Département de psychiatrie
Centre de neurosciences psychiatriques
Site de Cery
CH-1008 Prilly - Lausanne

Centre de Neurosciences Psychiatriques

CNP SEMINAR

ANNOUNCEMENT

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

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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.

1. Gül Dölen, Randall L. Carpenter, Timothy D. Ocain, Mark F. Bear. ***Mechanism-based approaches to treating fragile X***. Pharmacology & Therapeutics 127 (2010) 78–93

2. Aubin Michalon, Michael Sidorov, Theresa M Ballard, Laurence Ozmen, Will Spooren, Joseph G Wettstein, Georg Jaeschke, Mark F Bear and Lothar Lindemann. ***Chronic Pharmacological mGlu5 Inhibition Corrects Fragile X in Adult Mice.*** Neuron **74**(1):49-56 (2012) PMID 22500629

3. Jacquemont S, Curie A, des Portes V, Torrioli MG, Berry-Kravis E, Hagerman RJ, Ramos FJ, Cornish K, He Y, Paulding C, Neri G, Chen F, Hadjikhani N, Martinet D, Meyer J, Beckmann JS, Delange K, Brun A, Bussy G, Gasparini F, Hilse T, Floesser A, Branson J, Bilbe G, Johns D, Gomez-Mancilla B. ***Epigenetic modification of the FMR1 gene in fragile X syndrome is associated with differential response to the mGluR5 antagonist AFQ056.*** Sci Transl Med. 2011 Jan 5;3(64):64ra1.

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