Cellular mechanism of inhibition of superoxide anion generation in rat neutrophiles by the synthetic isoquinoline DMDI

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Abstract

This study was undertaken to assess the cellular localization of the inhibitory effect of a chemically synthetic isoquinoline compound 1-(3',4'-dimethoxybenzyl)-6,7-dichloroisoquinoline (DMDI) on the formyl-methionyl-leucyl-phenylalanine (fMLP)-induced respiratory burst in rat neutrophils. The DMDI concentration dependently inhibited the superoxide anion (O(2)(*-)) generation and O(2) consumption (IC(50) 12.2+/-4.9 and 15.2+/-8.4 microM, respectively) of neutrophils. DMDI did not scavenge the O(2)(*-) generated during the autoxidation of dihydroxyfumaric acid in a cell-free system. DMDI did not elevate cellular cyclic AMP levels. Inhibition of O(2)(*-) generation by DMDI in neutrophils was not reversed by a cyclic AMP-dependent protein kinase inhibitor, (8R,9S,11S)-(-)-9-hydroxy-9-hexoxycarbonyl-8-methyl-2,3,9,10-tetrahydro-8,11-epoxy-1H,8H,11H-2,7b,11a-triazadibenzo[a,g]cycloocta[cde]trinden-1-one (KT5720). The DMDI concentration dependently inhibited the late plateau phase but not the initial spike of fMLP-induced [Ca(2+)](i) changes in the presence of extracellular Ca(2+). However, DMDI had no effect on the fMLP-induced [Ca(2+)](i) changes in the absence of extracellular Ca(2+). In addition, DMDI did not affect the fMLP-stimulated phosphatidylinositol 3-kinase (PI3-kinase) activation. DMDI produced a concentration-dependent reduction in the formation of phosphatidic acid and phosphatidylethanol in the presence of ethanol from fMLP-stimulated neutrophils (IC(50) 13.3+/-4.0 and 9.4+/-4.3 microM, respectively). On the basis of the immunoblot analysis of the phosphorylation of the mitogen-activated protein (MAP) kinase, DMDI attenuated the fMLP-stimulated MAP kinase phosphorylation in a similar concentration range. Collectively, these results indicate that the inhibition of the respiratory burst by DMDI in rat neutrophils is mediated through the blockade of phospholipase D and MAP kinase signaling pathways.