Neurochemistry International 122 (2019) 1–7

Contents lists available at ScienceDirect

Neurochemistry International

journal homepage: www.elsevier.com/locate/neuint

Methoxetamine: A foe or friend?

Chrislean Jun Botanas[a], June Bryan de la Peña[a,b], Hee Jin Kim[a], Yong Sup Lee[c], Jae Hoon Cheong[a,*]

[a] Uimyung Research Institute for Neuroscience, Department of Pharmacy, Sahmyook University, 815 Hwarangro, Nowon-gu, Seoul, 01795, Republic of Korea
[b] Department of Biological Sciences, University of Texas Dallas, Richardson, TX 75080, United States
[c] Medicinal Chemistry Laboratory, Department of Pharmacy & Department of Life and Nanopharmaceutical Sciences, College of Pharmacy, Kyung Hee University, 26 Kyungheedae-ro, Seoul, 02447, Republic of Korea

ARTICLE INFO

Keywords:
Methoxetamine
Intoxication
Abuse liability
Antidepressant

ABSTRACT

Methoxetamine (MXE) is an *N*-methyl-D-aspartate (NMDA) receptor antagonist that is chemically and pharmacologically similar to other dissociative substances, such as ketamine and phencyclidine. There are reports on the misuse of MXE, which sometimes resulted in adverse consequences and death. Studies have also shown that MXE has abuse liability and stimulates dopamine neurotransmission in the mesolimbic reward pathway in the brain. These findings have contributed to the negative impression on MXE. However, recent preclinical studies have identified the antidepressant properties of MXE, which are attributed to its ability to affect the glutamatergic and serotonergic systems. MXE is also reported to have analgesic effects. These findings show some of the "redeeming qualities" of MXE and indicate its possible therapeutic uses. In this paper, we have reviewed the findings that provide insights into the adverse and potential therapeutic effects of MXE. We compiled studies on the toxicity, psychotomimetic effects, and abuse liability of MXE, as well as its promising antidepressant and analgesic properties. We also have discussed the mechanism of action that might mediate the somewhat paradoxical effects observed. Importantly, this review provides valuable information on MXE for future research and will enable a better understanding of its psychopharmacological properties and the mechanisms responsible for its unique effects.

1. Introduction

Methoxetamine [MXE; 2-(3-methoxyphenyl)-2-(ethylamino)cyclohexane] is a synthetic dissociative drug derived from ketamine (Corazza et al., 2012; Meyer et al., 2013). Similar to ketamine and phencyclidine, MXE is pharmacologically classified as an *N*-methyl-D-aspartate (NMDA) receptor antagonist (Corazza et al., 2013; Roth et al., 2013). Since its introduction to the market in 2010, MXE has become a popular recreational drug, particularly among adolescents (Morris and Wallach, 2014). This phenomenon is partially attributed to its ketamine-like dissociative effects, which can last longer than those of ketamine (Hofer et al., 2012; Kjellgren and Jonsson, 2013; Zawilska, 2014). MXE has been extensively marketed by head shops on the internet, most of which offer international shipping (Craig and Loeffler, 2014; Kjellgren and Jonsson, 2013). It is known by different street names such as "Mexxy", "M-ket", "MEX", "Kmax", "Special M", "MA", "legal ketamine", "Minx", "Jipper", and "Roflcoptr" (Roth et al., 2013; EMCDDA, 2013). Subsequently, there is an increasing number of reports on the misuse of MXE that has resulted in adverse effects, including death (Zawilska, 2014). Therefore, MXE has been categorized as a controlled/scheduled substance in countries such as Japan, China, Russia, United Kingdom, Turkey, Korea, and some European Union member states (EMCDDA, 2013; WHO, 2015).

On the contrary, MXE is hypothesized to possess antidepressant properties similar to those of ketamine (Coppola and Mondola, 2012). Over the past years, ketamine has been shown to produce rapid and robust antidepressant effects and improved depression symptoms, such as suicidal thoughts, anhedonia, and depressed mood; these effects occurred within hours following a single treatment with ketamine and persisted for at least a week (Berman et al., 2000; Murrough et al., 2013; Zarate et al., 2006). Although the exact mechanism remains to be determined, studies have suggested that the antidepressant effects of ketamine involves the activation of α-amino-3-hydroxy-5-methyl-4-isoxazole-propionic acid (AMPA) receptors and modulation of downstream signaling pathways that affect synaptic plasticity (Jourdi et al., 2009; Zanos et al., 2016; Zhou et al., 2014). Recently, we reported that MXE exerts rapid and sustained antidepressant effects in mice and that these effects are potentially mediated by the glutamatergic and

* Corresponding author.
E-mail address: cheongjh@syu.ac.kr (J.H. Cheong).

https://doi.org/10.1016/j.neuint.2018.10.020
Received 24 August 2018; Received in revised form 22 October 2018; Accepted 23 October 2018
Available online 24 October 2018

serotonergic systems (Botanas et al., 2017). In addition, MXE has also been proposed to have analgesic effects. It was reported that MXE is used in self-medication to relieve chronic foot pain (Maskell et al., 2016). These reports suggest that MXE has potential therapeutic uses. Although the discovery of the antidepressant efficacy of MXE may elicit excitement amongst scientists in the field, its potential therapeutic uses are limited by its capacity to induce toxic and psychotomimetic effects and its abuse liability.

In this paper, we have reviewed recent findings that provide insights into the adverse and potential therapeutic effects of MXE. We have compiled and discussed studies that have investigated its toxicity, psychotomimetic effects, abuse liability, and promising antidepressant and analgesic effects. We have also presented related underlying mechanisms that might be responsible for its paradoxical effects. For this review, we have comprehensively researched literature in PubMed and Google Scholar to identify all articles published to August 2018 with the term "methoxetamine". The inclusion criteria were: preclinical studies, case reports, editorials, letters, and surveys. Non-English articles or publications were excluded. Finally, this review aims to provide valuable information on the myriad effects of MXE to guide the design of future experiments and to address the very intriguing question: is MXE a foe or friend?

2. Physical, chemical, and pharmacological characteristics and metabolism of MXE

As shown in Fig. 1, MXE is different from ketamine in two ways: (1) the 2-chloro group in the phenyl ring of ketamine is replaced by a 3-methoxy group in that of MXE, which gives MXE weaker analgesic and anesthetic properties than those of ketamine; and (2) the *N*-methylamino group in ketamine is substituted by an *N*-ethylamino group in MXE, which confers increased potency and duration of action to MXE (Coppola and Mondola, 2012; Corazza et al., 2012). Compared with phencyclidine, MXE presents an ethyl amino group instead of a piperidine ring and a methoxy group inserted at position 3 of the phenyl ring; the former modification makes MXE more potent than phencyclidine, whereas the latter increases the affinity of MXE to the μ-opioid receptor (Adamowicz and Zuba, 2015; Corazza et al., 2013).

