

Exposure To Titanium Dioxide (TiO₂) Nanoparticles Increases Airway Reactivity And Neurogenic Inflammation In Rodent Lungs

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Environmental exposure to nanoparticles (defined as particulate matter, PM, having one dimension < 100 nm) has been associated with an increased risk of childhood and adult asthma. The fast-paced progression of nanotechnology has resulted in an increasing production and diffusion of nanomaterials which have peculiar chemical and physical properties compared to the same larger-sized material. Their higher surface area per unit mass ratio has been shown to result in a greater bioavailable dose in the peripheral lung and, therefore, an increased potential for biological interaction. In a previous study, we have shown that exposure to nanoparticles of TiO₂ (an immunological inert control material) up-regulates the expression of the prototypical neurotrophin nerve growth factor, NGF, in the lungs of weanling rats (2 week-old). Neurotrophins are key regulatory components of neuronal plasticity and responsiveness and control the expression of neuroregulatory peptides, such as substance P (SP), which are associated with abnormal airway responses including bronchoconstriction and hyperresponsiveness. In this study, we investigated the airway responses to inhaled methacholine following in vivo exposure to TiO₂ nanoparticles. Weanling Fisher F344 rats (2 week-old; n=6) were exposed to TiO₂ nanoparticles (particle size 100 nm) at a concentration of 12 mg/m³ for 5.6 hours a day for three consecutive days, achieving a cumulative lung burden of 100 mg of particulate. An equal number of age-matched control animals were exposed to filtered air according to the same protocol. One hour after the end of the last exposure, the airway responses to methacholine challenge (2.5, 5.0, 10.0 mg/ml) were obtained by using a newly developed acoustic whole-body plethysmograph which provided measurement of specific airway resistance (sRaw) in unrestrained rats comparable with those obtained with traditional double chamber plethysmographs. Exposure to TiO₂ nanoparticles resulted in higher baseline airway resistance in exposed animals compared to their age-matched controls (sRaw: 1.1±0.08 vs 0.9±0.03 cmH₂O*sec respectively; n=6 for both groups, p<0.01). In exposed animals, inhalational challenge with 10mg/ml methacholine caused a significantly higher increase in sRaw compared to control animals (110.1±23.4% vs 68.8±6.6% respectively; values are expressed as peak % change sRaw compared to baseline; n=6 for both groups, p<0.001). In conclusion, our results show that exposure to TiO₂ nanoparticles caused airway hyperresponsiveness in non-allergic animals and that this effect may be mediated by up-regulation of lung neurotrophins.

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