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Action of the Purinergic and Cholinergic Anti-inflammatory Pathways on Oxidative Stress in Patients with Alzheimer's Disease in the Context of the COVID-19 Pandemic

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Abstract—Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), the etiologic agent of the 2019 coronavirus disease (COVID-19), has affected more than 20 million people in Brazil and caused a global health emergency. This virus has the potential to affect various parts of the body and compromise metabolic functions. The virus-mediated neural inflammation of the nervous system is due to a storm of cytokines and oxidative stress, which are the clinical features of Alzheimer's disease (AD). This neurodegenerative disease is aggravated in cases involving SARS-CoV-2 and its inflammatory biomarkers, accelerating accumulation of β-amyloid peptide, hyperphosphorylation of tau protein, and production of reactive oxygen species, which lead to homeostasis imbalance. The cholinergic system, through neurons and the neurotransmitter acetylcholine (ACh), modulates various physiological pathways, such as the response to stress, sleep and wakefulness, sensory information, and the cognitive system. Patients with AD have low concentrations of ACh; hence, therapeutic methods are aimed at adjusting the ACh titers available to the body for maintaining functionality. Herein, we focused on acetylcholinesterase inhibitors, responsible for the degradation of ACh in the synaptic cleft, and muscarinic and nicotinic receptor agonists of the cholinergic system owing to the therapeutic potential of the cholinergic anti-inflammatory pathway in AD associated with SARS-CoV-2 infection.

Key words: SARS-CoV-2, Alzheimer's disease, Purinergic, Cholinergic, Oxidative stress.

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Abbreviations: 8-OHG, 8-hydroxyguanosine; ACE 2, Angiotensin-converting enzyme 2; ACh, Acetylcholine; AChE, acetylcholinesterase; AD, Alzheimer's diseas; Apo E, apolipoprotein E; APP, amyloid precursor protein; ARE, antioxidant response element; ATP, Adenosine Triphosphate; Aβ 1-42, 42 amino acid long beta-amyloid peptide; Aβ, β-amyloid; BBB, blood-brain barrier; Ca^{2+}, calcium ions; CAT, catalase; CKAP4, Cytoskeleton-associated protein 4; CNS, Central nervous system; COVID-19, acetylchoxxxlinesterase; CRP, C-reactive protein; CSF, cerebrospinal fluid; EO-FAD, early-onset familial Alzheimer disease; ER, endoplasmic reticulum; ETC, ETC; FDG-PET, fluorodeoxyglucose positron emission tomography; GAL-3, galactin-3; GPx, glutathione peroxidase; HCoVs, human coronaviruses; IL, interleukin; IsoPs, isoprostanes; KEAP 1, Kelch from stress sensor 1; LO-SAD, sporadic late onset Alzheimer disease; LTP, long-term potentiation; miRNA, microRNA; Na^{+}, sodium ions; NFTs, neurofibrillary tangles; NMDAR, N-methyl-D-aspartate receptor; NO, Nitric oxide; NOS, nitric oxide synthase; NPCs, neuronal precursor cells; Nrf2, Nuclear factor-erythroid 2 related factor 2; ORP, open reading frame; P1R, α 7 nicotinic acetylcholine receptor; P2X7R, P2X7 receptor; PANX-1, Pannexin 1; PGE2, prostaglandin E2; PNS, peripheral nervous system; PS1, Presenilin 1 gene; PS2, Presenilin 2 gene; PSEN1/2, presenilin genes; P-tau 181, phosphorylated tau on threonine 181; RNS, reactive nitrogen species; ROS, reactive oxygen species; SARS-CoV-2, Severe acute respiratory syndrome coronavirus 2; SOD, superoxide dismutase; TBI, Traumatic brain injury; TNF-α, tumor necrosis factor alpha; Zn, Zinc; α7nAChR, α 7 nixxxcotinic acetylcholine receptor.

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INTRODUCTION

AD is a progressive neurodegenerative disease, which is the most common cause of dementia in the elderly population worldwide. In the scenario of COVID-19, it has emerged as a key comorbidity, given the increased morbidity and mortality of COVID-19 in patients with AD due to multiple pathological changes. Among them, we can mention: the high expression of the viral angiotensin-converting enzyme 2 (ACE2) receptor, the increase in pro-inflammatory cytokines and several complications of AD (diabetes, changes in lifestyle, use of medication). Adding to the picture, the direct attack of the virus to the central nervous system (CNS) results in neurological symptoms, cognitive impairment, neuronal inflammation, hospitalization and post-COVID-19 delirium and syndrome (Xia et al., 2021). Furthermore, the COVID-19 crisis also worsens behavioral symptoms in uninfected AD patients and presents new challenges for preventing AD and controlling its progression.

Clinical signs have an insidious onset of memory deficits, with an emphasis on recent memory impairments, learning difficulties, mood, and behavioral

changes, which progress to variations in personality, language, calculation, visuospatial orientation, severe retrograde amnesia, and aphasia. In more advanced cases, in addition to psychotic symptoms, individuals present alterations in the sleep-wake cycle, irritability and aggressiveness, speech, gait and self-care difficulties (Ferreira et al., 2020). Among the risk factors, studies list more than 20 variants associated with AD including age, family heritage, exposure to aluminum, traumatic brain injury (TBI) and comorbidities such as vascular disease and infections.

