



Cannabinoids Δ^9 -tetrahydrocannabinol and cannabidiol may be effective against methamphetamine induced mitochondrial dysfunction and inflammation by modulation of Toll-like type-4(Toll-like 4) receptors and NF- κ B signaling

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ARTICLE INFO

Keywords:

Cannabinoids
Methamphetamine
Neuro-inflammation

ABSTRACT

The neurodegeneration, neuro-inflammation and mitochondrial dysfunction which occur by methamphetamine (METH) abuse or administration are serious and motivation therapeutic approaches for inhibition of these types of neurodegeneration. As we know, METH through Toll-like receptors (TLRs), specially type 4, and NF- κ B signaling pathway causes neuro-inflammation and mitochondrial dysfunction. Neuroprotective approach for management of METH-induced neurodegeneration, inflammation and mitochondrial dysfunction, through a novel neuroprotective agent is continuously being superior to any kind of other therapeutic strategy. Therefore, the clarification, introduction and development of efficacious novel neuroprotective agent are demanded. During recent years, using new neuroprotective agent with therapeutic probability for treatment of METH-induced neuro-inflammation and mitochondrial dysfunction has been astoundingly increased. Previous studies have stated the neuroprotective and anti-inflammatory roles of cannabinoid derivate such as cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ^9 -THC) in multiple neurodegenerative events and diseases. According to literature cannabinoid derivate, by inhibition of TLR4 and activation of NF- κ B signaling pathway, exerts their anti-inflammatory and neuroprotective effects and cause mitochondrial biogenesis. Thus we hypothesized that by using cannabinoids in METH dependent subject it would provide neuroprotection against METH-induced neurodegeneration, neuro-inflammation and mitochondrial dysfunction and probably can manage sequels of METH-induced neurochemical abuses via modulation of TLR4/NF- κ B signaling pathway. In this article, we tried to discuss our hypothesis regarding the possible role of CBD and Δ^9 -THC, as a potent neuroprotective and anti-inflammatory agents, in inhibition or treatment of METH-induced neurodegeneration, neuro-inflammation and mitochondrial dysfunction through its effects on TLR4/NF- κ B signaling pathway.

Introduction

The pharmacological properties of methamphetamine, which its pharmacological properties to induce hallucinogen, makes it a potential candidate for abuse [1,2] (Fig. 1). Misuses of methamphetamine has been increased in recent years [2,3]. Studies has indicated that methamphetamine can cause neurobehavioral and neurochemical disorder in human and animal subject [4,5]. Previous studies also showed that prolonged abuse of methamphetamine can cause neurodegeneration [6]. According to previous studies some parts of METH induced neurodegeneration is modulated by mitochondrial dysfunction and

occurrence of neuro-inflammation in some area of the brain, such as the hippocampus, is responsible for its neurobehavioral sequels [6,7]. Previous molecular studies have shown that methamphetamine abuse can lead to mitochondrial dysfunction which activates oxidative stress, neuro-inflammation and apoptosis [8,9]. Also other studies demonstrated that methamphetamine abuse can induce inflammation [10,11]. Moreover other works indicates that methamphetamine induced mitochondrial dysfunction and neuro-inflammation can cause DNA fragmentation in some brain region such as hippocampus [12].

Results indicate that Toll-like receptors (TLRs) family, especially TLR4, play an important role in METH-induced mitochondrial

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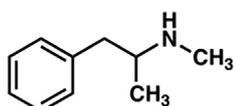


Fig. 1. Structure of methamphetamine.

dysfunction and neuro-inflammation and may be a potential gene target for therapeutics in METH-induced neuro-inflammation [13,14]. Toll-like receptors (TLRs) are type-I transmembrane glycoproteins which play a key role in mitochondrial function, innate immunity and neuro-inflammatory signaling pathway such as NF- κ B [14–16](Fig. 2). Specific roles of TLRs have been shown in CNS glia and neurons [16,17]. Experiments on neurological disease have shown that TLR4 plays a key role in the pathogenesis of a variety of neuro-inflammations expressed in microglia and neurons [18,19]. Current treatments for neurological disorder are based on regulating mitochondrial biogenesis, inflammation and neurotransmission, thus modulating the innate immune response by targeting TLRs and their signaling cascades such as NF- κ B in the CNS may represent a strong therapeutic strategy [19–22]. NF- κ B (nuclear factor kappa-light-chain-enhancer of activated B cells) is a protein complex that controls transcription of DNA, cytokine production and cell survival. Upregulation of NF- κ B in neurodegenerative event is a key point; inhibition of this protein can prohibit neurodegeneration progression and occurrence [21,23–26].

