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EFFECTS OF IMMUNOSUPPRESSANTS ON iNOS GENE EXPRESSION IN MACROPHAGES

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In the present study, the mechanism by which dexamethasone (DEX), acetylaminofluorene (AAF), and Δ^9-tetrahydrocannabinol (Δ^9-THC) inhibited iNOS gene expression in bacterial lipopolysaccharide (LPS)-activated RAW 264.7 cells was investigated. The decrease in NO, as demonstrated by measurement of nitrite was found to correlate well with a decrease in inducible nitric oxide synthase (iNOS) mRNA. Since the promoter in iNOS gene contains binding motifs for NF-κB/Rel, AP-1, NF-IL6, and Oct, which appear to be important in LPS-mediated iNOS induction, the effects of the chemicals on the activation of these transcription factors were examined. Treatment of DEX or AAF to RAW 264.7 cells induced a dose-related inhibition of NF-κB/Rel in chloramphenicol acetyltransferase activity and electrophoretic mobility shift assay. It has recently been shown that iNOS transcription is under the control of the cAMP signaling cascade. We demonstrate that Δ^9-THC, an inhibitior of cAMP signaling, inhibits the activation of NF-κB/Rel in response to LPS stimulation. Pyrrolidine dithiocarbamate, a relatively specific inhibitor of NF-κB/Rel, also inhibited the production of nitrite. Collectively, this series of experiments indicate that NF-κB/Rel is positively regulated by LPS to help initiate iNOS gene expression in macrophages. This activation of iNOS is attenuated by DEX, AAF, and Δ^9-THC through the inhibition of NF-κB/Rel.