European Journal of Pharmacology 919 (2022) 174800

Contents lists available at ScienceDirect

European Journal of Pharmacology

journal homepage: www.elsevier.com/locate/ejphar

Repositioning and development of new treatments for neurodegenerative diseases: Focus on neuroinflammation

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ARTICLE INFO

Keywords:
Alzheimer
Parkinson
Immunomodulators
Statins
Antidiabetics
Non-steroidal anti-inflammatory drugs

ABSTRACT

Neurodegenerative disorders, such as Alzheimer's and Parkinson's disease, are characterized by the progressive loss of neuronal cells, resulting in different clinical symptoms according to the affected brain region. Although there are drugs available for the treatment of these diseases, they present relatively low efficacy and are not capable of modifying the course of the disease or stopping its progression. In the field of drug development, drug repurposing could be an interesting strategy to search new therapeutic options against neurodegenerative diseases, since it involves lower costs and time for development. In this review, we discuss the search of new treatments for Alzheimer's and Parkinson's disease through drug repurposing. A focus was given to drugs that modulate neuroinflammation, since it represents a common point among neurodegenerative diseases and has been explored as a target for drug action.

1. Introduction

The increase in life expectancy in the world has been associated with a higher prevalence of neurodegenerative diseases, including Alzheimer's (AD) and Parkinson's Diseases (PD). Together, these diseases currently affect around 50 million people worldwide (GBD 2016 Disease and Injury Incidence and Prevalence Collaborators, 2017). They are characterized by progressive neuronal death in the brain, which produce different symptoms according to the location of vulnerable neurons (Fu et al., 2018). AD is associated with the accumulation of amyloid-beta (Aβ) and phosphorylated Tau (p-Tau), leading to cognitive dysfunction, including learning and memory impairment, and is the major cause of dementia (Scheltens et al., 2021). On the other hand, PD is associated with the loss of dopaminergic neurons in the substantia nigra, which leads to motor symptoms, including bradykinesia, muscular rigidity, rest tremor, and postural and gait impairment. Non-motor symptoms may also appear in PD patients, including cognitive impairment, olfactory dysfunction, psychiatric and sleep disorders, among other symptoms (Kalia and Lang, 2015). Despite their differences, AD and PD share common characteristics in their pathophysiology, including inflammation (Ransohoff, 2016), mitochondrial dysfunction, and oxidative damage (Lin and Beal, 2006).

The treatment for neurodegenerative diseases is limited and generally intended to control some symptoms, with no cure or disease-modifying treatments being available (Jamebozorgi et al., 2019; Long and Holtzman, 2019). The major pharmacological classes approved for AD treatment include acetylcholinesterase inhibitors (e.g. rivastigmine, galantamine, and donepezil) and N-methyl-D-aspartate (NMDA) receptor antagonists (e.g. memantine) (Scheltens et al., 2021). In addition, recently, aducanumab, a monoclonal antibody against Aβ, has been approved for AD treatment in the USA (Mullard, 2021; Tagliavini et al., 2021). On the other hand, PD is treated with drugs that regulate the activation of dopamine receptors. These drugs include levodopa (the precursor of dopamine), inhibitors of enzymes related to dopamine metabolism, such as monoamine oxidase-B (MAO-B) (e.g. rasagiline) and catechol-O-methyltransferase (COMT) (e.g. tolcapone and entacapone), and agonists of dopamine receptors (e.g. ropinirole and pramipexole) (Kalia and Lang, 2015).

In the USA, the economic impacts caused by dementia and PD are estimated to reach US$355 billion and US$52 billion in 2021,

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https://doi.org/10.1016/j.ejphar.2022.174800
Received 1 September 2021; Received in revised form 18 January 2022; Accepted 2 February 2022
Available online 5 February 2022

respectively (Alzheimer's Association, 2021; Parkinson's Foundation, 2021). Considering the high social economic impact caused by neurodegenerative diseases and the relatively low efficacy of the treatments currently available, it is crucial to work in the development of new treatments against these diseases.

Drug repurposing is a strategy for identifying new uses for investigational or approved drugs that are outside the scope of the original medical investigation. Generally, the repurposed drug presents a known safety profile, and this strategy is associated with reduced development costs and timelines (Pushpakom et al., 2019). The costs for bringing a repurposed drug to the market have been estimated to be US$300 million, while the costs for the development of a new drug are estimated to be US$2–3 billion (Nosengo, 2016). Therefore, the aim of this article is to discuss the search of new treatments for AD and PD through drug repurposing, focusing on drugs that could present anti-inflammatory effects.

2. The role of neuroinflammation in the pathophysiology of AD and PD

Neuroinflammation is an innate complex immune response of neural tissue aiming to restrain injury and infection. This response involves the action of different cell types, including microglia and astrocytes. When neuroinflammation is triggered, glial cells acquire a reactive phenotype associated to changes in their morphology and with the secretion of pro-inflammatory mediators that increase blood-brain barrier (BBB) permeability and attract peripheral immune cells that will help to eliminate cell debris, misfolded proteins, and pathogens. This cellular response is coordinated to protect tissues from secondary damage, and is related to cicatrization, often involving the formation of a glial scar, and tissue repair (Burda and Sofroniew, 2014; Yang and Zhou, 2019). However, despite its important roles in the response to injuries and infection, several studies have shown that persistent neuroinflammation is detrimental to neurons and is associated with the pathogenesis of chronic neurological diseases, including AD and PD.

Some decades ago, it was observed that inflammatory mediators could be detected in brain sections of AD and PD patients, which led to the hypothesis that neuroinflammation could be related to the progression of these diseases (for more details, see (Ransohoff, 2016)). One of the most common features shared by neurodegenerative diseases is the accumulation of aggregated misfolded proteins, including Aβ and p-Tau in AD and α-synuclein in PD and other synucleinopathies, which are able to trigger a neuroinflammatory response, activating glial cells that act in the clearance of these proteins (Choi et al., 2020; McAlpine et al., 2021; Rostami et al., 2021). Indeed, studies have shown that AD and PD may be related with an impairment in Aβ and α-synuclein clearance (Mawuenyega et al., 2010; Streubel-Gallasch et al., 2021). On the other hand, some studies have suggested that glial cells may not only internalize, but also be involved with the spread of p-Tau and α-synuclein (Asai et al., 2015; Fleeman and Proctor, 2021; Zheng and Zhang, 2021), and more studies are needed to clarify the role of glial cells in this context.

Robust evidence indicate that neurodegenerative diseases also share a common inflammatory mechanism involving the activation of inflammasomes and the release of proinflammatory cytokines (Piancone et al., 2021). Although there is some discrepancy between the reports regarding cytokine levels in AD and PD patients, studies have shown that AD and PD are associated with increased levels of some proinflammatory cytokines, including interleukin-1β (IL-1β) and interleukin-6 (IL-6) (Heneka et al., 2018; Karpenko et al., 2018). In addition, studies have also reported increased central levels of cyclooxygenase (COX)-2 and prostaglandin E_2 (PGE_2) in both AD and PD, stimulating research for evaluating the possible use of non-steroidal anti-inflammatory drugs for the treatment of neurodegenerative diseases (Yagami et al., 2016). As previously mentioned, the secretion of these proinflammatory mediators is associated with an increased permeability of the BBB in neurodegenerative diseases, attracting peripheral immune cells but also leading to synaptic dysfunction and neuronal injury (Sweeney et al., 2018).

Other evidence have also highlighted the role of neuroinflammation and glial cells in the pathogenesis of neurodegenerative diseases. Genetic studies have shown that genes mainly expressed by glial cells, such as *APOE, TREM2, APOJ*, and *SORL*, can lead to an increased risk of developing late onset AD, the most common form of the disease (Arranz and De Strooper, 2019). In the same fashion, studies have also suggested that mutations or changes in the expression of genes, such as *parkin, LRKK2*, and *DJ-1* in glial cells, could be related with the PD pathogenesis (Kam et al., 2020). Moreover, studies are trying to identify glial biomarkers for the early diagnosis of AD and PD (Bellaver et al., 2021; Zeng et al., 2020), and there is a significant increase in the number of studies regarding alterations in glial cells function during the progression of neurodegenerative diseases (Liddelow and Sofroniew, 2019).

Therefore, given the importance of glial cells and neuroinflammation in the development and progression of AD and PD, in the next sections, we will discuss the evidence regarding the repositioning of drugs and the development of new treatments for AD and PD, focusing on drugs that could present anti-inflammatory effects.

3. Repositioning of drugs and development of new treatments for AD and PD

3.1. Non-steroidal anti-inflammatory drugs (NSAIDs)

Cytokine-mediated inflammatory processes may play a central role in neurodegenerative disorders (Piancone et al., 2021). Consistent with this hypothesis, early epidemiological studies suggested that long-term treatment with NSAIDs decreased the risk of developing AD and PD (Chen et al., 2003, 2005; Szekely et al., 2004). It is worth mentioning, however, that there is some controversy about these findings, since later some studies have not observed an association between NSAIDs use and decreased risk of PD (Poly et al., 2019).

NSAIDs inhibit COX enzymes that catalyze the conversion of arachidonic acid (AA) to highly bioactive prostaglandins, which are known to increase the release of cytokines that promote inflammatory processes and are implicated in the pathogenesis of AD and PD (Kaduševičius, 2021). In addition to their classical mechanism of action, some NSAIDs have also been shown to present anti-amyloidogenic effects both *in vitro* and *in vivo*, and thus improve cognitive function in preclinical AD models (Heneka et al., 2005; Hirohata et al., 2006; McKee et al., 2008; Zhou et al., 2003).

Different studies have also shown that NSAIDs present beneficial effects in experimental models of PD. Teismann and Ferger (2001) showed that both acetylsalicylic acid and meloxicam were able to reduce the loss of nigral neurons, restore dopamine levels, and increase locomotor activity in mice exposed to 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP). Ibuprofen has also been shown to elicit neuroprotective actions in an experimental model of PD, presenting antioxidant effects, increasing tyrosine hydroxylase immunoreactivity and reversing motor deficits in rats exposed to rotenone (Zaminelli et al., 2014).

Celecoxib is a NSAID and analgesic agent that specifically inhibit COX-2. In an *in vitro* study with SH-SY5Y cells incubated with Aβ, celecoxib induced the translocation of nuclear factor erythroid 2-related factor 2 (Nrf2) to the nucleus, neutralizing the production of reactive oxygen species (ROS) and decreasing lipid peroxidation in a mechanism dependent on the upregulation of heme-oxygenase-1 (HO-1) (Mhillaj et al., 2020). In addition, it has been shown that celecoxib reduced COX-2 protein expression levels in the hippocampus, reduced morphological changes in microglia and astrocytes, decreased the levels of proinflammatory cytokines, induced synaptic plasticity, and prevented long-term memory impairment in rats treated with Aβ (Mhillaj et al., 2018).

The Alzheimer's Disease Anti-Inflammatory Prevention Test (ADAPT) was a primary prevention study to test the association of NSAIDs with the incidence of AD and changes in cognitive function over time in normal elderly people. This study involved 2528 patients over 70 years of age with a family history of AD, who received celecoxib, naproxen or placebo. The results showed that neither naproxen or celecoxib were able to improve cognitive function, and the treatments were suspended in the end of 2004 after increased cardiovascular risk was observed with celecoxib in another prevention trial (ADAPT Research Group et al., 2007; ADAPT Research Group et al., 2008). Later, a follow-up of this study corroborated the idea that the administration of celecoxib or naproxen for 1–3 years did not protect elderly adults with a family history of AD against cognitive decline (ADAPT-FS Research Group, 2015).

After the analysis of the data from the first ADAPT trials, the same group performed another study, this time with individuals without cognitive decline, with slow cognitive decline, and rapid cognitive decline. Their hypothesis was that naproxen or celecoxib treatment would slow cognitive decline in the slow decline group and accelerate cognitive decline in the rapid decline group compared to placebo subjects. The results involving naproxen administration were not clear and depended on the scale used to measure cognitive decline. Surprisingly, the results showed that celecoxib appeared to be harmful to individuals in the slow cognitive decline class, but with promising effects in individuals in the rapid cognitive decline class. Since COX-2 expression peaks early in the preclinical period of AD and then declines, the authors suggest that this process could be adaptive rather than detrimental, which could explain why COX-2 inhibition with earlier phase celecoxib (slow cognitive decline patients) seemed detrimental (Leoutsakos et al., 2012). In another study using the same dose of celecoxib in patients with mild-to-moderate AD, Soininen et al. (2007) showed that celecoxib did not attenuate the progression of the disease.

