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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-deficency 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_1 and CB_2 cannabinoid receptors are expressed in C6 cells, the effect of WIN-55,212-2 was uniquely due to CB_1 receptors, as shown by experiments carried out with selective CB_1 and CB_2 receptor agonists and antagonists. CB_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_1, but not and CB_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 cannabinoid 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_1 expression might be compensated for by an enhancement of the amounts of extracellular endocannabinoids available for CB_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.