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Immunoactive effects of cannabinoids: considerations for the therapeutic use of cannabinoid receptor agonists and antagonists

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Abstract

The active constituents of *Cannabis sativa* have been used for centuries as recreational drugs and medicinal agents. Today, marijuana is the most prevalent drug of abuse in the United States and, conversely, therapeutic use of marijuana constituents are gaining mainstream clinical and political acceptance. Given the documented contributions of endocannabinoid signaling to a range of physiological systems, including cognitive function, and the control of eating behaviors, it is unsurprising that cannabinoid receptor agonists and antagonists are showing significant clinical potential. In addition to the neuroactive effects of cannabinoids, an emerging body of data suggests that both endogenous and exogenous cannabinoids are potently immunoactive. The central premise of this review article is that the immunological effects of cannabinoids should be considered in the context of each prescribing decision. We present evidence that the immunological effects of cannabinoid receptor agonists and antagonists are highly relevant to the spectrum of disorders for which cannabinoid therapeutics are currently offered.

Keywords

Cannabinoids; signaling; GPCR; immunosuppression; metabolic disorders; neuroimmunology

1. Introduction

1.1. Cannabinoids and their receptors

The active constituents of *Cannabis sativa* have been used for centuries as recreational drugs and medicinal agents, primarily due to their ability to regulate neurobehavioral processes such as memory, mood and appetite [1, 2]. The 1974 identification of the most active and clinically relevant component, Δ^9-tetrahydrocannabinol (Δ^9-THC) in *C. sativa* extracts, by Mechoulam and Gaoni, initiated a novel field of pharmacological study, most recently developing into investigation of the therapeutic potential of cannabinoids and related compounds [3] (Table I). Cannabinoid pharmacological research expanded with the cloning of the two cannabinoid receptors, CB_1 and CB_2[4-6]. The cannabinoid receptors, CB_1 and

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CB_2 are single polypeptides with seven transmembrane α-helices, a glycosylated amino-terminus and an intracellular carboxyl-terminus [7-9]. Both cannabinoid receptors are G-protein-coupled receptors (GPCR) that couple to $G_{i/o}$- proteins [8, 10, 11]. CB_1 receptors have been shown to be highly concentrated in neuronal cells in the central nervous system (CNS), such as the basal ganglia, hippocampus and cerebral cortex, whereas, CB_2 receptors (or peripheral cannabinoid receptors) are expressed abundantly in the non-neuronal periphery, including immunocytes such as B-cells, monocytes, neutrophils, T-lymphocytes, macrophages, and mast cells [7-9, 12]. Shortly after the discovery of cannabinoid receptors CB_1 and CB_2, endogenous ligands including *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (2-AG) were identified [9, 13] (Table I).

1.2. Endocannabinoid control of physiological processes

Neurological roles of cannabinoids—The endocannabinoid system regulates numerous physiological processes. CB1 receptors have been shown to be highly concentrated in neuronal cells of the CNS, specifically in the presynapse. CB1 expression is mainly restricted to cells of the CNS; the cerebral cortex, hippocampus, lateral caudate-putamen, substantia nigra pars reticulata, globus pallidus, entopeduncular nucleus and the molecular layer of the cerebellum [8, 9, 13-16]. These patterns underlie documented effects of cannabinoids on cognition and brain function. CB1 agonists also have analgesic properties reflect the presence of CB1 receptors on pain pathways in the brain and spinal cord and at the peripheral axons of primary sensory neurons. CB1 receptors are present at low levels in the neurons innervating peripheral tissues, including the heart, vas deferens, urinary bladder and small intestine [8, 9, 17]. Ligation of the CB1 receptor, either by exogenous or endogenous endocannabinoids, can interrupt neurotransmission [14, 18, 19]. This may be attributed to their cAMP-dependent inhibition of calcium channels and activation of potassium channels.

Peripheral roles of cannabinoids—Within the CNS, endocannabinoids and their receptors modulate neuronal signaling and play key roles in the regulation of movement, sleep, emotion, appetite, regulation of body temperature, memory deposition, and pain perception [14, 19, 20]. In the periphery, endocannabinoids have been implicated in the control of neuroendocrine secretion, gastric motility and bladder function, and in the control of immunological responses [14, 19, 21-24]. While a considerable emphasis has been placed on the study of both exogenous and endogenous cannabinoids on the CNS, the effect of cannabinoids on the immune system has been considerably less investigated. However, there is an emergent body of work suggesting that cannabinoids, whether exogenous compounds from abusive or medicinal exposures, or the endogenous cannabinoid receptor ligands, are potent immunomodulators [21, 25-28]. In this review, we address the idea that immunological effects of medically applied cannabinoids are important considerations when assessing the potential utility of these medicinal compounds.

