Immunomodulatory effects of cannabinoids in human T-lymphocytes

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Background: Circulating levels of endocannabinoids are elevated in obese and hyperglycaemic patients and may contribute to immune dysfunction in obesity and diabetes. Cannabinoids have been shown to evoke both pro- and anti-inflammatory responses, acting via CB_1 and CB_2 receptors on immune cells. In the present study we compared the responses of human T-cells to varying concentrations (0.1–1000nM) of endocannabinoids (anandamide and 2-arachidonoylglycerol, 2-AG), a phytocannabinoid (Δ^9-tetrahydrocannabinol, Δ^9-THC), and a synthetic CB_2 receptor agonist (JWH-015).

Methods: Lymphocytes were isolated from the peripheral blood of healthy male and female subjects (*n*=12; aged 20-30 years), and cell surface expression of the T-cell activation marker CD69 was assessed on $CD3^+$, $CD4^+$ and $CD8^+$ T-cells following 24 h cannabinoid treatment, using four-colour flow cytometry. In addition, lymphocyte CB_1 and CB_2 receptor expression was measured by real-time RT-PCR. The human Jurkat T-cell line was used to assess the effects of cannabinoids on T cell migration, to the chemokine CXCL12, in single-well Boyden chemotaxis chambers (*n*=4-5).

Results: Endocannabinoids did not significantly alter T-cell activation, however, Δ^9-THC increased the proportion of CD3+ T-cells expressing CD69 (from 1±0 to 3.59±1.54; P=0.09) at low concentrations (0.1nM), and decreased (from 1±0 to 0.39±0.22; P<0.05) at high concentrations (100nM). JWH-015 suppressed PMA-induced %CD69 expression at all concentrations tested (from 1±0 to between 0.28±0.21 and 0.66±0.00; P<0.05). There were no significant differences between $CD4^+$ and $CD8^+$ T-cell phenotypes. CD69 was not correlated with CB_1 or CB_2 receptor mRNA expression. Endocannabinoids did not affect T-cell migration to CXCL12, while Δ^9-THC and JWH-015 reduced T-cell migration in a concentration-dependent manner (e.g. for Δ^9-THC: 100±0% cell migration score for control versus 93±7% at 1nM; 46±8% at 10nM; 27±19% at 100nM; and 0±0% at 1000nM; P<0.01).

Conclusions: These data reveal differences in the immunomodulatory effect of endo- versus synthetic and phyto-cannabinoids and concentration-dependent effects, with low Δ^9-THC concentrations stimulating and high concentrations inhibiting T-cell activation. Studies using selective CB_1 and CB_2 receptor antagonists are warranted to confirm the receptor involved in mediating these responses.