Propofol inhibits lipoteichoic acid-induced iNOS gene expression in macrophages possibly through downregulation of toll-like receptor 2-mediated activation of Raf-MEK1/2-ERK1/2-IKK-NFkappaB.

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Abstract

Our previous study showed that propofol suppressed Gram-negative bacterial LPS-induced NO biosynthesis. Lipoteichoic acid (LTA), an outer membrane component of Gram-positive bacteria, can induce septic shock. This study was further aimed to evaluate the effects of propofol on LTA-induced iNOS gene expression in macrophages and its possible molecular mechanisms. Exposure of macrophages to LTA increased production of nitrite and intracellular reactive oxygen species, but propofol reduced such enhancements in concentration- and time-dependent manners. Treatment of macrophages with LTA-induced iNOS mRNA and protein productions. Meanwhile, propofol at a clinically relevant concentration of 50 microM significantly inhibited LTA-caused augmentations of iNOS mRNA and protein syntheses. In parallel, exposure to LTA increased translocation of nuclear factor-kappa B (NFkappaB) from the cytoplasm to nuclei. Propofol at 50 microM decreased such translocation. Analyses by an electrophoretic mobility shift and reporter gene further showed that propofol could alleviate LTA-induced transactivation of NFkappaB. Sequentially, propofol decreased phosphorylation of IKK, ERK1/2, MEK1/2, and Raf in LTA-stimulated macrophages. Application of toll-like receptor 2 (TLR2) small interference (si)RNA decreased the translation of this receptor and Raf phosphorylation in LTA-stimulated macrophages. Co-treatment with propofol and TLR2 siRNA synergistically ameliorated LTA-induced iNOS mRNA expression and nitrite production. Thus, this study shows that propofol can downregulate NO biosynthesis via inhibiting iNOS gene expression. The suppressive mechanism occurs possibly through reduction of TLR2-mediated sequential activation of Raf-MEK1/2-ERK1/2-IKK-NFkappaB.