Immunological roles of cannabinoids—Immune cells express both CB_1 and CB_2 receptors and possess the ability to synthesize, secrete, transport and catabolize cannabinoids [21, 25, 26, 29, 30]. The roles of cannabinoids in immunity have been suggested by *in vitro* studies in both rodent and human model systems. A significant body of work has emerged that speaks to broadly immunosuppressive effects of exogenous cannabinoids (Table II) and the role of endocannabinoids as potent immunological mediators [19, 21, 25, 26].

In mice, deficiency in the anandamide-catabolizing enzyme Fatty Acid Amide Hydrolase (FAAH), causes a dramatic elevation in anandamide levels in the CNS and periphery. $FAAH^{-/-}$ mice show attenuated dermal inflammatory responses and DNBS-induced colitis, suggesting that physiologically anandamide is involved in terminating or dampening

immune responses [22, 31, 32]. Several lines of evidence suggest that endo- and exo-cannabinoids suppress various facets of the immune response. Exposure to THC alters the outcome of viral and protozoal challenges to the immune system [26, 33-36]. Several studies show that marijuana consumption decreases the proliferation of T cells [37-39]. It has also been shown that cannabis and certain cannabinoid receptor ligands have the ability to suppress serum immunoglobulin (Ig) levels [21, 25, 40]. Studies of human lung alveolar macrophages demonstrated that cannabinoid exposure caused metabolic and morphological changes. In mouse peritoneal macrophages, cannabinoid receptor ligands suppressed cell spreading and phagocytosis, cytolysis, cytokine production, and antigen presentation [41-44]. Similarly, in the context of both $CD8^+$ T cells and NK cells, published data show that cannabinoid exposure, either *in vitro* or *in vivo*, decreases cytotoxic effector functions and suppresses the killer function that is central to anti-viral immunity and tumor surveillance [36, 45, 46].

Mice deficient in either CB1 or CB2 have been generated, and the resulting knockouts have been assessed for the phenotypic effects of this deficiency. In CB1-deficient mice, neurological and behavioral phenotypes, especially those relating to appetite control, have been extensively studied. Perhaps because CB2 receptors outnumber CB1 by 10-100:1 in immune cells, there has not been a systematic study of the immunological phenotype of CB1-deficient mice. The potential phenotypes of CB1 deficiency that would be inferred from *in vitro* data may be subtle and highly cell-type specific. Intriguingly, Karsak et al show that CB1-deficient animals exhibit exacerbated contact hypersensitivity responses [31]. In contrast, and not unexpectedly, CB2 deficient mice have a range of defined immunological phenotypes. Several lines of evidence from CB2-/- mice support the idea that endocannabinoids are broadly immunosuppressive, and are responsible for attenuating inflammatory reactions and responses to pathogens [31, 47]. Macrophage infiltration of an inflammatory site, a chemotactic event that prolongs inflammation, is decreased in CB2-deficient animals [48]. Endocannabinoids that bind CB2 may also be involved in the suppression of autoimmunity, since CB2-deficient mice are more sensitive to EA-induced autoimmune encephalitis, a murine model of MS.

There is, however, evidence that all immunomodulation by cannabinoids cannot be considered as immunosuppressive. Again, reviewing data from CB2-deficient mice, it is clear that atherosclerotic lesions, which have inflammatory character, are more pronounced in CB2 deficient mice, due to attenuation of lipid-induced macrophage apoptosis. Moreover, certain methods of antigenic challenge suggest that endocannabinoids are involved in initiation of inflammation, promoting allergic reactions [49]. CB2 deficient mice mount more successful immune responses to parasitic challenge by *Plasmodium falciparum* than control animals [50]. This apparently paradoxical ability of cannabinoids to promote and enhance immune responses is also supported by *in vitro* data. For example, *in vitro* studies show that while cannabinoid exposure does inhibit $CD8^+$-mediated cytotoxic responses, the activity, cytokine production and clonal proliferation of $CD4^+$ TH2 cells is elevated following cannabinoid exposure [34, 51]. Moreover, while NK cell killing activity is indeed suppressed by cannabinoid exposure [36, 52], elevated IL-2R expression on these cells in response to cannabinoids would tend to suggest a longer-term elevation in NK-mediated activity. In macrophages, again acute suppression of phagocytic effector function is accompanied by a paradoxical elevation in the levels of IL-1 mRNA and hence a likely increase in the secreted levels of this pro-inflammatory cytokine [53, 54]. However, it is perhaps in the mast cell system that there is the strongest evidence for a dichotomy of cannabinoid effects [55-60].

