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REVIEW

Potential drugs for the treatment of Alzheimer's disease

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Abstract

It is well known that amyloid precursor protein (APP), the enzyme β-secretase 1 (BACE1), cyclooxygenase 2 (COX-2), nicastrin (NCT), and hyperphosphorylated tau protein (p-tau) are closely related to the development of Alzheimer's disease (AD). In addition, recent evidence shows that neuroinflammation also contributes to the pathogenesis of AD. Although the mechanism is not clearly known, such inflammation could alter the activity of the aforementioned molecules. Therefore, the use of anti-inflammatory agents could slow the progression of the disease. Nimesulide, resveratrol, and citalopram are three anti-inflammatory agents that could contribute to a decrease in neuroinflammation and consequently to a decrease in the overexpression of APP, BACE1, COX-2, NCT, and p-Tau, as they possess anti-inflammatory effects that could regulate the expression of APP, BACE1, COX-2, NCT, and p-Tau of potent pro-inflammatory markers indirectly involved in the expression of APP, BACE1, NCT, COX-2, and p-Tau; therefore, their use could be beneficial as preventive treatment as well as in the early stages of AD.

Keywords Alzheimer's disease · Inflammation · APP · BACE1 · NCT · COX-2 · p-Tau

Abbreviations

3,5,4′-Trihydroxy-trans-stilbene	Resveratrol
AD	Alzheimer's disease
AICD	APP intracellular domain
APH-1A/APH-1B	Anterior pharyngeal deficiency 1A or 1B
APP	Amyloid precursor protein
BACE1	Enzyme β-secretase 1
COX-2	Cyclooxygenase 2
CTFα	C-terminal fragment alpha
CTFβ	C-terminal beta
FDA	Food and drug administration
GSK-3β	Glycogen synthase kinase-3 beta
IFN-γ	Interferon gamma
IL	Interleukins
iNOS	Inducible nitric oxide synthase
MMP9	Matrix metallopeptidase 9
NADPH	Nicotinamide adenine dinucleotide phosphate
NCT	Nicastrin
NF-κβ	Nuclear factor kappa-light-chain-enhancer of activated B cells
NO	Nitric oxide
NOX	NADPH oxidase
NSAIDs	Non-steroidal anti-inflammatory drugs
p-Tau	Hyperphosphorylated Tau protein
PEN-2	Presenilin enhancer 2

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PGs	Prostaglandins
PS1/PS2	Presenilins
ROS	Reactive oxygen species
sAPPα	Soluble APPα peptide
sAPPβ	Soluble APPβ
SSRIs	Selective serotonin reuptake inhibitors
TGF-β	Transforming growth factor beta
TLR4	Toll-like receptors
TNF-α	Tumour necrosis factor-alpha
WHO	World health organization

Introduction

Dementia is defined as a clinical syndrome characterized by the progressive deterioration of two or more cognitive domains, affecting abilities related to memory, language, executive, and visuospatial functions that ultimately result in the loss of the ability to perform essential and/or basic activities of daily living, causing changes in the personality and behavior of the person affected by the disease [1]. According to the World Health Organization (WHO), there are 50 million people with dementia and Alzheimer's disease (AD) accounts for between 60 and 80% of cases [2].

The pathogenesis of AD is poorly understood as it is considered a multifactorial disease. However, the formation of amyloid plaques, the presence of abnormal p-tau aggregates, and neuroinflammation are the main mechanisms associated with disease progression [3]. Although the mechanism is not clearly known, several studies have shown that the inflammatory process is related to the formation of extraneuronal deposits of β-amyloid (Aβ) peptide and the presence of p-tau within the neuronal soma [4].

Overexpression of APP, BACE1, and nicastrin proteins have been linked to Aβ accumulation, which induces overexpression of COX-2 and hyperphosphorylation of tau [5, 6]. Therefore, the presence of Aβ and p-Tau is able to activate the inflammatory response. However, chronic activation of this process contributes to the neurodegenerative process characteristic of Alzheimer's disease.

A recent study suggests that the use of other drugs with anti-inflammatory activity may be key to delaying the symptoms of the disease [7].

Specifically, it has been suggested that nimesulide, resveratrol, and citalopram may reduce neuroinflammation and delay the development of AD.

Therefore, the aim of this study is to analyze and describe the information showing the mechanism of action and the effects of the three anti-inflammatory agents on the expression of APP, BACE1, nicastrin, COX-2, and p-Tau in order to provide an updated document that may support the use of citalopram, resveratrol, and nimesulide as adjunctive therapy in Alzheimer's disease.

Pathogenesis of Alzheimer's disease

The formation of amyloid plaques and p-tau protein aggregates, loss of synaptic processes, and the presence of microglia and astrocytes around the amyloid plaques are basic histopathologic features for the diagnosis of Alzheimer's disease. These events occur in brain regions related to cognitive function, which would explain the absence of memory as the first symptom [8].

The accumulation of amyloid plaques and p-tau aggregates creates a toxic environment that impairs normal brain activities. Therefore, Aβ-peptide and p-tau protein are able to induce microglial activation, probably as a mechanism for their elimination. However, chronic activation of the inflammatory response contributes to neurotoxic conditions caused by the release of inflammatory markers and oxidative species. It is known that pro-inflammatory cytokines and oxidative conditions increase the expression of COX-2 enzymes and induce the synthesis of various types of prostaglandins that activate microglia and allow exacerbation of neuroinflammation [9].

Amyloid precursor protein (APP)

The amyloid precursor protein is abundantly expressed in the mammalian brain [10]. Physiologically, APP is involved in brain development, synaptic transmission, neuronal plasticity, and memory; it also exerts neuroprotective effects on the adult and elderly brain [11, 12]. This protein is mainly localized in the axonal and somatodendritic compartments of neurons of the hippocampus and cerebral cortex.

APP is degraded by two different cleavage mechanisms: the amyloidogenic and the non-amyloidogenic pathways. In the non-amyloidogenic pathway, the protein is cleaved by the enzyme α-secretase located in the plasma membrane, producing a soluble APPα-peptide (sAPPα) that is released into the extracellular space. Subsequently, the remaining peptide, termed C-terminal fragment alpha (CTFα), is cleaved in the cytoplasm by γ-secretase, yielding an APP intracellular domain (AICD) and a 3-kilodalton product termed p3 [10].

In the second mechanism, the amyloidogenic pathway, BACE1 is the major β-secretase involved in the processing of the toxic Aβ-peptide. This enzyme resides in endosomes and cleaves APP to generate the fragments known as soluble APPβ (sAPPβ) and C-terminal beta (CTFβ). Finally, γ-secretase cleaves CTFβ to generate the corresponding AICD and Aβ peptides [10].

The AICD peptides generated by both metabolic pathways have similar amino acid sequences. However, they

are recognized by different metabolic systems. The AICD fragment generated by α-secretase is rapidly degraded in the cytoplasm by the endosomal/lysosomal system and the enzyme responsible for insulin degradation, while the AICD generated by β-secretase cleavage can bind to other proteins related to transcriptional activation factors that can regulate gene expression of APP and BACE1 [10].

