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**THC- and Nicotine-Induced Changes in Central and
Peripheral Extracellular Vesicle RNA Cargo**

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Given the recent increase in cannabis use in the US with legalization across states, there is an urgent need to more clearly understand the effects of THC on biological signaling mechanisms. Therefore, in these studies, we investigated the effects of THC aerosol inhalation on extracellular vesicle signaling in the brain and periphery, and we also compared these profiles with another drug commonly co-used with THC, nicotine. Adult Wistar rats were randomly assigned into 6 vapor-exposure treatment groups: control, low dose THC, high dose THC, nicotine, co-exposure nicotine/low dose THC, and co-exposure nicotine/high dose THC. Each group consisted of subgroups based on sex and acute (1 session) or chronic (14 daily sessions) of exposure. CSF and blood plasma were collected, and extracellular vesicles were extracted and then examined with small RNAseq. We found miRNAs in both serum and CSF extracellular vesicles, with 316 common in the blood and brain and 45 unique to the brain. Differential effects were found in CSF miRNAs following acute or chronic treatment, which was most significantly evident in the groups exposed to both THC doses. In the blood serum, an interesting sex-specific effect was observed, which was particularly evident in the groups exposed to nicotine or co-exposed to nicotine/high dose THC. Taken together, these findings provide evidence that vapor exposure to nicotine and/or THC, both acutely and chronically, induces differential release of RNA cargo in extracellular vesicles with sex-specific profiles.