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Cannabinoids – Influence on the Immune System and Their Potencial Use in Supplementary Therapy of HIV/AIDS

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1. Introduction

Cannabis sativa (Fig. 1.) has been valued for its medicinal as well as its psychotropic properties dating back to ancient times. In nineteenth century W.B. O'Shaughnessy used marijuana for pain relief and Jean-Jacques Moreau de Tours – French psychiatrist, said, that cannabis is very helpful in therapy of psychiatric disorders (Booth, 2004). Main constituents of *Cannabis sativa* were discovered in 1960's and named after the plant – cannabinoids. The identification of the chemical structure of *cannabis* components and the possibility of obtaining its pure constituents were related to a significant increase in scientific interest in this plant. This interest was renewed in the 1990's with the description of cannabinoid receptors and the identification of an endogenous cannabinoid system in the brain (Zuardi, 2006).

The most notable of the cannabinoids are: tetrahydrocannabinol (THC) – the most psychoactive substance found in the cannabis plant and cannabidiol – constituent which has displayed sedative effects. Both constituents can be found in the brown resin secreted by the hair which covers female plants (Truta et al., 2002). Cannabinoids bind to the cannabinoid receptors (CB receptors), change metabolism of the cells, moderate neurotransmission and hormones extraction, what affect main functions of the human body (Demuth et al., 2006, ElSohly et al., 2005).

The cannabinoid receptor family currently includes two types: CB1, characterized mostly in neuronal cells and brain, and CB2, characterized in immune cells (lymphocytes and macrophages) and tissues (spleen and tonsils) (Demuth et al., 2006). Both receptors are proteins and consist of seven transmembrane–spanning domains (Fig. 2.) (Joy et al., 1999). The CB1 molecule is larger than CB2. However, both receptor molecules are alike in four of the seven regions embedded in the cell membrane (known as the transmembrane regions). The intracellular loops of the two receptor subtypes are quite different, which might affect the cellular response to the ligand (Szulakowska&Milnerowicz, 2007). Human body also produces substances that activate CB receptors, they are known as endocannabinoids. The studies have revealed a broad role of endocannabinoids and cannabinoid receptors in a variety of physiological processes as neuromodulation, pain and appetite sensation, motor learning (Saito et al., 2010).



Fig. 1. *Cannabis sativa* (Kohler, 1887).

2. Cannabinoids and the immune system

The study of marijuana cannabinoid biology has led to many important discoveries in immunology; not only existence of a new physiological system - the endocannabinoid system, but also its role in the regulation of the immune system. Studies examining the effect of cannabinoids on immunity have shown that many cellular and cytokine mechanisms are suppressed by these agents (Klein&Cabral, 2006).

2.1 Cellular effects

Scientists have already suggested in 1970s that cannabinoids can change the number and function of T cells. Various functions from cytotoxic T cell killing to antibody production by B cells have been examined. Nong and Co. have studied the T-cell rosetting capacity of lymphocytes in CD4 and CD8 subsets - it was impaired in peripheral blood cells from marijuana users. Scientists examined also the effects on the number of lymphocytes in CD4 and CD8 subsets. The percentage of CD4 T cells was increased in peripheral blood cells from

marijuana smokers, with a mean CD4/CD8 ratio of 1.95 as opposed to 1.27 in controls (Nong et al., 2002; Massi et al., 2006). Finally, Klein and Co. proved that cannabinoids affect cytotoxic T lymphocytes (CTL) – after incubation with THC, the cytolytic activity of CTL was depressed by about 60% (Klein et al., 1991). It also appeared that cannabinoids can disrupt proliferation and cytolytic activity in natural killer cells (NK), which plays very important role in host defences against tumors and microbes (Massi et al., 2006).

