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Role of GSCAN Identified Genes in the Astrocytic Response to Nicotine

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Improved understanding of nicotine neurobiology is needed to reduce or prevent chronic addiction, the detrimental effects of nicotine withdrawal, and increase successful cessation of use. Nicotine use Genome wide association studies (GWAS) suggest an astrocytic role for nicotine responses. Previously, we found that AKT2 expression is restricted to astrocytes in mice and humans and may play a role in the nicotinic responses of astrocytes. To identify astrocyte-expressed genes that may be relevant to nicotine use in humans, we used TWAS results from the GWAS & Sequencing Consortium of Alcohol and Nicotine use (GSCAN) along with astrocyte expression data to identify genes of interest (GOI) to assess potential astrocyte involvement in nicotine responses. Using a CRISPR approach to knock down GOI expression, we are screening 25-50 GSCAN-identified genes that show expression in human and mouse astrocytes. Using area analysis, we are assessing the role of the GOI on astrocyte size and morphology in primary mouse astrocytes following nicotine treatment. The screen will establish a GOI for generating a new mouse model to assess the role of the astrocyte-expressed gene on nicotine behaviors and *in vivo* astrocyte response to nicotine. Behavioral assessments of astrocyte specific AKT2 deficient mice were conducted, revealing impacts of AKT2 loss on behaviors relevant to nicotine use providing proof of principle results for our ongoing GOI studies. These results will allow for the identification of potential novel drug targets and will improve the current understanding of the astrocytic response to nicotine.