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Understanding the molecular basis of nicotine addiction by integrative functional genomic analyses in a rat model and hiPSC-derived DA neurons

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Cigarette smoking is the largest preventable risk factor for mortality and a primary risk factor for many chronic diseases. Tobacco consists of more than 4,800 compounds, among which nicotine is responsible for the addictive nature of smoking. Repeated exposure to nicotine leads to sensitization, enhancing its self-administration. We aimed to identify transcriptome profile in nicotine addiction-relevant rat brain regions [ventral tegmental area (VTA); nucleus accumbens (NAc)] and in dopamine (DA) neurons derived from human-induced pluripotent stem cells (hiPSCs). We used F1 progeny of F344 and BN rat strains to analyze nicotine-associated trancriptome changes. Male and female F1s showed a dose-dependent increase in nicotine-induced locomotion; however, only males exhibited nicotine sensitization. We performed the transcriptome profiling of the F1s brains to determining whether these are similar to those observed in hiPSC-derived nicotine treated midbrain DA neurons. Compared to human postmortem brains from the Genotype-Tissue Expression and BrainSpan projects, hiPSC-DA neurons showed strong expression correlation with brain regions relevant to addiction, supporting the validity of hiPSC-DA neurons for the transcriptomic study of nicotine addiction. We subjected the hiPSC-derived DA neurons to microelectrode analysis and showed that acute nicotine treatment increases neuronal firing. Transcriptomic analysis suggests that nicotine sensitization is more associated with NAc core, while self-administration is more associated with VTA. Differentially expressed genes associated with sensitization and self-administration are relevant to nicotine addiction pathways. Identifying novel gene targets relevant to nicotine addiction will increase understanding of the neurobiology of human nicotine abuse and inform the development of more effective therapeutics.