Beta-secretase (BACE1)

The enzyme BACE1 is a type I aspartyl protease that contributes to the processing of proteins involved in synaptic and extracellular matrix interactions of astrocytes and oligodendroglia and modulates axon extension and axoglial interactions [13]. In the amyloidogenic pathway, it is the first endoprotease involved during APP processing, and therefore the rate-limiting enzyme for Aβ production in the context of Alzheimer's disease [14].

Approximately 90% of pathogenesis-related Aβ fragments consist of 40 amino acids, followed by isoforms containing 42 residues [10]. These oligomers and the shorter isoforms have a fibrillar morphology and a beta-folded conformation. Therefore, they have a stronger aggregation ability due to their higher hydrophobicity [10, 15]. Subsequently, the Aβ-peptides polymerize with each other and form insoluble fibrils that are deposited in the form of plaques, which together induce the activation of kinases leading to the formation of p-tau, causing its self-association and forming neurofibrillary tangles [16].

Nicastrin (NCT)

APP is cleaved by BACE1 to yield the sAPPβ fragment, which is released into the cytosol while CTFβ is bound to the membrane. It is a transmembrane fragment with 99 residues at the C-terminal end, which is why it is also called APPC99; it is sequentially cleaved by γ-secretase to form Aβ-isomers [17]. The products derived from the endoprotease γ-secretase positively regulate the expression of APP and BACE1; moreover, they are involved in Aβ-deposition. Therefore, recent research has focused on elucidating the mechanism of their cleavage [18].

The γ-secretase consists of four subunits; presenilins (PS1/PS2), NCT, anterior pharyngeal deficiency 1A or 1B (APH-1A/APH-1B), and presenilin enhancer 2 (PEN-2), highlighting the role of NCT as a substrate receptor and stabilizer of the complex. Amino acid residues 241, 242, and to a lesser extent 244 (belonging to the NCT ectodomain) are involved in the efficiency of successive APP cleavage and modulate the length of the resulting peptides [17, 19].

In humans, the NCT gene is encoded on chromosomal fragment 1q23.2. The physiological functions of NCT are not well known. However, it may be related to excitatory synapses and neuroprotective activities [20]. According to the literature, overexpression of wild-type NCT increases Aβ production [21]. Moreover, mutations in NCT increase substrate cleavage by binding to the amino-terminal end formed after proteolysis of the extracellular domains of APP [22], supporting its implications in the pathogenesis of AD.

Cyclooxygenase-2 (COX-2)

In the brain, COX-2 is consistently expressed in the postsynaptic dendrites and excitatory terminals of neurons in the cortex area. Under physiological conditions, it is involved in synapses and neuronal plasticity by participating in the signaling pathways of glutamate, dopamine, some serotonin receptors, and the endocannabinoid system [23]. In contrast, COX-2 is upregulated in the early stages of AD in response to stressful conditions. Previous studies have shown that COX-2 correlates with the severity of amyloid plaques and an increase in hippocampal slices, and thus could trigger severe dementia in AD pathology [24].

COX-2 is the limiting peroxidase enzyme in the synthesis of prostaglandins (PGs) involved in numerous inflammatory responses [9, 25]. It possesses a heme group that catalyzes the production of PGs from arachidonic acid [23, 24], thus it is likely to exert its effects through its metabolites: the prostaglandins PGE2, PGD2, PGI2 PGF2α, and thromboxane A2 [9].

The prostaglandins 15d-PGJ2, PGI2, and PGF2α indirectly induce p-tau formation through various mechanisms that may be indirectly regulated by the inflammatory process, as will be discussed later [5]. Therefore, modulation of inflammation through COX-2 inhibition may be key to lowering levels of this protein.

Formation of hyperphosphorylated tau (p-tau)

Tau protein is essential for the proper function of neurons. It is associated with DNA protection, regulation of gene expression, myelination, neurogenesis, and synaptic activity. It is also involved in cellular transport and stabilization of axonal microtubules for the proper transport of substances within neurons [26, 27].

The functions of the tau protein can be regulated by different phosphorylation states. However, hyperphosphorylation of this protein may be associated with various disease states [27]. Once hyperphosphorylated, tau precipitates and self-aggregates, forming clusters that contribute to neurodegeneration. The latter is caused by the disruption of the flow of nutrients and neurotransmitters necessary for the normal activities of neurons [6]. In the context of amyloid deposition, Aβ has been shown to contribute to tau phosphorylation, and both molecules exert a synergistic effect in the development of AD [6].

It is known that APP, BACE1, NCT, COX-2, and p-Tau proteins are involved in amyloid peptide formation and aggregation of hyperphosphorylated tau. In addition, both Aβ and p-Tau are molecules that can trigger the inflammatory activity of microglia and astrocytes, exacerbating the disease state [28]. Expression of APP, BACE1, NCT, COX-2, and p-Tau is also able to induce the synthesis of pro-inflammatory markers such as cytokines, which in turn regulate the expression of these proteins [29, 30], likely in response to activation of signaling pathways such as NF-κβ [29, 30]. Based on these observations, inflammation may be an important intervening mechanism in the pathogenesis of AD.

Neuroinflammation

In the neuroinflammatory process, microglia are activated in the presence of alarm signals and are differentiated into two states: M1 and M2. The first one can produce cytotoxic proinflammatory mediators such as cytokines, chemokines, and interleukins (IL-1β, IL-6, IL-12) and TNF-α. In addition, they express nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, reactive oxygen, and nitrogen species, which are potent inflammatory triggers. In contrast, M2 microglia produce anti-inflammatory cytokines such as IL-10 and transforming growth factor beta (TGF-β). M2-like cells are also involved in the deposition of extracellular matrix for tissue remodeling and repair. They also provide for the removal of toxic debris. However, when cells are unable to switch from the M1 to the M2 state, excessive accumulation of inflammatory factors caused by chronic activation of microglia results in neuronal damage to surrounding cells [31, 32].

The sequential development of amyloid plaques, microglial activation, and p-tau aggregates have led to the hypothesis of a relationship between Aβ-inflammation and p-tau. Accumulation of various Aβ species appears to induce microglial activation and production of pro-inflammatory cytokines [28]. Subsequently, increased cytokines such as IL-β stimulate the formation of neurofibrillary tangles that support the effects of neuroinflammation in AD [32].

In the context of APP, BACE1, NCT, COX-2, and p-Tau proteins, APP was observed to increase its expression following the release of inflammatory markers by activated microglia [33]. Similarly, BACE1 is involved in astrocyte activation, and its inhibition under toxicity conditions could reverse inflammation and the number of reactive astrocytes [34].

There is evidence that NCT plays an important role in the development of immune cells such as T and B lymphocytes. Therefore, it may be related to response and neurodegeneration [35]. LPS-induced neuroinflammation stimulates the activation and expression of NCT [36]. Similarly, NCT levels and immunoreactivity may increase in astrocytes and microglia following brain injury [37]. Altered expression, mutations, or the presence of polymorphisms in nicastrin is also associated with the occurrence of inflammatory diseases, cognitive activity, and neuroinflammation [38].

