DELTA^9-TETRAHYDROCANNABINOL INHIBITION OF TUMOR NECROSIS FACTORα PRODUCTION BY RAW264.7 MACROPHAGES

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Delta^9-tetrahydrocannabinol (Delta^9-THC), the major psychoactive component of marijuana, has been shown to be immuno-suppressive and to alter macrophage soluble cytolytic activity. The purpose of this study was to determine whether Delta^9-THC inhibited this function by altering tumor necrosis factorα (TNFα) production. The RAW264.7 macrophage cell line was used to produce macrophage conditioned medium (MØCM) containing TNFα which lysed L929 tumor cells. RAW264.7 macrophages were exposed to Delta^9-THC for 48 hours and were triggered with lipopolysaccharide (LPS) for 2 hours to 24 hours. Cytotoxicity assays demonstrated that MØCM produced by RAW264.7 macrophages exposed to 10^{-5} M Delta^9-THC was deficient in tumoricidal activity. Immuno-precipitation with an anti-TNFα antibody confirmed that RAW264.7 macrophages produced, and secreted, TNFα after triggering with LPS. In the presence of 10^{-5} M Delta^9-THC, less TNF was present in MØCM while intracellular levels of TNFα remained unaffected. Northern analysis revealed that Delta^9-THC had no effect on levels of TNFα messenger RNA (mRNA) from RAW264.7 macrophages triggered with LPS for 2 hours, 4 hours, or 6 hours. Although, slightly less TNFα mRNA was detected after triggering of cells with LPS for 24 hours. These results indicate that Delta^9-THC has no major effect on TNFα message. Radiolabel pulsing and pulse-chase experiments revealed that the intracellular conversion of the 26 kDa presecreted form of TNFα to the 17 kDa secreted form was inhibited by the drug. These results indicate that Delta^9-THC suppresses soluble macrophage tumoricidal activity, at least in part, by decreasing the intracellular conversion of presecretory TNFα to its 17 kDa secretory form.

ACKNOWLEDGEMENT:

Supported by National Institute on Drug Abuse grant RO1-DA05832, National Service Award F32 DA05448 to K. Fischer-Stenger, and Research Fellowship Award F31 DA05518 to D.A. Dove Pettit.

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