Prepulse inhibition defects and brain mitochondrial dysfunctions are rescued by selective stimulation of serotonin receptor 7 in a mouse model of CDKL5 Deficiency Disorder at an advanced stage of the disease

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CDKL5 Deficiency Disorder (CDD) is a rare neurodevelopmental syndrome characterized by severe behavioural and physiological symptoms for which no curative therapy is currently available. Such clinical condition has been associated with *de novo* mutations in the X-linked cyclin-dependent kinase-like 5 (CDKL5), a kinase which is abundantly expressed in the brain and plays a critical role in neurodevelopmental processes, such as neuronal morphogenesis and plasticity. Despite evidences demonstrating an age-dependent efficacy of pharmacological treatment strategies in a mouse model of CDD (*Cdkl5*-null), the progression of the disease pathogenesis has never been addressed so far. This study provides the first characterization of the neurobehavioural phenotype of *Cdkl5*-null mice at an advanced stage of the disease. Besides worse general health conditions, motor and cognitive impairments, *Cdkl5*-null mice present abnormal prepulse inhibition (PPI) and reduced brain energy status due to mitochondrial dysfunction, which constitute innovative neurobehavioural alterations for CDD. The first *in vivo* evidence that in mouse cortex Cdkl5 is involved in regulation of group I PAKs, a family of protein regulating several neuronal processes

potentially relevant for CDD, is also provided. Stimulation of the serotonin receptor 7 (5-HT 7R) with the agonist molecule LP-211 (0.25 mg/kg once/day for 7 days) partially rescues the abnormal phenotype displayed by fully symptomatic *Cdkl5*-null male mice. In particular, LP-211 treatment normalizes PPI defects and rescues the functional abnormalities of brain mitochondria and the abnormal cortical phosphorylation of rpS6 displayed by Cdkl5-null mice. Present results highlight innovative endophenotypes and druggable molecular targets for CDD.