MXE has mostly been encountered, in seized or collected samples, as a white, odorless, crystalline powder or as an "off-white", beige, or yellow powder (EMCDDA, 2013). Typically sold in powder form, it is also available as a tablet, capsule, or liquid (ACMD, 2012; Coppola and Mondola, 2012; EMCDDA, 2013). MXE is commonly administered by nasal insufflation, oral consumption, and intramuscular or intravenous injection (Corazza et al., 2012; Kjellgren and Jonsson, 2013), but sublingual and rectal administration have also been reported (Zawilska, 2014). Reports have indicated that the dose ranges of MXE are 20–100 mg by nasal insufflation, 40–100 mg by oral administration, and 10–80 mg by intramuscular injection (Zawilska, 2014). The onset of the desired effects is typically apparent 10–90 min after drug administration (Rosenbaum et al., 2012) and may last for approximately 1–7 h, depending on the route of administration (Corazza et al., 2012; Kjellgren and Jonsson, 2013).

As mentioned previously, MXE acts as an NMDA receptor antagonist. It has a high binding affinity to the phencyclidine site of the glutamate NMDA receptor (pKi = 6.59), an effect equipotential to that of ketamine (Roth et al., 2013); this feature is thought to be responsible for the dissociative effects of MXE. Unlike ketamine, MXE shows a similar appreciable affinity to serotonin transporter (pKi = 6.32), but not to opioid σ_1 and σ_2 receptors (Roth et al., 2013). MXE inhibits human dopamine transporter (IC_{50} = 33 μM), serotonin transporter (IC_{50} = 2 μM), and norepinephrine transporter (IC_{50} = 20 μM) in HEK293 cells by a fluorescence-based neurotransmitter transporter uptake assay (Hondebrink et al., 2017). It also inhibits the reuptake of and increases the level of electrical-release dopamine in an *in vitro* study (Davidson et al., 2014) Furthermore, MXE increases dopamine and serotonin concentrations in the medial prefrontal cortex (Fuchigami et al., 2015). Recently, MXE was shown to activate dopamine neurotransmission in the mesolimbic reward circuit, which may be the cause of its abuse liability (Mutti et al., 2016). It can also alter the expression of glutamatergic- and serotonergic-related genes in the hippocampus, which is attributed to its antidepressant effects (Botanas et al., 2017). Furthermore, MXE increases the phosphorylation of the ribosomal protein S6 in the medial prefrontal (prelimbic and infralimbic) and hippocampal areas (Zanda et al., 2017), which presents a preview of the neuroadaptive molecular effects of MXE which may be correlated with its behavioral or antidepressant effects. More details on the mechanism of action of MXE are discussed later in this review.

To date, there is little information about the metabolism of MXE. In a recent study, Meyer et al. (2013) identified phase I and phase II metabolites of MXE in human and rat urine. They found eight metabolites and hypothesized the following metabolic pathways: *N*-deethylation, *O*-demethylation, hydroxylation, and their combinations, as well as glucuronidation or sulfation of *O*-demethylated metabolites. This study showed that MXE is extensively metabolized in rats and humans and that the human cytochrome P450 enzymes, particularly CYP2B6 and CYP3A4, are involved in its initial metabolic steps. More recently, Menzies et al. (2014) identified five most abundant phase I and two phase II metabolites of MXE in human liver microsomes. These phase-I metabolites are *N*-desethyl(nor)methoxetamine, *O*-desmethyl methoxetamine, hydroxy-normethoxetamine, *O*-desmethyl-normethoxetamine, and dihydronormethoxetamine, whereas the phase-II metabolites are *O*-desmethylmethoxetamine glucuronide and *O*-desmethyl-normethoxetamine glucuronide. In addition, urine samples from three individuals with acute MXE toxicity revealed the presence of the majority of these metabolites except *O*-desmethyl-normethoxetamine glucuronide (Menzies et al., 2014), possibly because this particular metabolite was conjugated. Archer et al. (2012) reported that some of these metabolites were also detected in pooled urine samples from potable urinals in central London. The *N*-desethyl(nor)methoxetamine was the most abundant metabolite detected both *in vitro* and in urine samples.

3. MXE: the foe

3.1. MXE induces toxicity

Over the past few years, there has been a marked growth in reported

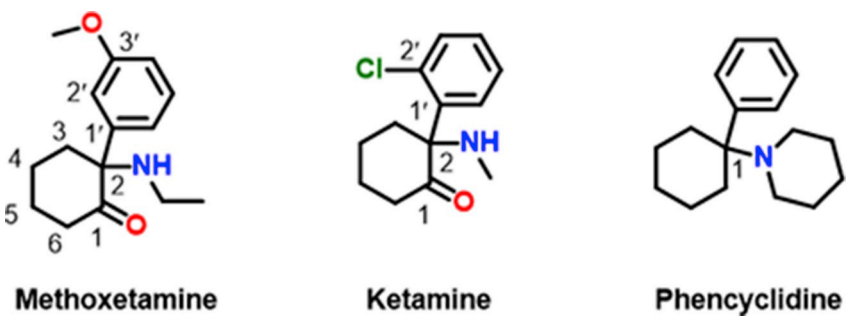

Fig. 1. Comparison of the chemical structures of methoxetamine, ketamine, and phencyclidine. Compared with ketamine, methoxetamine shows a 3-methoxy group instead of a 2-chloro group on the phenyl ring, and an *N*-ethylamino group instead of an *N*-methylamino group. Compared with phencyclidine, methoxetamine presents an ethyl amino group instead of a piperidine ring, and a methoxy group inserted at position 3 of the phenyl ring.

cases of fatal and non-fatal intoxication associated with MXE use. By 2013, a total of 110 non-fatal intoxications and 20 deaths were reported in several European Union states (EMCDDA, 2013). By 2015, 120 non-fatal intoxications and 22 deaths were recorded worldwide (WHO, 2015). The presence of MXE was analytically confirmed in almost half of all these cases. The varied blood or urine concentrations of MXE detected in those intoxication cases have been discussed in previous reports (WHO, 2015; Zanda et al., 2017; Zawilska, 2014). In addition, MXE was detected in several cases of drivers operating under the influence of drugs (Elian and Hacket, 2014; Fassette and Martinez, 2016). The reported symptoms of MXE-induced intoxication are nausea and severe vomiting, diarrhea, slow and/or irregular heart rate, loss of consciousness, difficulty breathing, seizures, disorientation, post-use depression, mental retardation, anxiety, catatonia, aggression, hallucinations, paranoia, and psychosis (WHO, 2015). In addition, symptoms of acute MXE intoxication include stimulant effects (e.g. agitation, tachycardia, and hypertension) and cerebellar features (e.g. ataxia and nystagmus) that are not expected to accompany acute ketamine intoxication (ACMD, 2012). However, not all reports of intoxication can be attributed to MXE alone because in several cases, other psychoactive compounds and their metabolites were detected in the blood of intoxicated patients; these compounds include amphetamine, alcohol, antipsychotics (olanzapine, clozapine), benzodiazepines (oxazepam, nordiazepam), cannabis, cocaine, synthetic cannabinoids (AM-2201, JWH-018), synthetic cathinones (methylone, fluoromethcathinone), and 3,4-methylenedioxymethamphetamine (MDMA) (Kjellgren and Jonsson, 2013; WHO, 2015). Therefore, it is possible that at least several symptoms of the reported MXE-induced intoxication were caused by other substances or their combination, instead of by MXE itself.

