Therapeutic Potential of Cannabinoids in the Treatment of Neuroinflammation Associated with Parkinson's Disease

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Abstract: The cannabinoid system is represented by two principal receptor subtypes, termed CB1 and CB2, along with several endogenous ligands. In the central nervous system it is involved in several processes. CB1 receptors are mainly expressed by neurons and their activation is primarily implicated in psychotropic and motor effects of cannabinoids. CB2 receptors are expressed by glial cells and are thought to participate in regulation of neuroimmune reactions. This review aims to highlight several reported properties of cannabinoids that could be used to inhibit the adverse neuroinflammatory processes contributing to Parkinson's disease and possibly other neurodegenerative disorders. These include anti-oxidant properties of phytocannabinoids and synthetic cannabinoids as well as hypothermic and antipyretic effects. However, cannabinoids may also trigger signaling cascades leading to impaired mitochondrial enzyme activity, reduced mitochondrial biogenesis, and increased oxidative stress, all of which could contribute to neurotoxicity. Therefore, further pharmacological studies are needed to allow rational design of new cannabinoid-based drugs lacking detrimental *in vivo* effects.

Keywords: Alzheimer's disease, fever, marijuana, microglia, mitochondrial dysfunction, oxidative stress, Δ9-tetrahydrocannabinol (THC), thermoregulation.

INTRODUCTION

Parkinson's disease (PD) is characterized by the degeneration of dopaminergic neurons, most significantly in the substantia nigra. This results in impaired signaling within the basal ganglia leading to the cardinal symptoms experienced by PD patients, which include tremor at rest, bradykinesia, rigidity and postural instability. The risk of developing PD increases with age. PD affects 0.5-1% of individuals aged 65-80 years and 3-5% of those over 85 years of age [1]. The healthcare cost of PD is estimated at 23 billion dollars per annum in the United States alone [2]. Currently, the availability of effective treatment for PD is limited and there is no cure; therefore research into potential therapeutics is warranted.

1. PATHOGENESIS OF PD AND THE CANNABINOID SYSTEM

There are numerous biological pathways and several key molecules implicated in the etiology and pathogenesis of PD (for reviews see [3-5]). Environmental triggers such as exposure to pesticides were implicated initially; however, recent studies demonstrate significant contribution of genetic factors. In addition, familial forms of PD have been described caused by mutations in a number of genes including PINK-1 (phosphatase and tensin homolog-induced putative kinase-1), parkin and DJ-1, which can lead to a deficiency in mitochondrial complex I and/or aggregation of the protein α-synuclein [6, 7]. The initial causative factors of PD are linked to several pathogenetic mechanisms such as increased oxidative stress, mitochondrial dysfunction and chronic neuroinflammation. These factors likely act independently and in combination to induce the critical loss of dopaminergic neurons and development of the characteristic symptoms [8].

The cannabinoid system has long been known to play a role in the functioning of the central nervous system. It involves two principal receptors, CB1 and CB2, along with numerous endogenous ligands. For an excellent overview of the cannabinoid system the reader is directed to several recent reviews on this topic [9-12]. In general, activation of CB1 receptors on neurons is associated with inhibition of excitation and is primarily implicated in psychotropic and motor effects. Chronic activation of CB1 receptors is also linked with cell death [13-15] and reduced mitochondrial biogenesis [16]. CB2 receptors are widely expressed on immune cells, including microglia in the brain, and have been shown to inhibit inflammatory responses [10, 17-19]. For chemical structures and biochemical properties (including receptor affinities) of various endogenous, plant-derived, and synthetic cannabinoids, please refer to the comprehensive review published in a previous issue of this journal by Campillo and Paez [20].

There is evidence that the cannabinoid system is altered in PD and may play a causative, supportive, or consequential role in disease progression (reviewed by [21-23]). CB1 receptor activation has been shown to be increased in the basal ganglia of post-mortem brain tissue obtained from PD patients compared to controls [24]. Studies in rodent models of PD indicate that CB1 receptors may initially decline, followed by an increase as Parkinson-like symptoms progress [21]. These findings suggest that overactivation of

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CB1 receptors may be involved in PD pathology [21, 24]. Levels of endocannabinoids measured in cerebrospinal fluid of PD patients were also higher compared to healthy control subjects [25]. Interestingly, levels of CB2 receptors appear not to be upregulated in PD patients or animal models of PD [26].