As for COX-2, it was observed that during the process of neuroinflammation, its levels increased in microglia and astrocytes. Likewise, its metabolites have been associated with the exacerbation of the neuroinflammatory response, acting as triggers of proinflammatory markers and cell recruitment [9, 23, 39]. Similarly, prostaglandins induce p-tau formation, which could also lead to microglial activation. According to several studies, abnormalities in tau protein contribute to glia activation and neuroinflammation during AD [40].

These data suggest that treatment of AD should be undertaken with consideration of the multiple targets that allow AD to develop. However, current pharmacological therapies are limited to treating clinical symptoms and regulating key neurotransmitters affected during the neurodegenerative process, which helps to delay disease exacerbation.

Anti-inflammatory drugs as possible experimental treatments

Nimesulide

Nimesulide is a medicine that belongs to the group of nonsteroidal anti-inflammatory drugs (NSAIDs). These drugs are used to treat various conditions such as arthritis, fever, and pain; they inhibit the COX-2-mediated synthesis of prostaglandins (PGs), allowing them to exert their pharmacological effects.

Several studies establish a link between neuroinflammatory processes and the development of AD. The use of anti-inflammatory medications as an adjunctive therapy has received increasing attention in recent years [41]. Preclinical and epidemiological studies have demonstrated an association between the use of nonsteroidal anti-inflammatory drugs and the prevalence of AD. These agents are able to minimize the risk of AD, slow its progression, delay the onset of dementia, and reduce the severity of cognitive symptoms [42].

NSAIDs are able to reduce the production of amyloid plaques through several mechanisms; they prevent the aggregation of Aβ by changing its conformation and inducing the synthesis of proteins that bind to the peptide to remove it; they bind to Aβ at the N-terminal hydrophobic site (residues 17–21) to block the binding site of the next monomer, which could prevent incoming amyloid molecules from expanding the preformed fibril [42]. NSAIDs have also been implicated

in p-tau formation. Ibuprofen, a non-selective cyclooxygenase inhibitor (COX) NSAID, decreases p-tau formation in APP/PS1/TauTg mice, leading to the hypothesis that the enzyme COX plays an important role in p-tau development [5].

Although NSAIDs appear to have a good effect on AD, those that inhibit both COX isoforms (COX-1 and COX-2) can produce gastrointestinal and renal toxicity [24]. Nimesulide is an NSAID that selectively inhibits COX-2, has anti-inflammatory activity and good gastrointestinal tolerance, supporting its chronic use. In patients with arthritis, nimesulide has been observed to protect against cartilage degradation by inhibiting metalloproteinases, preventing the proliferation of proinflammatory cytokines. Therefore, it is also considered to have a protective effect [41].

Clinical trials

In a randomized trial of the use of nimesulide in Alzheimer's disease, in which patients were administered 100 mg of nimesulide twice daily for 24 weeks, results showed that patients receiving the drug had no significant effect on the results of measures of cognition, clinical status, and activities of daily living compared with the control group. Therefore, it is concluded that further studies with nimesulide over a longer period of time are needed [43].

In a meta-analysis of several NSAIDs, including nimesulide and other drugs such as diclofenac, naproxen, rofecoxib, and celecoxib, no clinical or statistical significance was found in the treatment of people with Alzheimer's disease when cognitive tests such as the Mini-Mental State Examination (MMSE) were used [44].

Resveratrol

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a biomolecule belonging to the group of polyphenols, molecules biosynthesized by plants as secondary metabolites that possess potent antioxidant and anti-inflammatory capacities, prevent the pro-oxidative state, and modulate gene expression thus maintaining optimal brain function [45].

Recent evidence has supported the neuroprotective activity of resveratrol against mental illness. In several In-vitro and in-vivo models, this compound prevents cytotoxicity, apoptosis, and accumulation of oxidative stress-related molecules, reactive oxygen species (ROS), and nitric oxide (NO) [46].

In association with AD, resveratrol reduces the levels of insoluble Aβ1-40, soluble Aβ1-40, insoluble Aβ1-42, and soluble Aβ1-42 in the brains of resveratrol-fed mice when compared with homogenates of control group mice which supports its positive effects on AD [14]. Furthermore, it helps to reduce oxidative stress and mitophagy-mediated mitochondrial damage in cell models previously stimulated with Aβ, which increases resistance against neuroinflammation [14, 47]. In addition to this, resveratrol also manages to suppress the M1 state of microglia, activating the M2 state in both in vivo and in vitro models. Therefore, it could also decrease neuroinflammation during AD [48].

Clinical trials

Studies in patients with mild to moderate Alzheimer's disease were treated with resveratrol for 52 weeks at a dose of 1 g twice daily orally. The results obtained were a marked reduction of MMP9 in the cerebrospinal fluid with an increase in macrophage-derived chemokine, interleukin 4, and fibroblast growth factor compared to the placebo group. Treatment with resveratrol attenuated the decrease in mini-mental examination, Aβ42 levels, without altering Tau expression levels, thus concluding that resveratrol modulates neuroinflammation and may be feasible for the treatment or prevention of psychiatric disorders [49].

A randomized, double-blind study also of 52 weeks administering 500 mg orally once a day with dose increments of 500 mg every 13 weeks and ending with 1000 mg twice a day, was obtained as a result of the study a decrease of Aβ40 in plasma and cerebrospinal fluid with respect to the group that was only administered placebo, which concludes that being well-tolerated resveratrol would be important to do studies in combination with other drugs [50].

Another randomized study shows results in contrast to the two previous ones, where patients with mild to moderate Alzheimer's disease were administered 500 mg of resveratrol for 52 weeks without having a statistically significant effect with respect to the group that was administered only a placebo [51].

In a recently performed systematic review of 4 randomized clinical trials where resveratrol was administered to Alzheimer's patients, the results obtained are that the polyphenol acts in delaying cognitive decline in most patients when compared to the control group [52].

Citalopram

According to Zhou et al., 70–90% of patients diagnosed with Alzheimer's disease will develop behavioral and psychological symptoms within a given period; among these symptoms are depression [53]. Citalopram is the most frequently prescribed medication for the management of depressive symptoms such as social withdrawal, dysphoria, and anxiety [54]. Furthermore, according to pharmaco-epidemiological studies conducted on patients with dementia, citalopram is the most effective medication for the control of neuropsychiatric symptoms compared to placebos and other atypical antipsychotic medications [55].

It is a selective serotonin reuptake inhibitor involved in modulating memory formation and mood and emotional states and, according to previous studies, could significantly improve learning and memory by promoting synaptic plasticity [54]. In post-mortem studies, AD patients exhibited decreased levels of both serotonin and its receptors, which could be a result of AD's own neurodegeneration [56].

In-vivo and in-vitro models, serotonin signaling causes a reduction in the generation of Aβ and selective serotonin reuptake inhibitors (SSRIs), including citalopram, could ameliorate memory deficits related to Aβ accumulation during AD progression [56]. Patients who have used SSRIs as a treatment for depression exhibit a significant reduction in amyloid plaque formation in PET studies [57]. Adding to this, human CSF studies demonstrate that a single dose of SSRI reduces levels of newly formed Aβ with no apparent effect on its clearance in young people with normal cognitive activity [57, 58].