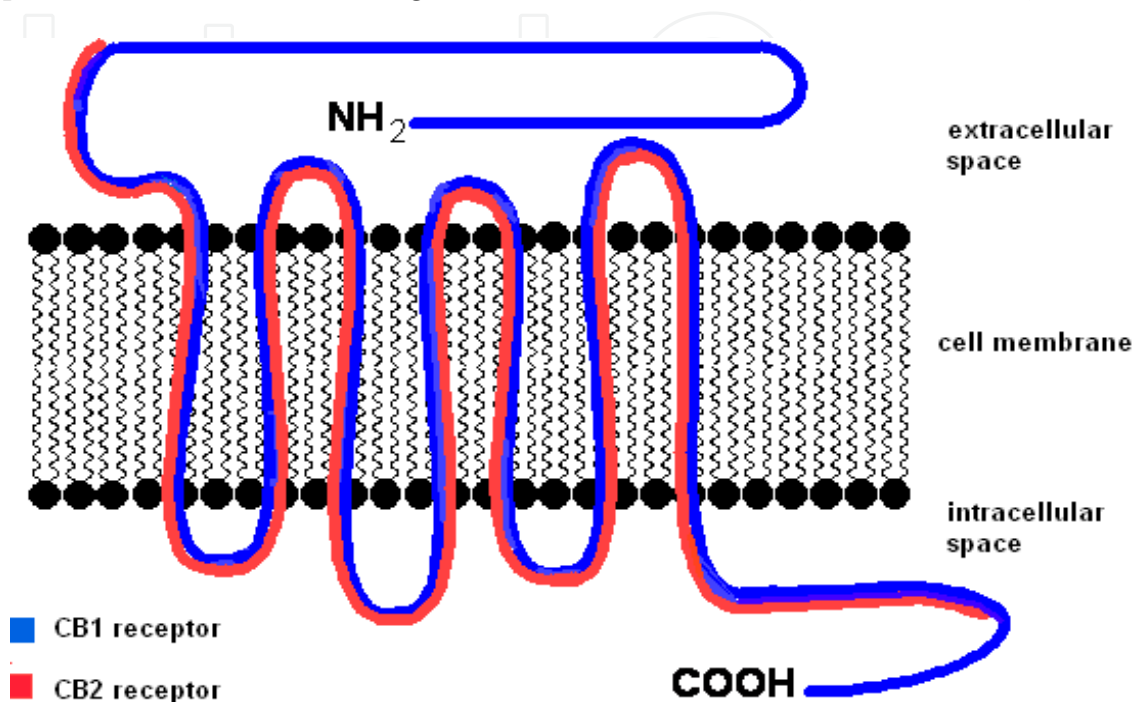


Fig. 2. Cannabinoid receptors CB1 and CB2 (Joy et al., 1999).

Functions of macrophages are also impaired by cannabinoids through either a receptor- or non-receptor-mediated mechanism. Studies with pulmonary alveolar macrophages showed that cannabinoids significantly lowered the level of tumor necrosis factor α (TNF α) in the bronchoalveolar lavage (Klein et al., 1991). Scientists proved that cannabinoids influenced the ability of macrophages to process antigens necessary for the activation of CD4⁺ T lymphocytes (McCoy et al., 1999), reduced chemotaxis (Sacerdote et al., 2000) and affect the production of arachidonic acid metabolites in macrophage cultures (Berdyshev et al., 2000). The influence of cannabinoids on NO production is still unclear (Massi et al., 2006).

2.2 Cytokines and hormones

Cannabinoids can modulate the action of cytokines mostly by affecting immune cells, for example macrophages or Th cells, their immunomodulatory properties are complex, what was shown in the Table 1.

Scientists proved that cannabinoids can modulate immune response also by affecting hormones release. For example administration of THC, may increase level of adrenocorticotrophic hormone and corticosterone, what is causing downstream release of immunoregulatory molecules as cortisol and sex hormones and inhibition of immune response (Massi et al., 2006; Tanasescu&Constantinescu, 2010; Baker et al., 2007).

Name of the cytokine	Cannabinoid influence	General result	References
IFN γ	Decreased level	Anti-inflammatory action	(Zheng et al., 1992, 1996)
TNF α	Decreased level	Anti-inflammatory action	(Zheng et al., 1992, 1996)
Il-1	Decreased level	Anti-inflammatory action	(Kozela et al., 2010)
Il-2	Decreased level	Anti-inflammatory action	(Zhu et al., 1993)
Il-4	Increased level	Action unclear	(Klein et al., 2000)
Il-6	Decreased level	Anti-inflammatory action	(Kozela et al., 2010)
Il-10	Decreased level	Action unclear	(Sacerdote et al., 2005)
Il-12	Decreased level (THC)/increased level (CBD)	Anti-inflammatory action (THC)/ Anti-inflammatory action	Massi et al., 2006; Klein et al., 2000; Sacerdote et al., 2005)