Indomethacin is an NSAID that can cross the BBB and acts as a potent non-selective inhibitor of COX-1 and COX-2 (Parepally et al., 2006). Preclinical studies have also found that indomethacin exerts beneficial effects in experimental models of AD and PD. It has been shown that indomethacin presents anti-amyloidogenic effects as well as a protective effect against Aβ *in vitro* (Fagarasan and Aisen, 1996; Hirohata et al., 2006). In addition, indomethacin-loaded lipid core nanocapsules suppressed glial and microglial activation and attenuated memory impairment in rats after Aβ administration. Interestingly, free indomethacin did not produce the same effects at the same dose of nanocapsules (Bernardi et al., 2012). In another model using Tg2576 mice, chronic administration of indomethacin reduced the amyloid pathology by blocking the activation of the nuclear factor kappa B (NF-κB) (Sung et al., 2004). Regarding PD, Kurkowska-Jastrzę;bska (2002) showed that indomethacin exerted neuroprotective effects in mice exposed to MPTP, decreasing microglial activation and lymphocytic infiltration in the injured areas. These results are corroborated by another study showing that indomethacin presented anti-inflammatory and pro-neurogenic effects in the dentate gyrus of mice exposed to MPTP (Hain et al., 2018).

Supported by the data provided by preclinical and epidemiological studies, clinical trials have also tried to evaluate if indomethacin could slow the progression of AD. Although an early study suggested that indomethacin (100–150 mg daily) could protect at some level patients with mild-to-moderate AD against cognitive decline, indomethacin was associated with important side effects, especially affecting the gastrointestinal tract, clearly limiting its use in this context (Rogers et al., 1993). Later, another phase II clinical trial was performed, involving the administration of indomethacin in association with omeprazole, aiming to decrease the side effects associated with indomethacin treatment. Although the typical side effects associated with indomethacin were attenuated with omeprazole administration, the treatment was not able to slow AD progression (de Jong et al., 2008). It is worth mentioning that both trials included a small number of patients, decreasing their statistical power.

In conclusion to this topic, although epidemiological and preclinical studies suggested that NSAIDs could decrease the risk or progression of AD, clinical trials were not able to detect robust evidence regarding their efficacy in this context. This incongruence may be due to confounding factors affecting the epidemiological findings or the wrong NSAIDs being tested in robust clinical trials. In this context, Rivers-Auty et al. (2020) recently published a very interesting study using logistic regression and an innovative approach of generalized negative binomial of linear mixed modelling to evaluate the effect of NSAIDs in AD prevalence and cognitive decline. The authors have found that the use of NSAIDs was associated with a lower prevalence of AD, but no associations were found regarding delayed cognitive decline, except for diclofenac use. Therefore, these findings suggest that the therapeutic window for the use of NSAIDs may be pre-symptomatic, inhibiting mechanisms involved in the initiating mechanisms of cognitive decline, while the use in the symptomatic phase of the disease may not be beneficial (Rivers-Auty et al., 2020). On the other hand, although some epidemiological studies have shown that NSAIDs may decrease the risk of PD (Chen et al., 2003, 2005), this effect has not been properly addressed by interventional clinical trials.

3.2. Antidiabetic drugs

Several studies have described the link between neurodegenerative disorders, including AD and PD, and Diabetes Mellitus (DM), a metabolic disease characterized by hyperglycemia due to chronic and/or relative insulin insufficiency (Forbes and Cooper, 2013). Epidemiological studies have shown an increased risk of AD and dementia in individuals with DM, especially DM type 2 (DM2) (Arvanitakis et al., 2004; Ott et al., 1999; Wang et al., 2012). In the case of PD, studies are still somewhat controversial. While some of them suggest that DM is a risk factor for PD (De Pablo-Fernandez et al., 2018; Schernhammer et al., 2011; Yang et al., 2017), others failed to show this association (Palacios et al., 2011; Simon et al., 2007).

The connection between neurodegenerative disorders and DM is not yet fully understood; however, both diseases share common pathological pathways, including inflammation, oxidative stress, and mitochondrial dysfunction (Labandeira et al., 2021). Furthermore, the phenomenon of insulin resistance, recognized as a central feature of DM2, has been proposed to occur also in the brain and play a crucial role in the neurodegeneration (Arnold et al., 2018; Aviles-Olmos et al., 2013b). The brain insulin resistance can be defined as the failure in the response of brain cells to insulin, and this non-responsiveness may result from the downregulation of insulin receptors, the inability of insulin to bind its receptor, or the defective activation of the insulin intracellular cascade. These changes in insulin signaling in the central nervous system has been related to impaired neuroplasticity and memory and the development of neurodegenerative disorders (Arnold et al., 2018; Batista et al., 2019). Of particular importance in both peripheral and central tissues, chronic inflammation accompanies insulin resistance (Kshirsagar et al., 2021). Inflammation increases the levels of cytokines, such as tumor necrosis factor-α (TNF-α), IL-1β, and IL-6, and these mediators activates cell stress kinases and down-regulate insulin receptor substrate-1 expression, which contributes to inhibit insulin signaling (De Felice et al., 2014).

The existence of common mechanisms between DM and neurodegenerative diseases boosted the study of antidiabetic drugs, as a drug repositioning strategy, for the treatment of these disorders. Antidiabetic drugs are primarily used to reduce blood glucose; however, other benefits that includes antioxidant, anti-inflammatory, and anti-apoptotic effects have been proposed to play a protective role in other conditions (Yaribeygi et al., 2020). Literature data suggest that antidiabetic drugs may act in the brain by improving insulin resistance, reducing neuroinflammation and metabolic and vascular changes, therefore promoting neuroprotection (Zhong et al., 2018). In this review, we will discuss the main antidiabetic drugs that have been investigated for AD

and PD, focusing on its modulatory role of neuroinflammation.

3.2.1. Metformin

Metformin, a drug from the class of biguanides, is the first line agent for treating DM2 and the most prescribed oral antidiabetic drug worldwide. The decrease in blood glucose levels induced by metformin is mainly due to the inhibition of the hepatic glucose production and increased glucose utilization (Brietzke, 2015; Flory and Lipska, 2019). Its action mechanism is attributed to the activation of AMP-activated protein kinase (AMPK). In the liver, the activation of AMPK suppresses the gluconeogenesis and fatty acid synthesis while, in the skeletal muscle, this activation increases the glucose uptake through the increase of glucose transporter 4 (GLUT4) to cell membrane (Kaneto et al., 2021; Zhou et al., 2001). The activation of AMPK is a consequence of the inhibition of complex I of mitochondrial respiratory chain, induced by metformin, that increases ADP:ATP and AMP:ATP ratio, triggering the activation AMPK (Stephenne et al., 2011).

In addition to the effects mentioned above, metformin presents other relevant properties, including the reduction of ROS production (Ionică et al., 2021; Kelly et al., 2015) and the modulation of inflammatory pathways (Bharath and Nikolajczyk, 2021). Some authors have demonstrated that metformin reduces the proinflammatory cytokines IL-6, IL-1β, and TNF-α in pre-clinical (Kelly et al., 2015; Soberanes et al., 2019) and also in clinical studies (Ali et al., 2019; Victor et al., 2015). It has been suggested that metformin blocks the activity of NF-κB through the inhibition of nuclear factor of kappa light polypeptide gene enhancer in B-cells (IκB) and IκB kinase (IKK)α/β phosphorylation, preventing the translocation of NF-κB to the nucleus (Moiseeva et al., 2013), consequently reducing proinflammatory gene expression.

The diversity of molecular targets for the action of metformin aroused the interest of researchers in studying its effect on neurodegenerative disorders. Evidence from cell and animal studies suggest a beneficial role of metformin in attenuating the pathological features of AD. Metformin attenuates spatial memory and learning impairments, the hippocampal neuronal loss, reduces the Aβ plaque load, promotes phagocytosis of Aβ and Tau proteins, increase neurogenesis, and decrease oxidative stress (Chen et al., 2021; Lu et al., 2020; Ou et al., 2018; Pilipenko et al., 2020; Xu et al., 2021). Furthermore, metformin mitigates microglia and astrocyte activation and suppresses pro-inflammatory cytokines, effects that can be due to AMPK activation that downregulates NF-κB activity (Lu et al., 2020; Ou et al., 2018). Other studies also indicate that neuroprotection induced by metformin is AMPK-dependent, suggesting AMPK as a potential therapeutic target in AD (Chiang et al., 2016; Zhao et al., 2019). Additionally, this drug has been shown to induce autophagy through AMPK activation and inhibition of Akt/mTOR pathway (Demaré et al., 2021). Despite several promising preclinical results, some studies have failed to demonstrate the beneficial effects of metformin or have even found an aggravation of experimental AD (Barini et al., 2016; Chen et al., 2009; Kuhla et al., 2019).

Several observational studies have investigated the association of the use of metformin in DM2 patients with the risk of cognitive dysfunction, dementia, and AD. A recent systematic review and meta-analyses evaluated 19 studies with 285,966 participants and found there was no significant effect on the incidence of neurodegenerative disorders with metformin exposure (Ping et al., 2020). In contrast, Zhou et al. (2020), in a meta-analysis accessing various antidiabetic drugs, verified that metformin decreases the risk of dementia in DM2 patients. Until now, only two clinical trials evaluated the effects of metformin for AD prevention and treatment. Luchsinger et al. (2016) conducted a pilot study in 80 patients with amnestic mild cognitive impairment that received metformin or placebo for 12 months. The authors evaluated clinical outcomes using scales to evaluate AD, levels of plasma $A\beta_{42}$, and relative glucose uptake in the posterior cingulate-precuneus in the brain. Metformin only significantly improved the verbal memory, after adjusting for baseline differences, but no differences were observed in the other outcomes. In a crossover study with 20 patients with mild cognitive impairment or dementia due to AD, receiving metformin for eight weeks followed by placebo or vice versa, metformin was associated with an improvement of executive function (Koenig et al., 2017). A phase II/III randomized placebo-controlled trial is recruiting patients with mild cognitive impairment to investigate the effects of metformin intervention. The outcomes evaluated will be changes in memory and cognitive tests, cortical thickness, white matter volume, Aβ and Tau burden, and plasma biomarkers of AD (NCT04098666).

Experimental evidence has shown that metformin is neuroprotective in PD models. In animal studies, metformin ameliorated motor dysfunctions, such as locomotor activity and motor coordination (Katila et al., 2017; Lu et al., 2016; Patil et al., 2014; Wang et al., 2020). In addition, it reduces the degeneration of dopaminergic neurons, restore dopamine depletion, inhibits α-synuclein phosphorylation and aggregation, decreases mitochondrial dysfunction and oxidative stress, modulates autophagy, and increases neurotrophic factors (Katila et al., 2017, 2021; Lu et al., 2016; Patil et al., 2014; Saewanee et al., 2021). In the management of neuroinflammation, studies have shown that metformin decreases the expression of proinflammatory cytokines (TNF-α, IL-1β and IL-6) and inducible nitric oxide synthase (iNOS), and mitigates microglial activation (Ismaiel et al., 2016; Lu et al., 2016; Tayara et al., 2018; Wang et al., 2020). Similar to what happens in AD, the mechanisms of anti-inflammatory effects of metformin seems to involve the activation of AMPK (Paudel et al., 2020). In a contradictory way, some studies have shown that, despite the anti-inflammatory effects, metformin fails to protect dopaminergic neurons (Tayara et al., 2018) or has even exacerbated dopaminergic damage (Ismaiel et al., 2016) in experimental models of PD.

Despite potentially interesting preclinical results, although sometimes controversial, research in humans have also shown conflicting results. The study from Shi et al. (2019) reported that the use of metformin decreases the risk of developing PD in DM2 patients. On the other hand, Kuan et al. (2017) showed an increased risk for PD in individuals using the antidiabetic drug. Recently, Qin et al. (2021), in a systematic review and meta-analyses, suggested a lack of association between metformin use and PD risk, while Ping et al. (2020) verified a significant increase in PD risk with metformin monotherapy. Until now, the benefits of metformin on PD remains inconclusive and randomized clinical trials with PD patients have not yet been developed.

3.2.2. Thiazolidinediones (TZDs)

TZDs act as peroxisome proliferator-activated receptor- γ (PPAR- γ) agonists to form heterodimers with retinoid-X receptors that bind to DNA response elements in the promoter region of target genes, resulting in the transactivation of gene products that increase insulin sensitivity, such as adipokines and trans expression of genes unfavorable to insulin action, such as NF-κB. Moreover, TZDs increases the uptake and storage of fatty acids in adipose tissue, and shifts lipid reserves from extra-adipose sites to adipose tissue (Brietzke, 2015; Nanjan et al., 2018).

PPAR-γ agonists also play an important role in inhibit proinflammatory gene expression and this property may be behind the beneficial effects of these drugs (Landreth et al., 2008). TZDs have been reported to block NF-κB-dependent gene expression, which includes the inhibition of pro-inflammatory cytokines, chemokines, COX-2, iNOS, and matrix metallopeptidases (Daynes and Jones, 2002; Straus and Glass, 2007). Furthermore, the anti-inflammatory activity of TZDs may be also mediated by the inhibition of pyrin domain-containing protein 3 (NLRP3) inflammasome, the expression of mitogen activated protein kinases (MAPK) phosphatase 1 and the activation of the caveolin-1-dependent pathway (Jankowska et al., 2019).

