Disruption of Hippocampal NRG3-ErbB4 Signaling Ablates Nicotine Withdrawal-Induced Anxiety-like Behaviors

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Addiction to nicotine and the ability to quit smoking are influenced by genetic factors. Identifying altered gene networks and how those networks contribute to nicotine dependence and withdrawal will only accelerate therapeutic development of new smoking cessation aids. Previous work from our lab and that of our collaborators demonstrate that SNPs across the Neuregulin 3 (NRG3) gene and its cognate receptor, ERBB4, are associated with smoking cessation outcomes. Our aim is to interrogate the functionality of this signaling pathway during nicotine and withdrawal, and examine how nicotine-induced changes in NRG3 and ErbB4 may contribute to anxiety-like withdrawal phenotypes in genetically modified mice. Our current studies show that both mRNA and protein levels of NRG3 and ErbB4 are upregulated selectively in the ventral hippocampus during nicotine and withdrawal, suggesting that aberrant NRG3 signaling in this structure may underlie select nicotine withdrawal phenotypes. While the dorsal hippocampus has a well-documented role in learning and memory, the ventral hippocampus contributes to affective and anxiety responses. To evaluate the role of ventral hippocampal NRG3-ErbB4 signaling in mediating nicotine withdrawal anxiety-like phenotypes, we disrupted this pathway via conditional hippocampal ErbB4 deletion in ErbB4-floxed mice and evaluated nicotine withdrawal anxiety-like behaviors. We found that ErbB4 deletion results in the ablation of withdrawal-induced anxiety-like behavior as measured by both the novelty-induced hypophagia test and the open field exploration task, demonstrating a potential role of this signaling pathway in mediating anxiety-related withdrawal phenotypes. Ongoing studies are utilizing single molecule fluorescence in situ hybridization coupled with immunofluorescence to identify the underlying cell type and circuit-specific modulation of NRG3 signaling by nicotine within the hippocampus of these animals. Collectively, these data will provide insight into NRG3-ErbB4 dependent mechanisms underlying nicotine withdrawal-induced phenotypes.