Table 1. Cannabinoid influence on cytokines profile

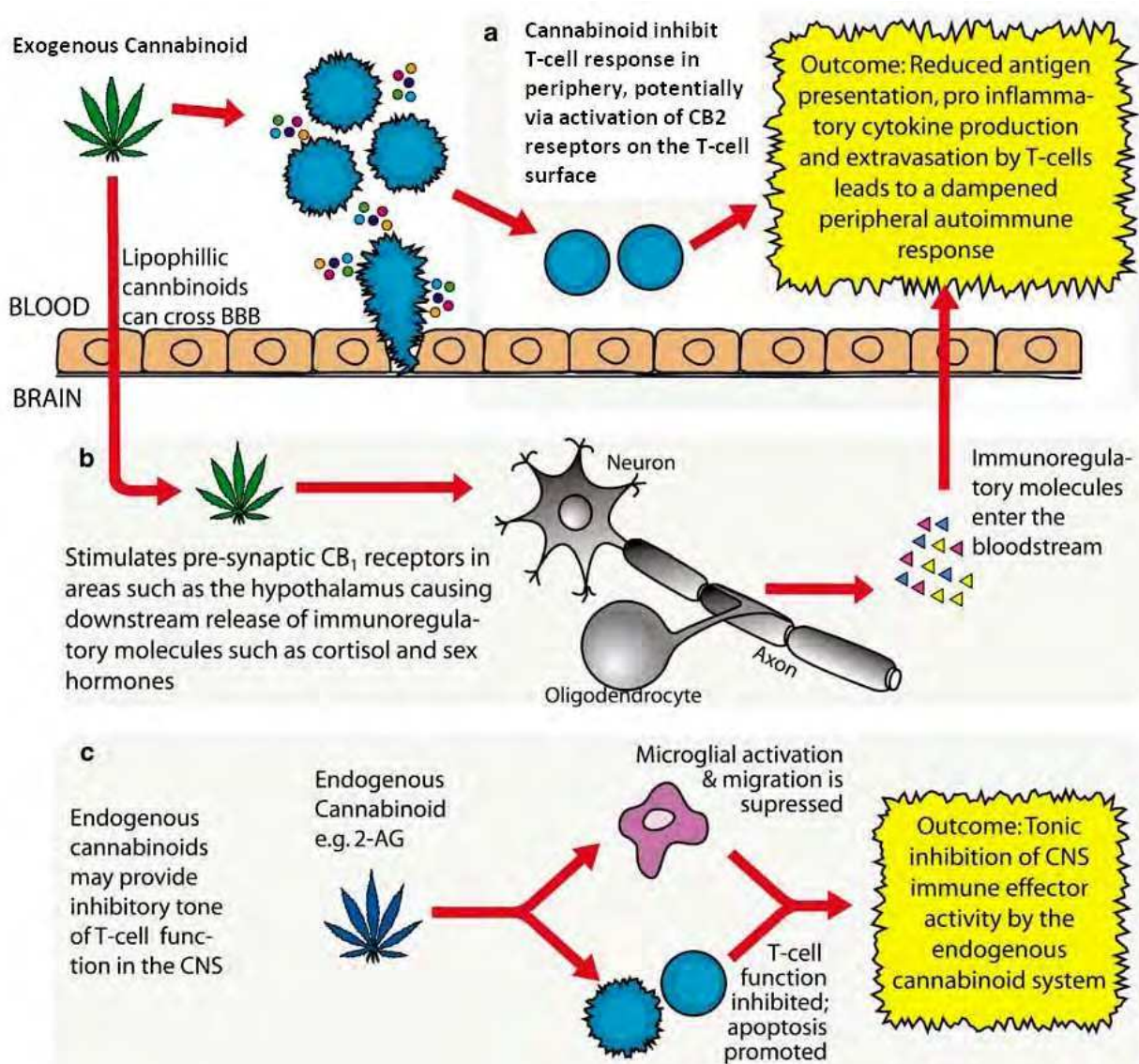


Fig. 3. Immune regulation by cannabinoids. Exogenously administered cannabinoids (a, b) or endocannabinoids (c) may inhibit the action of the immune response in either the periphery (a, b) or the central nervous system (CNS; c) via either a direct (a, c) or indirect (b) action on leukocytes (from Baker et al., 2007).

Cannabinoids can modulate immune reactions in the periphery but also in the brain, influence T cell subset balance and cytokine expression. Generally, they alter many functions of the immune response, what was shown in the Fig. 3. (Baker et al., 2007).

3. Immunological consequences of cannabinoids use by HIV/AIDS patients

Anti-inflammatory potential action of cannabinoids tends to be evident from the studies discussed in the previous paragraph. Cannabinoids do induce apoptosis in immune cells and alleviate inflammatory responses (Rieder et al., 2010). Even though the progressive failure of the immune system is a cause of AIDS disease, no conclusive data have been obtained as to potential risk associated with HIV infection and the use of cannabinoids. In 2003 Abrams and co. examined short-term effects of cannabinoids in patients with HIV-1

infection. Scientists measured HIV RNA level and CD4+ and CD8+ cell subsets, during 21 days of oral and smoked marijuana administration among 67 patients with HIV-1 infection. At days 0 and 21, HIV RNA was undetectable in 50% to 55% of patients in each group, the mean changes were decreases in both cannabinoid groups: marijuana group and dronabinol group. The unadjusted mean increases in CD4+ cell counts were greater for patients receiving cannabinoids than for patients receiving placebo. CD8+ cell counts were on average 20% greater for patients receiving marijuana than for patients receiving placebo and marginally greater (average 10%) for patients receiving dronabinol than for those receiving placebo. Authors concluded that smoked and oral cannabinoids did not seem to be unsafe in patients with HIV infection with respect to HIV RNA levels, CD4+ and CD8+ cell counts (Abrams et al., 2003).

