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GUEST COMMENTARY

Turning Over a New Leaf: Cannabinoid and Endocannabinoid Modulation of Immune Function

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Abstract Cannabis is a complex substance that harbors terpenoid-like compounds referred to as phytocannabinoids. The major psychoactive phytocannabinoid found in cannabis Δ^9-tetrahydrocannabinol (THC) produces the majority of its pharmacological effects through two cannabinoid receptors, termed CB_1 and CB_2. The discovery of these receptors as linked functionally to distinct biological effects of THC, and the subsequent development of synthetic cannabinoids, precipitated discovery of the endogenous cannabinoid (or endocannabinoid) system. This system consists of the endogenous lipid ligands *N*-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonylglycerol (2-AG), their biosynthetic and degradative enzymes, and the CB_1 and CB_2 receptors that they activate. Endocannabinoids have been identified in immune cells such as monocytes, macrophages, basophils, lymphocytes, and dendritic cells and are believed to be enzymatically produced and released "on demand" in a similar fashion as the eicosanoids. It is now recognized that other phytocannabinoids such as cannabidiol (CBD) and cannabinol (CBN) can alter the functional activities of the immune system. This special edition of the Journal of Neuroimmune Pharmacology (JNIP) presents a collection of cutting edge original research and review articles on the medical implications of phytocannabinoids and the endocannabinoid system. The goal of this special edition is to provide an unbiased assessment of the state of research related to this topic from leading researchers in the field. The potential untoward effects as well as beneficial uses of marijuana, its phytocannabinoid composition, and synthesized cannabinoid analogs are discussed. In addition, the role of the endocannabinoid system and approaches to its manipulation to treat select human disease processes are addressed.

Keywords Cannabinoids · Cannabinoid receptors · Endocannabinoids · Immune modulation · Neuroimmune effects · Marijuana · Phytocannabinoids

Introduction

In this special edition of the Journal of Neuroimmune Pharmacology, we present a collection of cutting edge articles on the medical implications of marijuana use and the functionality of the endocannabinoid system. It is our goal to provide an unbiased assessment of the state of research related to this topic and we have solicited articles from leading researchers in the field. The seven reviews and ten original articles in this special themed edition of the Journal describe the role of phytocannabinoids and the endocannabinoid system on neuroinflammatory processes in in vitro, laboratory animal, and human systems.

Translating in vitro and in vivo results derived from experimental animals to the human condition is fraught with substantial challenges. Marijuana users may consume other drugs that affect immune function, complicating our understanding of the relative contribution of a distinct phytocannabinoid. Furthermore, because marijuana contains a plethora of phytocannabinoids and other classes of chemicals, attributing a specified action to a single constituent is difficult. This complexity is further augmented by emerging scientific data that show that distinct phytocannabinoids may activate immune cells by receptor-mediated as well as by non-receptor-mediated modes. In order to garner insight into the potential linkage between marijuana use in humans and compromised immune function, investigators have resorted to the use of purified synthetic phytocannabinoid preparations in cell culture models or in experimental animals.

The Diversity of Cannabinoids

The discovery of the endogenous cannabinoid (endocannabinoid) system and concomitant explosion of basic knowledge pertaining to this system and cannabinoid pharmacology, combined with the controversy regarding potential medical benefits of cannabis versus its abuse and dependence liability, contribute to the impetus for disseminating the science appearing in this special edition. The long history of the use of cannabis for therapeutic and other purposes has been the subject of many reviews (Mechoulam et al. 1991; Russo 2007). Likewise, a detailed overview communicating the components of the endogenous cannabinoid system appears elsewhere (Blankman and Cravatt 2013; Howlett et al. 2011). To date, two cannabinoid-based medications have gained approval by the Food and Drug Administration, Marinol (dronabinol or Δ^9-tetrahydrocannabinol (THC)), the primary psychoactive constituent in cannabis, and Cesamet (nabilone), a synthetic cannabinoid (Pertwee 2009; Rahn and Hohmann 2009). These two medications have been approved for the treatment of chemotherapy-induced nausea and emesis. Marinol also may be prescribed as an appetite stimulant to treat cachexia in AIDS patients. A third medication, Sativex, consists of a sublingual spray formation that contains equivalent concentrations of THC and cannabidiol (CBD) that are extracted from cannabis and has been approved in many countries to relieve spasticity in multiple sclerosis (MS) patients (Syed et al. 2014). In this special issue, we describe key substances present in cannabis, their biological properties, and mechanisms of action. We also review the interdisciplinary research leading to our understanding of cannabinoid- and endocannabinoid-mediated modulation of immune function within the nervous system.

