Clonidine-induced enhancement of iNOS expression involves NF-κB

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摘要

Abstract

Background

Up-regulation of inducible nitric oxide synthase (iNOS) plays a crucial role in initiating systemic inflammatory response during sepsis. Clonidine, a widely used anti-hypertension agent and an effective adjunct to anesthesia/sedation and pain management, has been shown to enhance iNOS expression, but the mechanisms underlying its action remain unstudied. Among the possible mechanisms, enzyme induction and enzyme stability are two most likely ones. Endotoxin-induced iNOS induction is regulated by nuclear factor-κB (NF-κB). Stability of iNOS mRNA is regulated by RNA stabilizing factor, e.g., Hu antigen R (HuR), and RNA destabilizing factors, e.g., AU-rich element/poly(U) binding factor-1 (AUF-1) and tristetraprolin (TTP). We sought to elucidate which of these enzymes is involved in the clonidine-induced enhancement of iNOS expression.

Materials and methods

Confluent murine macrophages were randomized to receive 1× phosphated buffer saline, clonidine (100 μm), lipopolysaccharide (LPS, 100 ng/mL), or LPS plus clonidine (100 μm). Expression of iNOS and stability of iNOS mRNA were then measured. Expression of the aforementioned relevant enzymes in each group was also analyzed.

Results

Clonidine significantly enhanced LPS-induced iNOS expression. Clonidine also significantly enhanced LPS-induced NF-κB activation by enhancing the nuclear translocation of NF-κB as well as increasing the NF-κB-DNA binding activity. However, clonidine did not affect iNOS mRNA stability. The LPS-induced expression of AUF-1 and TTP but not HuR was significantly enhanced by clonidine.

Conclusions

NF-κB is involved in the clonidine-induced enhancement of iNOS expression in endotoxin-activated macrophages. Clonidine exerts its action on iNOS expression through

increasing enzyme induction instead of enzyme stability.