Genetic mutations stand out in rare forms of early-onset familial AD (EO-FAD), such as alterations in the amyloid precursor protein (APP) and presenilin genes (PSEN1/2), while late-onset sporadic AD (LO-SAD) presents a compilation of genetic and environmental factors. Thus, it may be related to age, genetic risk factors such as allelic variation in apolipoprotein E (Apo E) and many other genes, as well as infections, mitochondrial function, metal exposure, immune system defects, vascular disease, TBI, and risk factors associated with diet. From this perspective, the variables are reorganized to the point of acting together to: a) increase the concentration of oxygen free radicals, b) external factors acting on early and late regulatory genes (the 'double whammy' hypothesis) or c) increasing the 'cumulative allostatic' load on the body over a lifetime (Armstrong, 2019). Thus, the ways to modulate this pathogenesis are diverse, ranging from changes in habits to genetic management.

Among the hypotheses for the development of AD, it is believed that the protagonism of the β-amyloid protein. The Aβ hypothesis selects the imbalance between production and clearance of Aβ42 and Aβ peptides as an EO-FAD factor. Thus, knowing that the catalytic site of γ-secretase is presenilin, he oriented the causative factor of AD from the beginning on the alteration of the substrate, that is, on the APP or on the protease (presenilin) of the reaction that generates Aβ (Selkoe and Hardy, 2016). Thus, it is believed that the deposition of Aβ plaques results in neurodegeneration of brain tissue and this accumulation is the main influence on pathogenesis, followed by the formation of neurofibrillary tangles containing tau protein (Hardy and Selkoe, 2002). In addition, recent studies indicate that low Aβ42 concentration in the cerebrospinal fluid (CSF) and amyloid-PET positivity precede other manifestations of AD by many years, in addition to new results with three different Aβ antibodies (solanezumab, crenezumab and aducanumab) (Selkoe and Hardy, 2016). These suggested a slowing of cognitive decline in post hoc analysis of individuals with mild AD, leading to several factors that contribute to the development and progression of the disease (Selkoe and Hardy, 2016).

Thus, with mutations in presenilins implying alteration of the enzymatic activity of γ-secretase and the production of Aβ, the pathogenesis of hereditary AD in middle age results, although it is indistinguishable from sporadic and late AD. Mutations within and immediately flanking the Aβ region of APP cause aggressive forms of FAD. An increase in Aβ42-to-Aβ40 is understood to occur by mutations in presenilin, driven by a reduction in carboxypeptidase clipping and the increase in longer forms of Aβ, including membrane-associated forms Aβ45-Aβ49 (Wolfe, 2019). Relative increases in the production of Aβ42/43 peptides lead to a profound deposition of Aβ in middle age because they are hydrophobic species that self-aggregate easily (Selkoe and Hardy, 2016).

Certain biomarkers, such as interleukin (IL)-1 and IL-6, are also detected in the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. The new coronavirus is an enveloped virus with a single-stranded RNA, belonging to the family Coronaviridae, which has seven subtypes that affect humans and six other strains (Weiss and Navas-Martin, 2005; Rahman et al., 2021). This virus can cause neural tissue inflammation, and in patients with AD, it can aggravate the clinical picture, given that it uses the olfactory bulb to permeate the nervous tissue, inducing the activation of defense cells, reactive astrogliosis, and the necroinflammatory cascade (Zotova et al., 2013; Wu et al., 2020). Concomitantly, there is an increase in the levels of the plasma protein Galectin-3 (GAL-3), which is closely linked to the oligomerization of Aβ. Thus, there is a close association between SARS-CoV-2 infection and the poor prognosis of AD.

Another factor that boosts AD progression is the production of reactive oxygen species (ROS) and reactive nitrogen species (RNS), which at high concentrations trigger an imbalance in the homeostasis of antioxidant substances and is responsible for neutralizing and reducing damage caused by free radicals. Oxidative stress in the neuronal environment from the exacerbated production of free radicals by the mitochondria, a by-product of respiration, generates brain aging. This scenario is present both in aging and in the pathogenesis of AD, the so-called mitochondrial cascade hypothesis, in which damaged mitochondria produce beta-amyloid, a toxic oxidative stressor. Free radicals are capable of breaking unprotected mitochondrial DNA double strands without histones, as well as manipulating the epigenome and have far-reaching effects, from repression of cognitive genes by H3K9me3 to hypomethylation and activation of the APP promoter. Studies with mitochondrial antioxidants in aged animal models reduce oxidative stress and DNA damage, while restoration of mitophagy in AD models may minimize pathology (Ionescu-Tucker and Cotman, 2021). Thus, acting on different lines of attack against the progression of the disease can contribute to the reduction of neurodegeneration, although several pathways are interconnected to this process.

Such alterations are related to the development of neurodegenerative diseases, which can lead to the accumulation of Aβ and the generation of tau neurofibrillary tangles (NFTs), compromising axonal transport, synaptic processing, and neuronal death (Gauthier et al., 2016). Furthermore, oxidative stress can be amplified by the activation of the N-methyl-D-aspartate receptor (NMDAR) in the stress signaling pathways in neurons and by cytoplasmic calcium deposition induced by Aβ plaques, which also stimulates the extra-

cellular accumulation of glutamate. Upon activation of the central apoptotic pathway, cytochrome C is released to mediate the breakdown of synaptic proteins (Kamat et al., 2016).

