

Cognitive deficits in Down syndrome: the underlying molecular concepts

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With an incidence of one in 700-1000 live births worldwide, Down syndrome (DS) is the most common genetic cause of intellectual disability. As a contiguous gene syndrome encompassing the entirety of the long arm of human chromosome 21 (Hsa21), DS is particularly complex in the number and kinds of molecular/cellular perturbations it causes. DS is also difficult to model in mouse because orthologs of Hsa21 genes are distributed within regions of three mouse chromosomes. Nevertheless, based on results of preclinical evaluations in one partial trisomy mouse model, the Ts65Dn, a number of different drugs have been or are being used, and are being proposed for use, in human clinical trials for cognition in DS. To manage expectations for the outcomes of these trials, an understanding of the molecular basis of learning deficits and drug responses in DS would be helpful. In this presentation, I will review the gene content of Hsa21 and mouse models of DS and describe work my lab has done to characterize mouse models for perturbations in molecular processes normally subserving learning and memory, such as MAP kinase and MTOR pathways, NMDA receptor complexes and signaling, and immediate early gene responses. I will describe protein responses that occur in normal successful learning, how these are altered in mouse models of DS, and lastly, how they change when learning deficits are rescued with the NMDA receptor antagonist, memantine. Potential consequences for drug efficacy in full trisomy 21 will be discussed.