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A review article

Cannabinoids: A potent anti-inflammatory agent against neurodegenerative disorders

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Abstract

Cannabinoid based drugs exhibits promising results against neurodegenerative disorders such as Alzheimer's disease, Parkinson's disease and Huntington's disease in animal models and humans. Cannabinoid based drugs either acts in receptor dependent or receptor independent fashion and are known to exhibit antiepileptic, anti-nausea, anti-emetic, anti-inflammatory, anxiolytic, anti-psychotic, and anti-ischemic properties. Psychoactive and non-psychoactive cannabinoids based drugs majorly contains Δ9-THC and CBD. Activation of CB1 and CB2 receptors plays a vital role in regulating the inflammatory issues. Cannabinoid inhibits the pro-inflammatory signals, inhibits the inflammatory cytokines production, interrupts the JAK/STAT pathway and furthermore promotes the phagocytosis of Aβ and thus acts as a potent anti-inflammatory drug. The anti-inflammatory potential of these drugs has led to the testing of these drugs against other human diseases also. This review article describes the role of cannabinoids in combating the issues of neurodegenerative disorders by acting as an anti-inflammatory agent.

Keywords: Cannabinoids, neuroinflammation, neurodegeneration, neuroprotection

Introduction

Plant genus Cannabis belongs to the family Cannabaceae. Majorly three cannabis species have been described namely: *C. sativa*, *C. indica*, and *C. ruderalis*. Due to the long standing debates amongst taxonomists regarding classification of these variants into species, biochemical methods are generally used to classify cannabis variants. Cannabis possess high level of psychoactive cannabinoids and low levels of non/anti-psychoactive cannabinoid. Δ9-THC is a type of psychoactive cannabinoid on the other hand CBD falls under the category of non/anti-psychoactive cannabinoid which is generally referred as "marijuana". Cannabis which possess the high level of CBD and lower insignificant level of Δ9-THC are referred to as "industrial hemp," or "hemp."

Prominently leaves and flowering tops of cannabis plants contains cannabinoid compounds. Cannabis plant contains 489 distinct compounds belonging to 18 different chemical classes. Approximately 100 different phyto-cannabinoid compounds have been identified so far (1, 2). Cannabinoid compounds possess enormous potential to act as a therapeutic measures against various diseases. Several primary cannabinoids have been extensively studied so far namely Δ9-THC, CBD, cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV), although there are many others also (1, 3-6). Presence of different cannabinoids in cannabis plant depends on the cannabis strain, climate, soil, and techniques of cultivation. These factors are also responsible for the potential activity of cannabinoid either as a therapeutic measure or the ability to induce adverse effects (7, 8).

Delta9- THC is the prominent cannabinoid found to play a key role in physical and psychotropic effects of cannabis. All the cannabis species contains psychoactive compounds for e.g. Δ9-THC in variable amounts, *C. sativa* contains the highest concentration of Δ9-THC whereas *ruderalis* contains the least (9). On the other hand, other cannabinoids including CBD, CBN, and CBG either exhibits very little or no psychotropic properties, hence they are the prime focus of research because of their ability to act as an therapeutic measure against several deadly diseases. Δ9-THC was first isolated in 1964, and found to be a partial agonist of both CB1 and CB2 receptors, but also acts on other non-CB receptors too. CB1 receptor mediated action of Δ9-THC is found to be responsible for the psychoactive effects of cannabis, and is also thought to be mediated by to some extent by suppression of both glutamate and GABA release (10-14).

CBD was first isolated in 1963, and seems to lack psycho-activity property and do not exhibit binding affinity towards CB1 or CB2 receptors. CBD are found to be involved in interaction with several enzymes, ion channel or other receptors which are responsible for its analgesic, antiepileptic, anti-nausea, anti-emetic,

anti-inflammatory, anxiolytic, anti-psychotic, and anti-ischemic properties (10, 11, 15-18). Analgesics and anti-inflammatory activity of CBD are mediated by the inhibition of cyclooxygenase and lipoxygenase. CBD exhibits enormous potential to act as an anti-inflammatory agent. Studies conducted on animal studies have revealed that CBD exhibits hundred times more potential to act as anti-inflammatory agent in comparison to aspirin (8, 19). CBD and Δ9-THC also possess antioxidant activities, which is found to be even more than α-tocopherol and ascorbate. CBD and Δ9-THC also reduces NMDA, α-amino-3-hydroxyl-5-methyl-4-isoxazole-propionate and kainite receptor mediated neurotoxicities. (20-25). Hence CBD and Δ9-THC can be used as a potent drug to treat several neurodegenerative disorders.

