Chloroquine induces the expression of inducible nitric oxide synthase in C6 glioma cells.

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摘要

Abstract

Chloroquine, a well-known lysosomotropic agent, has long been used for the treatment of malaria and rheumatologic disorders. However, therapeutic doses of chloroquine are known to cause behavioral side effects. In the present study, we investigated whether chloroquine stimulates inducible nitric oxide synthase (iNOS) expression and nitric oxide (NO) synthesis in C6 glioma cells. Chloroquine caused dose-dependent increase in iNOS protein expression and NO production in C6 glioma cells. A tyrosine kinase inhibitor (genistein), a protein kinase C (PKC) inhibitor (Ro 31-8220), and a p38 mitogen-activated protein kinase (MAPK) inhibitor (SB 203580) all respectively suppressed chloroquine-induced iNOS expression and NO release from C6 glioma cells. Chloroquine activates p38 MAPK and stimulates PKC-α and -δ translocation from the cytosol to the membrane in C6 glioma cells. Chloroquine-stimulated p38 MAPK activation was blocked by genistein (20 μM), Ro 31-8220 (3 μM), and SB 203580 (10 μM). Incubation of lipopolysaccharide (LPS)-stimulated cells with chloroquine at non-toxic concentrations (10–100 μM) for 48 h increased iNOS expression, and led to a significant loss of adherent cells. Induction of DNA fragmentation in floating cells indicated that the C6 glioma cells were undergoing apoptosis. Taken together, our data suggest that chloroquine may activate tyrosine kinase and/or PKC to induce p38 MAPK activation, which in turn induces iNOS expression and NO production.

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