperalgesic effects of magnesium [93]. In addition, ketamine and magnesium have a synergistic effect [94].

Receptor Phosphorylation

Phosphorylation of the NMDA receptor plays a fundamental role in its activation. These phosphorylation mechanisms are the basis of long-term potentiation but also of hyperalgesia and morphine interactions with NMDA receptors [95]. Two phosphoproteins also modulate the NMDA receptor: phosphatase protein type I (PP1) and cAMP-dependent protein kinase (PKA). These two regulatory proteins are attached to the NR1 unit by another anchor protein called Yotiao (Figure 3A). This type of control (simultaneous presence of a kinase and a phosphatase that control the phosphorylation of a receptor) is typical of many ion channels [96,97].

Allosteric Inhibitors

Allosteric sites of the NR2 subunit also allow positive or negative modulation of the activity of the NMDA receptor. Some ions play an important role in the regulation of the channel opening by altering the spatial conformation of the receptor. These are protons and zinc ion (Zn^{2+}).

Protons (H^+ ions) are potent non-competitive inhibitors of NMDA receptors [98]. We do not know precisely the location of the proton detector, but it is known that protons act by stabilizing the closed state of the channel, independently of membrane polarization. Thus, tissue acidosis that accompanies ischemia or epileptic discharges reduces damage to neurons [99]. Receptors composed of NR2A or NR1a subunits have an intermediate reactivity to pH with an IC_{50} (concentration inhibiting 50% of the receptors) of 6.9 pH units, while the NR2C units provide the receptor with virtual insensitivity. In contrast, receptors composed of NR1a/NR2B or NR1a/NR2D dimers are extremely sensitive to pH. Their IC_{50} close to pH 7.40 explains that, under normal conditions, half of these receptors are under the influence of a tonic inhibition of opening by protons. Thus, even moderate changes in pH can participate in the opening of these NMDA channels, which illustrates an additional pejorative aspect of alkalosis.

The NTD domain of NR2A and NR2B subunits also plays an important role in NMDA receptor function modulation by selectively binding to non-competitive antagonists.

For the moment, only the zinc ion, often coreleased with glutamate in synaptic vesicles, has been identified as a ligand for NR2A and NR2B subunits [100] (Figure 3A). Zn^{2+} binds to the opening area of the NTD clam-shaped domain with an IC_{50} of 15 nmol and causes its closure. This closure relaxes a tension in the connections between the ABD and NTD domains, which in turn causes the separation of the interface between the two ABD domains of the receptor. This separation relaxes a stress exerted on a membrane segment, and this conformational change allows, with the bond to a proton, the closure of the channel. Zinc thus potentiates the channel closure, regulated by protons. It is possible that these mechanisms explain part of the pathophysiology of near-death experiences (NDE). In situations of cerebral ischemia or hypoglycemia, the NMDA channel is opened by neuronal depolarization and would hypothetically be modulated by zinc ions or protons. Prodils such as ifenprodil selectively inhibit NMDA receptors containing the NR2B subunit by binding in the slot of NTD domains, a site that partially overlaps with that of zinc binding [101]. Some synthetic compounds highly selective for the NTD domain of NR2B subunits, as traxoprodil, besonprodil, or radiprodil and other more recently described compounds, are used as pharmacological tools and may, in the future, become therapeutic agents as analgesics (including for chronic pain), neuroprotective agents, anticonvulsants, antidepressants or treatments for Parkinson's disease,

