Pharmacological treatment with Mirtazapine rescues cortical atrophy and respiratory deficits in MeCP2 null mice

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Loss of MeCP2 (Methyl CpG binding protein 2) in Rett syndrome (RTT) is known to cause brain weight decrease and shrinkage of the cortex due to the presence of neurons with reduced dendritic arborization. Other clinical signs of RTT includeautistic-like behavior,cognitive impairment, seizures and cardio-respiratory complications. The observed monoamine neurotransmitters reduction in RTT suggested antidepressants as a possible therapy. To test this hypothesis, we treated MeCP2-null mice for two weeks from postnatal-day 28 with the antidepressant desipramine, which was already tested in RTT, or mirtazapine, an antidepressant with limited side effects, known to promote GABA release. Mirtazapine was more effective than desipramine in restoring somatosensory cortex thickness by fully rescuing pyramidal neurons dendritic arborization and spine density and shape. Functionally, mirtazapine treatment normalized heart rate, breath rate, anxiety levels, and eliminated the hopping behavior observed in MeCP2-null mice, leading to improved phenotypic score, a measure of general animal wellbeing. These morphological and functional effects of mirtazapine were accompanied by reestablishment of the GABAergic and glutamatergic receptor activity recorded in cortex and brainstem tissues. These results suggest that mirtazapine has the potential to represent a new potential pharmacological treatment for the Rett syndrome (Supported by Telethon grant n. GGP08258).