NOVEL LSD1 IMPLICATIONS IN BRAIN PHYSIOLOGY AND RETT SYNDROME PATHOPHYSIOLOGY

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Rett Syndrome (RTT), mainly caused by mutations in Mecp2 gene, represents a severe X-linked neurodevelopmental pathology featuring early loss of acquired milestones including speech and operative skills. Young girls also experience severe epilepsy and intellectual disability, rarely surviving beyond the second/third decade of life. As learned from rodent models, RTT features synaptic dysfunction in the context of aberrant dendritic and spine plasticity. Convincing recent data obtained through analyses of Mecp2null RTT mouse hippocampus and primary neurons indicate a picture of i) enhanced IEGs stimuli-dependent transcription, ii) increased spontaneous and evoked excitatory synaptic transmission in the context of impaired Homeostatic Synaptic Plasticity (HSP) and iv) stimuli-independent LTP-like synapse potentiation. All these findings, together with hyperexcitable RTT human phenotype, indicate glutamate homeostasis as a major issue fostering Rett syndrome pathogenesis.

Lysine Specific Demethylase 1 (LSD1) and neuroLSD1 are respectively a transcriptional corepressor and its brain-specific dominant negative splicing isoform unable to repress transcription. Functionally, their relative amount (LSD1/neuroLSD1) concurs to set hippocampal circuitry excitability in such a way that neuroLSD1KO mice (models in which LSD1 represents the one and only isoform) display substantially decreased seizure susceptibility and impaired LTP. As symptomatic Mecp2Y/- mice feature neuroLSD1 increase in the hippocampus, double mutants Mecp2Y/-/neuroLSD1HET undergo neuroLSD1 decrease-mediated amelioration of RTT hyperexcitability. Pharmacological reduction of neuroLSD1 in primary neurons provides a functional perspective on the beneficial role, leading to decreased IEGs stimuli responsivity and diminished frequency and amplitude mEPSCs. Our work suggests neuroLSD1 normalization in RTT brain as a possible new approach to target Rett syndrome-associated epilepsy.