

Microglial Adaptations to Chronic Nicotine in the Cerebellum: Proteomic Evidence for Neuroimmune Vulnerability

Smoking is a major public health concern with widespread effects on multiple organ systems, including the immune system. Chronic nicotine exposure can alter immune cell function through nicotinic receptors expressed on peripheral macrophages and microglia in the brain. Recent evidence indicates that the cerebellum is impacted by nicotine, contributing to motor and non-motor outcomes, during drug use. In this study, we investigated the effect of chronic nicotine on microglia proteomes in the adult mouse cerebellum. Microglia were isolated by fluorescence-activated cell sorting (FACS) based on CD11b^{high} CD45^{low/intermediate} expression from male and female mice (n = 9 per group) exposed to 200 µg/mL nicotine (dissolved in 2% saccharin drinking water) for 30 days. Proteomic analysis was performed using liquid chromatography electrospray ionization (LC-ESI) mass spectrometry (MS) comparing the effect of nicotine relative to vehicle control. Our results reveal a sex-dependent effect of nicotine on microglial proteomes. While both males and females exhibited histone-related genomic responsiveness to nicotine, males demonstrated enrichment in cytoskeletal and metabolic proteins, and females showed complement-protein adaptations. The microglial proteome in male mice displayed nicotine-related adaptations in proteins that can contribute to neurodisorders including Huntington's disease and amyotrophic lateral sclerosis (ALS), of which smoking is a known risk factor. Together, these results highlight an effect of nicotine on the proteome of microglia providing insights into pathways that may contribute to smoking-related behaviors and disease.

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