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Review

Melatonin and cannabinoids: mitochondrial-targeted molecules that may reduce inflammaging in neurodegenerative diseases

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Summary. Generally, the development and progression of neurodegenerative diseases are associated with advancing age, so they are usually diagnosed in late adulthood. A primary mechanism underlying the onset of neurodegenerative diseases is neuroinflammation. Based on this background, the concept of "neuroinflammaging" has emerged. In this deregulated neuroinflammatory process, a variety of immune cells participate, especially glial cells, proinflammatory cytokines, receptors, and subcellular organelles including mitochondria, which are mainly responsible for maintaining redox balance at the cellular level. Senescence and autophagic processes also play a crucial role in the neuroinflammatory disease associated with aging. Of particular interest, melatonin, cannabinoids, and the receptors of both molecules which are closely related, exert beneficial effects on the neuro-inflammatory processes that precede the onset of neurodegenerative pathologies such as Parkinson's and Alzheimer's diseases. Some of these neuroprotective effects are fundamentally related to its anti-inflammatory and antioxidative actions at the mitochondrial level due to the strategic functions of this organelle. The aim of this review is to summarize the most recent advances in the study of neuroinflammation and neurodegeneration associated with age and to consider the use of new mitochondrial therapeutic targets related to the endocannabinoid system and the pineal gland.

Key words: Melatonin, Cannabinoids, Mitochondria, Inflammaging, Neuroinflammation, Neuroprotection

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Introduction

The aging world population is expanding, and this trend presents significant challenges for the current health system. The high percentage of people affected by neurodegenerative diseases worldwide reflects this phenomenon. The existing evidence has shown that neuroinflammation plays an essential role in pathologies such as Alzheimer's and Parkinson's diseases (Menzies et al., 2017; Chamera et al., 2020; Simon et al., 2019). In this sense, a requisite amount of variables that predispose the human brain to develop these neurodegenerative pathologies come into play. These variables include genetic, environmental, and nutritional factors related to different lifestyles. Fortunately, some molecules may positively influence these processes; these agents include cannabinoids and melatonin. These molecules seem to modulate several mechanisms related to mitochondrial and inflammatory aging processes responsible for the progression of these neurodegenerative diseases.

What is inflammaging?

Aging is the leading risk factor for a variety of chronic diseases, including cancer, metabolic, cardiovascular, and neurodegenerative diseases, which lead to poor life quality and an increase in morbidity and mortality. In this regard, the new frontiers of medicine are being redirected to the pathways responsible for the aging processes (Piber et al., 2019). One of these major pathways is the imbalance of the inflammatory processes that occur due to age, i.e., inflammaging. With aging, the immune system undergoes a number of functional alterations commonly referred to as "immunosenescence" characterized by a decrease in the number of hematopoietic stem cells, phagocytes, antigen-presenting cells, etc., and a reduction in the affinity of the antibodies for their antigens (De la Fuente, 2019). Inflammaging is a progressive increase in a chronic pro-inflammatory state that develops during the aging process and is one of the most characteristic features of immunosenescence (Franceschi et al., 2000). Currently, this phenomenon is being studied actively as a common pathophysiological factor underlying several types of age-related diseases that have been described.

Although the rate of aging processes varies widely among individuals due to gender, as well as genetic and environmental background, their differential characteristics are becoming increasingly apparent. Regardless of the different theories about the causes of these unavoidable changes, there is agreement that "inflammaging" belongs to unresolved inflammatory processes in multiple organs. Under normal conditions, inflammatory responses abate when proinflammatory factors due to infectious processes or tissue lesions are eliminated; thereafter a steady, active, and well-regulated state occurs, where inflammation resolution is finally reached (Nathan and Ding, 2010). However, as a result of some still unknown factors, the inflammatory process may not achieve a stable state of tissue repair. This leads to a persistent inflammation process with the inflammatory status not being resolved. A healthy state does not arise from the absence of inflammatory stimuli; instead, the maintenance of health requires precise control of specific actions within the immune system to suppress reactions against potentially inflammatory stimuli, but that does not require a complete immune response (Nathan, 2002).

Highest mechanisms of action proposed during "inflammaging"

It is not possible to discuss inflammation without mentioning cytokines; these molecules are largely responsible for the regulation of both proinflammatory and anti-inflammatory processes and therefore, depending on their balance, they are related to a healthy or pathological aging process (De La Fuente and Miquel, 2009). Recent studies demonstrated a positive association between age and the increased levels of interleukin-6 as well as the soluble tumor necrosis factor II receptor. However, no relationship was found between age and C-reactive protein, tumor necrosis factor, or nuclear factor kappa β (Piber et al., 2019).