On the other way during recent years, using new neuroprotective compounds with therapeutic probability for activation of mitochondrial biogenesis and inhibition of inflammation based on down regulation or inactivation of NF- κ B signaling pathway have been amazingly increased [25–27]. Many medicinal and psychological benefits have been reported for marijuana, as medicinal plant, since it was first reported in 2,600 BCE [28]. The phytocannabinoids, cannabidiol (CBD), and delta-9-tetrahydrocannabinol (Δ^9 -THC), (Fig. 3), are the most important extracts of *cannabis sativa* subspecies. Previous studies demonstrated that CBD and Δ^9 -THC could be effective as adjunctive therapy for some neurodegenerative disease such as Parkinson's disease (PD), Alzheimer's disease (AD) and multiple sclerosis (MS), these results emphasize on neuroprotective, anti-inflammatory, and immunomodulatory benefits of CBD and Δ^9 -THC [29–32]. These agents are being extensively considered as therapeutic mediators against neurodegenerative diseases and for management of neurobehavioral disorder [31–33].

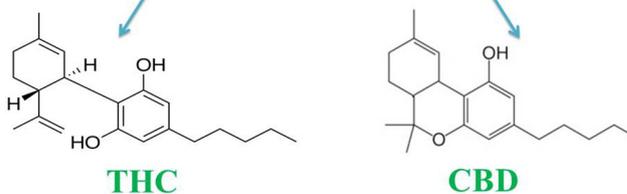
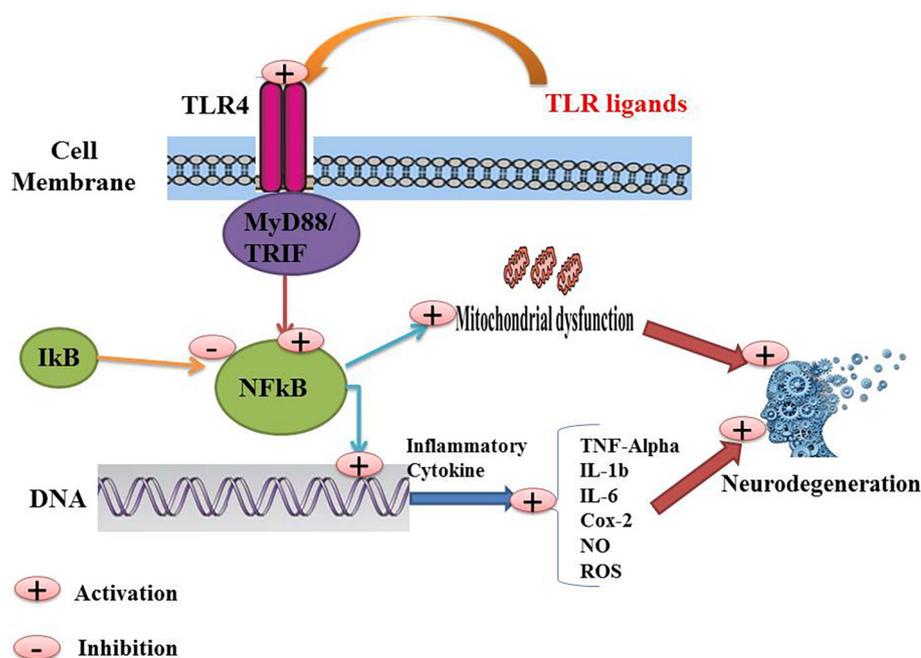


Fig. 3. Structure of cannabidiol (CBD) and delta-9-tetrahydrocannabinol (Δ^9 -THC).

Cannabinoids has possible antidepressant and cognitive enhancer properties in animal and humans subjects [34,35]. The antioxidant and anti-inflammatory behavior of Cannabinoids was approved in previous studies [35–40]. Cannabinoids treatment has shown to counteract apoptosis and reduce increase in apoptotic biomarkers in neurodegenerative event [41–43]. Both THC and CBD have been shown to exert anti-inflammatory properties, mitochondrial biogenesis and modulate immune cells function [40,44,45]. According to previous studies CBD and Δ^9 -THC are attributed to activation of the CB1 cannabinoid receptor [46].

