Reports of Cannabis and Dementia Research

Overview of the Endocannabinoid system

- Basic Science

The role of Cannabinoids in cognitive function

Basic Science and Clinical Dementia

Safety of cannabis Use

Cognitive enhancement

Prevention of cognitive loss

Mild Cognitive Impairment

Dementia: Mild, Moderate and Severe

NPI: Agitation, Delusions,

Overview of the Endocannabinoid system

A molecular link between the active component of marijuana and Alzheimer's disease pathology.
Eubanks LM1, Rogers CJ, Beuscher AE 4th, Koob GF, Olson AJ, Dickerson TJ, Janda KD.

Alzheimer's disease is the leading cause of dementia among the elderly, and with the ever-increasing size of this population, cases of Alzheimer's disease are expected to triple over the next 50 years. Consequently, the development of treatments that slow or halt the disease progression have become imperative to both improve the quality of life for patients and reduce the health care costs attributable to Alzheimer's disease. Here, we demonstrate that the active component of marijuana, Delta9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid beta-peptide (Abeta) aggregation, the key pathological marker of Alzheimer's disease. Computational modeling of the THC-AChE interaction revealed that THC binds in the peripheral anionic site of AChE, the critical region involved in amyloidgenesis. Compared to currently approved drugs prescribed for the treatment of Alzheimer's disease, THC is a considerably superior inhibitor of Abeta aggregation, and this study provides a previously unrecognized molecular mechanism through which cannabinoid molecules may directly impact the progression of this debilitating disease

Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation.[J Neurosci. 2005]
Abstract
Alzheimer's disease is the leading cause of dementia among the elderly, and with the ever-increasing size of this population, cases of Alzheimer's disease are expected to triple over the next 50 years. Consequently, the development of treatments that slow or halt the disease progression have become imperative to both improve the quality of life for patients as well as reduce the health care costs attributable to Alzheimer's disease. Here, we demonstrate that the active component of marijuana, Δ9-tetrahydrocannabinol (THC), competitively inhibits the enzyme acetylcholinesterase (AChE) as well as prevents AChE-induced amyloid β-peptide (Aβ) aggregation, the key pathological marker of Alzheimer's disease. Computational modeling of the THC-AChE interaction revealed that THC binds in the peripheral anionic site of AChE, the critical region involved in amyloidgenesis. Compared to currently approved drugs prescribed for the treatment of Alzheimer's disease, THC is a considerably superior inhibitor of Aβ aggregation, and this study provides a previously unrecognized molecular mechanism through which cannabinoid molecules may directly impact the progression of this debilitating disease.

Pharmacological treatments for alleviating agitation in dementia: a systematic review and network meta-analysis.

Kongpakwattana K1, Sawangjit R2, Tawankanjanachot I3, Bell JS4, Hilmer SN5, Chaiyakunapruk N1,6,7,8.

AIMS:
To determine the most efficacious and acceptable treatments of agitation in dementia.
METHODS:
MEDLINE, EMBASE, PsycINFO, CENTRAL and clinicaltrials.gov were searched up to 7 February 2017. Two independent reviewers selected randomized controlled trials (RCTs) of treatments to alleviate agitation in people with all-types dementia. Data were extracted using standardized forms and study quality was assessed using the revised Cochrane Risk of Bias Tool for RCTs. Data were pooled using meta-analysis. The primary outcome, efficacy, was 8-week response rates defined as a 50% reduction in baseline agitation score. The secondary outcome was treatment acceptability defined as treatment continuation for 8 weeks.
RESULTS:
Thirty-six RCTs comprising 5585 participants (30.9% male; mean ± standard deviation age, 81.8 ± 4.9 years) were included. Dextromethorphan/quinidine [odds ratio (OR) 3.04; 95% confidence interval (CI), 1.63-5.66], risperidone (OR 1.96; 95% CI, 1.49-2.59) and selective serotonin reuptake inhibitors as a class (OR 1.61; 95% CI, 1.02-2.53) were found to be significantly more efficacious than placebo. Haloperidol appeared less efficacious than nearly all comparators. Most treatments had noninferior treatment continuation compared to placebo, except oxcarbazepine, which was inferior. Findings were supported by subgroup and sensitivity analyses.
CONCLUSIONS:
Risperidone, serotonin reuptake inhibitors as a class and dextromethorphan/quinidine demonstrated evidence of efficacy for agitation in dementia, although findings for dextromethorphan/quinidine were based on a single RCT. Our findings do not support prescribing haloperidol due to lack of efficacy, or oxcarbazepine due to lack of acceptability. The decision to prescribe should be based on comprehensive consideration of the benefits and risks, including those not evaluated in this meta-analysis.

KEYWORDS:
Alzheimer's disease; agitation; dementia; network meta-analysis; pharmacological treatments

YOKUKANSAN: A TRADITIONAL KAMPO FORMULA FOR DEMENTIA

November 18, 2014; 83 (21) CLINICAL IMPLICATIONS OF NEUROSCIENCE RESEARCH

Synaptic effects of cannabinoids
Complexity, behavioral effects, and potential clinical implications
Eduardo E. Benarroch October 22, 2014

The discovery of (−)-Δ9-tetrahydrocannabinol (Δ9 THC) as the main psychoactive ingredient in cannabis (marijuana), the cloning of the cannabinoid receptors CB1R and CB2R, and the identification of the endocannabinoids as their endogenous ligands has stimulated extensive research on the role of the cannabinoid system in synaptic regulation in the CNS. The 2 major endocannabinoids in the nervous system are 2-arachydonoyl glycerol (2-AG) and N-arachidonoyl ethanolamide (also known as anandamide). They are lipid mediators that are released from neurons on demand in response to excitatory synaptic activity. Endocannabinoids function primarily as retrograde messengers that inhibit neurotransmitter release via presynaptic CB1Rs, which are distributed primarily in γ-aminobutyric acid (GABA)ergic and to a lesser extent glutamatergic and other presynaptic terminals. Retrograde endocannabinoid signaling participates in several mechanisms of short- and long-term plasticity (depression) of inhibitory and excitatory synapses. Endocannabinoids may also act via postsynaptic CB1Rs and, in the case of anandamide, also transient receptor potential, vanilloid type 1 (TRPV1) channels. Endocannabinoids also mediate interactions among neurons and different types of glial cells, regulating not only synaptic plasticity but also inflammatory responses in the CNS. By all these mechanisms, endocannabinoids affect the activity of neuronal networks involved in cognition, emotion, addiction and feeding behavior, motor control, and pain processing and participate in the mechanism of neuroprotection. The cannabinoid system thus provides a potential therapeutic target, with consequent increased interest in the use of cannabis for management of selected neurologic conditions. All these topics have been the subject of several comprehensive reviews.1–8

Clinical Evidence for Utilizing Cannabinoids in the Elderly

Medical Cannabis Significantly Safer for Elderly With Chronic Pain Than Opioids
Epidemiological characteristics, safety and efficacy of medical cannabis in the elderly.

