Targeting Mitochondria with Hydrogen Sulphide Attenuates Cigarettes Smoke-Induced Mitochondrial Dysfunction, Oxidative Damage, Inflammation and Lung Injury in Mice

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RATIONALE: Cigarette smoke (CS) is the predominant cause of chronic obstructive pulmonary disease (COPD), with 50% of lifelong smokers having chance of developing the disease. Thus, preventing/reversing CS-induced lung damage provides a novel treatment strategy for COPD. Mitochondrial (mt) dysfunction, oxidative stress and inflammation, the major triggers for COPD pathogenesis are caused by CS exposure. Hydrogen sulphide (H_2S), an endogenously produced gaseous signalling molecule, maintaining mt functions, regulating oxidative stress and inflammation is depleted in lungs of smokers and COPD patients. Inhibiting mt-H_2S production causes mt-dysfunction and oxidative damage and exacerbates inflammation in lungs, suggesting that H_2S is important in preventing lung injury. METHODS: We investigated the prophylactic (prevention) and therapeutic (reversal) potential of mt-targeted H_2S donors (mtH_2SDs) using a CS-induced mouse model of experimental COPD. To assess the prophylactic potential, BALB/c mice were exposed to CS (12 cigarettes, twice a day, 5 days/week) or air for 8 weeks and treated throughout CS exposure with 1.0 mg/kg (i.n)/day of mtH_2SDs. For therapeutic potential, mice were exposed to CS for 12 weeks and treated with 1.0 mg/kg (i.n)/day from 8-12 weeks. In addition, a separate group of mice terminated CS exposure after 8 weeks and treated from 8-12 weeks. Lung inflammation was assessed by enumerating immune cells (macrophages and neutrophils) in bronchoalveolar lavage fluid and inflammatory markers (pro-inflammatory cytokines and chemokines) using ELISA in lung homogenate. Oxidative stress markers (GCLC, HMOX1 and GPX2) and oxidative damage marker (4-HNE) were assessed using qPCR and western blot, respectively. Mt dysfunction, mt reactive oxygen species (ROS) and total cellular ROS levels were assessed using flow cytometry. Lung function and lung gas exchange capacity were assessed using forced oscillations and forced manoeuvre techniques and DFCO test, respectively. RESULTS: CS exposure reduced H_2S-synthesising enzyme expression, H_2S level and Caused mt-dysfunction, inflammation and oxidative damage in lungs. Treatment with mtH_2SDs attenuated CS-induced mt dysfunction, oxidative stress and significantly reduced immune cell influx into the lungs. Prophylactic and therapeutic treatment with mtH2SDs prevented/reversed CS-induced lung fibrosis in mice. CONCLUSIONS: mtH_2SDs may be a novel treatment for COPD and mt dysfunction related diseases.

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