Mast cells, which are potently pro-inflammatory, are established targets for the action of exo- and endo-cannabinoids. CB2 ligands suppress the release of certain inflammatory

mediators from mast cells. These data, together with evidence that cannabinoids suppress ongoing inflammation in both the respiratory and GI tracts, support intensive efforts to develop cannabinoids as anti-inflammatory therapeutics. However, studies of cannabinoids effects on mast cells suggest that cannabinoid exposure does not inevitably suppress immune responses [59, 60]. For example, ligation of the CB1 on mast cells actually stimulates the release of inflammatory mediators and activates a pro-inflammatory transcriptional program [60]. The initial description of CB1 on mast cells undermined the idea that CB1, and CB2 expression are restricted to cells of the nervous system and periphery, respectively. Subsequent published studies placing CB1 on various immunocytes, such as NK cells and neutrophils, suggest that there may be widespread potential for cannabinoid to act as immunostimulators.

It is clear that cannabinoids modulate numerous physiological processes. It is therefore unsurprising that these compounds are indicated as potential therapeutics in an equally numerous range of pathophysiological processes. Given that the evidence presented above that cannabinoid receptor ligands are potentially immunoactive, and may both suppress, or exacerbate, ongoing immune responses, we can propose that there may be immunological caveats to the use of cannabinoid therapeutics.

2. Clinical applications of cannabinoid therapeutics

2.1. The cannabinoid pharmacopoeia

There is an extensive pharmacopoeia of cannabinoid receptor ligands, comprising agonist, antagonist and inverse agonists derived from a range of pharmacophores (Table I). Structurally, these ligands include arachidonic acid derivatives related to anandamide (the eicosanoid cannabinoids), dibenzopyrans, aminoalkylindoles and diarylpyrazoles. The structures, SAR and receptor binding characteristics for many of these compounds are described extensively in several reviews [8, 13, 61, 62].

Therapeutically relevant cannabinoid receptor ligands include tetra-hydrocannabinol itself, its synthetic forms, and its closely related compounds. Clinical exposure to the former comes involves marijuana (both in prescribed and illicit preparations) and the recently developed vaporized delivery systems for purified THC (Sativex) [62, 63]. Dronabinol and Nabilone are synthetic, and derivatized synthetic, THC, respectively. Despite the development of cannabinoid receptor agonists that are important tools in both *in vitro* and *in vivo* model systems, THC and its derivatives remain the only clinically applied cannabinoid receptor agonists currently in use. High affinity, selective CB2 agonists have also been described but their therapeutic potential has not yet been established. Levonantradol (Nantrodolum) [64, 65] is a CB1/CB2 dual ligand with efficacy as an anti-emetic and analgesic, but which has largely been supplanted by Nabilone in the clinic. Interestingly, both CB1 and CB2-selective ligands modified for SPECT imaging are of potential clinical interest [66, 67].

Sanofi-Synthelabo has developed the most currently clinically applied cannabinoid receptor antagonist. The Sanofi compound SR141716 (Rimonabant, Accomplia), is a CB1 antagonist with a high degree of selectivity for CB1 over CB2 [68, 69]. Rimonabant has been widely prescribed for both management of obesity and smoking cessation, although recent data linking it to elevated risk of depression and even suicide has prompted withdrawal and serious concerns as to the safety of this therapeutic approach [70-72]. Sanofi also developed the SR144528 CB2 antagonist, which, while promising in pre-clinical studies, has not yet been approved for therapeutic use [73-75].

2.2. Indications for cannabinoid therapeutics

Cannabinoids have been used therapeutically in traditional medicine for centuries. Their more recent recognition as potentially mainstream therapeutic agents has centered around a spectrum of disorders summarized below and in Table III.

Neurological indications—The brain and CNS are primary sites of action for endogenous and exogenous cannabinoids. As described above, endogenous cannabinoids modulate various aspects of neuronal function, with concomitant effects upon learning, memory deposition, cognitive ability and anxiety [8, 14, 64, 76-78]. Cannabinoid receptor ligands are therefore proposed as potential therapeutics in neurodegenerative disorders where memory and learning pathways are severely compromised, such as Parkinson's and Alzheimer's diseases, and AIDS-related neurodegeneration. Cannabinoid therapeutics have also been proposed in the treatment of chronic, and affective, brain disorders [79-82]. A causal relationship between the endocannabinoid system and schizophrenia is supported by several lines of evidence, in particular, the association between prolonged marijuana usage and schizophrenia and bipolar pathology [83-85]. Also, polymorphisms in the CB1 receptor 5′ UTR are reportedly associated with the incidence of schizophrenia and mood disorders [86, 87]. Cannabinoids are also proposed as analgesics. On peripheral nociceptors cannabinoid receptor-mediated suppression of potassium channel activation by cyclic AMP is directly analgesic [88, 89]. Moreover, eicosanoid cannabinoids such as anandamide and palmitoylethanolamide, are direct agonists of the nociceptive TRPV1 and TRPA1 cation channels [90-92]. Thus, antagonists or inverse agonists based on the structures of these cannabinoids might reasonably be expected to act as analgesics.

