

Acute memantine injections enhance learning/memory in the Ts65Dn mouse model of Down syndrome. ACS Costa^{1,2,3}, Jonah Scott-McKean³, Melissa R Stasko¹

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Individuals with Down syndrome (DS) and Ts65Dn mice (a major animal model of DS) carry an extra copy of the *DSCR1* gene, which encodes for a protein that inhibits calcineurin. Calcineurin itself has been shown to modulate NMDA receptor activation kinetics by decreasing channel mean open time and opening probability. We hypothesize that the overexpression of DSCR1 in persons with DS and Ts65Dn mice would inhibit normal calcineurin activity and produce pathological increases in NMDA receptor mean open time and opening probability. These kinetic changes should in turn produce an increase in the apparent affinity of this receptor to open channel blockers. To test this hypothesis, we investigated the locomotor stimulating effects of MK-801 on Ts65Dn mice and have found that these mice display an increased sensitivity to this compound. Furthermore, we have found that acute injections of the uncompetitive NMDA receptor antagonist memantine rescue performance deficits of Ts65Dn mice on a fear conditioning test. The actions of memantine on NMDA receptor kinetics had been shown by others to mimic somewhat the actions of calcineurin. Therefore, we attribute this positive effect of memantine on Ts65Dn mice to a drug-mediated ‘normalization’ of the NMDA receptor kinetic parameters. To our knowledge, this is the first instance in which the acute injection of a pharmacological agent has improved the behavioral performance of Ts65Dn mice in a test of learning and memory. These results are quite exciting from a potential therapeutic perspective, given memantine status as an FDA approved drug.