Effects of histaminergic H_4R ligands in an animal model of lung fibrosis

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Pulmonary fibrosis is a pathophysiological response to chronic injury and inflammation characterized by excessive deposition of collagen and abnormal remodelling of lung parenchyma, resulting in airway stiffening and thickening of the air-blood membrane. The murine model of bleomycin-induced lung fibrosis is one of the most commonly used model. Bleomycin increases oxidative stress and the production of pro-inflammatory mediators. Moreover, histaminergic H_4 receptor (H_4R) has been identified as a target for inflammatory and immune disorders.

The aim of this study was to provide inside into the possible role of histaminergic H_4R in the pathophysiology of lung fibrosis, by investigating the protective effects of H_4R ligands in the reduction of the disease in C57BL/6 mice treated with bleomycin.

Fifty C57BL/6 male mice were treated with vehicle, JNJ7777120 (JNJ, selective H_4R antagonist) or with ST-1006 (partial H_4R agonist), ST-994 (H_4R neutral antagonist) and ST-1012 (inverse H_4R agonist) at equimolar doses, released by micro-osmotic pumps for 21 days. Airway resistance to inflation, a functional parameter related to fibrosis-induced lung stiffness, was assayed and lung tissue was processed to evaluate malondialdehyde (TBARS), 8-hydroxy-2'-deoxyguanosine (8OH*d*G), myeloperoxidase (MPO), COX-2 expression and activity as markers of oxidative stress and inflammation. The collagen deposition, a functional parameter of fibrosis, and airway remodelling were evaluated throughout transforming growth factor-b (TGF-b), percentage of positive Goblet cells and smooth muscle layer thickness determination.

Our results show that JNJ, ST-994 and ST-1012 reduce the amount of 8-OHdG, decreasing oxidative stress damage in the lung homogenates, and exert an anti-inflammatory effect, reducing the expression of the pro-inflammatory markers. They also decrease TGF-b production, smooth muscle layer thickness and Goblet cells hyperplasia, resulting in a decrease of airway functional impairment.

Our results indicated that H_4R antagonists or inverse agonists could be a novel therapeutic treatment for lung inflammatory and fibrotic diseases.