DELTA-9-TETRAHYDROCANNABINOL INHIBITION OF RAW MACROPHAGE TUMORICIDAL ACTIVITY IS DEPENDENT UPON THE ACTIVATION STIMULUS

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We have shown that peritoneal macrophages obtained from mice treated *in vivo* with Bacillus Calmétte-Guérin (BCG) and delta-9-tetrahydrocannabinol (THC), the major psychoactive component of marijuana, are impaired in their ability to effect cell contact-dependent cytolysis of tumor cells, amoebae, and virus-infected cells. However, these cells are able to bind their targets, suggesting that THC inhibits the induction and/or secretion of cytolytic molecules. We have employed an *in vitro* model system consisting of effector RAW264.7 macrophage-like cells and target murine tumor cells, susceptible to different macrophage cytolytic mechanisms, to determine whether THC exerts its effects on distinct macrophage killing pathways. RAW264.7 cells were treated with 10^{-5}M, 10^{-6}M, 10^{-7}M, or 10^{-8}M THC and were activated for 4h with 10 U/ml IFN-g plus 100 ng/ml LPS or with 1 µg/ml LPS. Cells, then, were employed in a chromium release assay using mouse L929 fibroblasts and P815 mastocytoma cells as targets. L929 cells are TNF-sensitive and nitric oxide (NO·)-resistant whereas P815 cells are TNF-resistant and NO·-sensitive. Results demonstrate that the protocol employed for macrophage activation is important in determining the effects of THC. TNF-dependent cell contact-dependent killing of macrophages was inhibited at both high and low concentrations of THC (10^{-5}M-10^{-7}M). Twenty hour conditioned medium (20h CM) obtained from macrophages treated with 10^{-5}M THC contained decreased levels of TNF when assayed using a TNF-specific enzyme-linked immunosorbent assay (ELISA). In contrast, L-arginine-dependent cell contact-dependent killing, in which NO· is the effector molecule, was inhibited only at high THC concentrations (10^{-5}M). Macrophage activation with IFN-g plus LPS overcame this drug-induced inhibition. Levels of NO^-_2 produced by RAW cells treated with IFN-g plus LPS or by LPS alone were assessed using the Griess reagent. Decreased levels of NO^-_2 were produced in response to activation with LPS but not with IFN-g plus LPS. These results indicate that at the higher drug concentrations (*i.e.,* 10^{-5}M). THC exerts a generalized inhibition of macrophage cell contact-dependent cytolytic activities. In contrast, at lower drug concentrations (*i.e.,* 10^{-7}M), THC specifically inhibits TNF-mediated killing.

ACKNOWLEDGEMENT:

This research was supported by NIDA grant RO1-DA05832.

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