Forskningsnyt om Cannabinoider og MS

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Udgangspunkt:
http://www.ncbi.nlm.nih.gov/pubmed
Søgeord: cannabinoid multiple sclerosis
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"Generelle" artikler

http://www.ncbi.nlm.nih.gov/pubmed/24115748

A review of the cultivation and processing of cannabis (Cannabis sativa L.) for production of prescription medicines in the UK.

Abstract

The quality demands of the pharmaceutical industry require prescription medicines to be consistent in their active ingredient content. Achieving this, using raw cannabis as a feedstock, is especially challenging. The plant material is extremely inhomogeneous, and the ratios of active ingredients are affected by a range of factors. These include the genetics of the plant, the growing and storage conditions, the state of maturity at harvest, and the methods used to process and formulate the material. The reasons for this variability are described, with particular emphasis on the botanical considerations. To produce the complex botanical medicine Sativex®, which contains the cannabinoids Δ9 -tetrahydrocannabinol (THC) and cannabidiol (CBD) and a range of other ingredients, GW Pharmaceuticals had to manage these variables. This medicine, for the treatment of spasticity due to multiple sclerosis, is the first cannabis-based medicine to be approved in the UK. The company's methodology for producing this and other chemotypes is described.

http://www.ncbi.nlm.nih.gov/pubmed/24006213

Therapeutic potential of cannabinoid medicines.

Abstract

Cannabis was extensively used as a medicine throughout the developed world in the nineteenth century but went into decline early in the twentieth century ahead of its emergence as the most widely used illicit recreational drug later that century. ***Recent advances in cannabinoid pharmacology alongside the discovery of the endocannabinoid system (ECS) have re-ignited interest in cannabis-based medicines. The ECS has emerged as an important physiological system and plausible target for new medicines. Its receptors and endogenous ligands play a vital modulatory role in diverse functions including immune response, food intake, cognition, emotion, perception, behavioural reinforcement, motor co-ordination, body temperature, wake/sleep cycle, bone formation and resorption, and various aspects of hormonal control.*** In disease it may act as part of the physiological response or as a component of the underlying pathology. In the forefront of clinical research are the cannabinoids delta-9-tetrahydrocannabinol and cannabidiol, and their contrasting pharmacology will be briefly outlined. The therapeutic potential and possible risks of drugs that inhibit the ECS will also be considered. This paper will then go on to review clinical research exploring the potential of cannabinoid medicines in the following indications: symptomatic relief in multiple sclerosis, chronic neuropathic pain, intractable nausea and vomiting, loss of appetite and weight in the context of cancer or AIDS, psychosis, epilepsy, addiction, and metabolic disorders.

http://www.ncbi.nlm.nih.gov/pubmed/23786660

The diagnosis and management of lower urinary tract symptoms in multiple sclerosis patients.

Abstract

Sixty-five percent of multiple sclerosis patients have moderate to severe urinary symptoms and up to 14% initially present with urinary symptomatology. Urinary retention, neurogenic detrusor overactivity, and detrusor sphincter dyssynergia, all increase the risk for urinary tract infections in patients with multiple sclerosis, and these infections may exacerbate their immune response, leading to symptom progression. Fewer than half of the patients with urinary symptoms have seen a specialist and only half have been treated for their neurogenic detrusor overactivity. ***Several***

treatments including pelvic floor muscle therapy, pelvic floor electrical stimulation, anticholinergics, desmopressin, sacral nerve neuromodulation, posterior tibial nerve stimulation, cannabinoids, and intravesical therapy with vanniloids, as well as botulinum toxin, have all been shown to be effective in treating urinary symptoms in those with multiple sclerosis. Clean intermittent catheterization is invaluable in patients with persistent urinary retention to avoid infection and upper tract dysfunction. Indwelling transurethral catheterization should be avoided because of the high risk of infection. Identification and successful treatment of these urinary conditions will improve the health and quality of life for these men and women.

http://www.ncbi.nlm.nih.gov/pubmed/23658734

Effects on immune cells of a new 1,8-naphthyridin-2-one derivative and its analogues as selective CB2 agonists: implications in multiple sclerosis.