Various phytocannabinoids isolated from cannabis plants as well as synthetic cannabinoids not only interact with the above two receptor subtypes, but are also reported to possess anti-oxidant activity [27, 28]. Thus, in addition to affecting motor function and inflammatory responses, exogenous cannabinoids may also reduce oxidative stress. As a result, administration of exogenous cannabinoids has been touted as a potential therapeutic target in neurodegenerative diseases [11, 12, 20, 29-33]. The purpose of this review is to highlight potential mechanisms and evidence for the therapeutic use of exogenous cannabinoids specific to PD. We will focus on the anti-inflammatory and anti-oxidant properties of cannabinoids in relevant models of PD. Due to the emerging role of the cannabinoid system in the regulation of mitochondrial content, we will also discuss the potential implications of cannabinoid treatment on the functions of brain mitochondria, which may be particularly relevant to the pathogenesis of PD.

2. ROLE OF NEUROINFLAMMATION IN PD

The progressive nature of PD may be attributed to neuroinflammation [4, 34]. The initial cause of neuroinflammation in PD and other neurodegenerative diseases is not well understood [4, 35], but may be related to the accumulation of α-synuclein [36-38], oxidative stress [39], or mitochondrial dysfunction [8]. Glial cells play a key role in neuroinflammation; elevated levels of activated microglia have been found in the substantia nigra of PD patient brains compared to the brains of control subjects [4, 35]. Upon activation, glial cells may release pro-inflammatory mediators, such as interleukin (IL)-1β, tumor necrosis factor (TNF)-α as well as neurotoxins, which include superoxide anion (O_2-•), glutamate [40-42], soluble Fas ligand (Fas L) [43], tissue plasminogen activator [44], cathepsin B [45, 46] and several proteases including metalloproteases [47] and chymotrypsin-like proteases [48]. Neuroinflammation in conjunction with oxidative stress and mitochondrial dysfunction may induce dopaminergic neuronal death observed in PD [4, 5, 8].

2.1. Cannabinoids as Therapeutic Anti-Inflammatory Agents in PD

Research on the anti-inflammatory properties of cannabinoids specific to PD is limited, but there is evidence that some cannabinoids, particularly CB2 receptor ligands, may reduce neuroinflammation [10, 17-19]. A series of studies using the intracerebral 6-hydroxydopamine (6-OHDA) injection as a rat model of PD also supports the finding that CB2 receptor agonists can be neuroprotective. In this model, the toxin 6-OHDA is injected into the medial forebrain bundle of rats, causing massive deterioration of catecholaminergic neurons that is accompanied by inflammation [49]. These animals then exhibit motor symptoms that are reminiscent of PD. Following 6-OHDA injection, daily treatment of rats with Δ9-tetrahydrocannabinol (Δ9-THC) or cannabidiol for 14 days reduced dopaminergic neuron loss [50]. Using similar *in vivo* methods, Garcia-Arencibia *et al.* [19] demonstrated that the synthetic CB2 receptor agonist HU-303 exhibited neuroprotective effects. Recently, transgenic rodents that overexpress the CB2 receptor were tested in this model and shown to have reduced dopaminergic neuron death and improved motor function following experimentally-induced PD [51]. Collectively, these studies indicate that, in the 6-OHDA model of PD, stimulation of CB2 receptors may reduce inflammation and protect against symptoms of PD.