Cannabinoid Receptors

Cannabis is a complex substance that harbors terpenoid-like compounds collectively referred to as phytocannabinoids. The

primary psychoactive constituent of cannabis, THC (Gaoni and Mechoulam 1964), produces the majority of its pharmacological effects through two cannabinoid receptors, termed CB_1 (Devane et al. 1988; Matsuda et al. 1990; Herkenham et al. 1990) and CB_2 (Munro et al. 1993). These two receptors share approximately 44 % amino acid homology (Munro et al. 1993). Both receptors have seven transmembrane domains, are coupled to G-inhibitory proteins, and are linked to signaling cascades that may involve adenylyl cyclase and cAMP, mitogen-activated protein (MAP) kinase, and the regulation of intracellular calcium (Howlett 2002). CB_1 is expressed heterogeneously throughout the nervous system (Herkenham et al. 1991) as well as in other organ systems (Gerard et al. 1991). CB_1 is predominantly responsible for the psychoactive effects of THC, and the stimulation of this receptor plays a role in regulating pain, stress responses, energy regulation and lipogenesis, and immune function. CB_2 is primarily associated with immune function and is expressed on immune cells, including microglial cells within the nervous system, but its expression in the CNS is of a much smaller magnitude than that of CB_1.

Cannabinoids bind to other receptors besides CB_1 and CB_2 (Breivogel et al. 2001; Di Marzo et al. 2000; Jarai et al. 1999), suggesting the existence of additional cannabinoid receptors or simply other binding sites (i.e., "off targets"). Included among these candidate cannabinoid receptors is GPR55, a seven-transmembrane G protein-coupled receptor first cloned and identified in silico from an expressed sequence tags database (Baker et al. 2006; Pertwee 2007; Sawzdargo et al. 1999). GPR55 is activated by THC and CBD, certain synthetic cannabinoids, and the endogenous cannabinoids N-arachidonoylethanolamine (anandamide; AEA) and 2-arachidonoylglycerol (2-AG) (Ryberg et al. 2007). However, unlike CB_1 and CB_2, GPR55 is coupled to a G-alpha (Gα) protein instead of a Gi/o protein (Ryberg et al. 2007), is not activated by the synthetic cannabinoid receptor agonist WIN 55212–2, and increases intracellular calcium levels upon activation (Lauckner et al. 2008). However, to date, a novel non-CB_1, non-CB_2 cannabinoid receptor that meets rigid pharmacological and functional criteria (i.e., is selective for cannabinoid ligands) has yet to be cloned and characterized at the molecular level (Breivogel et al. 2001; Di Marzo et al. 2000; Jarai et al. 1999; Wiley and Martin 2002; Pertwee et al. 2010).

