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Title: Role of the nitric oxide in the lung function and airway hyperreactivity in silicotic mice

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Body: Introduction: Silicosis is an inflammatory restrictive pulmonary disease caused by silica particle inhalation, characterized by intense fibrosis and granuloma formation. Several inflammatory mediators are involved in this disease, including nitric oxide (NO). Aim: To investigate the involvement of NO in silica-induced changes in lung function, hyperreactivity and airway morphology. Methods: Male wild-type C57BL/6 (iNOS+/+) and iNOS ko (iNOS-/-) mice were anesthetized and received a single intranasal instillation of silica (10 mg/50 µL) or saline (control). The analyzes were made 7 and 28 days after silica provocation and included: i) lung function and airways hyperrreactivity to methacholine, ii) quantification of nitric oxide levels in the bronchoalveolar lavage (BAL), iii) morphological and morphometric analyses and iv) treatment with NO donor DETANonoate (0.61 µmol/animal). Results: The animals exposed to silica showed higher lung function and airway response than the controls. In 7 days (11.5±2.6) (mean ± SEM) as soon as 28 days (7.8±0.6), the NO in BAL fluid was greater in silicotic mice as compared respectively to those of the controls (5.5±0.7) and (4.7±0.2). Instillation of DETANonoate led to an increase in lung resistance and elastance to methacholine. Yet all silica effects were abolished in iNOS -/- mice. Conclusion: Silica induced lung function compromise and airways hyperreactivity is directly associated with inflammation and granuloma formation. These responses were markedly suppressed in iNOS knockout mice, indicating that NO seems to significantly contribute to several features of the silicosis, including airways hyperreactivity and inflammation. Financial support: FAPERJ, CNPq.