In line with the above-mentioned MXE-induced symptoms, a recent study showed that MXE at 30 mg/kg induces cardiorespiratory alterations in mice. In particular, MXE induces reductions in basal heart and breathing rates that last longer than those induced by ketamine. It also transiently decreases peripheral capillary oxygen saturation (SpO2) level. Furthermore, MXE increases basal systolic and diastolic pressure in mice for an hour, similar to ketamine and phencyclidine (Ossato et al., 2018).

MXE was extensively marketed as a “bladder friendly” alternative to ketamine because the substance was designed in part to avoid urotoxicity related to chronic ketamine use. It was believed that the high potency of MXE would limit the accumulation of urotoxic metabolites in the bladder (Morris, 2011; Morris and Wallach, 2014). However, the chronic use of MXE has been reported to potentially cause urinary toxicity. Lawn et al. (2016) examined the prevalence of urinary symptoms in a group of MXE users who reported taking MXE within the past 12 months and had also used ketamine at least once in their lifetime, in the United States, United Kingdom, European Community, Australia, and Canada in 2012. Among the MXE users surveyed in 2012, 23.0% (98 of 427 respondents) reported urinary symptoms, with at least one urinary symptom associated with the frequency of MXE use in the last month. However, because all respondents had used ketamine once in their lifetime, previous ketamine use could not be excluded as a cause of these urinary symptoms. Thus, further studies in MXE users who have never used ketamine are required to confirm the relationship between urinary symptoms and MXE use.

Supporting these reported MXE-induced urinary symptoms, preclinical studies have shown that high-dose (30 mg/kg), chronic administration of MXE induces significant damage to rodent urinary tract. Dargan et al. (2014) revealed that daily administration of 30 mg/kg MXE to mice for 3 months causes bladder inflammation, followed by fibrosis and renal toxicity at a tubular and glomerular level. Similarly, Wang et al. (2017) reported that rats treated with 30 mg/kg MXE for 4 or 12 weeks experienced an increase in micturition frequency and bladder dysfunction, as well as damaged urothelial barrier, inflammatory cell infiltration, matrix disposition, and interstitial fibrosis. Furthermore, upregulated expression of pro-inflammatory cytokines, such as IL-1β, IL-6, CCL-2, CXCL-1, CXCL-10, NGF, and COX-2, was observed. These studies indicated that high-dose, chronic administration of MXE induces urinary toxicity comparable to that induced by ketamine.

3.2. MXE induces psychotomimetic effects

Self-reported experiences of users in web forums indicate that the desired psychological and behavioral effects of MXE are broadly similar to those reported of ketamine. These effects include euphoria, enhanced empathy and social interaction, pleasant intensification of sensory experiences (especially music), distorted sense of reality, vivid hallucinations, derealization, introspection, brief antidepressant effects, feelings of peacefulness and calmness, and spiritual and transcendental experiences (Corazza et al., 2012; EMCDDA, 2013 Zawilska, 2014). At high doses (> 40 mg), MXE produces a wide range unpleasant effects, including out-of-body or near-death experience, reduced ability to concentrate and focus, psychomotor agitation, intense psychedelic experiences, paranoia, anxiety, and distortions in the perception of time, distance, proportion, and body image (Corazza et al., 2013; Craig and Loeffler, 2014; Zanda et al., 2016).

Pre-pulse inhibition (PPI) is a behavioral test that measures sensorimotor gating in rodents, in which a strong startle response is inhibited by a preceding weaker non-startling stimulus (Valsamis and Schmid, 2011). Disruption in PPI is believed to mimic schizophrenia-like states in animals and humans. Indeed, such behavior is observed in patients with schizophrenia and schizotypal personality disorder (Mena et al., 2016). NMDA receptor antagonists, such as ketamine and phencyclidine, have been shown to disrupt PPI in rodents (Bakshi and Geyer, 1997; Cilia et al., 2007; Geyer et al., 2001). It is believed that this disruption may reflect the hallucinogenic effects of NMDA receptor antagonists (Halberstadt et al., 2016). Recent studies reported that MXE induces PPI disruption in rats (Halberstadt et al., 2016) and mice (Ossato et al., 2018). Halberstadt et al. (2016) reported that the rank order of PPI-disrupting potency of MXE and other NMDA antagonists, such as phencyclidine, S− (+)- and R- (−)- isomers of ketamine, and N-allylnormetazocine, is correlated with their affinities to the phencyclidine binding site (i.e., phencyclidine > MXE > S-(+)-ketamine > N-allylnormetazocine > R-(−)-ketamine), as previously reported (Roth et al., 2013). In addition to disrupting PPI, Ossato et al. (2018) also reported that MXE reduced visual object and placing responses. These findings validate MXE as a psychotomimetic drug, consistent with reports of its hallucinogenic and sensory-altering effects.

3.3. MXE produces addictive effects

Currently, there have been no published studies on the abuse liability of MXE in humans nor reports of people with suspected or proven MXE abuse. However, there are online self-reports of MXE misuse (Erowid, 2011) and reports of a growing prevalence of MXE use (WHO, 2015), which suggest that the substance has addictive effects. Thus, for example, Striebel et al. (2017) presented a case report of a 29-year-old male veteran who was in the Opioid Treatment Program. The man declared intermittent use of MXE to 50–70 mg/kg daily on his fourth year in the program which had progressed to 70 mg/kg two to three times daily on the fifth year, in addition to other substances like methamphetamine, heroin, and alprazolam (Striebel et al., 2017). Lawn et al. (2016) conducted a study on the prevalence of MXE use in 2011 and 2012 in the United States (n = 3830 in 2011; n = 3756 in 2012) and United Kingdom (n = 8184 in 2011; n = 7360 in 2012). They reported that lifetime, past 12 months, and last month uses of MXE appeared to increase in all respondents in the United States (2.1, 1.6, and 1.6% in 2011 and 5.4, 5.0, and 2.0% in 2012, respectively), but decrease in the United Kingdom (4.9, 4.2, and 2.4% in 2011 and 4.1, 3.0, and 0.7% in 2012, respectively). This trend may be attributed to the legal status of MXE in each country, as MXE was temporarily illegalized

in the UK in April 2012, whereas no federal law was in place in the US at the time of the study. Other factors such as availability of ketamine, popular culture, and even differences in the samples between 2011 and 2012 might have an impact on the reported use of MXE. Another study conducted in a gay nightclub in South London on the prevalence of novel psychoactive substances use reported that out of 315 individuals (predominantly men between 18 and 59 years of age), 6.4% reported occasional MXE use, 1.9% reported use in the last month, and 1.6% intended to use MXE on the night of survey (Wood et al., 2012). Furthermore, the online Global Drug Survey reported that among 7700 UK-based polydrug users, 326 (4.2%) and 197 (2.6%) used MXE in the past 12 months and in the last month, respectively (Winstock et al., 2016). Although the prevalence of MXE use does not necessarily reveal its addictive potential, it provides an indication that MXE is widely misused.