Endogenous Cannabinoids

The discovery of cannabinoid receptors that mediate the actions of THC and synthetic cannabinoids, precipitated the search for the endogenous ligands that bind these receptors. AEA (Devane et al. 1992) and 2-AG (Mechoulam et al. 1995; Sugiura et al. 1995) represent the primary endogenous ligands that bind and activate CB_1 and CB_2. Endocannabinoids have been identified in immune cells such as monocytes, macrophages, basophils, lymphocytes, and dendritic cells (Matias et al. 2002). These endocannabinoids are believed to be enzymatically produced and released "on demand" in a similar fashion as the eicosanoids. AEA and 2-AG are rapidly hydrolyzed by fatty acid amide hydrolase (FAAH; (Cravatt et al. 2001; Cravatt et al. 1996)) and monoacylglycerol lipase (MAGL (Dinh et al. 2002a; 2002b)), their respective chief degradative enzymes, though other enzymes play a role in endocannabinoid metabolism (Blankman et al. 2007; Hermanson et al. 2014). FAAH also hydrolyzes other bioactive fatty acid amides (Cravatt et al. 2001), such as N-palmitoylethanolamine and oleoylethanolamide each of which has been reported to possess anti-inflammatory actions through the PPARα receptor (Lo Verme et al. 2004). MAGL hydrolysis of 2-AG also represents an important pathway in the production of free arachidonic acid in the brain that may play a role in neuroinflammation (Nomura et al. 2011). Inhibitors of FAAH and MAGL as well as genetically modified mice that lack these enzymes represent useful tools to elucidate endocannabinoid function, and as a test of proof-of-principle of their potential as therapeutic agents.

Phytocannabinoids

Cannabis has long been used as a source of fiber for the manufacture of rope and clothing, but this material contains little THC. In contrast, illicit marijuana contains high levels of THC, which has steadily increased from approximately 3 % in the 1980s to 12 % in 2012 (Volkow et al. 2014). In addition to THC, over 100 other cannabinoids have been identified in the particulate phase of the marijuana plant (Husni et al. 2014) and its genome has recently been described (van Bakel et al. 2011). Other cannabinoids of interest including CBD, cannabinol (CBN), and cannabigerol (CBG) largely lack the ability to activate cannabinoid receptors, but are biologically active (Russo 2011). CBD has gained particular interest recently as a constituent in the medication Sativex, which has been found to alleviate spasticity associated with MS (Serpell et al. 2013; Syed et al. 2014), cancer pain in opioid-treated patients (Johnson et al. 2010), and marijuana withdrawal (Allsop et al. 2014). Additionally, CBD is under investigation in assorted clinical trials as an anti-epileptic (Devinsky et al. 2014). Preclinical studies reported that CBD elicits anticonvulsant (Consroe et al. 1982; Martin et al. 1987), anti-inflammatory (Li et al. 2013; Malfait et al. 2000), and anti-tumorgenic (McAllister et al. 2007) effects. Although its mechanism of action remains to be elucidated, it is known to inhibit adenosine uptake (Liou et al. 2008), down-regulate the enzymes FAAH and 5-lipoxygenase (Capasso et al. 2008; Massi et al. 2008), and bind both transient receptor potential vanilloid 1 (TRPV1) (Iannotti et al. 2014) and 5-

hydroxytryptamine (serotonin) receptor 1A (5-HT1A) receptors (Russo et al. 2005).

Upon heating, phytocannabinoids rapidly decarboxylate and at the temperature of pyrolysis (200° – 400 ° C) undergo aromatization (Nahas 1993). Polycyclic aromatic hydrocarbons have been identified in marijuana smoke and include higher molecular weight compounds, such as the carcinogens benzo(α)pyrene and benz(α)anthracene. The gas phase of marijuana smoke includes toxic substances including carbon monoxide, hydrogen cyanide, and nitrosamines, which also are present in equivalent concentrations in tobacco smoke (Nahas 1993). THC and other phytocannabinoids are lipophilic and sequester in liver, lung, spleen, and neutral fat (Nahas 1993). THC has an approximate half-life of 8 days in fat and may take up to one month for complete elimination of a single dose in humans (Nahas 1993). Furthermore, THC is a polar compound and is metabolized slowly into more water-soluble, nonpsychoactive metabolites. The bioavailability of inhaled and ingested THC is 20 and 6 %, respectively (Nahas 1993).

