Pharmacological inhibition of p21-Activated Kinase rescues the behavioral phenotype in a female mouse model of CDKL5 Deficiency Disorder

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Aim: Cdkl5 Deficiency Disorder (CDD) is a rare neurodevelopmental condition due to mutations in X-linked cyclin-dependent kinase-like 5 (*CDKL5*) gene. No cure is available for this disorder. *CDKL5* gene encodes for a kinase involved in several neurodevelopmental processes. Cdkl5-*null* male mice present brain overactivation of group I p21-activated kinases (PAKs), a family of Ser/Thr protein kinases involved in the spine morphogenesis and synapse formation, whose pharmacological inhibition rescues neurobehavioral defects in preclinical models of Fragile X and schizophrenia. The present study evaluated in a CDD mouse model the therapeutic efficacy of FRAX486, a brain penetrant inhibitor of group I PAKs.
Methods: symptomatic Cdkl5-Het female mice and wild-type (wt) littermates were treated with vehicle or FRAX486 for 5 days (20 mg/kg, daily subcutaneous injections). A battery of behavioral tests was performed to evaluate treatment efficacy.
Results: overactivation of group I PAKs was confirmed in the brain of symptomatic Cdkl5-Het mice, the condition which more closely recapitulates that of CDD patients. A 5-day long treatment with FRAX486 rescued the general health status of Cdkl5-Het mice and the social behavior in the Three-chamber social test, restoring wt sociability levels.
Conclusion: present results show that systemic treatment with FRAX486 rescues some behavioral alterations in a CDD mouse model. Group I PAK inhibitors may represent an innovative therapy for this disorder.