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Title: Converse airway effects of nicotine in vitro and in vivo

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Body: Cigarette smoke, which contains high concentrations of nicotine and endotoxin (LPS), plays a pivotal role in the development of asthmatic airway inflammation and hyperreactivity (AHR). But the mechanisms behind this are poorly known. The present study examines the effects of nicotine and LPS on murine airways both in vitro and in vivo. In the in-vitro model, murine tracheal segments were cultured in presence of nicotine (10 μM) and/or LPS (10 μg/ml) for 4 days. Smooth muscle contractibility was assessed with myograph and inflammatory mediator expressions measured with real-time PCR. In the in-vivo model, mice were exposed to nicotine (24 mg/kg/day) via osmotic pumps for 28 days followed by intranasal (i.n.) LPS (1 mg/ml) instillation during the last 3 days. Airway resistance was measured using FlexiVent® after i.v. methacholine challenge and inflammatory cells in the bronchoalveolar lavage fluid were counted. In vitro, nicotine increased contractions to bradykinin (BK) and des-Arg9-BK. Carbachol contractions only increased after combined nicotine and LPS exposure. Moreover, nicotine specifically up-regulated Toll-like receptor 2 and 4 as well as inflammatory mediators COX-2 and MCP-1. In vivo, nicotine had no effects alone, but i.n. LPS caused both AHR and acute pulmonary neutrophillic inflammation. 28-days of in-vivo nicotine exposure suppressed the LPS-induced AHR both in central and peripheral airways and prevented pulmonary neutrophil infiltration. It is interesting to note that the local smooth muscle effect of nicotine differs markedly from the in-vivo effect which involves a much more complex system of inflammatory cells and mediators. This is important to acknowledge when evaluating the toxic effect of nicotine.