IL-1β is the initiating cytokine of the proinflammatory cytokine cascade and, according to evidence, SSRI treatment decreases IL-1β levels. Being part of this pharmacological group could intervene in the inflammatory process through the modulation of pro-inflammatory cytokines [59].

Clinical trials

Several clinical trials have been conducted using citalopram/escitalopram on agitation in people with Alzheimer's disease. Agitation is a condition consisting of emotional distress, disruptive or aggressive behavior, and increased psychomotor activity. Doses used in clinical trials range from 10 to 15 mg per day for at least 9 weeks. The results of these trials determined that the condition of agitation decreased, as well as depression, showing a cognitive improvement in the MMSE [60–62].

Pharmacological activity

Neuroinflammation regulates the expression of APP, BACE1, NCT, COX-2, and p-tau

The emergence of amyloid plaques and p-Tau tangles leads to neuronal dysfunction. Injured neurons release cytokines and chemokines that induce neuroinflammation as a fundamental process for tissue repair and clearance of Aβ and p-Tau [63, 64]. However, chronic inflammation induces detrimental effects due to the excessive release of cytotoxic factors that aggravate brain injury [65]. Released species include cytokines and chemokines, ROS, and PGs, which aggravate neuroinflammatory conditions [66, 67].

Microglia and astrocytes are mainly responsible for the synthesis of cytokines, which contribute to the development of neuroinflammation during AD [68]. This activity is mainly due to the activation of NF-κβ, which is a transcriptional promoter of cytokines such as IL-1β, IL-6, IFN-γ, and TNF-α [69], which, indirectly intervene in the expression of APP, BACE1, NCT, COX-2, and p-Tau.

In endothelial cells and neurons, IL-1β and IL-1 synthesis induce APP mRNA and protein expression [33, 70, 71]. TNF-α and IFN-γ also increase APP expression in neurons and astrocytic cells [33]. APP expression also regulates the inflammatory process. In a study by Zhang and collaborators, APP overexpression induces the expression of TNF-α, IL-5, IL-13, and IFN-γ through two proteins named TNFRSF21 and APBB1, which are related to neurogenesis and apoptosis; added to this, APP is also able to induce IL-6 expression in animal models [72]. Despite these results, it should be emphasized that complete inhibition of APP is not effectuated. APP silencing not only reduces pro-inflammatory conditions, but it is also able to increase IFN-γ synthesis and decrease anti-inflammatory processes responsible for regulating neurodegeneration [73, 74], and therefore its regulation, but not its complete elimination, could be beneficial during the development of Alzheimer's disease.

NF-κβ could regulate BACE1 expression through cytokine synthesis. Chami and collaborators demonstrated that NF-κβ activation increases BACE1 promoter expression, whereas Alasmari and collaborators found that IFN-γ and TNF-α increase BACE1 expression [29, 33]. These data might suggest that NF-κβ regulates BACE1 expression through the synthesis of IFN-γ and TNF-α synthesis. On the other hand, inhibition of BACE1 reduces the expression of IL-1β, IL-6, and TNF-α [34, 75]. According to the study by Li et al., IL-1β does not affect BACE1 expression, but stabilizes APP-BACE1 binding to increase Aβ synthesis [70], demonstrating that the neuroinflammatory process affects BACE1 activity and its effect on AD.

Regarding NCT, there is data that could link this protein to neuroinflammatory activity. Mutations in NCT are able to increase IL-1β, IL-6, IL-17, IFN-γ, and TNF-α levels [76, 77]. At the same time, NF-κβ activation increases NCT promoter activation [29]. TNF-α and IFN-γ also stimulate γ-secretase activity [33] and because the activity and assembly of this enzyme is regulated by the interaction of its NCT and PS1 complexes [36], it is likely that the regulation of IL-1β, IL-6, IL-17, IFN-γ, and TNF-α through NF-κβ contribute to NCT expression and activity during AD.

NF-κβ induces mitogen-activated protein kinase (MAPK) pathway activity through the release of pro-inflammatory cytokines and, according to evidence, activation of both pathways is necessary for COX-2 expression [69, 78]. Wang et al., demonstrated that TNF-α, IL-1β, and IL-6 stimulate COX-2 mRNA and protein expression [5]. Therefore, it is likely that these cytokines induce COX-2 expression through the MAPK/NF-κβ pathway.

COX-2 overexpression also increases the production of PGs that could positively regulate NF-κβ activation and induce cytokine release. According to the studies, PGE2 increases NF-κβ activity, which increases IL-1β activity and induces TNF-α expression [9, 79]. Similarly, 15d-PGJ2 seems to pronouncedly stimulate TNF-α expression and accelerate cognitive decline through stimulation of apoptosis in APP/PS1 mice [3], while PGF2α and IL-1β exert synergistic activity to increase and induce IL-6 and COX-2 synthesis to enhance their pro-inflammatory effects [80], demonstrating that COX-2 regulates the inflammatory process through its metabolic products.

Regarding Tau protein, its phosphorylation has been shown to increase with the release of IL-6, IL-8, IL-1β [81–83]. The synthesis of p-Tau could also be affected by COX-2 activity. As previously shown, COX-2 accelerates the production of PGs such as PGF2α, PGI2, PGE2, and 15d-PGJ2, which are able to induce Tau phosphorylation through the activation of PI3K/Akt, ERK1/2 [5, 84]. According to the data provided up to this point, it can be concluded that the regulation of the inflammatory process plays an important role in the expression of APP, BACE1, NCT, COX-2, and p-Tau (Fig. 1). Nimesulide, resveratrol, and citalopram being anti-inflammatory agents, could regulate the expression of these proteins and exert beneficial effects on Alzheimer's disease. However, as will be discussed in the following sections, many of these effects are debatable.

