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Δ^9 Tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells

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Abstract

Marijuana, a widely abused drug in the US, and its derivatives (cannabinoids) have been used in AIDS and cancer patients for treatment of intractable nausea and cachexia. Yet, objective investigations of the effect of cannabinoids on the human immune system are few. We investigated the effect of Δ^9 tetrahydrocannabinol (THC) and cannabidiol (CBD) on cytokine production in vitro by human leukemic T, B, eosinophilic and $CD8^+$ NK cell lines as models. THC decreased constitutive production of IL-8, MIP-1α, MIP-1β, and RANTES and phorbol ester stimulated production of TNF-α, GM-CSF and IFN-γ by NK cells. It inhibited MIP-1β in HTLV-1 positive B-cells but tripled IL-8, MIP-1α and MIP-1β in B-cells and MIP-1β in eosinophilic cells but doubled IL-8. Both cannabinoids strongly inhibited IL-10 production by HUT-78 T-cells. Results indicate that THC and nonpsychotropic CBD have complex lineage and derivative specific effects on cytokines consistent with previous animal studies. These effects while of potential benefits in some inflammatory/autoimmune diseases may worsen HIV infection, tumorigenesis and allergic inflammation in the lung.

Keywords: Cytokines; Cannabinoids; Chemokines; HIV-1

1. Introduction

Marijuana remains a widely abused drug in the United States in 1997. Its use by younger teenagers has, in fact, been increasing over recent years. These children have been reported to have an increased incidence of infections, but normal immune studies, such as CBC, differential, and immunoglobulins (Spector, 1996). In addition, marijuana and its derivatives (cannabinoids) have been used in AIDS and cancer patients for treatment of intractable nau-

Abbreviations: THC = Δ^9 Tetrahydrocannabinol; CBD = Cannabidiol; HIV-1 = Human immunodeficiency virus 1; NK = Natural killer; IL-2 = Interleukin-2; MIP-1α = Macrophage inflammatory protein 1α; MIP-1β = Macrophage inflammatory protein 1β; RANTES = Regulated on activation normal T cell expressed and secreted; IL-8 Interleukin-8; IL-10 = Interleukin-10; TNF-α = Tumor necrosis factor α; GM-CSF = Granulocyte-macrophage colony stimulating factor; IFN-γ = Interferon gamma; TPA = 12-*O*-Tetrahydrocannabinol-13-acetate

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sea and cachexia (Mechoulam et al., 1996). The drug has been legalized for medical use in California, but its prescription by physicians was banned by the Federal Government. Yet, detailed scientific investigations of the effect of cannabinoids on the human immune system are few.

Recently, receptors for Δ^9 tetrahydrocannabinol (THC), the main psychoactive component of marijuana have been identified on immune cells (Bouaboula et al., 1993; Galieque et al., 1995; Daaka et al., 1996; Dove Pettit et al., 1996; Daaka et al., 1997). At higher concentrations, the highly lipid soluble THC may alter membrane function, resulting in nonreceptor-mediated alterations in immune cell activity as well (Klein et al., 1995). Other investigators have shown THC to alter killing by NK cells and the expression of cytokines such as TNF-α (Kusher et al., 1994; Spector and Lancz, 1991). THC adversely affects human neutrophil functions (Djeu et al., 1991). However, the effects of cannabinoids on chemokines, glycoproteins critical to inflammation and immune cell function, have not been determined. The CCR5 and CXCR4 chemokine receptors function as coreceptors for HIV-1 entry into $CD4^+$ cells (Unutmaz and Littman, 1997; Bleul et al., 1997; Cramer et al., 1997; Wells and Peitsch, 1997). The CC family of chemokines inhibit HIV-1 infection and replication (Cocchi et al., 1995). Thus, the modulation of chemokines and other cytokines by cannabinoids could effect HIV-1 infection and AIDS pathogenesis, as well as resistance to infections, tumor progression, and the inflammatory response.

Plasma levels of THC in humans range from 10^{-9}–10^{-6} M (Azorlosa et al., 1992). THC is concentrated 15–20 fold higher in some tissues, and has a long half life of approximately 4 days. It is lipid soluble and is stored in fat at 200 ng/g (Johansson et al., 1989).