Novack et.el. assessed the characteristics of elderly people (65+) using medical cannabis and to evaluate the safety and efficacy of the treatment. In a prospective study that included all patients above 65 years of age who received medical cannabis from January 2015 to October 2017 in a specialized medical cannabis clinic and were willing to answer the initial questionnaire. A Outcomes were pain intensity, quality of life and adverse events at six months.

they found that that the therapeutic use of cannabis is safe and efficacious in the elderly population. Their Cannabis use may decrease the use of other prescription medicines, including opioids..

During the study period, 2736 patients above 65 years of age began cannabis treatment and answered the initial questionnaire. The mean age was 74.5 ± 7.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%). After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0-10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose.

CONCLUSION:
Our study finds Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative.

Commentary:
Our study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids. Gathering more evidence-based data, including data from double-blind randomized-controlled trials, in this special population is imperative.

The impact of cannabis prescription on an elderly population, safety and well-being The therapeutic use of cannabis is safe and efficacious in the elderly population, a study by researchers of the Ben-Gurion University of the Negev in Be'er-Sheva, Israel, found in a group of 2736 patients above 65 years of age, who participated in a questionnaire. The mean age was 74.5 years. The most common indications for cannabis treatment were pain (66.6%) and cancer (60.8%).

After six months of treatment, 93.7% of the respondents reported improvement in their condition and the reported pain level was reduced from a median of 8 on a scale of 0-10 to a median of 4. Most common adverse events were: dizziness (9.7%) and dry mouth (7.1%). After six months, 18.1% stopped using opioid analgesics or reduced their dose. Authors concluded that their "study finds that the therapeutic use of cannabis is safe and efficacious in the elderly population. Cannabis use may decrease the use of other prescription medicines, including opioids."

Review of research about dementia and Cannabis

Cannabinoids for the treatment of dementia (Cochrane Review 2017)
Alzheimer's Disease – Medical Marijuana Research Overview (Medical Marijuana Inc)

Cannabinoids for the treatment of dementia (Cochrane 2017)

Discussion of Findings

The authors of the good-quality Cochrane systematic review concluded that the “review finds no evidence that cannabinoids are effective in the improvement of disturbed behavior in dementia or treatment of other symptoms of dementia” (Krishnan et al., 2009, p. 8). Subsequently, a larger good-quality RCT found no benefit from low-dose THC. We agree that the evidence is limited due to the small number of patients enrolled, limits in the study design and reporting, and inconsistent effects. The current limited evidence does not support a therapeutic effect of cannabinoids.

CONCLUSION 4-13 There is limited evidence that cannabinoids are ineffective treatments for improving the symptoms associated with dementia.

Cochrane Database Syst Rev. 2009 Apr 15;(2):CD007204. doi: 10.1002/14651858.CD007204.pub2.

Cannabinoids for the treatment of dementia.

Krishnan S1, Cairns R, Howard R.

Abstract

Following the discovery of an endogenous cannabinoid system and the identification of specific cannabinoid receptors in the central nervous system, much work has been done to investigate the main effects of these compounds. There is increasing evidence that the cannabinoid system may regulate neurodegenerative processes such as excessive glutamate production, oxidative stress and neuroinflammation. Neurodegeneration is a feature common to the various types of dementia and this has led to interest in whether cannabinoids may be clinically useful in the treatment of people with dementia. Recent studies have also shown that cannabinoids may have more specific effects in interrupting the pathological process in Alzheimer's disease.

OBJECTIVES:

To determine from available research whether cannabinoids are clinically effective in the treatment of dementia.

SEARCH STRATEGY:

The Specialized Register of the Cochrane Dementia and Cognitive Improvement Group (CDCIG), The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL and LILACS were searched on 11 April 2008 using the terms: cannabis or cannabinoid* or endocannabinoid* or cannabidiol or THC or CBD or dronabinol or delta-9-tetrahydrocannabinol or marijuana or marihuana or hashish. The CDCIG Specialized Register contains records from all major health

care databases (The Cochrane Library, MEDLINE, EMBASE, PsycINFO, CINAHL, LILACS) as well as from many clinical trials registries and grey literature sources.

SELECTION CRITERIA:

All double-blind and single (rater)-blind randomized placebo controlled trials assessing the efficacy of cannabinoids at any dose in the treatment of people with dementia.

DATA COLLECTION AND ANALYSIS:

Two reviewers independently examined the retrieved studies for inclusion according to the selection criteria. They then independently assessed the methodological quality of selected trials and extracted data where possible.

MAIN RESULTS:

Only one study met the inclusion criteria. The data in the study report were presented in such a way that they could not be extracted for further analysis and there was insufficient quantitative data to validate the results.

AUTHORS' CONCLUSIONS:

This review finds no evidence that cannabinoids are effective in the improvement of disturbed behaviour in dementia or in the treatment of other symptoms of dementia. More randomized double-blind placebo controlled trials are needed to determine whether cannabinoids are clinically effective in the treatment of dementia.

Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease.
Liu CS1,2, Chau SA1,2, Ruthirakuhan M2, Lanctôt KL1,2,3, Herrmann N4,5.

Abstract

Alzheimer's disease (AD) is frequently associated with neuropsychiatric symptoms (NPS) such as agitation and aggression, especially in the moderate to severe stages of the illness. The limited efficacy and high-risk profiles of current pharmacotherapies for the management of agitation and aggression in AD have driven the search for safer pharmacological alternatives. Over the past few years, there has been a growing interest in the therapeutic potential of medications that target the endocannabinoid system (ECS). The behavioural effects of ECS medications, as well as their ability to modulate neuroinflammation and oxidative stress, make targeting this system potentially relevant in AD. **This article summarizes the literature to date supporting this rationale and evaluates clinical studies investigating cannabinoids for agitation and aggression in AD.** Letters, case studies, and controlled trials from four electronic databases were included. While findings from six studies showed significant benefits from synthetic cannabinoids—dronabinol or nabilone—on agitation and aggression, definitive

conclusions were limited by small sample sizes, short trial duration, and lack of placebo control in some of these studies. Given the relevance and findings to date, methodologically rigorous prospective clinical trials are recommended to determine the safety and efficacy of cannabinoids for the treatment of agitation and aggression in dementia and AD.

Review Articles about Cannabis and Dementia

Cannabis and Alzheimer's Disease: A Systematic Review Of The Evidence
Santibanez, Rodrigo A. ; Sepehry, Amir Ali ; Robin Hsiung, Ging-Yuek
Alzheimer's & Dementia: The Journal of the Alzheimer's Association, July 2017, Vol.13(7), pp.P614-P614[Peer Reviewed Journal]

CNS Drugs. 2015 Aug;29(8):615-23. doi: 10.1007/s40263-015-0270-y.

The Use of Cannabinoids in Treating Dementia

Megan Weier1,2 & Wayne Hall Published online: 19 June 2017

Purpose of Review
To review and summarise the current evidence on the safety and efficacy of using cannabinoids to treat behavioural and neuropsychiatric symptoms of dementia. Recent Findings Two randomised controlled trials testing a synthetic form of tetrahydrocannabinol have shown that while well tolerated, there was no significant therapeutic effect, based on changes to scores on the neuropsychiatric inventory (NPI). Case reports and open label trials have indicated that there may be some therapeutic benefit of adding synthetic cannabinoids as an adjunctive therapy to reduce agitation, aberrant motor behaviour and nighttime behaviour.

