CBD AS AN ENCOURAGING THERAPEUTIC APPROACH TO ALZHEIMER'S

Alzheimer's And Dementia Defined

Alzheimer's disease, the most common form of dementia, is a neurodegenerative disorder characterized by a decline in cognitive function severe enough to interfere with remembering, reasoning, and planning; all requisite activities of daily living, and a disease that eventually leads to death ((Upadhyaya 2010; Stern 2008; Knopman 2012; Mayo Clinic 2011). According to the National Alzheimer's Association, Alzheimer's and dementia are described as such:

- **Alzheimer's is not a normal part of aging**, although the greatest known risk factor is increasing age, and the majority of people with Alzheimer's are beyond age of 65. Alzheimer's, however, is not just a disease of old age. Up to 5% of people with the disease have early onset Alzheimer's (known as younger-onset), which often appears when someone is in their 40's or 50's.
- **Dementia is not a specific disease. It is an overall term that describes a wide range of symptoms** associated with a decline in memory or other thinking skills severe enough to reduce a person's ability to perform everyday activities. Alzheimer's disease accounts for 60 to 80% of cases. Vascular dementia, which occurs after a stroke, is the second most common dementia type. But there are many other conditions that can cause symptoms of dementia, including some that are reversible, such as thyroid problems and vitamin deficiencies. Dementia is often incorrectly referred to as "senility" or "senile dementia," which reflects the formerly widespread but incorrect belief that serious mental decline is a normal part of aging.
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Alzheimer's disease is the consequence of several convergent factors including oxidative stress, inflammation, mitochondrial dysfunction, and accumulation of toxic protein aggregates in and around neurons (Luan 2012; Teng 2012; Rosales-Corral 2012; Wang 2007; Fonte 2011; Ittner 2011). Emerging, intriguing research implicates *chronic infection* with several pathogenic organisms in the development and progression of Alzheimer's disease as well (Miklossy 2011).

The inflammatory process appears to play the major role in the development of Alzheimer's disease. When high levels of amyloid beta accumulate in the brain, it activates the body's immune response, resulting in inflammation that damages neurons (Salminen 2009). Part of the inflammatory response to amyloid beta appears to be facilitated by tumor necrosis factor-alpha (TNF-α) (Tobinick 2008a). TNF-α is a pro-inflammatory cytokine that is often found in high levels in serum and cerebral spinal fluid (CSF) of Alzheimer's patients; it represents a potential target for novel Alzheimer's disease therapies (Culpan 2011; Ardebili 2011; Tobinick 2008a).

How does CBD assist in a treatment of Alzheimer disease? The substantial and well-documented antioxidant, anti-inflammatory, and neuroprotective properties of CBD have prompted researchers to test its effects in models of neurotoxicity and neurodegenerative disorders. In the investigation aimed at exploring CBD effects on b-amyloid-induced neurotoxicity, this phytocannabinoid was found to possess the ability to protect differentiated PC12 neural cells from detrimental action induced by peptide exposure. This is achieved through the combination of its antioxidant, anti-inflammatory and antiapoptotic properties. CBD antioxidant effects account mainly for the survival of cultured neurons, with potency higher than that exhibited by a-tocopherol. CBD prevents neurofibrillar tangle formation.

It also has been demonstrated that CBD decreased phosphorylation of stress-activated protein kinase, P38 mitogen activated protein kinase, thus preventing the translocation of nuclear factor (NF)-kB into the nucleus and the subsequent transcription of important pro inflammatory genes.

These encouraging results emphasize the relevance of CBD as a very promising pharmacological tool capable of mitigating B-amyloid-evoked neuroinflammatory and neurodegenerative responses. Found to prevent both glutamate neurotoxicity and radical oxygen species (ROS) - induced cell death, CBD also suppressed the decrease in cerebral blood flow due to the failure of cerebral microcirculation after

reperfusion, as well as it blunted metalloperoxidase activity after reperfusion for up to 3 days, showing potent long lasting neuroprotectant and anti-inflammatory effects.

