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Back to the future: ketamine and nitrous oxide in major refractory depression

Abstract

Major depression is a serious health problem that affects children, adolescents, adults and the elderly, most often in females. Traditional antidepressants have a high rate of therapeutic failure, with suicide being frequent during the beginning of treatment. Ketamine administered by diverse routes in subanesthetic doses and the inhalation of nitrous oxide have shown a sharp reduction of the indicators of major depression. The molecular mechanisms of action of these general anesthetics have been very controversial and most of the studies involve the NMDA receptor, although there is new evidence pointing to non-NMDA receptors as an important part of the rapid antidepressant effects of ketamine. ketamine (intravenous, nasal, sublingual, oral, intramuscular, subcutaneous) results in a rapid and effective treatment for depression with few side effects. It is most frequently given as 0.5 mg/kg intravenous infusion, and the results are perceived few hours after its administration, lasting up to 2 weeks. Future knowledge of the underlying molecular mechanisms, the therapeutic results and the immediate and long-term side effects of ketamine and nitrous oxide guarantee the development of a novel generation of fast-acting antidepressant drugs.

Volume 9 Issue 3 - 2017

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Received: December 20, 2017 | **Published:** December 28, 2017

Introduction

Major depression (MD) is a very common chronic mental illness that causes substantial disability in millions of adolescents and adults throughout the world. In the United States of North America there is an annual risk of depression of 6.6%. Unfortunately, only 30-40% of patients will remit with the usual antidepressant drugs and there is a high risk of suicide attempts during the first month of treatment. Patients who do not respond to antidepressants have a poor quality of life with symptoms and risks as diverse as panic disorders, phobias, anxiety, anhedonia, impaired sexual satisfaction, unacceptable social behavior, low mood, attempts to suicide, just to name a few. There are several options to treat major depressive disorder, including psychotherapy, pharmacotherapy, electroconvulsive therapy, transcranial magnetic stimulation, as well as non-traditional approaches.[1–4]

Selective serotonin reuptake inhibitor antidepressants (SSRIs) are the first-line of treatment for major depressive disorder, although selective inhibitors of norepinephrine reuptake and other drugs with related mechanisms that act on specific neurotransmitters are also used. [5]. Unfortunately, most antidepressants require many weeks or months to achieve their therapeutic effects, and in more than 50% of patients the result is not adequate. This has led to the investigation of new targets with antidepressant effects such as neurokinins, cytokines, corticotropin, release factor, opioids, cannabinoid receptor, and others.[6] The unapproved use (off label use) of drugs with approved indications for other pathologies is a notable option for patients who have diseases refractory to existing authorized treatment. Several drugs used in anesthesia have been studied off label use in several diseases or symptoms of systemic pathologies with fascinating results. The mechanisms of action of some these drugs are understood thanks to recent advances in the knowledge of membrane receptors, transmitters and their interactions. Ketamine and nitrous oxide are current examples off label use indications that have been the subject of various investigations in animals and humans. We review the most recent advances in the use of ketamine and nitrous oxide -antagonists of NMDA receptors- in the management of patients with refractory major depression to traditional antidepressants.

Glutamate system

Considering the extensive evidence of the involvement of the glutamate system in the pathophysiology of depression, it is important to review this system briefly. Glutamate is the main excitatory neurotransmitter in the CNS of mammals, including the human brain and is known to play an important role in cell plasticity. There are two large groups of glutamate receptors; ion channels (ionotropic receptors) and G-protein coupled receptors (metabotropic receptors), which play an important role for excitatory synaptic transmission and neuronal plasticity. The ionotropic glutamate receptors are multimeric sets of four and are divided into three groups based on their structural and pharmacological similarities; NMDA (N-methyl-D-aspartate), AMPA (α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate), and kainite receptors (kainic acid) (Figure 1). All ionotropic glutamate receptors are non-selective cation channels, which allows the passage of Na^+ and K^+, and in some instances small amounts of Ca^{2+}. NMDA, AMPA and kainate are formed from the association of protein subunits that can be mixed in various ways to produce a large number of receptor isoforms. The NMDA glutamate receptor subfamily also forms multiple subunits, non-selective cation channels include the subunits NR1, NR2 (NR2A-NR2D). It is thought that the glutamate binding site is in the NR2 subunit, while the NR1 subunit contains the binding site for glycine. Within the ion channel of this receptor is the site S and the site phencyclidine, the latter is the place where ketamine acts.[7–9] It has been shown that glutamate receptors mediate the excitatory responses in the CNS and their synaptic connections depend on the dynamic interaction of the NMDA, AMPA and kainate receptors.