Abstract

The efficacy of cannabinoids in the treatment of multiple sclerosis is widely documented; however their use is limited by psychoactivity mainly ascribed to the activation of the cannabinoid receptor CB1. Emerging findings support as alternative strategy in the treatment of neurodegenerative disorders, the application of compounds targeting the CB2 receptor, since likely unrelated to these side effects. Recently, a novel class of compounds, 1,8-naphthyridine, pyridine and quinoline derivatives have been demonstrated to show high CB2 receptor selectivity and affinity versus the CB1 receptor. Considering that the CB2 receptor is mainly expressed in cell and organs of the immune system, in this study we assessed the potential immune-modulatory effects of these compounds in activated lymphocytes isolated from MS patients with respect to healthy controls. These compounds blocked cell proliferation through a mechanism partially ascribed to the CB2 receptor, down-regulated TNF-α production and did not induce cell death. They also down-regulated Akt, Erk and NF-kB phosphorylation. Despite comparable effects observed in patients and healthy controls, these compounds, in particular, 1,8-naphthyridine and quinoline derivatives inhibited cell activation markers in MS patient derived lymphocytes more efficiently than in healthy control derived cells. Indeed, 1,8-naphthyridin-2-one derivative reduced the levels of Cox-2 in lymphocytes from patients whereas no effect was observed in control cells. ***Our findings suggest potential application of these drugs in neuro-inflammation, supporting further investigations of the effects of compounds in the therapy of MS, particularly on the aspects regarding activation and inflammation.***

http://www.ncbi.nlm.nih.gov/pubmed/23621668

Pharmacokinetic evaluation of nabiximols for the treatment of multiple sclerosis pain. (Red: nabiximold=Sativex)

Abstract

INTRODUCTION:

Pain associated with multiple sclerosis (MS) is frequent, and frequently not alleviated by currently available drugs. Nabiximols is a combination of two plant cannabinoids administered via an oromucosal pump spray and approved in Canada for the treatment of intractable central neuropathic pain due to MS and intractable cancer pain. Nabiximols exerts its analgesic effects through its interaction with the endocannabinoid system to modulate pain transmission via pain networks.

AREAS COVERED:

This review examines the characteristics of nabiximols, its pharmacokinetic properties and data on efficacy and tolerability in MS-related neuropathic pain. The authors, furthermore, provide information on the pharmacology and clinical data of nabiximols as neuropathic analgesic in MS.

EXPERT OPINION:

Nabiximols is an appropriate therapy for pain patients who tend to be particularly resistant to

pharmacological interventions. Its action depends on not only the local constellation of the endocannabinoid system signalling, but also the particular functional status of pain pathways and on the specific mechanism of neuropathic pain. It is therefore justifiable that further studies are initiated which aim to define the best responder profile and which explore the full potential of nabiximols in MS-related pain.

Forsøgspersoner:

http://www.ncbi.nlm.nih.gov/pubmed/24108959

Cannabinoid use in progressive inflammatory brain disease (cupid) MRI sub-study.

Abstract

INTRODUCTION:

In progressive Multiple Sclerosis (MS), there is no proven therapy for preventing accumulation of irreversible disability. The pathological substrate of irreversible disability in MS is neuroaxonal loss, and brain tissue volume loss on MRI can infer such pathology. There is experimental evidence to suggest that cannabinoids may have a neuroprotective and anti-inflammatory effect, although in a recent UK clinical trial (CUPID), oral cannabinoid did not slow the development of disability in progressive MS compared with placebo.

AIMS:

Using serial MRI brain scans obtained during the CUPID trial, we compared oral Delta 9-tetrahydrocannabinol (Δ9-THC) versus placebo for the following: (i) rates of new T2 hyperintense and new T1 hypointense lesions, and (ii) rate of brain atrophy.

METHODS:

A subset of progressive MS patients from the CUPID trial, who were randomised to either Δ9-THC or placebo, were followed up for 3 years with MRI scans at 4 time points: baseline, and years 1, 2 and 3. MRI sequences included axial dual echo, fast (turbo) spin echo proton density and T2 weighted scans, as well as a conventional T1 weighted spin echo scan. 46 contiguous 3 mm thick axial slices were performed for each acquisition. Scans from each time point were compared with the immediately preceding scan. New T2 lesions and new T1 lesions were marked by review of the electronic data using imaging software application JIM 6.0. If a scan had been missed, comparison was made with the last scan performed. Normalised brain volume (NBV) was estimated with SIENAX. Two-time-point percentage brain volume change (PBVC) was estimated with SIENA for three time-point pairs: baseline to year 1, year 1 to year 2, and year 2 to year 3.