We have, therefore, examined the effect of THC, at concentrations which may be achieved by marijuana users on chemokine/cytokine production by eosinophil, $CD8^+$ NK, T, and HTLV-1 positive B cell lines (Srivastava, 1990; Srivastava et al., 1993). We have also examined the effect of cannabidiol (CBD), a non-psychoactive, major constituent of marijuana, with a systemic availability 31% higher than THC, (Watzl et al., 1991) on chemokine expression.

2. Materials and methods

2.1. Cell lines

HUT-78, an HTLV-1 genome positive, virus negative T cell line; SRIS-EOSL, an eosinophilic leukemia cell line; SRIH-B (ATL), an HTLV-1 positive B cell line; and SRIK-NKL, an NK leukemia cell line were used in the present study. SRIK-NKL is positive for CD8, granzyme A, perforin, TIA antigen, kills K562 cells, and expresses high affinity IL-2 receptors (Srivastava, 1990; Srivastava et al., 1993). All cell lines, which grew as suspension cultures, were maintained in RPMI-1640 medium containing 5% heat-inactivated fetal calf serum without antibiotics, in a humidified CO_2 incubator at 37°.

2.2. Drug preparation

Stock solutions (2 mg/ml) of Δ^9 tetrahydrocannabinol, or cannabidiol in ethanol were diluted in

Table 1
Effect of ethanol on constitutive cytokine production (pg/ml) in SRIS-EOSL, SRIH-B (ATL) and HUT-78 and on TPA (5×10^{-9} M) induced cytokine production (pg/ml) in SRIK-NKL cells

Ethanol (%)	SRIS-EOSL		SRIH-B (ATL)		HUT-78	SRIK-NKL	
	IL-8	MIP-1α	IL-8	MIP-1α	IL-10	GM-CSF	TNF-α
0	312 ± 6	705 ± 5	464 ± 24	2490 ± 10	1400 ± 100	246 ± 100	250 ± 10
0.125	316 ± 4	697 ± 7	474 ± 14	2550 ± 50	1375 ± 25	200 ± 25	270 ± 10
0.25	316 ± 5	675 ± 15	440 ± 10	2650 ± 25	1175 ± 75	198 ± 75	260 ± 5
0.50	316 ± 6	663 ± 3	448 ± 32	2700 ± 100	1150 ± 50	–	–
P-value for Bootstrap trend *t*-test	0.7993	0.0218	0.4420	0.0536	0.0480	0.0088	0.4930

Table 2
Effect of THC on Chemokine production (pg/ml) in SRIK-NKL cell line

THC (μg/ml)	MIP-1α	MIP-1β	RANTES
0	650 ± 50	875 ± 25	525 ± 15
2.5	375 ± 25	422 ± 7	405 ± 35
5.0	302 ± 22	320 ± 5	405 ± 5
P-value for Bootstrap trend *t*-test	0.0175	0.0024	0.0302

RPMI-1640 5% fetal calf serum, to give 10 μg/ml, 5 μg/ml, or 2.5 μg/ml of drug. TPA was used at final concentration of 5×10^{-9} M. Ethanol 0.5% at the highest drug concentration was found to have no effect on cell viability (trypan blue), or cytokine production. To establish this fact, specifically with the cell lines used here, the effect of ethanol on cytokine production by these cell lines was tested.

2.3. Incubation

Cells were pelleted by centrifugation, suspended in fresh medium at $0.5–0.8 \times 10^6$ cells/ml with or without drug, and incubated in 12–24 well culture plates in a CO_2 incubator at 37°C. Following 24 h incubation, the culture supernatants were recovered by centrifugation for cytokine quantitation, or stored at −70° until used. Effect of ethanol on cytokine production by various cell lines was tested at 0.125, 0.25, and 0.5% ethanol, the concentrations corresponding to those encountered at 2.5 μg/ml, 5 μg/ml and 10 μg/ml of THC, respectively.

2.4. Cytokine quantitation

MIP-1α, MIP-β, RANTES, IL-8, IL-10, and IFN-γ were quantitated using R&D ELISA kits, TNF-α and GM-CSF by Biosource International ELISA kits, according to the manufacturer's instructions. Specificity of the ELISA kits for a particular cytokine had been established by the manufacturer. The values in the tables are the mean ± standard error of the mean for two separate experiments.

