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Title: Effects of soluble guanylate cyclase (sGC) stimulation in guinea pigs chronically exposed to cigarette smoke

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Body: Background: The nitric oxide-cyclic GMP signaling pathway is altered in pulmonary vessels of patients with chronic obstructive pulmonary disease (COPD). Activation of sGC improves vascular remodeling in experimental models of pulmonary hypertension. The effects of sGC stimulation in COPD remain unsettled. The aim of the study was to evaluate the low dose effects of the sGC stimulator BAY 41-2272 in a guinea pig model of COPD. Methods: 24 guinea pigs were exposed to cigarette smoke (CS) (6 cigarettes/day, 5 days/week) during 3 months. Half of them received BAY 41-2272, 3mg/kg daily (CS+BAY group), and the other half received vehicle (CS group). 16 guinea pigs, sham exposed to CS, were treated with BAY 41-2272 (Sham+BAY group) or vehicle (Sham group), and served as controls. Pulmonary artery pressure (PAP), cardiac output, % of muscularized intrapulmonary arteries (<50µm), airway resistance (enhanced pause, Penh), and mean interseptal distance (Lm) were assessed at the end of the study. Results are shown in the table:

	CS	CS+BAY	Sham	Sham+BAY
PAP (mmHg)	8.3±1.3*#	7.6±2.1*#	5.5±0.7	6.0±1.3
Cardiac Output (mL/min)	82±35#	88±28#	101±23	124±32
Muscularized vessels (%)	71±10*#†	54±13*#	28±12	31±8
Penh (AUC)	4.1±1.4*	4.1±1.4*	2.9±0.2	3.3±0.5*
Lm (µm)	75.3±5.5*#†	62.3±8.3	57.6±4.1	59.5±5.6

*p<0.05 vs Sham, #p<0.05 vs Sham+BAY, †p<0.05 vs CS+BAY

Conclusions: In the guinea pig, stimulation of sGC prevents the development of pulmonary vascular remodeling and emphysema induced by CS. At the given low dose, these effects were not translated into a reduction of pulmonary hypertension or airflow obstruction. Supported by grant FIS IS09-00536; Bayer

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