RESULTS:

273 patients were entered into the sub-study. 182 (67%) received active treatment, and 91 (33%) received placebo. 45 subjects missed one or more scan. Those that only had the baseline scan were excluded from all further analyses. Losses to follow up were 27 at 1 year, 18 at 2 years, and 18 at 3 years. 32 patients did not have a baseline NBV. There was no evidence of an association between treatment group and number of new T1 lesions or T2 lesions, at any of the three time-point pairs (new T1 lesions: baseline to year 1 p=0.99, year 1 to year 2 p=0.17, year 2 to year 3 p=0.90; new T2 lesions: baseline to year 1 p=0.55, year 1 to year 2 p=0.076, year 2 to year 3 p=0.90). Mean baseline NBV was 1420ml (SD 89.02) for all subjects, with no significant difference between the arms (p=0.7). At each of the three time-point pairs, there was no evidence of a difference in mean PBVC between active and placebo arms (baseline to year 1: active -0.60%, placebo -0.59%, p=0.93; year 1 to year 2: active -0.58%, placebo -0.65%, p=0.62; year 2 to year 3: active -0.88%, placebo -0.76%, p=0.39).

CONCLUSION:

Δ9-THC was not better than placebo at reducing the rates of new T1 or T2 lesions or brain atrophy in patients with progressive MS.

http://www.ncbi.nlm.nih.gov/pubmed/24035293

Clinical experiences with cannabinoids in spasticity management in multiple sclerosis.

Abstract

INTRODUCTION:

Spasticity is a common symptom among patients with multiple sclerosis (MS). This study aims to

assess the effectiveness and safety of the combination of delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) in clinical practice for the treatment of spasticity in MS.
METHODS:
Retrospective observational study with patients treated with inhaled THC/CBD between April 2008 and March 2012. Descriptive patient and treatment variables were collected. Therapeutic response was evaluated based on the doctor's analysis and overall impression.
RESULTS:
Of the 56 patients who started treatment with THC/CBD, 6 were excluded because of missing data. We evaluated 50 patients (42% male) with a median age 47.8 years (25.6-76.8); 38% were diagnosed with primary progressive MS, 44% with secondary progressive MS, and 18% with relapsing-remitting MS. The reason for prescribing the drug was spasticity (44%), pain (10%), or both (46%). Treatment was discontinued in 16 patients because of ineffectiveness (7 patients), withdrawal (4), and adverse effects (5). The median exposure time in patients whose treatment was discontinued was 30 days vs 174 days in those whose treatment continued at the end of the study. THC/CBD was effective in 80% of patients at a median dose of 5 (2-10) inhalations/day. The adverse event profile consisted of dizziness (11 patients), somnolence (6), muscle weakness (7), oral discomfort (2), diarrhoea (3), dry mouth (2), blurred vision (2), agitation (1), nausea (1), and paranoid ideation (1).
CONCLUSIONS:
THC/CBD appears to be a good alternative to standard treatment as it improves refractory spasticity in MS and has an acceptable toxicity profile.

http://www.ncbi.nlm.nih.gov/pubmed/23856559

Effect of dronabinol on progression in progressive multiple sclerosis (CUPID): a randomised, placebo-controlled trial.