The role of TZDs in neuroinflammation has been extensively explored in experimental models of neurodegenerative disorders. In animal models of AD, pioglitazone and rosiglitazone attenuate astroglial and microglial activation, and reduce pro-inflammatory cytokines (IL-6, TNF-α, IL-1β and interferon-γ (IFN-γ)), COX-2, and iNOS expression in

the brain tissue (Heneka et al., 2005; Mandrekar-Colucci et al., 2012; Papadopoulos et al., 2013; Prakash and Kumar, 2014; Sarathlal et al., 2021; Xu et al., 2014; Yu et al., 2015). Moreover, TZDs reduce amyloid plaques and Tau deposits, attenuate oxidative stress parameters, restore levels of neurotrophic factors and mitochondrial respiratory activity, and improve neuronal damage and memory and cognitive deficits (Mandrekar-Colucci et al., 2012; Prakash and Kumar, 2014; Sarathlal et al., 2021; Searcy et al., 2012; Yu et al., 2015).

Several observational studies have investigated the association of TZD treatment with the risk of dementia and AD. A recently published meta-analysis indicated that diabetic patients treated with TZDs present a lower risk for developing dementia (Zhou et al., 2020). A relevant number of clinical trials already investigated the effects of pioglitazone or rosiglitazone in AD patients. The initial studies were very promising; however, the clinical trials with a large number of patients did not show satisfactory results.

One of the earliest clinical studies providing evidence for the application of TZDs in AD was a placebo-controlled, double-blind, pilot study conducted in patients with AD or amnestic mild cognitive impairment that received rosiglitazone or placebo for six months. The results indicated that subjects who received the drug presented selective attention and delayed recall when compared to placebo, and the levels of plasma Aβ were preserved while it declined in the placebo group (Watson et al., 2005). Risner et al. (2006), in a randomized double-blind placebo-controlled study, showed that mild-to-moderate AD patients that were APOE-e4-negative, a genetic risk factor for AD, exhibited cognitive and functional improvement in response to rosiglitazone. Some years later, a phase III clinical trial, carried out at 134 centers in 19 countries, failed to demonstrate the beneficial effects of rosiglitazone in cognition and global functions in APOE-e4-negative AD patients. Additionally, no beneficial effects of drug monotherapy were found in the other populations analyzed (Gold et al., 2010). Rosiglitazone also failed to improve cognitive and global function when administrated as an adjunctive therapy to acetylcholinesterase inhibitors in two phase III clinical trials (Harrington et al., 2011). In another randomized, double blind, placebo controlled study, rosiglitazone was associated with a modest increase in glucose brain metabolism, but without affecting cognition and brain atrophy in AD patients (Tzimopoulou et al., 2011).

The pilot studies from Hanyu and colleagues (2010, 2009) were the first to suggest a beneficial effect of pioglitazone in subjects with AD and DM2. These studies evidenced a significant improvement in general cognition and verbal memory (Hanyu et al., 2009) and a reduction in TNF-α plasma levels associated with cognitive improvement (Hanyu et al., 2010), after pioglitazone treatment for six months. Moreover, pioglitazone improved the cerebral blood flow in parietal lobe from patients with AD and DM2 (Sato et al., 2011). On the other hand, the study from Geldmacher et al. (2011), initially designed to evaluate the safety of pioglitazone in patients with AD, did not verify any pioglitazone effects on the efficacy outcomes. In another pilot study, pioglitazone did not improve cognitive performance and did not modify inflammatory parameters in older adults with mild cognitive impairment (Hildreth et al., 2015). In 2013, a phase III, multicenter, randomized, double-blind placebo-controlled study (TOMORROW) started to investigate if a low dose of pioglitazone, lower than that used for DM2, could delay the onset of mild clinical impairment due to AD at high-risk subjects. Some years later, the study was stopped for lack of efficacy of pioglitazone (Burns et al., 2021).

As in AD, several preclinical studies have demonstrated the effects of TZDs on PD. In animal PD models, these drugs improve motor, cognitive, and olfactory dysfunctions, reduce dopaminergic neurodegeneration, and improve dopamine levels (Barbiero et al., 2014; Breidert et al., 2002; Carta et al., 2011; Pinto et al., 2016; Schintu et al., 2009). TZDs can decrease ROS production (Martin et al., 2012), increase paraoxonase-2 expression (Blackburn et al., 2020), and improve mitochondrial function (Wang et al., 2017). The mechanism of TZDs has been largely attributed to their anti-inflammatory activity. Attenuation of microglial and astroglial activation, and reduction of pro-inflammatory cytokines, such as TNF-α and IL-1β, COX-2, and NF-κB expression, were observed after TZDs treatment in PD experimental models (Breidert et al., 2002; Carta et al., 2011; Lee et al., 2012; Machado et al., 2019; Pinto et al., 2016; Pisanu et al., 2014; Schintu et al., 2009).

Despite the relevant preclinical evidence described above, studies conducted in humans are still quite limited. Recently, a meta-analysis of four observational studies concluded that subjects with DM2 treated with TZDs have a low risk for PD (Hussain et al., 2020). Despite evidence from observational studies, clinical trials conducted in PD patients are even more limited and disappointing. A randomized multicenter placebo-controlled study, developed by the Neuroprotection Exploratory Trials of Parkinson's Disease (NET-PD) program, investigated the neuroprotective effects of pioglitazone in PD patients. The study enrolled 216 subjects randomized in two groups that received pioglitazone in two different doses and placebo for 44 weeks. The results showed that pioglitazone is unable to modify PD progression. Furthermore, pioglitazone did not significantly modify peripheral biomarkers, including plasma IL-6, 8-hydroxydeoxyguanosine (a marker of oxidative DNA damage), and PPAR-γ coactivator 1-α and target gene expression. Based on the results, the authors did not recommend a larger clinical trial with this drug (Simuni et al., 2015).

3.2.3. *Glucagon-like Peptide-1 receptor agonists*

Glucagon-like Peptide-1 (GLP-1) is a hormone from the incretin family that is released from gut enteroendocrine cells in response to nutrients intake (Nauck et al., 2021). Peripherally, GLP-1 promotes insulin secretion by pancreatic β cells and reduces glucagon secretion by pancreatic α cells. GLP-1 also decreases gastric emptying and inhibits food intake, thus maximizing nutrient absorption and controlling weight gain (Drucker, 2018; Müller et al., 2019). Additional properties are also attributed to GLP-1, such as anti-inflammatory, antiapoptotic, cardioprotective, and neuroprotective (Müller et al., 2019). In the central nervous system, GLP-1 influences thermogenesis, blood pressure control, neurodegeneration, neurogenesis, energy homeostasis, satiety control, water intake, and stress reaction (Grieco et al., 2019).

GLP-1 actions to control hyperglycemia through insulin secretion and inhibition of glucagon release have led to the development of GLP-1 receptor agonists for DM2 treatment (Drucker, 2018; Nauck et al., 2021). The link between neurodegenerative diseases and impaired insulin signaling, combined with the ability of GLP-1 receptor agonists to cross the blood brain barrier, has led to interest in studying these drugs as a therapeutic strategy for modifying the progression of these disorders (Batista et al., 2019; Glotfelty et al., 2020).

GLP-1 receptor agonists have demonstrated neuroprotective properties in different experimental models of AD. In general, these drugs rescue spatial learning and memory deficits, and reduce brain levels of amyloid plaque load and soluble Aβ in both genetic and Aβ-induced models of AD in rodents (Bomfim et al., 2012; Cai et al., 2014; Duarte et al., 2020; Maskery et al., 2020; McClean et al., 2015; McClean and Hölscher, 2014; Solmaz et al., 2015). Moreover, reduction of Tau phosphorylation and neurofibrillary tangles, improvement of neurotrophic factors and neurogenesis, and reduction of oxidative stress were also observed after GLP-1 receptor agonists treatment (Bomba et al., 2019; Cai et al., 2018; Duarte et al., 2020; Géa et al., 2020; Holubová et al., 2019; McClean et al., 2015; Salles et al., 2020).

Regarding neuroinflammation, a number of studies have demonstrated that GLP-1 receptor agonists modulate inflammatory markers in AD. McClean et al. (2015) and Cai et al. (2018) showed a reduction in activated microglia in the cortex and hippocampus, respectively, after GLP-1 receptor agonists treatment in mouse models of AD. Exenatide reduced the levels of TNF-α in the brain of rats injected with streptozotocin (Solmaz et al., 2015), and liraglutide suppressed the levels of TNF-α and IL-1β in amyloid precursor protein plus presenilin-1 (APP/PS1) mice (Maskery et al., 2020). The anti-neuroinflammatory

effects of exenatide were also observed in rats exposed to lipopolysaccharide, through the reduction of hippocampal IL-6 levels (Géa et al., 2020). The mechanisms responsible for GLP-1 receptor agonists modulation of microglia and neuroinflammation remains uncertain; however, the downregulation of NF-κB, an important downstream target of the GLP-1 receptor/PI3K/AKT pathway can be involved (Athauda and Foltynie, 2016). Moreover, according to Cai et al. (2018), the activation of protein kinase A-cAMP response element-binding protein (PKA-CREB) signaling pathway and inhibition of p38-MAPK by GLP-1 receptor agonists can contribute to reduce neuroinflammation and to elicit neuroprotective effects.

The promising results obtained in preclinical studies have driven the development of clinical trials with GLP-1 receptor agonists for AD. Mullins et al. (2019) conducted a pilot phase II clinical trial with exenatide in participants with high probability of AD. Eighteen subjects completed the study, which was stopped before completion; therefore, the results should be analyzed with caution. Exenatide did not present differences when compared to placebo for cognitive measures, magnetic resonance imaging volume, and thickness, or biomarkers in cerebrospinal fluid and plasma, except for a decrease in $A\beta_{42}$ in plasma neuronal extracellular vesicles. Until now, two randomized double blind clinical trials were concluded using liraglutide as a potential drug for AD. Gejl et al. (2016) reported that the treatment with liraglutide in AD subjects for six months prevented the decline in cerebral glucose metabolism, which reflects disease progression, without affecting cognitive scores. The effects of liraglutide treatment for 12 weeks on the brain function of cognitively normal late middle-aged individuals with subjective cognitive complaints (with high risk for AD) were investigated in the study from Watson et al. (2019). The results showed a significant improvement in intrinsic connectivity, indicating a neural effect of liraglutide, also without affecting cognition. A larger clinical trial of liraglutide, with an estimated recruitment of 206 patients, is in progress and will evaluate cerebral glucose metabolism, microglial activation, levels of Aβ and Tau on cerebrospinal fluid, as well as changes in brain structure and cognition (NCT01843075).

GLP-1 receptor agonists have also been investigated as a therapeutic option for PD. Preclinical studies using animal models of neurotoxin-induced PD report the ability of GLP-1 receptor agonists to reduce dopaminergic degeneration, restore dopamine levels, and attenuate motor dysfunction (Bertilsson et al., 2008; Harkavyi et al., 2008; Kim et al., 2009; Y. Y. Li et al., 2009; Liu et al., 2015; Zhang et al., 2019, 2018). Additionally, GLP-1 receptor agonists mitigate α-synuclein accumulation, reduce oxidative stress, rebalance mitochondrial dynamics and inhibit mitophagy, increase autophagy-related protein expression, and increase glial cell line-derived neurotrophic factor expression and neurogenesis (Bertilsson et al., 2008; Lin et al., 2021; Zhang et al., 2018, 2019). Some studies have also found that GLP-1 receptor agonists are able to reduce neuroinflammation in PD. Exenatide, prevented MPTP-induced microglial activation and suppressed the expression of matrix metalloproteinase-3 and proinflammatory cytokines (TNF-α and IL-1β) in brain tissue (Kim et al., 2009). Similarly, liraglutide and semaglutide attenuated microglia and astrocytes activation in the striatum and substantia nigra of mice exposed to MPTP (Zhang et al., 2018, 2019).

Clinical trials have been developed with GLP-1 receptor agonists and, so far, the results have been interesting. A single-blind trial evaluated the progress of PD in 45 patients treated with exenatide or placebo for 12 months. The results show clinically relevant improvement in motor and cognitive functions after the drug treatment (Aviles-Olmos et al., 2013a). Of particular importance, 12 months after treatment interruption, the improvement in motor and cognitive symptoms remained in PD subjects, suggesting a disease modifying potential of exenatide (Aviles-Olmos et al., 2014). These promising results boosted the development of a randomized double-blind placebo control study to evaluate exenatide in patients with moderate PD. The study evaluated the effects of exenatide or placebo treatment for 48 weeks, in addition to regular medication in 62 patients. Positive and persistent effects on motor scores were observed after exenatide treatment, corroborating the results of the previous study (Athauda et al., 2017). In a *post hoc* exploratory analysis, Athauda et al. (2018) identified that patients treated with exenatide had greater improvement in individual non-motor symptom domains assessing mood dysfunction/depression. Moreover, exenatide increased the tyrosine phosphorylation of insulin receptor substrate 1 and Akt and phosphorylated mTOR expression in serum extracellular vesicles, indicating an increment in brain-insulin signaling in PD patients (Athauda et al., 2019). A phase III study is being conducted to assess the effects of exenatide on motor, non-motor, and cognitive scores in a larger number of patients (Vijiaratnam et al., 2021). In another clinical trial, the effects of exenatide will be evaluated on PD progression, using positron emission tomography (NCT04305002). Other GLP-1 receptor agonists, liraglutide, lixisenatide, and semaglutide, are being evaluated in phase II clinical trials (NCT02953665; NCT03439943; NCT03659682).