Chronic neuro-inflammation is found to be a major cause of neuro degeneration in alzheimer's disease, parkinson's disease and huntington's disease. Various studies using the animal models have been carried out to study the beneficial effect of cannabinoids against inflammatory disorders. Various mouse model studies have revealed that, JWH015 a synthetic cannabinoid inhibits the pro-inflammatory signals thus acts as a potent anti-inflammatory drug. The CB2 selective agonist, JWH015 reduces the interferon-γ-induced up-regulation of CD40 thus interrupts the JAK/STAT pathway in cultured mouse microglial cell and thus suppresses the pro-inflammatory cytokines production and furthermore promotes the phagocytosis of Aβ (26). In response to ATP, intracellular Ca2 mobilization leads to the activation of microglial cells and thus induces the inflammatory response in cultured mouse glial cells. CBD in combination with the other synthetic cannabinoids WIN 55212-2 which is a mixed CB1/CB2 receptor agonist and JWH-133, a CB2 receptor selective agonist reduces the ATP induced intracellular Ca2+ concentration in N13 microglial cell lines (27). The effects of these synthetic cannabinoids WIN 55212-2 and JWH-133 can be easily reversed by CB2 antagonist, SR144528 (100 nM). Hence it can be clearly said that CBD exhibits receptor dependent activity. Additionally, pro-inflammatory cytokine IL-6 which is induced by Aβ was reduced almost sixfold by 20 mg kg−1 CBD or 0.5 mg kg−1 WIN 55212-2 *in vivo* conditions (27). In vivo studies carried out by oral administration of JWH-133 (0.2 mg kg−1 day−1 for 4 months) in transgenic APP 2576 mice shows the reduction in microglial activation, reduced COX-2 and TNF-α mRNA and reduced cortical levels of Aβ, with no impact on cognitive performance (28).

Several studies have revealed that PPARγ plays a major role in inducing anti-inflammatory action of cannabinoids. PPAR belongs to the nuclear hormone receptor family which are known to be involved in lipid and glucose metabolism, gene expression and in inducing inflammatory response. Studies conducted on cultured rat astrocytes reveals that induction of reactive gliosis on treatment with 1 mg mL−1 Aβ for 24 h can be significantly reduced by CBD in a dosage dependent manner. Activity of CBD against

inflammatory response was reduced by PPARγ antagonism by GW9662, hence it can be clearly said that the antagonism of PPARγ affects the activity of CBD against inflammatory problems in a negative manner (29). Further, the studies have been confirmed by conducting the replicative study on hippocampal fractions isolated from adult rats. When the hippocampal fractions isolated from adult rats was injected with Aβ (10 μg mL−1) to the CA1 region and further on intraperitoneal treatment with the CBD (10 mg kg−1), the similar results were obtained *in vitro* as that of the previous research conducted by Esposito *et al.* Another study conducted by Fakhfouri *et al*. (30) also reveals the relationship between cannabinoids and PPARγ in *in vivo* conditions. They also said that when Aβ is administered intrahippocampally to adult rats, a significant increment in PPARγ transcriptional activity and protein expression is seen which was further increased due to the administration of WIN 55212-2. The partial antagonism of PPARγ due to the i.c.v. administration of GW9662 reduces the beneficial effects mediated by WIN 55212-2. Above conducted studies completely supports the fact that PPARγ acts as a key mediator in inducing anti-inflammatory action of cannabinoids.