Synthetic Cannabinoids

The purification and structural characterization of THC (Gaoni and Mechoulam 1964) have led to the chemical synthesis of various cannabinoid analogs that have been used extensively in structure–activity relationship studies to characterize cannabinoid-mediated bioactivity (e.g., Johnson and Melvin 1986; Mechoulam et al. 1987), and these efforts contributed directly to the discovery of the cannabinoid receptors (Devane et al. 1988; Herkenham et al. 1990; Matsuda et al. 1990; Munro et al. 1993). The extensive use of synthetic cannabinoid ligands has increased our understanding of the functional relevance and mechanism of action by which phytocannabinoids exert their effects on the immune system. For example, THC has been reported to suppress the antibody response of humans and animals (Klein et al. 1998) and to suppress a variety of activities of T lymphocytes (Kaminski 1998; Klein et al. 2004). Administration of THC to mice also has been reported to inhibit natural killer (NK) cytolytic activity and to reduce interferon gamma (IFNγ) levels (Massi et al. 2000). In addition, THC has been reported to abolish the functional activities of macrophages and macrophage-like cells, including macrophage-mediated cell contact-dependent cytolysis of tumor cells and the processing of antigens (Burnette-Curley et al. 1993; Klein et al. 1991; McCoy et al. 1999). It has been reported also that THC alters the production of chemokines and cytokines, leading to a perturbation in the homeostatic balance between pro-inflammatory (Th_1) cytokines, which promote systemic inflammation, and anti-inflammatory (Th_2) cytokines such as IL-4 and IL-10 that play an immunoregulatory role in controlling the inflammatory response. Such a shift in the cytokine profile to a Th_2 bias may contribute to altered inflammatory responses to infection with bacteria and viruses (Kidd 2003). It is now well recognized that other phytocannabinoids such as CBD and CBN can also alter the functional activities of the immune system (Cabral et al. 2014).

Immunomodulatory Activity of Cannabinoids

It has been suggested that the CB_1 has potential to serve as a molecular target for therapeutic attenuation of cognitive impairment and degeneration in select CNS disorders (Pryce et al. 2003; Pryce and Baker 2007; Shen and Thayer 1998), a caveat to this consideration is that activation of this receptor also engenders psychotropic effects, dependence, and cognitive impairment (Jones et al. 1976; Budney et al. 2007; Leweke and Koethe 2008; Vandrey and Haney 2009; Skosnik et al. 2012; Radhakrishnan et al. 2014). However, many neuropathogenic processes are characterized by progressive decline in cognitive functions that are accompanied by, if not caused by, inflammation. Much attention has been focused on CB_2 not only because of its expression primarily in cells and tissues of the immune system (Munro et al. 1993), but also because of its intricate involvement in immune function and its activation in the whole animal is largely devoid of psychotropic effects (Malan et al. 2003; Kinsey et al. 2011). The level of CB_2 expression varies among different immune cell populations, with B lymphocytes expressing the highest levels followed by macrophages, monocytes, NK cells, and polymorphonuclear cells, in that order (Galiegue et al. 1995; Schatz et al. 1997). Early studies concluded that the distribution of CB_2 was confined to peripheral non-neuronal sites. However, it is now recognized that this receptor is expressed by a variety of subsets of immunocompetent cells found in the CNS (Cabral and Marciano-Cabral 2005; Carlisle et al. 2002; Carrier et al. 2004; Fernandez-Ruiz et al. 2007; Nunez et al. 2004; Ramirez et al. 2005). Moreover, the CB_2 has been reported to be present also on neurons (Van Sickle et al. 2005; Zhang et al. 2014). In general, most of the immunomodulatory effects attributed to THC have been linked to activation of CB_2.