3.2.4. *Dipeptidyl peptidase-4 inhibitors*

Dipeptidyl peptidase-4 (DPP-4) inhibitors, also known as gliptins, are a class of oral antidiabetic approved to treat DM2. DPP-4 is an enzyme member of DPP family that has many substrates, including gastrointestinal hormones, neuropeptides, cytokines, and chemokines. GLP-1 is a substrate for DPP-4, and inhibitors of DPP-4 slows the degradation of this incretin, consequently enhancing and prolonging GLP-1 signaling (Baetta and Corsini, 2011; Drucker and Nauck, 2006; Giugliano et al., 2013). The main actions of GLP-1 were previously described.

The role of DPP-4 inhibitors in AD and PD has been investigated in preclinical studies. These drugs decrease Aβ load, Tau phosphorylation, neuronal apoptosis, and oxidative stress markers, modulate synaptic plasticity and reverse cognitive and memory deficits in experimental models of AD (Chen et al., 2019; Dong et al., 2019; Kosaraju et al., 2013b; Li et al., 2019; Ma et al., 2018; Rahman et al., 2020; Yossef et al., 2020). Moreover, the expression of GLP-1 and GLP-1 receptor in brain regions, cortex and hippocampus, were increased with DPP-4 inhibitors administration (Chen et al., 2019; Kosaraju et al., 2013a, 2013b; Siddiqui et al., 2021). It has also been shown that alogliptin maintained insulin sensitivity and prevented $A\beta_{1\text{-}42}$ mediated neurodegeneration in rats (Rahman et al., 2020). A reduction in the levels of pro-inflammatory cytokines, TNF-α and IL-1β, was observed in the cortex and hippocampus after treatment with DPP-4 inhibitors in animals induced to AD (Kosaraju et al., 2013a, 2013b; Rahman et al., 2020; Siddiqui et al., 2021; Yossef et al., 2020). Anti-inflammatory effects appear to involve reduced signaling of NF-κB pathway (Wiciński et al., 2018).

The neuroprotective effects of DPP-4 inhibitors in AD are the result of an increase in GLP-1 receptor activation, consequently influencing downstream pathways on AD. The GLP-1 receptor stimulation evokes an increase in cAMP and Klotho protein, which activates protein kinase A (PKA) and phosphoinositide 3-kinase (PI3K) that, in turn, activates downstream pathways, such as MAPK/ERK, AKT and JAK/STAT. Several intracellular events are modulated by its proteins, such as inhibition of apoptosis, inflammation, and Aβ aggregation (Chen et al., 2019; Cheng et al., 2020; Yossef et al., 2020). According to Chen et al. (2019), the beneficial effects of sitagliptin and saxagliptin in revert AD-like neurodegeneration is due to the partial improvement of GLP-1 signaling pathway, including PI3K-Akt and MAPK. Ma et al. (2018) attributed the improvement in cognitive functions mediated by vildagliptin to the activation of Akt and inhibition of glycogen synthase kinase 3 (GSK3β) signaling pathway.

Literature data about the effects of DPP-4 inhibitors in patients with AD are scarce, and so far, there are no clinical trials registered or in progress. A recent meta-analysis identified that patients with DM2 under treatment with DPP-4 inhibitors presented lower risk of dementia when compared to other oral antidiabetic drugs (Zhou et al., 2020). A prospective and observational study evaluated the effects of six months therapy with sitagliptin in elderly diabetic patients with or without AD.

The results showed that sitagliptin therapy was associated with an improvement of the cognitive function (Isik et al., 2017). Other studies demonstrated that treatment with DPP-4 inhibitors had a protective effect on cognitive function in older diabetic patients with or without mild cognitive impairment (Ates Bulut et al., 2020; Borzì et al., 2019; Rizzo et al., 2014). Although the findings look promising, further randomized controlled trials are needed to support these results.

Preclinical studies also evidenced the potential of DPP-4 inhibitors against PD. These drugs were effective in improving motor performance and memory deficits and reducing dopaminergic degeneration in animal models of the disease. Furthermore, it has been shown that DPP-4 inhibitors have anti-apoptotic properties, reduce oxidative stress, induce neurogenesis, and increases GLP-1 expression in brain tissue (Abdelsalam and Safar, 2015; Badawi et al., 2017; Kabel et al., 2018; J. Li et al., 2018; Nassar et al., 2015). Interestingly, some studies have shown that the combination of linagliptin or sitagliptin with levodopa had additional benefits over levodopa monotherapy against PD (Badawi et al., 2019; Kabel et al., 2018). A marked decrease of neuroinflammatory markers was observed after treatment with DPP-4 inhibitors, including reduction of pro-inflammatory cytokines (IL-1β, IL-6, TGF-β1, TNF-α, and intercellular adhesion molecule-1 (ICAM-1), iNOS, myeloperoxidase, decrease of microglia activation, and suppression of NF-κB (Abdelsalam and Safar, 2015; Badawi et al., 2017, 2019; Kabel et al., 2018).

Svenningsson et al. (2016) found, in a population-based case-control study, a significantly decreased incidence of PD among individuals with a record of DPP-4 inhibitor intake. More recently, in a longitudinal population-based cohort study, the use of DPP-4 inhibitors was associated with a lower PD risk compared to the use of other oral antidiabetic drugs in patients with DM2 (Brauer et al., 2020). To date there are no clinical studies registered or in progress that prove the effectiveness of treatment with these drugs in PD.

3.2.5. *Sulfonylureas*

Sulfonylureas are among the oldest prescribed oral antidiabetic drugs to DM2. These drugs stimulate insulin secretion through the closing of ATP-sensitive potassium channel (K_{ATP}), sulfonylurea receptor 1 (Sur1)-regulated channel, in membrane of pancreatic β-cell, thereby causing membrane depolarization, influx on calcium ions, and the release of insulin from storage vesicles (Brietzke, 2015; Zubov et al., 2020). Besides its hypoglycemic effects, sulfonylureas have been studied for its potential application in several pathologies, especially those involving inflammation (Mathews et al., 2016). In the central nervous system, Sur1 regulated channels, including K_{ATP} and Sur1-transient receptor potential melastatin 4 (Trpm4) channels (Sur1 regulated ATP and calcium-sensitive nonselective cation channels), both targets for the sulfonylureas action, are expressed in neurons, astrocytes, microglial cells, oligodendrocytes, and endothelial cells. Glibenclamide, a member of the class of sulfonylureas, inhibits microglial K_{ATP} channels and Sur1-Trpm4 channels, ameliorates neuroinflammation, and improves neurological function (Zhang et al., 2017).

Like other antidiabetic drugs, sulfonylureas are being investigated in the field of neurodegenerative diseases. In experimental AD, sulfonylureas improve memory and maintain synaptic plasticity, and inhibit acetylcholinesterase (Baraka and ElGhotny, 2010; Esmaeili et al., 2018; Ju et al., 2020; Salgado-Puga et al., 2017). When evaluating neuroinflammation, studies demonstrate that these drugs decrease microglia activation and levels of proinflammatory cytokines, TNF-α and IL-6, in the hippocampus of rodents undergoing experimental AD (Esmaeili et al., 2018; Ju et al., 2020). In a case control study, Imfeld et al. (2012) showed that the long term use of sulfonylureas was not associated with an altered risk for AD development. Zhou et al. (2020), in their meta-analysis, reported that sulfonylurea was associated with a decreased risk of dementia in DM2 patients in comparison to non-treated patients; however, the authors recommend caution about this data due to different results obtained in direct and indirect estimates. A recent study that investigated AD related neuropathology in a community-based autopsy cohort among patients treated with antidiabetic drugs concluded that five years of sulfonylureas was associated with lower levels of $A\beta_{1\text{-}42}$ compared to non-users (Barthold et al., 2021).

The therapeutic potential of sulfonylureas in PD has been investigated in preclinical studies. Sulfonylureas improve motor and memory impairment, decrease oxidative stress, attenuate α-synuclein expression, and prevent dopaminergic neuronal damage and apoptosis in toxin-induced experimental PD (Abdelkader et al., 2020; Ishola et al., 2019; Piri et al., 2017; Qiu et al., 2021). A reduction of microglia pro-inflammatory response, pro-inflammatory cytokines release, iNOS expression, and NF-κB activation was observed in the brain tissue of rodents induced to PD (Abdelkader et al., 2020; Ishola et al., 2019; Qiu et al., 2021). Qiu et al. (2021) demonstrated that glibenclamide suppress the activation of NLRP3 inflammasome, an intracellular complex that can be activated by pathogen and damage-associated molecular patterns that lead to caspase-1 activation and production of pro-inflammatory cytokines. This mechanism can contribute to reducing neuroinflammation and dopaminergic damage in PD. Despite some pre-clinical evidence, studies involving humans are scarce. Qin et al. (2021) did not find association between the use of sulfonylureas and PD risk by analyzing different antidiabetic drugs and their association with the risk of PD in diabetic patients, through a systematic review and meta-analysis. Clinical trials are needed to assess whether the use of sulfonylureas in the prevention or treatment of neurodegenerative diseases has any beneficial effect.

The repositioning of antidiabetic drugs for neurodegenerative diseases, despite showing evidence of a promising strategy, still fails to demonstrate real benefits for their clinical application. Long-term drugs for DM, such as TZDs and metformin, have failed or have shown slight benefits in the studies conducted so far. More recently, an investment has been made in the study of drugs that have been introduced more recently into the market, such as GLP-1 receptor agonists and DPP-4 inhibitors, and some results seem to be promising, despite the need to complete phase II and III clinical trials.

3.3. *3-Hydroxy-3-methyl-glutaryl-coenzyme A (HMG-CoA) reductase inhibitors*

Cholesterol plays an important role in the brain, acting in fundamental processes, such as the synthesis of myelin by oligodendrocytes and the functioning of the synapses (Koudinov and Koudinova, 2001; Mauch, 2001). Cellular cholesterol homeostasis is tightly regulated. A rise in cholesterol levels leads to the Aβ clearance reduction, affecting cellular membranes fluidity, due to Aβ raised levels, and causing accumulation of amyloid precursor protein (APP), possibly triggering a neuroinflammation state. High cholesterol levels prevent APP cleavage by α-secretase enzyme, enabling only APP cleavage *via* amyloidogenic pathway, which may result in increased Aβ production (Racchi et al., 1997; Simons et al., 2001). Some intermediates produced during the cholesterol synthesis process are responsible for proteins' post-translational modifications, such as the GTPase proteins family. GTPases regulate critical signaling pathways, including inflammation, by modulating NF-κB activation, for example (Montaner et al., 1998; Takai et al., 2001).

The HMG-CoA reductase is an enzyme responsible for catalyzing the conversion of HMG-CoA into mevalonate, a key intermediate in cholesterol synthesis (Pac-Soo et al., 2011). Statins are drugs that act inhibiting HMG-CoA reductase, decreasing cholesterol synthesis and being widely prescribed for the treatment of hypercholesterolemia. Since studies have associated high cholesterol levels with an increased risk of AD (Kivipelto et al., 2002; Pappolla et al., 2003), the use of statins for preventing and treating AD has been proposed (Pac-Soo et al., 2011). Indeed, studies have shown that statins present neuroprotective effects in experimental models of AD (Huang et al., 2017; H. Li et al., 2018),

presenting anti-amyloidogenic and anti-inflammatory effects, suppressing NF-κB phosphorylation, and reducing the expression of proinflammatory genes and the release of proinflammatory cytokines, counteracting the activation of microglia (Chu et al., 2015; Churchward and Todd, 2014; Rahman et al., 2020; Yongjun et al., 2013).

Clinical trials evaluating the use of statins in AD prevention and treatment have presented conflicting results. In the Alzheimer's Disease Cholesterol-Lowering Treatment Trial (ADCLT), initial results of a double-blind, placebo-controlled, and randomized pilot trial with a one-year exposure to atorvastatin calcium (80 mg/day) showed a positive effect on cognitive and behavioral decline in mild to moderate AD patients as a result of lowering cholesterol levels (Sparks et al., 2005). A subsequent study assessed whether the benefits of atorvastatin would be influenced by the severity of cognitive impairment across the same treatment regimen. Positive effects of the atorvastatin treatment on cognitive function were observed once again, and were more prominent between patients with less cognitive decline (higher mini-mental state exam (MMSE) scores), hypercholesteremic (cholesterol levels above 200 mg/dl), or who presented an APOE ε4 allele (Sparks et al., 2006).

