

Myelin Plasticity in the Ventral Tegmental Area is Required for Opioid Reward

Valcin, B.; Pomrenze, M.B.; Malacon, K.; Drexler, R.; Rogers, A.E.; Shamardani, K.; Chau, I.J.; Taylor, K.R.; Ni, L.; Contreras-Esquivel, D.; Malenka, R.C.; Monje, M.

Stanford University

Drugs of abuse induce modifications in the reward system of the brain, rendering neural circuits amenable for developing substance-use disorders. All drugs of abuse, including opioids such as morphine, target the midbrain dopaminergic reward system and induce changes in synaptic transmission and neural circuit function. While a significant role for microglia and astrocytes in these neural circuit adaptations is becoming increasingly apparent, oligodendroglial lineage cells, a glial cell type that is particularly well positioned with its functions and interactions to contribute to addiction, remain unknown. Oligodendrocytes generate myelin which ensheaths axons to modulate conduction velocity and provide metabolic support to axons therefore playing a fundamental role in shaping neural transmission. A recently appreciated mechanism of neural circuit plasticity is mediated through activity-regulated changes in myelin that can tune circuit function and influence cognitive behavior. However, the role of myelin plasticity in drug-evoked neural circuit adaptations is yet to be elucidated.

We demonstrate that dopaminergic neuron activity-regulated myelin plasticity is a key modulator of dopaminergic circuit function and opioid reward. Oligodendroglial lineage cells respond to dopaminergic neuron activity evoked by either optogenetic stimulation of dopaminergic neurons, optogenetic inhibition of GABAergic neurons, or by administration of morphine. These oligodendroglial changes are evident selectively within the reward center ventral tegmental area (VTA), but not along the axonal projections in the medial forebrain bundle nor within the target nucleus accumbens (NAc). Increased dopaminergic neuron activity induces myelination on dopaminergic axons within the reward system in a circuit- and region-specific manner, affecting proximal axonal segments of dopaminergic neurons within VTA. Morphine- or cocaine-induced conditioned place preference (CPP), a test for associative reward learning, promotes oligodendrogenesis in VTA. Conditional genetic blockade of oligodendrogenesis abrogates both morphine-induced oligodendrogenesis and CPP acquisition, highlighting oligodendroglial cells as critical players in opioid reward-related behavior. Because reward learning is highly correlated with dopamine release in NAc, we measured dopamine changes in real-time during CPP behavior using fiber photometry. We found that morphine-induced oligodendrogenesis in VTA alters dopamine release dynamics at NAc, demonstrating that myelin plasticity can modulate neural network synchronization in reward circuitry, and change the neurotransmitter release dynamics required for an opioid reward. Our results identify myelin plasticity as a previously unappreciated feature of the activity-dependent modifications of reward circuit function that critically contribute to the behavioral reinforcing effects of opioids.