Kosel and co. decided to examine effects of cannabinoids on the pharmacokinetics of indinavir and nelfinavir – protease inhibitors used as a component of highly active antiretroviral therapy to treat HIV infection and AIDS. Patients on stable regimens containing indinavir or nelfinavir were randomized to one of three treatments: 3.95% THC marijuana cigarettes, dronabinol 2.5 mg capsules or placebo capsules administered three times daily. The treatment lasted 14 days. Authors concluded that their results after marijuana treatment (statistically significant decrease in maximum concentration of nelfinavir - C(max)) by -17.4% ($P=0.46$) and the magnitude of changes in indinavir concentration - C(max) by -14.1% ($P=0.039$), are likely to have no short-term clinical consequence. The use of cannabinoids is unlikely to impact antiretroviral efficacy (Kosel et al., 2002).

4. Therapeutic use of marijuana for people living with HIV/AIDS

Over 40 million people are affected by HIV/AIDS in the world. There is still no cure available for this disease, although remarkable improvements in the quality and life expectancy have been achieved. Most of the patients are on long-term treatment with combinations of antiretroviral therapies and cope with the side effects of these therapies (nausea, vomiting, pain, reduced appetite, weight loss, headaches, diarrhea, constipation, anxiety and depression) (Woolridge et al., 2005). Recently, therapeutic use of marijuana has emerged as an important issue for people living with HIV/AIDS. Fogarty et al. reported that people with HIV/AIDS who use marijuana indicate improved moods, sensory experiences, creativity, increased socialising, elation and changes in appetite (Fogarty et al., 2007; Woolridge et al., 2005). In 2005 Woolridge et al. surveyed 143 HIV positive people who reported using marijuana to manage side effects of long-term anti-retroviral treatment. Results were shown in the table below (Table 2.) (Woolridge et al., 2005).

The ability of cannabinoid to treat pain, nausea, appetite loss, muscle spasm and a wide variety of other symptoms causes that more and more HIV/AIDS patients reach for marijuana as an alternative remedy. The actual numbers of HIV/AIDS patients that use marijuana to treat HIV related symptoms is a difficult number to quantify, but some researchers report that this number is quite significant (Cannon, 2010).

In 1998/1999, in Canada approximately 15% of 977 responders were using marijuana for medical purposes (Braitstein et al., 2001). In California in 2001 – 33.3% of the 442 responders reported the use of marijuana (Cannon, 2010). Regarding this data, in 2007 scientists examined people living with HIV/AIDS in Australia. The results show that among 408 participants, 59.8% reported some use of marijuana in the past six months. 244 (55.7% of

those) reported recreational use only of marijuana and 44.3% admitted mixed use of marijuana for therapeutic and recreational purposes (Fogarty et al., 2007). In 2007/2008 in South Africa only 3.7% of 618 admitted that was using marijuana in the past six month, mostly for stress relief (85.7%) and to a lesser extent for recreational purposes (relaxation) (23.5%) and pain relief (17.6%) (Peltzer et al., 2008). These results from different places in the world show that substantial proportion of people living with HIV/AIDS use marijuana for therapeutic purposes, despite considerable legal barriers, suggesting that cannabis represents another option in their health management (Fogarty et al., 2007). The small percentage of South Africans with HIV/AIDS using marijuana for therapeutic purposes may be caused by poverty (marijuana is more expensive than other alternative, supplementary methods like micronutrients, religious healing) and limited access to information about alternative therapy (Peltzer et al., 2008).

Symptom	Number of complaints	Much better [%]	Little better [%]	No change [%]	Little worse [%]	Much worse [%]
Lack of appetite	111	79	18	2	0	1
Pain in muscle	65	63	31	6	0	0
Nausea	62	56	37	3	2	2
Anxiety	98	64	49	3	2	2
Nerve pain	53	51	40	9	0	0
Depression	94	56	30	9	4	1
Tingling	46	37	48	9	7	0
Numbness	42	36	36	24	5	0
Weight loss	62	45	24	31	0	0
Headaches	46	35	30	33	2	0
Tremor	24	37	29	21	13	0
Constipation	24	21	29	46	4	0
Tiredness	60	17	33	33	15	2
Diarrhea	48	13	23	56	6	2
Vision dimness	22	9	27	55	9	0
Weakness	48	10	21	54	15	0
Memory loss	38	13	5	34	34	13
Slurred speech	9	11	0	78	11	0

Table 2. Effect of marijuana on Complaint of Symptoms in 143 HIV Patients (from Woolridge et al., 2005).

4.1 Pain management

Neuropathic pain and muscular pain is reported by people living with HIV/AIDS. Patients describe pain as “aching”, “burning” and “painful numbness” of legs and hands mostly (Cannon, 2010). Despite management with opioids and other pain modifying therapies, neuropathic pain continues to reduce the quality of life among 30% or more of HIV-infected individuals. Scientists suppose that pain perception is modulated by cannabinoid receptors in the central and peripheral nervous system (Ellis et al., 2009) via endocannabinoids, an endogenous system of retrograde neuromodulatory messengers that work in tandem with endogenous opioids (McCarberg, 2007).

