DART
DRUG ABUSE RESEARCH TRAINING

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Cocaine and memory: The Cell Type-Specific Role of NPAS4 in the Mouse Nucleus Accumbens

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Background: Drug seeking and relapse are driven, in part, by associations between the rewarding effects of drugs and the environment where the drug reward was experienced. Future exposure to this environment leads to an increase in drug-seeking behavior, which is partially driven by plasticity within the nucleus accumbens (NAc). The majority of neurons in the NAc are dopamine D1 or D2 receptor-expressing medium spiny neurons (MSNs), but the mechanisms mediating drug-context memories in these cell types is not well understood. We previously found that cocaine activates a sparse population of cells within the NAc that express the immediate early gene transcription factor, neuronal PAS domain 4 (NPAS4). NPAS4 has been shown to control the downstream expression of various genes involved in cocaine-related memories. When NPAS4 is removed from the NAc, there is a significant reduction in cocaine conditioned place preference (CPP), suggesting that the animals have trouble associating the environment with the cocaine reward experience. Given this, we hypothesized that NPAS4 acts in a cell type-specific manner within the NAc to promote cocaine-conditioned learning and memory. **Experiment 1: Methods:** To identify cell types inducing NPAS4, transgenic mice expressing cell type-specific labels were exposed to a drug-paired environment, followed by IHC for NAc Npas4. **Results:** We found that ~50% of NPAS4-positive cells are D1R or D2R-expressing MSNs. **Experiment 2: Methods:** To determine which cell type requires NPAS4 for cocaine-reward associations, we reduced NPAS4 expression in D1- or D2-MSNs and performed cocaine CPP. **Results:** D2-NPAS4 knockout mice showed reduced CPP, indicating that NPAS4 expression within D2-MSNs is required for the development of cocaine CPP. **Conclusion:** Our findings are consistent with previous literature suggesting a role for activated D2-MSNs in decreased cocaine-reward learning, and NPAS4 seems to be a key player in dampening the activity of these neurons to promote cocaine-conditioned behaviors. Future studies are being conducted to investigate the mechanism of D2-MSN activation after Npas4 knockdown.