Ultrafine particles affect the balance of endogenous pro- and anti-inflammatory lipid mediators in the lung: in-vitro and in-vivo studies.

Abstract: Exposure to ultrafine particles exerts diverse harmful effects including aggravation of pulmonary diseases like asthma. Recently we demonstrated in a mouse model for allergic airway inflammation that particle-derived oxidative stress plays a crucial role during augmentation of allergen-induced lung inflammation by ultrafine carbon particle (UfCP) inhalation. The mechanisms how particle inhalation might change the inflammatory balance in the lungs, leading to accelerated inflammatory reactions, remain unclear. Lipid mediators, known to be immediately generated in response to tissue injury, might be strong candidates for priming this particle-triggered change of the inflammatory balance. We hypothesize that inhalation of UfCP may disturb the balance of pro- and anti-inflammatory lipid mediators in: i) a model for acute allergic pulmonary inflammation, exposing mice for 24 h before allergen challenge to UfCP inhalation (51.7 nm, 507 µg/m3), and ii) an in-vitro model with primary rat alveolar macrophages (AM) incubated with UfCP (10 µg/1 x 106 cells/ml) for 1 h. Lungs and AM were analysed for pro- and anti-inflammatory lipid mediators, namely leukotriene B4 (LTB4), prostaglandin E2 (PGE2), 15(S)-hydroxy-eicosatetraenoic acid (15(S)-HETE), lipoxin A4 (LXA4) and oxidative stress marker 8-isoprostane by enzyme immunoassays and immunohistochemistry. In non-sensitized mice UfCP exposure
induced a light non-significant increase of all lipid mediators. Similarly but significantly in rat AM all lipids mediators were induced already within 1 h of UfCP stimulation. Also sensitized and challenged mice exposed to filtered air showed a partially significant increase in all lipid mediators. In sensitized and challenged mice UfCP exposure induced highest significant levels of all lipid mediators in the lungs together with the peak of allergic airway inflammation on day 7 after UfCP inhalation. The levels of LTB4, 8-isoprostane and PGE2 were significantly increased also one day after UfCP exposure. Immunohistochemistry localized highest concentrations of PGE2 especially in AM one day after UfCP exposure. Our results suggest that UfCP exposure affects the balance between pro- and anti-inflammatory lipid mediators. In allergic mice, where the endogenous balance of pro- and anti-inflammatory mediators is already altered, UfCP exposure aggravates the inflammation and the increase in anti-inflammatory, pro-resolving lipid mediators is insufficient to counterbalance the extensive inflammatory response. This may be a contributing mechanism that explains the increased susceptibility of asthmatic patients towards particle exposure.

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