Pioglitazone Pre-Treatment by Gavage Attenuates Particulate Matter Induced Lung Disease

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RATIONALE Peroxisome proliferator-activated receptor(PPAR)-agonists attenuate pulmonary fibrosis, acute lung injury, allergic/irritant induced airway inflammation and neutrophil recruitment. PPARγ polymorphisms are associated with obstructive airways disease. PPARγ agonists inhibit RAGE-mRNA and protein levels in mice, suggesting that PPARγ is a repressor of RAGE expression. Mice with deletion of PPARγ in the myeloid lineage have immature alveolar macrophages and are protected from the damaging effects of cigarette smoke. The potential therapeutic effects of pioglitazone(PioRx), an FDA-approved PPARγ agonist, on particulate matter (PM) induced pulmonary inflammation continues to be our focus. METHODS C57BL/6 female mice (Jackson) gavaged for 6-days with 60mg/kg pioglitazone (Santa Cruz) or an equal volume of 0.5% methylcellulose vehicle(n=12/exposure) were exposed on day 6 to WTC-PM_{53}(100 µg) or an equal volume of PBS. Lung mechanics, airway reactivity (Flexivent, SciReq), BAL and plasma(cardiac puncture) were collected 24 hour after exposure. Cytospins of BAL cell samples were H&E-stained and differentials obtained. Plasma and BAL were assayed for cytokines(Millipore MCYTOMAG-70K-PMX). RESULTS Prior data showed that PPARγ is strongly expressed in the lung and alveolar macrophages at baseline. Mice pre-treated with pioglitazone were resistant to lung function changes after PM exposure, specifically to significant increases in Newtonian resistance (R_n) and tissue elastance (H) compared to vehicle controls. G-CSF and IL-5 were induced in the plasma of Veh-PM mice but not PioRx-PM mice when compared to their PBS controls. In BAL, both IL-5 and IP-10 were significantly increased in Veh-PM but not PioRx-PM compared to their controls. CONCLUSIONS Pioglitazone is a potent PPARγ agonist, however we do not see complete protection from PM induced lung injury. The effects of PioRx rescue from PM associated lung disease will be secondary to the involvement of several pathways. Evidence that this may be true stems from our earlier biomarker studies that identified several associated pathways in the development of WTC-LI in the FDNY cohort. This study is not designed to investigate specific mechanisms or causality of PPARγ agonism and its involvement in the RAGE axis. Future studies will assay relevant proteins and signaling molecules downstream of RAGE and PPARγ in lung homogenates and BAL cell pellets. Furthermore, conditional knockouts may be used to investigate causality. This will provide insight on protein expression after PioRx that may guide future mechanistic and therapeutic studies designed to blunt the impact of the worldwide COPD epidemic.