Another mechanism of the inflammatory aging process is the sustained damage of telomeric and mitochondrial DNA, which results from exogenous and endogenous factors. These damage constituents can induce DNA replication or translation errors, which lead to specific mutations or chromosomal rearrangements and stress reactions through various signaling pathways; these eventually contribute to cellular senescence. Many of the inflammatory mechanisms are controlled by autophagy, a process that has active participation in terms of longevity. In the aging process, the efficiency of autophagy gradually decreases, which leads to an increase in reactive oxygen species (ROS) production and, consequently, to excessive oxidative stress especially at the mitochondrial level. Deficient autophagic function in aged tissues correlates with a growing expression of specific proteins such as Beclin 1, LC3, Atg5 and Atg7, and these correlate increasingly with the appearance of diabetes mellitus, a variety of tumors including colorectal cancer, lung diseases, or neurodegenerative conditions. This makes the autophagy process one of the most critical events of interest for many biomedical scientists (Fîlfan et al., 2017).

Knowing that hematopoietic stem cells are responsible for the maintenance and replacement of immune and hematopoietic cells throughout life, some authors support the idea that inflammaging is associated with different aging processes of these stem cells (Keenan and Allan, 2019; Watanabe et al., 2019). Persistent stimulation of different signaling pathways related to inflammatory processes including mTOR, JAK/STAT, among others, leads to the release of proinflammatory cytokines which produces chronic inflammation in the microenvironment thereby preventing the regenerative capacity of stem cells (Jones and Rando, 2011).

Neuroinflammaging

Chronic low-grade neuroinflammation associated with aging (neuroinflammaging) contributes to age-related cognitive impairment (Griñan-Ferré et al., 2016; Luo et al., 2019). Although this term was only recently coined, its consequences on neuronal pathophysiology have been studied for several years (Franceschi et al., 2000; Nathan and Ding, 2010).

One of the processes that have emerged as a central regulator of aging and neurodegeneration is autophagy (Menzies et al., 2017; Pandey et al., 2020). Studies have shown that the supply of toxic molecules and organelles to lysosomes during autophagy is crucial for the health and survival of neurons. Deregulation of this process also affects innate immune functions, such as phagocytosis and inflammation, which in turn contribute to the pathophysiology of aging and neurodegenerative

diseases (Plaza-Zabala et al., 2017). Thus, autophagy affects microglial phagocytosis of apoptotic cells, the neural deposition of amyloid-β peptide, synaptic materials, and myelin residues, among others, and promotes the progression of neurodegenerative diseases associated with age, e.g., Alzheimer's disease (Simon et al., 2019).

With advancing age, the dialogue between neurons and microglia becomes less efficient, making it a greater challenge to maintain healthy brain function, as well as to achieve adequate protection of the brain in response to injury. Postoperative cognitive dysfunction, which is frequently observed in the elderly, is proof of this. Disruptions in the functionality of the blood-brain barrier (BBB) initiate neuroinflammation processes characterized by microglial activation, specifically of type A1 astrocytes, and a progressive increase in the production of inflammatory cytokines (Luo et al., 2019). These morphophysiological changes in the glial cells towards a more pro-inflammatory profile during the normal aging process precede those apparent in neurons. This process possibly explains their leading role in the underlying mechanisms of the neuroinflammaging process (Lana et al., 2016; Chamera et al., 2020; Šimić et al., 2019) (Fig. 1A).

One of the initial areas where the loss of BBB occurs is the hippocampus (Montagne et al., 2015; Lana et al., 2016; Nation et al., 2019). The increase in the permeability of the barrier is accompanied among others by a rise in the concentration of cytokines and ROS, coupled with an imbalance of brain iron metabolism and downregulation of type 2 cannabinoid receptors.

In summary, the loss of BBB integrity causes the activation of signaling pathways that lead to a more proinflammatory microglia phenotype change (Luo et al., 2019). This change contributes to an increase in neuronal apoptotic activity, which leads to an early onset of cognitive deficits characteristic of neurodegenerative pathologies (Montagne et al., 2015; Nation et al., 2019) (Fig. 1A).

Mitochondrial role of melatonin in neuroinflammation and its relation with cannabinoids

Some melatonin receptors (MT1, MT2) and cannabinoid receptors are members of the family of G protein-coupled receptors (GPCRs) (Lahuna and Jockers, 2018). It is well known these receptors are located in the cell membrane. Additionally, GPCRs have also been localized in mitochondria from brain and muscle cells (Mendizabal-Zubiaga et al., 2016; Busquets-García et al., 2016; Melser et al., 2017; Suofu et al., 2017).