Generally in order to study the inflammation in the brain, the infusion of lipopolysaccharide into the fourth ventricle of young rats is commonly referred. Another study conducted by Marchalant *et al*. (31) reveals that administration of WIN 55212-2 (0.5 mg kg−1) injections daily significantly reduces the microglial activation in this model in the above mentioned young rat model. Natural process of aging also leads to the neuroinflammation. Cannabinoids can be used as a potent therapeutic measure to combat the issues of neuroinflammation in this context as well and thus efficiently provides neuroprotection. Another study conducted by Marchalant *et al*. (32) on 23 months aged rats, reveals that there is a significant reduction in the number of activated microglia in the hippocampus and dentate gyrus on the administration of WIN 55212-2 injections of 2 mg kg−1 i.p. for 4 weeks which would have induces the complications of neuroinflammation. They also highlighted another fact that, WIN 55212-2 on incubation with CB1 receptor antagonists SR141716A and SR144528 is unable to exhibit its anti-inflammatory action. These findings clearly indicates that the WIN 55212-2 works in a receptor dependent fashion. Treatment with WIN 55212-2 also reduces the mRNA levels of the pro-inflammatory cytokine IL-6 as well as the anti-inflammatory cytokine IL1-RA. A significant reduction in protein levels of TNF-α and IL-1β was observed along with the increment in IL1-RA (32). These findings strongly supports the role of cannabinoids in reducing the inflammatory burden during neurodegeneration at various stages. Hence, cannabinoids can be used as an effective measure to treat the complication of neurodegeneration.

Adult neurogenesis is referred to as the process in which new neurons are generated and gets integrated into the developed brain. A number of factors are found to be involved in the regulation of neurogenesis for e.g. neurotransmitter systems, inflammatory cytokines, adrenal and sex hormones and trophic factors. The production of new neurons and neuronal connections plays a pivotal role in order to sustain the normal neuronal functioning in various neurodegenerative disorders including AD and HD (33, 34). eCB system is found to be involved in the process of adult neurogenesis. DGLα and DGLβ are involved in the synthesis of endocannabinoid 2AG. DGLα and DGLβ null mice exhibits 80 and 50% reduction in 2AG synthesis respectively. These transgenic mouse were found to have impaired neurogenesis which may be due to the loss of 2AG-mediated transient suppression of GABAergic transmission at inhibitory synapses (35). Almost 50% reduction in neurogenesis in the dentate gyrus and subventricular zone has been observed in case of mice lacking CB1 receptors in comparison to the wild type (32, 36).

In response to seizure, ischaemia and excitotoxic and mechanical lesions, a significant increase in migration of neurons and proliferation of neuronal precursor cell in neurogenic regions has been observed which also indicates that they can be used as a possible contributing factor in lesioned circuit repair (37-40). The administration of CB1 receptor antagonist SR141716A reduces the proliferation of KA-induced neural progenitor cells in CB1 receptor deficient mice as well as in wild-type mice. This fact clearly indicates that the expression of basic fibroblast growth factor and epidermal growth factor is CB1-dependent (41). BDNF is said to be very essential to maintain the survival of new neurons. A significant reduction in BDNF is observed in neurodegenerative conditions for e.g. HD (42, 43). De March *et al* in their study reveals that, 2 weeks postexcitotoxic lesion in rats and the transient up-regulation of BDNF is highly related to high binding affinity and high protein expression level of CB1 receptor. On the contrary, under *in vitro* conditions BDNF (10 ng mL−1) increases the neuronal sensitivity towards the endocannabinoids 2AG and noladin ether as measured by Akt by phosphorylation (44). Activation of CB1 and CB2 receptors leads to the proliferation of neural progenitor cell which is vital for the generation and survival of new neurons (45, 41).

Conclusion

From all the evidences presented in this review, it can be clearly said that neuro- inflammation are key mediators of various neurodegenerative disorders. Neurodegenerative disorders such as AD, PD and HD are life threatening. Cannabinoids plays a miraculous role in combating the issues of neurodegeneration. Cannabinoids acts as an anti-inflammatory agent and thus efficiently inhibits the inflammatory signaling

pathways. They inhibits the pro-inflammatory signals, inhibits the inflammatory cytokines production, interrupts the JAK/STAT pathway thus acts as an effective measure to overcome the complication of neurodegeneration. Enormous potential of cannabinoids to act as an anti-inflammatory agent has led to the discovery of therapeutic measures which will help in combating the disease efficiently and will make us observe a drop in mortality rates due to complication of neurodegeneration.

Conflict of interest statement

There are no potential conflicts of interest among the authors regarding the publication of this manuscript.

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