Induction of cyclooxygenase-2 expression by methyl arachidonyl fluorophosphonate in murine J774 macrophages: role of protein kinase C, ERKs and p38 MAPK.

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摘要

Abstract

1.Methyl arachidonyl fluorophosphonate (MAFP), an inhibitor of phospholipase A2 (PLA2), has been widely used to assess the roles of PLA2 in various cell functions. Here, we report on a novel action of this compound at concentrations similar to those used for PLA2 inhibition.

2.The murine macrophage J774 released a large amount of prostaglandin E2 (PGE2) by MAFP (1–30μM), which was abolished by indomethacin and NS-398 but not by valeryl salicylate, and results from increased cyclo-oxygenase-2 (COX-2) protein levels and gene expression.

3.This PGE2 release was blocked by inhibitors of tyrosine kinase (genistein), protein kinase C (PKC) (Ro 31-8220, Go 6976 or LY 379196), mitogen-activated protein kinase kinase (MEK) (PD 098059) or p38 mitogen-activated protein kinase (MAPK) (SB 203580).

4.Consistent with these results, MAFP caused membrane translocation of PKCβI and βII isoforms and activated extracellular signal-regulated kinase (ERK) and p38 MAPK.

5.In accordance with these effects of MAFP, PKC activator phorbol 12-myristate 13-acetate (PMA) increased PGE2 release and caused activation of PKCβ, ERKs and p38 MAPK.

6.This is the first report that the PLA2 inhibitor, MAFP, can induce COX-2 gene expression and PGE2 synthesis via the PKC-, ERK- and p38 MAPK-dependent pathways. Thus, the use of MAFP as a PLA2 inhibitor should be treated with caution.