THE ENDOCANNABINOID SYSTEM PROTECTS RAT GLIOMA CELLS AGAINST HIV-1 TAT-
INDUCED CYTOTOXICITY: MECHANISM AND REGULATION

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Plant and synthetic cannabinoids modulate nitric oxide (NO) levels and exert both pro- and anti-apoptotic effects in cells of the CNS. Here we studied the effect in rat glioma C6 cells of cannabinoid receptor agonists on the release of NO and cell toxicity induced by the human immuno-deficiency virus-1 Tat protein (HIV-1 Tat). Activation of cannabinoid receptors by WIN55,212-2 inhibited the expression of inducible NO synthase (iNOS) and the subsequent release of NO caused by treatment of C6 cells with HIV-1 Tat and interferon-g (IFN-g). Although both CB\textsubscript{1} and CB\textsubscript{2} cannabinoid receptors are expressed in C6 cells, the effect of WIN-55,212-2 was uniquely due to CB\textsubscript{1} receptors, as shown by experiments carried out with selective CB\textsubscript{1} and CB\textsubscript{2} receptor agonists and antagonists. CB\textsubscript{1} receptor stimulation also inhibited HIV-1 Tat + IFN-g-induced, and NO-mediated, cell toxicity. On the other hand, cell treatment with HIV-1 Tat + IFN-g induced a significant inhibition of CB\textsubscript{1}, but not and CB\textsubscript{2}, receptor expression, thus suggesting that part of HIV-1 Tat cytotoxicity might be due to down-regulation of the neuroprotective tone exerted by the endogenous cannabino id system. However, HIV-1 Tat + IFN-g also induced a small albeit significant inhibition of the uptake of the endocannabinoid anandamide by C6 cells, with no effect on anandamide hydrolysis, thus indicating that the negative effect of HIV-1 Tat on CB\textsubscript{1} expression might be compensated for by an enhancement of the amounts of extracellular endocannabinoids available for CB\textsubscript{1} stimulation. These findings show that the endocannabinoid system is implicated in the control of HIV-1 Tat-induced cytotoxicity and is subject to regulation by HIV-1 Tat, through the elevation of NO production.