Effect of Diet-induced Obesity and Genetic Deficiency of G Protein-coupled Receptor 1 on Ozone-induced Increases in Airway Responsiveness

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RATIONALE: Serum levels of chemerin, a non-chemokine chemoattractant for natural killer cells, macrophages, and plasmacytoid dendritic cells, are increased in obese humans and rodents. Obese mice genetically deficient in G protein-coupled receptor 1 (Gpr1), one of three seven-transmembrane domain receptors for chemerin, exhibit diminished insulin secretion (Rourke et al., J Endocrinol, 2014). Hyperinsulinemia, a common sequela of obesity, exacerbates airway responsiveness in obese rats (Nie et al., Am J Respir Cell Mol Biol, 2014), and we previously reported that increases in airway responsiveness induced by acute inhalation exposure to ozone (O_3), a criteria pollutant, occupational irritant, and non-atopic asthma stimulus, are enhanced in obese mice that display hyperinsulinemia. Based on these observations, we hypothesized that diminished insulin secretion in obese mice genetically deficient in Gpr1 would lessen the severity of ozone-induced increases in airway responsiveness. METHODS: Wild-type C57BL/6J and mice genetically deficient in Gpr1 (Gpr1-deficient mice) were fed standard chow or a diet consisting of 60 kcal % fat in the form of lard (high-fat diet; HFD) from weaning until 30 weeks of age. At 30 weeks of age, mice were exposed to either filtered room air or O_3 (2 parts per million) for three hours. Twenty-four hours following cessation of exposure, mice were anesthetized, tracheostomized, and mechanically ventilated to measure responses to aerosolized acetyl-β-methylcholine chloride (methacholine) for total respiratory system resistance (R_{RS}) using the forced oscillation technique. RESULTS: Wild-type and Gpr1-deficient mice fed a HFD weighed approximately 72 and 59% more, respectively, than genotype-matched mice fed standard chow. In air-exposed mice fed a HFD, responses at the highest dose of methacholine (100 mg/ml) for R_{RS} were significantly lower in Gpr1-deficient as compared with wild-type mice. In comparison with genotype- and diet-matched air-exposed controls, exposure to O_3 increased airway responsiveness in wild-type and Gpr1-deficient mice. However, in mice fed a HFD, responses at the highest dose of methacholine for R_{RS} were again significantly attenuated in Gpr1-deficient as compared with wild-type mice. CONCLUSIONS: In mice with dietary obesity, Gpr1 has nominal effects on innate airway responsiveness as well as increases in airway responsiveness induced by acute inhalation exposure to O_3. Nevertheless, from these data, we cannot conclude if the observed phenomena are mechanistically coupled to the ability of Gpr1 to influence insulin secretion in the presence of obesity.

This abstract is funded by: CDC/NIOSH