Pyrimidinoceptor potentiation of macrophage PGE2 release involved in the induction of nitric oxide synthase.

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摘要

Abstract

1.We have previously demonstrated that Ca2+/calmodulin-dependent protein kinase (CaMK) mediates pyrimidinoceptor potentiation of LPS-elicited inducible nitric oxide synthase (iNOS) induction in murine J774 macrophages. In the present paper, we have explored the role of cyclo-oxygenase (COX)-dependent prostaglandin E2 (PGE2) formation in this event.

2.In J774 macrophages predominantly expressing P2Y6 receptors, the simultaneous addition of UTP and lipopolysaccharide (LPS) resulted in potentiated increase in PGE2 release.

3.UTP-induced increased PGE2 release was demonstrated by a concomitant increase in COX-2 protein expression, and was decreased by inhibitors specific for phosphatidylinositide-phospholipase C (PI-PLC), CaMK, protein kinase C (PKC), nuclear factor-kappa B (NF-κB) or COX-2.

4.NS-398 (a selective COX-2 inhibitor) reduced LPS plus UTP-elicited iNOS induction and nitrite accumulation, supporting for the positive regulation of iNOS gene expression by endogenous PGE2.

5.Moreover, the cyclic AMP/PKA-dependent up-regulation of iNOS expression mediated by PGE2 was drawn from the inhibitory effects of 2´,5´-dideoxyadenosine, KT5720 and H-89. Exogenous PGE2 induced NF-κB activation and potentiated nitrite accumulation in response to LPS.

6.In addition to COX-2 induction, arachidonic acid (AA) release and steady-state mRNA levels of type V secretory phospholipase A2 (sPLA2) and Ca2+-independent PLA2 (iPLA2) were also increased in the presence of LPS and UTP; the LPS-induced increase in iPLA2 activity was also potentiated by UTP.

7.Taken together, we conclude that UTP-mediated COX-2 and iPLA2 potentiation and PGE2 formation contribute to the iNOS induction, and that CaMK activation is

the primary step in the UTP enhancement of COX-2 induction.

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