New insights into methoxetamine mechanisms of action: focus on serotonergic 5HT-2 receptors in pharmacological and behavioral effects in the rat

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References:
Max 5 relevant references from the Authors in the following format:


Background (50 words): Methoxetamine (MXE) is a dissociative substance that we previously showed to possess ketamine-like discriminative and rewarding effects, affect brain processing involved in cognition and emotional responses and induce long-lasting behavioral abnormalities and neurotoxicity in rats. We then performed a multidisciplinary study to evaluate the potential mechanisms underlying its central effects.

Methods and Results (100 words): We first showed that MXE (0.25-0.5mg/kg) alters serotonin levels in the rat medial prefrontal cortex (mPFC) and nucleus accumbens. Then, we found that the serotonin 5-HT2 receptor antagonists ketanserin (0.1mg/kg) and MDL100907 (0.03mg/kg) attenuated MXE-induced hypermotility and visual sensory deficit and prevented the MXE-induced decrease of the prepulse inhibition. Finally, in-vitro electrophysiological studies revealed that MXE inhibits NMDA-mediated field postsynaptic potentials and GABA-mediated spontaneous current frequency in a dose-dependent manner. Conversely, MXE failed to alter both the AMPA component of field potentials and presynaptic glutamate release probability, and seems not to interfere with the endocannabinoid-mediated effects on mPFC GABAergic synapses.

Conclusions and Significance (50 words): Our results confirm that MXE is a NMDA receptor antagonist and shed new lights into its central mechanisms of action by pointing to 5-HT2 receptors as crucial players in the expression of MXE sensorimotor-altering effects, and to the NMDA and GABA receptors as potential further important targets of action.


**Thematic area:**
To be selected from the following areas of diseases and disorders:
- Psychiatric