Relaxation of Isolated Guinea Pig Trachea by Genistein via Inhibition of Phosphodiesterase

柯文昌

Lin CC;Chen JL;Ko WC

摘要

Abstract

We investigated the mechanisms of the relaxant action of genistein, an isoflavone, phytoestrogen and non-specific protein tyrosine kinase inhibitor. Changes in tension of guineapig tracheal segments were isometrically recorded on a polygraph. Genistein concentration-dependently relaxed histamine (30 μM)-, carbachol (0.2 μM)-, KCl (30 mM)- and leukotriene D4 (10 nM)-induced precontractions and inhibited cumulative histamine- and carbachol-induced contractions in a non-competitive manner. Genistein also concentration-dependently and non-competitively inhibited the cumulative, Ca2+-induced contractions in the depolarized (K-+, 60 mM) trachealis. The remaining nifedipine (10 μM)-induced tension of the histamine (30 μM)-induced precontraction was further relaxed by genistein, suggesting that regardless of whether voltage-dependent calcium channels are blocked genistein may have other mechanisms of relaxant action. These other mechanisms of the relaxant effect of genistein appeared to be epithelium-independent and were not affected by the presence of propranolol (1 μM), 2´,5´-dideoxyadenosine (10 μM), methylene blue (25 μM), glibenclamide (10 μM), Nω-nitro-L-arginine (20 μM) or α-chymotrypsin (1 U/mL), suggesting that the mechanisms are unrelated to activation of the β-adrenoceptor, of adenylate cyclase, of guanylate cyclase, of adenosine triphosphate-sensitive potassium channel opening, of nitric oxide formation or of neuropeptide release, respectively. However, genistein (17.5-35 μM) produced parallel, leftward shifts in the concentration-response curves of forskolin and nitroprusside and significantly increased the pD2 values of these two agonists. Both genistein and 3-isobutyl-1-methylxanthine at various concentrations (10-300 μM) concentration-dependently and significantly inhibited cAMP- and cGMP-phosphodiesterase (PDE) activities of the trachealis. The -log IC50 values of genistein were estimated to be 4.28 and 4.17, respectively. The above results reveal that the mechanisms of the relaxant action of genistein may be due to its non-selective inhibition of

both PDE activities.