There are different biomarkers considered for the biochemical diagnosis of AD and, based on different studies and much progress in this area, it was possible to validate three standard variables in the analysis of cerebrospinal fluid (CSF). Among them, the 42 amino acid long beta-amyloid peptide (Aβ 1–42), total tau protein (T-tau) and phosphorylated tau on threonine 181 (P-tau 181). They have been incorporated into research diagnostic criteria for AD and have added value both in diagnosis and exclusion in case of ambiguous clinical diagnoses of dementia (Bjerke and Engelborghs, 2018). Future researchers are leaning their studies on the implementation of the ratio of CSF Aβ 1-42 /Aβ 1-40A, acting directly on the analytical variability of the biomarker and early and differential diagnosis of AD. Based on many human biomarker studies, low CSF Aβ42 and positive amyloid PET precede other AD-related changes (increased CSF tau, decreased cerebral glucose metabolism, brain atrophy, clinical dementia) by years (Selkoe and Hardy, 2016). Furthermore, other studies analyze other pathological features of AD, such as incorrect amyloid metabolism, tau pathology or synaptic or neuronal degeneration, as well as neurodegenerative, vascular or inflammatory markers unrelated to AD (Bjerke and Engelborghs, 2018).

The neurotransmitter acetylcholine (ACh) is present in fundamental physiological pathways, such as the stress response in the cognitive system, sensory information, and sleep and wakefulness (Ferreira-Vieira et al., 2016); therefore, neurochemical changes in the cholinergic system have been linked to AD. The formation of Aβ in hyperphosphorylated tau plaques and tangles causes wear at the synapses and machinery, including the ACh pathways and cholinergic system, leading to a reduction in the concentration of this neurotransmitter in the synaptic cleft. ACh promotes neuron plasticity and is responsible, along with the serotonergic system, for cognitive, behavioral, and emotional regimes; therefore, a low concentration of ACh is considered one of the main characteristics of AD (Machado et al., 2020).

Damage to these chemical systems and mechanisms induces the development of AD (Rasch et al., 2006; Kuo et al., 2007) via presynaptic cholinergic lesions in nucleus basalis of Meynert neurons and axonal projections from the cerebral cortex, affecting local muscarinic and nicotinic receptors. Thus, maintaining adequate levels of ACh in the synapses can be used as a treatment method for AD. This can be achieved by administrating drugs that block the action of acetylcholinesterase (AChE), as they are capable of modulating the supply of ACh in the synaptic cleft (Rasch et al., 2006; Kuo et al., 2007).

Thus, the relationship between AD and COVID-19 is related to the neuroinflammatory process and neuronal oxidative state, and the association between these pathologies and its effect on the prognosis is evidenced by more than 50 million individuals with some type of dementia and the global reality of a highly infectious virus. Hence, it is possible to establish a close association between the cholinergic disorders present in both diseases, and modulation of the cholinergic anti-inflammatory pathway stands out for its therapeutic potential and must be focused on and applied in further research to enable the development of alternative therapies (Fig. 1).

NEUROCHEMICAL CROSS-TALK BETWEEN CORONAVIRUS DISEASE 2019 AND ALZHEIMER'S DISEASE

COVID-19 was initially detected as an outbreak with its epicenter located in Hubei Province, China, but quickly spread to other countries (Gómez-Mesa et al., 2021). The causal agent for COVID-19 is the SARS-CoV-2 virus, representative of the coronavirus family, which was first described in humans in 1966 when Tyrell and Bynoe observed the cultivation of viruses related to common cold (Chazal, 2021). Coronaviruses are named for their appearance, i.e., spherical-shaped with a central shell and surface projections that surround it like a crown (Velavan and Meyer, 2020). After the first reports of infection in 2019, it was identified that the responsible virus could be transmitted between humans (Baig et al., 2020). Based on the exponential increase in case notification rates across international, on March 11, 2020, the Emergency Committee of the World Health Organization declared that the outbreak of ''Corona Virus 2019," first diagnosed in a Chinese province, had become a global health emergency (Asselah et al., 2021).

Coronaviruses are enveloped, single-stranded, positive-sense RNA viruses ranging from approximately 26–32 kilobases in size (the largest genome known for an RNA virus) (Weiss and Navas-Martin, 2005). Four subfamilies are currently recognized and categorized as alpha, beta, gamma, and delta-coronaviruses. Alpha and beta coronaviruses are strongly associated with mammals in the order Chiroptera. In contrast, gamma and delta viruses originate from pigs and birds (Shu and McCauley, 2017; Zhou et al., 2020). Phylogenetically, the etiological agent of COVID-19 belongs to the subgenus Sarbecovirus, genus Betacoronavirus, subfamily Orthocoronavirinae, and family Coronaviridae (Cornidovirinea: Nidovirales) (Su et al., 2016). Among the seven subtypes of coronaviruses that infect humans, betacoronaviruses are associated with serious diseases and fatalities (Shu and McCauley, 2017; Zhou et al., 2020).

All coronaviruses have similar characteristics in their organization and expression, in which 16 non-structural proteins (nsp1 to nsp16) are encoded by the open reading frame (ORF) 1a/b at the 5′ end, followed by the peak expression of structural proteins (S), envelope (E), membrane (M), and nucleocapsid (N), which are encoded by other ORFs at the 3′ end (Kin et al., 2015). Currently, seven human coronaviruses (HCoVs) have been identified, namely HCoV-229E, HCoV-OC43, SARS-CoV, HCoV-NL63, HCoV-HKU1, Middle East respiratory syndrome coronavirus, and SARS-CoV-2 (Kin et al., 2015).