In contrast, some studies did not find any benefit of statin treatment against symptom progression and cognitive impairment in AD patients. Sano et al. (2011) showed that simvastatin treatment had no beneficial effects on symptom progression in mild-to-moderate AD patients when clinical signs were analyzed using the cognitive portion of the Alzheimer's Disease Assessment Scale (ADAS). Similar results were found in another double blind, randomized trial involving the administration of atorvastatin for 72 weeks in patients with mild-to-moderate AD (Feldman et al., 2010). An open-label trial evaluated the effects of simvastatin 40–80 mg/day for 12 weeks on brain cholesterol metabolism and plasma and cerebrospinal fluid biomarkers of AD, such as $A\beta_{40}$, $A\beta_{42}$, total Tau, and p-Tau. Even though inhibition of brain cholesterol synthesis was observed, simvastatin treatment did not alter the levels of AD biomarkers (Serrano-Pozo et al., 2010). Similar results were found by other studies showing that simvastatin was neither able to change plasma levels of Aβ nor of Aβ pattern (Höglund et al., 2004, 2005). Finally, trying to solve this controversy, Mcguinness et al. (2014) performed a meta-analysis of double-blind, randomized controlled trials of statins administered for at least six months in people diagnosed with dementia. Four trials, including 1154 patients, were found, and the analysis indicated that statins did not improve ADAS-Cog or MMSE.

Different studies also investigated the association between statin use and reduced risk of AD. Earlier cohort studies demonstrated that the use of lipid-lowering agents, especially statins, was associated with a lower risk of AD (Rockwood et al., 2002; Wolozin et al., 2000). Randomized clinical trials, however, showed controversial results regarding the use of statins to prevent AD. A randomized, placebo-controlled, double--blind, parallel-group design clinical trial evaluated the effects of simvastatin therapy in AD risk development. Asymptomatic middle-aged adults with a parental history of AD and high prevalence of APOE ε4 genotype were recruited and received simvastatin (40 mg/day) for four months. Although simvastatin did not change the levels of $A\beta_{42}$ and total Tau, the treatment improved the cognition function through verbal fluency and working memory measures (Carlsson et al., 2008). The prospective population-based Rotterdam Study showed that the use of statins, but not of non-statin cholesterol-lowering drugs, was associated with a decreased AD risk in the general population, and this effect was equal for lipophilic and hydrophilic statins users (Haag et al., 2009). Other studies, however, did not find a significant effect of pravastatin or simvastatin in cognitive decline (Collins et al., 2002; Shepherd et al., 2002).

On the other hand, the involvement between cholesterol homeostasis alterations and PD pathology remains elusive. It has been observed that Lewy bodies present different isoforms of isopentenyl diphosphate isomerase (IDI), an enzyme related to cholesterol biosynthesis (Nakamura et al., 2015). Studies conducted so far have related cholesterol and its metabolites with an acceleration of α-synuclein aggregation through proteasomes inhibition and activation of the liver X receptors (Marwarha et al., 2011; Schommer et al., 2018). Cholesterol facilitates interactions between α-synuclein oligomers while α-synuclein seems to be associated with the regulation of neuronal cholesterol (García-Sanz et al., 2021; Hsiao et al., 2017; Jakubec et al., 2021). Cholesterol metabolites can also inhibit the expression of tyrosine hydroxylase (TH), slowing down the dopamine synthesis, as well as leading to oxidative stress, cell death, and inflammation (Doria et al., 2016). In addition, cholesterol has been also associated with the synaptic damage induced by α-synuclein in a mechanism involving the activation of cytoplasmic phospholipase A2 (Bate and Williams, 2015).

However, although preclinical studies have already demonstrated a positive association between high levels of cholesterol and PD, human studies present controversial results. Studies have suggested that high cholesterol intake could be a risk factor for PD development (Johnson, 1999) and that patients with Lewy body dementia present increased cortical levels of cholesterol that may accelerate α-synuclein aggregation (Bosco et al., 2006). A retrospective study in a cohort of patients with PD showed that statins may have the potential effect of disease modifier since individuals using statins had a 9-year delay in the development of PD and a lower necessity in levodopa-daily dosage increase (Mutez et al., 2009). A historical cohort study investigated the incidence of PD among long-term statin users and non-users, and a significant decrease in PD risk was associated with statin use. Interestingly, this finding had no relation with baseline LDL cholesterol levels (Friedman et al., 2013). Another study found a strong reduction in the incidence of PD and dementia in simvastatin users, whereas atorvastatin showed a downward trend in the incidence of dementia and PD. However, the same was not observed between lovastatin users, which did not show a risk of PD decrease (Wolozin et al., 2007). A meta-analysis involving nine cohort and eight case-control studies has also suggested that statins (especially atorvastatin) could reduce the risk of PD (Yan et al., 2019). On the other hand, some studies showed that high levels of LDL cholesterol and triglycerides could be protective factors against PD (Fu et al., 2020; Rozani et al., 2018). Indeed, some studies have found that statin use could have a detrimental effect on nigrostriatal dopamine degeneration, and was associated with an increased risk of PD (Huang et al., 2015; Jeong et al., 2021; Liu et al., 2017).

In summary, to date, results from preclinical studies diverge from findings from clinical trials and epidemiological studies. Indeed, both in AD and PD, there are controversial results regarding the use of statins for preventing and treating these diseases. Future human observational studies or even large-scale well-designed trials with the purpose of unraveling molecular mechanisms of statins that may modulate pathways involved in AD and PD pathophysiology are required.

3.4. Anti-rheumatic drugs

As previously mentioned, TNF-α is a proinflammatory cytokine involved in the pathogenesis of neurodegenerative diseases. TNF-α has been shown to stimulate the expression of APP and the APP cleavage enzyme, β-secretase 1 (BACE1), in primary cultures of mouse astrocytes, as well as γ-secretase activity in other cell cultures, increasing the release of Aβ peptides in large amounts (Liao et al., 2004; Montgomery et al., 2013). In addition, it is known that TNF-α is elevated in the cerebrospinal fluid of aged patients and that it directly correlates with the progression of cognitive impairment (Hu et al., 2019; Tarkowski, 2003).

Etanercept was the first anti-cytokine-specific therapy to treat rheumatoid arthritis (Zhao et al., 2018). Etanercept is a dimeric fusion protein that can bind to two TNF-α molecules, thus acting as a receptor for this cytokine, preventing it from binding to its receptors and therefore inactivating it (Wong et al., 2008). Anti-TNF biological agents such as etanercept have rare but potentially serious adverse effects, including lymphoma, congestive heart failure, demyelinating disease, and lupus-like syndrome (Lin et al., 2008). Due to the possible role of TNF-α in AD, studies have explored the possible use of etanercept for the

treatment of AD.

In a preclinical study, it was shown that the subcutaneous administration of etanercept in Aβ-exposed mice counteracted working memory and long-term memory deficits evaluated through the Y-maze spontaneous alternation performance test and the inhibitory avoidance task test, respectively. In addition, etanercept decreased the levels of TNF-α in the hippocampus (Detrait et al., 2014).

In a pilot study of 12 patients with mild-to-severe AD, etanercept 25 or 50 mg was administered *via* perispinal injection once a week for six months. Although this study has several important limitations, investigators reported significant changes compared to the placebo group on several cognitive memory tests, verbal fluency, and comprehension. It was also reported that two dementia patients presented improvement in verbal fluency and aphasia in minutes after etanercept administration (Tobinick and Gross, 2008). In another small clinical trial involving 15 patients with rheumatoid arthritis, subjects who received etanercept showed a positive change in the baseline of MMSE after six months (Chen et al., 2010). These results are interesting, since etanercept is too large to cross the blood-brain barrier and directly target TNF-α within brain tissue (Chou et al., 2016). In this context, some evidence indicate that systemic inflammation plays a key role in AD, and therapies that reduce TNF-α activity peripherally may also act to reduce brain inflammation indirectly (Zhou et al., 2020).

Butchart et al. (2015) performed a randomized placebo-controlled, double-blind, phase II trial involving the administration of etanercept or placebo in 41 AD patients. After 24 weeks of treatment, etanercept was well tolerated. Although there were some trends favoring etanercept, no statistically significant changes in cognition, behavior, or global function were found. Since the primary goal of this study was to determine the safety of etanercept administration in AD patients, larger trials are still needed to evaluate its efficacy in this condition.

3.5. Chelating agents

Metals play vital roles in different biological processes; therefore, they are essential for the proper functioning of the central nervous system. Some of them are physiologically essential nutrients, acting as enzymatic cofactors and fundamental components for several biological molecules, and others are relatively harmful. Physiological levels of metals have to be tightly regulated since the limit between deficiency and toxic concentrations are relatively close and any excess can result in toxicity (Que et al., 2008). A considerable number of evidence have suggested the involvement of metal dyshomeostasis in neurodegenerative diseases, including AD and PD (Bourassa and Miller, 2012; Davies et al., 2014; Sensi et al., 2018).

Copper and zinc ions are involved in amyloid deposition in plaques and chelating agents may prevent metal-Aβ interaction since Aβ peptide has copper and zinc-binding sites (Cherny et al., 2001; Lovell et al., 1998; Smith et al., 1997). Protein Tau also has copper and zinc-binding sites, promoting its hyperphosphorylation when bound to these metals, contributing to brain oxidative damage; besides, it has been shown to promote the formation of the neurofibrillary tangles (Ma et al., 2006; Sun et al., 2012). On the other hand, copper and zinc act as cofactors and regulators of superoxide dismutase 1 (SOD1) an antioxidant enzyme whose impairment has been associated with several pathologies, including neurodegenerative diseases (Eleutherio et al., 2021; Krzyściak et al., 2010; M. Fetherolf et al., 2017). Studies have shown that AD patients present a decrease in copper and zinc levels that may reduce the expression of SOD1, leading to ROS accumulation and chronic neuroinflammation (Choo et al., 2013; Myhre et al., 2013; Ventriglia et al., 2012). In the same way that copper overload induces microglial activation and release of pro-inflammatory cytokines through the formation of Copper-Aβ complexes, copper homeostasis is important in preventing neuroinflammation as it regulates pro-inflammatory and anti-inflammatory microglial phenotypes (Rossi-George et al., 2012; Rossi-George and Guo, 2016).

Clioquinol was initially used as a topical antiseptic and an oral intestinal amebicide; however, it was later identified also as a metal-protein-attenuating compound, chelating zinc and copper and being suggested as a potential drug for AD treatment (Bush, 2008; Cuajungco et al., 2006; Huckle, 2005). An open randomized uncontrolled study investigated the effects of clioquinol on the pathogenetic processes of AD and its safety. Patients received 20 or 80 mg/day of clioquinol for 21 days. Individuals initially showed an increase in the CSF levels of Tau protein followed by a decrease after 21 days of clioquinol treatment. Authors related these findings with a possible release of Tau from the senile plaques and/or temporary brain cytotoxicity. Cognitive improvements were observed in patients treated with the higher dose and none had clioquinol-related adverse effects (Regland et al., 2001). On the other hand, a subsequent 36 weeks, pilot phase II, placebo-controlled trial evaluated clioquinol effects in moderately severe AD patients. Cognitive improvements were significant when the sample was stratified, with the treatment being more effective in patients presenting greater cognitive impairment. Clioquinol treatment significantly decreased $A\beta_{1\text{-}42}$ plasma concentrations and increased zinc plasma levels, while copper levels remained unchanged when compared to the baseline (Ritchie et al., 2003). Although a low incidence of possible adverse events related to clioquinol treatment was observed, a review conducted by Sampson et al. (2012) showed relevant negative aspects about this trial as sample size and randomization, as well as baseline differences in some variables. Finally, the period evaluated was not long enough to evidence a modification in AD course or long-term adverse effects.

D-penicillamine is a sulfhydryl-containing amino acid and a product of penicillin degradation used as a copper chelating agent in Wilson's disease treatment. In a 6-month, double-blind, placebo-controlled trial, D-penicillamine treatment decreased oxidative damage markers in AD patients, but no effect on copper levels or in clinical disease progression was observed (Squitti et al., 2002). Findings from another study showed that AD patients presented increased SOD activity, while D-penicillamine treatment decreased SOD activity in these patients. The decreased SOD activity after D-penicillamine treatment may be possibly related to a general depletion of bioavailable copper and could be an early diagnostic peripheral marker of AD (Rossi et al., 2002). It is important to mention, however, that both trials enrolled a small number of patients and presented a short evaluation period. In addition, Squitti et al. (2002) reported the occurrence of serious adverse effects related to D-penicillamine treatment, and these points should be considered for conclusions and future decisions.

