brain sciences

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Review

Role of Vitamin E and the Orexin System in Neuroprotection

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Abstract: Microglia are the first line of defense at the level of the central nervous system (CNS). Phenotypic change in microglia can be regulated by various factors, including the orexin system. Neuroinflammation is an inflammatory process mediated by cytokines, by the lack of interaction of specific receptors such as the OX2-OX2R complex, caused by systemic tissue damage or, more often, associated with direct damage to the CNS. Chronic activation of microglia could lead to long-term neurodegenerative diseases. This review aims to explore how tocopherol (vitamin E) and the orexin system may play a role in the prevention and treatment of microglia inflammation and, consequently, in neurodegenerative diseases thanks to its antioxidant properties. The results of animal and in vitro studies provide evidence to support the use of tocopherol for a reduction in microglia inflammation as well as a greater activation of the orexinergic system. Although there is much in vivo and in vitro evidence of vitamin E antioxidant and protective abilities, there are still conflicting results for its use as a treatment for neurodegenerative diseases that speculate that vitamin E, under certain conditions or genetic predispositions, can be pro-oxidant and harmful.

Keywords: vitamin E; neuroprotection mechanisms; neuroinflammation; central nervous system

1. Introduction

Oxidative stress refers to a condition caused by the imbalance between oxidants and antioxidants in a biological system [1]. Reactive oxygen species (ROS) are secondary metabolites and arise from various essential biological processes, such as mitochondrial respiration, yet they are potentially harmful to cells. Consequently, eukaryotic organisms present various antioxidant defenses to avoid possible damage induced by ROS. They include, for example, superoxide dismutase (SOD) and catalase, glutathione peroxidase (Gpx) and peroxyroxins, as well as non-enzymatic factors including glutathione, flavonoids and vitamins [2,3]. Oxidative stress occurs when the enzymatic defenses fail to counteract the production of ROS causing damage. The result of this imbalance is an excess of ROS or a malfunction of the antioxidant system [4]. Although oxygen is an essential building block for life and is involved in signal transduction, gene transcription and other cellular activities, it also has a deleterious effect on biomolecules when found in the form of free radicals and

ROS [1]. Another key molecule, involved in oxidative stress, is nitric oxide (NO); it regulates the relaxation and proliferation of vascular smooth muscle cells, leukocyte adhesion, angiogenesis, platelet aggregation, thrombosis, vascular tone and hemodynamics [5,6]. At physiological concentrations in the body, ROS are regulators of various physiological functions. In a chronic state of oxidative stress, reactive species can become harmful because they oxidize proteins and lipids and can damage DNA [7–9]. Reactive species may also mediate signaling, leading to microglia and primary astrocyte activation [10], resulting in a high secretion of pro-inflammatory cytokines and chemokines [11–13]. Numerous studies report that there is a significant connection between ROS and neurodegenerative diseases as well as aging [14–17], further suggesting a significant role of ROS and oxidative stress through a deleterious effect on biomolecules, in particular, on proteins. For example, in Alzheimer's Disease (AD), there is the deposition of protein aggregates, extracellular amyloid plaques (Aβ), intracellular tau (τ) or neurofibrillary tangles [18,19]; in Parkinson's Disease (PD), there is an impairment of dopaminergic neurons (DA) [20]; in amyotrophic lateral sclerosis (ALS) and Huntington Disease (HD), the mechanisms are still uncertain, but the substantia nigra is thought to have elevated levels of oxidized lipids, proteins and DNA [21–25].