These studies demonstrated that CBD and Δ^9 -THC can inhibit CB1 cannabinoid receptor and modulate TLRs (especially type 4) and by inhibition of this receptor, it can cause mitochondrial biogenesis and inactivation of neuro-inflammation [15,47,48]. Thus we suggested and theorized that by using phytocannabinoids, CBD and or Δ^9 -THC in METH addicted subject, it would provide neuroprotection against METH-induced mitochondrial dysfunction and neuro-inflammation. Also we hypothesized that CBD and or Δ^9 -THC, via inhibition of TLR4 and down regulation or inactivation of NF- κ B signaling pathway can inhibit METH-induced mitochondrial dysfunction, neurotoxicity and neuro-inflammation. In this article, we tried to discuss our hypothesis

Fig. 2. Role of TRL receptor in activation of NF- κ B in production of inflammatory mediators, by activation of inflammatory genes, and mitochondrial dysfunction. TLR; Toll-like receptors, TNF-Alpha; Tumor necrosis factor alpha, IL-1b; Interleukin-1b, IL-6; Interleukin-6, Cox-2; Cyclooxygenase, NO; Nitric Oxide, ROS: Reactive Oxygen Species.

regarding the possible role of CBD and or Δ^9 -THC, as a powerful neuroprotective agent, and also role of TLR4 and down regulation or inactivation of NF- κ B signaling pathway in treatment of METH-induced mitochondrial dysfunction and neuro-inflammation.

The hypothesis

During recent years, novel neuroprotective agents for treatment of METH Abuse side effects such as mitochondrial dysfunction, neurotoxicity and neuro-inflammation was amazingly increased. Rendering to stated neuroprotective properties of cannabinoids derivate, such as CBD and or Δ^9 -THC, in managements of neuro-inflammation, neurodegeneration and activation of mitochondrial biogenesis in brain areas such as hippocampus it is suggested that CBD and or Δ^9 -THC may protect hippocampal neurons against METH-induced neuro-inflammation, neurodegeneration and mitochondrial dysfunction.

Evaluation of the hypothesis

For evaluation of available information in the database regarding the role of neuroprotective properties of cannabinoid derivate such as CBD and or Δ^9 -THC, search was done in multiples data bank such as Elsevier Science Direct, Google Scholar, Web of Science, PubMed, Core Collection and Cochrane with the key words cannabinoids and or CBD and/or Δ^9 -THC plus methamphetamine. Also we did search about CBD and/or Δ^9 -THC plus methamphetamine and neuro-inflammation, neurodegeneration and mitochondrial dysfunction and role of TLR4/NF- κ B signaling pathway. The exploration was limited to English full-text articles just about CBD and/or Δ^9 -THC effects on methamphetamine induced neuro-inflammation, neurodegeneration and mitochondrial dysfunction and role of TLR4/NF- κ B signaling pathway in this manner. Apart from one paper about the role of Δ^9 -THC on methamphetamine induced neurotoxicity in glial cells in caudate-putamen, none of the articles discussed directly the anti-inflammatory role of CBD and/or Δ^9 -THC, by modulation of TLR4/NF- κ B signaling pathway, against METH induced neuro-inflammation, neurodegeneration and mitochondrial dysfunction.

Discussion

METH as a high potential psychostimulant agent exhibit neurotoxic effects [49]. Rendering to previous study, chronic administration or abuse of METH can cause neurochemical sequels which based on this changes neurobehavioral disorder will occur [1,49]. Also studies demonstrated that methamphetamine can increase lipid peroxidation level in multiple brain area such as hippocampus [50,51]. Previous findings indicated that management of lipid peroxidation play key role in inhibition of METH-induced mitochondrial dysfunction [52,53]. In consistent on METH effects on lipid peroxidation induction, some preceding works showed that methamphetamine administration can decrease mitochondrial GSH while increase GSSG level in the brain tissues. Converting of GSH to GSSG by methamphetamine, is a key change that can start and activate neurodegenerative signals in the brain [54,55], and this mechanism causes destructive effect on glutathione cycle and thus leading to neural cell death [56]. About the role of METH on antioxidant enzymes many previous data demonstrated that METH abuses can decrease antioxidant enzymes such as GPx, GR, SOD and CAT activities in brain tissues [55,57], which confirmed the reports about the role of METH abuse in reduction of antioxidant resistances and its consequences on neurodegeneration initiation [57]. It has been shown that GR is the key enzyme which modulate glutathione circle [56]. Thus, METH -induced reduction in GR activity results in destructive effect on glutathione cycle [56]. Rendering to these data, it seems that part of the damaging effects of METH is arbitrated through mitochondrial dysfunction and disturbance in oxidative and antioxidant balances. It was demonstrated that chronic administration of