In this issue, Eisenstein reviews the literature which addresses the effects of cannabinoids on immune function, with an emphasis on T-lymphocytes (Eisenstein 2015). Consistent with the identification of high levels of CB_2 on cells of the immune system, it is indicated that most of the modulatory effects of THC have been linked functionally to this receptor. Accordingly, it is proposed that selective CB_2 agonists possess promise as therapeutic agents for treatment of autoimmune diseases and for ablation of graft rejection under conditions of decreased incidence of side effects. The potential of select CB_2 agonists to ablate graft rejection is particularly relevant to the report by Robinson et al. that explores the mechanism by

which agonists selective for CB_2, such as O-1966, inhibit the Mixed Lymphocyte Reaction (MLR) (Robinson et al. 2015), an in vitro paradigm used as a correlate of organ graft rejection that is mediated predominantly through effects on T-lymphocytes. These investigators observed an increase in the percentage of regulatory T-cells (Tregs) in MLR cultures using mouse spleen cells. Furthermore, pretreatment with an antibody to the anti-inflammatory cytokine IL-10 (anti-IL-10) resulted in a partial reversal of the inhibition of proliferation and blocked the increase of Tregs. Their results bolster the argument that CB_2-selective agonists may represent useful therapeutic agents to prolong graft survival in transplant patients.

The expression of CB_2 appears to be modulated in monocytes and macrophages in response to various stimuli (Carlisle et al. 2002). CB_2 may be particularly responsive to cognate agonists when in a responsive state, i.e., a functional state that is associated with immune cell migratory activity (Carlisle et al. 2002). More work on this issue is clearly needed since the immunomodulatory activity of CB_2 may be dependent on the activation state of both the target cell population, as well as the vascular endothelial cells at the site of inflammation. This is particularly relevant to the report by Persidsky et al. in which brain microvascular endothelial cells (BMVEC) and monocyte-derived macrophages from human tissue were employed in an in vitro paradigm to show that CB_2 agonism may represent a strategy for treatment of CNS diseases associated with neuroinflammatory responses (Persidsky et al. 2015). These investigators found that activation of CB_2 blocks monocyte migration across BMVEC monolayers, dampens LPS-induced secretion of the pro-inflammatory cytokine tumor necrosis-alpha (TNF-α), reduces the expression of a large panel of pro-inflammatory genes activated by TNF-α in BMVEC, and blunts LPS-induced upregulation of genes associated with inflammation in primary human macrophages. Roth and colleagues macrophages report that THC inhibits the differentiation of human monocytes into antigen-presenting dendritic cells (Roth et al. 2015). These investigators report that THC and CB_2 agonists exert a robust CB_2-mediated effect on dendritic cells that results in failure to stimulate T cell proliferation or promote maturation into functional effector/memory T cells.

While a large body of data from in vitro studies and animal models indicates that the immunomodulatory activity of THC and CB_2 agonists can lead to decreased resistance to infectious agents, a comparable linkage in humans has yet to be demonstrated. A major challenge in resolving this issue is that individuals who use marijuana often also use other substances that have immune-suppressing potential. In addition, individuals who use marijuana, or cannabinoid formulations, for therapeutic purposes already possess underlying health conditions that may render them immunocompromised and susceptible to infection. Furthermore, the presence of CBD and other phytocannabinoids in marijuana may counteract the effects of THC and temper the overall immune functional outcome in vitro and in experimental animals. Thus, in order to more closely approximate the human condition, in particular to the impact of cannabinoid exposure on infection, investigators have resorted to the use of primate models. Molina et al. provide a comprehensive review of the consequences of chronic THC or ethanol exposure in rhesus macaques infected with simian immunodeficiency virus (SIV) (Molina et al. 2015) as a model of human immunodeficiency virus (HIV) infection. In comparison to chronic ethanol exposure that produced a plethora of deleterious effects and accelerated progression of end-stage disease, chronic THC exposure resulted in reduced viral load, viral replication, and inflammation. Furthermore, progression to end-stage disease was decreased or not affected. These results highlight the difficulty of translationally applying in vitro outcomes related to effects of cannabinoids on immune function to those anticipated in vivo in the context of an infectious process. Finally, Chen et al. present original research showing that THC produces a modest suppression of HIV gp120-induced IFNγ production through a CB_1/ CB_2 independent pathway (Chen et al. 2015). Their results indicate that THC can modulate immune responses through non-cannabinoid receptor targets.

