Signal transduction pathways of nitric oxide release in primary microglial culture

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摘要

Abstract

Between one-third and one-half of all cases of sepsis are known to be caused by gram-positive microorganisms through the cell wall component, e.g. lipoteichoic acid (LTA). Gram-positive bacteria are also known to induce encephalomyelitis and meningeal inflammation, and enhance the production of nitric oxide (NO) via expression of inducible nitric oxide synthase (iNOS) in murine tissue macrophages. It remains to be explored if LTA could activate microglia considered to be resident brain macrophages. We report here that LTA derived from gram-positive bacteria (Staphylococcus aureus) significantly induces NO release and iNOS expression in primary microglia. LTA-induced NO accumulation was detected at 2 h in microglial culture and was significantly attenuated by pretreatment with anti-CD14, complement receptor type 3 (CR3) or scavenger receptor (SR) antibodies. LTA activated mitogen-activated protein kinases (MAPKs) such as extracellular signal-regulated kinase, p38 MAPK or c-Jun N-terminal kinase in cultured microglia. LTA-elicited microglial NO production was also drastically suppressed by SB203580 (p38 MAPK inhibitor) or pyrrolidine dithiocarbamate (an inhibitor of nuclear factor KB), indicating that p38 MAPK and nuclear factor KB were involved in microglial NO release after LTA challenge. These results suggest that gram-positive bacterial product such as LTA can activate microglia to release NO via the signal transduction pathway involving multiple LTA receptors (e.g. CD14, CR3 or SR), p38 MAPK and nuclear factor KB. The in vivo studv further confirmed that administered intracerebrally LTA induced considerable noticeable iNOS, phospho-lKB and phospho-p38 MAPK expression in microglia/macrophages.