Discoveries and implications of molecular and cellular basis of substance use disorders

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Substance use disorders have devastating life consequence and are a huge social and economic burden to society. The behavioral consequences of drug use are mediated through long- term molecular adaptations in the brain. Thus, there is urgent need for effective treatment strategies that target these molecular adaptations. A major impediment to developing better treatments is a lack of knowledge of the molecular substrates that underlie selective brain circuitry and cell subtype adaptations, in the heterogeneous central nervous system. My research program aims to close this gap by elucidating molecular pathway processes in specific reward and basal ganglia circuit cell subtypes after psychostimulant and opioid exposure.

Methods: My laboratory uses intersectional mouse genetic and adeno-associated virus (AAV) tools to identify, probe the transcriptome, and manipulate selective reward and basal ganglia circuits in the brain, with chronic drug exposure. We employ models of substance use disorder, including cocaine intravenous self-administration and fentanyl access in the home cage drinking solution, to probe transcriptome changes in reward circuit and basal ganglia neuron subtypes. Using AAVs, including CRISPR tools, to alter gene transcripts in specific cell subtypes; we then probe the impact of these molecules on drug seeking and other behavioral states after drug exposure.

Results: Our studies have identified distinct transcriptional processes and their molecular targets that underlie cell subtype adaptations after cocaine or fentanyl exposure. Using AAVs to reverse these cell subtype molecular processes, we observe reduced drug seeking or disruption of other behaviors after drug exposure.

Discussion: Our studies provide a comprehensive understanding into the complex molecular orchestra that mediates cellular and circuit adaptations in the brain after psychostimulant and opioid exposure. These findings provide a foundation of cell subtype mechanisms with preclinical drug exposure that contribute to a broader understanding of the complex neurobiological processes in the heterogeneous brain in substance use disorders.

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