Lipoteichoic acid-induced TNF-α and IL-6 gene expressions and oxidative stress production in macrophages are suppressed by ketamine through downregulating toll-like receptor 2-mediated activation of ERK1/2 and NFκB

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Abstract

Lipoteichoic acid (LTA), a Gram-positive bacterial outer membrane component, can cause septic shock. Our previous studies showed that ketamine has anti-inflammatory and antioxidant effects on Gram-negative LPS-induced macrophage activation. In this study, we further evaluated the effects of ketamine on the regulation of LTA-induced tumor necrosis factor-[alpha] (TNF-[alpha]) and interleukin-6 (IL-6) gene expressions and oxidative stress production in macrophages and its possible mechanisms. Exposure of macrophages to a therapeutic concentration of ketamine (100 [mu]M) inhibited LTA-induced TNF-[alpha] and IL-6 expressions at protein or mRNA levels. In parallel, ketamine at 100 [mu]M reduced LTA-stimulated phosphorylation of extracellular signal-regulated kinase (ERK) 1/2. Sequentially, ketamine reduced the LTA-triggered translocation of nuclear factorkappaB (NF[kappa]B) from the cytoplasm to nuclei and its transactivation activity. Pretreatment with PD98059, an inhibitor of ERK, decreased LTA-enhanced NF[kappa]B activation and TNF-[alpha] and IL-6 mRNA syntheses. Co-treatment with ketamine and PD98059 synergistically suppressed the LTAinduced translocation and transactivation of NF[kappa]B and biosyntheses of TNF-[alpha] and IL-6 mRNA. Application of toll-like receptor 2 (TLR2) small interference (si)RNA into macrophages decreased the levels of this receptor, and simultaneously ameliorated LTA-augmented NF[kappa]B transactivation and consequent production of TNF-[alpha] and IL-6 mRNA. Co-treatment with ketamine and TLR2 siRNA synergistically lowered TNF-[alpha] and IL-6 mRNA syntheses in LTA-activated macrophages. Ketamine and TLR2 siRNA could reduce the LTA-caused increases in production of nitrite and intracellular reactive oxygen species in macrophages, and their combination had better effects than a single exposure. Thus, this study shows that one of possible mechanisms involved in ketaminecaused inhibition of LTA-induced TNF-[alpha] and IL-6 gene expressions and oxidative stress production is through downregulating TLR2-mediated phosphorylation of ERK1/2 and the subsequent translocation and

transactivation of NF[kappa]B.