Explanation of Terms – in order of usage throughout this document

mitochondrial RNAs: a unique set of tRNAs, mRNAs, rRNAs, transcribed from mitochondrial DNA by a mitochondrial-specific RNA polymerase, that account for about 4% of the total cell RNA that are transcribed

beta-amyloid: A4, β—amyloid Neurology A 4 kD polypeptide encoded on chromosome 21 arising from altered processing of amyloid precursor protein, an integral membrane glycoprotein secreted as a truncated carboxyl-terminal molecule; BA forms plaques in the brains of Pts with Alzheimer's disease–AD, Down syndrome, infectious encephalopathy, cerebral amyloid angiopathy; BA is found in skin, intestine, adrenal gland.

A-tocopherol: one of several forms of Vitamin E. A light yellow, viscous, odorless, oily liquid that deteriorates on exposure to light; it is obtained from wheat germ oil or by synthesis; an antioxidant retarding rancidity by interfering with autoxidation of fats.

Neurofibrillary tangle:
twisted masses of protein inside nerve cells that develop in the brains of people with AD.

Cannabidiol *in vivo* blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression

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Introduction

Alzheimer's disease (AD) is the most common age-related neurodegenerative disorder (Koo *et al*., 1999) whose specific hallmarks are neurofibrillary tangles (Terry, 1963) and senile plaques (Braak and Braak, 1997). While neurofibrillary tangles result from the deposition of hyperphosphorylated tau proteins (Lee *et al*., 1991), senile plaques represent more complex extracellular lesions composed of a core of *β*-amyloid (A*β*) aggregates, surrounded by activated astrocytes and dystrophic neuritis (Itagaki *et al*., 1989; Cotman *et al*., 1996). At present, although biochemical events leading to A*β* neurotoxicity still remain unclear, proposed mechanisms include production of oxygen free radicals (Behl *et al*., 1994), changes in cytosolic calcium homeostasis (Ueda *et al*., 1997; Mattson, 2002) and activation of Wnt pathway as well as of the transcription nuclear factor NF-*κ*B (Green and Peers, 2002; Caricasole *et al*., 2003). In addition to cytotoxic mechanisms directly affecting neurons, A*β*-induced glial cell activation, triggering inflammatory responses with subsequent release of neurotoxic cytokines, is present in the AD brain, contributing to the pathogenesis of disease (Craft *et al*., 2006). The possibility of interfering with this detrimental cycle by pharmacologically inhibiting reactive gliosis has been proposed as a novel rationale to develop drugs able to blunt neuronal damage and consequently slow the course of disease.

Cannabidiol (CBD), the main non-psychotropic component of the glandular hairs of *Cannabis sativa*, exhibits a plethora of actions including anti-convulsive, sedative, hypnotic, anti-psychotic, anti-nausea, anti-inflammatory and anti-hyperalgesic properties (Mechoulam *et al*., 2002; Costa *et al*., 2007). CBD has been proved to exert *in vitro* a combination of neuroprotective effects in A*β*-induced neurotoxicity, including anti-oxidant and anti-apoptotic effects (Iuvone *et al*., 2004), tau protein hyperphosphorylation inhibition through the Wnt pathway (Esposito *et al*., 2006a), and marked decrease of inducible nitric oxide synthase (iNOS) protein expression and nitrite production in A*β*-challenged differentiated rat neuronal cells (Esposito *et al*., 2006b).

In spite of the large amount of data describing the significant neuroprotective and anti-inflammatory properties of CBD *in vitro*, to date no evidence has been provided showing similar effects *in vivo*. To achieve this, the present study investigated the potential anti-inflammatory effect of CBD in a mouse model of AD-related neuroinflammation induced by the intrahippocampal injection of the human A*β* (1–42) fragment.

Discussion and conclusions

The urgent need for novel strategies for AD is apparent with the realization that the currently approved therapies are only palliative without significant and substantial disease modifying effects (Turner, 2006). In contrast, the present study suggests that CBD, here investigated with a primary focus on glial pathways, exhibits a potential to delay effectively the onset and progression of A*β* neurotoxicity. Actually, the current results provide evidence that CBD causes a clear-cut reduction of the transcription and expression of glial pro-inflammatory molecules in the hippocampus of an *in vivo* model of A*β*-induced neuroinflammation. They suggest CBD may be regarded as a promising tool able to affect the course of A*β*-related neuropathology, by reducing A*β*-generated reactive gliosis and subsequent neuroinflammatory responses, in addition to the previously demonstrated protective effects directly affecting neurons (Iuvone *et al*., 2004;Esposito *et al*., 2006a, 2006b). Indeed, the increasing body of immunohistological and molecular findings, showing that inflammatory processes are pre-eminent and constant aspects of the neuropathology generated by the A*β* toxicity, supports the notion that the previously under-appreciated glial activation plays a critical role in the pathogenesis of brain lesions subsequent to A*β* deposition (Craft *et al*., 2006). Although acute activation of glial cells may have important beneficial effects in the recovery of the CNS from a variety of insults, it is believed that a persistent activation amplifies inflammatory responses leading to a worsening of the consequences of injury (Ralay Ranaivo *et al*., 2006). In the scenario of reactive gliosis, the main features are astrocytic hypertrophy and proliferation, along with a marked overexpression of the intermediate filament proteins, such as GFAP, the best known hallmark of activated astrocytes (O'Callaghan and Sriram, 2005).

