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Genetic Disruption of Neuregulin Signaling in the PFC: Insights into Nicotine Exposure and Withdrawal

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Understanding the genetic underpinnings of nicotine dependence is crucial for developing targeted smoking cessation therapies. Our lab has identified the gene Nrg3 and its receptor tyrosine kinase, ErbB4, as key regulators of anxiety-like behaviors during nicotine withdrawal (WD) in a region-specific manner. The prefrontal cortex (PFC) plays a critical role in emotional regulation, decision-making, and cognitive functions, all of which are affected by nicotine use and withdrawal. This study investigates the role of PFC-specific ErbB4 signaling in the presentation of nicotine- or WD-related deficits.

Using an ErbB4-flox mouse model, we performed site-specific knockdown of ErbB4 in the medial PFC (mPFC) and subjected mice to chronic nicotine treatment followed by 24hr spontaneous WD. Behavioral assays indicate possible sex-specific differences in anxiety-like responses due to treatment. mPFC tissue was collected and both qPCR and RNAscope were employed to validate, characterize, and examine expression and co-localization of key targets, including Nrg3 and ErbB4. Results show a concurrent reduction in both ErbB4 and Nrg3 expression following ErbB4 knockdown, an atypical receptor-ligand relationship that warrants further exploration. Additionally, bulk RNAseq of murine PFC tissue from saline, nicotine, and 24hWD conditions revealed differentially expressed genes potentially involved in nicotine use and WD, providing a molecular framework for identifying alternative targets for further transcriptomic investigation. These findings offer a genetic mechanism for understanding nicotine dependence and inform future studies aimed at therapeutic targeting of the PFC in nicotine dependence.

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