2. The Orexin System

Hypocretins 1 and 2 (also known as orexin A and B, respectively, with the abbreviations OXA and OXB) are hypothalamic neurotransmitters involved in various regulatory processes. The precursor of hypocretin formation is prepro-orexin, which generates OXA and OXB through a proteolytic cleavage process [26,27]. Currently, two hypocretin receptors have been identified, the hypocretin 1 receptor (HcrtR1) and the hypocretin 2 receptor (HcrtR2) (i.e., the orexin 1/OX1R receptor and the orexin 2/OX2R receptor); these are G protein (OX1-OX2) coupled receptors [27–29]. Both OXA and OXB bind to HcrtR2 (OX2R), while OXA preferentially binds to HcrtR1 (OX1R) [27,30]. A possible imbalance of the hypocretin system can be associated with multiple diseases [31], narcolepsy [32,33] and emotional disorders, such as depression [28,34]. Furthermore, and of fundamental importance, they play an important role in neuroprotection by inhibiting oxidative stress and the inflammatory response through their type 1 and 2 receptors (OX1R and OX2R). In particular, some studies show that treatment with orexin A reduces the secretions of IL-1β, IL-6 and IL-8, as well as the production of reactive oxygen species (ROS) [35], which is why hypocretins may play a direct role in neurodegenerative diseases including PD and AD, although these mechanisms are less well known [36]. The functions of orexins prove to be different because of the multiple pathways involved, one of the main functions of orexin is neuroprotection [37]. The orexin system could lead to a decrease in oxidative stress, reducing the likelihood of neurodegenerative diseases. Currently, several in vitro studies have shown that OXA promotes both neuronal survival and neuronal protection from death caused by oxidative and hypoxic stress [38]. There are still few studies on the role of orexin on oxidative stress. Among those analyzed [39–41], we find a study by Butterick et al. [39] that shows how, in a hypothalamic cell line, the use of OXA leads to changes in cell survival following oxidative stress, particularly after H_2O_2; this study, in fact, has demonstrated that OXA is a neuroprotective molecule, partly because it reduces caspase-committed apoptosis and lipid peroxidation. There are also further studies regarding the orexin system and the reduction in oxidative stress, such as s study by Wang et al., which demonstrates how a neuroblastoma cell line reduces its oxidative stress induced by H_2O_2 following pretreatment with OXA [42]. H_2O_2 treatment is commonly used to induce oxidative stress [43]. These results indicate that orexin-A protects neuroblastoma cells from H_2O_2-induced neurotoxicity; moreover, the treatment with H_2O_2 reduces the antioxidant activity of SOD. It has been seen that this was attenuated by the pretreatment with OXA, in line with a study by Bihamta et al. conducted on cardiomyocyte cells [44]. This is believed to be thanks to the ability of OXA to activate the PI3K/MEK1/2/ERK1/2 signaling pathway and to attenuate the H_2O_2-induced increase in apoptosis and decrease

in SH-SY5Y cell viability [42]. In another set of experiments, Hah Y.S et al. showed how the level of ROS in TNF-α-induced fibroblast-like synoviocytes was found to be reduced in the presence of orexin A. It is thought to be related to the NF-κB pathway [45]. Therefore, the limiting effect of orexin A on the inflammatory response is exerted via the classic NF-κB signaling pathway. Consequently, OXA may be useful for treating neurodegenerative diseases associated with oxidative damage. However, further in vivo studies are needed to evaluate the clinical significance of OXA prior to its clinical use.

