Electronic-Cigarette Induces Dysregulated Repair Response and Extracellular Matrix Remodeling in Mouse Lung Via α7 Nicotinic Acetylcholine Receptor

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Rationale: Electronic cigarettes (e-cigs) are considered as less harmful alternative to tobacco smoke. However, there is very little knowledge on the pulmonary toxicology and respiratory health effects of e-cig exposure, especially on lung dysregulated repair and extracellular matrix (ECM) remodeling mechanisms. We hypothesized that sub-chronic (one month) e-cig exposure induces dysregulated repair and ECM remodeling process possibly via α7 nicotinic acetylcholine receptor (α7nAChR) in a sex-dependent manner. Methods: Adult C57BL/6J mice (WT) and α7nAChR knock out (KO) mice were exposed to e-cig aerosol containing propylene glycol (PG) with or without nicotine (24 mg/mL) for 30 days (2 hrs/day, 5 days/week). Total RNA and protein were isolated from mouse lungs for NanoString and Western blot analysis. Results: Sub-chronic e-cig aerosol exposure with or without nicotine caused dysregulation of several different matrix metalloproteinases such as MMP2, MMP8, and MMP9 in both male and female mice both at the level of protein abundance and gene expression. Further, MMP12 protein abundance was significantly increased in male mice only. Surprisingly, both MMP9 and MMP8 protein abundance were significantly decreased and MMP2 protein levels were increased in both male and female mice exposed to PG alone. Additionally, we found significantly downregulated protein abundance of tissue inhibitor of metalloproteinases (TIMP3), a negative regulator of MMP activity, was in female exposed to e-cig with or without nicotine. Furthermore, e-cig aerosol exposure significantly increased the protein levels of COL1A2 but decreased COL1A1 and fibronectin in both male and female mice. The α7nAChR KO mice exposed to e-cig aerosol showed attenuation of COL1A2 and fibronectin in male, but not in female mice. Similarly, protein levels of MMP2 and MMP12 were modulated in male mice. The rest of the protein abundances were not significant affected by α7nAChR KO. Conclusion: Overall, this study indicates that mice exposed to sub-chronic e-cig aerosol containing PG alone can cause significant effects on both dysregulated repair responses and ECM remodeling processes at the mRNA and protein levels possibly via α7nAChR in a sex-dependent manner. These findings support the long-term respiratory health effects of e-cig exposure leading to altered dysregulated repair responses and ECM remodeling of the lung in a sex-dependent manner. This work was funded by the NIH 1R01HL135613

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