Pharmacological correction of neurodevelopmental disorders in adult, a case for Fragile X Syndrome

Dr. Aubin Michalon
Postdoctoral Research Scientist
Discovery Neuroscience
F. Hoffmann-La Roche Ltd.
Basel, CH

Invited by Kim Do Cuénod
(Kim.Do@chuv.ch)

Salle Hirondelle, Hôpital Psychiatrique de Cery
Site de Cery, CH-1008 Prilly-Lausanne

Excessive mGlu5 signaling plays a central role in the pathophysiology of Fragile X syndrome (FXS), the most common monogenic form of intellectual disability and autism. The genetic reduction of mGlu5 expression level by 50% in the Fmr1 KO mice has been shown to prevent symptom onset, but a crucial unanswered question is whether chronic pharmacological mGlu5 inhibition is able to reverse an already established FXS phenotype. To address this issue, we have used the novel, long-acting, potent and selective mGlu5 inhibitor CTEP which enables uninterrupted high level of receptor inhibition in vivo during chronic treatment. Our results show that chronic mGlu5 inhibition corrects in adult mice, multiple cognitive, morphological and functional phenotypes directly related to FXS symptoms. These data suggest that many of the deficits seen in FXS are not caused by an irreversible alteration of brain development, and that mGlu5 inhibitors may offer widespread therapeutic benefit even when administered well after symptom onset.

Here below 3 publications providing a good overview of the topic: 1) a review of the mGlu5 hypothesis in FXS; 2) the recently published, preclinical results that will be presented and discussed; 3) results from a phase 2 clinical trial run by Novartis.

