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Methoxetamine: From drug of abuse to rapid-acting antidepressant

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ABSTRACT

Methoxetamine is a dissociative anaesthetic showing pharmacodynamic similarities with its analogue ketamine, a medication with demonstrated rapid-acting antidepressant effects. Like ketamine and other arylcyclohexylamine compounds, methoxetamine is thought to be both a noncompetitive NMDA receptor antagonist and a dopamine reuptake inhibitor. Furthermore, it acts as an agonist at dopamine D2, serotonin 5HT2, muscarinic cholinergic, sigma-1, opioid mu and k receptors. The hypothesis is that methoxetamine can produce rapid antidepressant effects in patients with resistant and non-resistant unipolar and bipolar depression.

Introduction

Mood disorders (MD) are chronic, recurring, disabilitating psychiatric illnesses that affect millions people worldwide [1,2]. In particular, major depressive disorder (MDD) is a seriously disabling public health problem that produces severe psycho-physical and socioeconomic consequences in the population [3]. MDD has a 12 month prevalence of 6.6% and a lifetime prevalence of 16.2% and it is twice as common in women than in men [4,5]. The World Health Organization (WHO) predicted that, by 2020, MDD will be the second leading cause of disability worldwide [6]. For more than 50 years, the treatment of MDD has been based on medications that increase the synaptic levels of biogenic amines, especially serotonin and norepinephrine [7]. Although the pharmacological treatments currently available can produce benefit in many patients, it is estimated that less than one third of depressed patients achieves remission with an adequate trial of a standard antidepressant, and only up two thirds responds after testing multiple medications [8,9]. Similarly, many patients with bipolar depression (BD) do not respond adequately to existing drugs [10,11]. Residual depressive symptoms, cognitive deficits, functional impairment, and increase in frequency of recurrences are often present in patients correctly treated [12,13]. Furthermore, antidepressants require not less than 3–4 weeks to produce a clinically significative improvement in depressive symptomatology and this delayed onset of action can produce important consequences on management of patients with high risk of suicide [14,15]. Several decades ago, preclinical studies have shown a potential involvement of the glutamatergic system in the pathophysiology of MD [16]. These studies showed that compounds which reduced transmission at *N*-methyl-D-aspartate (NMDA) receptors produced antidepressant effects in animal models of depression [17,18]. In recent years, some clinical studies have shown that an intravenous dose of ketamine, an *N*-methyl-D-aspartate (NMDA) receptor antagonist, produces a rapid antidepressant response within hours [19]. These studies include the treatment of resistant BD in two double-blind, randomized, cross-over, placebo-controlled, add-on trials [20,21], the treatment of resistant MDD and resistant MDD with suicidal ideation in open-label case series, in randomized, placebo-controlled, double-blind trials, including one with cross-over design and in several case report [22–25]. Furthermore, in an open-label study conducted in an emergency department was tested the efficacy of a single intravenous dose of ketamine in depressed patients with suicidal ideation. In this study, the patients experienced improvement in depressive symptoms including suicidal ideation [26]. In addition, some reports suggest that ketamine and ECT can produce synergistic antidepressant effects in patients with resistant depression [27–29]. Finally, family history of alcohol dependence and increased anterior cingulate cortical activity in response to fearful faces appear to predict a rapid initial antidepressant response to ketamine [30,31]. In 2010, methoxetamine (MXE), a ketamine derivative, was found in recreational products marketed as legal highs [32]. This substance, used by people for its dissociative effects, shows pharmacodynamic similarities with its analogue ketamine [33]. Unlike ketamine, the 2-chloro group on the phenyl ring has been replaced by a 3-methoxy group and the *N*-methyl group on the amine has been replaced by an *N*-ethyl group. The change from *N*-methyl to *N*-ethyl gives methoxetamine more potency and duration of action than ketamine while the change from 2-chloro to 3-methoxy gives methoxetamine less analgesic and anaesthetic properties than ketamine [34,35]. Pharmacodynamic comparison between MXE and ketamine suggests the hypothesis that these two arylcyclohexylamine derivatives can produce the same antidepressant effects.

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Methoxetamine information

Methoxetamine is a dissociative anaesthetic belonging to the arylcyclohexylamine class [35]. To date, there are no approved indications in human pharmacology and this drug is marketed only for research purpose by many suppliers, particularly in Asia [35–37]. These suppliers sell methoxetamine to a declared purity of more than 99% and generally discourage the use of this substance in laboratories without an analytical balance capable of weighing accurately 10/20 mg with a minimum accuracy of ±5 mg [35]. Methoxetamine, molecular weight 247,33 g/mol, is sold as a bright white powder with different brand names. This molecule has a density of 1,076 g/cm^3, a boiling point of 389,084 °C at 760 mm Hg, and a flash point of 189,111 °C [38]. There are no data about the safety of methoxetamine in humans.

The hypothesis

Recently, MXE, an arylcyclohexylamine derivative has emerged as a new potential drug of abuse [36]. Despite being marketed as research chemical and labeled as "not for human consumption", people use this substance for its ketamine-like effects [37]. The hypothesis is that MXE has antidepressant effects, is efficacious in the treatment of unipolar and bipolar depression and produces a rapid antidepressant response.