Cannabinoids have been shown to inhibit the experience of pain in both – animal and human studies. It was demonstrated in 2007 in a study conducted by Abrams et al. He decided to determine the effect of smoked cannabis on the neuropathic pain of HIV-associated sensory neuropathy and an experimental pain model. Scientists asked fifty patients to smoke either cannabis or identical placebo cigarettes with the cannabinoids extracted three times daily for 5 days. Reduction in pain intensity was measured. It occurred that smoked cannabis reduced daily pain by 34% with placebo. Greater than 30% reduction of pain was reported by 52% in the cannabis group and by 24% in the placebo group. The first cannabis cigarette reduced chronic pain by a median of 72% vs 15% with placebo (Abrams et al., 2007). Similar trial was conducted by American scientists in 2009. Ellis et al. examined 127 HIV-associated distal sensory predominant polyneuropathy and measured change in pain intensity by the Descriptor Differential Scale (DDS) from a pretreatment baseline to the end of each treatment week. Treatments were placebo and delta-9-tetrahydrocannabinol, smoked four times daily for 5 consecutive days during each of 2 treatment weeks, separated by a 2-week washout. Among all the patients, pain relief was greater with cannabis than placebo and the proportions of subjects achieving at least 30% pain relief with cannabis vs placebo were 0.46 and 0.18. Results were shown in Fig. 4. (Ellis et al., 2009). This study's findings are equivalent to those achieved by Abrams et al. in 2007 and consistent with other recent research supporting the short-term efficacy of cannabis for neuropathic pain (Ellis et al., 2009; Abrams et al., 2007).

Results of other studies show that cannabis can treat not only the neuropathic pain but also muscular and chronic pain. Woolridge study demonstrated that 94% of participants reported positive results for muscular pain management using marijuana (Cannon, 2010; Woolridge et al., 2005). Finally, as it was mentioned in the previous paragraph, 30% reduction in chronic pain was reported by 52% of the smoked cannabis group (Cannon, 2010; Abrams et al., 2007).

Scientists suppose that analgetic properties of cannabinoids are effect of additional receptor and non-receptor mechanisms of their activity. Synergy between opioids and cannabinoids may produce opioid-sparing effects, as well as extend the duration of analgesia and reduce opioid tolerance and dependence, what is very important in long-term palliative treatment (McCarberg, 2007; Karst&Wippermann, 2009).

4.2 Management of wasting syndrome

Wasting is big problem for people living with HIV/AIDS and is linked to disease progression and death. It is defined as the involuntary loss of more than 10% of normal body weight in addition to at least 30 days of diarrhea, fever and generalized weakness. It is caused by several factors:

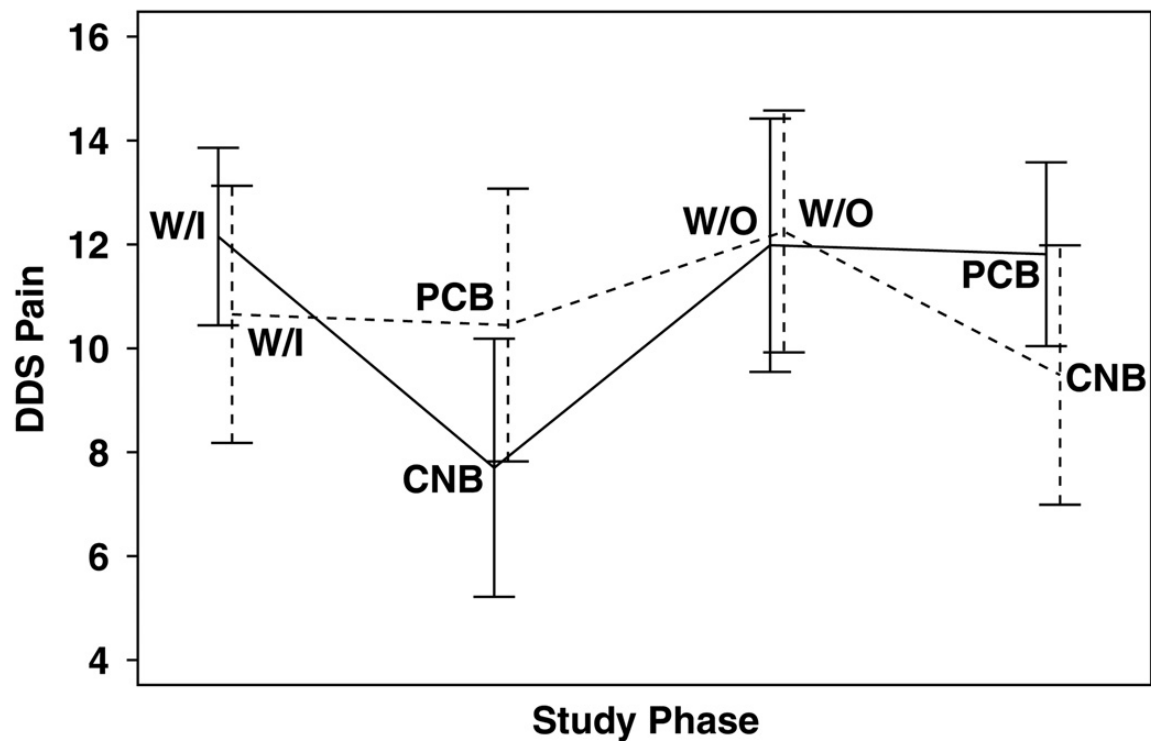


Fig. 4. DDS pain severity scores for participants in the cannabis (CNB) and placebo (PCB) arms before study treatment (W/I), during each of the 2 treatment weeks (1, 2) and during the Washout (W/O) between treatment weeks (from Ellis et al., 2009).

