Effect of fluticasone propionate and roflumilast on acute and chronic guinea pig models of asthma

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Acute or chronic ovalbumin (OVA) exposures cause early (EAR) and late asthmatic responses (LAR), airways hyperresponsiveness (AHR) and inflammatory cell influx into the airways in sensitised guinea pigs (Smith & Broadley, 2007), features associated with asthma. The aim of this study was to challenge guinea pigs with either a single or multiple exposures of OVA and examine the effects of an inhaled corticosteroid, fluticasone propionate (FP), or a phosphodiesterase-4 (PDE4) inhibitor, roflumilast, on these features.

Groups of six, male Dunkin-Hartley guinea pigs (200-250g) were sensitised with 100µg OVA and 100mg aluminium hydroxide in 1ml of pathogen-free saline on days 1 and 5. On day 15, acute and chronic groups were exposed to aerosolised 0.01% OVA for 60mins. For the chronic studies, exposure to 0.1% OVA, with 30mg/kg mepyramine, then occurred every 48 hours until day 29. On day 31, the OVA group was exposed to 0.1% OVA without mepyramine. EAR and LAR were measured in conscious animals by plethysmography giving values of specific airway conductance (sGaw). AHR was determined by exposing the guinea pigs to histamine (20s, 1mM) before OVA challenge and 24h post-final exposure. Total and differential cell counts in bronchoalveolar lavage (BAL) fluid were obtained following the final histamine inhalation. FP (0.51 mg/kg) or roflumilast (1 mg/kg) were administered respectively by inhalation and orally 24h and 30mins prior to and 6h after the final OVA challenge.

In acute OVA challenged guinea pigs, pre-treatment with FP inhibited the LAR (sGaw = -4.5±2.0% vs. -26.0±4.9%) and AHR to histamine (peak reduction in sGaw = -0.03±4.7% vs. -40.4±9.4%) compared to vehicle. Total cells in the BAL fluid were significantly reduced by FP (4.1±0.2x10⁶ vs. 6.2±0.6x10⁶ cells ml⁻¹) as were eosinophils (1.7±0.05x10⁶ vs. 3.9±0.1x10⁶ cells ml⁻¹). In the acute OVA challenged guinea pigs pre-treated with roflumilast the LAR was reduced significantly compared to the vehicle treated group (sGaw = -4.2±1.0% vs. -28.2±4.7%). AHR was eradicated (sGaw = +1.3±3.6% vs. -21.1±3.6%) and total cells (3.4±0.3x10⁶ vs. 6.7±0.5x10⁶ cells ml⁻¹) and eosinophils (1.3±0.3x10⁶ vs. 4.7±0.2x10⁶ cells ml⁻¹) in the BAL fluid were reduced. In the chronic OVA model, FP treatment inhibited the LAR compared to vehicle (sGaw = -3.1±1.0% vs. -28.1±2.6%), AHR was eliminated (sGaw = +1.0±1.2% vs. -38.4±9.0%) and total cells (3.8±0.2x10⁶ vs. 15.1±0.6x10⁶ cells ml⁻¹) and eosinophils (1.5±0.08x10⁶ vs. 7.3±1.9x10⁶ cells ml⁻¹) were reduced. Chronic OVA challenged guinea pigs treated with roflumilast had significantly reduced EAR (sGaw = -44.8±10.2% vs. -70.4±1.1%), LAR (sGaw = -4.3±0.7% vs. -31.2±4.9%) and AHR (sGaw = -1.2±1.4% vs. -33.8±5.9%) compared to vehicle. Total cells (3.2±0.1x10⁶ vs. 10.9±0.3x10⁶ cells ml⁻¹), macrophages (1.6±0.1x10⁶ vs. 4.7±0.3x10⁶ cells ml⁻¹) and eosinophils (1.4±0.07x10⁶ vs. 5.7±0.3x10⁶ cells ml⁻¹) were significantly reduced.

FP and roflumilast were effective against some features of the acute and chronic models, but roflumilast reduced all features in the chronic model, supporting the potential for PDE4 inhibitors in the treatment of asthma. RLE supported by a studentship from BBSRC & GSK.

Smith, N and Broadley, KJ. (2007). International Immunopharmacology, 7, 183-190