3. Orexin in Microglia Activation

Microglial cells are monocyte–macrophage cells resident in the brain. In brain tissue, under physiological conditions, microglia cells are found in a quiescent state throughout the brain parenchyma, accounting for about 15% of the cell population [46], they are responsible for maintaining brain homeostasis by ensuring and controlling neuronal tropism [47]. At the morphological level, the microglia have narrow soma and long dynamic branches, which act as sentinels of the surrounding microenvironment. After appropriate stimulation, the microglial cells continue the differentiation process, previously interrupted to maintain the state of quiescence, to become immunocompetent phagocytic cells, that is, they undergo a rapid activation assuming an amoeboid form [48]. There may be different phenotypes of activation of microglia, characterized by a multiplicity of responses such as the phagocytosis, migration, proliferation and release of bioactive molecules [49]. In particular, it is possible to distinguish the classic M1-type phenotype (classic activation) associated with the production of pro-inflammatory cytokines, and the alternative M2-type phenotype (alternative activation), associated with the production of anti-inflammatory cytokines [50,51]. In conditions of acute inflammation, M1 cells are activated by LPS/IFN-γ and increase pro-inflammatory mediators, including IL-1β, IL-6, ROS, iNOS and TNF-α, as well as IL-8 [52], inducing a state of inflammatory tolerance. The M2 activation state is induced by parasitic products or associated signals (IL-4 and IL-13) with a long-term function for resolution and repair [53–57]. In this step, cellular signaling occurs through the IL-4Rα receptor that determines the inhibition of the NF-κB signaling produced by the activation of M1. In fact, M2 macrophages facilitate the resolution of inflammation through anti-inflammatory factors (for example IL-10, IL-13, TGF-β, VEGF, EGF, Arg1) to deactivate cellular phenotypes of inflammation and restoring homeostasis [54,58–60]. Increased levels of cytokines and chemokines, prostaglandin (PG) and prostaglandins E2 (PGE2), ROS and reactive nitrogen species, produced during inflammatory responses, lead to blood–brain barrier (BBB) damage, resulting in further cell damage but also a loss of neuronal function [61]. This type of activation is observed after brain injury or infection, as well as during the development of neuropathies such as AD, stroke or demyelinating diseases such as multiple sclerosis (MS), or even in the event that there is a lack of cells mediated by communication receptors. Consequently, in response to stress, injury or absence of receptor interaction [62], microgliocytes assume a pro-inflammatory phenotype that could lead to profound neuronal damage if uncontrolled or dysregulated [61,63]. Therefore, maintaining homeostasis at the microglial level is important. The orexin system also contributes to this, in fact, recent studies affirm that they act by modulating microglia, playing a fundamental role in neuroprotection [64,65]. Therefore, a reduction in the quantity of orexins could lead to an increase in microglial dysfunction with a consequent increase in the probability of developing neurodegenerative diseases [66]. As mentioned, the orexin systems play a pivotal role in neuroprotection and neuroinflammation [67,68]. OXA and OXB regulate the homeostatic mechanisms of energy balance and metabolism [64] through the activation of two G proteins (OX1, OX2) coupled to receptors, OX1R and OX2R, respectively [68]. Recent studies in neuronal cell cultures have shown that orexin plays a role in neuroprotection [64,65] by reducing lipid peroxidation, apoptosis and neuronal inflammation [39,69–71]. The data suggest that the neuroprotective effects of orexin might be based on modulation of microglia, the brain's resident immune cells. OX2, also known as CD200, is a protein found in the first line of immune defense that belongs to the immunoglobulin

superfamily of cell surface proteins [72], which is mainly expressed by neurons [73], and interacts with a receptor, OX2R (CD200R), found mainly in microglia in the CNS [74,75]. Previous studies have indicated that OX2R activation reduces the activity of myeloid cells such as microglia and macrophages [76,77]. The interaction of OX2 with its receptor acts to suppress inflammatory responses [76,78–80]. OX2-deficient mice have been shown to exhibit a greater microglia response [73,81] and it has also been shown that CNS inflammation and neuronal degeneration are significantly exacerbated by OX2-OX2R-mediated silencing of macrophages [82]. Hence, OX2-OX2R signaling is crucial in the regulation of peripheral inflammation-induced neuroinflammation and neurodegeneration [73]. Furthermore, OX2 has been shown to play an important role not only in the control of autoimmunity and inflammation, but also in the development and spread of cancer, hypersensitivity and spontaneous fetal loss [83]. OX2-OX2R significantly inhibited the excessive activation of microglia and profoundly affected the microenvironment, including the decrease in the mRNA levels of proinflammatory factors (Il-1β, Il-6 and TNF-α) and the increase in levels mRNA of anti-inflammatory regulators (Il-4) [84]. Recent studies show that the reduction in the inflammatory response is given by the ability of the OX2/OX2R pathway to modulate the inflammatory response by controlling the activation of MAPK in vitro and in vivo [85,86]. A lack of OX2R activation in inflammatory situations produces an exaggerated microglia response, a phenomenon that has also been termed microglia priming [87]. In inflammatory situations, the absence or near absence of OX2-OX2R interaction will produce microglia priming mediated by an increase in microglial LPS/IFNγ receptors or other microglial PAMP/DAMP receptors such as Toll-like receptors (TLRs). This would also result in increased IFNγ-induced IL-6 production, increased iNOS-positive macrophages, and increased macrophage-mediated neuronal death [82]. Furthermore, according to some studies, orexin A exerts its anti-inflammatory actions with a direct effect on the signaling on hypothalamic cell line (designated mHypoA-1/2) [88]. Under normal circumstances, the pro-inflammatory agonist LPS increases the production of TNF-α in the BV-2 microglia cell line. In a study by Xiong et al. [71], the pretreatment of the BV-2 cell line with OXA before LPS stimulation led to a TNF-α reduction [89]. Alterations between OX2 and its OX2R receptor were found in both PD and AD. Precisely in this regard, studies have been carried out to study how the OX2-OX2R system determines a greater probability of the appearance of neurodegenerative diseases [67,90]. The well-established PD model that leads to the neurodegeneration of dopaminergic neurons is induced by intragastrically administered rotenone [91] or 6-hydroxydopamine (6-OHDA). It has been seen that in cases of enhanced OX2R blocking antibody neurotoxicity, causing an increase in some species of free radicals such as superoxide [92]. In addition to Parkinson's-like symptoms, a 6-OHDA injection also induced a marked activation of microglia [93]. These findings and observations from other groups over many years [94–98] have provided a significant support for the statement that activated microglia play an important role in the onset and/or progression of PD. AD is morphologically distinguished by the presence of senile plaques in the brain, mainly composed of several species of Aβ [99,100]. OX2 levels were found to be decreased in the AD brain mainly in the hippocampus and inferior temporal gyrus [90,101]. Data obtained from the brain tissues of AD patients showed that there is not only an OX2 deficiency but also an OX2R deficiency [90]. These results in several animal studies suggest that, therefore, in the brain, the enhancement of the OX2-OX2R system in AD, PD and also against other neurodegenerative diseases could be therapeutic.