- Low food intake – low appetite is common among HIV/AIDS patients and is mostly caused by anti-retroviral drugs (their side effects such as nausea, changes in the sense of taste, or tingling around the mouth also decrease appetite). Moreover, opportunistic infections in the mouth, throat or stomach may also reduce food intake.
- Poor nutrient absorption – opportunistic infections of the gastrointestinal tract can interfere with the absorption of nutrients. Moreover, HIV may directly affect the intestinal lining and reduce nutrient absorption; diarrhea may affect nutrient absorption indirectly – it flushes the system of needed nutrients and calories.
- Altered metabolism – HIV/AIDS affects food processing and protein building. It is probably caused by the increased activity of the immune system. People need more calories just to maintain their body weight (Cannon, 2010; The Body, 2011).

5. Antiemetic action

Scientists suppose that emesis (the side effect of anti-retroviral therapy) is caused by the stimulation of receptors in the central nervous system or the gastrointestinal tract. This stimulation appears to be caused by the drug used in treatment itself or a metabolite of the drug. The high concentration of cannabinoid receptors in the nucleus of the solitary tract, suggest that exogenous cannabinoids bind to receptors and prevent them from binding with drugs and metabolites (Szulakowska&Milnerowicz, 2007). Recent findings suggest that the mechanism of anti-emetic action of cannabinoids is more complex – CB1 agonist suppresses vomiting, which is reversed by CB1 antagonism, and CB1 inverse agonism promotes vomiting. Parker et al. proved that cannabinoid agonists -THC suppress nausea. It occurred

that cannabidiol (CBD) can also be used in the supplementary therapy of HIV/AIDS. The antiemetic effects of CBD may be mediated by indirect activation of somatodendritic 5-HT (1A) receptors in the dorsal raphe nucleus; activation of these autoreceptors reduces the release of 5-HT in terminal forebrain regions and inhibit nausea and emesis (Parker et al., 2010).

In 2001 Tramer et al. decided to search systematically for randomised controlled comparisons of the antiemetic efficacy of cannabinoids with any antiemetic or placebo (control) in chemotherapy, radiotherapy, surgery or HIV/AIDS. Scientist analyzed data from 30 randomised controlled trials published between 1975 and 1997 (1366 patients). Across all the trials, cannabinoids were more effective than active comparators and placebo. Results were shown in the Table 3. (Tramer et al., 2001).

	Cannabinoids % (number of patients)	Control % (number of patients)
Control of nausea and vomiting		
Complete control of nausea <i>vs</i> placebo	70 (81/116)	57 (66/115)
Complete control of vomiting <i>vs</i> placebo	66 (76/116)	36 (41/115)
Complete control of nausea <i>vs</i> active comparator	59 (122/207)	43 (93/215)
Complete control of vomiting <i>vs</i> active comparator	57 (111/194)	45 (90/201)
Patients' rating		
Cannabinoids <i>vs</i> placebo	76 (153/202)	13 (27/202)
Cannabinoids <i>vs</i> active comparator	61 (371/604)	26 (156/608)

Table 3. Control of nausea and vomiting and patients' preference for treatment in trials of cannabinoids against active antiemetic or control treatment (Tramer et al., 2001).

6. Appetite stimulation

Cannabinoids can also stimulate appetite and food intake. This property is connected with the presence of functional cannabinoid type 1 receptors in the digestive system, especially the liver. Hepatocytes express CB1 receptors, the activation of which increase the expression of lipogenic genes and *de novo* fatty acid synthesis, which contributes to the development of diet-induced obesity. Cannabinoids can also stimulate AMP-activated protein kinase in the hypothalamus, whereas they inhibit it in the liver and adipose tissues (Osei-Hyiaman, 2007). Moreover, scientists proved that CBs can activate fatty acid synthase (FAS), whereas the inhibition of FAS is a result of profound anorexia. These finding thus suggest that the same molecular pathway is involved in both central appetitive and the peripheral anabolic effects of cannabinoids (Szulakowska&Milnerowicz, 2007; Osei-Hyiaman et al., 2005).

