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In the search of safe therapies for Down syndrome

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No therapies currently exist for intellectual disability in Down syndrome (DS), a relatively high-incidence genetic condition (1:700/1000). Neurogenesis impairment starting from fetal life stages is considered a major determinant of intellectual disability in DS. We have previously shown that perinatal treatment with fluoxetine, an antidepressant, fully restores neurogenesis and cognitive performance in the Ts65Dn mouse model of DS. The finding that these effects were accompanied by an increase in the levels of brain-derived neurotrophic factor (BDNF) suggests that BDNF may be an important determinant of the proneurogenic effect of fluoxetine. This important discovery prompted us to find a therapy that is as effective as fluoxetine but that may pose fewer caveats for clinical application in children with DS. A therapy based on BDNF is impracticable due to its poor blood-brain barrier penetration. However, the naturally-occurring flavone 7,8-DHF is a BDNF mimetic that crosses the blood-brain barrier and binds to the BDNF TrkB receptor. Based on these premises, the goal of our study was to establish whether early treatment with 7,8-DHF can rescue trisomy-linked neurodevelopmental defects, similarly to fluoxetine. We found that neonatal treatment with 7,8-DHF increased neurogenesis and restored neuron maturation in the hippocampus of Ts65Dn mice. Importantly, Ts65Dn mice treated from birth to adolescence exhibited restoration of hippocampus-dependent memory. This study provides novel evidence that treatment with a natural compound 7,8-DHF restores brain development and cognitive performance in a DS mouse model. In view of the safe nature of 7,8-DHF our results, potentially, are readily transferable into clinical practice.

Biography

Fiorenza Stagni obtained her PhD in Biomedical Sciences at University of Bologna, Italy in 2014. She is currently involved as Postdoctoral fellow in an international project aimed at identifying a panel of drugs that may be safely used during pregnancy or in infants in order to counteract the neurodevelopmental defects linked to Down syndrome. In 2016, she was awarded by the Trisomy 21 Research Society for the Best Dissertation in the field of DS defended in 2014-2015. She has published more than 15 papers in the field of preclinical studies for the treatment of cognitive deficits in DS.

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