Summary

More well-controlled clinical trials in older populations with varying severity of dementia are needed to evaluate the effectiveness of cannabinoids in treating behaviour symptoms of dementia. We provide suggestions for designing such trials and evaluating possible adverse effects of cannabinoids on cognitive and neuropsychiatric functioning.

Cannabis and cognitive Function:
Marijuana May Boost, Rather Than Dull, the Elderly Brain

Senior mice treated with THC improved on learning and memory tests

Researchers led by Andreas Zimmer of the University of Bonn in Germany gave low doses of delta-9 tetrahydrocannabinol, or THC, marijuana's main active ingredient, to young, mature and aged mice. As expected, young mice treated with THC performed slightly worse on behavioral tests of memory and learning. For example, after receiving THC, young mice took longer to learn where a safe platform was hidden in a water maze, and they had a harder time recognizing another mouse to which they had previously been exposed. Without the drug, mature and aged mice performed worse on the tests than young ones did. But after the elderly animals were given THC, their performances improved to the point that they resembled those of young, untreated mice. "The effects were very robust, very profound," Zimmer says.

Role of Cannabinoids in Brain Function

Care Interventions for People With Dementia (PWD) and Their Caregivers
KEY QUESTIONS DRAFT November 9, 2018
https://effectivehealthcare.ahrq.gov/topics/care-interventions-pwd/key-questions

Considerations for the Design of a Systematic Review of Care
Interventions for Individuals with Dementia and Their Caregivers

Cannabis and dementia Alzheimer's Society UK
Some studies have that found taking cannabis could help to manage some behavioural symptoms of dementia. However, there is currently no evidence that cannabis can help to prevent the disease.

Medical marijuana has potential as Alzheimer's treatment, study says
By Susan Scutti, CNN
Updated 11:52 AM ET, Mon July 25, 2016

CNBC Feature Story

Medicinal Cannabis: Alzheimer's Disease, CME Information on the use of medicinal cannabis in Alzheimer's Disease and Related Dementias. Jefferson Medical College.

The Use of Cannabinoids in Treating Dementia

Marijuana: The Latest Scientific Findings and Legalization

RESEARCH AND CLINICAL DATA Physicians are developing protocols for treating patients with cannabis medicines. For example, the University of California Center for Medicinal Cannabis Research (CMCR) has completed a series of randomized clinical trials with patients and published guidelines for using cannabis in medical care 16. The researchers note that the decision to use cannabis therapeutics, like other treatment modes, should be based on careful assessment of the patient's condition with consideration for other possible treatments. They propose a treatment decision-tree for physicians, using neuropathic pain as an example, as reproduced below. This is similar to the guidelines established by the California Medical Board for doctors.

Cannabis and the Brain: Neuroprotection vs Toxicity
Cannabis use and cognitive dysfunction

Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia: An-Open Label, Add-On, Pilot Study
Article type: Short Communication

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Dr. Assaf Shelef, Abarbanel Mental Health Center, 15 KKL Street, Bat-Yam, 59100, Israel. Tel.: +972 3 5552611; E-mail: shelefmd@gmail.com.

Abstract: Background:Tetrahydrocannabinol (THC) is a potential treatment for Alzheimer’s disease (AD).

Objective: To measure efficacy and safety of medical cannabis oil (MCO) containing THC as an add-on to pharmacotherapy, in relieving behavioral and psychological symptoms of dementia (BPSD).

Methods: Eleven AD patients were recruited to an open label, 4 weeks, prospective trial.
Results: Ten patients completed the trial. Significant reduction in CGI severity score (6.5 to 5.7; $p < 0.01$) and NPI score were recorded (44.4 to 12.8; $p < 0.01$). NPI domains of significant decrease were: Delusions, agitation/aggression, irritability, apathy, sleep and caregiver distress.
Conclusion:Adding MCO to AD patients' pharmacotherapy is safe and a promising treatment option.

NEUROCOGNITIVE DISORDERS
https://www.ncbi.nlm.nih.gov/pubmed/25015040
http://onlinelibrary.wiley.com/doi/10.1111/bph.12492/full
https://www.ncbi.nlm.nih.gov/pubmed/23587650
http://rstb.royalsocietypublishing.org/content/367/1607/3326?sid=20cf2c23-e4fd-49e3-9398-ec8be2e00226

ALZHEIMER'S DISEASE
http://www.leafscience.com/2014/01/30/smoking-marijuana-might-best-way-prevent-alzheimers-disease/
https://www.ncbi.nlm.nih.gov/pubmed/28551012
https://www.ncbi.nlm.nih.gov/pubmed/25125475
http://www.neurobiologyofaging.org/article/S0197-4580%2813%2900240-6/abstract
http://www.sciencedirect.com/science/article/pii/S104474311300064X

Clinical Trials

Cannabis and Dementia/ Agitation:
Delta-THC in Behavioral Disturbances in Dementia

Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (AD) (THC-AD) (THC-AD) (Recruiting)

Brief Summary:

Alzheimer's disease (AD) is the most prevalent neurodegenerative disease of aging. Neuropsychiatric symptoms (NPS) in AD are a major cause of burden to patients, caregivers, and society and are near-universal at some point in the AD course. One of the most troubling of these symptoms is agitation (Agit-AD), typified by a variety of problem behaviors including combativeness, yelling, pacing, lack of cooperation with care, insomnia, and restlessness There is a great need for better interventions that target Agit-AD, a major source of patient disability as

well as caregiver burden and stress, particularly in the case of moderate to severe agitation. This pilot trial could open the door to "re-purposing" Dronabinol (Marinol®) as a novel and safe treatment for Agit-AD with significant public health impact.'

The medical use of cannabis improves cognitive performance

Following 3 months of treatment, cannabis patients demonstrated improved task performance accompanied by changes in brain activation patterns within certain brain regions (cingulate cortex and frontal regions). Authors wrote that after cannabis treatment, "brain activation patterns appeared more similar to those exhibited by healthy controls from previous studies than at pre-treatment, suggestive of a potential normalization of brain function relative to baseline." They concluded that their findings suggest that the medical use of cannabis "may result in different effects relative to recreational marijuana (MJ) use, as recreational consumers have been shown to exhibit decrements in task performance accompanied by altered brain activation." Patients also reported improvements in clinical state and health-related measures.

Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function

Results suggest that in general, MMJ patients experienced some improvement on measures of executive functioning, including the Stroop Color Word Test and Trail Making Test, mostly reflected as increased speed in completing tasks without a loss of accuracy. On self-report questionnaires, patients also indicated moderate improvements in clinical state, including reduced sleep disturbance, decreased symptoms of depression, attenuated impulsivity, and positive changes in some aspects of quality of life. Additionally, patients reported a notable decrease in their use of conventional pharmaceutical agents from baseline, with opiate use declining more than 42%. While intriguing, these findings are preliminary and warrant further investigation at additional time points and in larger sample sizes. Given the likelihood of increased MMJ use across the country, it is imperative to determine the potential impact of short- and long-term treatment on cognitive performance as well as the efficacy of MMJ treatment itself.

