Esmethadone (REL-1017) Shows Similar Effects to Ketamine in Manual Patch Clamp Studies

Ezio Bettini[1], Corrado Carignani[1], Sara De Martin[2], Charles E. Inturrisi[3], Andrea Mattarei[2], **Marco Pappagallo**[3,4], Stephen M. Stahl[5,6], Sergio Traversa[3], Paolo L. Manfredi[3]

[1]In Vitro Pharmacology Department, Aptuit, an Evotec Company, Verona, Italy, [2]Department of Pharmaceutical and Pharmacological Sciences, University of Padova, Padova, Italy, [3]Relmada Therapeutics, New York, NY, USA, [4]Department of Anesthesiology, Albert Einstein College of Medicine, Bronx, NY, USA, [5]University of California, San Diego, CA, USA, [6]Neuroscience Education Institute, San Diego, CA, USA

Background: Esmethadone (dextromethadone; REL-1017) is a novel NMDA receptor (NMDAR) antagonist that exerts robust and rapid antidepressant-like effects similar to ketamine. To characterize both drugs, we evaluated the onset and offset kinetic and trapping levels of REL-1017 and ketamine on NMDARs containing the GluN2C subunit.
Methods: Manual patch clamp recordings occurred at -70 mV. CHO cells expressing NMDARs with the GluN2C subunit were exposed for 30 seconds to L-glutamate and glycine (Glu/Gly) plus 10 µM REL-1017 or 1 µM ketamine, followed by a 50-second reexposure to Glu/Gly. Tau-on and tau-off were estimated by curve fitting to first order exponential equations. For trapping experiments, CHO cells were exposed for 5 seconds to Glu/Gly, followed by a 30-second reexposure to Glu/Gly plus REL-1017 or ketamine, then an 85-second application of glycine, and finally a 50-second reexposure to Glu/Gly.
Results: 10 µM REL-1017 and 1 µM ketamine comparably blocked the NMDAR, while 10 µM ketamine resulted in a significantly higher blockade. Tau-on results were similar for 10 µM REL-1017 and 1 µM ketamine and significantly faster for 10 µM ketamine. 10 µM REL-1017 and 1 µM ketamine had similar trapping effects on NMDARs, and both concentrations of REL-1017 and ketamine had similar offset kinetics.
Conclusions: REL-1017 is less potent and has a slower onset kinetic compared to ketamine. These subtle differences distinguish REL-1017 from ketamine and may partially explain the lack of dissociative side effects seen with REL-1017 in clinical studies.

Keywords: NMDA channel blocker, major depressive disorder (MDD), ketamine, dextromethadone, esmethadone