Studies on isolated brain cells indicated that the positive effects of cannabinoids on neuronal survival after 6-OHDA treatment were mediated by microglia [50]. Various exogenous CB receptor agonists, including Δ9-THC and Δ8-THC, were shown to suppress the release of pro-inflammatory cytokines IL-1 and TNF-α by human THP-1 monocytic cells [17]. In addition, the non-psychotropic *Cannabis sativa* derivative cannabidiol reduced IL-1 levels in inflamed hippocampal tissue homogenates of amyloid-treated mice brains [18]. These studies indicate that cannabinoids may function to reduce inflammation by blunting the chronic microglial activation that is implicated in PD. This effect is likely mediated through the CB2 receptors on microglial cells [10, 17]. As such, selective CB2 receptor agonists are hypothesized to have a potential as anti-neuroinflammatory agents in PD [10, 20, 23, 30-32].

3. CANNABINOIDS AND THERMOREGULATION: A NOVEL HYPOTHESIS FOR THE ANTI-INFLAMMATORY EFFECTS OF CANNABINOID TREATMENT IN PD AND OTHER NEURODEGENERATIVE DISORDERS

For several centuries it has been known that cannabinoids reduce body temperature (reviewed in [52]). Studies performed during the last 50 years have demonstrated that marijuana (cannabis) as well as purified cannabinoids, such as Δ9-THC and synthetic agonists of cannabinoid receptors, cause reductions in body temperature in a number of different species of homeotherms [41, 53, 54]. Recently, it has been demonstrated that endocannabinoids participate in thermoregulation and that they can both up- and down-regulate core body temperature [55, 56]. Even though the most likely mechanisms involve CB1 receptors found in the hypothalamic thermoregulatory centre, there is some evidence that the effects of cannabinoids on body temperature may also involve CB1-independent mechanisms [52].

Cannabinoids have been shown not only to induce hypothermia in normothermic animals, but also to have antipyretic activity in febrile animals [57]. Benamar *et al.* [56] showed that a nonhypothermic dose of the cannabinoid receptor agonist WIN 55,212-2 antagonized bacterial lipopolysaccharide-induced fever in rats. This effect was blocked by a selective CB1 antagonist, and was independent of the CB2 receptors. These data confirm that cannabinoids, including Δ9-THC, could be used as antipyretic agents and suggest that endocannabinoids and CB1 receptor subtypes could be important in regulation of fever. In their study,

Benamar *et al.* [56] also demonstrated that the antipyretic effect of WIN 55,212-2 was accompanied by reduced levels of circulating IL-6, which is in line with several previous studies showing immunosuppressive effects of cannabinoids on circulating pro-inflammatory cytokines including IL-1β, IL-6 and TNF-α [57-60]. The same cytokines are also known to be the endogenous pyrogens responsible for production of fever [61], and suppression of the circulating cytokines could be one of the mechanisms responsible for the antipyretic effect of cannabinoids. An alternative mechanism for the observed antipyretic effects of cannabinoids involves direct inhibition of biosynthesis of prostaglandin E_2 [62], which is the final mediator of febrile response [61].

The hypothermic and antipyretic effects of cannabinoids could offer neuroprotection in neurodegenerative diseases, including PD, through several mechanisms. First, Δ9-THC and the synthetic CB1 agonist HU201 have been shown to be neuroprotective in animal models of middle cerebral artery occlusion; this effect was shown to be dependent on the hypothermia induced by their administration [63, 64]. Physical hypothermia has been shown to be neuroprotective in various experimental stroke models as well as in clinical setting [65, 66]. It is widely accepted that therapeutic hypothermia benefits the brain in numerous ways including decreased accumulation of excitotoxic neurotransmitters, suppression of reactive oxygen species (ROS) generation and reduction of mechanisms related to post-ischemic remodeling [67]. Therefore, multiple methods of inducing hypothermia, including surface cooling, intranasal selective hypothermia, extraluminal vascular cooling and epidural cerebral cooling, are currently being tested for efficacy and safety [68]. Therapeutic manipulation of body temperature by targeted use of cannabinoids may represent a novel means of slowing down the progression of chronic neurodegenerative diseases, which include PD and Alzheimer's disease.

