Anti-inflammatory effect of heme oxygenase 1: Glycosylation and nitric oxide inhibition in macrophages.

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Abstract

Flavonoids including the aglycones, hesperetin (HT; ,7,30-trihydroxy-40-methoxyflavanone), and naringenin (NE; 5,7,40-trihydroxy flavanone) and glycones, hesperidin (HD; 5,7,30-trihydroxy-40-methoxy-flavanone 7-rhamnoglucoside) and naringin (NI; 5,7,40-trihydroxy flavanone 7-rhamno glucoside), were used to examine the importance of rutinose at C7 on the inhibitory effects of flavonoids on lipopolysaccharide (LPS)-induced nitric oxide production in macrophages. Both HT and NE, but not their respective glycosides HD and NI, induced heme oxygenase 1 (HO-1) protein expression in the presence or absence of LPS and showed time and dose-dependent inhibition of LPS-induced nitric oxide (NO) production and inducible nitric oxide synthase (iNOS) expression in RAW264.7, J774A.1, and thioglycolate-elicited peritoneal macrophages. Additive inhibitory effect of an HO-1 inducer hemin andNEor NI on LPS-inducedNOproduction andiNOS expression was identified, and HO enzyme inhibitor tin protoporphyrin (SnPP) attenuated the inhibitory effects of HT, NE, and hemin on LPS-induced NO production. Both NE and HT showed no effect on iNOS mRNA and protein stability in RAW264.7 cells. Removal of rutinose at C7 ofHDand NI by enzymatic digestion using hesperidinase (HDase) and naringinase (NIase) produce inhibitory activity on LPS-induced NO production, according to the production of the aglycones, HT and NE, by highperformance liquid chromatography (HPLC) analysis. Furthermore, the amount of NO produced by LPS or lipoteichoic acid (LTA) was significantly reduced in HO-1-overexpressing cells (HO-1/RAW264.7) compared to that in parental cells (RAW264.7). Results of the present study provide scientific evidence to suggest that rutinose at C7 is a negative moiety in flavonoid inhibition of LPS-induced NO production, and that HO-1 is involved in the inhibitory mechanism of flavonoids on LPS-induced iNOS and NO production. J. Cell. Physiol. 202: 579–590, 2005.