Characterization of Serotonin Neurochemistry in the Medial Prefrontal Cortex and Evaluation of Autism Spectrum Disorder Models

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Serotonin is a vital neurotransmitter whose exact roles are ill-defined. Dysfunctions in serotonin signaling are thought to underlie a myriad of neurological problems including depression and autism spectrum disorder (ASD). Prior to investigating serotonin’s role in disease states, one must understand more about the functionality of serotonin in healthy in vivo models. To study serotonin in vivo, fast-scan cyclic voltammetry (FSCV) and fast-scan controlled adsorption voltammetry (FSCAV) are employed to measure evoked and basal serotonin concentration, respectively. These methods, combined with mathematical modeling, provide information regarding regulatory mechanisms of serotonin neurotransmission. FSCV and FSCAV are first applied to characterize serotonin chemistry in the medial prefrontal cortex (mPFC), a brain region with abundant serotonin projections and associations with various diseases. In this region, we discover two unique populations of serotonin axons terminating in discrete reuptake domains. The mPFC serotonin signals are unique when compared to previously established brain regions. Mathematical modeling of the regions provides a unique tool to determine local tissue architecture. Establishing a model of serotonin neurotransmission in the mPFC of healthy mice allows us to begin to explore alterations during disease states and determine etiology.

Peripheral serotonin dysfunction is a common phenotype of ASD despite the underlying pathophysiology of this disorder remaining poorly understood. ASD is thought to result from a combination of genetic and environmental risk factors. To better understand serotonin’s role in the brain during ASD, we investigate two genetic ASD models and find similar alterations in evoked serotonin reuptake. To evaluate the contribution of lead as a risk factor for ASD, we use a low dose perinatal exposure model. Though no convincing evidence of ASD typical behaviors is induced by this exposure paradigm, acute effects at such low doses provides cause for concern and implies that compensatory mechanisms are employed to maintain the homeostasis of serotonin during long-term exposures.

In this dissertation, I present evidence for unique serotonin transmission in the mPFC and establish further evidence of serotonin neurotransmission disruptions in mouse ASD models. I evaluate lead for its effects on the serotonin system and provided support for further research into its contribution to ASD.