Immunomodulatory Role of Endocannabinoids

It has been suggested that 2-AG is the cognate functionally-relevant endocannabinoid for CB_2 (Sugiura et al. 2000; Parolaro et al. 2002). AEA also has been linked to modulation of immune function. However, whether this linkage involves activation of a cannabinoid receptor is uncertain. The immunomodulatory activity mediated by endocannabinoids may occur in an autocrine and paracrine fashion, impacting the functionality of immune cells in a localized environment. Furthermore, such mediated action may be short-lived because of the rapid degradation of endocannabinoids in the intracellular environment. It is now apparent that resident immune cells within the CNS harbor a constitutive endocannabinoid system (Suarez et al. 2010). Thus, it appears that the immediate effective action of endocannabinoids on immune function is at localized sites in the periphery and CNS. It is speculated that, in this context, endocannabinoids play an important role in maintaining the overall "fine tuning" of the immune homeostatic balance within the host.

There is also compelling evidence that the endocannabinoids may provide protective activity, particularly in the brain. However, the basis for the neuroprotection mediated by these endogenous cannabinoids is still rather poorly defined. In this regard, Espejo-Porras et al. describe their characterization of the endogenous cannabinoid system in the transactive response (TAR)-DNA binding protein-43 (TDP-43) transgenic mouse model of ALS during the early

symptomatic (70–80 days of age) and postsymptomatic (100–110 days of age) stages (Espejo-Porras et al. 2015). TDP-43 transgenic mice exhibit motor coordination deficits that are accompanied by a loss of motor neurons and reactive microgliosis with increased expression of CB_2 in the spinal cord. Varied small decreases were found on FAAH expression and increased endocannabinoid levels in spinal cord that were sex- and age-dependent. This initial characterization of the TDP-43 model of ALS sets the stage for testing of pharmacological agents targeting CB_2, FAAH, or other components of the endocannabinoid system. Thus, these studies may provide the basis for developing intervention strategies for treatment of certain neuroinflammatory diseases. One example of this type of development is described by Mann et al. who report the role of the fatty acyl amino acid (FAAA) palmitoyl-serine (PalmS) in the mouse closed head injury (CHI) model of traumatic brain injury (Mann et al. 2015). PalmS treatment improved neurobehavioral outcome, as indicated by neurological severity score (NSS), which examined reflexes, alertness, coordination, motor abilities and balancing. However, PalmS treatment had no effect on cognitive measures, rotarod performance or levels of biomarkers of brain injury (e.g., lesion volume, edema, or proinflammatory markers). Although PalmS does not bind cannabinoid receptors, its beneficial effects required the presence of CB_2. These investigators concluded that the reduction in NSS caused by PalmS is mediated by indirect activation of CB_2 and propose a model that involves receptor palmitoylation, which may result in the structural stabilization of the CB_2 and enhance its activity.

Nevertheless, at this point the physiological activities of the endogenous cannabinoids remain inadequately defined, and a greater understanding of the functional activities of these agents will be necessary in order to fully develop effective therapeutics. In this regard, Gómez et al. describe the effects of 2-AG on early stage oligodendrocyte progenitor cell (OPC) differentiation (Gomez et al. 2015). These investigators report that basal levels of 2-AG are required to maintain proliferation of early OPCs in vitro. Inhibition of 2-AG degradation with a MAGL inhibitor or exogenous administration of 2-AG, as well as that elicited by selective CB_1 or CB_2 agonists, further stimulated early OPC differentiation. The investigators propose a novel mechanism of action for 2-AG in oligodendrocytes coupled to Akt/mTOR signaling, an intracellular pathway important in regulating cell cycle. This exciting work has potential implications in the emerging field of brain repair. Similarly, recent research by Nass et al. shows that MAGL plays a protective role on thermoregulation in mice following endotoxin or cold ambient temperature challenge (Nass et al. 2015). While MAGL inhibition alone had no effect on body temperature in mice, it exerted a profound reduction in core temperature in mice challenged with LPS or cold ambient temperature. In view of these findings, the authors hypothesize that MAGL functions as a protective "brake" from immunological challenges by curtailing 2-AG activation of CB_1.

