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Downregulation of inducible nitric oxide synthase expression by a ceramide analogue in RAW 264.7 murine macrophages

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Nitric oxide (NO) has been studied and found to be an important intracellular modulator. The excess NO produced by the inducible nitric-oxide synthase (iNOS) is implicated in various inflammatory diseases and cellular injury. Inflammatory cytokines such as TNF- or IL-6 increase intracellular ceramide and ceramide may induce NO production and inflammation. In the present study, the effects of synthetic ceramide analogs on cellular cytotoxicity, iNOS expression and NO production were evaluated to find a molecule that specifically inhibits NO production. Of ten compounds tested, KY3336 and KY 3436 showed strong cytotoxic effects in human HL-60 cells. These analogues significantly inhibited the NO production in RAW 264.7 murine macrophage cells stimulated with lipopolysaccharide (LPS) and interferon (IFN)-gamma in a dose-dependent manner. Ceramide analogues also suppressed the iNOS level at 24 h. However, the expression of cyclooxygenase-2 was unaffected by analogue treatment. Our data demonstrate that the ability of ceramide analogues to inhibit iNOS may contribute to their anti-inflammatory activity.