

P2 PROSTAGLANDIN E₂ INHIBIT CYCLOOXYGENASE-2 INDUCTION IN LPS-TREATED ENDOTHELIAL CELLS THROUGH cAMP

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ABSTRACT

Cyclooxygenase (COX), which exists as COX-1 and COX-2 isoforms, is the first enzyme in the pathway in which arachidonic acid is converted to prostaglandins (PGs). PGE₂ is one of the PGs which have numerous cardiovascular and inflammatory effects. PGE₂ also exerts a variety of biological activities for the maintenance of local homeostasis in the body. Elucidation of PGE₂ involvement in the signalling molecules such as COX could lead to potential therapeutic interventions. Here, we have investigated the effects of PGE₂ on the induction of COX-2 in human umbilical vein endothelial cells (HUVEC) treated with lipopolysaccharide (LPS; 1 μ g/ml). COX activity was measured by the production of 6-keto-PGF_{1 α} , PGE₂, PGF_{2 α} and TXB₂ in the presence of exogenous arachidonic acids (10 μ M for 10 min) using enzyme immunoassay (EIA). COX-1 and COX-2 protein was measured by immunoblotting using specific antibody. Untreated HUVEC contained only COX-1 protein while LPS treated HUVEC contained COX-1 and COX-2 protein. PGE₂ (3 μ M for 24 h) did not affect on COX activity and protein in untreated HUVEC. Interestingly, PGE₂ (0.003, 0.03 and 3 μ M for 24h) can inhibit COX-2 protein, but not COX-1 protein, expressed in HUVEC treated with LPS (1 μ g/ml) in a dose dependent manner. Moreover, this inhibition was reversed by coincubation with forskolin (cAMP activator; 100 μ M). The increased COX activity in HUVEC treated with LPS was also inhibited by PGE₂ (0.03, 0.3 and 3 μ M for 24h) in a dose dependent manner. Similarly, forskolin (10, 50 or 100 mM) can also reverse the inhibition of PGE₂ on increased COX activity in LPS treated HUVEC. The results suggested that i) PGE₂ can be negative feedback regulation in the induction of COX-2 elicited by LPS in endothelial cells, ii) the inhibition of PGE₂ on COX-2 protein and activity in LPS treated HUVEC was mediated through cAMP and iii) the therapeutic uses of PGE₂ in the pathological conditions which COX-2 has been involved may have roles.