Analytical tools propel discoveries about dopamine neurotransmission

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The goal of my laboratory has been to discover how dopamine regulation mechanisms exert their effects during real-time neuronal communication deep within the brain, especially during behavior. To approach this problem, we developed very small, carbon-based chemical sensors designed to measure physiological fluctuations in dopamine concentrations. At the time, changes in extracellular dopamine had only been measured as slow fluctuations in basal concentrations. When we first used these sensors in freely moving animals we were surprised to observe rapid, transient dopamine concentration changes. Introducing novel stimuli or psychostimulants altered the frequency of transients. In behaving animals, dopamine transients also became time-locked to reward retrieval, or the presentation of a reward-predicting cue. Over the last 15 years, studies have shown that dopamine transients are an important component of monoamine transmission. New properties of transients are still being described, such as previously unappreciated cross-hemispheric dopamine signaling. Remarkably, we find that a majority of dopamine transients are synchronous between hemispheres, concurring with the physiological synchrony that is observed in many parts of the brain. To explore the specific actions of dopamine at its receptors we developed a method to chemotype dopamine receptors in situ. We use a modified form of iontophoresis enabling controlled delivery of dopamine receptor agonists and antagonists locally to the site of the recording electrode. We monitor their effects at dopamine autoreceptors by examining how they alter dopamine release. By pairing electrochemical measurements with electrophysiology, we can also monitor effects on postsynaptic receptors and cell-firing without disturbing animal behavior. These methods are sufficiently quantitative to generate dose response curves in multiple dopamine-rich microenvironments. Chemotyping enables real-time observations of dopamine interacting with different receptor subtypes to mediate animal behavior. New tools also enable us to explore unexpected facets of neurochemical communication in disease models and monitor previously undescribed dopamine release during spreading depression. As these examples indicate, our tools have enabled exploration of novel properties of dopamine neurotransmission, and sets a firm foundation for understanding the role of dopamine in behavior.

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