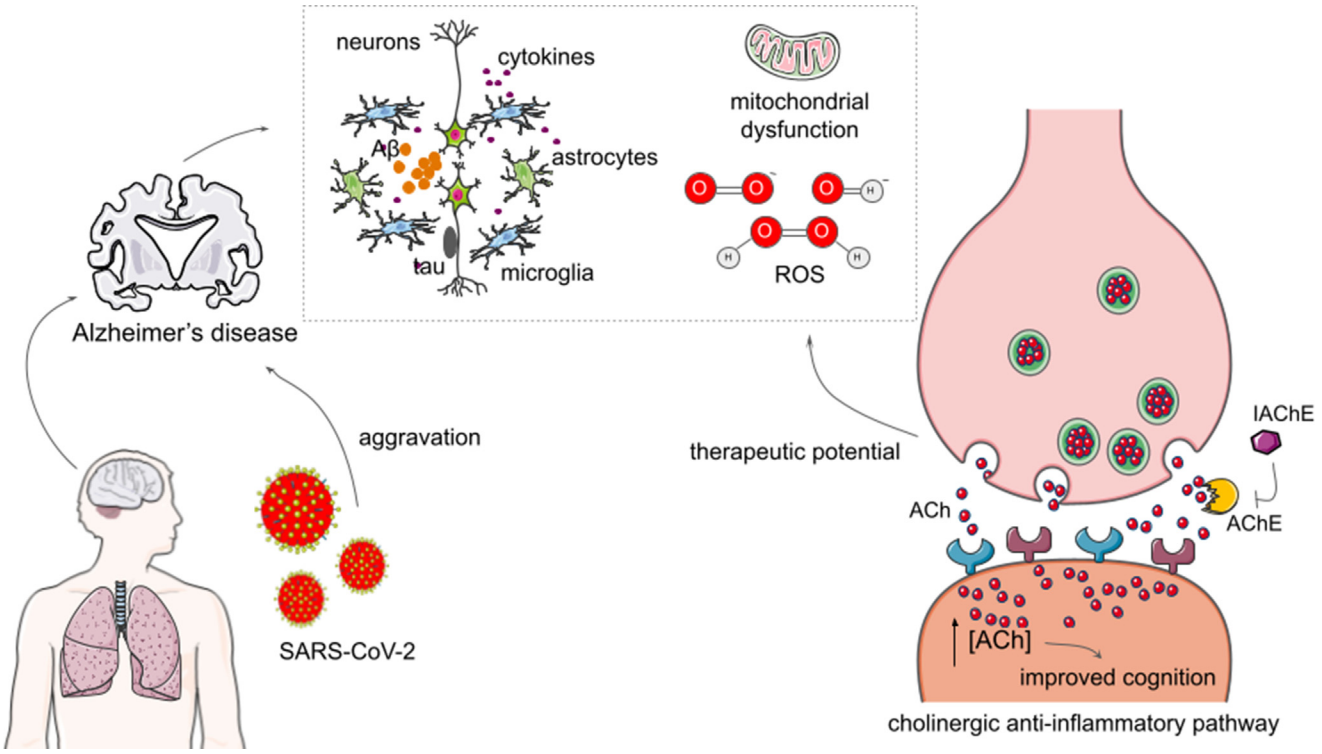

Fig. 1. Alzheimer's disease (AD) is caused either by genetic factors or by oxidative stress, inflammation, mitochondrial dysfunction, among others, which cause the accumulation of β-amyloid peptide (Aβ) and tau protein neurofibrillary tangles in the cleft synaptic, forming senile plaques. Neurochemical alterations in the cholinergic system are present in AD. The β-amyloid plaques erode the synapses and the mechanism of the acetylcholine (Ach) pathways, reducing the concentration of this neurotransmitter in the synaptic space, which modifies the stress response. SARS-CoV-2 can aggravate neurotissue inflammation by inducing reactive astrogliosis, defense cell activation, and the neuroinflammatory cascade, which is closely linked to Aβ oligomerization. β-amyloid peptide – Aβ, reactive oxygen species – ROS, acetylcholine – ACh, acetylcholinesterase – AChE, acetylcholinesterase enzyme inhibitors – IAChE.

SARS-CoV-2 primarily enters the host cell via the ACE2 receptor (Beacon and Davie, 2021). ACE2 is similar to ACE and acts in the regulation of blood pressure and electrolyte homeostasis in healthy individuals. ACE converts angiotensin I into angiotensin II, leading to vasoconstriction, renal sodium reabsorption and potassium excretion, increased aldosterone synthesis, and induction of inflammation and pro-fibrotic pathways. ACE2 cleaves angiotensin II into angiotensin (1–7), culminating in anti-inflammatory and vasodilatory effects (Bourgonje et al., 2020). Furthermore, ACE2 mediates the metabolism of bradykinins in the lungs, reducing pro-inflammatory effects such as vasodilation and increased vascular permeability (Bryce-Moncloa et al., 2021).

ACE2 is strongly expressed in alveolar and small intestinal epithelial cells, which are the sites frequently affected by SARS-CoV-2. Furthermore, the presence of this enzyme has been observed in vascular endothelial and smooth muscle cells (Hamming et al., 2004). SARS-CoV expresses an S1 peak protein for virion and cell membrane binding and interaction with the host cell's ACE2 receptor (Wrapp et al., 2020). Regarding the peak proteins between coronaviruses, the subtle differences in codon pair sequence alignments may explain the higher binding affinity between the spike protein of COVID-19 and the ACE2 receptor (Wrapp et al., 2020). According to the studies by Baig et al. (2020) proximal tubular cells of the urinary tract and neuronal and glial cells present in the CNS were also sites where the ACE2 receptor was found. Similar to the expression in pulmonary epithelial cells, the expression of ACE2 in blood–brain barrier (BBB) endothelial cells may allow HCoV to bind to pulmonary epithelial cells, thus causing viral dissemination in the CNS (Fu et al., 2020).