The present investigation focuses the ability of this phytocannabinoid, CBD, to negatively modulate GFAP transcription and expression as well as to significantly reduce IL-1*β* and iNOS upregulation, which importantly contribute to disease progression, through the propagation of inflammation and oxidative stress. Among the many active substances produced by A*β* stimulated microglia, IL-1*β* has proved to be substantially implicated in the cytokine cycle of cellular and molecular events responsible for the neurodegenerative consequences (Griffin *et al*., 1998). These include synthesis and processing of amyloid precursor protein (Buxbaum *et al*., 1992; Mrak and Griffin, 2000), as well as astrocyte activation with a subsequent iNOS overexpression and excessive production of NO (Das and Potter, 1995; Sheng *et al*., 1996). Increasing amounts of NO, a short-lived and diffusible free radical involved in all reported neuroinflammatory and neurodegenerative conditions (Murphy, 2000), accelerate neuronal protein nitration and cause a marked increase in tau protein hyperphosphorylation (Saez *et al*., 2004), encouraging the detrimental progression of A*β*-related pathology (Nathan *et al*., 2005).

Therefore, in this context where inflammatory pathways are believed to play relevant roles as driving forces of the A*β*-induced injury, they are identified as potential modulators of the neuronal damage and are reported as neuronal targets for effective therapeutic interventions. The present investigation provides the first evidence that substantial components of the neuroinflammatory response, set in motion by A*β*deposition and allowing for progression of neuropathology, are suppressed *in vivo* by CBD. The current data confirm and further reinforces the view that CBD can exhibit protective effects in models of neuroinflammation/neurodegeneration.

The seminal work describing CBD neuroprotective properties demonstrated its ability to protect cortical neurons in culture against glutamate-induced neurotoxicity. Such effects were found to be not antagonized by the established CB_1 antagonist SR141716A, suggesting that they were independent of CB_1 cannabinoid receptor involvement. Later CBD was shown to prevent A*β*-induced toxicity in PC12 pheocromocytoma cells, increasing survival while decreasing reactive oxygen species production, lipid peroxidation, caspas-3 levels, DNA fragmentation and intracellular calcium (Iuvone *et al*., 2004). In addition to this combination of anti-oxidant, anti-inflammatory and anti-apoptotic effects, subsequent studies, carried out under the same experimental conditions, demonstrated that CBD was able to operate as a Wnt/*β*-catenin pathway rescuer, inhibiting A*β*-induced tau protein hyperphosphorylation while attenuating iNOS protein expression and NO production (Esposito *et al*., 2006b). Such a wide range of

effects on pathophysiological processes implicated in neuroinflammatory/neurodegenerative diseases appears truly intriguing and encourages the clinical applicability of CBD for therapeutic use.