Ketamine

Ketamine hydrochloride (CI-581) is non-competitive anesthetic, with high affinity and antagonist of NMDA glutamate receptors. It is a drug related to phencyclidine (PCP, angel dust) that was synthesized in 1962 by Calvin Stevens when he was looking for a new intravenous anesthetic. Ketamine was first patented in Belgium in 1963, and introduced by Domino et al in clinical anesthesia in 1966.[10–12] It was approved for use in humans by the FDA in 1970. Since then, this compound has been used successfully in various anesthesia techniques, with patients of all ages, in a wide variety of clinical settings. In addition, several non-anesthetics uses of ketamine have been described as a bronchodilator, antidepressant, in chronic pain, as well as pre-emptive analgesic. Its main side effects are hallucinations, which can be reduced or avoided with benzodiazepines or butyrophenones such as droperidol. It is a racemic compound, where S-ketamine is 4 times more potent than the R-ketamine isomer (Figure 2). In hippocampal neurons, S-ketamine also inhibits NMDA receptors more potently than R-ketamine, reflecting relative stereoselectivity *in vivo*.[7]

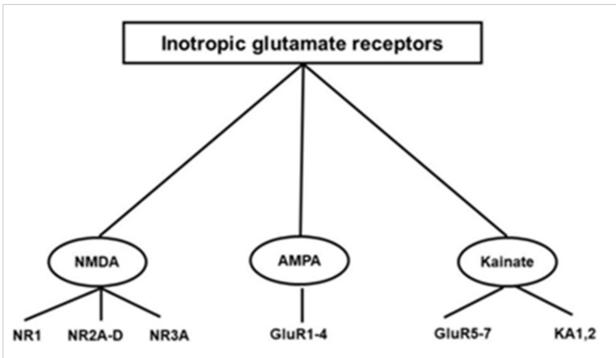

Figure 1 Classes of inotropic glutamate receptors.

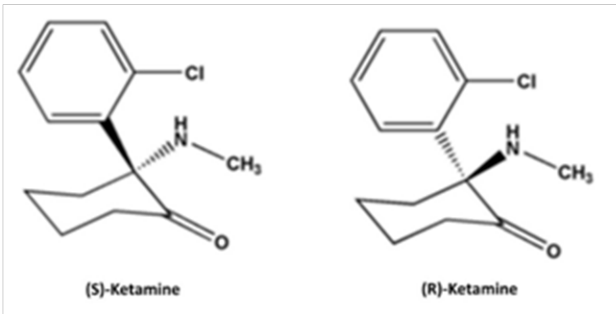

Figure 2 Ketamine S and R isomers.

The neuropharmacological properties of ketamine have prompted clinical research using it as a novel rapid and short-acting antidepressant. A single dose produces antidepressant effects within hours of administration, peak in less than a day, and last up to two weeks.[13–15]

Antidepressant mechanisms: The antidepressant mechanisms of ketamine are controversial and appear to be multiple; in part through the release of glutamate at NMDA receptors, the AMPA receptor contributes to the NMDA receptor and apparently to metabotropic receptors, which may represent a convergent mechanism for rapid antidepressant actions of ketamine.[16–19] However, these effects were also found in the 5-HT and dopamine receptors of the mammalian rapamycin pathway (mTOR).[17,20–22] Muthukumaraswamy et al.[23] mention that this antidepressant effect of ketamine may depend on its ability to change the balance of frontoparietal connectivity patterns.

