A mouse model of neuronal-specific MeCP2 overexpression

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Expression of MeCP2 in the brain occurs in both glial and neuronal cells. Neurons express approximately 6-7fold more MeCP2 protein than glia. It has been demonstrated that MeCP2 binds and recruits the NCoR complex to chromatin. In humans, mutations in the NCoR interaction domain (NID) cause Rett Syndrome. This shows that the NID is crucial for MeCP2 function. In addition, overexpression of wildtype MeCP2 leads to MeCP2 Duplication Syndrome, demonstrating that an excess of MeCP2 is detrimental. Using a previously established mouse model for MeCP2 Duplication Syndrome, we have knocked in either wildtype MeCP2 or MeCP2 with a mutation in the NID (R306C) into the neuronal-specific Tau gene. Analysing total brain extracts, both, Tau-MeCP2 and Tau-MeCP2-R306C are expressed at ~2-fold levels compared to endogenous MeCP2. Expression of Tau-MeCP2 rescues lethality and phenotypic scoring of MeCP2 null mice. Mice with heterozygous Tau-MeCP2 expression in a wildtype background are leaner than wildtype littermates, but viable and fertile. Homozygous expression of Tau-MeCP2 however is lethal between birth and weaning. In contrast, homozygous Tau-MeCP2-R306C mice which express wildtype levels of non-mutated MeCP2 plus ~4-fold levels of MeCP2-R306C are viable, fertile and phenotypically undistinguishable from wildtype littermates. This indicates that it is not solely the excess of MeCP2 protein in the nucleus, but the amplified interaction of NCoR with MeCP2, which is detrimental in MeCP2 duplication syndrome.