Proceedings of the British Pharmacological Society at http://www.pA2online.org/abstracts/Vol12Issue2abst0014P.pdf

Murine challenge models to assess mitochondrial dysfunction in airway compartments and the effect of mitochondria targeted antioxidants.

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Inflammation and oxidative stress play critical roles in chronic obstructive pulmonary disease (COPD). Targeted mitochondrial antioxidants may be of benefit to halt or reverse the effect of mitochondrial dysfunction. C57BL6 mice (n=8 per group) were exposed to a single dose of ozone (3ppm, 3hrs) or exposed for 6 weeks (3ppm, 3hrs, twice a week). Mice were injected (i.p.) one hour before each ozone treatement with MitoQ (5 mg/kg) or SS31 (2 mg/kg). Airway hyperresponsiveness (AHR) was measured 24hrs after the last ozone expose by whole body plethysmography with increasing doses of acethylcholine (0-264 mg/ml). BAL fluid and lung tissue were subsequently isolated. Intact mitochondria were isolated from lung tissue and probed with the fluorescent dyes JC-1 and mitoSOX to determine the transmembrane potential ($\Delta\Psi m$) and mitochondrial ROS content respectively. Acute and chronic ozone-exposed mice developed lung inflammation and AHR. BAL cytokines (KC,IFN-γ and TNFα) were increased in all ozone exposed groups. AHR measured as lung resistance (R_L) was increased in ozone exposed groups. These changes were associated with mitochondrial dysfunction reflected by decreased transmembrane potential ($\Delta\Psi m$), increased mitochondrial oxidative stress and reduced mitochondrial complex I, III & V expression. The mitochondrial-targeted antioxidant MitoQ reversed mitochondrial dysfunction in the acute ozone model which was associated with a reversal of AHR and lung inflammation. This effect was not apparent in the chronic ozone model. SS31 , another mitochondria-targeted antioxidant, reduced inflammation, AHR and mitochondrial dysfunction in both acute and chronic ozone-exposed mice. In addition, the elevated mitochondrial ROS production was decreased in SS31-treated mice indicating that mitochondrial ROS is an important mediator in this model. Mitochondrial dysfunction in an animal model of COPD is associated with excessive mitochondrial ROS that contributes to the enhanced inflammation. Targeting mitochondrial ROS with specific antioxidants represents a promising therapeutic approach in COPD.