Abstract
BACKGROUND:
Laboratory evidence has shown that cannabinoids might have a neuroprotective action. We investigated whether oral dronabinol (Δ(9)-tetrahydrocannabinol) might slow the course of progressive multiple sclerosis.
METHODS:
In this multicentre, parallel, randomised, double-blind, placebo-controlled study, we recruited patients aged 18-65 years with primary or secondary progressive multiple sclerosis from 27 UK neurology or rehabilitation departments. Patients were randomly assigned (2:1) to receive dronabinol or placebo for 36 months; randomisation was by stochastic minimisation, using a computer-generated randomisation sequence, balanced according to expanded disability status scale (EDSS) score, centre, and disease type. Maximum dose was 28 mg per day, titrated against bodyweight and adverse effects. Primary outcomes were EDSS score progression (masked assessor, time to progression of ≥1 point from a baseline score of 4·0-5·0 or ≥0·5 points from a baseline score of ≥5·5, confirmed after 6 months) and change from baseline in the physical impact subscale of the 29-item multiple sclerosis impact scale (MSIS-29-PHYS). All patients who received at least one dose of study drug were included in the intention-to-treat analyses. This trial is registered as an International Standard Randomised Controlled Trial (ISRCTN 62942668).
FINDINGS:
Of the 498 patients randomly assigned to a treatment group, 329 received at least one dose of dronabinol and 164 received at least one dose of placebo (five did not receive the allocated intervention). 145 patients in the dronabinol group had EDSS score progression (0·24 first progression events per patient-year; crude rate) compared with 73 in the placebo group (0·23 first progression events per patient-year; crude rate); HR for prespecified primary analysis was 0·92 (95% CI 0·68-1·23; p=0·57). Mean yearly change in MSIS-29-PHYS score was 0·62 points (SD

3·29) in the dronabinol group versus 1·03 points (3·74) in the placebo group. Primary analysis with a multilevel model gave an estimated between-group difference (dronabinol-placebo) of -0·9 points (95% CI -2·0 to 0·2). We noted no serious safety concerns (114 [35%] patients in the dronabinol group had at least one serious adverse event, compared with 46 [28%] in the placebo group).
INTERPRETATION:
Our results show that dronabinol has no overall effect on the progression of multiple sclerosis in the progressive phase. The findings have implications for the design of future studies of progressive multiple sclerosis, because lower than expected progression rates might have affected our ability to detect clinical change.

http://www.ncbi.nlm.nih.gov/pubmed/23369055

A new multiple sclerosis spasticity treatment option: effect in everyday clinical practice and cost-effectiveness in Germany.

Abstract
Sativex® (GW Pharmaceuticals PLC, Porton Down, UK; Laboratorios Almirall, SA, Barcelona, Spain), a cannabinoid oromucosal spray containing a 1:1 ratio of 9-δ-tetrahydrocannabinol and cannabidiol, has been licensed in Germany since July 2011 as add-on therapy for moderate-to-severe multiple sclerosis (MS) treatment-resistant spasticity symptoms. The 'MOVE 2' study evaluated clinical outcomes, treatment satisfaction, quality of life (QoL) and provision of care in MS patients with spasticity receiving Sativex in everyday clinical practice. ***Data from 300 patients were collected from 42 specialized MS centers across Germany and were available for this analysis. Assessments, including the MS spasticity 0-10 numerical rating scale, modified Ashworth scale, patients' and physicians' clinical impressions, and QoL scales were rated at baseline and at 1 and 3 months after starting treatment with Sativex. Sativex provided relief of MS-related spasticity in the majority of patients who were previously resistant to treatment. In addition, clear improvements were noted in MS spasticity-associated symptoms (e.g., sleep quality, bladder function and mobility), activities of daily living and QoL. Sativex was generally well tolerated. The majority of patients (84%) reported no adverse events, and there was only a limited risk of serious adverse reactions. Furthermore, based on data from Sativex clinical trials, a Markov model-based analysis has shown that Sativex is a cost-effective treatment option for patients with MS spasticity in Germany.***

http://www.ncbi.nlm.nih.gov/pubmed/23369054

Endocannabinoid system modulator use in everyday clinical practice in the UK and Spain.

Abstract
Spasticity is a disabling complication of multiple sclerosis. Some commonly used oral medications include baclofen, tizanidine, anticonvulsants and benzodiazepines, but their benefits are modest. Sativex® (GW Pharmaceuticals PLC, Porton Down, UK; Laboratorios Almirall, SA, Barcelona, Spain) is a unique cannabinoid-based medicine with two main active ingredients; 9-δ-tetrahydrocannabinol, which acts mainly on cannabinoid 1 receptors in the CNS and plays a key role in the modulation of spasticity and spasms, and cannabidiol, which has different properties, including minimization of the psychoactivity associated with 9-δ-tetrahydrocannabinol. Sativex is indicated for symptomatic improvement in adult patients with moderate-to-severe multiple sclerosis-related spasticity who have not responded adequately to other first- or second-line antispasticity medications, and who demonstrate clinically significant improvement in spasticity-related symptoms during an initial trial of therapy. Over the past couple of years, Sativex has been approved for use in a number of European countries and ongoing postmarketing studies are evaluating the possible risks associated with Sativex treatment by systematically collecting all

