PS2P20

NON-GENOMIC VASCULAR EFFECT OF 17β-ESTRADIOL INVOLVES ACTIVATION OF ADENYLYL CYCLASE AND PROTEIN KINASE G IN THE RAT MESENTERIC ARTERY

W. Keung, P.M. Vanhoutte and R.Y.K. Man

Department of Pharmacology, University of Hong Kong

Objective: The present study aims to elucidate the mechanism of 17β-estradiol-induced relaxation in the rat mesenteric artery.

Methods: Sprague-Dawley rats (10 weeks old) were employed in the study. Isometric tension was measured in rings of rat superior mesenteric arteries in functional studies. Tissue cAMP and cGMP contents were measured using enzyme-linked immunoassays. Protein kinase A and G activity were determined by measuring the rate of incorporation of 32P-labeled phosphate by cytosolic protein fractions after exposure to agonists.

Results: 17β-estradiol induced a concentration-dependent relaxation in mesenteric arteries of both male and female rats. This effect was found to be largely endothelium-independent. The classical estrogen antagonist, ICI 182 780 did not block this effect. Adminstration of the Gαs antagonist, NF449, partially inhibited the relaxation to 17β-estradiol while the Gαo antagonist NF023 did not. The adenylyl cyclase inhibitor, SQ22536 inhibited the relaxation to 17β-estradiol, as did the protein kinase G antagonist KT5823. However, co-administration of SQ22536 and KT5823 did not further inhibit this relaxation. The protein kinase A antagonist, KT5720, did not affect this response. Tissue cAMP content was found to increase by 2 fold following administration of 17β-estradiol for 30 min in preparations both with or without endothelium. In contrast, no change in cGMP content was observed. Administration of 17β-estradiol for 30 min resulted in a modest but significant increase in protein kinase G activity. However, no change in protein kinase A activity was observed.

Conclusions: 17β-estradiol elicited a concentration-dependent relaxation in rat mesenteric arteries. This relaxation appears to act, in part, via the activation of adenylyl cyclase in the vascular smooth muscle, leading to an increase in the cAMP level and the activation of protein kinase G. Activation of protein kinase A by cAMP was not observed and did not appear to contribute to the observed relaxation by 17β-estradiol.