



Cortical inhibitory mechanism governing auditory perception in MeCP2+/-

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Rett syndrome (RTT) is a neuropsychiatric disorder predominantly caused by mutations in the X-linked gene methyl CpG-binding protein 2 (Mecp2). RTT affects mainly females who are heterozygous for Mecp2 mutations (Mecp2+/-). Due to random X-inactivation, affected females exhibit a high degree of variability in RTT phenotypes, which include deficits in social behavior. How mutations in Mecp2 alter neural activity and gene expression, thereby, affecting adult social behavior remain unknown. We previously showed that impaired pup retrieval learning in an adult female mouse model of RTT (female mice with heterozygous deletion of Mecp2, Het) is caused by dysregulated adult plasticity in the auditory cortical inhibitory networks. Specifically, adult Het fail to learn from a wild-type mother to gather scattered pups. This failure to learn is associated with an abnormal transient increases of inhibitory proteins, parvalbumin (PV) and perineuronal net (PNN), in the auditory cortex. High expression of PV and PNNs are typically associated with suppressed plasticity during early development. It remains unknown how such increased inhibitory expressions in Het alter circuit and molecular plasticity in the auditory cortical inhibitory networks that results in impaired perceptual learning behavior. I hypothesize that pup retrieval learning triggers an abnormal molecular plasticity that leads to enhanced activity-dependent inhibition in the auditory cortical network of Het, thereby, inhibiting social perception and performance of the behavior. To test this hypothesis, I propose to 1) measure single-unit neural activity and determine the cellular identity of the recorded neurons in the auditory cortex of the awake mice, and 2) use single-cell Mu-Seq and next generation sequencing analysis of auditory cortical PV neurons to determine the genes and transcript isoforms that are dysregulated. I expect the learning experience will increase inhibitory activity in the auditory cortical inhibitory networks of Het by: 1) decreasing stimulus-evoked firing rate in excitatory neurons, and/or 2) increasing stimulus-evoked firing rate in inhibitory neurons (i.e. PV+ neurons). I expect the single-cell molecular analysis will reveal a discrete set of target genes dysregulated in Het. The results from this proposal will provide the first evidence for how mosaic MECP2 expression affect neural circuitry and molecular pathways, with cell-type identity, during a natural, social learning behavior in a clinically-relevant mouse model of RTT. The results will also provide novel gene targets that may be used for potential biomarkers for RTT patients.