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Baseline Characterizations of Novel D1R-CRISPRa and A2A-CRISPRa Mouse Lines

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It is critical to identify the underlying molecular mechanisms responsible for long-lasting changes in neural function that promote drug-seeking. The two main cell types in the nucleus accumbens(NAc), D1R-spiny projection neurons (D1R-SPNs) and D2R-spiny projection neurons (D2R-SPNs) have distinct roles in regulating reward-related and drug-seeking behaviors. Previous studies have demonstrated that distinct molecular mechanisms cause cell-type specific functions in behavior, however it is still unclear what transcriptional changes in SPNs are required for drug-seeking.

CRISPR-dCas9 viral systems allow for precise and spatially-controlled manipulation of neural gene expression, however there are limitations to these viral-based approaches related to packaging dCas9 fusion proteins. In an effort to overcome these limitations, here we characterized two mouse lines, D1R-dCas9p300 and A2A-dCas9p300, which would allow for cell-type specific transcriptional activation of specific gene targets with gene-specific guide RNAs (gRNAs). Without any gRNA, D1R- dCas9p300 mice exhibit several behavioral impairments, including repetitive spinning behavior and hyperlocomotion to their wild-type litter mates. However, A2A-dCas9p300 do not exhibit any changes in anxiety-like behavior, locomotion or operant food learning in comparison to their wild-type litter mates. On-going experiments to examine the underlying causes for this behavioral phenotype include differences in baseline gene expression and cellular function in the NAc. These data suggest considering potential limitations in CRISPR-dCas9 when implementing the system in transgenic mouse lines.