The release of cytochrome C (CytC) stimulated by increased mitochondrial Ca^{2+} concentration is blocked by melatonin, resulting in neuroprotection. Melatonin not only acts in cell membrane receptors but readily penetrates cell membranes including entering the mitochondria (Huo et al., 2017; Reiter et al., 2019). Additionally, melatonin is synthesized at the mitochondrial level and acts in a paracrine manner on their mitochondrial receptors (Lahuna and Jockers, 2018). Prado et al. (2018a,b) reported that melatonin attenuates inflammation, oxidative stress, mitochondrial edema, and damage of mitochondrial membranes. It is well established that deregulated mitochondrial respiratory mechanisms are involved in neurodegenerative and inflammatory pathologies associated with oxidative stress (Manucha, 2017). Alterations in the mitochondrial electron transport chain (ETC) generate an excess of free radicals including superoxide anions which are responsible for the oxidative stress that leads to aging and death cell. Due to its antioxidant actions (Tan and Reiter, 2019), melatonin protects the mitochondria ETC from harmful stimuli by reducing the production of nitric oxide (NO) by regulating inducible and neuronal nitric oxide synthases (iNOS, nNOS) and avoiding excessive concentrations of peroxynitrite. Finally, melatonin also improves intramitochondrial antioxidative defenses by enhancing reduced glutathione (GSH) levels and the induction of glutathione peroxidase and Mn-superoxide dismutase (Mn-SOD) in the mitochondrial matrix and Cu, Zn-SOD in the intermembrane space (Hardeland, 2017; Reiter et al., 2018a,b).

The endocannabinoids, including anandamide (AEA), have relevant anti-inflammatory properties (Martín Giménez et al., 2019). The endocannabinoids regulate neuroendocrine networks via their action on cannabinoid receptors, while the melatonin rhythm synchronizes these networks. It is well-established that there is a functionally active endocannabinoid system in the pineal gland (Koch et al., 2008). Thus, the levels of the endocannabinoid AEA cause rhythmic changes in the rat pineal gland when concentrations are elevated during the light period and are reduced in the early dark period. This behavior suggests that AEA and other endocannabinoids perform time-dependent autocrine and/or paracrine functions within the pineal gland. In addition, phytocannabinoids such as delta9-tetrahydrocannabinol (Δ9-THC) attenuate melatonin synthesis in pineal cells in culture. There are also endocannabinoid system components including cannabinoid receptors and several enzymes necessary for the synthesis and degradation of cannabinoids in the pineal gland. Moreover, endocannabinoids are released from the pineal gland into the cerebrospinal fluid and bloodstream (Koch et al., 2015). Of special interest is the observation that both melatonin and cannabinoids limit the damage associated with hypoxic-ischemic encephalopathy (HIE). Melatonin particularly acts in the first stage of HIE, that is, the acute phase of ischemia/hypoxia and reperfusion/reoxygenation due to its antiapoptotic, antioxidative and antiinflammatory effects, it does this with a very good safety profile. The cannabinoids are useful in the second stage of HIE when it enters in the subacute phase; the beneficial actions relate to its regulatory function on the central nervous

system (CNS) including neurogenesis and neuroprotection mediated by hypothermia or mitochondrial protection (Hassell et al., 2015; Pac-Soo et al., 2015; Solevåg et al., 2019) (Fig. 1B) (Table 1).

Participation of cannabinoids in mitochondrial processes associated with central and peripheral inflammation: pros and cons

The cannabinoid receptors type 1 (CB1) are mainly found in the outer mitochondrial membrane and are capable of regulating the mitochondrial function (Gutiérrez-Rodríguez et al., 2018). The activation of mitochondrial CB1 impacts several mitochondrial functions related to the modulation of synaptic transmission and ATP and ROS production, calcium buffering, neurotransmitters metabolism and apoptosis, etc. (Djeungoue-Petga and Hebert-Chatelain, 2017). The activation of mitochondrial CB1 receptors triggers the intramitochondrial signaling pathway that involves G proteins, protein kinase A (PKA) and soluble adenylyl cyclase (sAC) (Ye et al., 2019). Via these receptors, cannabinoids may specifically modulate different intramitochondrial signaling pathways and respiration (Melser et al., 2017).

Of particular interest, it was observed a beneficial effect from fatty acid amide hydrolase inhibitors on hippocampal cells with mitochondrial damage produced by moderate epileptic seizures. These inhibitors increase the bioavailability of different endocannabinoids such as AEA and 2-arachidonoylglycerol by the blockade of the enzyme that metabolizes them (Mikheeva et al., 2017). Moreover, mitochondrial CB1 receptors are involved in neuroprotection during cerebral ischemia or neurons in culture. This protection is related to an inhibition of the opening of the transition pore of mitochondrial permeability (Ma et al., 2018a,b). The excitotoxic effects of quinolinic acid which participate in neurodegeneration are modified by different cannabinoids including AEA, WIN and other synthetic agonists of cannabinoid receptors. Additionally, these cannabinoids inhibited mitochondrial dysfunction and the oxidative