In addition to the ACE2 receptor, coronaviruses can use the olfactory bulb to enter neural tissue, taking advantage of the trans-synaptic pathway existing at the site (Steardo et al., 2020). Once in the CNS, SARS-CoV-2 induces reactive astrogliosis (inflammation of neural tissue), activation of immune defense cells (microglia), and a neuroinflammatory cascade. Simultaneously, viral spread in lung epithelial cells can cause a systemic inflammatory response, producing increased levels of pro-inflammatory cytokines, which also interfere with the CNS (Wu et al., 2020). In addition, the ventilatory function in lungs altered by infection can lead to respiratory failure and intense hypoxia, with consequent cerebral vasodilation and risk of evolution to edema and cerebral ischemia (Wu et al., 2020).

Rahman et al. (2021) revealed that biomarkers can be identified to track the progression of COVID-19 owing its significant role in the CNS. Some of these biological markers have also been identified in AD. IL-6 is a mediator with several effects on different cell groups (pleiotropic effects), acting in the inflammatory process, immune response, and hematopoiesis. At the onset of inflamma-

tion, IL-6 is synthesized at the injured site, travels to the liver via the bloodstream, and induces the production of positive acute phase proteins, such as C-reactive protein (CRP), serum amyloid A, fibrinogen, haptoglobin, and α1-antichymotrypsin. Simultaneously, IL-6 also acts by decreasing the production of fibronectin, albumin, and transferrin (negative acute phase proteins)(Zotova et al., 2013; Tanaka et al., 2014). The 11 family groups of antagonist ligands and receptors (IL-1α, IL-1β, IL-18, IL-33, IL-36α, IL-36β, IL-36g, IL-1Ra, IL-36Ra, IL-38, and IL-37) for IL-1 are responsible for independently mediating local or generalized inflammatory processes or inducing anti-inflammatory responses (Mendiola and Cardona, 2018).

SARS-CoV-2 activates IL-1 at the beginning of infection, which stimulates the secretion of TNF, IL-6, and other pro-inflammatory cytokines, causing a cytokine storm (Conti et al., 2020). Zhao et al. (2020) concluded that certain markers, including C—C motif chemokine ligand 5 levels and IL-1RA and IL-10 in the blood (individually and in combination), may be useful in prognosis and to guide treatment strategies, (Zhao et al., 2020). In patients with AD, the increase of pro-inflammatory ILs in plasma has been analyzed owing to its inflammatory response (Culjak et al., 2020). The changes in IL-1α, IL-10, and TNF-α concentration in patients with AD partially confirmed its association with the neuroinflammatory response in AD (Culjak et al. 2020). Therefore, monitoring these levels may aid in our understanding of various AD stages and the effect of SARS-CoV-2 infection on the prognosis, given that elevated serum pro-inflammatory cytokines are associated with an increased rate of decline in cognitive impairment in AD (Ide et al., 2016; Lin et al., 2022).

However, from a broader perspective, in a study that included the elderly as a control group, the variables IL-6 ($p = 0.138$), TNF-α ($p = 0.451$), and CRP ($p = 0.07$) were not significant, indicating that patients with AD do not have higher differentiation markers than other elderly patients (Ng et al., 2018).

Clinical evidence has linked the cascade of cytokine release to the presence of viral infection and is a prominent cause of mortality in patients with −19 (Culjak et al., 2020). In patients compromised by SARS-CoV-2, the marked elevation of plasma GAL-3 levels (belongs to the galectin family of proteins) stands out compared to that of healthy controls. These lectins can interact with other proteins through the carbohydrate recognition domain of a galectin with a β-galactoside conjugate on a specific protein, which mediates several physiological effects (Barondes et al., 1994; Machado et al., 2020). GAL-3 is a carbohydrate-binding protein expressed in lung cells, such as macrophages, epithelial cells, and alveolar cells (Reyfman et al., 2019). An increase in this substance is observed in patients affected by COVID-19, which is precisely explained by the association of galectin with the immune system and the activation of pro-inflammatory macrophages (McGonagle et al., 2020).

Tao et al. (2020) observed that GAL-3 promoted Aβ oligomerization and Aβ toxicity in animal models of AD. Evidence indicates that Aβ oligomers are responsible for altering the integrity of the bilipid membranes (membrane lipid bilayers), causing an increase in the influx of sodium (Na^+) and Ca^{2+} ions, causing a deficit in synaptic transmission and contributing to the pathology of AD (Fändrich, 2012; Salahuddin et al., 2016). Thus, GAL-3 can be considered a biomarker of inflammation related to both COVID-19 and AD, and the modulation of bioavailability seems to be promising in the treatment of these manifestations.

Cytoskeleton-associated protein 4 (CKAP4) is another protein of equal importance as a potential biomarker for both conditions. CKAP4, also known as CLIMP-63 and ERGIC-63, is a non-glycosylated type II transmembrane protein present in the endoplasmic reticulum (ER) of all tissues. In the ER, the cytoplasmic region of CKAP4 binds to the microtubules, creating a link between microtubules and the ER. (Osugi et al., 2019). Furthermore, CKAP4 is a Dicer-binding protein that regulates the microRNA (miRNA) pathway and mRNA translation by anchoring Dicer to the ER (Pépin et al., 2012). A study by Cancino (2013) suggested that CKAP4 is essential for maintaining the appropriate number of neuronal precursor cells (NPCs) in neurons born in the adult hippocampus. Furthermore, the removal (ablation) of P63 from the site leads to an increase in the apoptosis of NPCs via the pro-apoptotic p53-PUMA pathway, which culminates in neuronal memory deficits and decreased learning capacity (Cancino et al., 2013). Analysis of the serum proteomic profile of patients affected by SARS-CoV-2 identified 6 proteins related to disease severity, including CKAP4 (Poyiadji et al., 2020).

