PKC- and ERK-dependent activation of IkB kinase by lipopolysaccharide in macrophages: enhancement by P2Y receptor-mediated CaMK activation.

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摘要

Abstract

1. Although accumulating studies have identified I kappa B kinase (IKK) to be essential for controlling NF-kappa B activity in response to several cytokines, the upstream kinases that control IKK activity are still not completely known. We have previously reported that G protein-coupled P2Y(6) receptor activation by UTP potentiates lipopolysaccharide (LPS)-induced I kappa B phosphorylation and degradation, and NF-kappa B activation in J774 macrophages. In this study, we investigated the upstream kinases for IKK activation by UTP and LPS. 2. In murine J774 macrophages, LPS-induced NF-kappa B activation was inhibited by the presence of PDTC, D609, Ro 31-8220, PD 098059 and SB 203580. 3. Accompanying NF-kappa B activation, LPS induced I kappa B degradation and IKK activation were reduced by PDTC, D609, Ro 31-8220 and PD 098059, but not by SB 203580. 4. Although UTP itself slightly induced IKK activation, this response was synergistic with LPS. BAPTA/AM and KN-93 (a calcium/calmodulin-dependent protein kinase (CaMK) inhibitor) attenuated UTP- but not LPS-stimulated IKK activity. Synergistic IKK activation between LPS and thapsigargin was further demonstrated in peritoneal macrophages. 5. LPS and UTP co-stimulation additively increased p65 NF-kappa B phosphorylation. In vitro kinase assays revealed that LPS and UTP induced extracellular signal-regulated protein kinase (ERK) and p38 mitogen-activated protein kinase activation were respectively inhibited by PD098059 and SB 203580. 6. Taken together, we demonstration that Gq protein-coupled P2Y(6) receptor activation can potentiate LPS-stimulated IKK activity. While PKC and ERK participate in IKK activation by LPS and UTP, the phosphatidylinositide-phospholipase C-dependent activation of CaMK plays a major role in UTP potentiation of the LPS response.