4. Vitamin E and Microglia Mediated Neuroprotection

Vitamin E is a fat-soluble vitamin that plays the role of antioxidant against oxidative stress. As summarized in Table 1, the following eight isoforms of vitamin E have been identified: α-, β-, γ- and δ-tocopherol (αTOC, βTOC, γTOC and δTOC) and α-, β-, γ- and δ-tocotrienol (αT3, βT3, γT3 and δT3) [102,103]. The most studied isoform of vitamin E is α-Tocopherol (αTOC). The difference between the two major groups is the presence of an unsaturated side chain with three double bonds in the farnesyl isoprenoid tail of

TOCs and an isoprenoid tail with three double bonds in T3s [104,105]; moreover, α-, β-, γ- and δ- are differentiated by the number and position of methyl groups on the chromanol ring. Vitamin E is known for its antioxidant properties and for its role in neuroplasticity, which could explain its neuroprotective effects. An "antioxidant" is any substance that can protect against oxidative stress damage caused by free radicals. Older cells decrease their ability to prevent and reduce oxidative damage. Thus, cellular senescence is associated with increased levels of oxidants, decreased body defenses against ROS and decreased effectiveness of repair mechanisms; factors that result in increased end products of oxidative damage [104]. The neuroprotective role of vitamin E in the brain, therefore, has been linked to neurogenesis, neuronal differentiation, hippocampal synaptic function and cell signaling pathways [105]. Antioxidants act in the following two ways: they prevent neuronal death due to oxidative stress (scavenging free radicals and, thus, preventing lipid peroxidation) and reduce the activation of transcription factors [106]. Transcription factors (themselves activated by oxidative stress) [107] are involved in the control of nerve cell survival and antioxidant-induced neuroprotection, although, to date, this mechanism is not fully understood [108]. Tocopherol is the most effective fat-soluble antioxidant, breaking chain reactions initiated by free radicals between Polyunsaturated fatty acids (PUFAs) in biological membranes, i.e., counteracting free radical reactivity by donating a hydrogen atom from an intact hydroxyl group to the free radical, thus stabilizing it [109]. Each tocopherol molecule can donate two electrons [110] before being "consumed"; the tocopherol molecule is then reduced to its previous state and can then be reused. Importantly, this reduction process is most likely carried out by ascorbic acid [110], which is why there are many studies reporting the antioxidant capacity of vitamin E linked to vitamin C [111]. A combination of different antioxidants, therefore, may offer additional benefit [112] because antioxidants may together have different protective effects. The long-term treatment with vitamin E tends to increase the concentration of tocopherol in the brain over time, thus, increasing its effectiveness as an antioxidant [113]. Clinical studies suggest that vitamin E would play an important role in the prevention of neurodegenerative diseases [114] thanks to its ability to act at the level of the microglia, causing a reduction in its activation, reducing inflammation [115–117]. This review aims to explore the pivotal role that tocopherol and the orexin system may play in the prevention and treatment of microglia inflammation and, consequently, in neuro-degenerative diseases.

