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Title: Comparing the effects of orally and intranasally administered IKK2 inhibitors in a 4 day tobacco-smoke exposed model of COPD

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Body: Orally dosed IKK2 inhibitors are effective anti-inflammatory agents in tobacco smoke (TS) based COPD models. Their development is limited by systemic side effects. Lung administration may overcome these liabilities if localised IKK2 inhibition is sufficient to inhibit the inflammatory response. The effects of orally (p.o.) and intranasally (i.n.) administered IKK2 inhibitors were compared. Methods Mice were exposed to TS for 4d and killed 24h after the last exposure, the lungs lavaged and cells counted. The IKK2 inhibitor PHA-408 (Sommers et al. J. Pharm. Exp. Ther. 330, 337-388, 2009) at 3, 10 or 30mg/kg or the PDE4 inhibitor Roflumilast (5mg/kg), were orally dosed 1h prior to each TS-exposure. The IKK2 inhibitor PF-184 (Sommers et al.) at 0.03, 0.1 or 0.3mg/kg or the p38 inhibitor PF-03715455 (0.1mg/kg), were dosed i.n. 1h prior to each TS-exposure. For pharmacokinetic (PK) determinations, mice were dosed with PHA-408 (10mg/kg p.o.) or PF-184 (0.1mg/kg i.n.) Results TS-exposure caused a lung neutrophilia that was significantly inhibited by orally dosed PHA-408 (68%, $p<0.001$). The inhaled inhibitor PF-184 also inhibited neutrophilia (55%, $p<0.001$), similar to that seen with PF-03715455. PK assessment showed PF-184 had a lung $t_{1/2}$ of >24h, with low plasma levels and rapid clearance from the circulation (plasma $t_{1/2}$ 0.42h), supporting the hypothesis that its action is locally driven. Conclusions IKK2 inhibitors, dosed orally and intranasally, inhibited TS-elicited lung inflammation to a similar degree. PK data showed that local delivery and lung retention can deliver pulmonary anti-inflammatory activity similar to that observed with PF-03715455.