Recently, Zanos et al.[24] proposed that (2S,6S;2R,6R)-hydroxynorketamine (HNK) - a metabolite of racemic ketamine- produces antidepressants effects in mice. These actions are independent of NMDAR inhibition but implicate early and sustained activation of α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid receptors (non-NMDA receptors). This theory was also mentioned by Hashimoto.[25] This enantiomer lacks ketamine related side effects. This novel hypothesis has motivated interesting comments[26,27] and new therapeutic possibilities will surely be opened without the undesirable effects of ketamine, including the possibility of addiction when used chronically. On the other hand, Shirayama and Hashimoto[28] found that the HNK (20 and 40 mg/kg) does not have antidepressant effects in a rat model of depression.

Although there are currently many studies in animals and humans, the clinical data to treat patients with psychiatric disorders resistant to the usual treatment such as unipolar and bipolar depression, refractory obsessive disease, post-traumatic malaise, anxiety and suicide, exhibit controversial results since there are many questions without satisfactory answers.

In just two hours after the administration of ketamine, patients improve the symptoms of MD, which contrasts with the slow response to the traditional antidepressants. This rapid response has cataloged ketamine as a novel ultra-rapid onset antidepressant that begins to have an important place in therapeutic armamentarium for these patients.

The first double-blind study comparing intravenous ketamine 0.5 mg/kg versus placebo[29] in patients with MD demonstrated significant improvement measured with the Hamilton scale in the patients treated with ketamine. Carrier and Kabbak[30] found that female rats are more sensitive to the antidepressant effect of low doses of ketamine when compared to male rats and female ovariectomized rats where no antidepressant effect was found. These authors suggest an important hormonal role. This animal data is relevant since MD affects more women than men.

There is no consensus on the dose and ideal route for the administration of ketamine as an antidepressant in MD disorders. Most studies have used intravenous infusions with subanesthetic doses ranging from 0.25 to 0.5 mg/kg administered in 40 to 60 minutes in a variety of schemes: a weekly infusion for two weeks, 3 to 5 times a week for a week.[16,31] Correll and Futter [32] described two patients managed with very low doses (0.1-0.2 mg/kg/h) and adjusted to 0.27 mg/kg/h with excellent results.

The antidepressant effect lasting up to two weeks after the infusion of ketamine 0.5 mg/kg has been related to the family history of alcoholism.[33] Pennybaker et al.[34] treated 93 patients with MDD or bipolar depression with a single infusion of ketamine 0.5 mg/kg that only 12.9% had response criteria two weeks later. These authors found that ketamine responder have a positive family history of alcoholism in a first-degree relative and greater dissociative effect during ketamine administration. They also mentioned that better measurements in sadness, failure to feel, and difficulty concentrating at day 1 after ketamine infusion correlated most powerfully with antidepressant effects at two weeks evaluation.

The antidepressant effect of ketamine occurs almost immediately after the intravenous administration is completed; the onset occurs within two hours post infusion and persists significantly for a week evaluated with the Hamilton scale. Like its use in anesthesiology, ketamine as antidepressant drug has been administered intravenous, oral, sublingual, subcutaneous, intramuscular and intranasal, with promising results.[35–37] In a randomized, double-blind, crossover study that included 20 patients with MD, Lapidus and his group[38] found that 50 mg of intranasal ketamine for two consecutive days had a rapid antidepressant effect with minimal side effects. Children aged 9-19 years suffering bipolar disorder (Fear of Harm (FOH) phenotype) were treated with intranasal ketamine producing marked improvement in all symptoms.[39] The nasal route could be the ideal approach in the management of these patients since it is easily accessible compared with parenteral options. In elderly patients with resistant depression ketamine produced significative and sustained improvement of depressive symptoms.[40]

Suicidal thoughts and suicide are an important part of people affected by MD. The rapid effect of ketamine on MD decreases the frequency of suicidal ideation, and this is one of the greatest advantages of this novel treatment.[41].Single ketamine intravenous infusion 0.5 mg/kg over 40 minutes administered in patients with MDD and bipolar depression could reduce suicidal ideas by reducing nocturnal wakefulness by an unknown mechanism.[42] In a recent randomized clinical trial including 80 patients suffering MDD Grunebaum et al.[43] compared 0.5 mg/kg i.v. ketamine versus 0.02 mg/kg i.v. midazolam and measured SSI score 24 hours after, and found that ketamine demonstrated a larger and faster reduction in suicidal thoughts within 24 hours compared with midazolam. Ketamine side effects were brief, and clinical improvement lasted up to 6 weeks with additional optimized standard pharmacotherapy in an uncontrolled follow-up.

