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INTRODUCTION

Ketamine was synthesized in 1962 by Calvin Lee Stevens, a professor of Chemistry at Wayne State University, while looking for a short-acting derivative of phencyclidine (PCP), with a more favorable tolerability profile, such as lower risk of hypertension and post-operative delirium. In 1966, Corssen and Domino published the first clinical study of ketamine as a “dissociative anesthetic”. Having been approved by FDA in 1970, ketamine received wide use as an anesthetic during the Vietnam War and it has remained one of the most utilized anesthetics ever since. Additionally, it is employed for pain management in emergency medicine, as an alternative to opioids. During the 1970ies, it was also tried as an adjunct for psychotherapy in Latin America, with limited success (Khorramzadeh & Lotfy 1973). In recent times, racemic ketamine and, more frequently, its (S)+ enantiomer (esketamine) have been used in acute treatment of depression, due to their fast-acting antidepressant, antisuicidal and antianhedonic effects. We are going to discuss ketamine’s action as a novel antidepressant, in light of its potential side effects and its possible diversion as a recreational drug.

PHARMACOLOGY

Ketamine is considered a “dirty drug” modulating various biological targets. Its full mechanism of action is not fully understood. Ketamine’s proposed mode of action is via open-channel uncompetitive antagonism (K_i=0.25-0.66 μM) of the N-methyl-D-aspartate (NMDA) receptors, which are ionotrophic glutamate receptors (Tyler et al. 2017). It binds to dizocilpine (MK-801) site of the NMDA receptor (which is also known as the PCP site of this receptor).

Arketamine and esketamine bind to this site with unequal affinities, with esketamine showing roughly 3 to 4 fold stronger affinity for this receptor than arketamine. Ketamine is also a ligand of the μ-, κ-, and δ-opioid receptors (MOR partial agonist, agonist of KOR and DOR), a sigma σ1 and σ2 receptor agonist, a (presumably agonistic) ligand of the serotonin 5-HT_2A receptor, a weak (presumably antagonistic) potentiator of the serotonin 5-HT_1 receptor, as well as a competitive muscarinic acetylcholine receptor antagonist, acting mainly on M_1, the most common muscarinic subtype in the cortex and hippocampus. It also acts as a negative allosteric modulator of nicotinic acetylcholine receptors (mainly α7, α4β2), as well as an indirect agonist of the AMPA receptor. It is also a weak inhibitor of nitric oxide synthase and a cholinesterase inhibitor. Its inhibitory effects on the reuptake of serotonin, norepinephrine and dopamine, although measured, are dose-dependent, with SERT inhibition being the weakest of the three. Ketamine’s partial agonism the high-affinity state of the dopamine D2 receptor is still considered controversial and open to interpretation and further research (Can et al. 2016). Ketamine’s complex pharmacodynamics becomes evident in situations of overdose when even receptors with weak affinity may be activated. Ketamine’s main antidepressant mode of action was long thought to be through the modulation of glutamate transmission (Zhang & Hashimoto 2019). Via antagonism of the NMDA receptor on GABA-ergic inhibitory interneurons, it was thought to stimulate glutamate release.
by pyramidal cells in the prefrontal cortex, which should lead to increased synaptogenesis in this part of the brain (Abdallah et al. 2014). Glutamate transmission basis of ketamine’s antidepressant action has recently been criticized, given that preclinical studies indicated that (2R,6R)-hydroxynorketamine, a metabolite of arketamine with negligible affinity for the NMDA receptor, may be more a effective antidepressant than esketamine (Garay et al. 2018, Hashimoto 2019). For these reasons, in 2019, arketamine and (2R,6R)-hydroxynorketamine both entered clinical trials for the treatment of depression. The antidepressant effect of ketamine is thought to be achieved by activation of the connections between the anterior cingulate cortex and amygdala and acute inhibition of the lateral habenula which can be considered "anti-reward center" in the limbic system, projecting to and inhibiting the mesolimbic reward pathway and modulating other limbic areas (Chen et al. 2018). Furthermore, ketamine affects neuroplasticity in an indirect way, through the enhancement of brain-derived neurotrophic factor (BDNF) production, via the inhibition of glycogen synthase kinase 3 and through the stimulation of mammalian target of rapamycin (mTOR) signaling in the prefrontal cortex (Roy et al. 2020).

Esketamine has approximately 3 to 4 times stronger affinity for NMDA receptors, compared to racemic ketamine. Unlike racemic formulation, it has not been found to interact with sigma receptors. While, as of yet, no antidepressant superiority of intravenous esketamine over arketamine or racemic ketamine has been found, intranasal esketamine seems less potent than racemic intravenous infusion, because of 50% lower bioavailability of the intranasal formulation. Nevertheless, esketamine was found to offer better neurocognitive protection, including, but not limited to faster reha- bilitation of neuronal functioning (through atrophy reversal and neurogenesis promotion) as well as fewer episodes of anterograde amnesia, compared to other formulations of ketamine. This may be due to eske- tamine’s superior mTOR signaling in the prefrontal cortex, which has not been detected in arketamine studies, so far. On the other hand, arketamine was found to possess less dissociative side effects and is therefore less prone to diversion and possible abuse. Arketamine could, thus, be a safer alternative to both esketamine and racemic ketamine.