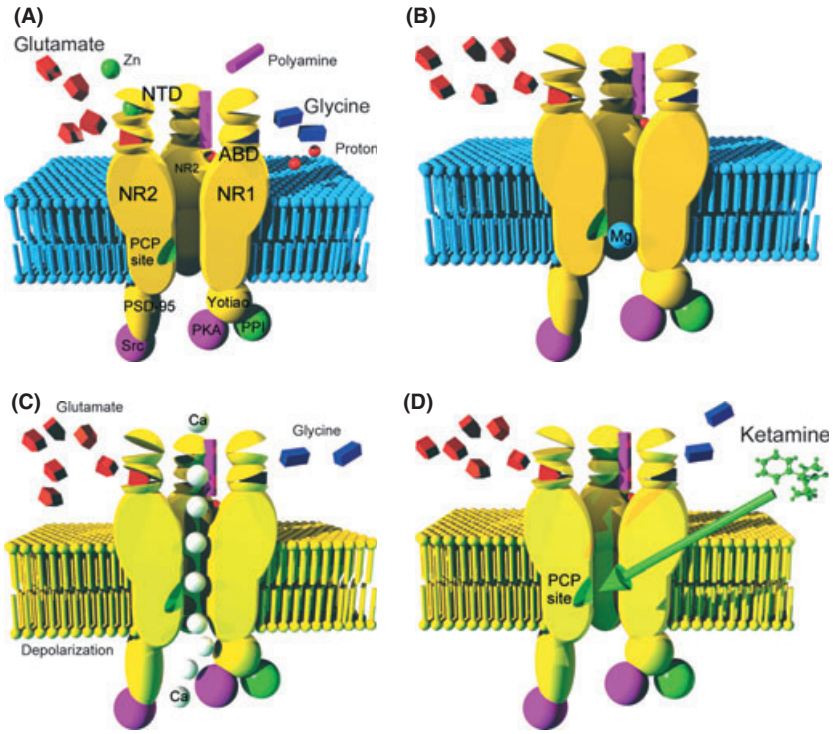

Figure 3 The NMDA receptor is anchored in the membrane (sky blue) by the PSD-95 protein, linked to the Src tyrosine kinase. The four sub-units (2 NR1 and 2 NR2) form an NMDA receptor channel selective for the cathions, which is shown open in (**A**). (**A**) The binding site of glutamate (red polyhedron), selectively activated by NMDA, is in ABD clam shaped NR2 subunit. The site for glycine (dark blue polyhedron), which acts as a co-agonist of glutamate, is located in the ABD area of the NR1 subunit. We do not know exactly where polyamines (magenta cylinder) bind, but certainly in close connection with one or the other clam-form fields in NR2 unit. Zinc ion (green spheres) binds to the NTD domain of NR2 subunit. Protons (red sphere) are an essential regulator mechanism that promotes closed state of the channel. The site of the proton detector is unknown, but it is assumed that it is ane area near ABD domain. Protein phosphatase type I (PP1) and cAMP-dependent protein kinase (PKA) are attached to the NR1 subunit by an anchor protein named Yotiao. (**B**) When the membrane is not depolarized, even when agonists occupy ABD sites, the channel is blocked by Mg^{2+} ion (sky blue sphere). The binding site of magnesium is near the intracellular part of the receptor. (**C**) In contrast, a membrane depolarization (phospholipids represented in yellow) causes the departure of the Mg^{2+} ion (voltage-dependent block) and allows a massive influx of calcium (white spheres), if the two coagonists occupy their binding site. (**D**) The molecule of ketamine or other derivatives of phencyclidine inactivate the receptor by binding to the intraductal PCP site (green slot), which partially covers the magnesium binding site.

and other neurodegenerative diseases. In the same way as zinc, they promote occlusion of the NMDA channel under the influence of protons. They are promising in the sense that they inhibit the receptor most involved in pathological phenomena, but also because they are much more active when the channel has been previously opened.

Polyamines: Endogenous Allosteric Activators

Polyamines, putrescine, spermine, and spermidine, are basic aliphatic amines, positively charged at normal pH. They are synthesized from ornithine, a metabolite in the urea cycle, and spread throughout the body. They are released in neurons in a calcium-dependent manner. Without being critical, they potentiate channel opening under the joint action of glutamate and glycine (Figure 3A). Polyamine deprivation has an analgesic effect in some animal models [102].

Other endogenous substances may allosterically modulate NMDA receptors; it is the case of neurosteroids, such as pregnenolone sulfate. The release of these substances can be triggered by stress.

Consequences of the Opening of the NMDA Channel

The increase in intracellular calcium concentration is the starting point for the synthesis of second and third messengers, prostaglandins and nitric oxide (NO), which facilitate the presynaptic release of glutamate, thus initiating the amplification of a vicious circle.