Apolipoprotein E (APOE), the main cholesterol transporter in the CNS, is another protein involved in the maintenance of neuronal function and is a constituent of very low-density lipoproteins (Hultman et al., 2013). Among its three alleles (ε2, ε3 and ε4), the ε4 allele (allele of the APOE gene) is the greatest risk factor for the development of AD (Serrano-Pozo et al., 2016) because the APOE ε4/4 genotype induces an increase in fibrinogenesis in the brains of these individuals (Hultman et al., 2013). Normally, astrocytes (and to a lesser degree, microglia) are primarily responsible for expressing and secreting APOE (Serrano-Pozo et al., 2016). Among the variables, the APOE ε4 allele is the best-established risk factor for AD. ApoE4 carriers have already been included in typical LO-SAD. This allele has been found to markedly increase the risk of AD and decrease cerebral Aβ clearance, leading to excess Aβ aggregation and downstream AD-typical neuropathology (Selkoe and Hardy, 2016). Whitwell et al (2021) evaluated the relationship between APOE genotype, age of onset, Aβ deposition, and typical versus atypical clinical presentations in AD. As a result, it highlighted the heterogeneous nature of AD and that the APOE genotype varies according to the studied variables. It can be mentioned that its frequency increased with the age of onset in atypical AD, although it presented a bell-shaped curve in typical AD, with higher frequencies between 65 and 70 years. Comparing typical and atypical AD, the former presented higher APOE ε4 frequencies only between the ages of 57 and 69 years. Finally, the overall proportions of standard Aβ absorption values did

not differ according to APOE e4 status in either group (Whitwell et al., 2021).

APOE is one of the genes co-expressed with the ACE2 receptor gene in type II alveolar cells, which is the route of coronavirus entry (Zhao et al., 2020). Thus, individuals with AD carrying the APOE4 allele are at a higher risk of developing severe COVID-19. ACE2 is primarily responsible for the invasion of SARS-CoV-2 into the host cells (Chaudhry et al., 2020). Thus, the level of ACE2 receptor expression is a crucial determinant of viral replication and pathogenesis. Notably, ACE2 is not expressed or localized in all human cells, and its main site of concentration is the surface of type II alveolar epithelial cells (AT2 pneumonocytes) (Hamming et al., 2004). In view of the difference in tissue concentrations, the expression of the ACE2 gene increased tenfold in the nerve cells of individuals with AD compared to those without the disease (Lim et al., 2020). Thus, individuals with AD have a higher risk of contracting COVID-19.

One of the most prominent manifestations of COVID-19 is anosmia, which can be defined as the loss of the ability to detect odors (Moein et al., 2020). Simultaneously, several neurodegenerative diseases such as Parkinson's disease and AD present olfactory dysfunction as one of the initial symptoms prior to the appearance of motor symptoms and cognitive decline (Marin et al., 2018). Being the second most abundant metal in the human body, zinc is an essential micronutrient. Zinc deficiency (zincopenia) is related to the manifestation of anosmia and ageusia (taste dysfunction) because carbonic anhydrase, an enzyme responsible for maintaining the function of smell and taste, is a zinc-dependent metalloenzyme (Equils et al., 2021). Given the anti-inflammatory properties of zinc, zincopenia induces an increase in the expression of IL-6 and IL-1β, pro-inflammatory cytokines, and intercellular adhesion molecule 1, which are important for leukocyte extravasation (Dhama et al., 2020). According to Equils et al. (2021), SARS-CoV-2 infection induces an immune response in the nasopharyngeal mucosa that can lead to local zinc deficiency. Such a decrease in zinc (Zn) levels is also observed in patients with AD, contributing to the progression and severity of the disease (Sensi et al., 2018).

Nitric oxide (NO) is a gaseous molecule that can easily diffuse into body tissues and is produced by the enzymatic activity of the NO synthase (NOS) family. In neural tissues, neurons, glial cells, and vascular cells can express NOS and are potential sources of local NO (Tajes et al., 2013). Activation of NMDAR in the hippocampus induces a cascade of reactions involving NO production. The diffusion of gas from the postsynaptic to the presynaptic termination stimulates the release of vesicles via a mechanism independent of guanylyl cyclase, forming an activation cycle called long-term potentiation (LTP), which is attributed to the physiological mechanisms of learning and memory (Picón-Pagès et al., 2019). SARS-CoV-2 can decrease neuronal NO production; thus, patients with AD who have contracted COVID-19 may show increased behavioral and cognitive decline owing to the low concentration of this neurotransmitter (Alkeridy et al., 2020) (Fig. 2).

ACh is another neurotransmitter involved in both the manifestations. It is a fast-acting point-to-point neurotransmitter in the neuromuscular junction and autonomic ganglia. Its main function is to control interneuronal and muscular communications. It also acts in the maintenance of movement, heart rate, digestion, breathing, and other autonomic functions (Picciotto et al., 2012). In addition to these well-characterized processes, ACh is involved in other activities such as vasodilation and action on the immune system (Cox et al., 2020).