Second, post mortem analysis show elevated levels of IL-1β and TNF-α in the substantia nigra of PD patients; these pro-inflammatory cytokines have been implicated in the pathogenesis of PD (reviewed in [69]). The antipyretic effects of cannabinoids could be mediated by lowering both circulating and brain levels of these cytokines thus conferring neuroprotection indirectly by inhibiting neuroinflammatory processes. Sustained upregulation of pro-inflammatory cytokines could also lead to chronically elevated temperature, which could be detrimental to neurons by enhancing neuroinflammatory processes [70]. Even though this has not been demonstrated in PD patients, a meta-analysis of data from six different studies showed a significant increase of core body temperature of Alzheimer's disease patients [71]. This phenomenon could be a direct consequence of local inflammatory reactions in the brain. If similar chronic hyperthermia is present in PD, the hypothermic and antipyretic properties of cannabinoids could be used for therapeutic purposes [72].

4. ROLE OF OXIDATIVE STRESS IN PD

Increased oxidative stress has long been associated with PD (reviewed in [73, 74]). Oxidative stress is a term used to describe an imbalance between the production and removal of ROS. The main source of cellular ROS is thought to be the mitochondria, where electrons can be transferred to molecular oxygen to produce O_2-• within the mitochondrial electron transport chain (ETC). The main source of extracellular ROS under inflammatory conditions is likely NADPH oxidase, a multi-subunit enzyme present on the cell membrane of activated immune cells that produces O_2-•. Cannabinoids have been shown to possess anti-oxidant activity *in vitro* by virtue of their phenolic side group [28]. Based on this property, anti-oxidant cannabinoid treatment has been suggested for preventing PD and other neurodegenerative disorders [19, 21, 50].

5. SOURCES OF OXIDATIVE STRESS IN PD

5.1. Mitochondrial ROS Production in PD

Mitochondria-derived ROS have been implicated in PD pathology as various studies have reported impaired mitochondrial function and increased markers of oxidative cellular damage in brains of PD patients (reviewed in [74]). In particular, reduced activity of complex I of the mitochondrial ETC and the resultant O_2-• formation have been hypothesized to play a causal and exacerbating role in PD [75]. Interestingly, α-synuclein appears to directly interact with complex I to impair its activity and increase ROS production in PD brain [76]. Furthermore, PD is modeled in cell culture and animals by administering toxins such as rotenone and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) that impair mitochondrial ETC complex I activity and increase ROS production [77, 78].

5.2. NADPH Oxidase and Microglia-Mediated Oxidative Stress

More recently, studies *in vitro* and *in vivo* have highlighted a role for O_2-• produced by microglial NADPH oxidase in promoting dopaminergic neuron damage in PD [79, 80]. In addition to direct damage, O_2-• produced by NADPH oxidase can combine with nitric oxide produced by inducible nitric oxide synthase (NOS) to generate the damaging free radical peroxynitrite and lead to characteristic nitration and nitrosylation of proteins seen in PD brain [81, 82]. Levels of NADPH oxidase are increased in the substantia nigra of post-mortem PD brain and in animal models of toxin-induced PD [79]. Upregulation of NADPH oxidase coincides with increased markers of oxidative stress and is thought to promote neuroinflammation [79]. More direct evidence that microglial NADPH oxidase plays a causal role in the development of PD comes from findings that MPTP injection into murine brain results in oxidative damage *via* enhanced microglial NADPH oxidase activation [83]. This oxidative damage is secondary to direct neuronal damage caused by MPTP, suggesting cross-talk between neuronal mitochondrial dysfunction and microglial NADPH oxidase activation [83]. Interestingly, in experimentally-induced PD models, NADPH oxidase-null mice show reduced secondary neuronal damage and have lower parkinsonism-like symptoms [79, 80]. This strongly supports a pathogenic role for extracellular free radicals produced by microglial NADPH oxidase in the progression of PD. Furthermore, inhibitors of NADPH oxidase reduce neuronal damage induced by rotenone in neuron-glial co-cultures and

primary microglial cultures from NADPH oxidase-deficient mice show reduced neurotoxicity when co-cultured with rotenone-treated neurons [80]. These findings highlight a potential role for anti-oxidants, including certain cannabinoids, in the prevention and treatment of PD.

