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Title: Determinants of inflammatory and functional toxicity of silver nanospheres in rat lung

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Body: Nanoparticle size, shape and surface chemistry are major contributing factors to their toxicity. The effects of silver nanoparticles (AgNPs) delivered via the airways may also be determined by the inflammatory state of the lungs. We studied the effects of intratracheally administered AgNPs, with differing sizes and capping agents (20 nm or 110 nm; PVP or citrate-capped, 0.1 mg/Kg) in Brown Norway (BN) rats with a pulmonary eosinophilic granulomatous inflammation and Sprague Dawley (SD) rats with normal lungs. In BN rats, at day 1, BAL neutrophils increased for all NP, with the greatest increase for 20nm NPs, while there was also a small eosinophilic response. At 7 days, there was a prominent eosinophilia for all 4 NPs, with persistence of neutrophilia, except with 110nm PVP. In SD rats, exposed to the 20 nm NPs, there was a large neutrophil response at day 1, which was greater for the citrate capped NP. In BN rats, total protein and KC levels in BAL were increased at 1 and 7 days for all NPs while in the SD rats, there was a small increase in protein levels at 7 days but no increase in KC. In BN rats, pulmonary resistance increased and compliance decreased at 1 and 7 days. 20nm PVP and citrate capped NPs but not the 110 nm PVP, caused an increase in bronchial hyperresponsiveness (BHR) to acetylcholine at 1 day. BHR persisted at 7 days for the citrate capped NPs. Overall, the 20 nm and citrate-capped AgNPs were more proinflammatory than the 110 nm and PVP-capped NPs. A pre-existing eosinophilic lung inflammation in BN rats, led to a smaller early neutrophilic and a late-onset eosinophilic response associated with greater effects on lung function and bronchial hyperreactivity.