Its antioxidant and neuroprotective actions are presumably related in part to a potential as a scavenger of free radicals due to its structural characteristics (Hampson *et al*., 2000), although there is room for alternative mechanisms. Ruling out the possibility that transient receptor potential vanilloid type 1 channels may be involved in the suppression of reactive gliosis exerted by CBD (personal data), a potential involvement of the CB_2 receptor might be taken into account. The recently provided *in vitro* evidence that CBD can display CB_2 receptor inverse agonist properties (Thomas *et al*., 2007) might offer an explanation of the anti-neuroinflammatory effects we have shown here. In A*β* neurotoxicity, several results have related CB_2 receptors to events involved in the progression of brain damage by affecting reactive gliosis at neuroinflammatory lesion sites (Walter and Stella, 2004). Further, we have recently reported that, in a rodent model of A*β*-induced reactive gliosis, CB_2 receptors were overexpressed (van der Stelt *et al*., 2006), paralleling the changes in cannabinoid receptor expression occurring in AD brain, where, in astrocyte-associated plaques, CB_2 receptors were also found to be up-regulated (Ramirez *et al*., 2005). Interestingly, some of our recent unpublished results suggest that pharmacological interactions at glial CB_1 and CB_2receptors result in a marked and opposite regulation of reactive astroglial response, with CB_2 receptor blockade suppressing astroglial activation. These findings would imply a function for CB_2 receptors in the regulation of CBD actions and would encourage further study of how pharmacological interactions at this receptor could influence the effects of CBD. Although more research will be needed to elucidate fully the molecular mechanisms implicated in the CBD actions described in this paper, the current data showed that the early administration of CBD markedly attenuated *in vivo* the reactive gliosis induced by A*β* injury. The relevance of these results stems from the fact that a proper control of glial cell function, which is compromised by the persistence of inflammatory events, is critical to provide an environment capable of ensuring neuronal survival and function. For this reason, on the basis of the present results, CBD, a drug well tolerated in humans, may be regarded as an attractive medical alternative for the treatment of AD, because of its lack of psychoactive and cognitive effects.

Cannabidiol Reduces Aβ-Induced Neuroinflammation and Promotes Hippocampal Neurogenesis through PPARγ Involvement

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3230631/

Introduction

Despite a significant increase in the understanding of the pathogenesis of Alzheimer's disease (AD) over the past two decades, therapeutic options for treating this condition are still very disappointing.

Depending on the heterogeneity of pathways that could initiate and drive sporadic AD, effective treatment for this illness rests on the ability to develop a multi-targeted approach, as used in current practice for other multi-factorial disorders [1]. According to this assumption, both natural and synthetic cannabinoids have been proposed as novel potential pharmacological tools able to blunt underlying disease processes, thus ameliorating symptoms and slowing down illness progression [2], [3].

Unfortunately, *Cannabis* derivatives are therapeutically limited by their unwanted psychotropic effects. However, one interesting exception to this is represented by cannabidiol (CBD), the major constituent of the plant, which lacks any undesired psychomimetic action. Converging evidence provided over the last years, also by our group, demonstrated that CBD may account for a significant reduction of β amyloid (Aβ) induced neuronal cell death, due to its ability to scavenge reactive oxygen species and reduce lipid peroxidation [4]. That CBD exerts anti-inflammatory properties, impairing the inducible form of nitric oxide synthase (iNOS) and interleukin 1β (IL-1β) expression which consequently decreases their release was also proved in an *in vivo* model of AD [5]. Moreover, CBD was reported to blunt τ hyperphosphorylation in cultured neurons by reducing phosphorylation of glycogen synthase kinase 3β (GSK3β), acting as a Wnt/β-catenin pathway rescuer, although alternative mechanisms may be implicated in inducing this

effect [6]. Indeed, since GSK3β also promotes amyloid precursor protein (APP) processing, and so increasing Aβ generation [7], the CBD-mediated inhibition of GSK3β is likely to be effective in reducing the amyloid burden. Moreover, CBD was also described to protect neurons against glutamate toxicity [8], an effect occurring independently of the cannabinoid receptor 1 (CB1) signalling[9]. Despite such impressive properties and promising actions, the precise site at which CBD could exert its neuroinflammatory and neuroprotective effects is still not fully elucidated. The recently discovered ability of different cannabinoids, including CBD, to display an extra-cannabinoid receptor binding activity has been highlighted by the observation that these compounds may go nuclear to exert their activity through the interaction with peroxisome proliferator-activated receptors (PPARs) [10]. The PPARs belong to the family of nuclear hormone receptors and their activity is generally regulated by steroids and lipid metabolites. At present three different PPAR isoforms (PPARα, PPARβ, also called δ, and PPARγ) have been identified [11]; they have been reported to control the expression of genes related to lipid and glucose homeostasis and inflammatory responses [12]. A growing body of evidence suggests PPARs as drug targets for treating several dysmetabolic conditions and inflammatory degenerative diseases, as well. PPARγ is expressed in the CNS at low levels under physiological condition [13]. However, in some pathological situations, including AD, PPARγ expression, but not other isoforms, was shown to be elevated[14]. These findings suggested that PPARγ could play a role in regulating pathophysiological features of AD and established the basis for modulation of PPARγ activity in the treatment of the disease.