High concentrations of iron in the brain induce Haber-Weiss and Fenton reaction, directly leading to ROS generation (Sayre et al., 2001). It has been observed that glial cells, especially microglia and astrocytes, accumulate higher iron content and might seem to be more resistant to oxidative damage when compared to neuronal cells (Oshiro et al., 2000). However, iron accumulation in these cells could compromise their function (Lopes et al., 2008). Iron deposition in substantia nigra has been associated with PD pathogenesis since dopaminergic neurons express high levels of neuromelanin that play a protective role in attenuating oxidative damage *via* direct inactivation reactive species or chelation of metals such as iron ions. Degeneration of dopaminergic neurons release neuromelanin that leads to microglial activation and neuroinflammation (Zhang et al., 2011; Zucca et al., 2017).

Deferiprone is a chelating agent already used as a treatment of iron overload disorders such as thalassemia and Friedreich ataxia (Boddaert et al., 2007). After Kwiatkowski et al. (2012) demonstrated in a case report a decrease in iron levels and positive improvement in the clinical conditions of a PD patient as a result of long-term deferiprone treatment, some clinical trials have been conducted. A pilot, double-blind, placebo-controlled randomized clinical trial explored the effects of deferiprone in early-stage PD. Patients submitted to a 12-month treatment with deferiprone (30 mg/day) showed a decrease in substantia nigra iron deposits and amelioration of the motor symptoms related to disease

progression. In addition, the treatment avoided systemic changes in iron levels (Devos et al., 2014). A subsequent trial with the same regimen treatment evaluated the involvement of ceruloplasmin, a ferroxidase that mediates iron oxidation in iron accumulation in the substantia nigra and PD progression. Deferiprone treatment reduced the iron levels in the substantia nigra and displayed clinical improvements in PD patients that showed higher levels of ceruloplasmin activity (Grolez et al., 2015). In another small phase II, randomized, double-blinded, clinical trial, Martin-Bastida et al. (2017) showed that deferiprone administration for six months in early PD patients was well tolerated. The treatment decreased the iron content in dentate and caudate nucleus, but most patients did not present changes in the iron levels in the substantia nigra. Also, no changes in mood and motor and cognitive functions were observed (Martin-Bastida et al., 2017).

Unlike the metals mentioned above, aluminum is a non-essential metal for human health and is considered a systemic intoxicant responsible for causing cerebral impairments. Crucial brain processes such as gene expression, intracellular signal transduction, synaptic transmission, neurotransmitter synthesis, and inflammatory responses can be influenced by aluminum (Altmann et al., 1999; Klotz et al., 2017). Some studies report exposure to aluminum in drinking water as a risk factor for AD, due to the high incidence or mortality found in contaminated areas (Flaten, 2001; Forbes and McLachlan, 1996; Martyn et al., 1989). Aluminum induces neurofibrillary degeneration (Boni et al., 1976; Savory et al., 1995) and Tau aggregation (Nübling et al., 2012), and disrupts Aβ metabolism, leading to its aggregation and to memory impairment (Luo et al., 2009; Sakamoto et al., 2006). Aβ-aluminum complexes are more toxic than Aβ itself and lead to membrane disruption besides perturbing neurons' calcium homeostasis and mitochondrial respiration (Drago et al., 2008; Ricchelli et al., 2005). Neurons and glia compete for aluminum uptake in the brain, but aluminum is preferentially taken up by glial cells, where it induces pro-inflammatory cytokines production, NF-κB up-regulation, and glia activation (X. Li et al., 2009; Lukiw et al., 2005).

Desferrioxamine is an aluminum chelating agent that has been studied as a potential drug to modify AD progression. Two single-blind, placebo-controlled trials investigated whether desferrioxamine (125 mg/twice daily, i.m.) could slow AD progression. Both trials used activities of daily living as primary outcomes assessed by a videotaped home behavior. Desferrioxamine-treated patients showed a decrease in the decline rate of daily living skills, which, when compared to the non-treated group, was twice slower (McLachlan et al., 1991, 1993). Moreover, desferrioxamine treatment lowered brain aluminum concentrations near to those presented by non-treated individuals (McLachlan et al., 1993). Some adverse effects such as appetite and weight loss were reported and reversed after desferrioxamine treatment suspension (McLachlan et al., 1991). Although not being used as a preventive option, aluminum chelators may potentially slow the clinical progression of cognitive decline associated with AD.

3.6. Neuroactive steroids

Neuroactive steroids are defined as natural or synthetic steroids that can act on the nervous system. These molecules can be synthesized naturally in the central nervous system by neurons or glial cells and the so called neurosteroids, or even in the peripheral nervous system, in the adrenal glands, or in gonads (Giatti et al., 2019). Neuroactive steroids regulate several neural functions as nervous system development, neural plasticity, and inflammatory responses under normal or pathological conditions (Giatti et al., 2012, 2019). Different studies have suggested the association between age-associated decline of endogenous steroid levels and risk of developing neurological disorders, including AD and PD (di Michele et al., 2013; Luchetti et al., 2011; Pike, 2017; Rosario et al., 2011; Weill-Engerer et al., 2002).

3.6.1. Estrogens

Since studies have shown that brain levels of estrogens are decreased in women with AD (Manly et al., 2000; Rosario et al., 2011), preclinical studies were performed to evaluate the neuroprotective effects of estrogens in experimental models of AD, as well as its role in AD development. It has been demonstrated that estrogen depletion through ovariectomy or aromatase inhibition leads to memory impairment, Aβ accumulation, and increased activation of NF-κB (Yue et al., 2005; Yun et al., 2018). Interestingly, the administration of estradiol was able to exert neuroprotective effects against Aβ, presenting anti-inflammatory effects and decreasing cognitive impairment (Shang et al., 2010; Yun et al., 2018; Zheng et al., 2017). These effects might be related with an increased clearance of Aβ and decreased NF-κB activation, which consequently leads to a reduced expression of inflammatory genes, such as COX2, iNOS, IL-1β, and TNF-α (Li et al., 2002; Valles et al., 2010; Vegeto et al., 2006; Yun et al., 2018).

Most of the trials conducted so far had focused on evaluating hormone therapy in postmenopausal women with AD. A preliminary study assessed the effects of estrogen administration in the cognitive and neuroendocrine response of postmenopausal women with mild-to-moderate AD. The 17β-estradiol treatment *via* skin patch for eight weeks enhanced cognitive function through verbal memory and attention, which was positively correlated with estradiol plasma levels (Asthana et al., 1999). Accordingly, two subsequent studies from the same or related research group, with a higher dose of estrogen (Asthana et al., 2001) and a longer period of treatment (Wharton et al., 2011), also exhibited favorable multiple cognitive effects, in addition to improvements in visual and semantic memory of women with AD. Both studies showed suppression of insulin-like growth factor-1 (IGF-1) system of women who received estrogen (Asthana et al., 1999, 2001); however, the role of IGF-1 in AD development and progression is controversial. Different studies reported that IGF-1 presents neuroprotective effects in experimental AD models (Aguado-Llera et al., 2005; Carro et al., 2002, 2006; Westwood et al., 2014), and Westwood et al. (2014) showed that lower serum levels of IGF-1 are associated with an increased risk of AD. On the other hand, some studies have suggested that the suppression of IGF-1 signaling could present protective effects against Aβ, decreasing cognitive impairment and neuroinflammation (George et al., 2017; Kim et al., 2019; Parrella et al., 2013; Suh et al., 2008). Two meta-analyses available in the literature focused on the relationship between alteration in IGF-1 levels and AD concluded that the IGF-1 factor has a critical personalized behavior influenced by age and AD progression, requiring large clinical trials to understand this association (Hu et al., 2016; Ostrowski et al., 2016).

Effects of estrogen replacement were also investigated in the cognitive function of women with AD using cholinergic therapy. Women taking estrogen in association with tacrine, an acetylcholinesterase inhibitor, showed cognitive improvements in different outcome measures in a 30-week, randomized, double-blind, placebo-controlled, multicenter, clinical trial (Schneider et al., 1996). Nevertheless, a subsequent study evaluated whether estrogen and progesterone replacement enhance response of rivastigmine in women with AD, and no significant changes in hormone therapy were observed on any parameters evaluated (Rigaud et al., 2003).

More recent studies suggest an interaction of hormone therapy and APOE genotype. A 12-month randomized, double-blind, placebo-controlled study evaluated the effects of hormone therapy (17β-estradiol and norethisterone) on cognition and mood of women with AD. Women without the APOE ε4 allele that received hormone therapy showed lower depressive symptoms and improvements in mood and cognition (Valen-Sendstad et al., 2010). Kantarci et al. (2016) showed that transdermal 17β-estradiol administration in recently menopausal women reduced Aβ deposition assessed by PET imaging, especially in those carrying the APOE ε4 allele.

Although some clinical studies demonstrated beneficial effects of hormone therapy and AD progression, it is important to mention that

other trials failed to show beneficial effects of estrogens in this context. Two studies involving the administration of estrogens in female AD patients for 12 or 16 weeks showed that the treatment did not improve cognitive performance, dementia severity, mood, behavior, and cerebral perfusion (Henderson et al., 2000; Wang et al., 2000). In addition, another trial involving the admistration of estrogen for one year in women with mild-to-moderate AD also failed to show any improvement in disease progression or in cognitive, motor, or mood outcomes (Mulnard et al., 2000).

The Woman's Health Initiative Memory Study evaluated the effects of estrogen plus progestin on the incidence of dementia and mild cognitive impairment in postmenopausal women, and this was the largest trial conducted to date in this area. Women receiving combined hormone therapy showed increased risk in the development of dementia, with AD being the most common classification of dementia in the study groups. In addition, treatment did not prevent mild cognitive impairment (Shumaker et al., 2003). A subsequent trial showed that estrogen alone also failed to decrease the incidence of mild cognitive impairment or dementia (Shumaker et al., 2004). Therefore, data from these trials do not support the use of hormone therapy to prevent cognitive decline or dementia in elderly women.

In contrast to AD, there is a higher incidence of PD in men than in women (Hirsch et al., 2016). Several studies have associated estrogen levels with a positive effect on PD risk, which could explain the decreased risk of PD in women (Bourque et al., 2019; Villa et al., 2016). These results are supported by preclinical studies showing that estrogen treatment exerts beneficial effects on dopamine and its metabolite levels and protects the integrity of dopaminergic neurons, preventing neuronal loss in PD models (Bourque et al., 2009; Morale et al., 2006; Tripanichkul et al., 2006). Furthermore, glial cells seem to be involved in the estrogen neuroprotection, since estrogens receptors are expressed by these cells in the striatum (Almey et al., 2012). In this context, estrogens or other modulators of estrogens receptors reduce inflammatory mediators, such as IL-1, TNF-α, IL-6, iNOS, and prostaglandin E2 (PGE2) in microglia, as well as IL-6 and IFN-γ in astrocytes, preventing glial activation (Brown et al., 2010; Cerciat et al., 2010; Soucy et al., 2005; Vegeto et al., 2001; Wu et al., 2015).

Clinical studies have shown that estrogen levels decline as a result of the postmenopausal period worsening of PD-related symptoms (Sandyk, 1989), whereas estrogen replacement diminished the severity of symptoms in women with PD. Estrogen replacement therapy decreased the risk of developing dementia in women with PD (Marder et al., 1998). Saunders-Pullman et al. (1999) showed through a retrospective study that estrogen therapy lowers symptom severity in women with early PD before levodopa use.

Patients exposed to long-term levodopa treatment commonly present motor fluctuations, also referred to as "on-off" times (Weiner, 2006). A short-term pilot study investigated the effects of 17β-estradiol on levodopa-induced dyskinesia in postmenopausal women with mild to moderate PD and showed a reduction in antiparkinsonian threshold dose of levodopa, showing a slight prodopaminergic/antiparkinsonian effect, although it did not consistently alter dyskinesias (Blanchet et al., 1999). A prospective study showed that the adjunctive administration of low-dose estrogen was well tolerated and decreased motor disability in postmenopausal women with PD associated with motor fluctuations (Tsang et al., 2000). Furthermore, a small clinical trial involving 11 PD postmenopausal women presenting levodopa-induced peak-dose dyskinesias showed that the combined administration of estrogen and medroxyprogesterone did not worsen motor symptoms and improved peak-dose dyskinesia (Nicoletti et al., 2007). Finally, a more recent randomized pilot trial also involving postmenopausal women with PD and motor fluctuations demonstrated that estrogen therapy was well-tolerated after eight weeks. Women treated with estrogen presented a trend in the improvement of motor symptoms, but the differences were not statistically significant. Anyway, since the primary outcome of this study was related to treatment safety, the authors suggested that larger studies should be performed to evaluate the efficacy of estrogen replacement in this context (Parkinson Study Group POETRY Investigators, 2011).

3.6.2. Progesterone and allopregnanolone

As similar to estrogens, reduced levels of progesterone during aging could increase the risk of AD (Barron and Pike, 2012). Progesterone administration blocked $A\beta_{25-35}$-mediated increase in TNF-α and IL-1β expression and improved behavioral performance and neuronal survival in rat hippocampus (Liu et al., 2013). Attenuation of the inflammatory responses in astrocytes, as well as prevention of inflammasome activation in microglia, were also observed in *in vitro* studies using progesterone (Hong et al., 2016, 2018; Slowik et al., 2018). Furthermore, allopregnanolone, a progesterone metabolite that may play an important role in the neuroprotective effects of progesterone, also produced beneficial effects in AD animal models, decreasing Aβ plaques formation and microglial activation and improving cognitive function (Chen et al., 2011; Singh et al., 2012; Wang et al., 2010).

