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Title: A robust translational model of acute exacerbations in the tobacco-smoke and poly IC treated mouse

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Body: Exposure to tobacco smoke (TS) for 4 days induces steroid-insensitive lung inflammation in mice. The effect of adding the viral mimetic poly IC (PIC) to TS-exposed mice was examined. Methods. Mice were exposed daily to either TS or air for 4d. Saline or PIC was administered intra-nasally. The time course of lung inflammation was examined 4-120hrs after the last exposure and cell numbers measured in the BAL fluid. The acute effects of oral Dexamethasone (DEX 0.3mg/kg) or Roflumilast (ROF 5mg/kg) on the peak inflammation were examined. The effects of DEX on the kinetics of the enhanced inflammation were also examined. Results TS caused a lung inflammation which was inhibited by ROF but not by DEX. PIC alone induced an inflammation that was not inhibited by DEX or ROF. Dosing PIC in addition to TS induced an exaggerated response that was significantly greater than the additive effect of the two stimuli. The enhanced response peaked 24hrs after the last exposure then slowly declined. Neutrophils were predominant over the first 48 hrs. Macrophage numbers increased at 24-72hrs and lymphocyte numbers peaked at 48-72hrs. The peak inflammation after TS/PIC exposure was significantly inhibited by ROF (53%, $p<0.05$) and DEX (56%, $p<0.05$), in contrast to the lack of efficacy of DEX against TS or PIC alone. A single dose of DEX after the last exposure reduced the exaggerated response over the entire 120hr study period, but did not fully resolve the inflammation. Conclusions TS exposure for 4 days induced a steroid-insensitive lung inflammation. Addition of PIC markedly enhanced the inflammatory response which was sensitive to both steroids and roflumilast, mimicking features of human COPD.