Relapse to cocaine self-administration is regulated by medial habenula Nr4a2

Jessica E Childs, Samuel Morabito, Sudeshna Das, Caterina Santelli, Kelly Kusche, Vanessa Alizo Vera, Fairlie Reese, Rianne R Campbell, Dina P Matheos, Vivek Swarup, Marcelo A Wood

Recent studies have implicated the medial habenula in cocaine-associated behaviors, yet the role of the medial habenula in regulating reinstatement of cocaine self-administration remains unknown. The lab recently identified the histone deacetylase 3 (HDAC3; a powerful epigenetic regulator of gene expression) target gene, nuclear orphan receptor subfamily4 groupA member2 (*Nr4a2)*, as an important regulator of cocaine-associated behavior. NR4A2 is a transcription factor that regulates aspects of dopamine signaling during development, and is densely expressed in the medial habenula. Further, *Nr4a2* expression is altered by cocaine exposure. We hypothesized that reducing medial habenula NR4A2 function would reduce reinstatement of cocaine self-administration.

Methods: The dominant negative form of NR4A2 (NURR2C) was expressed in medial habenula cholinergic neurons of ChAT-Cre mice trained to self-administer cocaine. To facilitate reinstatement behavior, an incubation of craving model was used in which animals were given 30 days of homecage withdrawal after 12 days of self-administration. On the last day of testing, animals were extinguished for 5 hours, and were then re-exposed to drug-associated cues to drive cued reinstatement. for single nucleus RNA sequencing. To develop a more in-depth understanding of the medial habenula response to reinstatement of cocaine-seeking, one hour after reinstatement, brains were collected and flash frozen for single nuclei RNA sequencing.

Results: While there were no differences in rates of cocaine self-administration or extinction, NURR2C mice had dramatically reduced reinstatement compared to GFP controls. After reinstatement, transcriptome perturbation analysis revealed that clusters of both medial and lateral habenula neurons are highly perturbed by the medial habenula NURR2C manipulation.

Discussion: These findings necessitate consideration of the medial habenula and *Nr4a2* as pivotal components of the reward circuit and identify the nuclear orphan receptor NR4A2 (with recently identified exogenous ligands) as a therapeutic target for medicinal chemistry to develop agonists/antagonists that may be relevant for addiction treatment. Lastly, transcriptomic changes in lateral habenula nuclei indicate more interplay between the medial and lateral habenula than previously thought, which needs further study.

References:

Rogge, G. A., Singh, H., Dang, R., Wood, M.A. (2013). HDAC3 is a negative regulator of cocaine context-associated memory formation. J. Neurosci. 33(15) 6623–32. 10.1523/JNEUROSCI.4472-12.2013.

López, A. J., et al. (2019) Epigenetic regulation of immediate-early gene Nr4a2/Nurr1 in the medial habenula during reinstatement of cocaine-associated behavior. Neuropharm. 153, 13-19. 10.1016/j.neuropharm.2019.04.016.

Morabito, S., Miyoshi, E., Michael, N., Shahin, S, Martini, A.C., Head, E., Silva, J., Leavy, K., Perez-Rosendahl, M., Swarup, V. (2021). Single-nucleus chromatin accessibility and transcriptomic characterization of Alzheimer's disease. Nat. Genet. 53, 1143–1155.

Funding for this work was provided by UCI startup funds, NIA grant 1RF1AG071683 and the Adelson Medical research foundation (AMRF), NIDA grants R01DA047441 and R01DA047981, and NIDA fellowship F32 DA055438 as well as support from the George E. Hewitt Foundation.