Table 3
Effect of THC on TPA (5×10^{-9} M) induced cytokine production (pg/ml) in SRIK-NKL cell line

Drugs	TNF-α	GM-CSF	IFN-γ
None	105 ± 5	150 ± 5	3
TPA	503 ± 3	1150 ± 50	46 ± 2
TPA + 5 μg/ml THC	87 ± 3	300 ± 20	8 ± 2
P-value for Bootstrap trend *t*-test	0.0001	0.0001	0.0001

Table 4
Effect of THC on cytokine production (pg/ml) in HUT-78 cell line

THC (μg/ml)	IL-8	MIP-1α	IL-10
0	102 ± 28	720 ± 60	750 ± 30
2.5	90 ± 5	750 ± 10	565 ± 55
5.0	140 ± 5	675 ± 25	185 ± 15
10.0	125 ± 15	735 ± 15	32 ± 2
P-value for Bootstrap trend *t*-test	0.1759	0.8601	0.0002

2.5. Statistical analysis

We applied a linear trend test to each dose response curve with the multitest *t*-test for the mean procedure with bootstrap resampling (10,000 bootstrap samples for each test) with the SAS statistical software package, version 6.12 (Cary, 1997). A reasonable criterion for a significant trend was to require the *P*-value to be less than 0.05.

3. Results

The data presented in Table 1 show that ethanol at the concentrations encountered in THC/CBD experiments in various cell lines had no significant effect on IL-8 and TNF-α production. Although significant

Table 5
Effect of THC on cytokine production (pg/ml) in SRIS-EOSL cell line

THC (μg/ml)	IL-8	M-IP-1α	MIL-1β
0	245 ± 35	785 ± 165	265 ± 5
5	450 ± 100	1525 ± 25	255 ± 15
10	975 ± 175	2300 ± 100	445 ± 45
P value for Bootstrap trend *t*-test	0.0281	0.0024	0.0191

Table 6
Effect of THC on cytokine production (pg/ml) in SRIH-B (ATL) cell line

THC (μg/ml)	IL-8	MIP-1α	MIP-1β
0	850 ± 50	640 ± 10	415 ± 5
2.5	1200 ± 10	605 ± 12	405 ± 15
5	1450 ± 150	641 ± 4	375 ± 5
10	2600 ± 100	660 ± 10	321 ± 5
P value for Bootstrap trend *t*-test	0.0005	0.0997	0.0001

Table 8
Effect of cannabidiol on chemokine production (pg/ml) in SRIH-B (ATL) cell line

Cannabidiol (μg/ml)	IL-8	MIP-1α	MIP-β
0	1750 ± 150	1900 ± 180	343 ± 70
2.5	1575 ± 125	–	–
5	1775 ± 75	1500 ± 120	146 ± 16
10	740 ± 40	910 ± 60	26 ± 13
P-value for Bootstrap trend *t*-test	0.0099	0.0286	0.0218

by trend *t*-test, MIP-1α production was only weakly effected (< 10%) and IL-10 and GM-CSF mildly inhibited (16–20%) by the highest doses of alcohol.

Cannabinoids THC and CBD significantly affected cytokine expression by all cell lines tested, but were not uniform in action, or across cell lineages. The results with THC on constitutive and TPA-stimulated cytokine expression by SRIK-NKL cells are depicted in Tables 2 and 3, respectively. THC strongly inhibited (54–64%) MIP-1α and MIP-Iβ, and moderately inhibited (23%) RANTES production. THC also greatly diminished (> 80%) the TPA-induced increase of TNF-α, GM-CSF, and IFN-γ in these natural killer cells. These alterations in cytokine production were far more than 10% change observed for MIP-1α and 16–20% inhibition for IL-10 and GM-CSF with highest concentration of alcohol.

In the HUT-78 T cell line, THC strongly inhibited (96%) IL-10 production, but had no significant effect on IL-8 or MIP-1α (Table 4). IL-10 inhibition at the highest alcohol concentration was only 18% (Table 1).