Table 1. Biological activities of each type of vitamin E.

Type of Vitamin E	Biological Activity	Study Model	References
α-tocopherol	Reduces astrocytosis and microglia activation	Cell rat hippocampus	Ambrogini et al. [108]
α-tocopherol	Inhibits Microglia Activation	Pheochromocytoma cell line: PC12 cells	Li et al. [118]
α-tocopheryl acetate	Increases microglial activation and RAGE expression	Astroglial cell of mice	Bialowas-McGoey et al. 2008 [119]
α-tocopherol	Blocks glutamate release	Sprague Dawley rats	Barger et al. 2007 [120]
α-tocopherol	Attenuates expression of COX-2 and the production of proinflammatory cytokines	Cell rat hippocampus	Annàhazi et al. 2007 [121]
α-tocopherol	Reduces proinflammatory cytokines and production of ROS	Primary glial cultures	Stolzing et al. [122]
α-tocopherol	Decreases lipid peroxidation and IL-6 secretion	BALB/c mice	Godbout et al., 2004 [123]
Tocotrienols	Prevents death of HT4 cells treated with glutamate	HT4 hippocampal neuronal cells	Sen et al., 2000 [124]

Table 1. *Cont.*

Type of Vitamin E	Biological Activity	Study Model	References
δ-tocotrienol	Reduces NO production and IL-1β expression, inhibits PGE2 expression	BV2 microglia cells	Tan et al., 2020 [125]
α-, γ- and δ-tocotrienol	Reduce NO release	BV2 microglia cells	Tan et al., 2011 [126]
α-tocopherol	Attenuates COX-2 protein synthesis	BV2 microglia cells	Egger et al. [127]
γ-Tocopherol	Inhibits cyclooxygenase activity and nitrite accumulation	Murine RAW264.7 macrophages	Jiang Q et al., 2000 [128]

The neuroprotective roles of vitamin E have been well documented in both in vivo and in vitro studies [113,116–118]. As antioxidants, tocopherols and tocotrienols protect tissue lipids from free radicals by reducing chemical species such as peroxyl, hydroxyl and superoxide radicals and singlet oxygen. Vitamin E has often been referred to as nature's best chain antioxidant. Typically, one molecule of the vitamin protects about 100 membrane phospholipids [129]. In vivo, vitamin E and other endogenous antioxidants work in concert or synergistically by maintaining a reduced environment [130]. The effects of vitamin E on microglial cells have been studied in the short term, most studies, in line with the idea that microglial activation is a harmful process, have shown that vitamin E suppresses inflammatory activation of microglia, thus providing some neuroprotection [115,131]. Recent studies highlight how vitamin E is able to improve the various vital functions of N9 microglial cells; this includes the enhancement of protein turnover, the regulation of oxidative activity, the amount of proinflammatory agents and the absorption and degradation of extracellular protein material [132–134]. These effects could be explained not only by pure antioxidant effects [135], but also by the role of vitamin E as a hormone-like substrate, as proposed by Azzi et al. [136]. As regards the various isoforms at the level of the central nervous system, alpha tocopherol is the most biologically active form; in fact, a-tocopherol reduces the radicals of intracellular peroxide induced by stimulation with LPS at the level of the microglia [137]. As far as other isoforms are concerned, for example, tocotrienols may offer a greater bioavailability than tocopherols because their unsaturated hydrocarbon tails allow for better penetration into fatty tissue such as the brain [138]. A drastic decrease in ROS production by α-tocopherol has already been demonstrated in macrophages and is related to the inhibition of protein kinase C (PKC) [139]. The inhibition of PKC leads to the inhibition of NADPH-oxidase assembly [140] and, thus, reduces the production of superoxide. α-tocotrienol protects neurons from a glutamate-induced death better than γ-tocotrienol [141]. Interestingly, this effect is not related to the differential uptake of δ-tocotrienols in cells: γ-tocotrienols are absorbed more efficiently by neurons than α-tocotrienol [142]. To directly show the involvement of vitamin E in neuroprotection through the modulation of microglial responses, several papers have treated microglia cells with vitamin E alone, or with LPS alone, or pre-treated with vitamin E and then stimulated with LPS [115], the most commonly used pro-inflammatory stimulus for microglia, both in vitro and in vivo. Various studies show that vitamin E significantly suppressed LPS-induced microglia activation by decreasing the associated NO production and induction of IL-1α, TNF-α and iNOS expression. Indeed, Li et al. showed that incubating cells with 50 μM of vitamin E for 24 h significantly inhibited LPS-induced NO production (68%) and also reduced the expression of IL-1α (89%), TNF -α (32%) and iNOS (55%) [118]. More specifically, it was seen that the δ-tocotrienol taken up by BV2 microglia was 71% retained in BV2 cells even 24 h after its removal. The inhibitory effects of δ-tocotrienol on NO production by BV2 microglia could be partly attributable to δ-tocotrienol retention, as inhibition continued 48 h after stimulation with LPS [143]. Indeed, it showed that although various isoforms of tocotrienol at various concentrations were able to reduce the NO produced by BV2, δ

