Abstract

Serotonin signaling plays a key role in the regulation of development, mood and behavior. Selective serotonin reuptake inhibitors (SSRIs) have been the standard of treatment for several mental disorders, including depression. However, our understanding of their effects is incomplete and the serotonergic system in mammals is complex, making it difficult to study. *Drosophila* is well suited for the study of the basic mechanisms of serotonergic signaling, but the small size of its nervous system has previously precluded the direct measurements of neurotransmitters. We have developed a novel combination of methods to study serotonergic signaling in the larval *Drosophila* central nervous system. Fast-scan cyclic voltammetry at inserted microelectrodes is used to detect serotonin elicited by channelrhodopsin-2 (ChR2) mediated depolarization. This dissertation demonstrates the first real-time measurements of serotonin dynamics in a single larval *Drosophila* nerve cord. A characterization of serotonin release and clearance in the fly, including the estimation of Michaelis-Menten constants, shows that they are analogous to those in mammals, making this simple organism more useful for the study of the basic physiological mechanisms of serotonergic signaling.

The effects of pharmacologically inhibiting serotonin synthesis or reuptake on the releasable pool of serotonin are probed with multiple stimulation experiments. Reuptake is shown to be important for the clearance of serotonin from the extracellular space as well as the rapid replenishment of the releasable pool. Synthesis is critical to the longer-term replenishment of the releasable pool, especially when reuptake is concurrently inhibited. Decreases in serotonin are rescued by inhibiting action potential propagation with tetrodotoxin, implicating endogenous activity in depletion of neuronal serotonin. These results give insight into the possible effects of SSRIs on the serotonergic system and the important role that synthesis may play in this phenomenon as well as in overall

serotonergic neuron function. The have also paved the way for future use of *Drosophila* for large-scale genetic analysis of neurotransmitter dynamics. This dissertation was completed under the direction of Jill Venton, PhD, in the Department of Chemistry and Neuroscience Graduate Program.