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Nicotine Mediates Extracellular Vesicle RNA Signaling in the Brain

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Circulating extracellular vesicles (EVs) in the cerebrospinal fluid (CSF) contain a variety of signaling factors, including RNA transcripts, proteins and enzymes. While EVs have been implicated in several cell-to-cell signaling contexts, the vast majority of prior studies are based on cell culture conditions, which do not represent the complexity of signaling in the brain. In this talk, I will discuss our recent findings demonstrating that nicotine alters EV RNA transport in the CSF *in vivo*. Although nicotine appears to decrease the overall density of CSF EVs, increased expression of multiple small RNA transcripts and EV- associated protein markers are found, suggesting a biased signal-to-noise ratio. Interestingly, one target miRNA, mir-204, was found to be differentially expressed in both the CSF and choroid plexus of the dorsal third ventricle, a tissue that releases EVs into the brain ventricle. Nicotine's direct actions on EV mir-204 cargo loading and/or release could be prevented by administration of the nicotinic receptor antagonist, mecamylamine. Further, injection of labeled EVs into a recipient brain provides evidence that CSF- localized EVs integrate into the neuronal parenchyma, including habenular neurons. Finally, our most recent studies have demonstrated that dopaminergic neurons also release EVs *in vivo,* and our current investigations are isolating and identifying RNA transcripts present in this EV subpopulation circulating in the extracellular environment. Taken together, our novel findings reveal that nicotine intake alters extracellular RNA communication in the brain, which has important implications for both normal and pathological disease states.