-tocotrienol has the most potent effect, reducing NO levels by approximately 50%, even after 48 h [138]. Some studies have reported that vitamin E reduces the expression of iNOS, on human monocytic cells [144]. Indeed, vitamin E inhibits the phosphorylation of p38 MAPK and the activity of NFκB [115]. The vitamin E-induced inhibition of microglial responses after stimulation with LPS is, therefore, linked to the suppression of activation of p38 MAPK and NFκB, both of which regulate cytokine and iNOS expression [115]. In addition, vitamin E has also been reported to interact with the cyclooxygenase-2 (COX-2) signaling pathway, which is linked to pro-inflammatory signals [145] in BV2 cells. In this regard, several studies, including seminal observations from the Ames laboratory [146,147], suggest that c-tocopherol possesses significant anti-inflammatory activities that are distinct from its classical free radical defense action. Both c-tocopherol and δ-tocotrienol are more potent than a-tocopherol in inhibiting the catalytic function of Cyclooxygenase (COX) in BV2 cells [146]. COX, particularly inducible COX-2, are key inflammatory enzymes that mediate the conversion of arachidonic acid to prostaglandin E2 (PGE2) [148]. Finally, among the protective effects, a recent publication demonstrated that δ-tocotrienol is able to inhibit inflammation activation and subsequent IL-1β production in iJ774 macrophages [117]. The production of IL-1b, a key cytokine that mediates the inflammatory response, was found to be significantly reduced in vitamin E-treated microglia after 7 days in vitro, confirming the results of previous studies [115,131]. These findings indicate that antioxidants can be used to mitigate cytokine expression in the brain and protect against damage due to microglia activation. Regarding the ability of tocopherol to modulate the cell signaling pathways, in vitro and in vivo models have shown that vitamin E lowers the inflammatory responses that induce activation of microglia [115,149]. The chronic activation of microglia probably plays an important role in neurodegenerative disorders related to oxidative stress such as PD, AD [150,151] and ALS [115,152]. Vitamin E would, thus, suppress the harmful activation of microglia, thus offering possible neuroprotection [131]. Despite this, there are some studies that claim that antioxidants and their radicals often undergo other side reactions that can be classified as pro-oxidants [153,154]. One of the mechanisms hypothesized by Miller et al. [150] is that vitamin E supplementation has a pro-oxidant effect. There is a potential for vitamin E compounds to act as pro-oxidants, particularly the tocopheroxyl radical [155]. When the concentration of the tocopheroxyl radical is high enough, several undesirable side reactions can occur, which, in turn, can initiate a chain reaction that increases lipid peroxidation. In suspensions of the low-density lipoproteins isolated from blood, vitamin E can accelerate the peroxidation of polyunsaturated fatty acids [156]. The pro-oxidant radicals of vitamin E analogues caused intracellular LPO, GSH oxidation and cytotoxicity, which were prevented by an antioxidant [157]. A pro-oxidant effect of high-dose vitamin E may explain the increased mortality observed in adults taking high-dose vitamin E supplements for more than one year [150]. This suggests that the current recommendations for the maximum vitamin E dosage of 1000 mg/day of any form of α-tocopherol supplement (corresponding to synthetic vitamin E 1100 IU/day or natural vitamin E 1500 IU/day) should be revised in light of the new data [158].

