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Degeneration of norepinephrine-ergic system in mouse models of down syndrome prospects for therapy

Down syndrome (DS) is the most common cause of cognitive disabilities in children. While there has been an incredible progress in improving life expectancy in people with DS, that has not been paralleled with reduction in the severity of cognitive dysfunction in these individuals. In addition, almost all individuals with DS will develop Alzheimer pathology in their adulthood. The most widely used mouse model for DS is the Ts65Dn mouse with a triplication of around 140 genes orthologous to those on human chromosome 21. Among the triplicated genes in this mouse, amyloid precursor protein (App), i.e. a major player in Alzheimer's disease, is believed to play a significant role in the pathophysiology of cognitive dysfunction in DS. We have identified App overexpression as both necessary and sufficient to cause degeneration of multiple systems in Ts65Dn mice. Locus coeruleus (LC) in the brainstem is the sole source of norepinephrine-ergic terminals for the cortex and hippocampus. We found that LC neurons undergo significant degeneration in Ts65Dn mice. A process that was linked to failure in contextual learning in these mice. Accordingly, Increasing brain NE levels in Ts65Dn mice led a significant improvement in contextual learning in these mice. Our recent data suggest that LC neurons degeneration in Ts65Dn mice can be linked to failure in trophic factor signaling in these mice. We suggest that improving NE system by either increasing NE levels or improving trophic factor signaling would be a potentially successful strategy in restoring cognitive function in people with DS.

Biography

Ahmad Salehi obtained his MD in Tehran, Iran and his PhD in the field of neurobiology at the Netherlands Institute for Brain Research. During his postdoctoral training in Amsterdam, he was chosen as the best junior scientist in the field of Alzheimer's disease in the Netherlands (Boerhaave Commissie, University of Leiden). Following a second postdoctoral training at Stanford Medical School, he worked for several years as a senior scientist at the Department of Neurology and Neurological Sciences at Stanford Medical School, in Palo Alto, California. His work on the neurobiological basis of Down syndrome has been covered and featured around the word. In fact, due to the use of multiple mouse models to understand the role of individual genes in Down syndrome, in November 2009, he was honored with the World Technology Award in the field of Biotechnology from the World Technology Network in New York. Currently, he is a clinical associate professor at the Department of Psychiatry and Behavioral Sciences, Stanford Medical School and the Palo Alto Health Care System. His very recent study on the role of trophic factors polymorphism in predicting the rate of decline in skilled task performance in healthy individuals was among the top ten downloaded papers for the first three months after publication in Translational Psychiatry.

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