Different clinical trials have been proposed aiming to evaluate the effects of allopregnanolone in AD. Hernandez et al. (2020) performed a phase Ib/IIa clinical trial aiming to evaluate safety, tolerability, and pharmacokinetics of allopregnanolone in early AD patients. This randomized, double-blinded, placebo-controlled clinical trial involved the administration of allopregnanolone or placebo for 12 weeks, with a one-month follow up. A total of 24 patients completed the trial, and the results showed that allopregnanolone was safe and well tolerated (Hernandez et al., 2020). These results prompted the registration of a phase II trial, aiming to investigate the efficacy of allopregnanolone to restore the structural integrity and cognitive function of mild AD patients, as well as its long-term safety (NCT04838301). It is estimated that the study should be completed in 2024, and the results will be essential to evaluate if allopregnanolone could be a viable therapeutic alternative for AD patients.

3.6.3. Dehydroepiandrosterone (DHEA)

DHEA is an adrenal hormone whose levels also decline during aging (Aldred and Mecocci, 2010). Indeed, low DHEA and dehydroepiandrosterone sulphate (DHEA-S) levels may also be associated with AD pathology, since AD patients present low serum levels of these hormones compared to age-matched healthy individuals (Aldred and Mecocci, 2010; Hillen et al., 2000; Luchetti et al., 2011). A protective effect of DHEA/DHEA-S in AD is supported by studies showing that these hormones present anti-apoptotic activity against Aβ-induced cytotoxicity (Cardounel et al., 1999; El Bitar et al., 2014; Li et al., 2010) and antioxidant properties (Aly et al., 2011). The effects of DHEA may also be related to the enhancement of mitochondrial respiration and the regulation of neuronal bioenergetic activity (Grimm et al., 2014; Patel and Katyare, 2006). Neuroprotective DHEA/DHEA-S effects attenuated Aβ-induced impairments in memory in a mice model of AD (El Bitar et al., 2014), as well as improved cognitive performance in a mice model with an age-dependent accumulation of APP and Aβ (Farr et al., 2004).

Few clinical trials have been conducted to investigate the effects of DHEA in patients with cognitive impairment. Wolkowitz et al. (2003) performed a randomized, double-blind, placebo-controlled pilot study that evaluated the effects of six-month DHEA in AD patients, and no significant improvement in cognitive performance or even in overall parameters of disease severity were observed. Another study, however, observed that DHEA administration produced some benefits in the cognition of aged women with mild-to-moderate cognitive impairment (Yamada et al., 2010). On the other hand, DHEA supplementation in healthy elderly people does not seem to improve cognitive function (Grimley Evans et al., 2006).

3.6.4. Androgens

Similar to estrogens, androgens such as testosterone also gradually decline during aging, and this could be associated with increased risk of

AD in men (Hogervorst et al., 2001; Moffat et al., 2004). Testosterone levels seem to be inversely correlated with Aβ concentrations in early AD pathology and may contribute to disease progress (Rosario et al., 2011). Preclinical studies suggest that testosterone present neuroprotective effects against Aβ (Pike, 2001), improving cognitive performance and decreasing AD-like neuropathology (Benice and Raber, 2009; Rosario et al., 2006). Since studies have shown that testosterone and its metabolites inhibit the expression and release of pro-inflammatory cytokines and chemokines, besides decreasing reactive gliosis on microglia and astrocytes (Barreto et al., 2007; Malkin et al., 2004; Rettew et al., 2008), anti-inflammatory effects could be related to the protective effects of testosterone that were observed in preclinical models of AD.

The role of testosterone in cognitive impairment is controversial. While some studies demonstrated an association between testosterone treatment and improvements in cognitive function (Cherrier et al., 2005; Wahjoepramono et al., 2016), other studies have failed to demonstrate beneficial effects of testosterone administration in the cognitive function of older men with low-to-normal testosterone levels (Huang et al., 2016; Resnick et al., 2017). Clinical research of androgen replacement as an alternative therapy for AD is limited. A small pilot study demonstrated improved cognitive function in AD hypogonadal male patients treated with testosterone, while the placebo-treated group deteriorated gradually (Tan and Pu, 2003). Subsequent studies observed that testosterone replacement therapy through intramuscular injections or gel applied at skin improved spatial and verbal memory and overall quality of life of AD patients, respectively (Cherrier et al., 2005; Lu et al., 2006).

Similar to AD, an association between low levels of testosterone and PD has also been suggested (Okun et al., 2004). However, findings from preclinical studies that investigated the neuroprotective activity of testosterone are not favorable. Different studies have shown that testosterone or its metabolites are not able to prevent dopamine depletion and its metabolites in PD models induced by MPTP or methamphetamine (Dluzen, 1996; Ekue et al., 2002; Gao and Dluzen, 2001; Lewis and Dluzen, 2008).

Case report studies reported beneficial effects of testosterone treatment in motor and non-motor symptoms in PD (Mitchell et al., 2006; Okun, 2002); however, clinical trials conducted so far have not shown favorable results after testosterone administration in PD patients. A prospective open-labeled pilot study investigated the testosterone effects on cognitive function and motor and non-motor symptoms in men with PD. Transdermal testosterone gels improved testosterone deficiency symptoms and there were some trends toward improvement in PD symptoms, but in most cases the differences did not reach statistical significance (Okun et al., 2002). A subsequent small trial conducted by the same research group failed again in showing improvements in motor and non-motor features of PD in men receiving intramuscular testosterone when compared to the placebo group (Okun et al., 2006).

To conclude this topic, the benefits of neurosteroids-based therapy on neurodegenerative disorders such as AD and PD are not yet clear. Findings from preclinical and human studies diverge probably due to different reasons. One important factor is sex differences observed between men and women steroid levels that imply different susceptibility and outcomes in response to these therapies: women seem to be more susceptive to AD than men while they show a decreased risk of PD. Other hypotheses are related to the optimal timing of starting the intervention, type, dose, administration route, and duration of the hormonal replacement therapy. Finally, clinical trials have used relatively small sample sizes in most of the cases, assuming a possible lack of statistical power to detect treatment effects, generally providing insufficient evidence.

3.7. Antibodies and immunomodulators

3.7.1. α-synuclein and Aβ-related antibodies

Immunotherapeutic approaches comprise passive and active immunization, consisting of the infusion of monoclonal antibodies and vaccination with specific antigens that induce adaptive immune responses (Arevalo-Villalobos et al., 2017). Since neuroinflammation is a prominent event associated with the pathophysiology of PD and AD, these pathologies are considered targets for immunotherapy (Fakhoury, 2015). Indeed, different trials have been developed in the last decade trying to assess the efficacy and safety of antibodies aiming to reduce the levels of proteins that usually accumulate during the progression of PD and AD, such as α-synuclein and Aβ, respectively. Although not being examples of repurposed drugs, we believe that it is worthwhile to discuss the data on these agents since these studies attracted a lot of attention in the past decade and are also related to neuroinflammation.

Active immunization against PD has been performed in animal models and early clinical trials (Schneeberger et al., 2016). Vaccination can be used for large populations and is less invasive than other treatments. In addition, frequent injections are not required, which can reduce stress for patients (Schneeberger et al., 2016). Thus, active immunization could be suitable for patients with early-stage PD and high-risk populations. PD01A is a new therapeutic vaccine candidate containing a short peptide designed to induce an antibody response, specifically targeting oligomeric α-synuclein. A phase I clinical trial showed that repeated administration of PD01A was safe and well tolerated, producing a substantial humoral immune response (Volc et al., 2020). Further phase II clinical trials are needed to investigate the efficacy and safety of PD01A for PD treatment.

Other studies targeting α-synuclein have also been performed. Schenk et al. (2017) and Jankovic et al. (2018) presented data from a phase I clinical trial that revealed that a humanized 9E4 antibody prasinezumab (PRX002) was well tolerated and presented dose-dependent effects, thus being able to reduce free unbound α-synuclein levels in serum up to 97%. These data led to a phase II multicenter, randomized, double-blind, clinical trial aiming to address the efficacy of intravenous prasinezumab versus placebo over 52 weeks in participants with early PD (NCT03100149). The primary outcome of the study is the change from baseline in the total score of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS). Secondary outcomes include changes in the subscores of MDS-UPDRS, analysis of dopamine transporter density in the striatum, changes from baseline in the Montreal Cognition Assessment (MoCA), Clinical Global Impression of Improvement (CGI-I), Patient Global Impression of Change (PGIC), Schwab and England Activity of Daily Living (SE-ADL) scores, time to worsen motor or non-motor symptoms and starting time of the dopaminergic PD treatment. Partial results available at clinicaltrials.gov show that the administration of prasinezumab does not seem to improve outcomes in comparison with placebo.

Another phase I clinical study evaluated the safety, tolerability, and pharmacokinetics of a single-dose of BIIB054 (15 or 45 mg/kg i.v.), a monoclonal antibody of human origin that preferentially binds to aggregated α-synuclein in patients with PD (Brys et al., 2019). BIIB054 was well tolerated, and its pharmacokinetics profile supports further clinical studies. All PD patients presented nearly completed saturation of the BIIB054/α-synuclein complex formation in plasma. However, the development of BIIB054 was discontinued after a phase II clinical trial sponsored by Biogen, called SPARK, failed to meet its primary and secondary outcomes (NCT03318523).

In addition to PD, studies have also evaluated the use of immunotherapy for the development of new treatments for AD, including the use of antibodies aiming to prevent Aβ aggregation and the neuroinflammatory response associated with the disease. Verubecestat and semagacestat are antibodies targeting the enzymes β- and γ-secretase, which are the enzymes related to the synthesis of Aβ. Phase III clinical trials have failed to demonstrate any benefit regarding the administration of these antibodies in AD patients (Doody et al., 2013; Egan et al., 2018, 2019). Antibodies directly targeting Aβ were also tested in clinical trials, including bapineuzumab, solanezumab, gantenerumab, and aducanumab. Although negative results have been found in different phase III clinical trials involving the use of these antibodies (Doody

et al., 2014; Knopman et al., 2019; Ostrowitzki et al., 2017; Salloway et al., 2014), aducanumab has recently been approved in the USA for the treatment of AD after a controversial process (Mullard, 2021; Tagliavini et al., 2021).

In addition to the trials presented above, there are currently some other ongoing phase II clinical trials in AD patients with neflamapimod, canakinumab, and lenalidomide (NCT03435861; NCT04795466; NCT04032626), which are antibodies targeting different proteins and cytokines related to neuroinflammation.

3.7.2. Neflamapinod

Neflamapimod or VX-745 is a highly selective and orally bioavailable inhibitor of the mitogen-activated protein kinase p38 alfa (p38α) activity that presents anti-inflammatory activity and that was introduced by the Vertex pharmaceutical industry as a potential anti-inflammatory treatment for rheumatoid arthritis in phase II clinical trials in the late 1990s (Haddad, 2001). The expression of p38α in the neuron is associated with the formation of Aβ, inflammation, and synaptic dysfunction (Gee et al., 2020). In addition, microglial p38α is involved in the stimulatory effects of Aβ in the production of pro-inflammatory cytokines and modulates the activation state of microglia (Bachstetter and Van Eldik, 2010). In this context, Alam (2015) has shown that the administration of neflamapimod to aged rats led to significantly improved performance in the Morris water maze test (MWM) and a significant reduction in protein levels of IL-1β in the hippocampus. The role of p38α in AD pathogenesis is also corroborated by studies showing that the downregulation or the knockout of its gene improved synaptic transmission, decreasing memory loss and reducing amyloid pathology (Colié et al., 2017; Schnöder et al., 2016).

Two clinical trials have evaluated the effects of neflamapimod in patients with early AD. In a preliminary clinical trial without a placebo control involving 16 patients, Scheltens et al. (2018) suggested that neflamapimod could improve episodic memory and potentially impact Aβ production after 12 weeks. Later, in a phase II double-blind placebo controlled clinical trial, Prins et al. (2021) showed that the administration of neflamapimod for 24 weeks did not improve episodic memory in mild AD patients. However, since the treatment decreased some CSF markers of synaptic dysfunction, the authors concluded that a study involving the administration of a higher dose of neflamapimod for a longer period is warranted to assess effects on AD progression. Currently, there is still an ongoing phase II clinical trial aiming to evaluate the effect of a 12-week treatment of neflamapimod on microglial activation, brain structure, and other inflammatory markers in AD patients (NCT03435861).