5. Vitamin E in the Orexin System

There is still little evidence for this concept, but several studies correlate vitamin E with the hypocretin system. For example, a work conducted by Sanita Masoudi et al. studies the effect of an AS03 adjuvanted influenza vaccine (Pandemrix) against H1N1 swine flu. ASO3, a squalene-based immunological adjuvant used in various vaccine products, also contains α-tocopherol [155]. It has been hypothesized that α-tocopherol, through Nrf2 activation in neuronal cells, affects hypocretin expression and turnover. Factor 2, related to nuclear erythroid factor 2 (NRF2), is a transcription factor [159]. Nrf2 triggers the expression of cytoprotective genes, i.e., the active catalytic subunits of the constitutive proteasome, by binding to the antioxidant response element (ARE) [160]. Activating this pathway protects cells from oxidative stress-induced cell death. Increased oxidative stress leads to the death of neuronal cells during the pathogenesis of various chronic

neurodegenerative diseases, such as AD, PD, HD and amyotrophic lateral sclerosis [161]. It was found that hypocretin also has an ARE site in its promoter region and could, therefore, be activated in a Nrf2-dependent manner [162]. It has been observed that the α-tocopherol AS03 component activates Nrf2 in neuronal cells that leads, on the one hand, to a greater expression of hypocretin with the consequent turnover of hypocretin and the formation of many hypocretin-specific peptides in the cells [162]. This could be achieved in two ways. On the other hand, α-tocopherol can freely cross the blood–brain barrier by increasing the amount of hypocretin with a consequent increase in the level of the educt. Moreover, α-tocopherol could influence the turnover of hypocretin resulting in high hypocretin fragments (the product). This underlines the potential of α-tocopherol to impart the increased formation of hypocretin fragments. This indicates that α-tocopherol has the potential to increase the amount of specific hypocretin fragments by increasing the expression of hypocretin and, in parallel, increasing the turnover of de novo synthesized hypocretin. However, in cases of a particular genetic predisposition, the use of vitamin E could be associated with an increase in narcolepsy [162]. Narcolepsy is closely associated with a specific human leukocyte antigen (HLA) allele. Of patients with narcolepsy, 90–100% carry HLA-DQ0602, a heterodimer encoded by DQA1 * 0102 (α chain) and DQB1 * 0602 (β chain) [159,160]. Due to this high association with HLA-DQ0602, narcolepsy is thought to be caused by an autoimmune-mediated process [161,162]. However, it is assumed that T cell mediated autoimmunity affects hypocretin neurons and could lead to the loss of hypocretin and, thus, to the development of narcolepsy [163,164]. In cases of genetic predisposition (DQB1 * 602), the hypocretin specific peptides/fragments are presented with greater affinity to the HLA subtype DQB1 * 602 on the cell surface and recognized by the immune system as foreign, which ultimately leads to the destruction of the respective cells. However, tocopherol by itself is not considered inductive to narcolepsy. It must be considered as an important factor in a multifactorial process, such as the interaction between genetic predisposition (DQB1 * 602), and the abrupt increase in the concentration of tocopherol [155].

As summarized in Figure 1, orexins act, at the neuronal level, on OX2, a G protein coupled to the OX2R receptor, located at the level of the microglia. A possible imbalance of the hypocretin system can be associated with the absence of the interaction between OX2 and its OX2R receptor, which causes the microglia to trigger a proinflammatory M1 phenotype, with the consequent formation of interleukins, cytokines and ROS typical of an inflammatory response, which could lead to an increased likelihood of developing neuro-degenerative diseases. However, a correct interaction between the G protein and its receptor, mediated by orexins, determines an anti-inflammatory response of the microglia towards an M2 state and the production of secondary typical metabolites, providing neuroprotection. We have seen how the use of vitamin E can act directly both at the microglia level, causing a shift from the M1 state to the M2 state, but also at the level of the orexinergic system [160–165]. Despite the few studies published to date, it is hypothesized that vitamin E is involved in the activation of the NRF2/ARE pathway, which appears to be linked to the orexin system, causing an increase in its turnover and formation, thus providing greater neuroprotection.

