Heme Oxygenase 1 Involves in Flavonoids Inhibition of Lipopolysaccharide-Induced Nitric Oxide Production in RAW264.7 Macrophages

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摘要

Abstract

The role of heme oxygenase-1 (HO-1) played in the inhibitory mechanism of flavonoids in lipopolysaccharide (LPS)-induced responses remained unresolved. In the present study, flavonoids, including 3-OH flavone, baicalein, kaempferol, and quercetin, induced HO-1 gene expression at the protein and mRNA levels in the presence or absence of LPS in RAW264.7 macrophages. This effect was associated with suppression of LPS-induced nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) protein expression. Hemin induced HO-1 protein expression and this was associated with the suppression of LPS-induced NO production and iNOS protein expression in a dose-dependent manner. In addition, an increase in bilirubin production was found in flavonoid- and hemin-treated cells. Hemin, at the doses of 10, 20, and 50 μM, dose-dependently stimulated the flavonoid (50 pM)-induced HO-1 protein expression, and enhanced their inhibitory effects on LPS-induced NO production and iNOS protein expression. Pretreatment of the HO-I inhibitor, tin protoporphyrin (10 μM), attenuated the inhibitory activities of the indicated flavonoids on LPS-induced NO production. Morphologic analysis showed that 3-OH flavone, baicalein, kaempferol, quercetin, hemin, and tin protoporphyrin did not cause any change in cell viability in the presence or absence of LPS. In contrast, only 3-OH flavone showed a significantinhibition of cell growth using the MTT assay. Transfection of an HO-I vector in macrophages (HO-1/RAW264.7) resulted in a 3-fold increase in HO-1 protein compared with that the parental RAW264.7 cells. NO production mediated by LPS in HO-I over-expressed RAW264.7 cells (HO-1/RAW264.7) was significant less than that in parental RAW264.7 cells. 3-OH Flavone, baicalein, kaempferol, and quercetin showed a more significant inhibition on LPS-induced NO production in HO-1/RAW264.7 cells than in parental RAW264.7 cells. These results provide evidence on the role of HO-I in the

inhibition of LPS-induced NO production by flavonoids. A combination of HO-1 inducers (i.e. hemin) and flavonoids might be an effective strategy for the suppression of LPS-induced NO production