The organization of inhibitory interneurons in the cerebral cortex of Mecp2 mutant mice

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Rett syndrome (RTT) is a complex and severe X-linked neurological disorder with no efficient treatment that manifests mainly in girls during childhood after an apparently normal early development. RTT is typically characterized by a broad range of deficits including loss of language skills and hand use, cognitive and motor alterations. Mutations in the gene encoding Methyl−CpG−Binding Protein 2 (MeCP2), a transcription modulator that binds methylated DNA regulating chromatin remodelling and gene expression, cause most RTT cases. Male mice lacking MeCP2 ($Mecp2^{-/y}$), following a brief period of normal development, manifest severe locomotor and neurological dysfunctions, tremor, weight loss and premature death. The absence of gross macroscopic neuroanatomical defects and neurodegeneration suggests that dysfunctions may occur at the microcircuit level, affecting synaptic connectivity and, consequently, the balance between excitation and inhibition. Although a number of studies reported defects in the structural and molecular organization of excitatory circuits in the cerebral cortex of mutant mice, the impact of Mecp2 dysfunction on the establishment of GABAergic connectivity is still largely unknown. Recently, the characterization of a conditional mouse model in which MeCP2 was ablated specifically in inhibitory interneurons, demonstrated that GABAergic cells are critical mediators of RTT phenotypes. Interestingly, these mice recapitulate many features of RTT, including repetitive behaviours, impaired motor coordination, learning/memory deficits, respiratory disrhythmia and premature lethality. However, the cellular and molecular determinants of such dysfunctions are still largely unknown. In this study we assessed the morphological organization of the major GABAergic interneurons subpopulations and the architecture of inhibitory synapses in the S1 neocortex. We found that the density of both parvalbumin (PV) and calretinin (CR) interneurons, but not somatostatin (SST) cells, is increased in $Mecp2^{-/y}$ mice. Such abnormalities are detectable even at an early asymptomatic age and exacerbate when symptoms occur. Moreover, both the morphology and the biochemical differentiation of the CR-positive subpopulation are affected in Mecp2 mutants. In particular, we found an increased density of a specific subpopulation of CR-SST co-expressing cells, characterized by multipolar dendritic arborizations. Moreover, we found a significant increase in perisomatic neuroligin-2-positive synapses in $Mecp2^{-/y}$ cortices, but no differences in the number of VGAT-positive terminals. These result suggest that the expression of important adhesion synaptic molecules may be modulated by MeCP2 expression. Interestingly, we found that ageing heterozygous female mice ($Mecp2^{+/-}$), a model closely mimicking many aspects of human patients, recapitulate most of the alterations found in symptomatic $Mecp2^{-/y}$ male mice. Finally, we found that a conditional mouse model (Dlx5/6-$Mecp2^{-/y}$), carryingMeCP2 deletion only in cortical interneurons, shows a similar phenotype, supporting a cell autonomous role of MeCP2 in the organization of GABAergic circuits. Thus, our data suggest that MeCP2 expression is directly involved in the establishment of inhibitory circuits, and that the GABAergic system may represent an important target for future studies on therapeutic treatments for RTT.