OMICS Group Conferences
Accelerating Scientific Discovery

2nd International Conference and Exhibition on
Neurology & Therapeutics

June 17-19, 2013, Hilton Chicago/Northbrook, Chicago, USA

Improving noradrenergic signaling in the treatment of cognitive dysfunction in the Ts65Dn mouse model of Down syndrome

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Abstract

Down syndrome (DS) is the leading cause of cognitive dysfunction in children, affecting over 5 million individuals in the world. In addition to cognitive impairment, all people with DS develop Alzheimer's disease (AD) pathology, implicating the role of *App* gene, which is involved in AD pathogenesis and is among the triplicated genes in DS. We have previously identified a significant age-dependent degeneration of the locus coeruleus (LC) in the mouse model of DS, Ts65Dn, which is trisomic for at least 130 of the genes on human chromosome 21. Consistent with the loss of LC neurons, we showed that adult Ts65Dn mice exhibited decreased norepinephrine (NE) levels in the hippocampus, suggesting a failure of NE signaling in Ts65Dn mice. More importantly, we found that increasing brain NE levels in Ts65Dn mice via administration of L-DOPS, i.e. an NE prodrug, can improve their cognitive function. In this study, we aimed to improve the cognitive function of adult Ts65Dn mice using atomoxetine (ATMX), a selective norepinephrine reuptake inhibitor, L-DOPS, and/or a combination of the two. We found that the effects of ATMX and low-dose L-DOPS (200 mg/kg) by themselves were unremarkable on cognitive function. However, when ATMX was administered in combination with L-DOPS, adult Ts65Dn mice exhibited significantly improved contextual learning and reduced velocity during open field tests, as compared to untreated mice. Our results suggest that L-DOPS in combination with NE potentiating drugs could have synergistic positive effects on learning and memory in people with DS.

Biography

Ahmad Salehi, MD, Ph.D, is a clinical Associate Professor at the Department of Psychiatry and Behavioral Sciences, Stanford Medical School and the Director of Translational Laboratory at the VA Palo Alto Heath Care system. He obtained his PhD in the field of neurobiology from the Netherlands Institute for Brain Research in Amsterdam. During his studies in the Netherlands, he was awarded as the best junior scientist in the field of Alzheimer's disease in the country. In 2010, he was awarded World Technology Award, from the World Technology Network in New York. His multiple publications and contributions have been featured on the cover of multiple journals including Science, Science Translational Medicine, Cell-Stem Cell, and Biological Psychiatry.