Evaluation of the hypothesis

To date, no human or animal studies has evaluated the antidepressant properties of MXE, however, the pharmacological similarities with ketamine, a dissociative anaesthetic producing a rapid antidepressant action, suggest that MXE can produce the same therapeutic effects. Like ketamine and other arylcyclohexylamine compounds, MXE is thought to be both a noncompetitive NMDA receptor antagonist and a dopamine reuptake inhibitor [39]. Furthermore it acts as an agonist at dopamine D2, serotonin 5HT2, muscarinic cholinergic, sigma-1, opioid mu and k receptors [40].

Activity at NMDA receptors

Glutamate is the major excitatory neurotransmitter in the human brain and modulates synaptic excitability and plasticity in many central nervous system (CNS) circuits, including those involved in the MD [41]. The neurobiological mechanisms underlying the ketamine induced rapid antidepressant effects have not been completely understood, but some data have shown that the block of NMDA receptors produces both an increase in the glutamate AMPA receptors activation and an increase in AMPA/NMDA receptor activity ratio and subsequently, an activation of mammalian target of rapamycin (mTOR) signaling through the release of brain derived neurotrophic factor (BDNF) [42]. The mTOR pathway appears to be of main importance in the synaptic protein synthesis, synaptogenesis and rapid antidepressant effects induced by NMDA antagonists [43].

Activity at opioid receptors

Like monoamine systems, the endogenous opioid systems are involved in the regulation of mood and behavior and are both expressed in brain areas known to play a key role in the pathophysiology of depression [44]. Some data have shown that opioids produce antidepressant effects and those dual action antidepressants such as venlafaxine and duloxetine can produce analgesic action [45]. Furthermore, mu receptor has also been genetically associated with citalopram response in MDD [46] while antidepressant effects of venlafaxine are abolished in mu opioid receptor knockout mice [47]. Finally, studies in mice model of depression have shown that the combination between classical monoaminergic antidepressants and opioid receptor agonists can produce synergistic antidepressant effects [48].

Activity at sigma-1 receptors

Numerous evidence suggest that sigma-1 receptors play a key role in the pathophysiology of depression and other neuropsychiatric disorders, as well as in the mechanism of action of some therapeutic drugs, including monoaminergic antidepressants [49]. The activation of sigma-1 receptors appear to be involved in the enhancement of the prefrontal dopaminergic neurotransmission and in the antidepressant effects mediated by some drugs such as fluvoxamine, fluoxetine, citalopram, sertraline, clorgyline, and imipramine [40–54]. In an open study, a small sample of depressed patients was treated with JO-1784, a sigma-1 receptor agonist, which induced a 50% reduction of intensity of depressive symptoms on the Hamilton depression scale. Furthermore, data emerged by a double-blind placebo controlled study showed that a dose of 20 mg/day of JO-1784 was superior to placebo and to 20 mg/day of fluoxetine in the treatment of depressive symptoms. However, at 100 mg/day, JO-1784 was not different from the placebo in antidepressant efficacy [55,56]. In addition, sigma-1 agonists can modulate both glutamatergic and serotonergic neurotransmission supporting the hypothesis of a potential involvement of sigma-1 receptors in the pathophysiology of depression [56].

Activity at muscarinic cholinergic receptors

The implication of cholinergic system in the pathophysiology of depression was postulated several decades ago. A recent post-mortem study has found that depressed patients showed a decreased binding of M2 and/or M4 muscarinic receptors in the dorsolateral prefrontal cortex [57]. Furthermore, M2 receptors appear to be involved in the pathophysiology of depression by single-nucleotide polymorphism association studies [58,59]. Finally, M1 receptor could play a key role in the amelioration of mood disorder-associated cognitive deficits, given its role in cognition [60].

Consequences of the hypothesis

Antidepressants currently available are principally based on the monoaminergic hypothesis of depression [61]. Although these medications can produce some benefits, they take weeks to achieve the full effect and patients receiving these drugs remain vulnerable to the global functioning impairment and are at high risk of suicide [62]. In recent years, the rapid antidepressant effect of the intravenous infusion of a sub-anesthetic dose of ketamine, has triggered research endeavors on this novel potential class of antidepressants [63]. Experimental confirmation of the hypothesis may demonstrate some predicted effects of MXE: [1] clinically significant antidepressant effects in patients with resistant and non-resistant unipolar and bipolar depression; [2] a rapid onset of antidepressant effect within hours of initial administration; [3] antidepressant properties in animal models of depression (e.g., forced swimming, learned helplessness); [4] response associated with both a block of NMDA receptors and an increase in AMPA/NMDA receptor activity ratio. These predictions will be critical to testing the hypothesis. Other predictions such as the pharmacodynamic action at serotonin 5HT2, muscarinic cholinergic, sigma-1, opioid mu and k receptors are desirable but not critical to testing the hypothesis. The developments of rapid-acting antidepressants are the new frontier in the pharmacological treatment of

depressive disorders and NMDA receptor antagonists are potential candidates to become a new generation of antidepressants.

Conflicts of interest statement

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