The Grass Might Be Greener: Medical Marijuana Patients Exhibit Altered Brain Activity and Improved…

The vast majority of states have enacted full or partial medical marijuana (MMJ) programs, causing the number of…www.frontiersin.org

Patients' Brain Function Improve Using Cannabis for 3 Months

Following 3 months of treatment, MMJ patients demonstrated improved task performance accompanied by changes in brain activation patterns within the cingulate cortex and frontal regions. Interestingly, after MMJ treatment, brain activation patterns appeared more similar to those exhibited by healthy controls from previous studies than at pre-treatment, suggestive of a potential normalization of brain function relative to baseline. These findings suggest that MMJ

use may result in different effects relative to recreational marijuana (MJ) use, as recreational consumers have been shown to exhibit decrements in task performance accompanied by altered brain activation. Moreover, patients in the current study also reported improvements in clinical state and health-related measures as well as notable decreases in prescription medication use, particularly opioids and benzodiazepines after 3 months of treatment. Further research is needed to clarify the specific neurobiologic impact, clinical efficacy, and unique effects of MMJ for a range of indications and how it compares to recreational MJ use.

The Grass Might Be Greener: Medical Marijuana Patients Exhibit Altered Brain Activity and Improved Executive Function after 3 Months of Treatment. Gruber SA, Sagar KA, Dahlgren MK, Gonenc A, Smith RT, Lambros AM, Cabrera KB, Lukas SE. Pharmacol. 2018;8:983.

Commentary:

The medical use of cannabis improves performance of tasks testing cognition. This is the result of research by scientists of the McLean Hospital in Belmont, USA. Participants were tested before starting the intake of cannabis and 3 months later. Patients completed the Multi-Source Interference Test (MSIT) while undergoing functional magnetic resonance imaging (fMRI). The MSIT was designed to study normal human cognition and psychiatric pathophysiology.

The Pilot Study was reported here Splendor in the Grass? A Pilot Study Assessing the Impact of Medical Marijuana on Executive Function.

Synthetic marijuana compound reduces agitation, improves appetite

Study results suggest dronabinol, a synthetic version of THC, the active ingredient in marijuana, may reduce agitation and lead to weight gain in patients with AD, according to data presented in August at the annual meeting of the International Psychogeriatric Association. “Our research suggests dronabinol may reduce agitation and improve appetite in patients with Alzheimer’s disease, when traditional therapies are not successful,” said Joshua Shua-Haim, MD, lead investigator in the study and medical director of the Meridian Institute for Aging, a continuum of senior health programs and services in central New Jersey affiliated with Meridian Health System. “In the study, dronabinol appeared to be safe and effective for these patients.” Dronabinol, marketed under the trade name Marinol, is synthetic delta-9-tetrahydrocannabinol (delta-9- THC), which is also a naturally occurring component of Cannabis sativa L (marijuana). Dronabinol is the only cannabinoid approved by the FDA and is indicated for the treatment of anorexia in patients with HIV/AIDS and for the treatment of nausea and vomiting associated

with cancer chemotherapy. Agitation is the most frequently encountered type of behavioral disturbance associated with AD, affecting an estimated 75 percent of people with the disease. Weight loss, a common problem with AD patients, is a predictive factor of mortality and may derive from the deterioration of patients' cognitive abilities, resulting in an inability to recognize hunger and thirst. The study examined 48 patients (mean age = 77) residing in a dementia unit of an assisted living facility or nursing home. All patients met the DSM-IV and NINCDS-ADRDA criteria for possible AD and, according to their family or caregivers, had unsatisfactory control of their agitation. Both the Mini-Mental State Examination (a test to measure a person's basic cognitive skills) and an assessment of activities of daily living were used to evaluate patients prior to treatment with dronabinol and at one month. Patients initially received 5 mg/day of dronabinol in two doses. The treatment was titrated up to a maximum of 10 mg/day. In addition, all patients were treated with atypical neuroleptics and at least four medications to control behavior. The evaluation by caregivers following one month of treatment found 31 patients (66 percent) experienced a significant improvement in agitation. Functional improvement was observed in 33 (69 percent) of the patients. Prior to the study, all patients experienced weight loss and had been diagnosed with anorexia. After treatment with dronabinol, all patients had gained weight. No adverse events, such as falls, syncope, seizures, or exacerbation of agitation or depression, were reported as a result of treatment. (Source: International Psychogeriatric Association, 20 August 2003.)

Warning letters could cut high prescribing rates

A new study suggests that firing off a strongly worded warning letter to providers who prescribe high amounts of an antipsychotic could curb prescription rates. Quetiapine is often used off label in patients with dementia, but has been tied to potentially harmful side effects among elderly patients. Public health researchers ran a randomized trial with more than 5,000 primary care doctors with high quetiapine prescribing rates. Some received a letter that flagged that their rates were higher than their peers and warned that abusive prescribing can lead to audits or a loss of Medicare billing privileges. Over two years, prescribing rates fell much more among doctors who received the letter. The authors say that suggests the letters might serve as a way to push physicians to take another look at their prescribing habits.

Cannabis in Alzheimer's Treatment

Scientists at the Salk Institute have recently discovered that tetrahydrocannabinol, or THC, among other compounds in marijuana can increase the cellular removal of amyloid, a toxic protein found in the brains of Alzheimer's patients.

David Schubert, Salk Professor and lead writer of the study, told Salk News,

“Although other studies have offered evidence that cannabinoids might be neuroprotective against the symptoms of Alzheimer’s, we believe our study is the first to demonstrate that cannabinoids affect both inflammation and amyloid beta accumulation in nerve cells.”
Read the full article
The THC activates receptors that conduct intercellular signaling in the brain, thus reducing amyloid beta levels and killing off inflammation in the brain. Inflammation is a serious side effect of Alzheimer’s, contributing to the mental and physical health decline in patients.
The study points to the importance of integrating cannabis into treatment of high-risk diseases such as Alzheimer’s.
Read the full study published in the Aging and Mechanisms of Disease journal entitled “Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids”.

Integrated Approach Best for Alzheimer's-Associated Agitation

http://www.psychiatryadvisor.com/alzheimers-disease-and-dementia/integrated-approach-best-for-alzheimers-associated-agitation/article/357977/

Basic Science and Animal Studies

Elimination of senescent cells prevents neurodegeneration in mice
Aggregation of the protein tau is implicated in neurodegenerative diseases in humans. It emerges that eliminating a type of damaged cell that no longer divides can prevent tau-mediated neurodegeneration in mice.

Reversal of age-related cognitive impairments in mice by an extremely low dose of tetrahydrocannabinol.

