The novel psychoactive substance methoxetamine (MXE) affects the brain reward pathway and emotional processing in the rat

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Methoxetamine (MXE) is a new synthetic drug, an arylcyclohexylamine derivative with 3-methoxy and N-ethylamino groups with ketamine (KET)-like properties but with a much longer duration of action and intensity of effects. MXE is perceived as safe by users despite its severe adverse consequences and toxicity, and its use is increasing worldwide. Yet, although almost nothing is known about the pharmacological profile of this new substance, the effects of acute and chronic exposure to MXE being still to be investigated. Here we provide the first evaluation of its effects on behavior, mood, and reward.

In this study we first tested the effect of an acute intraperitoneal (i.p.) administration of MXE (1, 2.5 or 5 mg/kg) on motor activity, attention function, analgesia and emotional states in male Sprague-Dawley (SD) rats. Data showed that MXE transiently but significantly affected motor activity in a dose- and time-related manner, with low and high doses inducing hyper- and hypomotility, respectively, during the first 20 minutes after administration. As compared to controls, MXE dose-dependently also decreased the startle amplitude of rats in the pre-pulse inhibition (PPI) test, which provides an operational measure of sensorimotor gating reflecting the ability of an animal to successfully integrate and inhibit sensory information. As concerns analgesia, the highest dose tested (MXE 5 mg/kg) induced a transient thermal threshold analgesia after 30-45 minutes from administration, as revealed by tail flick and hot plate tests. This high dose of MXE induced anxiety-like state too, as suggested by the higher amount of time spent by MXE 5 mg/kg-treated rats in the closed arms of the elevated plus maze (EPM) with respect to VEH-treated animals. We then tested MXE in the marble burying test (MBT), an animal model frequently used for assessing either anxiety-like and/or repetitive-like behaviors in rodents as well as neophobia and/or obsessive-compulsive behavior. We found that rats treated with MXE 0.5 and 1 mg/kg buried a significantly higher number of marbles than controls, suggesting an anxious and/or obsessive-compulsive trait. Moreover, in the forced swim test (FST) model of depression, MXE 5 mg/kg reduced immobility and climbing while significantly increasing swimming activity, which suggests an antidepressant effect. Altogether, these results indicate that acute MXE administration differentially alters spontaneous motor activity, induces analgesia and spatial anxiety (EPM) and increases swimming time (FST) at high doses, while inducing repetitive/perseverative (obsessive-compulsive) behaviors (MBT) at low doses.

In parallel, different groups of animals were tested for abuse- and reward-related effects of MXE. When tested in a self-administration (SA) substitution protocol, the intravenous (i.v.) dose of MXE 0.25 mg/kg fully substituted for KET 0.5 mg/kg (i.v.), with significant differences from saline but not from KET. Conversely, MXE 0.125 mg/kg (i.v.) showed a partial substitution only, while MXE 0.5 mg/kg (i.v.) did not substitute for KET. In addition, MXE (0.5 and 0.25 mg/kg, i.v.) induced a significant and time-dependent enhancement of dopamine extracellular levels with respect to basal values in the nucleus accumbens shell. Consistently, MXE (0.031-0.5 mg/kg, i.v. cumulative doses) stimulated the activity of dopamine neurons in the ventral tegmental area. These last results indicate that at appropriate doses MXE is able to substitute for KET in the SA paradigm suggesting that it possesses rewarding effects, a notion supported by both neurochemical and electrophysiological data.

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