THE MULTIPLE EFFECTS OF THE KETAMINE ANALOG METHOXETAMINE: PRECLINICAL EVIDENCE

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Among the novel psychoactive substances currently available on the drug market and sold as "legal highs" or "research chemicals", the ketamine analog methoxetamine (MXE) is emerging at an unprecedented rate on the Internet. MXE-induced dissociative effects and acute toxicity have been reported, but its toxicology and pharmacology is still poorly investigated. Preclinical studies focused on its behavioral and toxicological effects start explaining MXE effects and frequent occurrence of adverse effects after its use (Zanda et al., 2016). We recently showed that MXE fully substitutes for ketamine interoceptive stimulus in a two-lever operant drug discrimination paradigm in rats trained to discriminate ketamine from saline, in a manner very similar to the NMDA channel blocker MK-801, thus showing to possess discriminative stimulus similar to ketamine (Chiamulera et al., 2016). Moreover, MXE substituted for ketamine in a drug substitution study (Mutti et al., 2016), showing to share common reinforcing properties with ketamine, i.e. the self-administration training drug, and hence to possess relative reinforcing properties by its own. We also examined a range of behavioral effects induced by acute intraperitoneal (i.p.) administration of MXE (0.5-5 mg/kg) in rats, and whether the observed behavioral responses correlated to rapid neuroadaptive molecular changes such as protein translation. Data showed that MXE (0.5-5 mg/kg) significantly affected spontaneous motor activity in a dose- and time-dependent manner, inducing hypermotility and hypomotility at low and high doses, respectively. At low-intermediate doses (0.5 and 1 mg/kg) MXE induced anxious and/or obsessive-compulsive traits (marble burying test), slightly (but not significantly) increased sociability (social interaction test) but did not induce spatial anxiety (elevated plus maze test). At the highest dose tested (5 mg/kg), MXE induced transient analgesia (tail flick and hot plate test), significantly decreased social interaction time (social interaction test) and significantly reduced immobility time while increasing swimming activity (forced swim test), suggesting an antidepressant effect. Immunohistochemistry study showed that the behaviorally active doses of MXE 1 and 5 mg/kg increased the expression of phosphorylated ribosomal protein S6 (rpS6P) in medial prefrontal cortex and hippocampus. Altogether, results indicate that depending on the dose tested MXE may differentially affect spontaneous motor activity, behavior and emotional states in rats (Zanda et al., under revision). As recently reported for ketamine, the expression of rpS6P protein was increased in MXE-treated animals thus providing a potential correlate of rapid neuroadaptive changes induced by MXE. In light of the growing number of MXE-induced intoxications, knowledge of its short- and long term effects is urgently needed. On the other hand, MXE hypothetical rapid antidepressant activity suggested by its chemical analogy with ketamine and supported by recent preclinical findings deserves further investigation.

Chiamulera et al. (2016). Behav Pharmacol 27(2-3), 204-210.

Mutti A et al. (2016). Psychopharmacology 233, 2241-2251.

Zanda et al. (2016). Behav Pharmacol 27(6), 489-496.

Zanda et al. Under revision.