Dimethylacetyl-β-cyclodextrin as a Novel Antagonist of Septic Shock Induced by Lipopolysaccharide and D-galactosamine in Mice

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Purpose. To identify whether hydrophilic cyclodextrin derivatives (CyDs) improve septic shock induced by lipopolysaccharide (LPS)/D-galactosamine (D-gal) in mice.

Methods. Natural, methylated, sulfobutyl ether, hydroxyalkeyalted and branched CyDs were used. The effects of CyDs on nitric oxide (NO) and tumor necrosis factor-α (TNF-α) production in several mouse macrophages stimulated with LPS in vitro were investigated. Nitrite, iNOS and TNF-α were determined by Griess method, Western blotting and ELISA, respectively. The mRNA of *iNOS* and *TNF-α* were determined by RT-PCR analysis. The interaction of LPS with CyDs was evaluated by utilizing a competitive inclusion phenomenon. The binding of FITC-labeled LPS to the surface of RAW264.7 cells and the expression of CD14 and Toll-like receptor 4 (TLR4)/MD2 complex were measured by a flow cytometry. The effects of CyDs on septic shock were evaluated by the survival rate of mice after intraperitoneal injection of saline containing LPS/D-gal in the absence and presence of CyDs.

Results. Of 15 CyDs, dimethyl-α-CyD (DM-α-CyD) and dimethylacetyl-β-CyD (DMA-β-CyD) have greater inhibitory activity than do the other CyDs against NO production in mouse macrophages stimulated with LPS. Likewise, DM-α-CyD and DMA-β-CyD impaired the TNF-α production in the macrophages. DMA-β-CyD, but not DM-α-CyD, had a greater interaction with LPS. On the contrary, DM-α-CyD, not DMA-β-CyD, released CD14 from lipid rafts of RAW264.7 cell membranes into the medium, although no CyDs affected the level of TLR4/MD2 complex on the membranes. DMA-β-CyD, not DM-α-CyD, markedly improved a survival rate of septic mice treated with LPS/D-gal, reflecting the attenuation of the plasma TNF-α level after co-administration of DMA-β-CyD.

Conclusions. These results suggest the potential use of DMA-β-CyD as an antagonist of septic shock induced by LPS.

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