Cannabinoids and Development

The high incidence of cannabis use by adolescents and young adults of childbearing age, raises the question of the potential impact of cannabinoids on brain development. Chronic and/or recurrent use of cannabis may alter brain and/or immune system development and exert effects that are less apparent in adults. A review by Zumbrun et al. in this issue investigates the implications of marijuana use during pregnancy on the offspring (Zumbrun et al. 2015). These authors also address whether maternal or paternal cannabinoid exposure can trigger epigenetic changes, such as altered microRNA, DNA methylation and histone modification, that have long-term immunological implications on offspring and can be carried across generations. Since much of the current data have been derivative of in vivo rodent and in vitro studies, in this review a case is made for the importance of conducting translational research to provide insights applicable to humans. However, it is clear that additional work in this topical area will be necessary in order to develop an understanding of the capacity of cannabis use to alter either neuronal or immune cell development. A review by Moretti et al. describes results of preclinical studies in which the long-term consequences of THC exposure on adolescent mice were examined (Moretti et al. 2015). Whereas THC did not affect levels of brain cytokines in adult mice, it was found to decrease those of proinflammatory cytokines in the adolescent brain. Following a 1.5 month hiatus from the final THC exposure, brain levels of the anti-inflammatory cytokine IL-10 were decreased. These studies demonstrated that chronic exposure of adolescent mice to THC suppressed immunity immediately after treatment. However, after a washout period, THC induced a long-lasting opposite modulation towards a proinflammatory and T-helper-1 phenotype in adulthood, an outcome comparable to that reported previously to occur at peripheral sites. These findings raise the intriguing possibility that cannabis exposure in adolescents leads to increased vulnerability to immune and neuroinflammatory diseases in adulthood. Finally, the report by Cloak et al. in this issue compares salivary cortisol levels, immunological responses (i.e., salivary IL-1β, TNF-α and IL-6 levels), and psychiatric symptoms in adolescent marijuana users and nonusers (Cloak et al. 2015). While cortisol and salivary cytokine levels did not differ between the marijuana users and controls, self-reported and clinician-rated psychiatric (particularly anxiety-related) symptoms were increased in the marijuana users compared with controls. The age of onset was

negatively correlated with symptoms and the quantity of lifetime marijuana use was correlated positively with symptoms, while days of abstinence were correlated negatively with symptoms. Although levels of cortisol and cytokines did not correlate with cannabis use or psychiatric symptoms, this work suggests that marijuana use in adolescents may contribute to an aberrant relationship between stress response and psychiatric symptoms.

Clinical Implications

Cannabinoid agonists exert a variety of effects in the brain on neuronal function and can modulate neuroinflammatory disease levels in several neurodegenerative disease states. Because CB_2 activation dampens inflammatory responses in the absence of psychotropic effects, it has the potential to serve as a molecular target for attenuating inflammation linked to pathogenic disorders such as MS (Maresz et al. 2007; Zhang et al. 2009b), ischemic/perfusion injury following an induced stroke (Zhang et al. 2007, 2009a), rheumatoid arthritis (Sumariwalla et al. 2004), inflammatory bowel disease (Storr et al. 2008, 2009), inflammatory autoimmune diabetes (Li et al. 2001), spinal cord injury (Adhikary et al. 2011; Baty et al. 2008), sepsis (Tsch p et al. 2009), autoimmune uveoretinitis (Xu et al. 2007), osteoporosis (Ofek et al. 2006), pain (Kinsey et al. 2011; Malan et al. 2001, 2003; Quartilho et al. 2003; Anand et al. 2009; Deng et al. 2015), hepatic ischemia-reperfusion (I/R) injury (Batkai et al. 2007), and systemic sclerosis (Servettaz et al. 2010). Thus, it is not entirely surprising that cannabinoids alter the antitumor immune response, and McAllister et al. review literature describing the well established antitumor activity of CBD, a cannabinoid that does not bind CB_1 or CB_2, in a variety of cancer cell lines, including those derived from glioblastoma, breast, lung, prostate and colon cancer (McAllister et al. 2015). These authors also discuss potential targets of this non-psychoactive phytocannabinoid, as well as the underlying mechanisms of action for its plethora of antitumor effects, elegantly illustrated in Table 1 of their review (McAllister et al. 2015).

