Boris Ferko et al., J Allergy Ther 2017, 8:3(Suppl)
DOI: 10.4172/2155-6121-C1-006

Preclinical development of a novel glutarimide derivative – a candidate oral drug for allergic asthma therapy

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We tested the efficacy of a novel biogenic peptidoamine compound, glutarimide histamine (XC8) in mouse, rat and guinea pig asthma models. Sensitized animals underwent oral treatments for at least 10 consecutive days with titrated doses of XC8 or corticosteroid reference drugs. In mice, XC8 efficiently inhibited eosinophilic lung inflammation of acute asthma disease onset, suppressed mucus hypersecretion, antigen-specific serum IgE or IgG1 titres, and methacholine-induced airway hyperresponsiveness (AHR). In Sephadex-induced migration of eosinophils in a rat model XC8 decreased the content of eosinophils in bronchalveolar lavages (BAL) 2.6-6.4 times. In guinea pig models of asthma and antigen-induced bronchospasm, XC8 reduced the number of degranulated mast cells and basophils in the lung tissue and the degree of degranulation. Moreover, XC8 also reduces hyperactivity of the lungs and reduces mortality of the animals from anaphylactic reactions. Chronic toxicity studies in rats and dogs revealed an excellent safety profile of XC8. In vitro experiments indicated that the mode of XC8 action might be associated with the suppression of glutaminyl cyclase - an enzyme that converts the immature form of chemokines (CCL2, CCL7, CCL8, CCL13) into the mature form by the reaction of pyroglutamination, thus suppressing the chemokine-driven migration of eosinophils and other cells into the inflammation area and the degranulation of mast cells and basophils. Our data demonstrate that XC8 efficiently suppresses experimental allergic asthma and provide support for its use as a treatment for human allergic asthma.

Biography

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