Esmethadone (REL-1017) Reduces Glutamate-Induced Currents in NMDA Receptors in a Concentration Dependent Manner

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Background: NMDA receptor (NMDAR) channel blockers are an emerging class of rapid acting antidepressants. Esmethadone (dextromethadone; REL-1017) is a safe and well-tolerated novel NMDAR channel blocker currently in Phase 3 trials as an adjunctive treatment for major depressive disorder (MDD). We investigated REL-1017 ability to block NMDARs in the presence of 1 μM L-glutamate and extracellular Mg^{2+} at negative membrane potentials.
Methods: CHO cells stably expressing recombinant diheteromeric human NMDARs were used in manual whole-cell patch-clamp experiments. In the presence of 1 mM extracellular Mg^{2+}, cells were clamped at –60 mV holding potential. The voltage protocol included 5 depolarizing 2 s step pulses to +40 mV, followed by a 2 s ramp back to holding potential. The voltage stimulation was repeated 5 times at 15 s intervals. Meanwhile, a 120 s perfusion of 1 μM L-glutamate was performed in the presence of 10 μM glycine, 1 mM Mg^{2+}, and 1, 3, 10, 30, and 100 μM of REL-1017. The varying concentrations of REL-1017 were assessed to calculate concentration response curves in NMDARs containing GluN2A, -2B, -2C, and -2D subunits.
Results: IC_{50} values of 63.1 μM, 41.7 μM, 28.4 μM, and 13.5 μM for GluN2A, GluN2B, GluN2C, and GluN2D subunits, respectively, were observed.
Conclusions: REL-1017 blocks 1 μM L-glutamate-induced current in NMDARs in the presence of extracellular Mg^{2+}. REL-1017 preference for NMDARs containing GluN2D subunits in the presence of relatively low glutamate concentration may help explain ~~play a role in~~ its therapeutic antidepressant effect in the absence of cognitive side effects and may help improve our understanding of the pathophysiology of MDD.

Keywords: NMDAR channel blocker, major depressive disorder (MDD), glutamate, dextromethadone, esmethadone