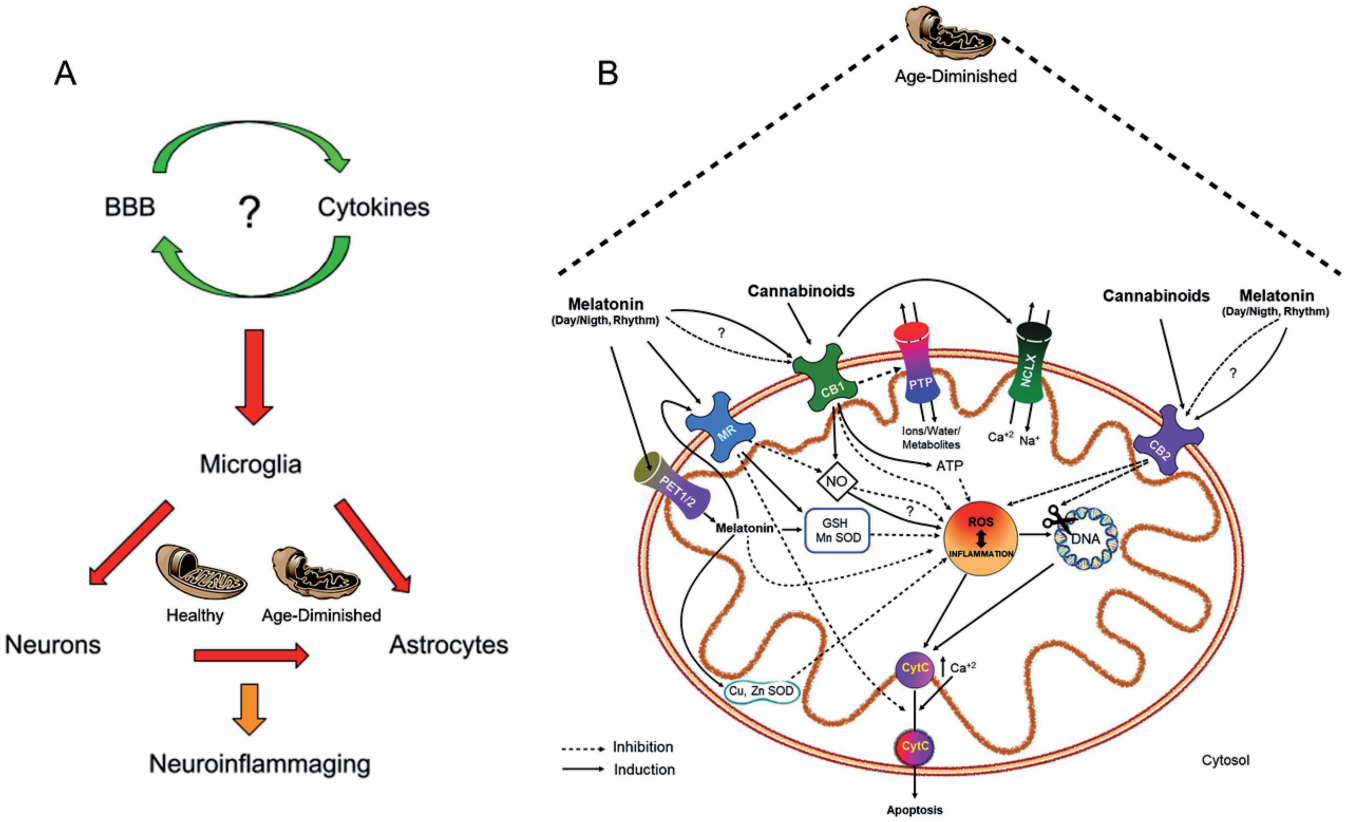

Fig. 1. Graphical overview about common signaling pathways between melatonin and cannabinoids as mitochondrial-targeted molecules that may reduce inflammaging in neurodegenerative diseases. On the left of the panel **(A)**, in the advancing age, the dialogue between neurons and microglia becomes less efficient, making it a more significant challenge to maintain healthy brain function, as well as to achieve adequate protection of the brain in response to injury. However, on the right of the panel **(B)**, it is shown a protective/ strategic mitochondrial location of melatonin/cannabinoids (and their receptors), as well as their ability to regulate oxidative stress and inflammation, which have advantages by taking advantage of signaling pathways common to both systems that interconnect, complement or enhance each other.

stress induced by quinolinic acid, suggesting a beneficial role for these molecules in the early stages of excitotoxic processes (Rangel-López et al., 2015). Furthermore, macamides, which are vegetal structural analogous of AEA, also have exhibited neuroprotective effects. These effects may be mediated by CB1 receptors and others such as the peroxisome proliferator-activated receptor-gamma (PPARγ) which regulates the mitochondrial metabolic and energetic balance and modulates neuroinflammation (Gugnani et al., 2018). Also, cannabidiol exerts neuroprotective actions through the modulation of Na^{+}-Ca^{2+} exchanger in mitochondria which regulates intracellular calcium concentrations. Via this means, cannabidiol may reduce the neurotoxicity associated with oxidative stress which occurs in different pathologies (Brenneman et al., 2018). Cannabidiol also repairs mitochondrial damage caused by iron accumulation in the brain which contributes to the development of several neurodegenerative disorders. Cannabidiol administration in a rodent model of brain iron accumulation reversed the mitochondrial epigenetic and ferritin modulation of mitochondrial DNA and re-established the succinate dehydrogenase activity impaired by iron (da Silva et al., 2018).

