NF-κB inhibitors stabilize the mRNA of high-affinity type-2 cationic amino acid transporter in LPS-stimulated rat liver

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摘要

Abstract

BACKGROUND: Induction of inducible nitric oxide synthase (iNOS) results in nitric oxide (NO) overproduction during endotoxemia. Cellular uptake of L-arginine, modulated by the isozymes of type-2 cationic amino acid transporters (CAT), including CAT-2, CAT-2A and CAT-2B, has been reported to be a crucial factor in the regulation of iNOS activity. We sought to elucidate the expression of CAT-2 isozymes and the role of nuclear factor-kappaB (NF-kappaB) in this expression in lipopolysaccharide (LPS)-treated rat liver. METHODS: Adult male Sprague-Dawley rats were randomly given intravenous (i.v.) injections of normal saline (N/S), LPS, LPS preceded by an NF-kappaB inhibitor (PDTC, dexamethasone or salicylate) or an NF-kappaB inhibitor alone. After injection, rats were sacrificed at different times and enzyme expression and liver injury were examined. Hepatic and systemic NO production were also measured. RESULTS: CAT-2, CAT-2A and CAT-2B were constitutively expressed in un-stimulated rat liver. LPS stimulation not only significantly increased iNOS mRNA and NO concentrations but also decreased the mRNA concentrations of CAT-2 and CAT-2B, but not CAT-2A, in a time-dependent manner. LPS-induced hepatic and systemic NO overproduction was associated with hepatocellular injury. Pre-treatment with NF-kappaB inhibitors significantly attenuated LPS-induced iNOS induction as well as CAT-2/CAT-2B mRNA destabilization, which was associated with significant inhibition of NO biosynthesis and less liver injury. CONCLUSION: NF-kappaB inhibitors stabilize CAT-2 and CAT-2B mRNA in LPS-stimulated rat liver. The hepatic CAT-2/CAT-2B pathway may be a constitutive part of cytoprotective mechanisms against sepsis.