DRUG REINFORCEMENT IMPAIRS COGNITIVE FLEXIBILITY VIA INHIBITING STRIATAL CHOLINERGIC NEURONS

H Gangal[1, 2], X Xie[1], Z Huang[1], Y Cheng[1], X Wang[1], J Lu[1], X Zhuang[1], A Essoh[1], Y Huang[1, 2], R Chen[1, 4], L. N. Smith[1, 2], R. J. Smith[2, 3], J Wang[1, 2, *]

[1]Department of Neuroscience and Experimental Therapeutics, College of Medicine, Texas A&M University Health Science Center

[2]Institute for Neuroscience, Texas A&M University

[3]Department of Psychology and Brain Sciences, Texas A&M University

[4]Department of Toxicology, Texas A&M University

Reinforcing behaviors are associated with deficits in cognitive flexibility, wherein a subject is required to extinguish an old behavioral strategy and explore a new one if the old strategy is no longer rewarding. The neural circuitry underlying this flexibility deficit is not known. Cholinergic interneurons (CINs) in the dorsomedial striatum (DMS) are known to play a critical role in behavioral flexibility. In this study, we used chronic cocaine and alcohol exposure as reinforcement models to investigate the role of DMS CINs in the reversal of instrumental learning. We found that chronic cocaine or alcohol exposure increased GABAergic inputs to DMS CINs and reduced their spontaneous firing activity. Morphological and physiological studies demonstrate that the major GABAergic input to the DMS CIN originates from the direct-pathway medium spiny neurons (dMSNs) and this input was potentiated by chronic cocaine or alcohol exposure. To artificially mimic the inhibition of DMS CINs, we employed chemogenetic and time-locked optogenetic approaches to downregulate DMS CIN activity, which led to deficits in behavioral flexibility. The dMSN to SNr (Substantia Nigra Reticulata) pathway is known to mediate reinforcing behaviors. Functionally, we test that dMSNs also send collateral inhibitory connections to the CINs. Therefore, we propose that, on one hand dMSN to SNr pathway causes reinforcement, at the same time dMSN to CIN pathway leads to inflexibility, thus providing the neural substrate for deficits in flexibility caused by reinforcing behaviors.