Cannabidiol has important antioxidant and antiinflammatory properties and its use significantly improved the damage to cardiac mitochondrial function and biogenesis induced by doxorubicin, suggesting that these effects could contribute to the beneficial properties of cannabidiol in several models of tissue injury associated to mitochondrial dysfunction, such as cardiovascular and neuroinflammatory diseases (Hao et al., 2015).

Finally, isoflurane preconditioning, through the activation of CB1 receptors, provokes mitochondrial protection and enhances the brain tolerance during cerebral ischemia, which would constitute a new neuroprotective mechanism mediated by the endocannabinoid system (Cai et al., 2017). Δ9-THC acid caused an increase in the mitochondrial mass of neuroblastoma cells and overcame the cytotoxicity caused by serum deprivation in cell models of Huntington's disease; this indicates a strong neuroprotective effect of phytocannabinoid acids on other similar neuroinflammatory and neurodegenerative pathologies (Nadal et al., 2017). Δ9-THC may act as neuroprotective cannabinoid through the reduction in oxidative stress and the enhancement of mitochondrial biogenesis in a mechanism mediated by PPARγ. The antioxidant effect at the mitochondrial level produced by Δ9-THC would be beneficial for the treatment of Parkinson's disease which is usually associated with mitochondrial dysfunction (Zeissler et al., 2016)

The neuroprotective effects of cannabinoids against oxygen-glucose-deprivation/reperfusion injury in hippocampal neurons are well documented. These benefits stem, at least in part, from the attenuation of oxidative stress, the improvement in mitochondrial bioenergetics, and the modulation of glucose metabolism (Sun et al., 2017a,b). The synthetic cannabinoid WIN induced protective effects on mitochondrial dysfunction induced by endogenous metabolites involved in severe organic acidemias which usually produce neuro-degenerative effects. These toxic agents include glutaric, propionic, 3-hydroxyglutaric and methylmalonic acids. WIN prevents the ROS production and lipid peroxidation provoked by these metabolites (Colín-González et al., 2015).

Related to cannabinoid receptors type 2 (CB2), their deletion produces mitochondrial dysfunction at the

Table 1. The main differences between melatonin and endocannabinoids activity are summarized during neurodegenerative and neuroprotective processes.

Molecules	Neuroprotective effects	Neurodegenerative effects
Melatonin	• Blockade of mitochondrial Cytochrome C release. • Attenuation of inflammation, oxidative stress, mitochondrial edema, and damage of mitochondrial membranes. • Antiapoptotic, antioxidative and anti-inflammatory effects during the first stage of hypoxic-ischemic encephalopathy.	• Not observed.
Cannabinoids	• Hypothermia and mitochondrial protection during the second phase of hypoxic-ischemic encephalopathy. • Inhibition of the opening of the transition pore of mitochondrial permeability. • Inhibition of mitochondrial dysfunction and oxidative stress-induced in the early stages of excitotoxic processes. • Modulation of Na^{+}-Ca^{2+} exchanger in mitochondria which regulates intracellular calcium concentrations. • Reparation of mitochondrial damage caused by iron accumulation in the brain. • Reduction in oxidative stress and enhancement of mitochondrial biogenesis by peroxisome proliferator-activated receptor-gamma (PPARγ). • Attenuation of oxidative stress, improvement in mitochondrial bioenergetics, and modulation of glucose metabolism during oxygen-glucose-deprivation/reperfusion injury. • Prevention of ROS production and lipid peroxidation provoked by different acid metabolites.	• Reduction in synaptic transmission, mitochondrial mobility and memory formation through the activation of mitochondrial CB1 receptors at the hippocampus level. • Increase in oxidative stress and stimulation of brain mitochondrial dysfunction related to the development of strokes in young cannabis users. • Mitochondrial signaling alterations related to the disturbed neuronal activation produced by Δ9-THC. • Inhibition of mitochondrial respiration induced by Δ9-THC.

central nervous system in mice. CB2 receptors are involved in Alzheimer's disease development; therefore, these cannabinoid receptors could be a novel drug target for the treatment of this pathology (Wang et al., 2018). Peroxisome proliferator-activated receptor-gamma coactivator-1α (PGC-1α), a transcription protein, modulates mitochondrial biogenesis. In this context, it has been found that PGC-1α mediates the antiinflammation produced by CB2 receptors agonist AM1241 in microglial cells, and this mechanism would be associated with the rise of mitochondria biogenesis at the microglial level (Ma et al., 2018a,b).

