



A carbon monoxide-releasing molecule (CORM-3) attenuates lipopolysaccharide- and interferon- γ -induced inflammation in microglia

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Abstract:

The development of carbon monoxide-releasing molecules (CO-RMs) in recent years helped to shed more light on the diverse range of anti-inflammatory and cytoprotective activities of CO gas. In this study, we examined the effect of a ruthenium-based water-soluble CO carrier (CORM-3) on lipopolysaccharide (LPS)- and interferon- γ (INF- γ)-induced inflammatory responses in BV-2 microglial cells and explored the possible mechanisms of action. BV-2 microglial cells were stimulated with either LPS or INF- γ in the presence of CORM-3 and the inflammatory response evaluated by assessing the effect on nitric oxide production (nitrite levels) and tumor necrosis factor- α (TNF- α) release. Similar experiments were also performed in the presence of inhibitors of guanylate cyclase (ODQ), NO synthase (L-NAME), heme oxygenase activity (tin protoporphyrin IX) or various mitogen-activated protein kinase (MAPK) inhibitors. CORM-3 significantly attenuated the inflammatory response to LPS and INF- γ as evidenced by a significant reduction ($p < 0.001$) in nitrite levels and TNF- α production ($P < 0.05$). Such effect was maintained in the presence of ODQ, L-NAME or tin protoporphyrin without showing any cytotoxicity. The use of an inactive form of CORM-3 that does not contain carbonyl groups (Ru(DMSO)₄Cl₂) failed to inhibit the increase in inflammatory markers suggesting that liberated CO mediates the observed effects. In addition, inhibition of phosphatidylinositol-3-phosphate kinase (PI3K) and extracellular signal-regulated kinase (ERK) pathways seemed to amplify the anti-inflammatory effect of CORM-3, particularly in cells stimulated with INF- γ . These results suggest that the anti-inflammatory action of CORM-3 could be exploited to mitigate microglia activation in neuro-inflammatory diseases.

Key words:

carbon monoxide-releasing molecules (CO-RMs), BV-2 microglia, LPS, interferon- γ , inflammation