In contrast to its effects in NK cells, THC increased IL-8, MIP-1α, MIP-1β production 2–4 fold in SRIS-EOSL eosinophilic leukemia cell line (Table 5). In the HTLV-1 positive B-cell line, THC tripled IL-8 production, suppressed MIP-1β, but had no significant effects on MIP-1α production (Table 6). SRIH-B(ATL), produced only modest amounts of virus, characteristic of HTLV-1 positive B cells. This viral expression inside cells also remained unchanged with THC, as revealed by indirect immunofluorescence staining of acetone-fixed cells using monoclononal antibodies to viral protein p19 (data not shown), but viral shedding into supernatant was not examined in this study. IL-8 production was not altered by alcohol and MIP-1α production was only effected < 10% by highest dose of alcohol.

CBD, like THC, strongly inhibited (77%) IL-10 production in the HUT-78 T-cell line, and doubled IL-8 production in SRIS-EOSL cell line (Table 7). CBD also increased MIP-1α (140% of control) and MIP-1β (200% of control) production by the eosinophilic cell line at 2.5–5 μg/ml, but returned to baseline at 10μg/ml. However, in contrast to

Table 7
Effect of cannabidiol on chemokine production (pg/ml) in SRIS-EOSL cell line and IL-10 production in HUT-78 cell line

Cannabidiol (μg/ml)	SRIS-EOSL Cell Line			HUT-78
THC (μg/ml)	IL-8	MIP-1α	MIP-1β	IL-10
0	735 ± 15	810 ± 10	165 ± 5	755 ± 5
2.5	790 ± 10	930 ± 30	265 ± 15	440 ± 20
5	1175 ± 75	1150 ± 50	345 ± 5	305 ± 10
10	1300 ± 10	890 ± 10	135 ± 5	175 ± 5
P-value for Bootstrap trend *t*-test	0.0028	0.0281	0.8150	0.0001

THC, which tripled IL-8 production in SRIH-B (ATL) cells, CBD inhibited (60%) IL-8 production by the B cells. CBD also inhibited MIP-1α (> 50%) and MIP-1β (93%) production in the SRIH-B(ATL) cell line (Table 8).

4. Discussion

This study demonstrates for the first time the modulation by cannabinoids of constitutive and stimulated chemokine production in pure populations of human immune cells, with significant differences between cell lineages and cannabinoid derivatives. These findings are relevant in relation to the use of these compounds in AIDS, cancer, inflammation, and infection.

THC has been used with success in controlling the severe cachexia seen in patients with cancer or AIDS (Razdan, 1986; Mechoulam et al., 1996). This may be partially explained by the ability of THC to decrease TNF-α production, (Kusher et al., 1994) which we confirm in our study (Srivastava et al., 1996). However, additional results on chemokine production presented here pose serious question regarding the safety of cannabinoids in HIV-1 infection and malignancy as a deleterious effect on susceptibility to infection, disease progression, and even tumorigenesis may be postulated.

The CC chemokines (MIP-1α, MIP-1β and RANTES) produced by $CD8^+$ T cells have been shown to inhibit HIV-1 (Cocchi et al., 1995). These chemokines are all also produced in large amounts by leukemic (HTLV-1/II positive or negative) and normal B cells, leukemic T (HTLV-1 or genome positive), eosinophilic, $CD8^+$ NK cell line, and dendritic cells (Srivastava, 1994). CC chemokine production is also upregulated in these cells, and myeloid cells, by activation by antigen, modeled by the protein kinase C activator TPA (Srivastava, 1994). Furthermore, upregulation of chemokine/HIV-1 coreceptors CCR-5 and CXCR4, as well as cannabinoid receptors on immune cells, can occur upon activation (Bleul et al., 1997). The distribution of these receptors on immune cells is known to vary with cell lineage (Bleul et al., 1997).

Given our findings that THC decreased CC chemokine production by NK cells, and CBD both CXC (IL-8) and CC chemokines by B cells, all the aforementioned, parameters may be adversely affected by cannabinoids, increasing a patient's risk of infection with HIV-1, other infectious organisms, or allowing the disease to progress.

