Heme oxygenase 1, nuclear factor E2-related factor 2, and nuclear factor kappaB are involved in hemin inhibition of type 2 cationic amino acid transporter expression and L-Arginine transport in stimulated macrophages.

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BACKGROUND: L-Arginine transport mediated by type 2 cationic amino acid transporter (CAT-2) is one crucial mechanism that regulates nitric oxide production mediated by inducible nitric oxide synthase. Heme oxygenase (HO)-1 induction has been reported to significantly attenuate inducible nitric oxide synthase expression and nitric oxide production. The authors sought to explore the effects of HO-1 induction on CAT-2 expression and L-arginine transport. The effects of HO-1 induction on nuclear factor E2-related factor 2 (Nrf2) and nuclear factor kappaB (NF-kappaB) were also investigated. METHODS: Murine macrophages (RAW264.7 cells) were randomized to receive lipopolysaccharide, lipopolysaccharide plus hemin (an HO-1 inducer; 5, 50, or 500 microm), lipopolysaccharide plus hemin (5, 50, or 500 microm) plus tin protoporphyrin (an HO-1 inhibitor), or lipopolysaccharide plus hemin (5, 50, or 500 microm) plus hemoglobin (a carbon monoxide scavenger). Then, cell cultures were harvested and analyzed. RESULTS: Lipopolysaccharide significantly induced Nrf2 activation and HO-1 expression. Lipopolysaccharide also significantly induced NF-kappaB activation, CAT-2 expression, and L-arginine transport. In a dose-dependent manner, hemin enhanced the lipopolysaccharide-induced Nrf2 activation and HO-1 expression. In contrast, hemin, also in a dose-dependent manner, significantly attenuated the lipopolysaccharide-induced NF-kappaB activation, CAT-2 expression, and L-arginine transport. Furthermore, the effects of hemin were significantly reversed by both tin protoporphyrin and hemoglobin.

CONCLUSIONS: HO-1 induction significantly inhibited CAT-2 expression and L-arginine transport in lipopolysaccharide-stimulated macrophages, possibly through mechanisms involved activation of Nrf2 and inhibition of NF-kappaB. In addition, carbon monoxide mediated, at least in part, the effects of HO-1 induction on CAT-2 expression and L-arginine transport.