Binding protein PSD-95 appears to be essential to the sequence, which links the increased synthesis of NO and calcium influx [103]. The NR2 unit, rich in tyrosine residues on the cytoplasmic side, is linked to an intracellular tyrosine kinase of the Src family, by means of the anchoring PSD-95 protein (Figure 3A). A major function of Src in the adult CNS is to regulate glutamatergic transmission and synaptic plasticity [104]. PSD-95 is also linked to other intracellular enzymes, in particular NO-synthase [105].

The increase in intraneuronal calcium causes secondary activation of kinases that regulate the activity of receptors and modulate downstream early gene expression like c-fos. These transcriptional processes support long-term memory.

Because of an increase of intracellular calcium, the NMDA receptor stimulation by glutamate liberated in the nociceptive afferents leads to the activation of a neuronal NO-synthase (NO-s) and the production of NO from L-arginine [106]. NO stimulates the synthesis of cyclic guanosine monophosphate 3′5′ (c-GMP), which plays a role in the central transmission of pain messages ("nitroxidergic" transmission) [107]. It has been demonstrated that NO and c-GMPc participate in the central sensitization and hyperalgesia processes, after a peripheral inflammation for example [108].

Mechanism of Action of Ketamine at the NMDA Receptor Level

Ketamine and other NMDA receptor non-competitive antagonists (PCP, MK801, dextromethorphan, and memantine [109]) are fastened to an intrachannel site called phencyclidine site (Figure 3D). Ketamine intrachannel binding decreases the channel opening time. Ketamine decreases the amplification of the response to a repeated stimulation (stimuli summation called "wind up", considered as an elementary form of sensitization of the CNS) [110,111]. The antagonism is more important if the NMDA channel has been previously opened by the glutamate fixation. This "use dependence" concept can explain why ketamine analgesic properties are efficient if the pain is important or chronic [112].

Fixing of ketamine at a second site located in the hydrophobic domain of the NMDA receptor decreases the frequency of channel opening [113]. Ketamine is also an allosteric antagonist of the receptor, with a marked tropism for NR2B unity, particularly involved in the phenomena of emotional perception and memory of pain. Independently of its action on NMDA receptors, ketamine might directly inhibit NO-synthase, which could act in its analgesic and anesthetic effects [114].

S(+)-ketamine affinity for the PCP site could be three times higher than that of R(−)-ketamine [94], which confers to S(+)-ketamine a strong analgesic and anesthetic effect, at least two times stronger compared to the racemic mixture [115].

NMDA Receptors and Opioid-Induced Hyperalgesia

Interactions between opioid and NMDA receptors explain the antihyperalgesic properties of ketamine [116]. Relations between ketamine and opioid system are not unequivocal [117]. On the one hand, morphine has a low affinity for NMDA receptors. Morphine also decreases glutamatergic transmission in the cortex [118]. Conversely, it has become clear, in recent years, that opioids favor phenomena of acute and chronic tolerance, termed opioid-induced hyperalgesia [119–121]. These effects, which are not universally found [122], but are dose dependent, result from the involvement of NMDA receptors in the CNS [123]. There are cross-talks between NMDA and opioid receptors on the surface of the same cells. Following the activation of opioid receptors and protein kinase C [124], especially its γ isoform [125,126], phosphorylation of the NMDA receptor suppresses the magnesium plug of the channel, allowing the entry of Ca^{2+} into the cell, starting point of a cascade of events (activation of protein kinase C, of prostaglandin and nitric oxide systems, transcriptional changes) that leads to a down-regulation (underlying tolerance) and a blunted response of opioid receptors (underlying hyperalgesia). The antagonism of NMDA receptors allows ketamine to exert a preventive action of these phenomena, one of the molecules most explored aspects for more than 10 years [127–129].