Immunological indications—As described above, exogenous cannabinoids are broadly immunosuppressive. A significant body of work suggests that this suppressive potential extends to acute, and ongoing, inflammatory responses. Mechanistically, cannabinoid-mediated inhibition of adenylyl cyclase, activation of beta-gamma mediated pathways and modulation of intracellular free calcium levels, may all negatively impact the release of inflammatory mediators and the induction of pro-inflammatory transcriptional programs. For example, cannabinoid exposure antagonizes antigen-, and secretagogue-mediated release of prostaglandins, histamine and the matrix-active proteases from mast cells [60]. The phagocytic function of macrophages is also suppressed by cannabinoid exposure. Cannabinoids also suppress inflammation at a secondary, chronic level by down-regulation of the production of cytokine such as TNF-alpha, interferon-gamma, and interlukin-1. Moreover, Th2-mediated production of interleukin-4, which is critical to maintain B-cell class switching to IgE in the case of allergic reactions, is also negatively regulated by cannabinoids [25, 27, 28, 93, 94].

The promise of cannabinoid receptor agonists as a novel class of anti-inflammatories has led to intensive investigation into this area. In terms of clinical application, the anti-inflammatory effects of the endocannabinoids are of limited utility, because these structures are chemically labile and likely to exhibit poor bioavailability. Inhaled or ingested THC can acutely suppress ongoing airway or gastrointestinal inflammation, leading to a particular interest in the development of cannabinoid therapeutics prescribed for treatment of asthma, COPD, and Crohn's Disease/IBD. Indeed, at the cellular level, chronic exposure of mast cells to CB1 ligands has been shown to potentiate secretion of inflammatory mediators and to activate transcriptional programs that include multiple pro-inflammatory cytokine genes [60]. In mast cells, as in many other immunocytes, the activation of CB2 receptors is central to the suppressive effects of CB, while apparently pro-inflammatory effects of cannabinoids appear to be attributable to the expression of CB1 receptors [60]. Given the growing evidence of the expression of the CB1 receptor on numerous immunocytes, it would seem

that the clinical promise of cannabinoids as anti-inflammatories may only be realized as the development of highly selective CB2 agonists is made a priority.

Metabolic indications—Cannabinoid therapies have been proposed for control of eating disorders, including anorexia, cancer- and AIDS-associated cachexia, obesity, and the metabolic syndrome [95-97]. These proposed therapeutic approaches are based on the evident role of the endogenous cannabinoid system in metabolic homeostasis. It is known that the endocannabinoids affect the particular neuronal circuits that control food intake and energy expenditure, as well as the metabolic functions of various peripheral tissues, including skeletal muscle, the gastrointestinal tract, liver and adipose tissue. Endocannabinoids actively promote food-seeking behavior, and increase the incentive value of foods presented. Endocannabinoids also cross-regulate peptide signaling pathways that regulate eating behavior (notably exemplified by the fact that blockade of CB1 prevents the orexigenic actions of the hunger signaling hormone Ghrelin) [98, 99]. Endocannabinoids positively reinforce the perceived hedonic value of foods, through the induction of the synthesis of endogenous opioids. Excessive excitation of the cannabinoid system induces food intake that is consequently followed by an accumulation of adipose tissue, and hyperphagia attributable to hypothalamic stimulation. In contrast, mice genetically deficient in CB1 have a decreased tendency towards obesity when fed a high caloric diet. With these data in mind, synthetic Δ9-THC (Dronabinol) has been a prescribed drug for the treatment of anorexia and wasting syndromes in both cancer and aids patients due to these weight increasing and orexigenic characteristics. There is growing interest in the application of cannabinoids such as Dronabinol to appetite promotion for elderly patients who exhibit anorexia associated with the failure-to-thrive (FTT) syndrome [20, 100]. In contrast, antagonism of the CB1 receptor has been shown to suppress appetite. Appropriately, selective antagonists of the CB1 receptor have been proposed as potential therapeutic agents to be used in the treatment of several metabolic disorders such as obesity and metabolic syndrome.

