STIMULATION OF THE BRAIN SEROTONIN RECEPTOR 7 RESCUES SENSORY-MOTOR GATING IMPAIRMENTS, EMOTIONAL MEMORY DEFICITS AND BRAIN MITOCHONDRIAL DYSFUNCTION IN A MOUSE MODEL OF RETT SYNDROME

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Objectives Rett syndrome (RTT) is a rare neurodevelopmental disorder, characterized by severe behavioral and physiological symptoms. Mutations in the methyl CpG binding protein 2 gene (*MECP2*) cause more than 95% of classic cases, and currently there is no cure for this disorder. Recently, we have demonstrated that neurobehavioral and brain molecular alterations can be rescued in a RTT mouse model, by pharmacological stimulation of the brain serotonin receptor 7 (5-HT7R). The 5-HT7R is crucially involved in the regulation of brain structural plasticity and cognitive processes and can be stimulated by systemic repeated treatment with LP-211, a brain-penetrant selective agonist.

Purpose: The present study verified whether repeated systemic treatment with LP-211 affects emotional memory and sensorymotor gating in RTT female mice. We also explored whether mitochondrial dysfunction can be rescued targeting the brain serotonin receptor 7 in RTT mouse brain.

Methods: MeCP2-308 female mice and wild type littermates were daily ip injected with either LP-211 (0.25 mg/kg, once per day for 7 days) or vehicle. After the treatment, mice were tested in the Prepulse Inhibition (PPI) task and the cued Fear conditioning test (CFC). The brains were subsequently collected to investigate mitochondria functionality in RTT mouse brain and LP-211 effects thereon.

Results: The LP-211 treatment rescued sensory-motor gating impairments (PPI) and emotional memory-associative learning deficits (CFC) in RTT female mice. Moreover, LP-211 treatment rescued mitochondrial respiratory chain impairment and the reduced energy status in the brain of RTT female mice.

Conclusions: The present study demonstrates that the LP-211 treatment provides a widespread beneficial effect on the neurobehavioural phenotype of a RTT mouse model and provides the first evidence that RTT brain mitochondrial dysfunction can be rescued targeting the brain serotonin receptor 7.