6. Conclusions and Future Scenarios

This mini review provides further support for the potential protective effects of vitamin E on neuroinflammation, the orexin system and its correlation with neurodegenerative diseases. Therefore, vitamin E could help reduce the chances of developing neurodegenerative diseases thanks to its fundamental role on microglia and its correlation with the orexin system. Further studies need to be conducted to better understand the mechanisms involved in the neuroprotective role of vitamin E and the benefit of its integration in our diet.
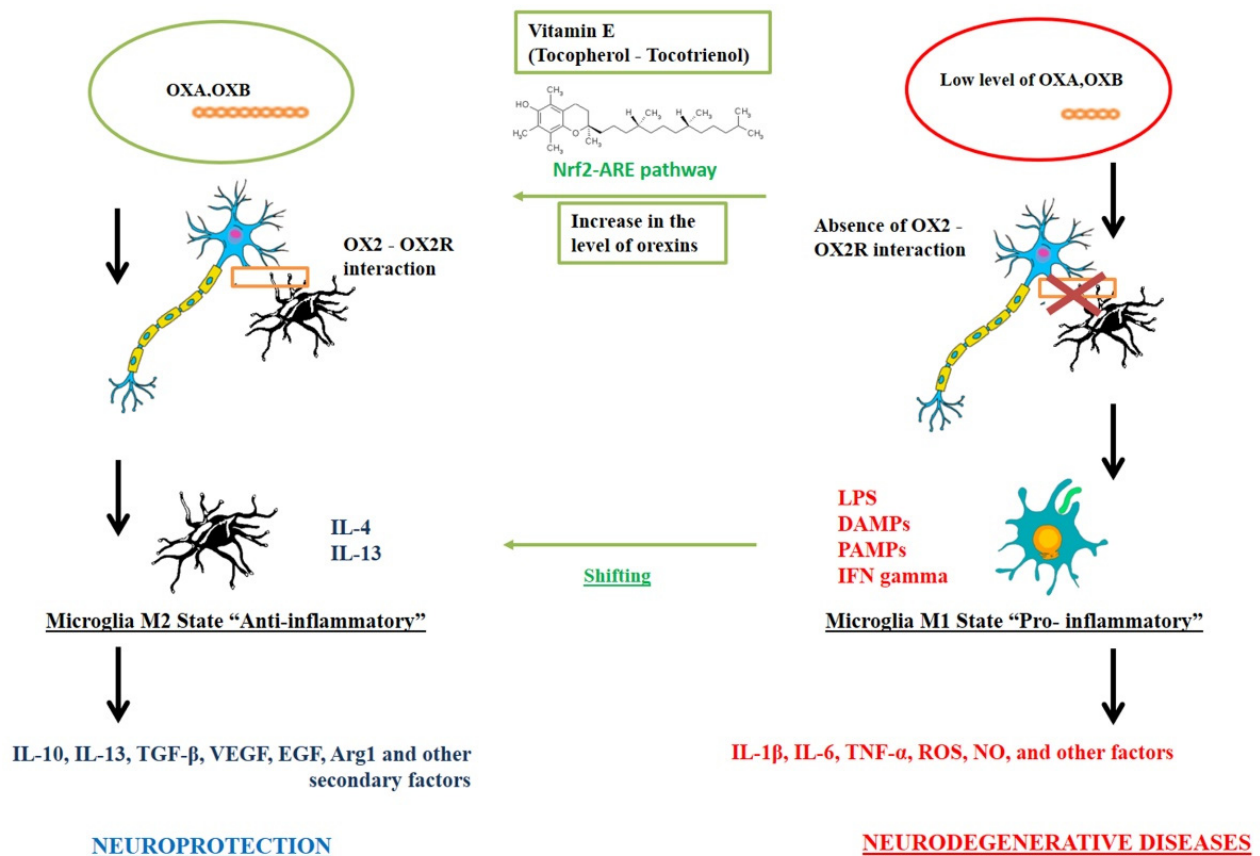
Figure 1. Role of vitamin E on the orexinergic system for neuroprotection.

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