5.3. Cannabinoids as Therapeutic Anti-Oxidants in PD

Cannabinoids contain phenolic ring moieties [28] and have been shown to exhibit anti-oxidant activity and protect against glutamate-induced neurotoxicity *in vitro* [27]. More recent studies in rodents indicate that by reducing oxidative stress exogenous cannabinoid treatment may protect against neuronal damage in diabetic neuropathy [84] and cognitive impairment induced by experimental sepsis [85]. Infusion of H^3-labelled Δ9-THC in dogs demonstrates accumulation of cannabinoids within brain mitochondria [86]. Cannabinoids have also been shown to influence activities of various mitochondrial enzymes *in vitro* [87-89]. A recent study directly assessed the influence of synthetic cannabinoids on mitochondrial ROS-induced damage caused by paraquat treatment and found protective effects [90]. Taken together, these findings support the hypothesis that exogenous cannabinoids with anti-oxidant properties may be able to influence mitochondrial ROS production in PD brain. Presumably cannabinoids could also exhibit anti-oxidant properties in the extracellular space to reduce microglial NADPH oxidase-induced neuronal damage, but this has not been directly assessed yet. A recent study in rodents with cisplatin-induced nephropathy demonstrated that the anti-oxidant cannabidiol blunted the increase in NADPH oxidase expression and lessened markers of oxidative stress, inflammation, and cell death in kidneys [91]. Whether cannabidiol might act similarly to reduce NADPH oxidase expression and limit oxidative damage within PD brain has yet to be tested.

There is evidence to support that cannabinoids may protect against PD pathology in rodent models due to their anti-oxidant properties. Using the 6-OHDA model in rats, synthetic cannabinoids with anti-oxidant properties were shown to protect against biochemical features of experimentally-induced PD [19, 50]. Cannabidiol and AM404, which demonstrate anti-oxidant activity *in vitro* and have little to no affinity for CB receptors [20], demonstrated neuroprotective effects. Although the direct effects of cannabinoids on markers of oxidative stress were not assessed, cannabinoid treatment did prevent a decline in mRNA levels of the endogenous cytosolic anti-oxidant copper-zinc superoxide dismutase following 6-OHDA injection [19]. Further direct support of a reduction in neuronal or brain oxidative stress and/or an increase in *in vivo* anti-oxidant capacity with cannabinoid therapy is therefore needed, but cannabinoids as anti-oxidants do show promise in the treatment of PD at least in cell culture and animal models.

6. POTENTIAL NEGATIVE EFFECTS OF CANNABINOIDS IN PD: INFLUENCE ON MITOCHONDRIA

There is substantial evidence that mitochondrial dysfunction is present in the brain of patients with PD [75]. There is also evidence suggesting that cannabinoids may have a negative influence on brain mitochondrial function, calling into question possible use of cannabinoids as therapies for PD. Δ9-THC treatment of rats promotes uncoupling of brain mitochondria [89] and Δ9-THC also impairs complex I activity *in vitro*, particularly in mitochondria isolated from the cerebral cortex [87]. In addition to possible direct insult to mitochondrial enzymes, cannabinoids may impair mitochondrial biogenesis; a process recently shown to be downregulated in PD brain [92].

Mitochondrial biogenesis is a complex process involving the incorporation of new proteins into existing organelles. This requires the coordinated expression of genes encoded by both the nuclear and mitochondrial genome, which are regulated by several transcription factors and co-activators (reviewed in [93]). Chief among these regulatory proteins is the transcriptional co-activator peroxisome proliferator-activated receptor γ co-activator-1 (PGC-1), which is regarded as a master regulator of mitochondrial biogenesis in various cell types [93, 94, 95].