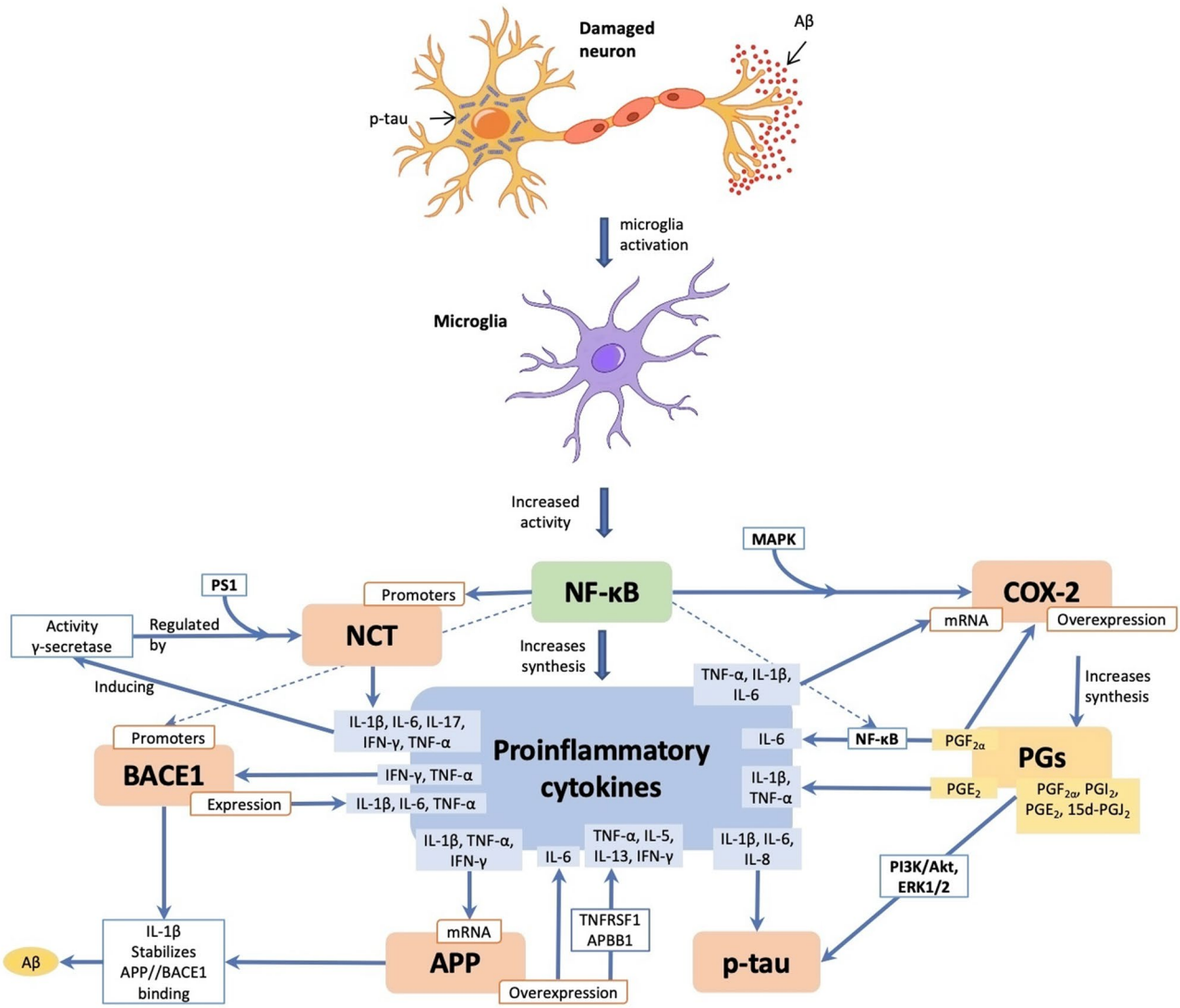

Fig. 1 Regulation of inflammation and expression of APP (Amyloid precursor protein), BACE1 (Enzyme β-secretase 1), NCT (Nicastrin), COX-2 (Cyclooxygenase 2), and p-tau (hyperphosphorylated Tau protein)

Nimesulide regulates the inflammatory process related to APP, BACE1, NCT, COX-2, and p-tau expression

According to a study by Martínez-Díaz et al. [85], nimesulide reduces the expression of BACE1, NCT, COX-2, and p-Tau, without affecting APP levels in cells previously treated with lipopolysaccharide (LPS). LPS stimulation induces NF-κβ activation and the synthesis of cytokines such as TNF-α, IFN-γ, IL-1β, and IL-6, likewise, increases the expression of ROS and other inflammatory markers such as PGs [86, 87], which, as previously demonstrated, regulate the expression of APP, BACE1, NCT, COX-2, and p-Tau.

In rat astrocytoma cells, nimesulide reduces NF-κβ and mRNA and protein expression of IL-1β, IL-6, and TNF-α [88]. In the rat hippocampus and cerebral cortex, nimesulide reduces the synthesis of IL-6, IFN-γ, and TNF-α and increases the levels of IL-10, which is a highly anti-inflammatory cytokine [89]. Polat and collaborators demonstrated that nimesulide reduces IL-1β, TNF-α, and COX-2 levels simultaneously. However, it is difficult to determine whether COX-2 induces cytokine expression or whether cytokines induce COX-2 expression [90].

As discussed previously, APP, BACE1, NCT, COX-2, and p-Tau can increase their expression in response to stimulation of the inflammatory process, so the following scheme presents the possible mechanism by which nimesulide carries out its effects (Fig. 2). Despite the previous information, the effects of nicastrin on Alzheimer's proteins are debatable because there is insufficient information to support its effects on APP, BACE1, NCT, COX-2, and p-Tau. According to previous information, nimesulide is involved in signaling multiple inflammation-associated targets that could more robustly support its effects on these proteins.

Nimesulide regulates Alzheimer's protein expression indirectly

AD brains exhibit high levels of oxidative species because of neuroinflammation [65]. NF-κβ regulates the expression of ROS and NO through transcriptional regulation of the enzymes NADPH oxidase (NOX) and inducible nitric oxide synthase (iNOS) [30, 66, 69, 91]. At the same time, increased oxidative stress enhances NF-κβ activity and the release of inflammatory markers [69].

Oxidative conditions induce BACE1 promoter and protein expression, enhance COX-2 expression and increase p-Tau formation in animal models [24, 92, 93]. Nimesulide decreases the production of oxidative species and increases the release of antioxidants [94]. It also reduces iNOS expression in response to the reduction of NF-κB and IL-1β, IL-6, and TNF-α [88], and decreases the levels of ROS [25]. These data suggest that nimesulide interferes with the expression of BACE1, COX-2, and p-Tau through NF-κβ and oxidative stress.

Protein glycogen synthase kinase-3β (GSK-3β) is also related to inflammation as it is involved in the release of cytokines and ROS by regulating NF-κβ stability and activity [72, 91, 93, 95]. According to evidence, GSK-3β is related to the regulation of BACE1 and p-Tau transcription and expression. Furthermore, it regulates APP metabolism [10, 70, 91, 96], NCT [97], COX-2 [98], and p-Tau [99, 100].

Nimesulide reduces COX-2 expression which prevents GSK-3β activation and Tau phosphorylation through its metabolic products [5, 101]. These data agree with the results of Martínez-Díaz et al. [85], where COX-2 and p-Tau reduction is demonstrated after nimesulide treatment.

This contrasts with other results where nimesulide is observed to increase GSK-3β activity through phosphorylation of PI3K, which is an upstream regulator of the GSK-3β pathway [102]. However, a study has shown that nimesulide has no effect on the treatment of Alzheimer's disease [43].

Resveratrol regulates the inflammatory process related to APP, BACE1, NCT, COX-2, and p-tau expression

Following the results of Martinez et al., resveratrol markedly reduces the expression of NCT and p-Tau. Paradoxically, it increases COX-2 levels and keeps APP and BACE1 levels unchanged [85]. These data contrast with different studies. In mouse hippocampal samples, resveratrol reduces APP mRNA and protein expression, in addition to reducing BACE1 levels. It also attenuates the expression of sAPPα and sAPPβ fragments, demonstrating its effects on α- and β-secretase enzymes and APP processing [14]. Other studies demonstrate that resveratrol down-regulates transcription and subsequent expression of COX-2 [103, 104].