suspected adverse reactions that occur in patients from the start of treatment. ***Interim data from the UK as well as Spanish Sativex safety registries confirm that clinical benefit is maintained over the longer term despite the expected trend for deterioration owing to disease progression. Even after more than 2 years of use, no new safety/tolerability signals have emerged with Sativex, including no evidence of driving impairment and no relevant incidence of falls or other adverse events of concern, such as psychiatric or nervous system events. Sativex appears to be a well-tolerated and useful add-on therapy in patients who have not achieved an adequate response with traditional antispastic agents.***

http://www.ncbi.nlm.nih.gov/pubmed/23180178

A double-blind, randomized, placebo-controlled, parallel-group study of THC/CBD oromucosal spray in combination with the existing treatment regimen, in the relief of central neuropathic pain in patients with multiple sclerosis.

Abstract

Central neuropathic pain (CNP) occurs in many multiple sclerosis (MS) patients. The provision of adequate pain relief to these patients can very difficult. Here we report the first phase III placebo-controlled study of the efficacy of the endocannabinoid system modulator delta-9-tetrahydrocannabinol (THC)/cannabidiol (CBD) oromucosal spray (USAN name, nabiximols; Sativex, GW Pharmaceuticals, Salisbury, Wiltshire, UK), to alleviate CNP. Patients who had failed to gain adequate analgesia from existing medication were treated with THC/CBD spray or placebo as an add-on treatment, in a double-blind manner, for 14 weeks to investigate the efficacy of the medication in MS-induced neuropathic pain. This parallel-group phase of the study was then followed by an 18-week randomized-withdrawal study (14-week open-label treatment period plus a double-blind 4-week randomized-withdrawal phase) to investigate time to treatment failure and show maintenance of efficacy. A total of 339 patients were randomized to phase A (167 received THC/CBD spray and 172 received placebo). Of those who completed phase A, 58 entered the randomized-withdrawal phase. The primary endpoint of responder analysis at the 30 % level at week 14 of phase A of the study was not met, with 50 % of patients on THC/CBD spray classed as responders at the 30 % level compared to 45 % of patients on placebo ($p = 0.234$). However, an interim analysis at week 10 showed a statistically significant treatment difference in favor of THC/CBD spray at this time point ($p = 0.046$). During the randomized-withdrawal phase, the primary endpoint of time to treatment failure was statistically significant in favor of THC/CBD spray, with 57 % of patients receiving placebo failing treatment versus 24 % of patients from the THC/CBD spray group ($p = 0.04$). The mean change from baseline in Pain Numerical Rating Scale (NRS) ($p = 0.028$) and sleep quality NRS ($p = 0.015$) scores, both secondary endpoints in phase B, were also statistically significant compared to placebo, with estimated treatment differences of -0.79 and 0.99 points, respectively, in favor of THC/CBD spray treatment. ***The results of the current investigation were equivocal, with conflicting findings in the two phases of the study. While there were a large proportion of responders to THC/CBD spray treatment during the phase A double-blind period, the primary endpoint was not met due to a similarly large number of placebo responders. In contrast, there was a marked effect in phase B of the study, with an increased time to treatment failure in the THC/CBD spray group compared to placebo. These findings suggest that further studies are required to explore the full potential of THC/CBD spray in these patients.***

http://www.ncbi.nlm.nih.gov/pubmed/22878432

Sativex long-term use: an open-label trial in patients with spasticity due to multiple sclerosis.

Abstract

Sativex is an endocannabinoid system modulator principally containing Δ(9)-tetrahydrocannabinol