In the pipeline

Tonix announced that the Food and Drug Administration (FDA) has granted Fast Track designation to TNX-102 SL (cyclobenzaprine HCl) sublingual tablet for the treatment of agitation in Alzheimer's disease. Currently, there are no approved treatments for this indication.
The Company plans to evaluate the safety and efficacy of TNX-102 SL dosed at bedtime in a Phase 2 study involving patients with agitation in Alzheimer's disease. The researchers also plan on analyzing genomic DNA to identify biomarkers associated with treatment response.
TNX-102 SL, a low-dose cyclobenzaprine HCl formulation, is thought to work by blocking the serotonin 2A receptor, the alpha-1 adrenergic receptor, and the histamine-1 receptor. Blocking

these receptors may increase slow wave sleep and decrease waking-after-sleep-onset, as well as reduce trauma-related nightmares and sleep disturbance.

The Potential Therapeutic Effects of THC on Alzheimer's Disease

Article type: Research Article
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Abstract: The purpose of this study was to investigate the potential therapeutic qualities of Δ9-tetrahydrocannabinol (THC) with respect to slowing or halting the hallmark characteristics of Alzheimer's disease. N2a-variant amyloid-β protein precursor (AβPP) cells were incubated with THC and assayed for amyloid-β (Aβ) levels at the 6-, 24-, and 48-hour time marks. THC was also tested for synergy with caffeine, in respect to the reduction of the Aβ level in N2a/AβPPswe cells. THC was also tested to determine if multiple treatments were beneficial. The MTT assay was performed to test the toxicity of THC. Thioflavin T assays and western blots were performed to test the direct anti-Aβ aggregation significance of THC. Lastly, THC was tested to determine its effects on glycogen synthase kinase-3β (GSK-3β) and related signaling pathways. From the results, we have discovered THC to be effective at lowering Aβ levels in N2a/AβPPswe cells at extremely low concentrations in a dose-dependent manner. However, no additive effect was found by combining caffeine and THC together. We did discover that THC directly interacts with Aβ peptide, thereby inhibiting aggregation. Furthermore, THC was effective at lowering both total GSK-3β levels and phosphorylated GSK-3β in a dose-dependent manner at low concentrations. At the treatment concentrations, no toxicity was observed and the CB1 receptor was not significantly upregulated. Additionally, low doses of THC can enhance mitochondria function and does not inhibit melatonin's enhancement of mitochondria function. These sets of data strongly suggest that THC could be a potential therapeutic treatment option for Alzheimer's disease through multiple functions and pathways.
Keywords: Alzheimer's disease, amyloid-β peptide, cannabinoid, CB1 receptor, CB2 receptor, delta(9)-tetrahydrocannabinol, neurodegeneration
DOI: 10.3233/JAD-140093
Journal: Journal of Alzheimer's Disease, vol. 42, no. 3, pp. 973-984, 2014 16 September 2014

Research overview: The potential role for cannabinoids with the elderly population

Review of the current literature
Approach to the patient
Cannabinoids and delivery systems
General information on cognitive function-Dementia

Cannabinoids may have more specific effects in Alzheimer's disease pathology, as they can reduce excitotoxicity, mitochondrial dysfunction, oxidative stress, neuroinflammation, and the formation of amyloid plaques and neurofibrillary tangles (Ahmed 2015; Aso 2014). Several studies have shown the protective effect of cannabinoids against amyloid-β peptide and tau phosphorylation (reviewed in: Aso 2014), which are the neuropathological hallmarks of AD. (Cochrane)

http://onlinelibrary.wiley.com/doi/10.1002/14651858.CD012820/full

Observational studies using biomarkers, such as neuroimaging markers, of brain health in older patients taking cannabinoids for various durations may give us a better understanding of their long-term safety and tolerability and the monitoring required to assess long-term burden of specific cannabinoids in real-world samples.[52] Additionally, clarifying the role and the place within the clinical armament can provide an important tool to address a devastating clinical situation. However, because of various biases, observational data may not provide answers to all questions,[53] and a major challenge is that the number of published RCTs specific to geriatric patients is not growing substantially. Pharmacotherapy evidence is not keeping up with demographic trends. Key developments in RCTs will be the inclusion of biomarkers via neuroimaging, drug serum or brain levels, and genetic profiling. Because of the modest findings of benefits of antipsychotics in dementia and safety concerns addressing brain health in preclinical or early stages, identification of effective nondrug interventions and identifying true disease-modifying agents will be the next challenges of dementia research.

General information on Cognitive function-Dementia

Interventions for Preventing Cognitive Decline, Mild Cognitive Impairment, and Alzheimer's Disease

Delta-THC in Behavioral Disturbances in Dementia (See below)
Delta-THC in Behavioral Disturbances in Dementia

Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (AD) (THC-AD) (THC-AD) (Recruiting)

Handb Exp Pharmacol. 2015;231:233-59. doi: 10.1007/978-3-319-20825-1_8.

Endocannabinoids and Neurodegenerative Disorders: Parkinson's Disease, Huntington's Chorea, Alzheimer's Disease, and Others.

Fernández-Ruiz J[1,2,3], Romero J[4,5], Ramos JA[6,7,8].

Abstract

This review focuses on the role of the endocannabinoid signaling system in controlling neuronal survival, an extremely important issue to be considered when developing new therapies for neurodegenerative disorders. First, we will describe the cellular and molecular mechanisms, and the signaling pathways, underlying these neuroprotective properties, including the control of glutamate homeostasis, calcium influx, the toxicity of reactive oxygen species, glial activation and other inflammatory events; and the induction of autophagy. We will then concentrate on the preclinical studies and the few clinical trials that have been carried out targeting endocannabinoid signaling in three important chronic progressive neurodegenerative disorders (Parkinson's disease, Huntington's chorea, and Alzheimer's disease), as well as in other less well-studied disorders. We will end by offering some ideas and proposals for future research that should be carried out to optimize endocannabinoid-based treatments for these disorders. Such studies will strengthen the possibility that these therapies will be investigated in the clinical scenario and licensed for their use in specific disorders.

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Endocannabinoid system in neurodegenerative disorders.
J Neurochem. 2017 Sep;142(5):624-648. doi: 10.1111/jnc.14098. Epub 2017 Jul 5

Basavarajappa BS1,2,3,4, Shivakumar M1, Joshi V1, Subbanna S1.

Most neurodegenerative disorders (NDDs) are characterized by cognitive impairment and other neurological defects. The definite cause of and pathways underlying the progression of these NDDs are not well-defined. Several mechanisms have been proposed to contribute to the development of NDDs. These mechanisms may proceed concurrently or successively, and they differ among cell types at different developmental stages in distinct brain regions. The endocannabinoid system, which involves cannabinoid receptors type 1 (CB1R) and type 2 (CB2R), endogenous cannabinoids and the enzymes that catabolize these compounds, has been shown to contribute to the development of NDDs in several animal models and human studies. In this review, we discuss the functions of the endocannabinoid system in NDDs and converse the therapeutic efficacy of targeting the endocannabinoid system to rescue NDDs.

KEYWORDS:

Alzheimer's disease; CB1 receptors; Huntington's disease; Loss of neurons; Parkinson's disease; motor and memory behavior

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The therapeutic potential of the phytocannabinoid cannabidiol for Alzheimer's disease.
Karl T, Garner B, Cheng D. Behav Pharmacol. 2017 Apr;28 (2 and 3 - Special Issue):142-160. doi: 10.1097/FBP.0000000000000247.