Despite the multiple beneficial effects of cannabinoids in inflammation, under certain circumstances, the mitochondrial CB1 receptor activation provokes undesirable side effects such as alteration and limitation of neuronal mitochondrial energetic activity, which is closely related to synaptic plasticity, memory, and learning. Hence, the activation of mitochondrial CB1 receptors at the hippocampus level provokes a reduction in synaptic transmission, mitochondrial mobility and memory formation through soluble-adenylyl cyclase and protein kinase A signaling pathway, processes that are regulated by mitochondrial energetic metabolism (Hebert-Chatelain et al., 2016; Djeungoue-Petga and Hebert-Chatelain, 2017; Harkany and Horvath, 2017; Mancini and Horvath, 2017). Although recent studies have shown that the consumption of cannabinoids is related to an increased probability of developing a cerebrovascular accident, it is not yet known with certainty whether this relationship responds to an over activation of CB1 receptors (Desai et al., 2019). Moreover, it is known that through CB1 receptor activation, Δ9-THC causes an increase in oxidative stress and stimulates brain mitochondrial dysfunction, which could be related to the development of strokes in young cannabis users (Wolff et al., 2015; Wolff and Jouanjus, 2017). In this regard, and as previously mentioned, it has been suggested that the endocannabinoid system plays a harmful role in ischemic stroke favoring neuroinflammation; also, the administration of CB receptor antagonists such as hinokiresinols would inhibit the migratory activity of mitochondria which reduces the migratory capability of microglia into the ischemic lesion and decreases inflammation at this site (Jalin et al., 2015). Neurons treated with Δ9-THC show mitochondrial signaling alterations that may be related to the disturbed neuronal activation observed in pathologies such as schizophrenia (Guennewig et al., 2018). Moreover, it has been proven that cannabinoids such as Δ9-THC inhibit mitochondrial respiration and, inverse agonists or antagonists of mitochondrial CB1 receptors such as AM251 have the opposite effect, causing an increase in mitochondrial respiration even in the presence of Δ9-THC, due to a competitive displacement (Fišar et al., 2014).

On the other hand, contradictory findings to those mentioned above that argue the positive effects of endocannabinoids and stroke have been discussed very recently (basic and clinical evidence). Thus, several studies in rodent models of ischemia after stroke have shown that activation of CB1/CB2 protects against acute stroke with hypothermia induction, reduction of the brain edema/infarcted tissue volume, improvement of the blood-brain barrier (BBB) disruption, neurological outcome, and cerebral microcirculatory function. However, double knockout of the CB1 and CB2 improved recovery after stroke, suggesting as yet unknown compensatory mechanisms. Of interest, patients who received palmitoylethanolamide with luteolin during rehabilitation post-stroke improve spasticity, pain, cognitive impairments, and independence in their frequent activities. In addition, Nabiximols -a specific Cannabis extract- is currently being evaluated as an add-on therapy for post-stroke spasticity (Cristino et al. 2020).

At the peripheral level, the activation of CB1 receptors in mitochondria of metabolically active renal proximal tubular cells caused mitochondrial fission and other harmful cell processes, such as an increase in cellular oxidative stress, elevated levels of lactate, mitochondrial dysfunction, and a reduction of ATP synthesis, among others (Drori et al., 2019). The evaluation of the effects of synthetic cannabinoids on human proximal tubule (HK-2) cells showed that they induce hyperpolarization of the mitochondrial membrane and increase the production of ATP and Bax translocation from the cytosol to mitochondria. These changes stimulate apoptotic cell death pathways dependent on energy mediated by the rise in the activity of caspase-3 and condensation of chromatin (Silva et al., 2018).

Cannabidiol also causes apoptosis of immune cells through a mechanism related to mitochondrial oxidative stress. Especially in monocytes, cannabidiol induced mitochondrial membrane potential depolarization, cardiolipin (one of the most important lipids of the inner mitochondrial membrane) oxidation, and CytC release; these events occur due to the opening of the mitochondrial permeability transition pore (Wu et al., 2018). This mitochondrial dysfunction may be the main cause of the cytotoxicity provoked by cannabidiol in other immune cells (Schultze et al., 2017) (Tables 1, 2).

Finally, several effects of endocannabinoids on mitochondria are independent of cannabinoid receptors and are a result of a reduction in calcium sensitivity and a perturbation in different properties of the mitochondria membrane (Singh et al., 2015) (Fig. 1B).

