Ketamine inhibits tumor necrosis factor-α and interleukin-6 gene expressions in lipopolysaccharide-stimulated macrophages through suppression of toll-like receptor 4-mediated c-jun N-terminal kinase phosphorylation and activator protein-1 activation

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Abstract

Our previous study showed that ketamine, an intravenous anesthetic agent, has anti-inflammatory effects. In this study, we further evaluated the effects of ketamine on the regulation of tumor necrosis factor-α (TNF-α) and interlukin-6 (IL-6) gene expressions and its possible signaltransducing mechanisms in lipopolysaccharide (LPS)-activated macrophages. Exposure of macrophages to 1, 10, and 100 μM ketamine, 100 ng/ml LPS, or a combination of ketamine and LPS for 1, 6, and 24 h was not cytotoxic to macrophages. A concentration of 1000 μMof ketamine alone or in combined treatment with LPS caused significant cell death. Administration of LPS increased cellular TNF-α and IL-6 protein levels in concentrationand time-dependent manners. Meanwhile, treatment with ketamine concentration- and time-dependently alleviated the enhanced effects. LPS induced TNF-α and IL-6 mRNA syntheses. Administration of ketamine at a therapeutic concentration (100 μM) significantly inhibited LPS-induced TNF-α and IL-6 mRNAexpressions. Application of toll-like receptor 4 (TLR4) small interfering (si)RNA into macrophages decreased cellular TLR4 levels. Co-treatment of macrophages with ketamine and TLR4 siRNA decreased the LPS-induced TNF-α and IL-6 productions more than alone administration of TLR4 siRNA. LPS stimulated phosphorylation of c-Jun N-terminal kinase and translocation of c-Jun and c-Fos from the cytoplasm to nuclei. However, administration of ketamine significantly decreased LPS-induced activation of c-Jun N-terminal kinase and translocation of c-Jun
and c-Fos. LPS increased the binding of nuclear extracts to activator protein-1 consensus DNA oligonucleotides. Administration of ketamine significantly

ameliorated LPS-induced DNA binding activity of activator protein-1. Therefore, a clinically relevant concentration of ketamine can inhibit TNF-α and IL-6 gene expressions in LPS-activated macrophages. The suppressive mechanisms occur through suppression of TLR4-mediated sequential activations of c-Jun N-terminal kinase and activator protein-1.

Keywords: Ketamine; Macrophages; LPS; TNF-α; IL-6; TLR4; JNK/AP-1