Chiurchiu et al. discuss the immunomodulatory effects of cannabinoid signaling on immune cells in the brain (Chiurchiu et al. 2015). The modulatory impact on brain immune responses supports the concept that select cannabinoids have potential as therapeutic agents for management of neuroinflammatory disorders, such as Alzheimer's disease, MS, Huntington's disease, amyotrophic lateral sclerosis (ALS), and Parkinson's disease. The review of Pryce et al. addresses the effects of phytocannabinoids in an experimental autoimmune encephalomyelitis (EAE) model of MS in mice (Pryce et al. 2015). These authors include original data indicating that THC and CBD dampen the behavioral signs and motor deficits associated with EAE. Synthetic CBD was shown to slow down the accumulation of disability from the inflammatory penumbra during relapsing EAE in ABH mice, possibly through blockade of voltage-gated sodium channels. However, while subthreshold doses of each compound given in combination enhanced subjective clinical scores significantly, the experimental conditions applied did not lend themselves to classification of the nature of the drug interaction. In addition, the investigators describe the outcome of a phase III clinical trial aimed at testing the efficacy of oral THC in progressive MS. Although the study did not yield a positive outcome, an a priori analysis of a subgroup of patients who presented with decreased disability revealed that THC reduced disease progression. In addition, CB_2 agonists have recently been demonstrated to be protective against the reinforcing effects of cocaine in mice (Xi et al. 2011; Zhang et al. 2014). Although activation of CB_2 produces well described antinociceptive effects in preclinical studies (Ibrahim et al. 2006), the general outcome of clinical trials has been disappointing (Atwood et al. 2012; Dhopeshwarkar and Mackie 2014).

Finally, given the continued controversy surrounding the issue of "medical marijuana", using the scientific process to discern the safety and efficacy of cannabinoid-based medications remains of paramount importance. To this end, Lynch and Ware provide an in depth analysis of recent clinical trials testing the efficacy of endocannabinoid-based drugs in treating non-cancer pain in humans (Lynch and Ware 2015). A variety of cannabinoids was examined in these studies, including the FDA-approved synthetic cannabinoid receptor agonist nabilone, an oral mucosal cannabis spray, the FAAH inhibitor PF-04457845, oral or inhaled cannabis extract, and smoked cannabis. The majority of these studies revealed modest analgesic effects of these formulations without serious side effects, lending credence to the idea that cannabinoid-based medications ultimately may be a reasonable treatment option for chronic non-cancer pain. However, on a cautionary note, these studies generally have been conducted under conditions of short duration, using relatively small sample sizes and modest effect sizes.

Conclusions

The potential deleterious effects as well as beneficial uses of cannabis, its phytocannabinoid composition, and synthetic cannabinoid analogs are discussed in these papers. In addition, the role of the endocannabinoid system and approaches to its manipulation to moderate select human disease processes are addressed. It is our aim to place the potential benefits and risks of marijuana use in perspective. As the Guest Editors, we believe this is an excellent opportunity to present the latest works related to this important topic.

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Conflict of Interest The authors declare that they have no conflict of interest.

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