

Network hyperexcitability in hippocampal slices from *Mecp2* mutant mice revealed by voltage-sensitive dye imaging

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Our recent work discovered the cellular bases for seizure and epilepsy disorders in the *Mecp2* mutant mouse model of Rett syndrome, in addition to providing a novel pre-clinical end-point for the evaluation of therapeutic approaches. Proper development of excitatory and inhibitory neurons and their synapses leads to a finely tuned “excitation-to-inhibition balance”, which has been recently found to be dysfunctional in several mouse models of autism spectrum disorders. Due to its high degree of inter-connectivity, keeping this balance is absolutely critical in a region of the brain called the hippocampus, one of the main focal points of epileptogenesis in the brain. Our work in the hippocampus of *Mecp2* mutant mice describes for the first time a pronounced network hyperexcitability that is caused by an excitation-to-inhibition imbalance. The origin of this imbalance is two-fold: reduced inhibitory input and enhanced excitatory input to CA3 neurons. We are currently evaluating the hypothesis that the development of GABAergic interneurons – the main inhibitory elements in the brain – is impaired in *Mecp2* mutant mice because of reduced BDNF signaling. It is well known that GABAergic interneurons depend on BDNF for their maturation (including inhibitory synapse formation), despite not producing it themselves. Importantly, BDNF dysregulation contributes to Rett-like pathologies in mouse models, and its genetic or pharmacological overexpression reverses several impairments. In current pre-clinical studies, we are testing 2 different types of BDNF mimetics (because BDNF does not cross the blood-brain barrier) in an attempt to enhance GABAergic interneuron maturation and prevent the development of an epileptogenic hippocampus.

The transition of my research interest from the basic biology of BDNF and hippocampal neurons and synapses to the role of *Mecp2* in synapse function and the potential dysregulation of BDNF signaling as underlying cause of several phenotypes and clinical manifestations would not have been possible without funding support from the IRSF. My first NIH grant on *Mecp2* and BDNF was co-funded by the IRSF and NINDS, and 3 of my postdocs have had fellowships from the IRSF. In addition, the Rett scientific community and the Rett families welcomed me with open arms and allowed me to learn and share our work during the annual meetings. It has been exciting and highly motivational to become part of this community, and I hope to be able to continue my active participation as a basic and pre-clinical neuroscientist.

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