Cilostazol Attenuates MCP-1 and MMP-9 Expression in vivo in LPS-administrated Balloon-injured rabbit aorta and in vitro in LPS-Treated THP-1 Cells

林豐彥

Tsai CS;Lin FY;Chen YH;Yang TL;Huang GS;Lin CY;Tsai YT;Li CY

摘要

Abstract

Monocyte chemoattractant protein-1 (MCP-1) and matrix metalloproteinase-9 (MMP-9) are involved in vascular inflammation. We tested the hypothesis, and explored the underlining mechanisms that cilostazol, a phosphodiesterase 3 inhibitor with antiplatelet and antithrombotic properties, inhibits lipopolysaccharide (LPS)-induced MCP-1 and MMP-9 expression. In a rabbit aorta balloon-injury model, administration of LPS increased macrophage infiltration and MCP-1 and MMP-9 expression; cilostazol supplementation prevented this phenomenon and reduced intimal hyperplasia. In contrast, the reverse zymography showed that cilostazol did not affect TIMP-1 expression in serum. In monocytic THP-1 cells, cilostazol and N6,O2'-dibutyryl-cAMP (dioctanoyl-cAMP, a cAMP analog) dose-dependently inhibited LPS-induced MCP-1 protein expression and MMP-9 activation, but did not affect the tissue inhibitor of metalloproteinase-1. Quantitative real-time polymerase chain reaction (PCR) showed that cilostazol inhibited MCP-1 and MMP-9 mRNA expression. Cilostazol significantly inhibited LPS-induced activation of p38, JNK, and nuclear factor-kappaB, and the respective inhibitors of p38 and JNK greatly reduced the level of LPS-induced MCP-1 and MMP-9, suggesting the involvement of the p38 and JNK pathways. In conclusion, cilostazol administered with LPS in vivo reduced neointimal hyperplasia and macrophage infiltration in the balloon-injured rabbit aorta; in vitro, cilostazol inhibits LPS-induced MCP-1 and MMP-9 expression. These data suggest that cilostazol may play an important role in preventing endotoxin- and injured-mediated vascular inflammation.