The endocannabinoid system as therapeutic target for fragile X syndrome and other cognitive disorders

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Fragile X syndrome is the most common monogenetic form of intellectual disability and is a leading cause of autism. This syndrome is produced by the reduced transcription of the fragile X mental retardation (FMR1) gene, and it is characterized by a range of symptoms heterogeneously expressed in patients such as cognitive impairment, seizure susceptibility, altered pain sensitivity and anxiety. The recent advances in the understanding of the pathophysiological mechanisms involved have opened novel potential therapeutic approaches identified in preclinical rodent models as a necessary preliminary step for the subsequent evaluation in patients. Among those possible therapeutic approaches, the modulation of the metabotropic glutamate receptor or the GABA receptor signaling have focused most of previous the attention. New findings in animal models open now other possible therapeutic approaches, such as the endocannabinoid system. In this regard, we have shown that the CB1 receptor antagonist/inverse agonist rimonabant (1 mg/kg) normalized a number of core features in the Fmr1 knockout mouse. Low doses of rimonabant (from 0.01 mg/kg) equally normalized the cognitive deficit in the mouse model of FXS. These doses of rimonabant were from 30 to 300 times lower than those required to reduce body weight in rodents and to presumably produce adverse effects in humans. Furthermore, NESS0327, a CB1 receptor neutral antagonist, was also effective in preventing the novel object-recognition memory deficit in Fmr1 KO mice. In addition, we have obtained recent data demonstrating the effectiveness of CB1 blockade in other congenic cognitive deficits, which underlines the interest of targeting CB1 receptors as a relevant potentialtherapy for these cognitive disorders.