Resveratrol regulates the expression of pro-inflammatory genes, COX expression, and the release of ROS through toll-like receptors (TLR4), which affect the expression of MAPK and NF-κβ mRNA and proteins [104, 105]. This activity regulates the release of IL-1β, IL-6, and TNF-α, without affecting IL-8 and IL-1 levels [106–108]. According to the literature, resveratrol reduces COX-2 expression through the NF-κβ pathway [109]. Furthermore, this anti-inflammatory down-regulates both COX-2 and PGE2 expression, which reduces inflammation in animal models [110, 111]. Although there is no further evidence determining its effect on the other proteins through inflammation, it is likely that resveratrol intervenes indirectly.

The Fig. 3 summarizes the possible mechanisms by which resveratrol regulates the expression of APP, BACE1, NCT, COX-2, and p-Tau through its effects during the inflammatory process.

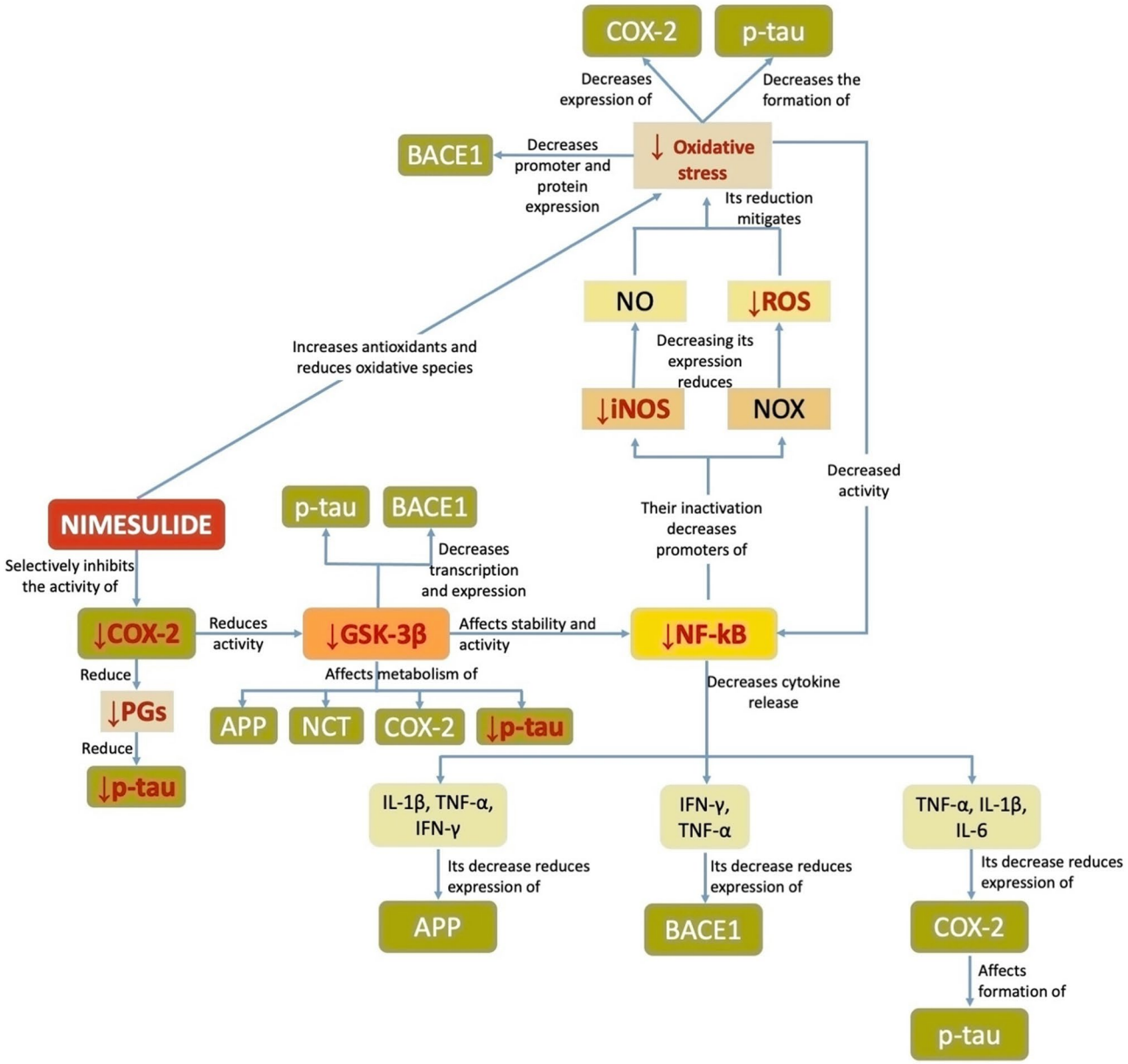

Fig. 2 In-direct regulation of APP (Amyloid precursor protein), BACE1 (Enzyme β-secretase 1), NCT (Nicastrin), COX-2 (Cyclooxygenase 2), p-Tau (hyperphosphorylated Tau protein) expression, and the inflammatory process by nimesulide. Nimesulide acts by inhibiting COX-2 expression and inhibits glycogen synthase kinase-3 beta activity, which indirectly, by decreasing the release of pro-inflammatory cytokines, will reduce the expression of APP, BACE1, Nicastrin and may prevent the formation of p-tau

Resveratrol regulates Alzheimer's protein expression indirectly

Resveratrol possesses strong antioxidant activity that contributes to the reduction of NF-κβ activity [65, 104]. According to research, resveratrol reduces BACE1 and p-Tau levels by regulating the expression of EROs and decreases COX-2 levels in models expressing NOX, iNOS, and their respective products [92, 112–114], providing it with a strong effect on the expression of these proteins. There is no information on the effects of resveratrol on APP through its antioxidant power. However, it is likely that its effect is through a decreased synthesis of ROS [115].

Resveratrol reduces the activity of ERK/GSK-3β and Akt/GSK-3β pathways which prevent Tau phosphorylation [14, 111, 113, 114]. Likewise, it reduces Akt activity in different inflammation-related diseases [116, 117]. Akt depletion affects NCT stability which reduces γ-secretase