In 2007 Haney et al. decided to check tolerability and efficacy of smoked marijuana and oral dronabinol in HIV-positive marijuana smokers. This placebo-controlled within-subjects study evaluated marijuana and dronabinol across a range of eating topography and mood. Scientists administered 4 times daily for 4 days each dronabinol and marijuana, but only one drug was active per day. Administration of drugs was separated

by four days of placebo washout. Results were shown in the Fig. 5. In comparison to placebo, marijuana and dronabinol increased daily caloric intake and body weight. It is probably caused by the increased number of eating occasions – marijuana and dronabinol increased the number of eating occasions but didn't alter the number of calories intake. Moreover, marijuana and dronabinol produced significant shifts in the distribution of macronutrient administration by enhancing the proportion of calories derived from fat. The final effect of increased caloric intake and macronutrients administration was weight gain – 1.2 kg after 4 days of dronabinol and 1.1 kg after 4 days of marijuana (Haney et al., 2007).

6.1 Mood control

Scientists consider that prevalence of psychiatric disorders (mostly depression) is really high among the people living with HIV/AIDS. In 2001 in the USA nearly half of the population screened positive for a psychiatric disorder (36% major depression, 26.5% dysthymia, 15.8% generalized anxiety disorder, 10.5% panic attack)(Bing et al., 2001). Psychiatric disorders may be triggered by side effects of medications or the effects of HIV on the brain. Research show that depression can limit the energy needed to keep focused on staying health and may accelerate HIV's progression to AIDS (The Body, 2002).

Clinical data suggests that cannabinoids can strongly modulate mood of the people living with HIV/AIDS. Marijuana and dronabinol can help to overcome psychiatric disorders like anxiety, depression and sleeping disorders. In 2004 Prentiss et al. reported that 60.3% of 133 people living with HIV/AIDS and coping with psychological disorders recently used marijuana to alleviate the symptoms. Only few of them (9.1%) reported smoking marijuana/using dronabinol ineffective (Prentiss et al., 2004). Moreover, Haney et al. showed also that cannabinoids from marijuana or dronabinol can improve mood without producing disruptions in psychomotor functioning and add benefit of improving rating of sleep (Haney et al., 2007). In general, people living with HIV/AIDS reported that using marijuana cause reduction in stress, relief from anxiety and improve sleep (Cannon, 2010; Fogarty et al., 2007).

Scientists suppose that anti-depressive properties of THC and CBD are probably effect of involvement of these cannabinoids in the modulation of serotonergic signaling by their capacity to increase the availability of circulating tryptophan (precursor necessary for the biosynthesis of the 5-HT). The compensation of tryptophan degradation might be an important mechanism, by which THC and CBD may improve mood disturbances – mainly cause by alteration of serotonergic activity) (Jenny et al., 2010).

7. Medical marijuana use – Legal issues

Scientists from all over the world have explored the use of medical marijuana. Many of them have clearly reported that cannabinoids have therapeutic benefits (Cannon, 2010). According to this information, many countries, including Canada, Australia, The Netherlands and Switzerland, have legalized marijuana for medical purposes. The process of legislation of medical marijuana began in the United States in 2005. Today medical marijuana is legal at least in thirteen states (Active State Medical Marijuana Programs, 2011). Table 4. shows a summary of the main features of medical marijuana programs in different countries (Cannon, 2010).