3. Counter-indications for cannabinoid therapeutics

3.1. Documented Side-effects of cannabinoid exposure

Likely side effects of cannabinoid therapeutics must be identified from the known effects of cannabinoid compounds upon the human body. Each of these may be considered as a potential side effect, desirable or undesirable, of cannabinoid therapeutics. The systemic effects of cannabinoids have been relatively well-described. Cannabinoid exposure is associated with euphoric mood alterations, with marijuana users reporting an enhanced sense of well-being, relaxation, sedation and alleviating inhibition. Conversely, disphoric mood alterations associated with marijuana usage include anxiety, panic, and in rare situations does this develop into psychosis [72, 83, 101, 102]. Potential side effects of cannabinoid therapeutics also lie within the spectrum of neuropsychological effects reported for these compounds. Thus, cannabinoids are psychomotor suppressors, and altered memory deposition may result from exposure [103, 104]. Within the cardiovascular system, the hypotensive effects of cannabinoids may be significant risk factors for syncope, transient ischemic attack and stroke. Modulation of appetite is also a consequence of both abuse, and use, of cannabinoids. The immediate stimulation of appetite that is associated with cannabinoid exposure may translate, over a chronic time courses, to weight gain, hypoactivity and associated health problems. Finally, there is an inherent risk that highly purified THC preparations (eg. Sativex) may induce chronic respiratory or GI irritation that reflects the apparent pro-inflammatory potential of this compound. Outright allergy to marijuana is rare but has been described, with contact urticaria and rhinoconjunctivitis reported [105, 106].

3.2. Potential immunological side-effects of cannabinoid exposure

The systemic immunological effects of cannabinoids have been inferred from evidence ranging from the anecdotal to defined *in vivo* studies. At the anecdotal level, those who use or abuse marijuana report increase incidences of common infectious diseases, respiratory symptoms and mild GI pathology, each associated with the route of administration [40, 107-110]. To date, there has been relatively little description of immunological side effects for cannabinoid drugs in humans, a fact that is somewhat at odds with the extensive literature, referred to above, that documents cannabinoid immunoactivity. This apparent paradox may be rooted in the interpretation of data measuring immune system function in AIDS patients who reported self-medication or abuse of marijuana. Early studies addressing this question suggested a lack of gross alteration in immune status with continued exposure to inhaled or ingested marijuana. Bredt *et al* reported upon immune phenotype in HIV-1 infected patients exposed to a 25 day regimen of Dronabinol (2.5mg daily) or Δ9-THC (in the form of a 3.5% THC cigarette), or to placebo. This study is of particular interest since it is oft-cited as indicating no gross alterations in immune function. Indeed, no statistically significant decline in absolute numbers of the major lymphocyte subsets were observed during the trial [111, 112]. However, significant changes were seen in the numbers of $CD8^+HLA^-DR^+$ cells (increased in smoked marijuana versus placebo) and in a number of other variables, such as a decline in the numbers of $CD8^+CD38^+HLA\text{-}DR^+$ and $CD4^+CD38^+HLA^-DR^+$ cells in smoked marijuana versus placebo. The smoking preparation obviously confounds some aspects of analysis, since both of these latter subsets were increased in patients exposed to Dronabinol versus placebo. Similarly, increases in median levels of intracellular TNFα, IFNγ and IL-2 were increased in Dronabinol-exposed patients *versus* placebo, and THC exposure stimulated NK cell function were observed, which was significantly suppressed when the THC cigarettes were the delivery vehicle. While the data of Bredt *et al* are in agreement with the Kaslow *et al* Multipatient AIDS Cohort Study, suggesting that, at least, cannabinoid exposure does not accelerate loss of immune competence in HIV-1 infected patients, it can also be argued that these data support the idea that chronic exposure to cannabinoids alters the human immune system [113]. In marijuana users, Pacifici et al showed that cannabis use was associated with a decrease in NK cell numbers, suppressed lymphoproliferative responses to lectins and suppressed IL-2 levels, but enhanced levels of the pro-inflammatory cytokines IL-10 and TGF1 [114, 115]. Perhaps of particular interest is the elevation of cytokines such as TNFα, IL-10 and TGF1, since these messengers have the potential to exert profound phenotypic changes in immunity.

Further suggestions that we may be currently under-estimating the potential for cannabinoid exposure to modulate immunity can be derived from review of studies published in the 1970s. Inhibition of cell-mediated immunity in marijuana smokers published in 1974 was echoed subsequently by *in vivo* experiments from the Klein laboratory [37]. Moreover, enhanced mitogen sensitivity and a tendency towards PHA-induced transformation were also observed in lymphocytes isolated from marijuana smokers. Numerous studies in the last two decades have shown that cannabinoid exposure causes a suppression in responsiveness to infectious disease, and the work of the Tashkin laboratory gives us compelling evidence that, even when the confounding effects of smoke components are accounted for, cannabis smoking causes profound inflammatory changes in the respiratory tract [110].

As a final note on this topic, literature dating back to the 1970s documents the consumption of cannabinoids in the form of marijuana and their effect on immunity to infection. It had been suggested that there is a strong correlation between cannabis consumption and an increased susceptibility to various viral infections [35, 116]. Numerous animal studies followed, involving infectious agents such as the herpes simplex virus, *Listeria monocytogenes*, *Staphylococcus albus*, *Treponema pallidum* and *Legionella pneumophila*.