Article conclusion:
This review presents a brief introduction to AD biology and current treatment options, outlines CBD biology and pharmacology, followed by in-vitro and in-vivo evidence for the therapeutic potential of CBD, discusses the role of the endocannabinoid system in AD, comments on the potential future of CBD for AD therapy (including safety aspects).

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive loss of cognition. Over 35 million individuals currently have AD worldwide. Unfortunately, current therapies are limited to very modest symptomatic relief. The brains of AD patients are characterized by the deposition of amyloid-β and hyperphosphorylated forms of tau protein. AD brains also show neurodegeneration and high levels of oxidative stress and inflammation. The phytocannabinoid cannabidiol (CBD) possesses neuroprotective, antioxidant and anti-inflammatory properties and reduces amyloid-β production and tau hyperphosphorylation in vitro. CBD has also been shown to be effective in vivo making the phytocannabinoid an interesting candidate for novel therapeutic interventions in AD, especially as it lacks psychoactive or cognition-impairing properties. CBD treatment would be in line with preventative, multimodal drug strategies targeting a combination of pathological symptoms, which might be ideal for AD therapy. Thus, this review will present a brief introduction to AD biology and current treatment options before outlining comprehensively CBD biology and pharmacology, followed by in-vitro and in-vivo evidence for the therapeutic potential of CBD. We will also discuss the role of the endocannabinioid system in AD before commenting on the potential future of CBD for AD therapy (including safety aspects).

Cannabinoids and Dementia: A Review of Clinical and Preclinical Data.
Walther S1, Halpern M 2. Pharmaceuticals (Basel). 2010 Aug 17;3(8):2689-2708.
Abstract
The endocannabinoid system has been shown to be associated with neurodegenerative diseases and dementia. We review the preclinical and clinical data on cannabinoids and four neurodegenerative diseases: Alzheimer's disease (AD), Huntington's disease (HD), Parkinson's disease (PD) and vascular dementia (VD). Numerous studies have demonstrated an involvement of the cannabinoid system in neurotransmission, neuropathology and neurobiology of dementias. In addition, several candidate compounds have demonstrated efficacy in vitro. However, some of the substances produced inconclusive results in vivo. Therefore, only few

trials have aimed to replicate the effects seen in animal studies in patients. Indeed, the literature on cannabinoid administration in patients is scarce. While preclinical findings suggest causal treatment strategies involving cannabinoids, clinical trials have only assessed the suitability of cannabinoid receptor agonists, antagonists and cannabidiol for the symptomatic treatment of dementia. Further research is needed, including in vivo models of dementia and human studies.]

The role of the endocannabinoid system in Alzheimer's disease: facts and hypotheses.

Curr Pharm Des. 2008;14(23):2299-3305. Bisogno T1, Di Marzo V.

Abstract

Unlike other neuroinflammatory disorders, like Parkinson's disease, Huntington's disease and multiple sclerosis, little is still known of the role of the endocannabinoid system in Alzheimer's disease (AD). This is partly due to the poor availability of animal models that are really relevant to the human disease, and to the complexity of AD as compared to other neurological states. Nevertheless, the available data indicate that endocannabinoids are likely to play in this disorder a role similar to that suggested in other neurodegenerative diseases, that is, to represent an endogenous adaptive response aimed at counteracting both the neurochemical and inflammatory consequences of beta-amyloid-induced tau protein hyperactivity, possibly the most important underlying cause of AD. Furthermore, plant and synthetic cannabinoids, and particularly the non-psychotropic cannabidiol, might also exert other, non-cannabinoid receptor-mediated protective effects, including, but not limited to, anti-oxidant actions. There is evidence, from in vivo studies on beta-amyloid-induced neurotoxicity, also for a possible causative role of endocannabinoids in the impairment in memory retention, which is typical of AD. This might open the way to the use of cannabinoid receptor antagonists as therapeutic drugs for the treatment of cognitive deficits in the more advanced phases of this disorder. The scant, but nevertheless important literature on the regulation and role of the endocannabinoid system in AD, and on the potential treatment of this disorder with cannabinoids and endocannabinoid-based drugs, are discussed in this mini-review.

RESEARCH PROTOCOL

Potential Therapeutic Targets of the Endocannabinoid System in Common Neurodegenerative Disorders and Organic Acidemias

The cannabinoid chemistry is currently being addressed in preclinical approaches as a viable therapeutic alternative for the management of a wide range of signs, symptoms, and some biochemical hallmarks of many neurological pathologies (such as neuroinflammation and neurodegeneration). This clinical orientation is grounded on the consistent promissory profile that cannabinoid compounds have shown, and the great necessity of feasible options to

undergo such disorders. Even though at early research stages, metabolic disorders are starting to rise as potential targets of cannabinoid alternatives; approaches in this term could, in turn, aim to modulate the endocannabinoid response for therapeutic purposes. This review recalls the pathologic scenarios endured in the course of neurological diseases of high occurrence and the most typical metabolic disorders, while discussing the neuroprotective mechanisms of cannabinoid agonists in the central nervous system, and the potential targets of the endocannabinoid system and metabolic disorders.

The therapeutic potential of the phytocannabinoid cannabidiol for Alzheimer's disease. Karl T1, Garner B, Cheng D. Behav Pharmacol. 2017 Apr;28(2 and 3-Spec Issue):142-160.

Abstract

Alzheimer's disease (AD) is the most common neurodegenerative disorder, characterized by progressive loss of cognition. Over 35 million individuals currently have AD worldwide. Unfortunately, current therapies are limited to very modest symptomatic relief. The brains of AD patients are characterized by the deposition of amyloid-β and hyperphosphorylated forms of tau protein. AD brains also show neurodegeneration and high levels of oxidative stress and inflammation. The phytocannabinoid cannabidiol (CBD) possesses neuroprotective, antioxidant and anti-inflammatory properties and reduces amyloid-β production and tau hyperphosphorylation in vitro. CBD has also been shown to be effective in vivo making the phytocannabinoid an interesting candidate for novel therapeutic interventions in AD, especially as it lacks psychoactive or cognition-impairing properties. CBD treatment would be in line with preventative, multimodal drug strategies targeting a combination of pathological symptoms, which might be ideal for AD therapy. Thus, this review will present a brief introduction to AD biology and current treatment options before outlining comprehensively CBD biology and pharmacology, followed by in-vitro and in-vivo evidence for the therapeutic potential of CBD. We will also discuss the role of the endocannabinioid system in AD before commenting on the potential future of CBD for AD therapy (including safety aspects).

Randomized double-blind placebo-controlled multicenter trial of Yokukansan for neuropsychiatric symptoms in Alzheimer's disease.
Our data did not reach statistical significance regarding the efficacy of YKS against BPSD; however, YKS improves some symptoms including "agitation/aggression" and "hallucinations" with low frequencies of adverse events. Geriatr Gerontol Int 2017; 17: 211-218.

Br J Clin Pharmacol. 2018 Jul;84(7):1445-1456. doi: 10.1111/bcp.13604. Epub 2018 May 14.