NOVEL ANTIDEPRESSANT

Depression is one of the most frequent mental dis- orders, with prevalence up to 20-25% in general popula- tion. While psychotherapy and social therapy play a great role in depression rehabilitation, antidepressant psychopharmacotherapy remains the golden standard in the initial treatment of depressive episodes, even though in one third of cases, patients will fail to respond to the antidepressant therapy. Whereas most current antidepressants produce some benefits within the first ten days of use, full improvement might not be seen for two or three months. Rapid-acting antidepressant therapeutics may be limited to older drugs with a significant side effect burden (clomipramine), novel drugs (agomelatine) or non-anti- depressant drugs (low-dose sulpride, low-dose amisul- pride). The local availability of these medications can be a limiting factor in treatment, more often than not. Ketamine and esketamine have been used as anesthetics for several decades all around the world, with known pharmacokinetics and side effect profiles. In 2000, it was found that administration of a subanesthetic dose of ketamine lead to the rapid remission of an acute depression case. The first placebo-controlled study by Berman and colleagues found noticeable results in reduction of depressive symptoms, as measured by Hamilton Depression Rating Scale (HAM-D) and self-rated Beck Depression Inventory, after a single intravenous infusion of a racemic mixture of ketamine (given as 0.5 mg/kg). Since then, numerous studies have proven fast-acting antidepressant effects of intravenous and intranasal ketamine in patients with depression. In the majority of patients, its antidepressant effects may linger up to seven days. Repeated applications of keta- mine have been proposed in first-treatment non-respon- ders since no tachyphylactic effects to antidepressant properties of ketamine has ever been detected (Rakesh et al. 2017). Ketamine has antidepressant, antisuicidal and antianhedonic actions, all of which may be independent one from another.

Intravenous or intranasal ketamine has been used as a rapid-acting antidepressant as well as a therapy of choice in treatment-refractory depression, in which it can rival (or be used synergistically with) electroconvul- sive therapy. Along with lithium salts and clozapine, it is one of the few psychotropic drugs with proven anti- suicidal effects, but with an additional advantage of rapid onset of action, with effects observed within minutes. Positron emission tomography imaging findings have shown that reductions in suicidal ideation after intravenous ketamine infusion correlate with decreased regional cerebral glucose metabolism in the infralimbic cortex (Brodmann area 25). BDNF may be involved in enhanced antisuicidal response to ketamine (Levinstein & Samuels 2014). Ketamine’s antidepressants effects are beneficial in both unipolar and in bipolar depression, that is, there is no associated risk of manic switch. Low subanesthetic doses of ketamine have also been tried in the treatment of substance use disorders, including alcoholism, with some success (Azhari et al. 2020).

RISKS

Even antidepressant, subanesthetic doses of keta- mine, have some abuse potential, due to its psycho- mimetic, primarily dopaminergic effects (Strong & Kabbaj 2018). Increased dopamine levels in frontal
Ketamine should not be taken together with alcohol, benzodiazepines, sodium oxybate, or γ-butyrolactone, because of the increased risk of ataxia and sedation. There is no single antidote for ketamine overdose. Supportive therapy is used. Opioid antagonists like naloxone, which were found to have antidiissociative effects in treatment of derealization and depersonalization symptoms, were found to attenuate antidepressant and antisuicidal effects of ketamine. This could convey an impression of ketamine’s antisuicidal and antidepressant mechanism being intertwined with its dissociative effects. Still, more studies are needed to prove (es)ketamine therapeutic efficacy, in direct comparison with standard therapeutic options for conditions esketamine is indicated for, such as lithium, clozapine or electroconvulsive therapy.
CONCLUSION

Many psychoactive drugs are prone to abuse and diversion. When psychoactive drug rescheduling or legalization is done, it should be so to benefit users and/or to prevent them from possible harm caused by exposure to a psychotropic drug. There is such a loose line between "soft" and "hard" drugs. Drugs like ketamine can exert devastating effects on their users, including psychotic states and unpredictable behavior. Therefore, preventive strategies must be developed in order to reduce harm in susceptible individuals while providing optimized therapeutic effects in controlled, expert-guided situations, to those who may benefit from their treatment. The line between a psychoactive drug of abuse and a licensed medication can be blurry, and the trends and patterns of therapeutic use and illicit abuse are prone to cultural, social and political factors. Strict guidelines on ketamine medical use in psychiatry must be developed in order to prevent its overprescribing and consequent misuse, abuse or diversion.

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Contribution of individual authors:
All authors contributed to writing of this paper equally.

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