Esmethadone (REL-1017) Reduces Glutamate-Induced Currents in NMDA Receptors with the GluN2D Subunit

**INTRODUCTION**

- Esmethadone (REL-1017; dextromethadone; DXT) is a novel NMDA receptor (NMDAR) antagonist currently in Phase 3 trials for the treatment of major depressive disorder (MDD).

**OBJECTIVES**

- To characterize esmethadone ability to block heterodimeric NMDARs, in the presence of physiological concentrations of extracellular magnesium and at different membrane potentials.

**METHODS**

- CHO cells stably expressing recombinant heterodimeric human NMDARs were used in automated depolarizing clamp experiments (QPatch HTX).
- Cells were clamped at -80 mV holding potential.
- Voltage protocol included a depolarizing 2 seconds step pulse to +60 mV followed by a 2 seconds ramp back to holding potential.
- Currents were induced by 10 µM or 1 µM L-glutamate with 1 mM extracellular MgCl₂ and with or without 10 µM esmethadone.

**RESULTS**

Figure 1 - Voltage protocol diagram

Figure 2 - L-glutamate CRC in presence of 1 mM magnesium

Figure 3 - Voltage dependence of 1 mM magnesium block

**CONCLUSIONS**

- Esmethadone preferentially reduced 1 µM-L-glutamate induced currents at NMDAR including GluN2D subunit, in the presence of 1 mM MgCl₂.
- Since GluN2D subunit is expressed in inhibitory interneurons, esmethadone might affect interneuron activity in presence of low ambient L-glutamate concentrations.

**REFERENCES**


**DISCLOSURES**

* This research was sponsored by Relmada Therapeutics, Inc. Drs. Interani, Stahl, Pappagallo, and Manfredi are paid consultants for Relmada Therapeutics. Drs. Interani and Manfredi are inventors on esmethadone patents and other patents and patent applications.

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