In vivo treatment of *Mecp2*$^{-/y}$ mice with the radical scavenger Trolox

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Rett syndrome (RTT) is a progressive neurodevelopmental disorder affecting almost exclusively girls. After the first year of life, complex disease symptoms start to manifest, including pronounced cognitive impairment, epilepsy, motor dysfunction, and severe breathing disturbances. Rating mitochondrial function in male Rett mice (*Mecp2*$^{-/y}$) revealed an intensified mitochondrial respiration, a less efficient cellular redox homeostasis, and oxidative stress. As these alterations become evident already at neonatal stages, they may facilitate disease progression. In the isolated hippocampus of symptomatic *Mecp2*$^{-/y}$ mice Trolox dampens neuronal hyperexcitability, reinstates synaptic plasticity, ameliorates cellular redox balance, and improves hypoxia tolerance. Therefore, we now started a chronic *in vivo* Trolox treatment of *Mecp2*$^{-/y}$ mice at very young, presymptomatic stages. For most reliable compound dosing we performed intraperitoneal injections of either saline, 10 or 40 mg Trolox/kg body weight. Trolox-treated *Mecp2*$^{-/y}$ mice showed a normalization of blood glucose levels. Furthermore, low doses of Trolox improved the hypoxia-tolerance and synaptic short-term plasticity of *Mecp2*$^{-/y}$ hippocampus. Lipid peroxidation in cortical tissue samples was less pronounced in high-dose Trolox treated *Mecp2*$^{-/y}$ mice. Systemic Trolox administration did, however, not rescue body weight or size, regular breathing, or motor function. Rather, the frequent animal handling and intraperitoneal injections dampened the phenotypic differences among WT and *Mecp2*$^{-/y}$ mice, which may have masked potential merits of Trolox. In conclusion, our findings show that radical scavengers may be promising for the treatment of various aspects in RTT. The route of compound administration and frequent animal handling are, however, critical parameters to be optimized.

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