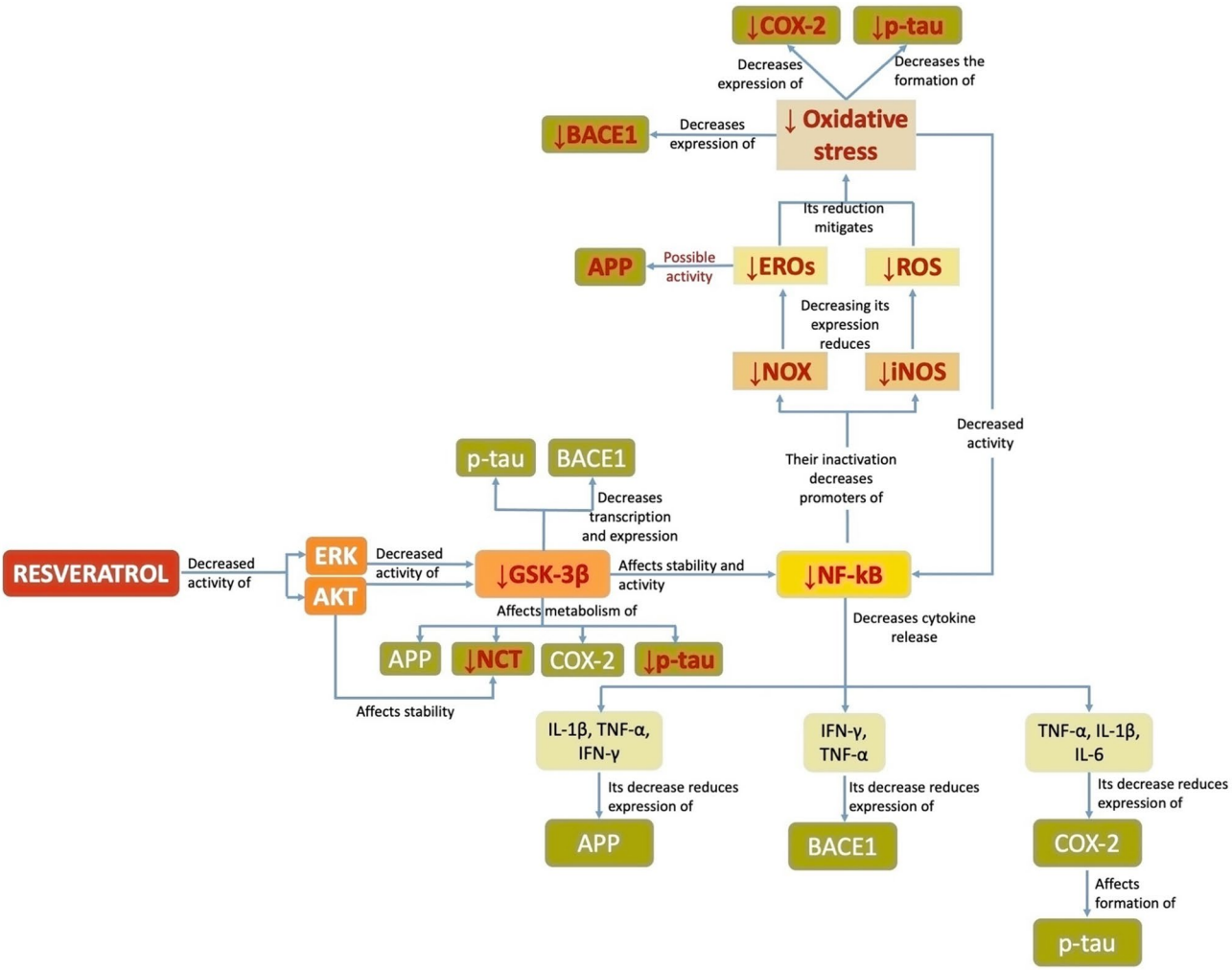

Fig. 3 In-direct regulation of APP (Amyloid precursor protein), BACE1 (Enzyme β-secretase 1), NCT (Nicastrin), COX-2 (Cyclooxygenase 2), p-Tau (hyperphosphorylated Tau protein) expression, and the inflammatory process by resveratrol. Resveratrol decreases ERK/AKT pathway activity, affecting GSK-3β and NF-κβ activity, which will decrease the expression of APP, BACE1, Nicastrin, and p-tau, by decreasing the release of pro-inflammatory enzymes

activity [118], thus resveratrol might exert effects on NCT expression and APP processing through Akt. Despite these conjectures, further evaluations are needed to demonstrate that resveratrol exerts an effect on these proteins.

Citalopram regulates the inflammatory process related to APP, BACE1, NCT, COX-2, and p-tau expression

Although citalopram is the most frequently prescribed drug [55], escitalopram has more published research papers. The first one is a racemic mixture of the R- and S-citalopram enantiomers, where the S- conformation is the one that exerts the pharmacological activity while escitalopram is a drug that only contains the active form [58]. Therefore, in this work, data from both drugs will be used to establish the possible effects of citalopram on AD.

Martinez et al., showed that citalopram reduces APP, COX-2, and p-Tau levels in a pronounced way. However, it does not seem to exert results on BACE1 and increases NCT expression [85, 119]. Studies in human-derived neuronal cells demonstrate the beneficial effect of citalopram on the reduction of the Aβ1-42:40 ratio, increasing the non-amyloidogenic processing pathway [120]. In the hippocampus of 3xTgAD mice, citalopram decreases APP expression and reduces CTFβ levels, which is a metabolic product obtained by BACE1 activity. Therefore, the effect of citalopram on the expression and activity of BACE1 would not be ruled out [121]. However, more research is needed as there is even research indicating a contradictory effect of SSRIs on BACE1 [58, 122].

Citalopram could regulate AD protein expression through the regulation of the inflammatory process. In depression, IL-2, IL-4, and IFN-γ levels are altered. However, SSRI use normalizes their concentrations. Treatment with citalopram suppresses IL-2, IL-4, and IL-17 production in animal models of depression [123]. However, there are no effects on pro-inflammatory markers associated with APP, BACE1, NCT, COX-2, and p-Tau. Likewise, citalopram reduces NF-κβ expression and the activity of some of its signaling pathways [124, 125]. In Fig. 4, the possible mechanism by which it intervenes in Alzheimer's protein expression through modest regulation of inflammation is shown.

Citalopram regulates APP, BACE1, NCT, COX-2, and p-tau expression indirectly

The inflammatory process is also related to serotonin signaling, which could explain the activity of SSRIs on AD. In human dendritic cells, activation of serotonin or 5-Hydroxytryptophan (5-HT) receptors reduces the expression of IL-12, IL-6, and TNF-α [123, 126]. Likewise, 5-HT and its metabolites have been shown to reduce NF-κβ activity and plasma concentrations of TNF-α, IL-6, IL-10, and IL-1β, which, decreases iNOS expression and plasma NO levels, demonstrating that 5-HT also exerts beneficial effects on oxidative stress [126, 127].

