

Nicotinic Modulation of the Choroid Plexus and Altered Circulating MicroRNA Expression During Chronic Nicotine Self-Administration

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Given the recent identification of circulating microRNAs (miRNAs) in the cerebrospinal fluid and documented effects of nicotine on the secretion of protein from the choroid plexus, we sought to determine whether chronic nicotine self-administration alters the expression of choroid plexus derived miRNAs. First, we investigated whether nicotine could act on the choroid plexus via a direct mechanism. We found that choline acetyltransferase and nicotinic acetylcholine receptor (nAChR) subunits are expressed at varying levels across the choroid plexus ventricular sites. These data support the notion that endogenous cholinergic signaling can regulate the function of choroid plexus ependymal cells. Next, we examined whether chronic intravenous nicotine self-administration would alter the expression of nAChR subunits and transthyretin, a choroid plexus-specific protein. Interestingly, we found that transthyretin expression was selectively increased in choroid plexus derived from the dorsal third ventricle, but not in tissue from the lateral or fourth ventricles. Given the localization of the dorsal third ventricle adjacent to the habenula, these data suggest that nicotine can selectively alter signaling factors released into the cerebrospinal fluid for potential integration into the habenula. This was further supported by the finding that labeled exosomes injected into the dorsal third ventricle integrate into the neuronal parenchyma. Finally, we conducted a miRNA microarray and identified several miRNAs differentially expressed in the choroid plexus and cerebrospinal fluid during chronic nicotine self-administration. Taken together, these data support the hypothesis that nicotine alters extracellular transfer of miRNAs, which could potentially lead to downstream changes in neuronal gene expression mediating the drug dependence state.

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