New approaches on cannabinoids and melatonin during neuroinflammation process: Implications of endogenous and exogenous levels

While there is still-controversial evidence between beneficial and harmful effects of the activation of cannabinoid receptors, mainly CB1 and its relationship with stroke (Desai et al., 2019), ultralow doses of Δ9-THC protects the mouse brain from inflammation-

induced cognitive damage (Fishbein-Kaminietsky et al., 2014). On the other hand, several studies have shown increased levels of endocannabinoids -as an adaptive response- in inflammatory lesions, neurotoxicity, and even Parkinson's disease models (Concannon et al., 2015; Vázquez et al., 2015; Carr et al., 2020). CB1 activation in neurons of substantia nigra pars compacta (SNpc) has a neuroprotective effect in models of Parkinson's disease (PD). At the same time, a decrease in both microglial activation and expression of pro-inflammatory cytokines and a consequent decline in production has been demonstrated (Chung et al., 2011). On the other hand, CB1 is expressed at low yet functional levels in peripheral organs involved in regulating energy homeostasis, including liver, skeletal muscle, adipose tissue, and endocrine pancreas. Consequently, the pharmaceutical industry has focused on the development of CB1 antagonists for the treatment of obesity (Cinar et al., 2020).

Regarding CB2, new studies have been developing different treatments such as cannabidivarin or highly selective cannabinoid CB2 agonist with potent immunomodulatory activity in neurodegenerative disease model (Annunziata et al., 2017; Burgaz et al., 2019; Zamberletti et al., 2019). Additionally, growing evidence suggests there is a high relationship between CB2 activity and a shift in pro-inflammatory microglial phenotype M1 to the M2 phenotype, which mediates anti-inflammatory responses (Franco and Fernández-Suarez, 2015). Besides, there is an increase in CB2 expression in recruited (Navarrete et al., 2018) and activated microglial cells within the SNpc of PD patients. Moreover, the activation of CB2 with a selective agonist HU-308 reversed LPS model of PD effects such as an increase in pro-inflammatory microglial CD68 immunostaining, iNOS activity and reduction of tyrosine hydroxylase (TH) immunostaining, all of them in the striatum neurons (Gómez-Gálvez et al., 2016). Although there is not yet a specific study that demonstrates or describes the effects of the anti-

Table 2. The table summarizes a dosage comparison -in original units- between melatonin and cannabinoids system, as well as disorders studies and described effects.

Molecule	Dose	Pathology/alteration	Effects
Melatonin	2.5 mg/kg	Kainic acid and Excitotoxicity in neurons.	Protects neurons in vitro from excitotoxicity mediated by kainate-sensitive glutamate receptors, and from oxidative stress-induced DNA damage and apoptosis.
	100 nM	Methamphetamine and neuroinflammation model in neuroblastoma human cell.	Decreases the iNOS protein expression and TNF-α mRNA levels.
	50 and 100 mg/kg	Multiple sclerosis (Cuprizone Model of Demyelination).	Improves motor behavior deficits, decreases the mean number of apoptotic cells via decreasing caspase-3 and Bax, as well as increasing Bcl-2 levels. Enhances nuclear factor-κB activation and decreases heme oxygenase-1 level.
	10 and 30μM	Neuroinflammation (oxygen-glucose-deprivation (OGD) and glutamate excitotoxicity).	Reduces lactate dehydrogenase released, reverts neuronal injury, restores the reduction of GSH, and diminishes the oxidative stress produced in the reoxygenation period.
	20 mg/kg	Acute ethanol neurotoxicity.	Upregulates endogenous antioxidant Nrf2 and heme oxygenase-1. Reverses the acute ethanol-induced elevated ROS and oxidative stress.
	10 mg/kg/day	Neuroinflammaging model.	Attenuates increase of CD11b, GFAP, IL-1β, IL-6, TNF-α, and pNFκB. Reverts down regulations of NMDA receptor subunits NR2A, and NR2B, CaMKII, and BDNF.
	50 μg/ml	Model of Alzheimer disease.	Reduces Amyloid Aβ deposits and improves behavioral deficit.
Anandamide	100 ng		Interacts with Hsp70, modulating the level of p-tau and synaptic proteins, and preventing cognitive impairments.
THC	0.002 mg/kg	Neuroinflammation.	Neuroprotective effect reduces prostaglandin-producing enzyme cyclooxygenase-2 and improves cognitive performance.
β-caryophyllene (phytocannabinoid)	50 mg/kg	Neuroinflammation and Model of Parkinson disease.	Rescues dopaminergic neurons, decreases microglia, and astrocyte activation.
HU-308, CB2R Agonist	5 mg/kg	LPS-Model of Parkinson disease.	Reverts LPS-induced elevation of CD68, reduction iNOS activity, and protects damage of TH positive neurons.
COR167, CB2-selective high affinity agonist	10^{-9} M to 10^{-5} M (Cell culture)	Multiple Sclerosis.	Shift of Th1 phenotype towards Th2 phenotype associated with slight reduction of IL-4 and IL-5, strongly reduced levels of Th17-related cytokines. Reduces in vitro migration of stimulated immunocompetent cells through human brain endothelium associated with a significant reduction of levels of several chemokines.
VCE-003.2 (amino-quinone derivative of cannabigerol)	10 and 20 mg/kg	Inflammatory model of Parkinson's disease.	Neuroprotective properties come from its activity in the γ receptor activated by peroxisome proliferator.
Cannabidivarin (Phytocannabinoid)	20 mg/kg	Model of Autism Spectrum Disorder.	Reverts social impairments, social novelty preference, short-term memory deficits, repetitive behaviors, and hyper locomotion.
Cannabidiol and cannabigerol	2.5 and 5 μM	Amyotrophic lateral sclerosis.	Anti-inflammatory, anti-oxidant, and anti-apoptotic properties.