3.7.3. Canakinumab

IL-1β is a pro-inflammatory cytokine involved in the pathophysiology of different neuroinflammatory diseases, capable of activating astrocytes and microglia, further inducing the release of other cytokines, which will have effects on neuronal function and integrity (Kaur et al., 2019; Mendiola and Cardona, 2018). Studies have shown that Aβ and α-synuclein trigger IL-1β release (Lučiūnaitė et al., 2020; Pike et al., 2021). Therefore, the blockade of IL-1β actions could reduce pathological changes and decrease cognitive impairment in AD and PD experimental models (Gonzalez et al., 2009; Kitazawa et al., 2011; Long-Smith et al., 2010; Wu et al., 2002).

Given its importance, several therapeutic biological inhibitors of IL-1β have been developed and are currently clinically available. One of these inhibitors is canakinumab or ACZ885, a human monoclonal anti-IL-1β antibody that neutralizes the activity of human IL-1β and suppresses inflammation, and that is currently approved for the treatment of different autoinflammatory diseases (Chakraborty et al., 2012).

To date, a randomized, placebo-controlled, phase II clinical trial of canakinumab (NCT04795466) with patients with mild cognitive impairment or mild AD with evidence of peripheral inflammation was recently registered. Patients will receive subcutaneous injections of canakinumab for 20 weeks and the outcome assessment will consist of several globally established neuropsychological tests that provide a thorough assessment of the cognitive domains affected by early AD, in particular, memory, executive function, attention, and verbal fluency. In addition, the drug's safety and tolerability, and the effects on the central and peripheral inflammation will be evaluated.

3.7.4. Lenalidomide

Lenalidomide is a thalidomide analogue that has potent anti-inflammatory and anti-angiogenic activities. Currently, it is prescribed for the treatment of multiple myeloma and myelodysplastic syndromes (Galustian and Dalgleish, 2009). Its main mechanisms of action include the inhibition of TNF-α and IL-1, IL-6, and IL-12 production, induction of T-cell proliferation and increased production of IL-2 and IFN-γ, as well as the regulation of ubiquitination processes (Zhu et al., 2013).

Preclinical studies showed beneficial effects of lenalidomide in PD models. Valera et al. (2015) showed that lenalidomide reduced microgliosis, pro-inflammatory cytokines expression, and NF-κB activation, ameliorating dopaminergic fiber loss in the striatum and reducing motor behavioral deficits in mThy1-α-syn transgenic mice. More recently, another study showed that lenalidomide (100 mg/kg for 28 days) increased brain-derived neurotrophic factor (BDNF) expression in the substantia nigra, improving neuronal survival, preventing the reduction of dopamine levels and decreasing motor deficits in rats treated with rotenone (Cankara et al., 2020).

Although there are no completed clinical trials regarding the use of lenalidomide in PD patients, there is currently an ongoing phase II clinical trial in patients with AD-related mild cognitive impairment (MCI) (NCT04032626). Patients will receive 10 mg/day of lenalidomide for 12 months, followed by a six-month washout period. Cognitive measures, brain imaging, and blood of individuals will be evaluated, as well as the tolerability and safety of this drug, aiming to determine whether lenalidomide could be a possible therapeutic option for the treatment of AD (Decourt et al., 2020).

3.8. Drug therapy combination

The multifactorial characteristic and the different mechanisms involved in the pathogenesis of neurodegenerative diseases have aroused interest in the use of drug combination therapies. The combination of drugs, with multiple targets of action, can be an interesting strategy to increase efficacy and decrease resistance to treatment (Kabir et al., 2020; Löscher and Klein, 2022). Some studies have investigated the effects of the association of drugs that modify the neuroinflammatory process to existing therapies for PD and AD.

In PD, the benefit of combination of drugs with levodopa have been examined in clinical trials. Exenatide, a GLP-1 receptor agonist, demonstrated a positive effect in patients with PD using conventional medications for PD (Athauda et al., 2017). Moreover, DPP-4 inhibitors combined with levodopa presented additional benefits in patients with PD when compared to monotherapy (Badawi et al., 2019; Kabel et al., 2018). In addition to improving disease symptoms, combination therapy may decrease adverse effects of levodopa, which are not well tolerated by patients. It has been reported that patients treated with levodopa and receiving estrogens presented less motor fluctuations and dyskinesia (Nicoletti et al., 2007; Tsang et al., 2000).

Despite the rationality of combination therapy, in AD, most clinical trials using the previously mentioned drug classes have not shown promising results. For example, the antidiabetic drug, rosiglitazone, and statins, such as atorvastatin and simvastatin, were not effective in showing beneficial effects when associated with acetylcholinesterase inhibitors or memantine in clinical trials (Feldman et al., 2010; Harrington et al., 2011; Sano et al., 2011). Also, hormone replacement therapy with estrogen and progesterone did not enhance the response to rivastigmine in patients with AD (Rigaud et al., 2003). Although not all results are promising, the combination of drugs, especially repositioned

drugs, still needs to be further explored in clinical trials.

4. Conclusion

The difficulties encountered in discovering new drugs for neurodegenerative diseases have led researchers to invest in the drug repositioning strategy. This approach can be very interesting due to the already known profile of previously approved drugs and the reduced cost compared to research and development of new drugs. Moreover, the translation of a drug candidate into an approved drug can often take around 15 years (Agrawal, 2015). However, despite the numerous advantages, studies that prove the effectiveness of a re-profiled drug need to be conducted.

The investigation of drugs that modulate neuroinflammation, a common feature of different neurodegenerative pathologies, has proven to be an interesting approach. As seen in this review, an effort has been made to repurpose drugs for AD and PD, especially those with anti-inflammatory properties. In this context, classic drugs, such as NSAIDs, anti-diabetic, and statins, as well as drugs more recently introduced in the market have been investigated in pre-clinical and clinical trials in a possible attempt to apply them in the treatment of neurodegenerative diseases. The common mechanisms of action of these drugs are illustrated in Fig. 1. Although preclinical studies have shown promising results for several of these drugs, most of them have failed in phase II and III clinical trials. However, some of them are still being studied, waiting for results that can prove its effectiveness. In addition,

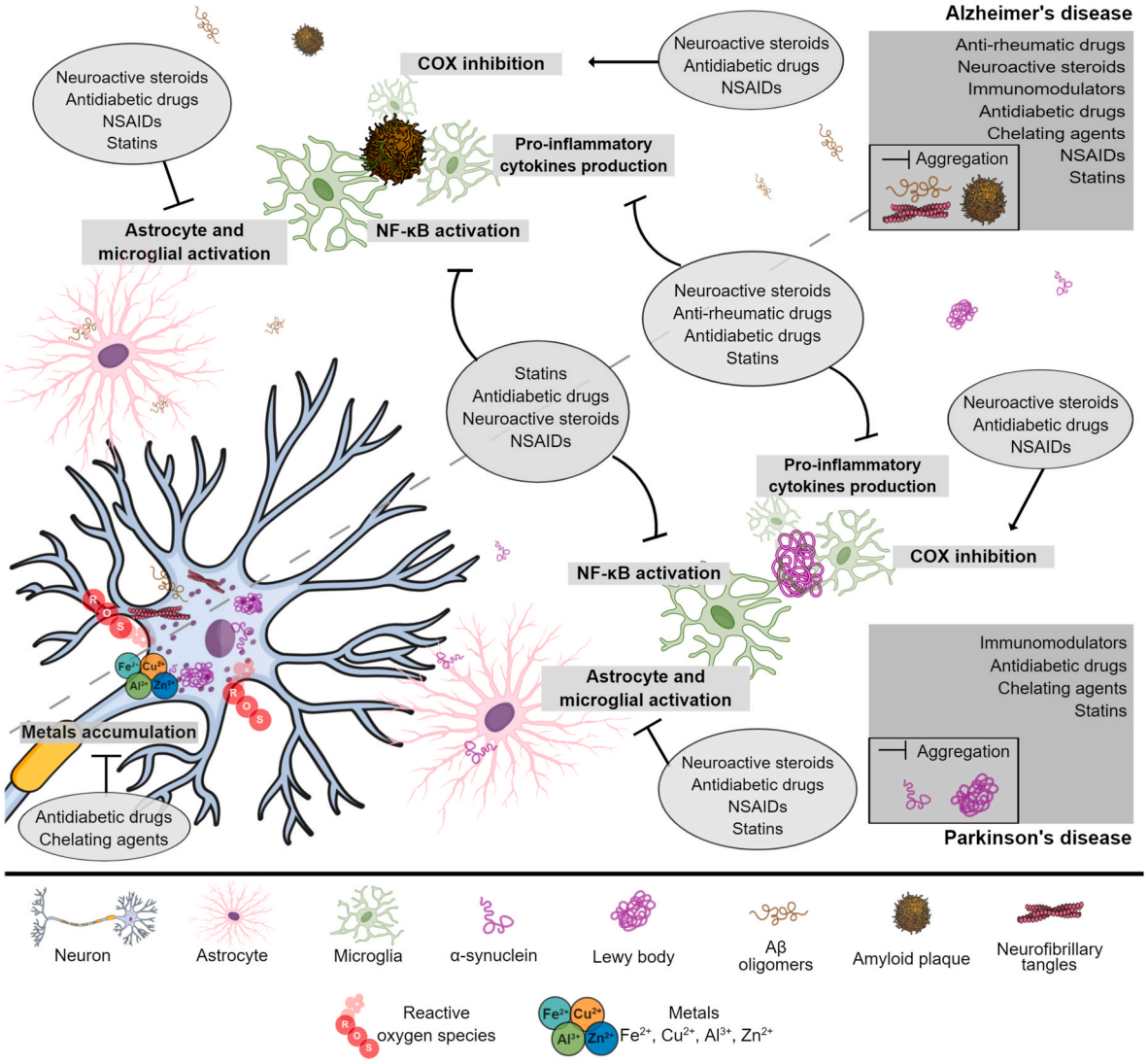

Fig. 1. Neuroinflammation as a target in the repositioning of drugs for AD and PD treatment. Besides inhibiting COX, NSAIDs might act by limiting astrocyte and microglial activation by interfering with NF-κB activation or by reducing Aβ loading. Neuroactive steroids exert anti-inflammatory effects by suppressing the expression of proinflammatory cytokines, chemokines, and inflammatory mediators, as well as preventing astrocyte and microglial activation and Aβ-induced NF-κB activation. Statins might also have effects on the amyloidogenic pathway, in addition to decreasing α-synuclein aggregation. Statins can also suppress NF-κB phosphorylation, reducing the expression of proinflammatory genes as well as the release of proinflammatory cytokines by counteracting the activation of microglia. Antidiabetic drugs present anti-inflammatory effects by reducing proinflammatory cytokines and microglial activation, in addition to preventing the translocation of NF-κB to the nucleus. Antidiabetic drugs also have actions on AD by decreasing the Aβ plaque load and promoting phagocytosis of Aβ and tau proteins, as well as in PD through the inhibition of α-synuclein phosphorylation and aggregation, besides decreasing oxidative stress. Anti-rheumatic drugs can bind to TNF-α, preventing the inflammatory effects of this cytokine. Dyshomeostasis of metals seems to be also related to both AD and PD pathogenesis. Chelating agents act decreasing the accumulation of metals that have a high affinity to Aβ and tau, besides inhibiting α-synuclein aggregation and decreasing oxidative stress. Chelating agents also prevent astrocyte and microglial activation and counteract the overproduction of pro-inflammatory cytokines. Finally, immunomodulators aim to reduce the levels of proteins that usually accumulate during the progression of AD and PD, such as α-synuclein and Aβ. Abbreviations: AD: Alzheimer's disease; Aβ: amyloid-beta; COX: Cyclooxygenase; NF-κB: Nuclear factor kappa B; NSAIDs: Non-steroidal anti-inflammatory drugs; PD: Parkinson's disease; TNF-α: Tumor necrosis factor-alpha.

more studies are needed to evaluate the combination of repurposed drugs with current approved therapies for the treatment of AD and PD.

Finally, it is important to mention that drug repositioning has challenges that must be taken into account. A successful repositioning requires the understanding of biological and molecular pathways that can be modulated by the drug and its interaction with endogenous biomolecules. This knowledge can contribute to the discovery of a new mechanism of action, a new pharmacological target, and a new therapeutic indication. Another relevant issue is the need for expensive and high-risk clinical trials, especially in the case of neurodegenerative diseases that require long-term/chronic treatments and elderly patients, who often have comorbidities and take other medications. In the end, there are no hard and fast regulatory guidelines for repurposing candidate drugs, and the intellectual property rights of the original drug can make the repositioning process difficult (Agrawal, 2015; Parvathaneni et al., 2019; Shineman et al., 2014). Despite existing barriers and limitations, drug repositioning for neurodegenerative diseases still seems to be a promising field, especially when the currently existing therapeutic options still fail to treat the diseases and improve the patient's quality of life.

Funding

This study was supported by the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq – Chamada Universal 429639/2018-0) and by the Coordenação de Aperfeiçoamento de Pessoal de Nível Superior – Brasil (CAPES) [Finance Code 001].

Declaration of competing interest

None.

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