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Airway nerve mediated reflex hyperresponsiveness in offspring of obese mothers

Kayla R. Williams, Gina N. Calco, Zhenying Nie.
Kayla Williams

Keywords

Maternal obesity, hyperinsulinemia, hyperinnervation, airway hyperresponsiveness

Abstract

Background: Children born to obese mothers are at a higher risk of developing asthma, but the underlying mechanisms are unclear. We used a diet induced maternal obesity mouse model to investigate the effects of maternal obesity on offspring airway reflex responsiveness.

Method: 6-week wild-type FVB female mice were fed either high-fat diet (HFD) or regular chow (RCD) for 8 weeks before breeding and throughout pregnancy and lactation. All offspring were fed a regular chow diet. Airway hyperresponsiveness was measured in anesthetized, paralyzed, and ventilated 16-week offspring. Tracheas were collected from 3- and 16-week offspring. Samples were fixed, stained for the pan neuronal marker PGP9.5, optically cleared and imaged using confocal microscopy. 3D remodels of nerve architecture were created using IMARIS software for analysis.

Result: Dams on a HFD had higher body fat when compared to dams on RCD, indicating diet induced maternal obesity. Bronchoconstriction induced by inhaled 5-hydroxytryptamine was significantly increased in 16-week offspring of HFD dams vs. offspring of dams fed RCD ($p<0.05$). Increased bronchoconstriction was blocked by vagotomy, indicating airway nerves mediate this reflex hyperresponsiveness. Epithelial sensory nerve density was significantly increased in both 3- and 16-week-old offspring of HFD dams compared to offspring of RCD dams. Substance-P, a neuropeptide can cause bronchoconstriction by directly binding to neurokinin-1 receptors on airway smooth muscle or indirectly by potentiating nerve function through neurogenic inflammation. Substance-P was significantly increased in offspring from dams on a HFD.

Conclusion: We have demonstrated that intrauterine exposure to maternal obesity changes the structure, neurotransmitter content, and function of airway epithelial nerves in offspring. We show that maternal obesity increases airway sensory innervation in offspring, leading to increased airway hyperresponsiveness.