Nicotine-Mediated Modulation of Choroid Plexus Function and Altered Circulating MicroRNA Expression

Valeria Lallai and Christie D. Fowler

Department of Neurobiology and Behavior, University of California Irvine,
Irvine, CA 92617, USA

Circulating extracellular microvesicles have been recently identified to contain a variety of signaling factors, such as proteins, enzymes, DNA and RNA species. Interestingly, nicotine has been proposed to modulate choroid plexus function, and thus, nicotine-mediated release of factors into the cerebrospinal fluid (CSF) may underlie the drug's effects in the brain. In the current studies, we sought to determine whether nicotine acts directly on the choroid plexus and whether chronic nicotine self-administration would alter the expression of choroid plexus-derived circulating miRNAs. In the first series of studies, choline acetyltransferase (ChAT) and nicotinic acetylcholine receptor (nAChR) subunit mRNA expression were examined in the choroid plexus. Next, rats underwent chronic intravenous nicotine or saline self-administration, and choroid plexus tissue and CSF were assessed for changes in miRNAs and mRNA expression of nAChR subunits and the choroid plexus-specific protein transthyretin. Our findings reveal the expression of ChAT and nAChR subunits in the lateral, dorsal third and fourth ventricle choroid plexus sites, indicating that endogenous cholinergic signaling mechanisms regulate the function of choroid plexus ependymal cells. Transthyretin expression was selectively increased in choroid plexus derived from the dorsal third ventricle, but not in tissue from the lateral or forth ventricles. Finally, miRNAs were found to be differentially expressed in the choroid plexus and exosomal fractions of the CSF with chronic nicotine self-administration, and these findings were further validated with *in vitro* studies. These data support the hypothesis that nicotine alters extracellular transfer of miRNAs, which could potentially lead to downstream changes in neuronal gene expression. In addition to nicotine dependence, findings from these studies may provide insight into normal physiological function and other pathological disease states.

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