PKCe dependent pathway of extracellular signal-regulated protein kinase activation by P2Y1 and P2Y2 purinoceptors that activate cytosolic phospholipaseA2 in endothelial cells.

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摘要

Abstract

The aim of this study was to investigate the stimulating effects on arachidonic acid release of P2Y1 and P2Y2 receptor-selective agonists, 2-methylthio-ATP (2MeSATP) and UTP, respectively, in bovine pulmonary artery endothelial cells. Exposure of cells to 2MeSATP and UTP led to the release of arachidonic acid, a response which was abolished by the removal of extracellular Ca2+ and methyl arachidonyl fluorophosphonate. Phorbol 12-myristate 13-acetate (PMA) itself not only stimulated arachidonic acid release but also played a permissive role in the response to UTP. However, PMA failed to enhance the arachidonic acid response induced by 2MeSATP, probably due to greater attenuation of the [Ca2+]i increase caused by 2MeSATP than UTP. Inhibition of protein kinase C with Ro 31-8220 (1-[3-(amidinothio) propyl-1H-indoyl-3-yl]-3-(1-methyl-1H-indoyl-3-yl)-maleimide-methane sulphate) and staurosporine, but not with Go 6976 (12-(-2-cyanoethyl)-6,7,12,13-tetrahydro-13-methyl-5-oxo-indolo(2,3-a)pyrrolo(3,4-c)carbazole), reduced the arachidonic acid response of 2MeSATP, UTP and PMA. PMA-induced potentiation of the UTP response reached a maximum after a 1-h preincubation, then declined and eventually lost its effect when the preincubation lasted up to 8 h. Among the protein kinase C isoforms present in endothelial cells, βI and could be down-regulated by treatment with PMA for 4–24 h. PD 098059 (2-(2-Amino-3-methoxyphenyl)-4H-1-benzopyran-4-one) inhibited extracellular signal-regulated protein kinase activation, cytosolic phospholipase A2

phosphorylation and arachidonic acid release caused by 2MeSATP, UTP and PMA. Taken together, our results demonstrate that P2Y1 and P2Y2 purinoceptors mediate arachidonic acid release by activating cytosolic phospholipase A2 through an elevation of [Ca2+]i and protein kinase C -, extracellular signal-regulated protein kinase-dependent phosphorylation.

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