The abuse liability of MXE has been investigated in preclinical studies using different behavioral approaches, including the locomotor activity test, conditioned place preference, drug discrimination, and self-administration. The ability of a drug to induce locomotor activation has been correlated with its potential to produce positive reinforcement effects and its abuse liability (Robinson and Berridge, 2001). This correlation is thought to occur because the neural substrate that mediates locomotor activation is similar to the neural substrate responsible for the rewarding effects of drugs, namely the mesolimbic dopamine system (Robinson and Berridge, 2001). The conditioned place preference test gauges the conditioned rewarding value of a drug, which relies on the ability of a subject to associate a particular environment with the psychopharmacological effects of the drug (Prus et al., 2009). Drug discrimination is a paradigm in which subjects learn to recognize the effects of a drug from the absence of it or from a different pharmacological effect produced by other drugs (Stolerman, 1993). It relies mainly on operant responding procedures. The self-administration test measures the reinforcement (primarily hedonic) efficacy of a drug, in which animals undergo operant conditioning to obtain a reward (Prus et al., 2009). These behavioral paradigms are not isomorphic measures of drug reward; however, they may provide complementary information on drug-taking behavior. Furthermore, a combination of these tests may yield a better understanding on the abuse liability of a drug beyond the information obtained by each procedure alone.

It has been reported that MXE at several doses induces locomotor alterations in rodents. Several studies showed that low, sub-anesthetic doses (0.5–30 mg/kg) of MXE induce locomotor stimulation (Halberstadt et al., 2016; Horsley et al., 2016; Zanda et al., 2017; Ossato et al., 2018). This effect was observed to diminish within 40–60 min after drug administration. Intriguingly, some studies showed contrasting findings. In a study by Zanda et al. (2017), locomotor activity in rats was increased by intraperitoneal 1 mg/kg MXE, but transiently decreased by 5 mg/kg MXE. Conversely, Halberstadt et al. (2016) showed that subcutaneous 1 mg/kg MXE induces transient hypomotility, whereas 10 mg/kg MXE enhances the locomotor response in rats. Horsley et al. (2016) also showed that subcutaneous 5 and 10 mg/kg MXE increases the motor activity in rats. Furthermore, Ossato et al. (2018) showed an increased locomotor activity in mice intraperitoneally injected with 30 mg/kg MXE. In our previous study, MXE (1.5, 2.5, and 5 mg/kg intraperitoneal) did not induce any significant alteration in the distance moved and movement duration during a conditioned place preference test in rats (Botanas et al., 2015). Berquist et al. (2018) also found that no locomotor response is induced by MXE (0.3, 1, 3, 10, and 30 mg/kg intraperitoneal) in an 8-h test in mice. However, these studies measured only the cumulative locomotor activity; therefore, identification of transient locomotor alterations was difficult. These contrasting findings on the locomotor effects of MXE may be attributable to the varied methodological differences (e.g. route of administration, strain, and parameters) among the studies; hence, additional experiments are required to clarify the effects of MXE on locomotor activity. However, these results are clear indications of the complexity of the dose-response relationship between MXE and locomotor activity.

MXE also elicits conditioned place preference and supports self-administration behavior (Berquist et al., 2018; Botanas et al., 2015; Mutti et al., 2016). These findings suggested the ability of MXE to produce rewarding and reinforcing effects. However, the reinforcing efficacy of MXE was observed to be weaker than those of ketamine and phencyclidine (Berquist et al., 2018; Botanas et al., 2015). That is, ketamine and phencyclidine induce higher maximal infusion levels and lever responses in self-administration conditions than those induced by MXE. A possible reason for the difference in reinforcing efficacy between MXE and ketamine might be related to the onset of action of MXE, which is slower than that of ketamine (Corazza et al., 2013). Previous studies have suggested that the onset of action of a drug may influence its ability as a reinforcer; that is, the reinforcing effects of drugs with a rapid onset of action are stronger than those of drugs with a slower onset of action (Ko et al., 2002; Winger et al., 2002). Thus, the slower onset of action of MXE may cause its limited reinforcing effects, which results in lower response rates than those induced by ketamine. However, the study by Corazza et al. (2013) investigated the oral consumption of MXE by humans; thus the variations in the reinforcing effects MXE and ketamine may be influenced by differences in absorption kinetics. Another plausible explanation is the affinity of MXE to serotonin transporter and its ability to increase extracellular serotonin levels in the brain (Davidson et al., 2014; Fuchigami et al., 2015; Roth et al., 2013). Previous studies have suggested that serotonin inversely affects the reinforcing effects of certain drugs of abuse (Müller and Homberg, 2015). In particular, a recent study showed that serotonin limits the acquisition of reliable self-administration of MDMA (Bradbury et al., 2014). Thus, these factors, among others, may have influenced the reinforcing effects of MXE and may be interesting subjects for future studies.

In addition to inducing place preference and self-administration response, MXE can act as a complete substitute for ketamine in self-administration experiments (Mutti et al., 2016) and in a two-lever operant drug discrimination test trained to distinguish ketamine from saline (Chiamulera et al., 2016; Mutti et al., 2016). These findings suggested that MXE and ketamine share common reinforcing properties. MXE was also shown to substitute for phencyclidine; however, only two out of the five rats observed successfully self-administer MXE, and that MXE induces a reduction in response rate (Berquist et al., 2018). Thus, this result should be interpreted with caution. Repeated administration of MXE, in a dose-dependent manner, alleviates the phencyclidine withdrawal-induced suppression of the response rate to food (Berquist et al., 2018). This suggests that the administration of arylcyclohexylamine analogs or related compounds may improve withdrawal symptoms caused by abrupt cessation of exposure to arylcyclohexylamine.

It has been suggested that the rewarding and reinforcing effects of most abused drugs are attributable to their ability to stimulate dopamine neurotransmission in the brain reward circuit. The brain reward circuit is a collection of dopaminergic neurons projected from the ventral tegmental area to the ventral striatum, including the nucleus accumbens, and the prefrontal cortex. Similar to other abused drugs, MXE activates dopamine neurotransmission in the brain reward region. As mentioned above, MXE increases dopamine levels in an *in vitro* release model (Davidson et al., 2014) and a brain microdialysis study (Fuchigami et al., 2015). Recently, Mutti et al. (2016) showed that MXE, in a dose-dependent manner, activates the mesolimbic dopamine neurotransmission by enhancing the firing rate of dopamine neurons in the ventral tegmental area projecting to the nucleus accumbens. Subsequently, it increases the extracellular dopamine concentration in the nucleus accumbens shell of rats to different extents, depending on the dose and time (Mutti et al., 2016). Based on these data, the ability of MXE to stimulate dopamine neurotransmission in the brain reward circuit may be the cause of its addictive properties.

4. MXE: the friend

4.1. MXE produces antidepressant effects

Depression (major depressive disorder; MDD) is a serious mental disorder that affects approximately 16% of the global population and has become one of the leading causes of economic and disability burden (Whiteford et al., 2013). The currently available pharmacotherapies, such as monoamine-based antidepressants, require an extended period of administration to achieve improvements and have high rates of absent and partial responses (Gaynes et al., 2009; Rush et al., 2006). These limitations underscore the need to develop antidepressant drugs with a rapid onset of action and low rates of absent or partial responses. Previous studies have suggested that the glutamatergic system also plays a role in the pharmacotherapy of depression (Hashimoto, 2009; Sanacora et al., 2008). Ketamine, an NMDA receptor antagonist, has shown rapid-acting and long-lasting antidepressant effects in preclinical (Li et al., 2010; Zanos et al., 2016) and clinical studies (Murrough et al., 2013; Zarate et al., 2006). This newfound clinical efficacy of ketamine has enabled the development of a new generation of glutamate-based antidepressants.