(THC) and cannabidiol (CBD). During a 6-week randomised controlled trial, Sativex had a clinically relevant effect on spasticity associated with multiple sclerosis (MS). Patients self-titrated oromucosal Sativex to symptom relief or maximum tolerated dose (maximum of 130 mg THC and 120 mg CBD daily). The primary objective was to evaluate the safety and tolerability of long-term treatment by recording the incidence and severity of adverse events (AEs). Secondary outcomes were to determine evidence of developing tolerance and to assess the long-term dosing profile of Sativex. A validated 11-point Numerical Rating Scale of spasticity severity was used to assess efficacy. A total of 146 patients elected to enter this open-label follow-up safety trial. Mean treatment exposure was 334 days (standard deviation, SD = 209 days), and patients administered on average 7.3 (SD = 4.42) actuations per day. Fifty-two (36 %) patients withdrew from the study in the first year, 14 % due to AEs and 9 % due to lack of efficacy. Most AEs were mild/moderate in severity. Common (>10 %) treatment-related AEs were dizziness (24.7 %) and fatigue (12.3 %). ***Serious AEs occurred in five patients (3.4 %), with two psychiatric events reported by one patient. No psychoses, psychiatric AE trends, or withdrawal symptoms occurred following abrupt cessation of treatment. Baseline symptoms including spasticity did not deteriorate but were maintained to study completion in those patients who did not withdraw. No new safety concerns were identified with chronic Sativex treatment, and serious AEs were uncommon. There was no evidence of tolerance developing, and patients who remained in the study reported continued benefit.***

http://www.ncbi.nlm.nih.gov/pubmed/22784399

A questionnaire survey of patients and carers of patients prescribed Sativex as an unlicensed medicine.

Abstract
AIM:
To identify the areas of daily function most affected by the introduction of Sativex, a cannabis-based medicine, and the impact on caregivers and people with multiple sclerosis (MS).
BACKGROUND:
Cannabinoid medicines have recently become available on prescription in several parts of the world, principally for the treatment of spasticity in people with MS. Their efficacy and safety have been demonstrated in the setting of randomised controlled clinical trials. Results of such studies may not always reflect the wider effectiveness that a medicine shows when used in clinical practice.
METHODS:
A short questionnaire survey consisting mostly of multiple-choice questions, along with some free-text questions aimed at the patient and primary caregiver (ie, partner, mother, nurse or outside carer). The questionnaire was developed in consultation with a patient representative organisation, field tested, ethics approval gained, then distributed to prescribers in the United Kingdom, with the request that they in turn forward it to any patients who had received repeat prescriptions for Sativex within the previous 16 weeks. Patients were seen in both a primary care (general practice) and a secondary care (hospital) setting. There was no control group in this study. Most patients had MS, and the primary reasons for using Sativex were spasticity and pain.
FINDINGS:
The response rate was 57%, with 124 questionnaires returned. The majority of respondents and their caregivers reported improvements across a range of daily functional activities, alongside a reduction in the use of concomitant anti-spasticity medication and in the use of other healthcare resources.

Forsøgsdyr:

http://www.ncbi.nlm.nih.gov/pubmed/24121462

Control of spasticity in a multiple sclerosis model using central nervous system-excluded CB1 cannabinoid receptor agonists.

Abstract

The purpose of this study was the generation of central nervous system (CNS)-excluded cannabinoid receptor agonists to test the hypothesis that inhibition of spasticity, due to CNS autoimmunity, could be controlled by affecting neurotransmission within the periphery. Procedures included identification of chemicals and modeling to predict the mode of exclusion; induction and control of spasticity in the ABH mouse model of multiple sclerosis; conditional deletion of CB1 receptor in peripheral nerves; side-effect profiling to demonstrate the mechanism of CNS-exclusion via drug pumps; genome-wide association study in N2(129×ABH) backcross to map polymorphic cannabinoid drug pump; and sequencing and detection of cannabinoid drug-pump activity in human brain endothelial cell lines. Three drugs (CT3, SAB378 and SAD448) were identified that control spasticity via action on the peripheral nerve CB1 receptor. These were peripherally restricted via drug pumps that limit the CNS side effects (hypothermia) of cannabinoids to increase the therapeutic window. A cannabinoid drug pump is polymorphic and functionally lacking in many laboratory (C57BL/6, 129, CD-1) mice used for transgenesis, pharmacology, and toxicology studies. This phenotype was mapped and controlled by 1-3 genetic loci. ABCC1 within a cluster showing linkage is a cannabinoid CNS-drug pump. Global and conditional CB1 receptor-knockout mice were used as controls. ***In summary, CNS-excluded CB1 receptor agonists are a novel class of therapeutic agent for spasticity***.

http://www.ncbi.nlm.nih.gov/pubmed/23892791

Cannabinoids Decrease the Th17 Inflammatory Autoimmune Phenotype.