Mitochondrial biogenesis is becoming more appreciated as a potential therapeutic target in PD for two main reasons. First, increased mitochondrial biogenesis would incorporate new mitochondrial proteins - devoid of oxidative damage - into existing organelles. This would act to replace or reduce the burden of dysfunctional mitochondria caused by oxidatively damaged mitochondrial enzymes present in PD brain [75]. Second, there is accumulating evidence that PD is associated with impaired mitochondrial biogenesis in brain [92]. Specifically, reduced expression of PGC-1 and its downstream targets are hypothesized to play a causal role in PD pathology [91]. A recent study examining a large set of post-mortem PD brain tissues using laser-capture micro-dissection of dopaminergic neurons coupled with gene-set enrichment analyses identified genes controlled by PGC-1 as being co-ordinately down-regulated in PD brain compared to healthy controls [92]. Interestingly, CB1 receptor activation inhibits [16] and antagonism promotes [96] mitochondrial biogenesis across a wide variety of cell types. This appears to occur through reduced expression of PGC-1 acting through impairment of endothelial NOS [16], which is important for maintenance of basal mitochondrial content. Thus, if similar processes occurred in neurons, cannabinoids acting through the CB1 receptor could exacerbate PD by reducing PGC-1 expression and mitochondrial biogenesis within the brain. Along with the direct effects of certain cannabinoids on brain mitochondrial function [89], these findings suggest that there is potential for cannabinoids to have a negative influence on mitochondrial bioenergetics. This should be considered if cannabinoids are to be utilized in the treatment of PD in terms of oxidative stress and mitochondrial function.

The effects of cannabinoids on mitochondrial biogenesis and function in neurons and other brain cells appear to be an area that requires further study. The negative effects of cannabinoids on PGC-1 expression and mitochondrial biogenesis are likely due to their interaction with CB1 receptors [16]; recent findings also indicate that activation of CB1 receptors increases oxidative stress in various cell types [97, 98]. Therefore, the best strategy for the treatment of PD