These data suggest that therapeutic cannabinoids may have the side effect of suppressing host resistance to infection [117].

Taken together with data on *in vitro* and *in vivo* modeled effects of cannabinoid exposure, these studies indicate significant potential for immunological side effects of cannabinoid compounds in humans. While no single, or systematic, study of these effects has been performed, emergent themes would seem to be alterations in cell-mediated immunity, dysregulated production of cytokines, altered intensity of cytokines production, changes in susceptibility to infectious agents and chronic exacerbation of inflammation.

4. Immunological considerations in current therapeutic applications of cannabinoids

We can identify two emergent therapeutic applications of cannabinoids in which a consideration of potential immunological side-effects is appropriate. These are the applications of cannabinoid agonists to promote eating in patients with AIDS, cancer, anorexia or FTT-associated cachexia; and the application of cannabinoid receptor antagonists to suppress appetite and weight gain mechanisms in patients with obesity and the metabolic syndrome. The immunological caveats to these therapeutic regimens are deserving of attention first, because they are chronic disorders in which sustained exposure to the cannabinoid therapeutic is likely, creating the potential for phenotypic changes in the patient's immune status. Second, each of these patient groups already present with a dysfunctional immune system (reviewed below). The question of whether the effect of the cannabinoid therapy is to redress these immunological imbalances or exacerbate them is key. Despite the focus here on these chronic disorders, it should also be noted that consideration of cannabinoid-based therapeutics as analgesics, and anti-inflammatories, as well as the recreational use of cannabinoids, should be weighed in light of their potential effects on the immune system.

4.1. Immunological context in AIDS-, cancer- and other cachexias

In AIDS patients, the dysregulation of the immune system has been extensively described. Briefly, plummeting $CD4^+$ T cell levels leave the human body vulnerable to opportunistic infections, primarily pneumocystic pneumonia, TB, meningitis and encephalitis [118-120]. Deficient T- and dendritic-mediated surveillance allows tumor progression, especially in the skin. The respiratory and GI tracts are prone to chronic intractable inflammation, unresolved in the absence of effective T cell and macrophage responses. It is not difficult to reason that cannabinoid exposure in an HIV-infected patient, while promoting appetite, may nevertheless adversely effect an already failing immune system, through suppression of T-mediated immunity that would combat these infections in a normal patient.

Moreover, in cachexics, either with AIDS, or with cancer, anorexia or geriatric failure-to-thrive (FTT), the immune system is further compromised, with impaired cell-mediated responses, decreased IgA production, suppressed phagocyte activity and depleted complement [121, 122]. This immunosuppression would likely be exacerbated by prolonged exposure to cannabinoids. However, cachexics also display a systemic inflammatory syndrome (likened to a ‘cytokine storm’) characterized by elevated plasma levels of IL-6, IL-11, IL-1, and TNFα. The elevations in these cytokines are believed to be related to both lipolysis in adipose tissue and the breakdown of muscle tissue, with the products of the latter also causing acute pyremia and fever. Thus the effect of cannabinoid exposure on the immunological status of a cachexic is likely to be multi-faceted. An exacerbation of immunosuppression following cannabinoid exposure could, in turn, exacerbate the impairment in the above-mentioned immune responses. In contrast, cannabinoids may act to

suppress the systemic inflammation that attends the elevated circulating cytokine levels found in cachexics. Clear predictions as to the immunological caveats of cannabinoid exposure in these individuals are thus hard to make in the absence of clinical, multi-parameter, data collected from individuals who are cachexic and prescribed nabilone or dronabinol.

4.2. Immunological context in obese/metabolic syndrome patients

In obese individuals, a systemic, low level, inflammation has been described. In broad terms, the plasma of obese individuals contains elevated levels (2-4 fold above basal) of pro-inflammatory cytokines, cytokine antagonists and acute phase proteins [123-125]. This systemic inflammation lacks intensity, but is a consistent predictor of mortality in the general population and in people with cardiovascular disease and obesity. In addition to systemic plasma elevation in cytokine levels, it is clear that locally, within the adipose, production of the pro-inflammatory cytokine TNFα is elevated, arising from an apparent increase in lipolytic activity by adipose seeking to self-regulate the adipose volume. Moreover, at the epidemiological level, an increased prevalence of atopic diseases such as asthma and allergy are associated with obesity, likely due to both an exercise-induced asthma type presentation where increased body mass causes respiratory stress, and to underlying immunological changes that exacerbate inflammatory reactions. There is also evidence that immune tolerance is decreased in obese individuals, where increased body weight increases IL-6, TNFα and leptin levels [126]. The latter suppress Treg activity and the individual is shifted to a Th2 cytokine profile that is associated with increased prevalence of atopic disease and autoimmune diseases such as Type II diabetes.

