NF-kB inhibitors significantly attenuate the transcription of high affinity type-2 cationic amino acid transporter in stimulated rat kidney

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摘要

Abstract

BACKGROUND: Sepsis-induced renal failure is closely related to inducible nitric oxide synthase (iNOS) upregulation and nitric oxide (NO) overproduction. Trans-membrane L-arginine transportation mediated by type-2 cationic amino acid transporter (CAT-2) isozymes, including CAT-2, CAT-2A, and CAT-2B, is one of the crucial mechanisms that regulate NO biosynthesis by iNOS. We previously had shown that endotoxemia significantly upregulated renal CAT-2 and CAT-2B but not CAT-2A expression. This study was, thus, conducted to further explore the role of nuclear factor-kappaB (NF-kappaB) in regulating the expression of CAT-2 isozymes in lipopolysaccharide (LPS)-treated rat kidney. METHODS: Adult male Sprague-Dawley rats were randomly given intra-peritoneal injections of normal saline (N/S), LPS, LPS plus NF-kappaB inhibitor pre-treatment (PDTC, dexamethasone, or salicylate), or an NF-kappaB inhibitor alone. The rats were sacrificed at 6 hours after LPS injection and enzyme expression and renal injury were examined. RESULTS: Renal iNOS, CAT-2, and CAT-2B were significantly upregulated in LPS-stimulated rat kidney. NF-kappa B inhibitors significantly attenuated this upregulation induced by LPS and resultantly attenuated renal NO biosynthesis and renal injury induced by LPS. In contrast, renal CAT-2A expression was not affected by either LPS or NF-kappaB inhibitors. CONCLUSIONS: LPS co-induces iNOS, CAT-2 and CAT-2B expression in LPS-stimulated rat kidney. Furthermore, inhibition of NF-kappaB significantly attenuates NO biosynthesis through inhibition of iNOS, CAT-2, and CAT-2B, and, in turn, significantly reduces endotoxemia-induced renal injury.