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Title: The role of soluble guanylyl cyclase in chronic obstructive pulmonary disease

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Body: Rationale: Soluble guanylyl cyclase (sGC), a cyclic guanosine 5'-monophosphate (cGMP) generating enzyme, regulates smooth muscle tone and exerts anti-inflammatory effects in animal models of asthma and acute lung injury. In Chronic Obstructive Pulmonary Disease (COPD), primarily caused by cigarette smoke (CS), lung inflammation persists and smooth muscle tone remains elevated, despite ample amounts of nitric oxide (NO) that could activate sGC. Objective: To determine the expression and function of sGC in a murine model of COPD and in patients with COPD. Methods: Expression of sGC α 1, α 2 and β 1 subunits was examined in lungs of never smokers, smokers without airflow limitation and patients with COPD; and in C57BL/6 mice after 3 days, 4 and 24 weeks of CS exposure. The functional role of sGC was investigated in vivo by measuring bronchial responsiveness to serotonin (5-HT) in mice using genetic and pharmacological approaches. Results: Pulmonary expression of sGC, both at mRNA and protein level, was decreased in smokers without airflow limitation and in patients with COPD, and correlated with disease severity (FEV₁%). In mice, exposure to CS reduced sGC, cGMP levels and protein kinase G activity. CS exposure induced bronchial hyperresponsiveness (BHR) to 5-HT in wildtype mice, which was even more pronounced in CS-exposed sGC α 1 -/- mice (wildtype mice vs. sGC α 1 -/- mice: p<0.05). Activation of sGC by BAY58-2667 restored the sGC signaling and attenuated BHR in CS-exposed mice. Conclusion: Downregulation of soluble guanylyl cyclase due to cigarette smoke exposure contributes to airflow limitation in COPD. Funding: Ghent University BOF/GOA/01601009, FWO Flanders (G.0195.09 en G.0194.10) and IUAP P7/30.