Therefore the present study was aimed at exploring whether CBD neuroprotective effects depend upon its activity on PPARs receptors, particularly on PPARγ isoform. To this purpose, the involvement of PPARs receptors in mediating anti-inflammatory and neuroprotective effects of CBD both *in vitro* in primary cultured astrocytes and *in vivo*, in a rat model of AD-related neuroinflammation induced by the intrahippocampal injection of fibrillar Aβ (1–42) peptide was evaluated.

Discussion

Chronic neuroinflammation implicates protracted activation of both microglial and astroglial cells, with the consequent sustained release of pro-inflammatory molecules [15], [16], that act in an autocrine way to self-perpetuate reactive gliosis and in a paracrine way to kill neighboring neurons, thus expanding the neuropathological damage. Once started, neuroinflammation promotes neuronal death, powering a vicious cycle responsible for the progression of the pathology [17]. The possibility of interfering with this detrimental cycle by molecules which can reduce reactive gliosis has been proposed as a novel rationale to develop drugs able to blunt neuronal damage and consequently slow the course of AD.

Results from the present study prove the selective involvement of PPARγ in the anti-inflammatory and neuroprotective effects of CBD here observed either *in vitro* and *in vivo*. In addition, CBD significantly promoted neurogenesis in Aβ injured rat hippocampi, much expanding its already wide spectrum of beneficial actions exerted in AD models, a non negligible effect, due to its capability to activate PPARγ.

CBD was already reported to exert a marked anti-inflammatory effect through the A2A and 5HT1A receptors [18], [19], as well as to improve brain function [20]. In addition, it has been already demonstrated that CBD markedly downregulate reactive gliosis by reducing pro-inflammatory molecules and cytokine release that strongly occurs in Aβ neurotoxicity. This activity was linked to its ability to act as a potent inhibitor of NFκB activation induced by Aβ challenge [21]. The present findings, confirming the formerly obtained results and extending our knowledge about CBD pharmacology, indicate that a selective PPARγ activation occurs upstream to CBD-mediated NFκB inhibition. Such activation appears to be responsible for a large plethora of CBD effects. Indeed, the interaction of CBD at the PPARγ site results in a profound inhibition of reactive gliosis as showed by the reduction of both GFAP and S100B protein expression together with a marked decline of pro-inflammatory molecules and cytokine release observed in Aβ challenged astrocytes.

The *in vitro* findings were replicated in *in vivo* experiments, since once again CBD treatment resulted in a profound inhibition of astrocytic activation surrounding CA1 area Aβ-injected and induced a rescue of CA1 neuronal viability in comparison to control.

Along this line, results from hippocampal homogenates fully matched with *in vitro* data previously obtained from primary cultured astrocytes. Also in this case, CBD through the activation of PPARγ provoked a marked reduction of NO, TNFα, and IL-1β release in association with a parallel decline of GFAP, S100B, and iNOS protein expression. The observation that in the hippocampus the selective

activation of PPARγ caused a decrease in p50 and p65 protein expression, further reinforces the importance of the sequence of events PPARγ activation/NFκB inhibition as responsible for the CBD anti-inflammatory effect. The PPARγ mediated inhibition of S100B induced by CBD represents a crucial step in interrupting self-perpetuation of the reactive gliosis cycle. Indeed, the over-release of this astroglial-derived neurotrophin actively exacerbates the pro-inflammatory cytokine loop fuelled by Aβ stimulation, massively accelerates amyloidogenicity by promoting cleavage of APP to Aβ and induces tau protein hyperphosphorylation, by disrupting the Wnt pathway [22]–[24].

Notably, both *in vivo* and *in vitro*, a selective involvement of PPARγ at the base of the neuroprotective and anti-gliotic effect of CBD appears peremptory, since a complete loss of any beneficial pharmacological activity of this phytocannabinoid occurs when it was co-administered with the PPARγ antagonist GW9662.