MXE has been hypothesized to possess antidepressant properties because of its pharmacodynamics similarities to ketamine (Coppola and Mondola, 2012). Indeed, recent studies have shown that MXE, at subanesthetic doses, induces antidepressant effects in rats (Zanda et al., 2017) and mice (Botanas et al., 2017). In particular, our previous study showed that MXE induces rapid (30 min after administration) and sustained (for 24 h after administration) antidepressant effects in various behavioral experiments (i.e. forced swimming test, tail suspension test, sucrose preference test, and novelty-suppressed feeding test) (Botanas et al., 2017). MXE also produces anxiolytic effects, as evidenced by an increase in time spent in the open arms of the elevated plus maze test (Botanas et al., 2017). In contrast, Zanda et al. (2017) reported that MXE induces anxiogenic effects in rats. These discrepancies may be ascribed to methodological differences (e.g. species differences between Sprague-Dawley rats and ICR mice) between the two studies; thus, further studies are required to clarify these findings. Nevertheless, antidepressant and anxiolytic properties of MXE would be beneficial considering that depression is often comorbid with anxiety, and that antidepressants and anxiolytics are frequently used in combination to treat depression (Furukawa et al., 2001; Kessler et al., 2003; Sartorius et al., 1996). Interestingly, MXE is reportedly used in self-medication to treat post-traumatic stress disorder symptoms owing to its calming effects (Striebel et al., 2017). Although there have been contrasting findings on the effects of MXE in locomotor activity, as mentioned above, our previous study showed that MXE does not increase locomotor activity in mice, suggesting that the antidepressant effects of MXE are not due to the alterations in locomotor activity (Botanas et al., 2017). Collectively, these findings provide an evidence that MXE exerts antidepressant activities and may be a potential treatment for depression.

Previous studies have suggested that the antidepressant effects of ketamine are facilitated by the activation of AMPA receptors that results in increased brain-derived neurotrophic factor (BDNF) release and stimulation of the mammalian target of rapamycin (mTOR) signaling in the brain (Jourdi et al., 2009; Koike et al., 2011; Zhou et al., 2014). The protein BDNF acts on certain neurons in the nervous system, supporting the survival of existing neurons, and promoting the growth and differentiation of new neurons and synapses (Acheson et al., 1995). mTOR is a serine/threonine protein kinase that regulates the initiation of protein translation and is abundantly expressed during the dendritic development that controls protein synthesis (Duman et al., 2012). Substantial evidence has shown that decreases in BDNF expression and mTOR signaling in the brain are involved in the pathophysiology of depression (Bocchio-Chiavetto et al., 2010; Duman et al., 2016; Jernigan et al., 2011). Given the pharmacodynamic similarities between MXE and ketamine, it is likely that the antidepressant effects of MXE would also involve similar mechanisms to those of ketamine.

Our previous study (Botanas et al., 2017) have shown that the AMPA receptor antagonist NBQX blocks the antidepressant action of MXE in a forced swimming test in mice. MXE also increases the hippocampal mRNA expression of the AMPA receptor subunits GluA1, GluA2, BDNF, and mTOR. Similar results were also observed for ketamine. These findings suggest that the antidepressant action of MXE is facilitated by the activation of AMPA receptors and increased BDNF and mTOR mRNA expression in the hippocampus.

As mentioned above, MXE has affinity to serotonin transporter, acts as a serotonin reuptake inhibitor, and increases extracellular serotonin concentration in the brain (Fuchigami et al., 2015; Hondebrink et al., 2017; Roth et al., 2013), indicating its influence in the serotonergic system. We (Botanas et al., 2017) have shown in a forced swimming test that the antidepressant effects of MXE are inhibited by ketanserin, a selective 5-HTR2a antagonist. Furthermore, MXE increases the mRNA expression of the serotonin receptors (5-HTR) 1a, 5-HTR2a, and 5-HTR2c, as well as that of serotonin transporters in the hippocampus. In contrast, the effects of ketamine were not blocked by ketanserin and nor did ketamine alter hippocampal serotonergic-related mRNA expression. These findings were consistent with those of previous studies, in which the antidepressant effects of ketamine were shown to be independent of the serotonergic system (Gigliucci et al., 2013). Furthermore, low doses of ketamine were not reported to affect the serotonin activity of the brain (El Iskandrani et al., 2015). Nevertheless, in addition to its glutamatergic system, the antidepressant effects of MXE were also mediated by the serotonergic system. At present, preclinical and clinical data are insufficient to support the idea that MXE could be used as an antidepressant drug; thus, further research is necessary to explore and elucidate the antidepressant effects of MXE and its mechanistic correlation.

4.2. MXE induces analgesic effects

Similar to ketamine, MXE is suggested to have analgesic or antinociceptive properties with enhanced potency and duration of action because of the chemical modifications mentioned above. A study reported that MXE is used in self-medication to alleviate chronic foot pain after a surgery (Maskell et al., 2016). Although the user, who reportedly ingested 5–10 mg of MXE every 4 h for 5 days at a previous week, was brought in to the emergency department owing to intoxication, the analgesic efficacy of MXE was indicated.

Recently, Zanda et al. (2017) investigated the antinociceptive effects of MXE using the tail-flick and hot plate tests in rats, and showed that MXE 5 mg/kg exhibits analgesic effects. In contrast, ketamine induces antinociceptive effects only when administered at high dosages (50–160 and 25 mg/kg in the tail flick test and hot plate test, respectively) (Baumeister and Advokat, 1991; Shikanai et al., 2014), and not at subanesthetic doses (Getova and Doncheva, 2011; Huang et al., 2005). More recently, Ossato et al. (2018) also showed that MXE increases mechanical (tail-pinch test) or thermal (tail withdrawal test) nociceptive threshold in mice more effectively than ketamine. This suggests that action of MXE is more potent than that of ketamine, which could be attributed to the substitution of the N-ethylamino group and/or of the 3-methoxy group that increases the affinity of MXE to the μ-opioid receptors. However, MXE was found to have no affinity to the opioid σ_1 and σ_2 receptors (Roth et al., 2013); hence, other mechanisms (i.e. different brain sites or neurotransmitter systems) might be involved in the antinociceptive effects of MXE. Nevertheless, the ability of MXE to induce antinociceptive effects suggests potential use of MXE as a potent analgesic drug. Additional studies are needed to characterize the analgesic effects of MXE and explore its mechanism of action.

