

Effects of Memantine on NMDA-Induced Long-Term Depression in the Ts65Dn Mouse

Jonah J. Scott-McKean¹, Karen E. Smith², Mark L. Dell'Acqua^{1,2}, Alberto C. S. Costa^{1,3}

1) Neuroscience Training Program, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO

2) Department of Pharmacology, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO

3) Division of Clinical Pharmacology and Toxicology, Department of Medicine, University of Colorado Denver, Anschutz Medical Campus, Aurora, CO

The Ts65Dn mouse is the most complete animal model for Down syndrome that is widely available. Recently, our research group has shown that the Ts65Dn mouse displays pharmacological responses consistent with a dysfunction in molecular pathways coupled to the gating of NMDA receptors; these include the finding that the uncompetitive NMDA receptor antagonist memantine rescues learning and memory deficits in these mice. In the present study, we used electrophysiological and biochemical techniques to probe potential mechanisms underlying these observations. NMDA mediated long-term depression (LTD) was induced in the CA1 region of acute hippocampal slices from Ts65Dn and euploid control mice. This form of chemically-induced LTD (Chem-LTD) was elicited by bath application of 20 μ M NMDA for 3 min, and the resulting depression of field postsynaptic potentials was assessed 60 min after application. We found that Ts65Dn mice showed a greater synaptic depression when compared to euploid littermate controls. To determine whether memantine could rescue this phenotype in the Ts65Dn mice, half of the hippocampal slices were treated with 1 μ M memantine before Chem-LTD treatment. Interestingly, we found that memantine-treated hippocampal slices from Ts65Dn mice presented control levels of Chem-LTD. Currently, phosphorylation of the AMPA receptor GluR1 subunit is being assessed on hippocampal slices from Ts65Dn and control mice, which were flash frozen under control and Chem-LTD conditions, with or without drug. Our goal is to determine whether Chem-LTD-induced dephosphorylation of this subunit is dysregulated in Ts65Dn mice and whether memantine treatment rescues this molecular phenotype.

This study confirms our previous finding that molecular pathways coupled to the gating of NMDA receptors are altered in the Ts65Dn mouse and brings us a step closer to understanding the role of NMDA receptors in the pathogenesis of the cognitive deficits associated with Down syndrome.

Support Contributed By: HD056235, Anna & John J. Sie Foundation, The Coleman Institute