Ecosystem

Older Americans Are Flocking to Medical Marijuana https://nyti.ms/2G4TQNg

Minnesota OKs medical marijuana to treat Alzheimer's HealthMPR News Staff · St. Paul · Dec 3, 2018

Potential Mechanism of Action with relevance to AD

The dual neuroprotective-neurotoxic profile of cannabinoid drugs.
Review article
Sarne Y, et al. Br J Pharmacol. 2011.

The Potential Therapeutic Effects of THC on Alzheimer's Disease

THC found to reduce amyloid-beta levels and enhance mitochondria function, thus demonstrating potential as an Alzheimer's disease treatment option.

THC prevented amyloid-beta aggregation, the key pathological marker of Alzheimer's disease.
A molecular link between the active component of marijuana and Alzheimer's disease pathology.

Cannabinoids stimulate the removal of beta amyloid, block the inflammatory response, and provide neuroprotective effects.

Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids.
http://www.nature.com/articles/npjamd201612–

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The Use of Cannabinoids in Treating Dementia
Weier, Megan ; Hall, Wayne Aug 2017
Current Neurology and Neuroscience Reports, Vol.17(8), pp.1-9[Peer Reviewed Journal]

March 23, 2016
The Role of Phytochemicals in the Treatment and Prevention of Dementia
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J Psychopharmacol. 2017 Feb;31(2):184-191. doi: 10.1177/0269881116665357. Epub 2016 Sep 27.

Agitation and aggression are commonly present symptoms in Alzheimer's disease (AD). Six trials have administered synthetic cannabinoids for the treatment of agitation and/or aggression in patients diagnosed with dementia or AD.

Cannabinoids may offer a therapeutically relevant and efficacious treatment option for the management of agitation and aggression in AD.

Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease

The Potential therapeutic effects of THC on Alzheimer's Disease. Cao C et al. J Alzheimer's Dis. 2014.42:973-84

Amyloid proteotoxicity initiates an inflammatory response blocked by cannabinoids. Currias A et al. npj Aging and Mechanisms of Disease. 2016; 2:16012. doi:10.1038/npjamd.2016.12

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THC in behavioral disturbances in dementia.van den Elsen et al. Am J Geriatr Psychiatry. 2015; 23: 1214-24.

Atypical antipsychotic use in patients with dementia: managing safety concerns. Steinberg M, Lyketsos CG. Am J Psychiatry. 2012;169(9):900-906.

Research
A molecular link between the active component of marijuana and Alzheimer's disease pathology
Eubanks LM, Rogers CJ, Beuscher AE 4th, Koob GF, Olson AJ, Dickerson TJ, Janda KD
Department of Chemistry and Immunology, The Skaggs Institute for Chemical Biology, The Scripps Research Institute, La Jolla, California 92037, USA

Letter

A chronic low dose of Δ9-tetrahydrocannabinol (THC) restores cognitive function in old mice

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Abstract

The balance between detrimental, pro-aging, often stochastic processes and counteracting homeostatic mechanisms largely determines the progression of aging. There is substantial evidence suggesting that the endocannabinoid system (ECS) is part of the latter system because it modulates the physiological processes underlying aging[1,2]. The activity of the ECS declines during aging, as CB1 receptor expression and coupling to G proteins are reduced in the brain tissues of older animals [3,4,5] and the levels of the major endocannabinoid 2-arachidonoylglycerol (2-AG) are lower[6]. However, a direct link between endocannabinoid tone and aging symptoms has not been demonstrated. Here we show that a low dose of Δ9-tetrahydrocannabinol (THC) reversed the age-related decline in cognitive performance of mice aged 12 and 18 months. This behavioral effect was accompanied by enhanced expression of synaptic marker proteins and increased hippocampal spine density. THC treatment restored hippocampal gene transcription patterns such that the expression profiles of THC-treated mice aged 12 months closely resembled those of THC-free animals aged 2 months. The transcriptional effects of THC were critically dependent on glutamatergic CB1 receptors and histone acetylation, as their inhibition blocked the beneficial effects of THC. Thus, restoration of CB1 signaling in old individuals could be an effective strategy to treat age-related cognitive impairments.

The role of the endocannabinoid system in Alzheimer's disease: facts and hypotheses

Bisogno T, Di Marzo V
Endocannabinoid Research Group, Institute of Biomolecular Chemistry, Consiglio Nazionale delle Ricerche, Via Campi Flegrei 34, Pozzuoli (Naples), Italy

Abstract
Unlike other neuroinflammatory disorders, like Parkinson's disease, Huntington's disease and multiple sclerosis, little is still known of the role of the endocannabinoid system in Alzheimer's disease (AD). This is partly due to the poor availability of animal models that are really relevant to the human disease, and to the complexity of AD as compared to other neurological states. Nevertheless, the available data indicate that endocannabinoids are likely to play in this disorder a role similar to that suggested in other neurodegenerative diseases, that is, to represent an endogenous adaptive response aimed at counteracting both the neurochemical and inflammatory consequences of beta-amyloid-induced tau protein hyperactivity, possibly the most

important underlying cause of AD. Furthermore, plant and synthetic cannabinoids, and particularly the non-psychotropic cannabidiol, might also exert other, non-cannabinoid receptor-mediated protective effects, including, but not limited to, anti-oxidant actions. There is evidence, from in vivo studies on beta-amyloid-induced neurotoxicity, also for a possible causative role of endocannabinoids in the impairment in memory retention, which is typical of AD. This might open the way to the use of cannabinoid receptor antagonists as therapeutic drugs for the treatment of cognitive deficits in the more advanced phases of this disorder. The scant, but nevertheless important literature on the regulation and role of the endocannabinoid system in AD, and on the potential treatment of this disorder with cannabinoids and endocannabinoid-based drugs, are discussed in this mini-review

http://www.ncbi.nlm.nih.gov/pubmed/18781980

Prevention of Alzheimer's disease pathology by cannabinoids: neuroprotection mediated by blockade of microglial activation

Ramírez BG, Blázquez C, Gómez del Pulgar T, Guzmán M, de Ceballos ML
Neurodegeneration Group, Cajal Institute, Consejo Superior de Investigaciones Científicas, 28002 Madrid, Spain

Abstract
Alzheimer's disease (AD) is characterized by enhanced beta-amyloid peptide (betaA) deposition along with glial activation in senile plaques, selective neuronal loss, and cognitive deficits. Cannabinoids are neuroprotective agents against excitotoxicity in vitro and acute brain damage in vivo. This background prompted us to study the localization, expression, and function of cannabinoid receptors in AD and the possible protective role of cannabinoids after betaA treatment, both in vivo and in vitro. Here, we show that senile plaques in AD patients express cannabinoid receptors CB1 and CB2, together with markers of microglial activation, and that CB1-positive neurons, present in high numbers in control cases, are greatly reduced in areas of microglial activation. In pharmacological experiments, we found that G-protein coupling and CB1 receptor protein expression are markedly decreased in AD brains. Additionally, in AD brains, protein nitration is increased, and, more specifically, CB1 and CB2 proteins show enhanced nitration. Intracerebroventricular administration of the synthetic cannabinoid WIN55,212-2 to rats prevent betaA-induced microglial activation, cognitive impairment, and loss of neuronal markers. Cannabinoids (HU-210, WIN55,212-2, and JWH-133) block betaA-induced activation of cultured microglial cells, as judged by mitochondrial activity, cell morphology, and tumor necrosis factor-alpha release; these effects are independent of the antioxidant action of cannabinoid compounds and are also exerted by a CB2-selective agonist. Moreover,

cannabinoids abrogate microglia-mediated neurotoxicity after beta A addition to rat cortical co cultures. Our results indicate that cannabinoid receptors are important in the pathology of AD and that cannabinoids succeed in preventing the neurodegenerative process occurring in the disease

