Phosphodiesterases inhibitors and transient receptor potential ankyrin 1 channel antagonists exert anti-fibrotic effects on human lung fibroblasts

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Asthma is a chronic inflammatory lung disease, characterized by prolonged airway inflammation and remodelling. Many of drugs have been used in anti-asthmatic therapy including inhaled/systemic corticosteroids, β₂-agonists, anti-leukotrienes or cromones. Most of them reduce inflammation and limit its harmful effects, whereas airway remodelling is still not the direct goal of any therapeutic strategy. Recently, a particular attention has been paid to inhibitors of phosphodiesterases (PDEs), enzymes that are responsible for increasing the intracellular level of second messengers. It is known that their elevated levels can cause anti-fibrotic effects on inflammatory and lung structural cells. On the other hand, a latest findings indicate that transient receptor potential ankyrin 1 (TRPA1) channel may be involved in the asthma pathogenesis. In the response to the above premises, a series of 7,8-disubstituted purine 2,6-dione derivatives with PDEs and/or TRPA1 activity has been synthesized. From this group we selected three compounds: PDEs inhibitor (comp 1), TRPA1 antagonist (comp 2) and PDEs inhibitor/TRPA1 antagonist (comp 3) and compared their potency of inhibiting profibrotic responses. To address this we used transforming growth factor type β (TGF-β₁) induced human lung fibroblast cell line (MRC-5). Comp 3 showed the highest ability to limit the TGF-β₁-induced fibroblasts migration and transition into myofibroblasts. Dual PDEs inhibitor/TRPA1 antagonist, from the group of purine-2,6-dione derivatives, exerted its action via canonical, Smad-dependent pathway of TGF-β signalling. The obtained data suggest that amplification of anti-fibrotic properties may be achieved by simultaneous PDEs and TRPA1 inhibition. This opens a new perspective in the search for an efficacious anti-asthmatic drugs.

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