Neuroprotective effects exerted by PPARγ agonists in neuropathological conditions, including Aβ induced neuroinflammation and neurodegeneration have been largely described in the past years [25]. Besides microglial cells, emerging data indicate astrocytes and neurons as fundamental cell type targets for the beneficial role of PPARγ ligands [26]. Astrocytes represent the most abundant glial cells type in the CNS. Once these cells undergo reactive activation, they produce cytokines and other molecules involved in inflammatory response, which are thought to significantly contribute to expand brain damage. Interestingly astrocytes express the highest level of PPARγ in the CNS [27], [28], and accumulating evidence over the last decade indicate that PPARγ agonists may finely regulate their detrimental functions during a protracted activation exerting a profound anti-inflammatory and neuroprotective effects [29].

Such well-defined and highly effective beneficial activity due to PPARγ activation has recently demonstrated to functionally inactivate NFκB promoters inducing a massive down regulation of the activation of this transcription factor. Traditional PPARγ agonists like thiazolidinediones were reported to inhibit the overproduction of NO, IL-6, and TNF-α as well as the increased expression of the inducible enzymes iNOS and COX2 induced in LPS-stimulated astrocytic and microglial cultures [30]–[32]. Taken together all these findings fully match those concerning the anti-inflammatory and neuroprotective activities exhibited by CBD in this study.

AD neuroinflammation is a highly important feature that has been considered responsible for the progressive worsening of the disease. Given the tremendous complexity of AD, however, it appears to be oversimplified reasoning to consider only reactive astrogliosis and neuronal degeneration as the unique factors at the basis of the functional decline provoked by the course of the illness.

Neuropathological investigation has provided evidence that in AD brains progressive neuronal loss is not accompanied by a new neuronal replacement while alterations in neurogenesis have been reported to occur[33]. Both aspects are considered to be important in contributing to the long-term development of disease. Therefore the disease symptoms could partly be due to the impaired replacement of new hippocampal neurons from endogenous neuronal stem cells [34], [35], which is believed to promote learning and memory. Although there were some controversies over whether neurogenesis is increased or reduced in the pathogenesis of AD, later studies have confirmed deficient maturation of new neurons in AD patients [36]. As a result, an approach to enhance neurogenesis and/or maturation should be considered potential therapies for AD.

Moreover, activation of PPARγ has been reported to promote neurogenesis and agonists at these receptors regulate neuronal stem cell proliferation and differentiation as well [37]. In addition PPARγ activation promotes neurite outgrowth in mature neurons, significantly contributing to a proper neuronal connectivity in neuronal networks [38]. According to these observations, results from the current investigation demonstrate that CBD-mediated activation of PPARγ is associated with a significant neurogenic activity in the granule cell layer of the hippocampal DG. Results indicate that CBD markedly counteracts the massive reduction of neurogenesis in the DG caused by Aβ exposure towards control animals and this effect is consequential, as expected, to a selective PPARγ involvement.

It has been recently asserted that CBD could promote adult hippocampal neurogenesis by activating CB1 receptors [39]. Such an assumption was supported by the observation that the CBD neurogenic effect was lost in CB1 knock-out mice, suggesting that the pro-neurogenic action of this phytocannabinoid was clearly dependent on the interaction at the CB1 receptor, which shows a wide expression over the entire

DG, including the neuronal precursor cells. However, the observation that Δ9-tetrahydrocannabinol, a preferential agonist at CB1 receptor site, failed in the same investigation to affect hippocampal neurogenesis, tempers the notion that CB1 receptor activation and CBD neurogenetic properties are linked in a straightforward way. Since CBD exhibits negligible affinity to CB1 receptors and the majority of actions appears to be cannabinoid receptor independent, it is possible to assume that the CBD effect on neurogenesis could only involve CB1 receptor sites indirectly.

In conclusion, results of the present research demonstrate that CBD may exert protective functions through a PPARγ dependent activation, which leads to a reduction in reactive gliosis and consequently in neurodegeneration. Moreover, in the current experimental conditions this phytocannabinoid appears to stimulate neurogenesis since it increases DCX immunopositive cell proliferation rate in rat DG.

Innovative therapeutic approaches which could significantly improve AD course require new molecules that will be able to have an impact on different pathological pathways, which converge at the progressive neurological decline. CBD has shown a capability to profoundly reduce reactive astrogliosis and to guarantee both direct and indirect neuronal protection in Aβ induced neuroinflammation/neurodegeration. So far, the lack of understanding of the precise molecular mechanism involved in CBD pharmacological actions, has had limited interest and has puzzled investigators. Currently, findings of the present study throw some light on the issue, and frame CBD as a new PPARγ activator.