Excitotoxicity

NMDA receptors are involved in neuronal tissue physiology and in synaptic plasticity, but in certain circumstances, also in acute or chronic neurotoxic effects. The concept of excitotoxicity, issued from the work of John Olney [130], confers to glutamate the status of "excitotoxin." While excitotoxicity could be mediated by any of the ionotropic receptors, the calcium conductance of the NMDA receptor makes it the privileged mediator of these phenomena. Indeed, a massive increase in calcium concentration inside the neuron is likely to produce a cascade of deleterious events, whose ultimate outcome is cell death. The cytoplasmic Ca^{2+} activates many enzymes such as protein kinase C (PKC), phospholipases A2 and C (PLA2 and PLC), protein kinase II Ca^{2+}, and calmodulin-dependent NO-synthase as well as proteases and endonucleases. This sequence of reactions has been proposed as a pathogenic model of cerebral ischemia and traumatic brain injury [131]. In case of hypoxia or ischemia, the collapse of the activity (or an activity in reverse mode) of the high-affinity transporter, which normally removes glutamate from the synaptic cleft, provokes a significant increase in extracellular glutamate [132]. The collapse of ATP-dependent ion pumps (Na/K-ATPase) increases extracellular potassium concentrations, which in turn causes a depolarization of neurons that terminates the magnesium block and reduces the effectiveness of high-affinity transporter glutamate whose energy source is the transmembrane sodium gradient [130]. In addition, potassium stimulates the secretion of glutamate and inhibits its glial capture. Finally, an injured cell glutamate content is an important source of excitatory amino acids. A potassium current, independent of calcium, also intervenes in the apoptotic phenomena [133]. Ischemia is finally associated with the stimulation of ornithine decarboxylase, which leads to the synthesis of polyamines. Thus, excitotoxicity is the efferent common pathway of pathological processes, all compromising cellular energy intake. The glutamatergic system would thus be involved in chronic neurological pathologies, such as amyotrophic lateral sclerosis and Huntington's, Alzheimer's, or Parkinson's diseases. NMDA antagonists experimentally have neuroprotective properties because they are able to reduce neuronal apoptosis or brain injury induced by hypoxia or brain trauma [131]. There exists a window of opportunity with respect to the ischemic penumbra, during the hours following cerebral infarction, because the effectiveness of NMDA antagonists in this area is highly dependent on the precocity of their administration [134,135]. Regarding neurodegenerative diseases, amantadine [136], originally used in the treatment of influenza, and its derivative meman-

tine [137] are NMDA antagonists, which improve the symptoms of Parkinson's disease. A recent study reported improved Parkinsonian symptoms (dyskinesia and tremor) in the minutes following the injection of low doses of ketamine (10 mg two bolus IV) [138].

Ketamine Neurotoxicity

Experimentally, NMDA antagonists and ketamine are clearly known to exhibit a potential neurotoxicity [139,140] and may promote neuronal apoptotic lesions [141]. On the contrary, in usual anesthetic practice, ketamine does not induce neurotoxicity. Possible but rare neurotoxicity cases have scarcely been reported [142]. The consequences of high doses, repeatedly administered for more than 24 h, are not known. Psychodysleptic effects could be linked to transient neurotoxic effects [139]. Cognitive disturbances are frequent in ketamine chronic users [143], as well as frontal white matter abnormalities [144].

Recently, several experimental studies have raised the possibility of neurotoxic effects in the developing brain [145]. Animal studies suggest that neurodegeneration, with possible cognitive sequelae, is a potential long-term risk of anesthetics in neonatal and young pediatric patients. The existing experimental data implicate not only NMDA receptor antagonists, but also drugs that potentiate gamma-aminobutyric acid signal transduction, as potentially neurotoxic to the developing brain [146].

Conclusions

Having been in use for more than 50 years, ketamine has proven to be a safe anesthetic drug with potent analgesic properties. It has been widely used to induce narcosis, because of the preservation of cardiovascular and respiratory functions, and in the context of an emergency, because it allows the preservation of pharyngeal and laryngeal reflexes.

The so-called psychodysleptic effects explain a fall in ketamine use during the 1980s. But during the 90s, its peculiar antihyperalgesic properties renewed the interest for this agent, which allows a reduction of opioid tolerance in the context of postoperative pain. More recently, an antidepressive activity has been demonstrated that may participate in the recovery from the disability resulting from chronic pain syndromes. Ketamine and other anti-NMDA derivatives are being explored in the prevention of the excitotoxicity phenomenons involved in acute and chronic brain damage. Some safety concerns have been advocated, especially in the context of chronic administration, or in the case of administration during pregnancy and in a pediatric setting.

Conflict of Interest

The authors declare no conflict of interest.

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