METH significantly rises the level of pro-inflammatory cytokines such as IL- β and TNF- α in the hippocampus [11]. It has been proposed that methamphetamine-induced rise of pro-inflammatory cytokines is responsible for the neurodegenerative properties of METH [11,58]. In addition to oxidative stress and inflammation, preceding study confirms METH-induced cell death which is mediated by increasing apoptosis in the brain. According to these studies, METH via activation of multiple apoptotic cascades can cause DNA damages which results disturbance in normal brain function [9,12].

Toll-like receptors (TLRs) are a class of immunological pattern recognition receptors [17,22]. Toll-like receptor 4 (TLR4) is one of the most widely studied receptors in the TLR family because it is the only one that can induces NF- κ B activation, thereby mediating mitochondrial dysfunction and inflammatory and pro-inflammatory cytokine production [22,59–61]. Studies have reported that drug abuse such as heroin and cocaine can induce the activation of TLR4 on the cell surface, which in turn mediates the occurrence of mitochondrial dysfunction and inflammatory responses [62–64]. It was demonstrated that METH exposure induces the expression of TLR4, prompting NF- κ B expression and leading to increase of mitochondrial dysfunction and production of inflammatory cytokines [13]. Thus it can be suggested that by inactivation or inhibition of METH induced over expression of TLR4/NF- κ B, increase of mitochondrial dysfunction and production of inflammatory cytokines will be inhibited and possible neurodegeneration will not occur. Conferring to our hypothesis we suggested that cannabinoids derivate such CBD and/or Δ^9 -THC, by modulation of TLR4/NF- κ B signaling pathway, can be used for management of METH induced sequels such as neuro-inflammation, neurodegeneration and mitochondrial dysfunction as previous results somehow indicates that Δ^9 -THC could alter the METH-induced glial cell toxicity but role of TLR4/NF- κ B signaling pathway and changes in mitochondrial function and neuro-inflammation situation remain unclear in this manner [65]. Many previous works showed that cannabinoids derivate such as CBD and/or Δ^9 -THC, as novel generation of neuroprotective agent can recover damaged brain cell functions [29,38,66]. One study results suggest that cannabinoids system paly key role in behavioral deficits in subject with METH addiction [65]. This study indicates that Cannabinoids had controversy effects on behavioral sensitization in methamphetamine subjects [65]. Other studies demonstrated that cannabinoids antagonist can act as behavioral modulator and can be useful in management of methamphetamine withdrawal syndrome [67,68]. About the role of cannabinoids derivate such as CBD and/or Δ^9 -THC on inhibition of oxidative stress occurrences, previous studies indicates that this agent attenuates rise in lipid peroxidation in the brain [66]. Furthermore, it has been showed that cannabinoids exerts some parts of its neuroprotective effects by inhibiting the formation of lipid peroxidation in neurodegenerative event [29,37,66]. The role of cannabinoids derivate as a scavenger of free radicals is well-evident in this type of disorder [44,69]. Based on previous works CBD and/or Δ^9 -THC can activate glutathione antioxidant pathway [69]. These results have also been described that cannabinoids, by activation of glutathione circle, can be therapeutically beneficial against neurodegenerative events [69,70]. Also some other similar studies demonstrated that cannabinoids derivate can recover the activity of antioxidant enzymes such as SOD, CAT, GR and GPx and by this mechanism can increase mitochondrial biogenesis [29,36,69]. According to protective role of cannabinoids in management of oxidative stress in multiple situations we could suggest that cannabinoids can inhibit methamphetamine induced mitochondrial dysfunction in brain multiple area. On the other hand, CBD and/or Δ^9 -THC has shown to have the therapeutic efficacy for inhibition of neuroinflammation signaling cascades, thereby protecting the brain against inflammation and its damage [37,38,71]. TLR4/NF- κ B signaling pathway play key role in initiation of immune responses in the CNS and this system is critical for elimination of pathogens [27,63]. Dysregulation of this system by exogenous agents such as METH is associated with neuro-inflammation and degeneration [13],