Abstract

Cannabinoids, the Cannabis constituents, are known to possess anti-inflammatory properties but the mechanisms involved are not understood. Here we show that the main psychoactive cannabinoid, Δ-9-tetrahydrocannabinol (THC), and the main nonpsychoactive cannabinoid, cannabidiol (CBD), markedly reduce the Th17 phenotype which is known to be increased in inflammatory autoimmune pathologies such as Multiple Sclerosis. We found that reactivation by MOG35-55 of MOG35-55-specific encephalitogenic T cells (cells that induce Experimental Autoimmune Encephalitis when injected to mice) in the presence of spleen derived antigen presenting cells led to a large increase in IL-17 production and secretion. In addition, we found that the cannabinoids CBD and THC dose-dependently (at 0.1-5 μM) suppressed the production and secretion of this cytokine. Moreover, the mRNA and protein of IL-6, a key factor in Th17 induction, were also decreased. Pretreatment with CBD also resulted in increased levels of the anti-inflammatory cytokine IL-10. Interestingly, CBD and THC did not affect the levels of TNFα and IFNγ. The downregulation of IL-17 secretion by these cannabinoids does not seem to involve the CB1, CB2, PPARγ, 5-HT1A or TRPV1 receptors. ***In conclusion, the results show a unique cannabinoid modulation of the autoimmune cytokine milieu combining suppression of the pathogenic IL-17 and IL-6 cytokines along with boosting the expression of the anti-inflammatory cytokine IL-10.***

http://www.ncbi.nlm.nih.gov/pubmed/23851307

Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors.

Abstract

Inflammation in the central nervous system (CNS) is a complex process that involves a multitude of

molecules and effectors, and it requires the transmigration of blood leukocytes across the blood-brain barrier (BBB) and the activation of resident immune cells. Cannabidiol (CBD), a non-psychotropic cannabinoid constituent of Cannabis sativa, has potent anti-inflammatory and immunosuppressive properties. Yet, how this compound modifies the deleterious effects of inflammation in TMEV-induced demyelinating disease (TMEV-IDD) remains unknown. ***Using this viral model of multiple sclerosis (MS), we demonstrate that CBD decreases the transmigration of blood leukocytes by downregulating the expression of vascular cell adhesion molecule-1 (VCAM-1), chemokines (CCL2 and CCL5) and the proinflammatory cytokine IL-1β, as well as by attenuating the activation of microglia. Moreover, CBD administration at the time of viral infection exerts long-lasting effects, ameliorating motor deficits in the chronic phase of the disease in conjunction with reduced microglial activation and pro-inflammatory cytokine production.*** Adenosine A2A receptors participate in some of the anti-inflammatory effects of CBD, as the A2A antagonist ZM241385 partially blocks the protective effects of CBD in the initial stages of inflammation. Together, our findings highlight the anti-inflammatory effects of CBD in this viral model of MS and demonstrate the significant therapeutic potential of this compound for the treatment of pathologies with an inflammatory component.

http://www.ncbi.nlm.nih.gov/pubmed/23173851

Cannabidiol (CBD) enhances lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice.

Abstract

Cannabidiol (CBD) is a plant-derived cannabinoid that has been predominantly characterized as anti-inflammatory. However, it is clear that immune effects of cannabinoids can vary with cannabinoid concentration, or type or magnitude of immune stimulus. The present studies demonstrate that oral administration of CBD enhanced lipopolysaccharide (LPS)-induced pulmonary inflammation in C57BL/6 mice. The enhanced inflammatory cell infiltrate as observed in bronchoalveolar lavage fluid (BALF) was comprised mainly of neutrophils, with some monocytes. Concomitantly, CBD enhanced pro-inflammatory cytokine mRNA production, including tumor necrosis factor-α (Tnfa), interleukins (IL)-5 and -23 (Il6, Il23), and granulocyte colony stimulating factor (Gcsf). These results demonstrate that the CBD-mediated enhancement of LPS-induced pulmonary inflammation is mediated at the level of transcription of a variety of pro-inflammatory genes. The significance of these studies is that CBD is part of a therapeutic currently in use for spasticity and pain in multiple sclerosis patients, and therefore it is important to further understand mechanisms by which CBD alters immune function.