inflammatory action of cannabinoids on non-motor symptoms (SNM) of PD, there is an improvement in cognition after treatment with cannabinoids (Sun et al., 2017a,b).

On the other hand, the anti-inflammatory potential of melatonin has been demonstrated since the 1990s, and is associated with a neuroinflammatory and neurodegenerations diseases, including Alzheimer's disease (AD) and PD (Chung and Han, 2003; Spuch et al., 2010; Cecon and Markus, 2012; Permpoonputtana and Govitrapong, 2013; Patiño et al., 2016). One of the main anti-inflammatory actions of melatonin is done through the direct inhibition of NF-ϰB expression (Franco and Markus, 2014), contributing to attenuate specific behavioral, molecular, and histopathological changes on neurodegenerative disease such as in multiple sclerosis, PD among others (Vakilzadeh et al., 2016; Lee et al., 2018; Taniguti et al., 2018). Nevertheless, in different inflammatory processes, it is necessary a temporary reduction of melatonin secretion to trigger an initial inflammatory response (Pontes et al., 2006). Therefore, in response to a first harmful stimulus on some tissue, both NF-ϰB and TNF-α inhibit melatonin night secretion by modulating the transcription of arylalkylamine-N-acetyltransferase (AA-NAT), the critical enzyme involved in the synthesis of melatonin (Fernandes et al., 2006; Muxel et al., 2012). In this sense, the NF-ϰB pathway is required to regulate a switch synthesis of melatonin from the pineal gland to immunocompetent cells; which trigger a local anti-inflammatory response (Markus et al., 2018). Additionally, another melatonin pathway of homeostasis control on these inflammatory processes is the stimulation of the sirtuin (SIRT) expression, which inhibits NF-ϰB and, therefore, results in negative regulation of pro-inflammatory cytokines such as COX2 and iNOS (Liu et al., 2017). The control of the concentrations of SIRT by melatonin is of great interest, particularly with the progression of neuroinflammatory disorders present in Alzheimer's disease, PD as well as in depression (Donmez and Outeiro, 2013; Noseda et al., 2014).

Other anti-inflammatory actions that characterize melatonin are closely related to the inhibition of TNF-α. Moreover, this inhibitory effect of TNF-α by melatonin has raised the possibility of developing new pharmacological treatments in neurodegenerative diseases because it prevents apoptosis, increases neurogenesis and induces antidepressant effects (Hoehn et al., 2016; Brymer et al., 2019). After the inflammatory process is over, melatonin production by the pineal gland is restored (Fernandes et al., 2006). However, decreased melatonin levels are observed in PD patients (Bolitho et al., 2014) and animal models of the disease (Meng et al., 2015). Advanced stages of PD are associated with reduced plasma melatonin levels (Lin et al., 2014), while long-term administration of melatonin attenuates neuroinflammaging in the mouse brain (Permpoonputtana et al., 2018) (Table 2).

Collectively, all these findings suggest the possibility of joint melatonin utilization and different types of cannabinoids, causing an essential synergistic effect. Therefore, this new paradigm could become a potential therapeutic agent, not only to control or reduce neuroinflammatory processes but also to improve psychiatric symptoms such as anxiety, depression, and cognitive impairment.

Conclusion and prospects

Melatonin and cannabinoids of both exogenous and endogenous origin have multiple relationships so far as they have been explored. The strategic mitochondrial location of its receptors and the production of these active compounds at the level of this organelle and their ability to regulate oxidative stress and inflammation have advantages by taking advantage of signaling pathways common to both systems that interconnect, complement or enhance each other (Fig. 1A,B). This opens the possibility of designing new therapies involving these molecules.

It is of special interest to enhance knowledge about the interrelationship between the endocannabinoid system and melatonin since this information would enrich the understanding of the mitochondrial mechanisms of anti-inflammation and antioxidation that may be beneficial not only in the development of new treatments oriented to neurodegenerative pathologies related to aging but also in other types of conditions associated with inflammatory and oxidative imbalances, such as hypertension, cancer, etc.

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