Bronchodilatory effects of S-isopetasin, an antimuscarinic sesquiterpene of Petasites formosanus, on obstructive airway hyperresponsiveness

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摘要

Abstract

In the presence of neostigmine (0.1 μM), S-isopetasin competitively antagonized cumulative acetylcholine-induced contractions in guinea pig trachealis, because the slope [1.18 ± 0.15 (n = 6)] of Schild's plot did not significantly differ from unity. The pA2 value of S-isopetasin was calculated to be 4.62 ± 0.05 (n = 18). The receptor binding assay for muscarinic receptors of cultured human tracheal smooth muscle cells (HTSMCs) was performed using [3H]-N-methylscopolamine ([3H]-NMS). Saturation binding assays were carried out with [3H]-NMS in the presence (non-specific binding) and absence (total binding) of atropine (1 μM). Analysis of the Scatchard plot (y = 0.247−1.306x, r2 = 0.95) revealed that the muscarinic receptor binding sites in cultured HTSMCs constituted a single population (nH = 1.00). The equilibrium dissociation constant (Kd) and the maximal receptor density (Bmax) for [3H]-NMS binding were 766 pM and 0.189 pmol/mg of protein, respectively. The − logIC50 values of S-isopetasin, methoctramine, and 1,1-Dimethyl-4-diphenylacetoxypiperidinium iodide (4-DAMP) for displacing 0.4 nM [3H]-NMS-specific binding were 5.05, 6.25, and 8.56, respectively, which suggests that [3H]-NMS binding is predominantly on muscarinic M3 receptors of cultured HTSMCs. The inhibitory effects of S-isopetasin on enhanced pause (Penh) value were similar to that of ipratropium bromide, a reference drug. The duration of action of S-isopetasin (20 μM), also similar to that of ipratropium bromide (20 μM), was 3 h. In contrast to ipratropium bromide, which non-selectively acts on muscarinic receptors, S-isopetasin preferentially acts on muscarinic M3 receptors. In conclusion, S-isopetasin may be beneficial as a bronchodilator in the treatment of chronic obstructive pulmonary disease and asthma exacerbations.