Esmethadone (REL-1017) Antagonizes NMDA Receptors and Reduces Ca^{2+} Entry in Presence of Quinolinic Acid and Gentamicin

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Background: Esmethadone (dextromethadone; REL-1017) is a novel NMDA receptor (NMDAR) antagonist currently in clinical development for major depressive disorder (MDD). To better understand its role as an NMDAR channel blocker, we examined the functional interaction between REL-1017 and quinolinic acid, an endogenous partial agonist at the glutamate binding site of the NMDAR, and REL-1017 and gentamicin, an antibiotic that modulates NMDAR potentiation.
Methods: We applied 10 µM REL-1017 for 5 minutes in the presence of glycine alone or L-glutamate and glycine (Glu/Gly) to CHO cells stably expressing human recombinant diheteromeric NMDA receptors. We measured intracellular Ca^{2+} levels using a fluorescence imaging plate reader (FLIPR) at different drug concentrations. 1000 µM quinolinic acid was tested for 5 minutes in presence of glycine and with or without 10 µM REL-1017. 10 µg/ml gentamicin was tested for 5 minutes in the presence of Glu/Gly and with or without 10 µM REL-1017.
Results: 1000 µM quinolinic acid significantly increased Ca^{2+} levels in all NMDARs except those expressing GluN2C subunits. 10 µM REL-1017 significantly reduced Ca^{2+} entry in NMDAR cell lines expressing GluN2A/B/D subunits. Similarly, 10 µg/mL gentamicin significantly increased Ca^{2+} entry in all NMDARs, and 10 µM REL-1017 significantly reduced Ca^{2+} entry in all NMDARs.
Conclusions: REL-1017 effectively blocked NMDARs and reduced Ca^{2+} entry induced by quinolinic acid and gentamicin in vitro. These results suggest that even in the absence of increased glutamate, REL-1017 effectively blocks excessive Ca^{2+} entry across multiple scenarios where endogenous and exogenous agents may impact the NMDAR.

Keywords: Major depressive disorder (MDD), glutamate, NMDA channel blocker, dextromethadone, esmethadone