We do not know whether this systemic inflammation is causal or an effect of increased adipose mass. It seems clear that in the case of TNFα there is a direct relationship between elevated cytokine levels and increased adipose volume. Anti-inflammatory effects of inhaled or ingested cannabinoids such as suppression of TNF transcription could, in a sense, be counter-productive since TNF over-production appears to be an attempt at homeostatic lipolysis. However, the most likely modality of exposure to cannabinoid receptor ligands in the clinical setting for obese patients is treatment with cannabinoid receptor antagonists such as Rimonabant. Here the effect of endogenous cannabinoids on CB1 would be blocked in the CNS and periphery, including in cells of the immune system. Since CB1-active endocannabinoids appear to contribute to basal immune function, there may be significant caveats to the use of these compounds immunologically. As a final point, the application of CB1 antagonists may be immunostimulative, in the sense that the homeostatic role of endo-cannabinoids in dampening immunocyte activation could be over-ridden, and would be predicted to change the profile of responses to subsequent infection.

5. Perspectives

The physiological effects of cannabinoids on the immune system have been relatively understudied. Similarly, the attention paid to potential immunological side effects of cannabinoid exposure is considerably less than that paid to the neurological implications. Both endogenous and exogenous cannabinoids are potently active in multiple aspects of physiology. Hence, the exciting potential of cannabinoid derived drugs in diseases as disparate as obesity, anorexia, neurodegeneration and anxiety. Given their immunoactivity, as cannabinoids enter our pharmacopoeia, the immunological status of patients receiving these drugs should be considered as cannabinoids have the potential to further compromise an already challenged immune system. Clearly, more research is required on all aspects of this problem.

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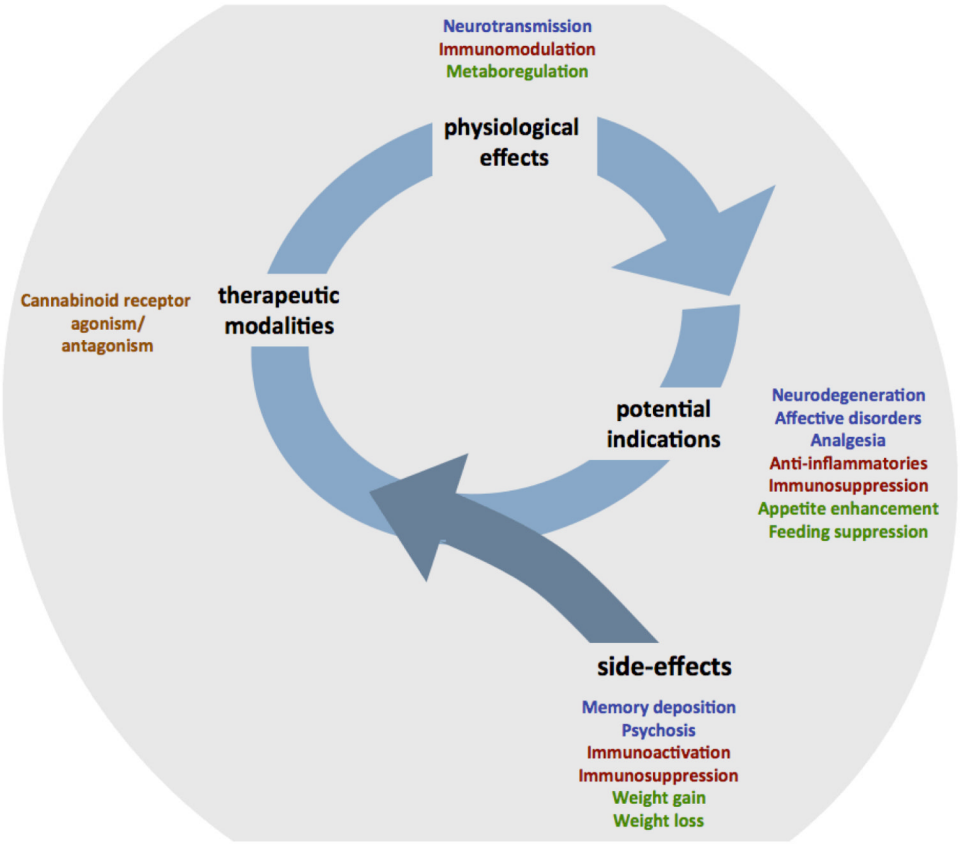

Figure 1. Considerations in the therapeutic application of cannabinoids

The documented physiological effects of cannabinoids inform their proposed uses as therapeutic agents. Literature that documents side effects of cannabinoid exposure can further inform the design of actual therapeutic modalities to optimize benefit and minimize risk.

