Inhibitory mechanisms of PMC and YC-1 in the induction of iNOS expression by lipoteichoic acid in RAW 264.7 macrophages.

許準榕
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Abstract

In the present study, the signal pathways involved in NO formation and iNOS expression in RAW 264.7 macrophages stimulated by LTA were investigated. We also compared the relative inhibitory activities and mechanisms of PMC, a novel potent antioxidant of alpha-tocopherol derivatives, with those of YC-1, an sGC activator, on the induction of iNOS expression by LTA in cultured macrophages in vitro and LTA-induced hypotension in vivo. LTA induced concentration (0.1-50 microg/mL)- and time (4-24 hr)-dependent increases in nitrite (an indicator of NO biosynthesis) in macrophages. Both PMC (50 microM) and YC-1 (10 microM) inhibited NO production, iNOS protein, mRNA expression, and IkappaBalpha degradation upon stimulation by LTA (20 microg/mL) in macrophages. On the other hand, PMC (50 microM) almost completely suppressed JNK/SAPK activation, whereas YC-1 (10 microM) only partially inhibited its activation in LTA-stimulated macrophages. Moreover, PMC (10 mg/kg, i.v.) and YC-1 (5 mg/kg, i.v.) significantly inhibited the fall in MAP stimulated by LTA (10 mg/kg, i.v.) in rats. In conclusion, we demonstrate that YC-1 shows more-potent activity than PMC at abrogating the expression of iNOS in macrophages in vitro and reversing delayed hypotension in rats with endotoxic shock stimulated by LTA. The inhibitory mechanisms of PMC may be due to its antioxidative properties, with a resulting influence on JNK/SAPK and NF-kappaB activations. YC-1 may be mediated by increasing cyclic GMP, followed by, at least partly, inhibition of JNK/SAPK and NF-kappaB activations, thereby leading to inhibition of iNOS expression..