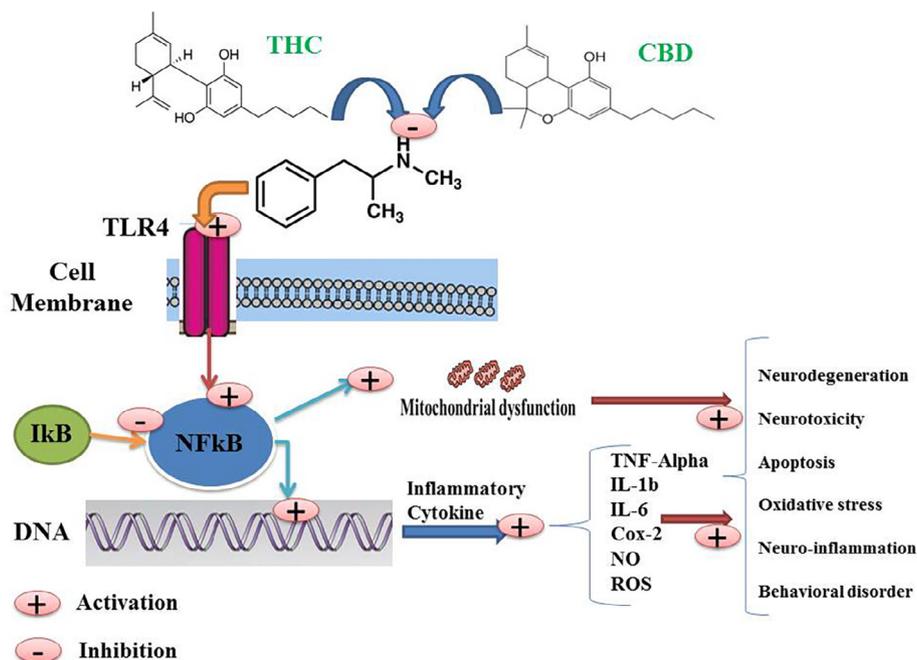


Fig. 4. Possible inhibitory role of CBD and/or Δ^9 -THC on methamphetamine (METH) induced activation in TLR4 and NF- κ B signal pathway, CBD and/or Δ^9 -THC might be act as neuroprotective agent against NF- κ B induced inflammation and mitochondrial dysfunction.

but cannabinoids are recognized as anti-inflammatory agents which inhibit this system [48]. It is clear that cannabinoid impact on the TLR system presents a pharmacological target with promising therapeutic potential for METH induced dysregulation in TLR4/NF- κ B signaling pathway. Based on this claim we can suggest that treatment of METH abuser by cannabinoids can inhibit inflammatory destructive process, by inhibition of TLR4/NF- κ B signaling pathway, and mitochondrial dysfunction which occurs in METH abuses. On the other hand, previous results demonstrated that CBD and/or Δ^9 -THC have anti-apoptotic effect. It seems that some parts of anti-apoptotic effects of this agent are modulated through inhibition of TLR4/NF- κ B signaling pathway [41]. In fact it was suggested that cannabinoids can inhibit cell death by reserve of DNA fragmentation in apoptosis process during neurodegenerative process of METH abuses [72,73]. Endocannabinoid exerts neuroprotection after traumatic brain injury, by inhibition of NF- κ B transactivation, can act as pharmacological profile and as novel candidates for treatment of traumatic brain damages [73,74]. Taken together, according to mentioned literatures reports it can be suggested that cannabinoids derivate such as CBD and/or Δ^9 -THC can be effective against METH-induced mitochondrial dysfunction, neuro-inflammation, and neurodegeneration, in both human and animal subject. Also it can be suggested that CBD and/or Δ^9 -THC can decline METH-stimulated mitochondrial and neurotoxicity via mediation (possible inhibition) of TLR4/NF- κ B signaling pathway (Fig. 4), but additional study should be intended for confirming or declining this hypothesis.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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