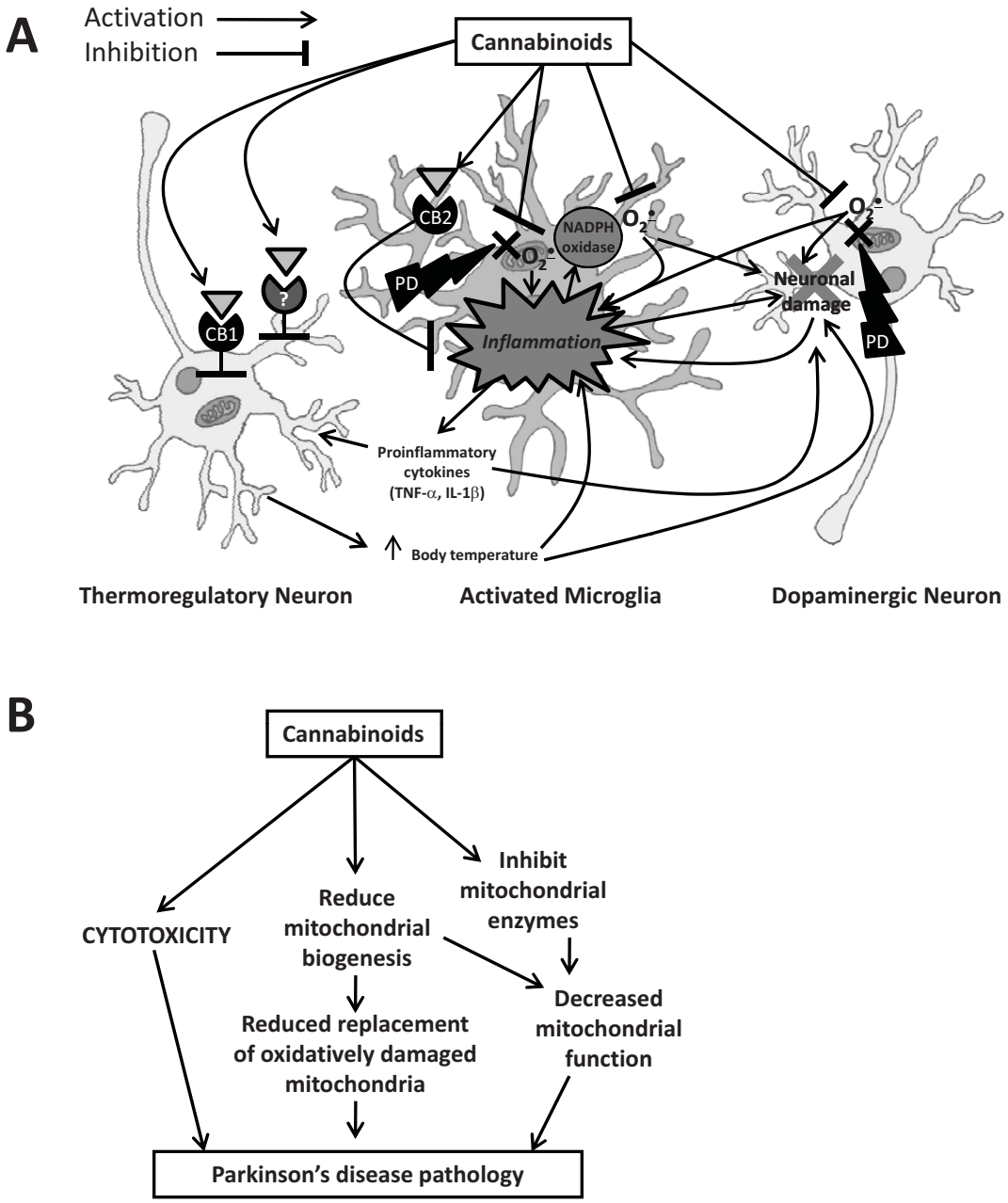

Fig. (1). A) Potential neuroprotective effects of cannabinoids in PD. Cannabinoids acting as anti-oxidants or through CB2 receptors may reduce microglia-mediated inflammatory damage to dopaminergic neurons. Reducing body temperature may represent an additional anti-inflammatory effect of cannabinoids, which may act through CB1 receptors or unknown pathways in thermoregulatory centre of the hypothalamus. **B**) Possible mitotoxic effects of cannabinoids in PD. Direct cytotoxicity, reduced mitochondrial biogenesis, or inhibition of mitochondrial enzymes may contribute to elevated oxidative damage and increased PD pathology. See text for additional details and citations. PD, Parkinson's disease.

appears to be either selective targeting of CB2 receptors [99] or use of cannabinoids with anti-oxidant properties, which do not interact with the CB1 receptor [19, 50].

7. SUMMARY AND CONCLUSIONS

There is a significant body of evidence supporting the potential therapeutic use of cannabinoids in neurodegenerative diseases. The therapeutic effects may result from the anti-oxidant properties of some cannabinoids and/or the immunomodulatory influence of those cannabinoids that are CB2 receptor agonists (Fig. **1A**). However, as noted above, cannabinoids may also trigger signaling cascades leading to neurotoxicity, impaired mitochondrial enzyme activity, reduced mitochondrial biogenesis, and increased oxidative stress (Fig. **1B**). Consequently, it is not surprising that cannabinoids have been reported to cause toxic effects in a number of animal models [12, 100-102]. There is also significant clinical evidence of detrimental effects of chronic cannabis use in humans [101, 103]. These adverse effects may be mediated by the CB1 receptors, but could also involve other receptor

types, including vanilloid receptor 1 (VR1) also known as the transient receptor potential cation channel subfamily V member 1 (TrpV1) [104].

It is apparent that the effects of drugs affecting cannabinoid signaling depend on the cell types, animal models and other experimental conditions used. Therefore, further studies of the pharmacological mechanisms of cannabinoids are needed to allow rational design of neuroprotective drugs lacking detrimental effects *in vivo*. Nevertheless, initial mechanistic studies on the potential therapeutic role of cannabinoids in PD and other neurodegenerative disorders are promising and propose an area of exciting discovery.

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ABBREVIATIONS

6-OHDA = 6-hydroxydopamine

CB1 = cannabinoid receptor type 1

CB2 = cannabinoid receptor type 2

ETC = electron transport chain

IL = interleukin

MPTP = 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

PD = Parkinson's disease

PGC-1 = peroxisome proliferator-activated receptor γ co-activator-1

ROS = reactive oxygen species

O_2-• = superoxide anion

Tfam = mitochondrial transcription factor A

THC = tetrahydrocannabinol

TNF = tumor necrosis factor

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