According to the cholinergic theory, the decline in cognitive function in patients with AD is largely related to structural changes in cholinergic synapses, the loss of specific subtypes of ACh receptors, and the death of ACh-generating neurons, resulting in decreased cholinergic neurotransmission (Stanciu et al., 2019). Depending on the calcium ion influx, ACh release occurs via exocytosis of synaptic vesicles. They fuse with the presynaptic membrane, eliminating their neurotransmitter content in the synaptic cleft, where they activate muscarinic and nicotinic receptors (Stanciu et al., 2020). Effect of ACh stimulation on nicotinic receptors in macrophages was observed, which resulted in a concentration-dependent inhibition of the synthesis and release of pro-inflammatory cytokines, such as IL-1β, TNF-α, IL- 6 and HMGB1, without changing the concentration of anti-inflammatory cytokines, such as IL-10 (Hoover, 2017). A cytokine storm is characterized by the accentuated expression of IL-2, IFN-γ, IL-4, and IL-13. SARS-CoV-2 can rapidly activate pathogenic Th1 cells to secrete pro-inflammatory cytokines (Petrone et al., 2021). Therefore, treatment with nicotinic substances and the cholinergic system could reduce the generation of the inflammatory storm observed in patients infected with the new HCoV, while simultaneously being useful in the maintenance of neuronal functions in patients with AD (Farsalinos et al., 2020) (Fig. 2).

In addition to AD biomarkers concomitantly related to COVID-19, some AD-specific features should be emphasized. Among them, AD is mainly characterized by the formation of extracellular aggregates of Aβ outside neurons: the Aβ protein, the APP 21q21 gene and the long arm of chromosome 21 (Xie et al., 2020). Aβ plaques begin to develop in the basal, temporal, and orbitofrontal regions of the brain's neocortex and then progress to other regions such as the neocortex, hippocampus, amygdala, diencephalon, and basal ganglia. In severe AD, Aβ plaques are observed throughout the midbrain, lower brainstem, and cerebellar cortex (Goedert, 2015). In the pathogenesis of AD, the deposition of misfolded amyloid fibrils into plaques causes the activation of kinases, hyperphosphorylation of tau protein associated with microtubules, and its polymerization into NFTs. The formation of extracellular Aβ plaques and NFT tangles formed by hyperphosphorylated tau protein act directly on the recruitment and activation of microglia, with a local inflammatory response and increased neurotoxicity (Pinheiro and Faustino, 2019; Tiwari et al., 2019) (Fig. 2).

