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Regulation of airway contractile response by the free fatty acid 4 receptor

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Introduction: Free fatty acid 4 (FFA4) receptor is a G protein-coupled receptor that responds to medium and long chain fatty acids[1]. The receptor has been shown to play a key role in regulating metabolic responses and inflammation and has been considered an important drug target for the treatment of type 2 diabetes and obesity[2]. The receptor is also expressed in the lung[3], although its function in such tissue is unknown. In this study, we investigate the role of FFA4 in the lung using pharmacological tools and animal models of respiratory disease.

Methods: FFA4 expression profiling in lung tissue was performed using RT-PCR, immunohistochemistry and β-galatosidase staining with GALS kit. Lung slices (200µm) were prepared from 2% agarose-inflated lungs of wild-type and FFA4-KO mice and used in contraction and relaxation experiments. *Ex vivo* myography using human lung tissue was performed by Biopta. Ligands were applied directly to the tissue for 15-20min. Whole body lung resistance experiments were performed on healthy and ozone (3ppm, 3hr) or cigarette smoke (daily, 1-week)-exposed mice with ligands nebulised for 3min. Data (3 or more independent experiments) are presented as mean ± SEM of % basal airway area or saline control, with statistical comparison made using ANOVA and Bonferroni's post-hoc test.

Results: FFA4 was detected at mRNA and protein levels in the lung. Treatment of lung slices with FFA4 selective agonists (TUG891, TUG1197 and Merck CpdA) did not alter the basal airway diameter but causes relaxation in pre-contracted airways. The levels of relaxation was partial (82.59±5.48% TUG891, 70.31±4.37% TUG1197 and 72.42±15.59% Merck CpdA) and significantly reduced in the presence of FFA4 selective antagonist, AH7614 (46.82± 3.74% relaxation for TUG1197) and in FFA4-KO mice (46.61± 9.39% relaxation for TUG1197). In mouse lung slices, TUG891 and TUG1197 caused airway relaxation with pEC50 of 4.60±0.10 and 4.77±0.15 respectively. Whole body lung function tests showed that TUG1197 was also able to reduce airway resistance evoked by muscarinic agonists in healthy mice (53.26±9.85% reduction) and in mouse models of COPD resulting from exposure to ozone (47.06±28.61% reduction) and cigarette smoke (81.87±6.52% reduction).

Conclusion: FFA4 receptor is expressed in the lung and mediates airway smooth muscle relaxation in isolated lung tissues. In vivo experiments also indicate that FFA4 is able to block bronchoconstriction.

References:

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