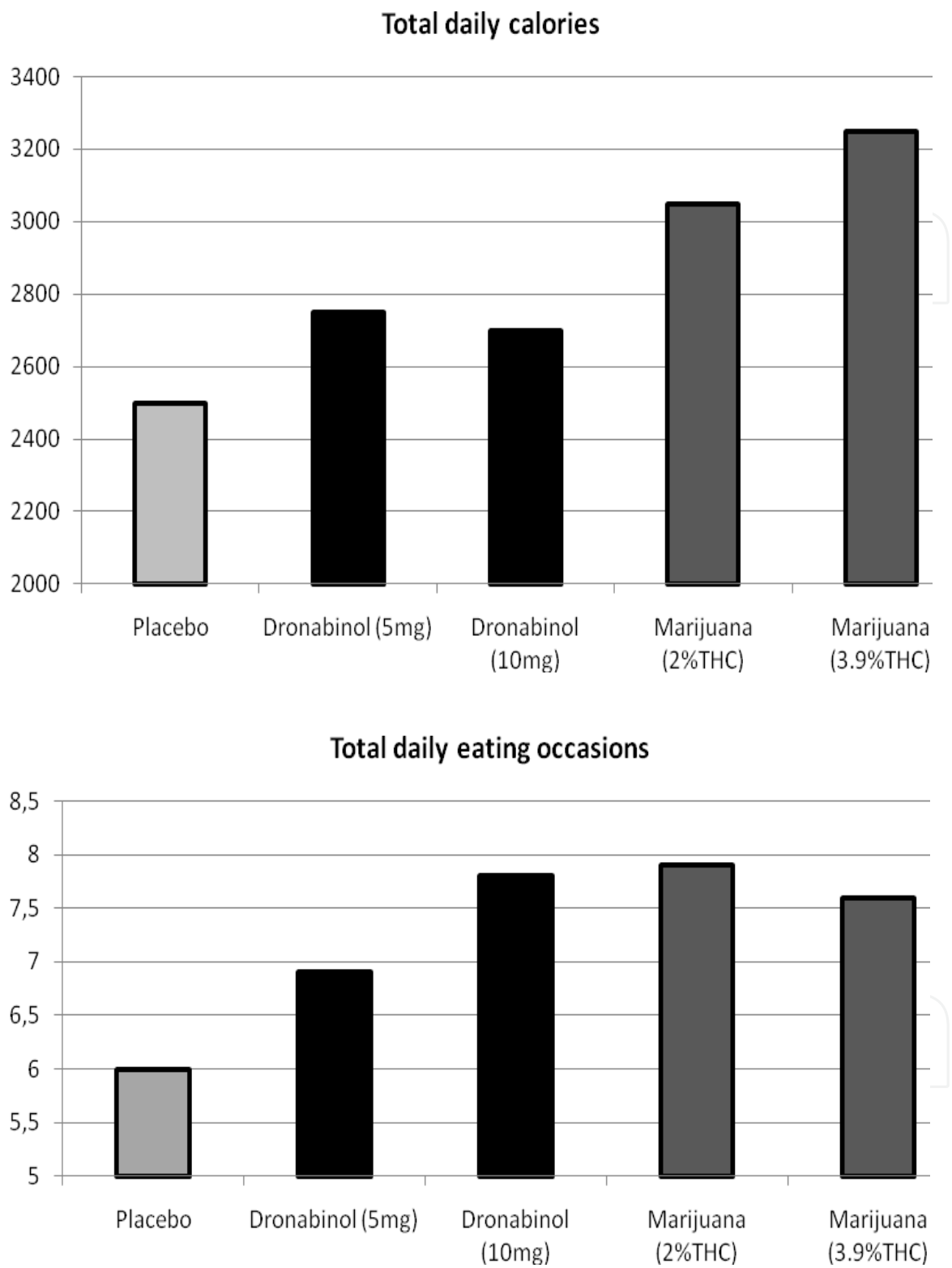


Fig. 5. Mean total daily caloric intake and total number of eating occasions as a function of marijuana (MJ) and dronabinol (Dronab) dose (Haney et al., 2007).

Country	Legal issues	Eligible health conditions	Access
United States of America	Legal for medical purposes in 13 states	HIV/ AIDS Cancer Arthritis Anorexia Chronic pain Spasticity Glaucoma Migraine	Patients must receive a prescription from a physician
Canada	Legal for medical purposes	HIV/ AIDS Cancer Multiple Sclerosis Spinal cord injury/ disease Severe arthritis Epilepsy Part of a palliative care treatment program	Patients must become licensed by the Medical Marijuana Resource Centre to access marijuana
The Netherlands	Illegal – exception for personal use	HIV/ AIDS Cancer Multiple Sclerosis Tourette’s Syndrome Chronic pain Spasticity	Patients must voluntarily apply through the Department of Public Health to join the program and be issued with an identification car

Table 4. A summary of the main features of the medical marijuana programs in different countries (Cannon, 2010).

8. Conclusion

There is constant debate whether cannabis should be considered therapeutic for HIV/AIDS patients. According to the literature, management of HIV-associated symptoms is one of the most common applications ascribed to medical marijuana (Prentiss et al., 2004). More and more studies have characterized the extent of cannabis use for medical benefit to address HIV-related symptoms like nausea (Parker et al., 2010), lack of appetite (Tramer et al., 2001), emesis (Parker et al., 2010), pain (McCarberg, 2007), depression (Bing et al., 2001), anxiety Haney et al., 2007) and weight loss (Fogarty et al., 2007). However, it has to be mentioned, that use of cannabinoids can have side effects. Several scientists have warned about the negative effects of marijuana use on the cardiovascular, respiratory and nervous system (Cannon, 2010; Corless et al., 2009), and psychological dysfunction including loss of memory (Seamon et al., 2007) and pointed out the necessity for further investigation of the effects of cannabinoids. Moreover, recent legislative efforts to support legalization of medical marijuana suggest the need for more precise understanding of the typical patterns and determinants of marijuana use, and

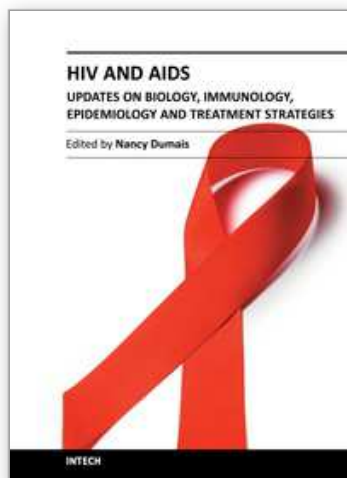
better characterization of the epidemiology of cannabis use for relief of symptoms commonly associated with HIV/AIDS (Cannon, 2010; Abrams et al., 2007).

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