Fatigue is an accompanying symptom of depression that can be treated with ketamine. A recent study showed that 0.5 mg/kg of ketamine administered in 40 minutes significantly reduced for two weeks the fatigue scores in patients with bipolar disorders when compared to placebo in a double-blind crossover study.[44] While there are abundant clinical and animal references, a recent review has called into question the antidepressant effects of ketamine and mentions the need for more research.[45]

As it has been reviewed, ketamine in low doses has a fast antidepressant effect in MD, in bipolar depression, and in depression with suicidal ideas.[13,44,45] One limitation to this novel management is the relatively short time that ketamine has as an antidepressant and the addictive potential that patients could develop.[46,47]

Nitrous oxide

Named “dephlogisticated nitrous air” by its creator, nitrous oxide (N_2O) was first prepared by Joseph Priestley in 1722. In 1800 Sir Humphry Davy mentioned the possibility of using it in surgery due to its analgesic properties. Since then, the gas of laughter has had a well-known history with personalities such as William Parker, Gardner Q. Colton, Horacio Wells, William Morton, John Collins Warren. Curiously, it was Horacio Wells who introduced N_2O as an anesthetic gas in his failed presentation at the Massachusetts General Hospital. Wells had data compatible with MD and seasonal affective disorder that recurred in the winter and resolved in the spring and is known to self-breathe N_2O,[48] which would make him the first patient to receive N_2O -pure serendipity- for MD.

Nagele and his group[49] based their research on the fact that being N_2O an NMDA receptor antagonist could have a therapeutic effect on resistant MD[50] like that described with ketamine. They studied 20 patients with resistant MD comparing 50% N_2O in oxygen versus a mixture of 50% nitrogen-O_2 administered for 60 minutes. Symptoms of MD improved significantly at 2 and 24 hours compared with the placebo group. In three of 10 patients, N_20 was discontinued, 4 had reduction ≥50% on the Hamilton scale, and 3 had complete remission. There were no severe side effects. Zarate and Machado-Viera[51] commented on the results of Nagele and the possibilities of N_2O in the management of resistant MD. Yang and Hashimoto[52] also comment on the study of Nagele and his group adding comments on the effect of isofluorane and scopolamine on the NMDA receptor.

The toxicity of N_2O could be a limiting factor to the chronic use in patients with resistant MD since it interacts with vitamin B12 inhibiting methionine synthetase, a key enzyme in the metabolism of methionine and folates. Although the classic exposure during anesthesia is not considered harmful, chronic exposure could cause megaloblastic depression in the bone marrow, neurological symptoms. A relationship between anesthesia with N_2O and hyperhomocysteinemia has also been found, which is an independent risk factor for coronary heart disease.[53,54]

Conclusion

The modulating effect of general anesthetics on neuronal activity could exert long-term therapeutic results in certain psychiatric conditions such as MD disorders.[52,55] The off-label use of drugs is accepted in medicine as long as it is based on studies in animals and humans that show encouraging results, with minimal or no side effects. This is the case of advances in the management of refractory MD and other psychiatric pathologies that have benefited from the antagonism of glutamate receptors by modifying human pathological behaviors by changing the chemical interactions of neurotransmitters/membrane receptors.[56,57] Ketamine and N2O are two general anesthetics from the past that have opened a range of future therapeutic possibilities in psychiatry by demonstrating promising results where traditional antidepressants have a high failure rate. As experts in the safe use of these two drugs, but unaware of psychiatric diseases, anesthesiologists can actively co-participate in this new modality of resistant MD management. In fact, most of the clinics that have opened in the United States of America are directed by anesthesiologists interested in this topic.

Acknowledgments

None.

Conflicts of interest

The authors declare no conflicts of interest.

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Citation: Whizar-Lugo VMMD, Heredia-Mota CMD, Alejandro CMD. Back to the future: ketamine and nitrous oxide in major refractory depression. *J Anesth Crit Care Open Access.* 2017;9(3):419–423. DOI: 10.15406/jaccoa.2017.09.00345