Lithium Induces Heme Oxygenase-1 Expression and Suppresses Lipopolysaccharide-induced Inducible Nitric Oxide Synthase Expression in C6 Glioma Cells.

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摘要

Abstract

Lithium has been widely used to treat manic depression and bipolar behavior. In the present study, we show that treatment of C6 glioma cells with lithium induced HO-1 expression at both mRNA and protein levels. Lithium increased intracellular production of reactive oxygen species (ROS). Inhibition of intracellular ROS production by N-acetylcysteine resulted in a decreased HO-1 expression in C6 glioma cells. Lithium activated the phosphatidylinsitol 3-kinase (PI 3-K) /Akt pathway and increased phosphorylations of PDK-1 and Akt/PKB. Inhibition of PI 3-K/Akt pathway by LY294002 reduced lithium-induced HO-1 expression. Lithium suppressed LPS-induced inducible nitric oxide synthase (iNOS) expression and nitrite accumulation. Inhibition of HO-1 by tin protoporphyrin reversed the suppression of LPSstimulated nitrite accumulation by lithium. A CO releasing molecule, tricarbonyldichloro-ruthenium (II) dimmer, suppressed LPS-induced nitrite accumulation in C6 glioma cells. Scavenging CO by hemoglobin significantly attenuated the suppressive effects of lithium. Taken together, these data indicate that lithium may increase ROS production, which triggers Akt/PKB signaling pathway and HO-1 induction. The induction of HO-1 leads to CO generation, which in turn suppresses LPSinduced iNOS expression in C6 glioma cells.