In particular, NK cells, the distinct population of cytotoxic lymphocytes that act as a first line of defense against transformed (malignant) or virus-infected cells, as well as B cells, important in humoral and cellular immunity, strongly express the CB2 cannabinoid receptor (Galieque et al., 1995). These cells, therefore, may be more sensitive to the effects of cannabinoids, potentially permitting tumorigenesis, growth and even metastasis, via inhibition of NK and chemokine function, and escape of malignant clones. The inhibition of proinflammatory cytokines TNF-α, IFN-γ, and GM-CSF by THC in our SRIK-NKL cell line (Srivastava et al., 1996) is consistent with suppression of NK cytotoxicity (Spector and Lancz, 1991), as is the previously reported decreased TNF-α and IFN-γ production by PBMN cells (Kusher et al., 1994; Watzl et al., 1991), a mixture of T, B, and monocytes. It would be interesting to examine whether NK functions, such as K562 cell killing, perforin expression, granzyme A, and T1A antigen expression are also altered by cannabinoids, with further inhibition of anti-cancer activity.

Lokensgard et al. (1997) have reported that proinflammatory cytokines possess anti-HIV-1 activity in the CNS, with TNF-α strongly inhibiting HIV production in mixed brain cell culture, and increasing the release of RANTES, MIP-1α, and MIP-1β in the supernatant. Thus, TNF-α or CC chemokine downregulation in the brain by THC, could allow increased HIV-1 replication in microglial cells, percentage of infected cells, and viral load, permitting progression of the damaging effects of HIV-1.

Also, both THC and CBD strongly inhibited IL-10 production by HUT-78 T cells. Given previous reports that IL-10 inhibits HIV-1 expression by infected macrophages (Poli and Fauci, 1993; Moriuchi et al., 1996; Cramer et al., 1997), this could be another mechanism whereby HIV-1 production would be upregulated by marijuana.

Surprisingly, both THC and CBD clearly increased IL-8, MIP-1α, and MIP-1β production in SRIS-EOSL cells, demonstrating cell lineage specific effects of these compounds on immune cell function

as has been reported in previous studies using rodent immune cells (Klein et al., 1995). Eosinophils are cells with key roles in allergic inflammatory diseases, such as asthma. Direct exposure of high concentrations of cannabinoids to lung eosinophils, as occurs with illicit use of smoked marijuana, could significantly worsen preexisting asthma/allergic pulmonary disease.

In the HTLV-1 positive B cell line, THC and CBD demonstrated significant differences between cannabinoid derivations on immune cell modulation. Whereas both inhibited MIP-1β CBD was more effective and also decreased IL-8 and MIP-1α. THC had no significant effect on MIP-1α, and more than tripled IL-8. Consistent with its more potent anti-inflammatory effects, CBD has previously been shown to be better than THC in inhibiting IL-1, TNF-α, and IFN-γ release by PBMN cells (Watzl et al., 1991).

Thus, the nonpsychoactive component CBD (Razdan, 1986), or the related endogenous intestinal 2-arachidonyl glycerol (Mechoulam et al., 1996), may have utility in the treatment of inflammatory diseases in which this pattern of cytokines, and T/B immune cell activation, is abnormally increased, such as inflammatory bowel disease, rheumatoid arthritis, or multiple sclerosis. and may be mediated by affects on transcription factors (Kaminski, 1996). CBD, combined with antibiotics, could also prove useful in treating destructive infections such as *Mycobacterial leprae*, in which TNF-α overexpression may be disfiguring, and alternative therapies dangerous, such as with thalidomide.

In conclusion, results presented here indicate that of both psychotropic (THC) and nonpsychotropic (CBD) cannabinoids have widespread, yet lineage and derivative specific effects on chemokine/cytokine expression by pure populations of human T, B, NK, and eosinophil cells. These effects, while being of potential benefit in some autoimmune/inflammatory diseases, may worsen HIV infection, disease progression, tumorigenesis, metastases, and exacerbate allergic inflammation in the lung. Clearly, more detailed, scientific study of the effects of cannabinoids on cytokine/chemokine expression, transcription factor modulation, receptor expression, immune cell activation and function are needed in vitro, as well as clinical studies of patients being treated with these potent immunoactive compounds.

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