5. Conclusion

MXE is a new synthetic drug with a wide range of effects, some of which are similar to those of ketamine and phencyclidine. It is a potent NMDA receptor antagonist that has been reported to be misused by humans owing to its hallucinogenic and dissociative effects. Preclinical studies have shown that MXE has an abuse liability, as evidenced by its ability to induce rewarding and reinforcing effects in various animal models of drug addiction, and to stimulate dopamine neurotransmission in the brain reward circuit. In contrast, MXE also produces rapid and sustained antidepressant effects that are most likely mediated by the glutamatergic and serotonergic systems. This antidepressant effect of MXE may be beneficial owing to the limited effectiveness (i.e. delayed onset of therapeutic effects and high non-response rate) of the current generation of antidepressants (monoaminergic antidepressants). Given the recent increase in interest in antidepressants targeting the glutamatergic system, MXE deserves to be explored as a potential treatment for depression. Additionally, MXE induces analgesic effects that are more potent than those induced by ketamine. However, it should be noted that potential use of MXE as a therapeutic drug poses a number of challenges owing to its adverse side effects and abuse liability. Nonetheless, classifying MXE as a foe or friend requires a further research to fully understand its psychopharmacological properties and the mechanisms responsible for its unique effects.

6. Conflicts of interest

None.

Acknowledgement

This study was supported by the Bio and Medical Technology Development Program of the National Research Foundation and the Korean government (MSIT) (NRF-2017M3A9G2077568), the National Research Foundation of Korea (2017R1D1A1A02018695), and the Ministry of Food and Drug Safety of Korea (14182MFDS979).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.neuint.2018.10.020.

References

Acheson, A., Conover, J.C., Fandl, J.P., DeChiara, T.M., Russell, M., Thadani, A., Squinto, S.P., Yancopoulos, G.D., Lindsay, R.M., 1995. A BDNF autocrine loop in adult sensory neurons prevents cell death. Nature 374, 450–453.

Advisory Council on the Misuse of Drugs (ACMD), 2012. Methoxetamine report. Available at: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/119087/methexetamine2012.pdf, Accessed date: 5 March 2018.

Adamowicz, P., Zuba, D., 2015. Fatal intoxication with methoxetamine. J. Forensic Sci. 60, S264–S268.

Archer, J., Dargan, P., Hudson, S., Wood, D., 2012. Analysis of anonymous pooled urine from portable urinals in central London confirms the significant use of novel psychoactive substances. QJM: Int. J. Med. 106, 147–152.

Bakshi, V.P., Geyer, M.A., 1997. Phencyclidine-induced deficits in prepulse inhibition of startle are blocked by prazosin, an alpha-1 noradrenergic antagonist. J. Pharmacol. Exp. Therapeut. 283, 666–674.

Baumeister, A., Advokat, C., 1991. Evidence for a supraspinal mechanism in the opioid-mediated antinociceptive effect of ketamine. Brain Res. 566, 351–353.

Berman, R.M., Cappiello, A., Anand, A., Oren, D.A., Heninger, G.R., Charney, D.S., Krystal, J.H., 2000. Antidepressant effects of ketamine in depressed patients. Biol. Psychiatry 47, 351–354.

Berquist, M.D., Hyatt, W.S., Bauer-Erickson, J., Gannon, B.M., Norwood, A.P., Fantegrossi, W.E., 2018. Phencyclidine-like in vivo effects of methoxetamine in mice and rats. Neuropharmacology 134, 158–166.

Bocchio-Chiavetto, L., Bagnardi, V., Zanardini, R., Molteni, R., Gabriela Nielsen, M., Placentino, A., Giovannini, C., Rillosi, L., Ventriglia, M., Riva, M.A., 2010. Serum and plasma BDNF levels in major depression: a replication study and meta-analyses. World J. Biol. Psychiatr. 11, 763–773.

Botanas, C.J., de la Peña, J.B., Custodio, R.J., dela Peña, I.J., Kim, M., Woo, T., Kim, H.J., Kim, H.I., Cho, M.C., Lee, Y.S., 2017. Methoxetamine produces rapid and sustained antidepressant effects probably via glutamatergic and serotonergic mechanisms. Neuropharmacology 126, 121–127.

Botanas, C.J., de la Peña, J.B., Dela Pena, I.J., Tampus, R., Yoon, R., Kim, H.J., Lee, Y.S., Jang, C.G., Cheong, J.H., 2015. Methoxetamine, a ketamine derivative, produced conditioned place preference and was self-administered by rats: evidence of its abuse potential. Pharmacol. Biochem. Behav. 133, 31–36.

Bradbury, S., Bird, J., Colussi-Mas, J., Mueller, M., Ricaurte, G., Schenk, S., 2014. Acquisition of MDMA self-administration: pharmacokinetic factors and MDMA-induced serotonin release. Addict. Biol. 19, 874–884.

Chiamulera, C., Armani, F., Mutti, A., Fattore, L., 2016. The ketamine analogue methoxetamine generalizes to ketamine discriminative stimulus in rats. Behav. Pharmacol. 27, 204–210.

Cilia, J., Hatcher, P., Reavill, C., Jones, D.N., 2007. (±) Ketamine-induced prepulse inhibition deficits of an acoustic startle response in rats are not reversed by antipsychotics. J. Psychopharmacol. 21, 302–311.

Coppola, M., Mondola, R., 2012. Methoxetamine: from drug of abuse to rapid-acting antidepressant. Med. Hypotheses 79, 504–507.

Corazza, O., Assi, S., Schifano, F., 2013. From "Special K" to "Special M": the evolution of the recreational use of ketamine and methoxetamine. CNS Neurosci. Ther. 19, 454–460.

Corazza, O., Schifano, F., Simonato, P., Fergus, S., Assi, S., Stair, J., Corkery, J., Trincas, G., Deluca, P., Davey, Z., 2012. Phenomenon of new drugs on the Internet: the case of ketamine derivative methoxetamine. Hum. Psychopharmacol. Clin. Exp. 27, 145–149.

Craig, C.L., Loeffler, G.H., 2014. The ketamine analog methoxetamine: a new designer drug to threaten military readiness. Mil. Med. 179, 1149–1157.

Dargan, P., Tang, H., Liang, W., Wood, D., Yew, D., 2014. Three months of methoxetamine administration is associated with significant bladder and renal toxicity in mice. Clin. Toxicol. 52, 176–180.

Davidson, C., Hashemi, G., Gant, A., Fergus, S., Benha, C., Lione, L., 2014. Effects of methoxetamine in rat bladder and nucleus accumbens brain tissue. Res Adv Psychiatry 1, 39.

Duman, R.S., Aghajanian, G.K., Sanacora, G., Krystal, J.H., 2016. Synaptic plasticity and depression: new insights from stress and rapid-acting antidepressants. Nat. Med. 22, 238.

Duman, R.S., Li, N., Liu, R.-J., Duric, V., Aghajanian, G., 2012. Signaling pathways underlying the rapid antidepressant actions of ketamine. Neuropharmacology 62, 35–41.

El Iskandrani, K.S., Oosterhof, C.A., El Mansari, M., Blier, P., 2015. Impact of subanesthetic doses of ketamine on AMPA-mediated responses in rats: an in vivo electrophysiological study on monoaminergic and glutamatergic neurons. J. Psychopharmacol. 29, 792–801.