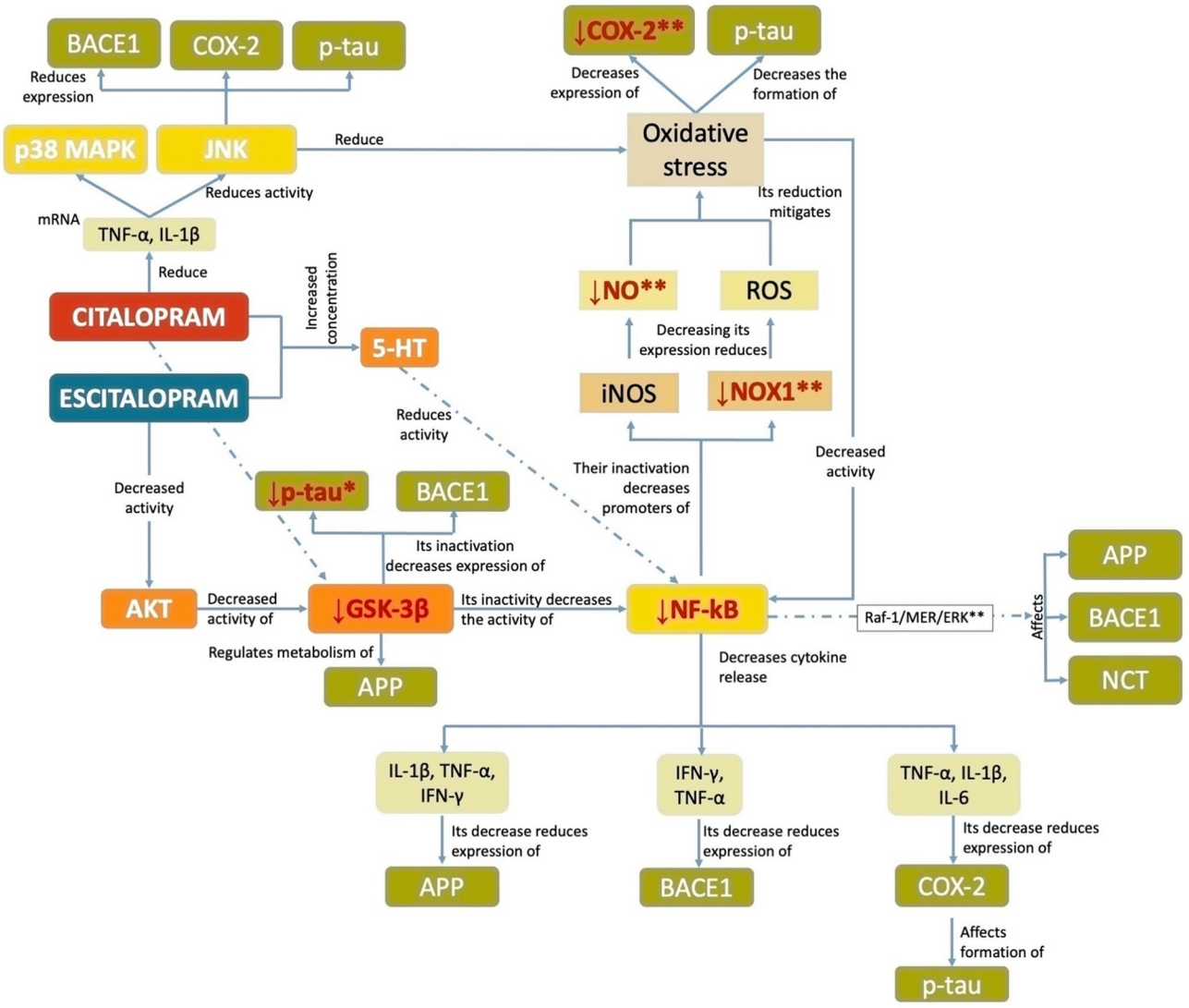

Fig. 4 In-direct regulation of APP (Amyloid precursor protein), BACE1 (Enzyme β-secretase 1), NCT (Nicastrin), COX-2 (Cyclooxygenase 2), p-Tau (hyperphosphorylated Tau protein) expression, and the inflammatory process by citalopram. Citalopram or escitalopram could decrease the release of pro-inflammatory cytokines and decrease AKT activity respectively, leading to a reduction of APP, BACE1, Nicastrin, and p-tau expression

Citalopram could also be related to the regulation of inflammation through its antioxidant effects. In animal models, escitalopram decreases NOX1 gene expression by 63% when compared to the untreated group [91]. In addition, it reduces NO synthesis and COX-2 expression in rats exhibiting oxidative stress. This fact could support the effects of SSRIs on COX-2 and p-Tau by reducing oxidative stress and inflammation.

Studies in mouse models have shown that citalopram improves cognitive behavior, due to an increase in spine density and synaptic activity [119].

NF-κβ activation is involved in Raf-1/MEK/ERK pathway signaling. According to studies, serotonin activates the Raf-1/MEK/ERK pathway which increases the non-amyloidogenic processing of APP and reduces BACE1 and γ-secretase expression, the latter, potentially intervening in NCT expression [58, 91]. In animal models, treatment with escitalopram decreases Raf-1, MEK, and ERK activity pronouncedly. Therefore, it is likely that citalopram has similar activity on this signaling pathway.

Citalopram inhibits TNF-α, IL-1β mRNA, and proteins which also reduce JNK and p38 MAPK activity [128]. According to previous reports, JNK is associated with pro-inflammatory cytokine release, oxidative stress, and neuroinflammation [98, 129, 130]According to previous studies, JNK contributes to the overexpression of BACE1, COX-2, and p-Tau formation [91, 131, 132], thus, it is likely that citalopram exerts effects on BACE1, COX-2, and p-Tau through the regulation of inflammation and subsequent JNK signaling.

There is no information that can prove the direct relationship of the anti-inflammatory effects of citalopram with the expression of p-Tau; however, it could exert its effects through GSK-3β/NF-κβ. The only work demonstrating the activity of citalopram on p-Tau was elaborated by Ren et al., in which, a pronounced decrease of p-Tau is observed, probably as a result of GSK-3β activity, which, could be demonstrated with current works where escitalopram is used [133]. The latter reduces Tau mRNA phosphorylation and synthesis through decreased Akt/GSK-3β activity [4, 134], demonstrating that both citalopram and escitalopram could have a positive effect on the Tauopathy exhibited during AD.

Conclusion

The treatment of AD, being a multigenic pathology, is complicated due to the intervention of multiple related mechanisms; however, the inflammatory process is one of the most studied in recent years due to its close relationship with the onset of neurodegenerative diseases. Therefore, it seems necessary to find therapeutic agents that effectively intervene in a large number of therapeutic targets related to inflammation. Nimesulide, resveratrol, and citalopram seem to obtain good results in the control of therapeutic targets related to the inflammatory process and the expression of APP, BACE1, NCT, COX-2, and p-Tau. Therefore, it cannot be discarded that they represent good options as a concomitant treatment for the prevention and treatment of AD during its early stages.

Unfortunately, no clinical trials have been reported for the treatment of the disease in which the 3 drugs are administered at the same time. This could be since clinical studies in patients with AD have not been completely conclusive as to their effectiveness. However, it would be interesting to do pre-clinical studies on the effectiveness of these drugs together in the treatment of AD, since it is very important to decrease neuroinflammation before using drugs that have been approved by the Food and Drug Administration (FDA).

For the treatment of the disease, only 5 drugs were approved by the FDA. However, even though at the beginning of the treatment patients respond positively, over time they continue to deteriorate cognitively. This may occur because the drugs do not target the root cause of the disease, such as the neuroinflammation that leads the patient to continue to deteriorate at an increasing rate.

An interesting proposal would be to combine nimesulide, resveratrol, and citalopram with one of the FDA-approved drugs.

This could probably be of benefit to the patient and prevent him from deteriorating at an alarming rate.

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Declarations

Conflict of interest The authors have nothing to disclose.

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