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Single-Nucleus Transcriptomic Analysis Reveals Sex-Specific Hippocampal Cell-Type Responses to Nicotine Vapor Exposure and Withdrawal

Nicotine withdrawal induced hippocampal dysfunction contributes to both affective dysfunction and cognitive deficits symptomologies, both of which are major predictors of lapse to smoking behavior. Therefore, we investigated the sex- and cell-type specific impacts of chronic nicotine vapor exposure and spontaneous withdrawal on the murine hippocampus. Nicotine was administered via a custom-built passive administration E-vape system (La Jolla Alcohol Research, Inc.). We exposed adult mice to nicotine vapor or air for 14 sessions, with each session lasting 12hr from 2000 to 0800 the next morning. Mice marked for 24hr withdrawal did not receive nicotine vapor exposure during the 14th session. Mice were sacrificed 2 hours after the 14th exposure session and hippocampal tissues were collected. We performed single-nucleus RNA-sequencing (10x Genomics) on the hippocampi of air control (Air), chronic nicotine (Nic), and 24hr withdrawal (WD) mice (N=3 treatment*sex). A total of 27,992 cells passed quality control metrics and 23 cell types were identified through clustering analysis. Differential expression analysis (WD vs Air, Nic vs Air, and WD vs Nic) was performed on males and females separately, identifying a total of 14,488 and 879 differentially expressed genes in males and females respectively. In both sexes glutamatergic cells experienced the largest alterations in transcriptome, with cells from the dentate gyrus and dorsal CA1/3 most impacted in males and cells in the prosubiculum and subiculum were most impacted in females. Further, we constructed cell to cell communication networks which suggested Lamp5+ GABAergic interneurons may act as a hub of dysfunction in males, while a loss of Oligodendrocytes mediated signaling may contribute to female hippocampal dysfunction. These preliminary results suggest a possible sex convergence process where nicotine withdrawal induced hippocampal dysfunction is mediated by sex specific cell types, but results in similar affective dysfunction and cognitive deficits during withdrawal in both sexes.

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