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CBD & THC are Neuroprotective Antioxidants

http://ropevilleraider.tumblr.com/post/156415187503/cannabis-and-neurogenesis

Cannabinoids can help remove dangerous dementia proteins from brain cells, researchers say

Pre- and post-conditioning treatment with an ultra-low dose of Δ9-tetrahydrocannabinol (THC) protects against pentylenetetrazole (PTZ)-induced cognitive damage.
Randomized controlled trial
Assaf F, et al. Behav Brain Res. 2011.
Long-term behavioral and biochemical effects of an ultra-low dose of Δ9-tetrahydrocannabinol (THC): neuroprotection and ERK signaling.Fishbein M, et al. Exp Brain Res. 2012.

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J Neurochem. 2017 Sep;142(5):624-648. doi: 10.1111/jnc.14098. Epub 2017 Jul 5.

Endocannabinoid system in neurodegenerative disorders.

Basavarajappa BS1,2,3,4, Shivakumar M1, Joshi V1, Subbanna S1.

Author information

Abstract

Most neurodegenerative disorders (NDDs) are characterized by cognitive impairment and other neurological defects. The definite cause of and pathways underlying the progression of these NDDs are not well-defined. Several mechanisms have been proposed to contribute to the development of NDDs. These mechanisms may proceed concurrently or successively, and they differ among cell types at different developmental stages in distinct brain regions. The endocannabinoid system, which involves cannabinoid receptors type 1 (CB1R) and type 2 (CB2R), endogenous cannabinoids and the enzymes that catabolize these compounds, has been shown to contribute to the development of NDDs in several animal models and human studies. In this review, we discuss the functions of the endocannabinoid system in NDDs and converse the therapeutic efficacy of targeting the endocannabinoid system to rescue NDDs.

CLINICAL STUDY RESOURCES:

Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease
The therapeutic potential of the endocannabinoid system for Alzheimer's disease
Endocannabinoid signalling in Alzheimer's disease
A molecular link between the active component of marijuana and Alzheimer's disease pathology
Neuroprotective effect of CBD… on beta-amyloid-induced toxicity in PC12 cells
Cannabinoids for the treatment of dementia
CBD in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression
CBD: A promising drug for neurodegenerative disorders?
The role of the endocannabinoid system in Alzheimer's disease
Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic
Can Marijuana Prevent Alzheimer's?
Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia
Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease
Natural Phytochemicals in the Treatment and Prevention of Dementia: An Overview
CBD Modulates the Expression of Alzheimer's Disease-Related Genes in Mesenchymal Stem Cells

In vivo Evidence for Therapeutic Properties of CBD for Alzheimer's Disease
Neurological aspects of medical use of CBD

ALZHEIMER'S DISEASE

The therapeutic potential of the endocannabinoid system for Alzheimer's disease

Endocannabinoid signalling in Alzheimer's disease

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The Potential Therapeutic Effects of THC on Alzheimer's Disease

The Role of Endocannabinoid Signaling in the Molecular Mechanisms of Neurodegeneration in Alzheimer's Disease

Cannabinoids for the treatment of dementia

CBD in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression

- CBD: A promising drug for neurodegenerative disorders?
- Cannabinoid receptor 1 deficiency in a mouse model of Alzheimer's disease leads to enhanced cognitive impairment despite of a reduction in amyloid deposition
- The role of the endocannabinoid system in Alzheimer's disease
- The role of phytochemicals in the treatment and prevention of dementia
- Cannabinoids for the treatment of dementia
- Cannabidiol Promotes Amyloid Precursor Protein Ubiquitination and Reduction of Beta Amyloid Expression inSHSY5YAPP+ Cells Through PPARγ Involvement
- Cannabinoids for treatment of Alzheimer's disease: moving toward the clinic
- Can Marijuana Prevent Alzheimer's?
- Safety and Efficacy of Medical Cannabis Oil for Behavioral and Psychological Symptoms of Dementia
- Cannabinoids for the Treatment of Agitation and Aggression in Alzheimer's Disease
- Natural Phytochemicals in the Treatment and Prevention of Dementia: An Overview
- Delineating the Efficacy of a Cannabis-Based Medicine at Advanced Stages of Dementia in a Murine Model

- CBD Modulates the Expression of Alzheimer's Disease-Related Genes in Mesenchymal Stem Cells
- In vivo Evidence for Therapeutic Properties of CBD for Alzheimer's Disease
- Neurological aspects of medical use of CBD

NIH Alzheimer's Disease Research Summit 2018 National Institute on Aging, NIH
May 24, 2018

The 2018 NIH AD Research Summit will bring together researchers and opinion leaders from academia, industry, federal agencies, private foundations and public advocacy groups working on Alzheimer's and other complex diseases with the goal to evaluate progress towards the AD research implementation milestones and to continue the development of an integrated, multidisciplinary, translational research agenda necessary to address critical knowledge gaps and enable precision medicine for AD. Key to achieving this goal is the identification of: 1) resources/infrastructure and multi-stakeholder partnerships necessary to successfully implement this research agenda and 2) strategies to engage patients, caregivers and citizens as direct partners in research.

This key strategic planning event is tied to the implementation of the first research goal of the National Plan to Address Alzheimer's (NAPA), to treat and prevent Alzheimer's disease by 2025. The 2018 Summit builds on the foundation laid by the NIH AD Research Summits held in 2012 and 2015 and the NIH ADRD Research Summits of 2013 and 2016.

The meeting program will be organized around 7 major themes/sessions:

Novel Mechanistic Insights into the Complex Biology and Heterogeneity of AD
Enabling Precision Medicine for AD
Translational Tools and Infrastructure to Enable Predictive Drug Development
Emerging Therapeutics
Understanding the Impact of the Environment to Advance Disease Prevention
Advances in Disease Monitoring Assessment and Care
Building an Open Science Research Ecosystem to Accelerate AD Therapy Development

Each session will feature progress achieved towards key research implementation milestones and highlight emerging research trends, followed by a moderated panel discussion focused on outstanding questions/knowledge gaps/research needs.

The general program will be followed by a writing session during which a select group of experts together with NIA/NIH staff and NAPA Council members will evaluate progress to date and formulate recommendations which will be used as the basis for updating and refining the

research implementation milestones for measuring progress towards the goal to prevent and treat AD by 2025.

Appendix 1. Screened references for review

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(54) **CANNABINOIDS AS ANTIOXIDANTS AND NEUROPROTECTANTS**

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