Elian, A.A., Hackett, J., 2014. A polydrug intoxication involving methoxetamine in a drugs and driving case. J. Forensic Sci. 59, 854–858.

Erowid, 2011. Available at: https://www.erowid.org/. [Accessed 5 March 2018].

European Monitoring for Drugs and Drug Addiction (EMCDDA), 2013. Methoxetamine. EMCDDA – Europol Joint Report on a new psychoactive substance: methoxetamine (2-(3- methoxyphenyl)-2-(ethylamino) cyclohexanone). http://www.emcdda.europa.eu/attachements.cfm/att_222602_EN_TDAS14004ENN-1.pdf, Accessed date: 5 March 2018.

Fassette, T., Martinez, A., 2016. An impaired driver found to be under the influence of methoxetamine. J. Anal. Toxicol. 40, 700–702.

Fuchigami, Y., Fu, X., Ikeda, R., Kawakami, S., Wada, M., Kikura-Hanajiri, R., Kuroda, N., Nakashima, K., 2015. Evaluation of the neurochemical effects of methoxetamine using brain microdialysis in mice. Forensic Toxicol. 33, 374–379.

Furukawa, T.A., Streiner, D., Young, L.T., Kinoshita, Y., 2001. Antidepressant plus benzodiazepine for major depression. Cochrane Database Syst. Rev. 2.

Gaynes, B.N., Warden, D., Trivedi, M.H., Wisniewski, S.R., Fava, M., Rush, A.J., 2009. What did STAR* D teach us? Results from a large-scale, practical, clinical trial for patients with depression. Psychiatr. Serv. 60, 1439–1445.

Geyer, M.A., Krebs-Thomson, K., Braff, D.L., Swerdlow, N.R., 2001. Pharmacological studies of prepulse inhibition models of sensorimotor gating deficits in schizophrenia: a decade in review. Psychopharmacology 156, 117–154.

Getova, D., Doncheva, N., 2011. Effects of ketamine on memory and nociception in rats. Folia Med. 53, 53–59.

Gigliucci, V., O'Dowd, G., Casey, S., Egan, D., Gibney, S., Harkin, A., 2013. Ketamine elicits sustained antidepressant-like activity via a serotonin-dependent mechanism. Psychopharmacology 228, 157–166.

Halberstadt, A.L., Slepak, N., Hyun, J., Buell, M.R., Powell, S.B., 2016. The novel ketamine analog methoxetamine produces dissociative-like behavioral effects in rodents. Psychopharmacology 233, 1215–1225.

Hashimoto, K., 2009. Emerging role of glutamate in the pathophysiology of major depressive disorder. Brain Res. Rev. 61, 105–123.

Hofer, K.E., Grager, B., Müller, D.M., Rauber-Lüthy, C., Kupferschmidt, H., Rentsch, K.M., Ceschi, A., 2012. Ketamine-like effects after recreational use of methoxetamine. Ann. Emerg. Med. 60, 97–99.

Hondebrink, L., Kasteel, E.E., Tukker, A.M., Wijnolts, F.M., Verboven, A.H., Westerink, R.H., 2017. Neuropharmacological characterization of the new psychoactive substance methoxetamine. Neuropharmacology 123, 1–9.

Horsley, R.R., Lhotkova, E., Hajkova, K., Jurasek, B., Kuchar, M., Palenicek, T., 2016. Detailed pharmacological evaluation of methoxetamine (MXE), a novel psychoactive ketamine analogue—behavioural, pharmacokinetic and metabolic studies in the Wistar rat. Brain Res. Bull. 126, 102–110.

Huang, C., Long, H., Shi, Y.-S., Han, J.-S., Wan, Y., 2005. Ketamine enhances the efficacy to and delays the development of tolerance to electroacupuncture-induced