Table I
Overview of cannabinoid receptor ligands

Endogenous and exogenous (synthetic) cannabinoids ligate two G-Protein coupled receptors, CB1 and CB2. In addition, binding of arachidonic acid-derived cannabinoids to the ionotropic cannabinoid receptors TRPV1 and TRPA1 has been described. Inverse agonist character of some cannabinoids is reviewed in [9, 127].

Ligand	Activity	Selectivity
Endocannabinoids		
Anandamide	Agonists	CB1>CB2; TRPV1, TRPA1, CB2>CB1
2-arachidonylglycerol		CB1 and CB2
Noladin ether		CB1 and CB2
Homo-γ-linolenoylethanolamide		CB1 and CB2
Docosatetraenoylethanolamide		
Synthetic Cannabinoids		
R1-Methanandamide,	Agonists	CB1, TRPV1, TRPA1
ACEA		
ACPA.		
O-1812		
HU-308	Agonists	CB2
L-759633		
L-759656		
JWH015		
JWH133		
JWH139		
Δ^9 tetrahydrocannabinol,	Classical agonist	CB1 and CB2
Cannabidiol	Classical agonist	
HU210	Classical agonist	
CP55940	Non-classical agonist	
CP47497	Non-classical agonist	
CP55244	Non-classical agonist	
WIN55212	Aminoalkylindole agonist	
SR171416A (Rimonabant)	Antagonist	CB1
LY320135		
AM251		
AM281		
SR144528	Antagonist	CB2
AM630		
WIN56098		
WIN54461		

Table II
Cannabinoid receptor agonist effects upon immunocytes

Both rodent and human model systems have established that both endo-and exo- cannabinoids effect multiple facets of immunocyte effector function including cytokine release, cell proliferation, and levels of effector enzymes.

Cell type	Effect	Ligand Applied
Cytokine modulation		
Splenocytes	[r]Decrease IFNy	[r]Anandamide, D^9-THC
	[r]Decrease IL-2	[r]Δ^9-THC
	[r]Increase IL-4	[r]Δ^9-THC
	[r]Increase IL-10	[r]Δ^9-THC
	[r]Decrease IL-1	[r]11-hydroxy THC
Macrophage	[r]Decrease Th1 cytokines	[r]Δ^9-THC
	[r]Increase Th2 cytokines	[r]Δ^9-THC
	[r]Decrease NO	[r]Δ^9-THC, dexanabinol (HU-211)
	[r]Decrease IL-1β	[r]Δ^9-THC
	[r]Decrease TNFα	[r]Δ^9-THC, dexanabinol
	[r]Increase IL-1β	[r]Δ^9-THC
	[h]Increase NO	[h]Anandamide
	[h]Increase TNFα	[h]Δ^9-THC
	[h]Decrease IL-1β	[h]Δ^9-THC
	[h]Decrease IL-6	[h]Δ^9-THC
Lymphocytes	[r]Decrease IL-2, biphasic	[r]Δ^9-THC
	[h]Decrease IL-2	[h]Δ^9-THC
	[h]Decrease TNFα	[h]Δ^9-THC
	[h]Decrease IFNγ	[h]cannabinol
	[h]Decrease IL-8	[h]cannabinol
	[h]Decrease MIPα	[h]cannabinol
	[h]Decrease MIPβ	[h]cannabinol
	[h]Decrease RANTES	[h]cannabinol
	[h]Decrease IL-10	[h]cannabinol
Mononuclear cells	[h]Decrease IL-1β	[h]cannabinol
	[h]Decrease TNFα	[h]cannabinol
Effector functions		
Fibroblasts	[h]Elevated PLA2	anandamide
Proliferation		
Natural killer cells	[h]Decrease proliferation	[h]Δ^9-THC
	[r]Decrease proliferation	[r]Δ^9-THC

Cell type	Effect	Ligand Applied
Macrophages	[r]Increased apoptosis	[r]Anandamide, [r]Δ^9-THC
Lymphocytes	[r]Increased apoptosis	[r]Δ^9-THC

Table III

Overview of potential indications for cannabinoid therapeutics

Given the varied physiological effects of cannabinoids, it is unsurprising that drugs based upon their structures are either proposed or current therapies for a range of disorders. Both agonist and antagonist of cannabinoid receptors have been incorporated into this emergent pharmeceutical approach.

Drug	Use	Indication
CB1 agonists		
Peripheral Central	Appetite stimulation Appetite stimulation	Anorexia Cancer cachexia AIDS-related cachexia Failure to thrive
CB1 antagonists		
	Memory enhancement Weight loss Decrease hedonistic behaviors	Neurodegeneration, Alzheimer's Obesity Alcohol addiction
CB2 antagonists		
	Anti-inflammatory Analgesia	Colitis, dermatitis, arthritis, neurogenic inflammation Acute pain, neuropathy