antinociception in rats. Neurosci. Lett. 375, 138–142.
Jernigan, C.S., Goswami, D.B., Austin, M.C., Iyo, A.H., Chandran, A., Stockmeier, C.A., Karolewicz, B., 2011. The mTOR signaling pathway in the prefrontal cortex is compromised in major depressive disorder. Prog. Neuro Psychopharmacol. Biol. Psychiatr. 35, 1774–1779.
Jourdi, H., Hsu, Y.-T., Zhou, M., Qin, Q., Bi, X., Baudry, M., 2009. Positive AMPA receptor modulation rapidly stimulates BDNF release and increases dendritic mRNA translation. J. Neurosci. 29, 8688–8697.
Kessler, R.C., Berglund, P., Demler, O., Jin, R., Koretz, D., Merikangas, K.R., Rush, A.J., Walters, E.E., Wang, P.S., 2003. The epidemiology of major depressive disorder: results from the National Comorbidity Survey Replication (NCS-R). Jama 289, 3095–3105.
Kjellgren, A., Jonsson, K., 2013. Methoxetamine (MXE)–a phenomenological study of experiences induced by a "legal high" from the Internet. J. Psychoact. Drugs 45, 276–286.
Ko, M., Terner, J., Hursh, S., Woods, J., Winger, G., 2002. Relative reinforcing effects of three opioids with different durations of action. J. Pharmacol. Exp. Therapeut. 301, 698–704.
Koike, H., Iijima, M., Chaki, S., 2011. Involvement of AMPA receptor in both the rapid and sustained antidepressant-like effects of ketamine in animal models of depression. Behav. Brain Res. 224, 107–111.
Lawn, W., Borschmann, R., Cottrell, A., Winstock, A., 2016. Methoxetamine: prevalence of use in the USA and UK and associated urinary problems. J. Subst. Use 21, 115–120.
Li, N., Lee, B., Liu, R.-J., Banasr, M., Dwyer, J.M., Iwata, M., Li, X.-Y., Aghajanian, G., Duman, R.S., 2010. mTOR-dependent synapse formation underlies the rapid antidepressant effects of NMDA antagonists. Science 329, 959–964.
Maskell, K.F., Bailey, M.L., Rose, S.R., 2016. Self medication with methoxetamine as an analgesic resulting in significant toxicity. Pain Med. 17, 1773–1775.
Mena, A., Ruiz-Salas, J.C., Puentes, A., Dorado, I., Ruiz-Veguilla, M., De la Casa, L.G., 2016. Reduced prepulse inhibition as a biomarker of schizophrenia. Front. Behav. Neurosci. 10, 202.
Menzies, E., Hudson, S., Dargan, P., Parkin, M., Wood, D., Kicman, A., 2014. Characterizing metabolites and potential metabolic pathways for the novel psychoactive substance methoxetamine. Drug Test. Anal. 6, 506–515.
Meyer, M.R., Bach, M., Welter, J., Bovens, M., Turcant, A., Maurer, H.H., 2013. Ketamine-derived designer drug methoxetamine: metabolism including isoenzyme kinetics and toxicological detectability using GC-MS and LC-(HR-) MSn. Anal. Bioanal. Chem. 405, 6307–6321.
Morris, H., 2011. Interview with a ketamine chemist, or to be more precise, an arylcyclohexylamine chemist. Vice Magazine 18.
Morris, H., Wallach, J., 2014. From PCP to MXE: a comprehensive review of the non--medical use of dissociative drugs. Drug Test. Anal. 6, 614–632.
Müller, C.P., Homberg, J.R., 2015. The role of serotonin in drug use and addiction. Behav. Brain Res. 277, 146–192.
Murrough, J.W., Iosifescu, D.V., Chang, L.C., Al Jurdi, R.K., Green, C.E., Perez, A.M., Iqbal, S., Pillemer, S., Foulkes, A., Shah, A., 2013. Antidepressant efficacy of ketamine in treatment-resistant major depression: a two-site randomized controlled trial. Am. J. Psychiatry 170, 1134–1142.
Mutti, A., Aroni, S., Fadda, P., Padovani, L., Mancini, L., Collu, R., Muntoni, A.L., Fattore, L., Chiamulera, C., 2016. The ketamine-like compound methoxetamine substitutes for ketamine in the self-administration paradigm and enhances mesolimbic dopaminergic transmission. Psychopharmacology 233, 2241–2251.
Ossato, A., Bilel, S., Gregori, A., Talarico, A., Trapella, C., Gaudio, R.M., De-Giorgio, F., Tagliaro, F., Margherita, N., Fattore, L., Marti, M., 2018. Neurological, sensorimotor and cardiorespiratory alterations induced by methoxetamine, ketamine and phencyclidine in mice. Neuropharmacology 141, 167–180.
Prus, A., James, J.R., Rosecrans, J.A., 2009. Conditioned place preference. In: Methods of Behavioral Analysis in Neuroscience. J. Buccafusco. Boca Raton (FL). CRC Press.
Robinson, T.E., Berridge, K.C., 2001. Incentive-sensitization and addiction. Addiction 96, 103–114.
Rosenbaum, C.D., Carreiro, S.P., Babu, K.M., 2012. Here today, gone tomorrow and back again? A review of herbal marijuana alternatives (K2, Spice), synthetic cathinones (bath salts), kratom, Salvia divinorum, methoxetamine, and piperazines. J. Med. Toxicol. 8, 15–32.
Roth, B.L., Gibbons, S., Arunotayanun, W., Huang, X.-P., Setola, V., Treble, R., Iversen, L., 2013. The ketamine analogue methoxetamine and 3-and 4-methoxy analogues of phencyclidine are high affinity and selective ligands for the glutamate NMDA receptor. PloS One 8 e59334.
Rush, A.J., Trivedi, M.H., Wisniewski, S.R., Nierenberg, A.A., Stewart, J.W., Warden, D., Niederehe, G., Thase, M.E., Lavori, P.W., Lebowitz, B.D., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR* D report. Am. J. Psychiatry 163, 1905–1917.
Sanacora, G., Zarate, C.A., Krystal, J.H., Manji, H.K., 2008. Targeting the glutamatergic system to develop novel, improved therapeutics for mood disorders. Nat. Rev. Drug Discov. 7, 426.
Sartorius, N., Üstün, T.B., Lecrubier, Y., Wittchen, H.-u., 1996. Depression comorbid with anxiety: results from the WHO study on" Psychological disorders in primary health care. Br. J. Psychiatr. S30, 38–43.
Shikanai, H., Hiraide, S., Kamiyama, H., Kiya, T., Oda, K., Goto, Y., Yanagawa, Y., Shimamura, K.-i., Goda, Y., Togashi, H., 2014. Subanalgesic ketamine enhances morphine-induced antinociceptive activity without cortical dysfunction in rats. J. Anesth. 28, 390–398.
Stolerman, I., 1993. Drug Discrimination, Techniques in the Behavioral and Neural Sciences, vol. 10. Elsevier, pp. 217–243.
Striebel, J.M., Nelson, E.E., Kalapatapu, R.K., 2017. "Being with a Buddha": a Case Report of Methoxetamine Use in a United States Veteran with PTSD. Case Reports in Psychiatry 2017.
Valsamis, B., Schmid, S., 2011. Habituation and prepulse inhibition of acoustic startle in rodents. JoVE: JoVE 55 (55), e3446.
Wang, Q., Wu, Q., Wang, J., Chen, Y., Zhang, G., Chen, J., Zhao, J., Wu, P., 2017. Ketamine analog methoxetamine induced inflammation and dysfunction of bladder in rats. Int. J. Mol. Sci. 18, 117.
Whiteford, H.A., Degenhardt, L., Rehm, J., Baxter, A.J., Ferrari, A.J., Erskine, H.E., Charlson, F.J., Norman, R.E., Flaxman, A.D., Johns, N., 2013. Global burden of disease attributable to mental and substance use disorders: findings from the Global Burden of Disease Study 2010. Lancet 382, 1575–1586.
Winger, G., Hursh, S., Casey, K., Woods, J., 2002. Relative reinforcing strength of ThreeN-methyl-d-aspartate antagonists with different onsets of action. J. Pharmacol. Exp. Therapeut. 301, 690–697.
Winstock, A.R., Lawn, W., Deluca, P., Borschmann, R., 2016. Methoxetamine: an early report on the motivations for use, effect profile and prevalence of use in a UK clubbing sample. Drug Alcohol Rev. 35, 212–217.
Wood, D., Hunter, L., Measham, F., Dargan, P., 2012. Limited use of novel psychoactive substances in South London nightclubs. QJM: Int. J. Med. 105, 959–964.
World Health Organization (WHO), 2015. Methoxetamine (MXE) Critical Review Report 37th ECDD Agenda Item 5.9. Available at: http://www.who.int/medicines/access/controlled-sub stances/5.9_Methoxetamine_CRev.pdf, Accessed date: 5 March 2018.
Zanda, M., Fadda, P., Antinori, S., Di Chio, M., Fratta, W., Chiamulera, C., Fattore, L., 2017. Methoxetamine affects brain processing involved in emotional response in rats. Br. J. Pharmacol. 174, 3333–3345.
Zanda, M.T., Fadda, P., Chiamulera, C., Fratta, W., Fattore, L., 2016. Methoxetamine, a novel psychoactive substance with serious adverse pharmacological effects: a review of case reports and preclinical findings. Behav. Pharmacol. 27, 489–496.
Zanos, P., Moaddel, R., Morris, P.J., Georgiou, P., Fischell, J., Elmer, G.I., Alkondon, M., Yuan, P., Pribut, H.J., Singh, N.S., 2016. NMDAR inhibition-independent antidepressant actions of ketamine metabolites. Nature 533, 481.
Zarate, C.A., Singh, J.B., Carlson, P.J., Brutsche, N.E., Ameli, R., Luckenbaugh, D.A., Charney, D.S., Manji, H.K., 2006. A randomized trial of an N-methyl-D-aspartate antagonist in treatment-resistant major depression. Arch. Gen. Psychiatr. 63, 856–864.
Zawilska, J.B., 2014. Methoxetamine–a novel recreational drug with potent hallucinogenic properties. Toxicol. Lett. 230, 402–407.
Zhou, W., Wang, N., Yang, C., Li, X.-M., Zhou, Z.-Q., Yang, J.-J., 2014. Ketamine-induced antidepressant effects are associated with AMPA receptors-mediated upregulation of mTOR and BDNF in rat hippocampus and prefrontal cortex. Eur. Psychiatr. 29, 419–423.