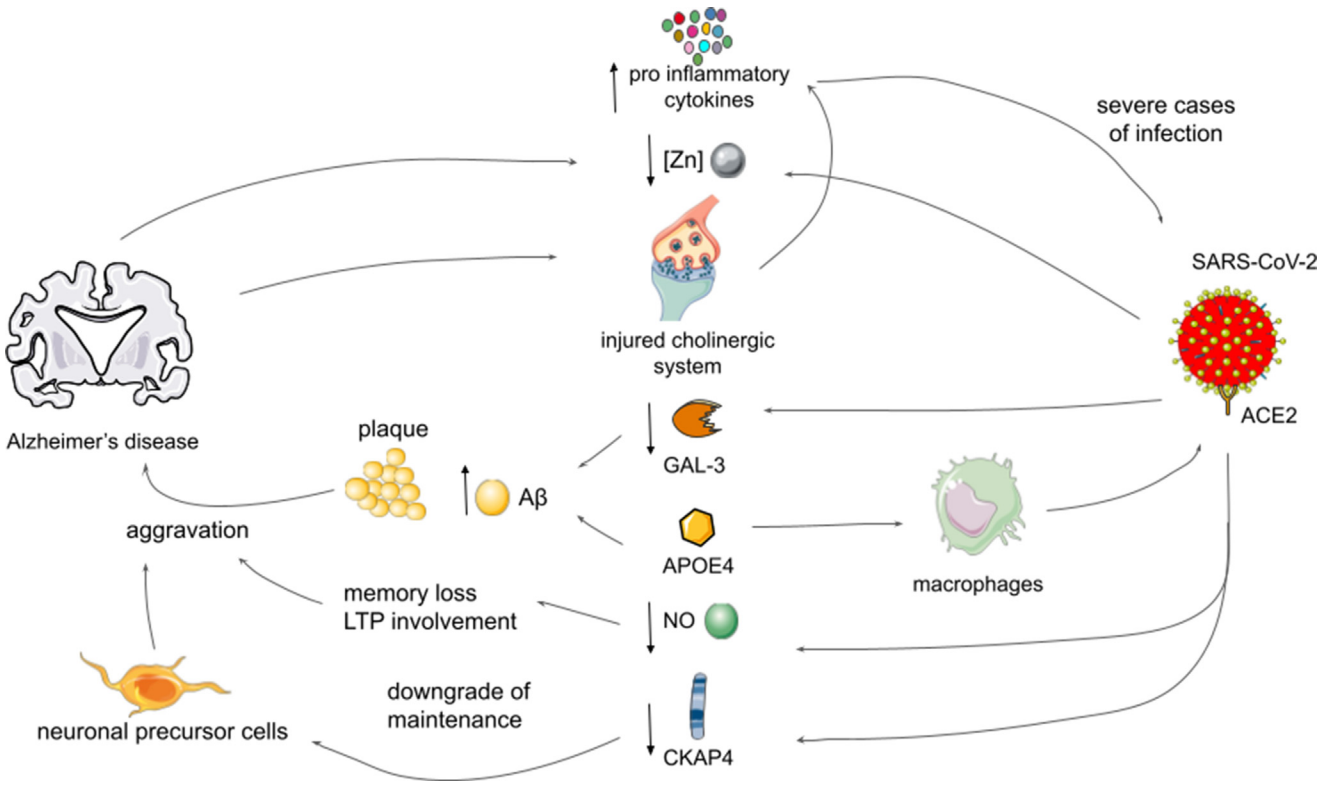

Fig. 2. In patients with COVID-19, there is an indirect reduction of critical factors, which also decrease in Alzheimer's disease (AD). The reduction of nitric oxide (NO), a molecule involved in the learning and memory process, and the cytoskeleton-associated protein 4 (CKAP4 protein), which acts in the maintenance of the appropriate number of neuronal precursor cells, and reduction in the level of this protein culminates in a deficit in the memorization process. One of the roles of SARS-CoV-2 in the host organism is linked to the low expression of galectin-3 (GAL-3), with a consequent increase in β-amyloid peptide (Aβ) oligomerization, a condition that characterizes the pathogenesis of AD. Apolipoprotein E (APOE 4) is another molecule that is associated with pathological Aβ deposition, which also acts to increase the activation of circulating pro-inflammatory macrophages, a factor that increases the risk of severe COVID-19 in an individual. Finally, the reduction of zinc in patients with AD and infected with COVID-19, together with profound alterations in the functioning of the cholinergic system in these patients, proved to be a stimulatory condition for the activation of already activated pro-inflammatory cells owing to the SARS-CoV-2 infection. In this scenario, patients with AD may have a worse prognosis of COVID-19 compared to age-matched controls. **Zn** – Zinc**; GAL-3** – protein Galectin-3; **APOE4** – apolipoprotein E; **NO** – **nitric oxide; CKAP4** – cytoskeleton-associated protein 4; **LTP** – long-term potentiation; **ACE 2** – angiotensin-converting enzyme 2;

However, tau is another factor that contributes to the possible development of AD. Tau is a microtubule-associated protein that plays a key role in microtubule stability (Gauthier et al., 2016). Furthermore, several functions of tau, such as maintenance of genomic DNA integrity, regulation of neuronal activity, neurogenesis, and iron export, have been elucidated in recent years (Gao et al., 2018; Peña-Bautista et al., 2019). The Tau protein is encoded on chromosome seventeen of MAPT gene. Alternative splicing of eight of the 16 exons of the MAPT gene allows the expression of six Tau isoforms in the CNS and six additional isoforms in the peripheral nervous system (PNS), ranging from 58 kDa to 66 kDa and one isoform of 110 kDa (Naseri et al., 2019). Post-translational modifications may occur during AD progression, and tau phosphorylation at various sites is the main characteristic of AD progression (Neddens et al., 2018).

Phosphorylation of serine and threonine residues near or within the microtubule-binding domain causes changes in the conformation of microtubules. This alteration releases stored tau, leading to its accumulation in the somatodendritic compartment of a pair of helical filaments and other abnormal conformations (Wesseling et al., 2020). Shigemoto et al. (2018) suggested that low levels of tau deposition, together with lower amyloid deposition, induce compensatory responses against early neuronal damage or chronic inflammation due to aging (Gauthier et al., 2016). In contrast, the coexistence of amyloid deposition and increased tau concentration induces a decrease in neuronal connectivity, contributing to the progression of AD (Shigemoto et al., 2018).

Presenilin 1 (PS1) is a ubiquitous transmembrane protein with several biological roles, such as cell adhesion, apoptosis, calcium homeostasis, and synaptic plasticity. Despite being rare and representing only 0.5% of all AD cases, FAD has attracted growing interest in the scientific community. This autosomal dominant inherited condition is characterized by highly penetrating mutations in three genes (Canevelli et al., 2014): (a) the APP gene on chromosome 21 (Goate et al., 1991); (b) the presenilin 1 gene (PSEN1) on chromosome 14 (Sherrington et al., 1995); and (c) the presenilin 2 gene (PSEN2) on chromosome 1 (Levy-Lahad et al., 1995). Changes in these variables are associated with increased production and/or deposition of β-amyloid (Aβ) (Selkoe, 1997; Walker et al., 2005; Canevelli et al., 2014). As a

clinical presentation, humans with trisomy 21 (Down syndrome), who harbor 3 copies of APP, invariably have the neuropathologically typical AD. Furthermore, on biopsy in early adolescence, abundant diffuse Aβ plaques are found without neuritic dystrophy, microgliosis, astrocytosis, and tangle formation, all of which gradually accumulate in such individuals in late adolescence and beyond (Selkoe and Hardy, 2016).

Another factor that causes neuronal effects and AD manifestation is the occurrence of mitochondrial defects (Macdonald et al., 2018), as normal synaptic function requires a high energy demand (Velavan and Meyer, 2020). In addition, neuroimaging studies using fluorodeoxyglucose positron emission tomography (FDG-PET) have demonstrated that the brains of individuals with AD absorb less glucose than those of cognitively normal controls. Therefore, a reduction in the cerebral metabolic rate of glucose, as measured by FDG-PET, is now considered a hallmark of AD (Zhou et al., 2018).

Genetics plays a vital role in AD risk and pathogenesis (Shao et al., 2017). miRNAs are a 19–23 nucleotide class of single-stranded non-coding RNA involved in post-transcriptional epigenetic regulation of mRNA (Bradley-Whitman and Lovell, 2013). Features such as size, amphipathic nature, and high solubility make miRNAs extremely mobile in the brain. The pathogenic miRNA gene families in the neocortex, hippocampus, limbic system, and CNS in general make miRNAs prime candidates for modulating the expression of many mRNA targets in complex, progressive, and ultimately lethal CNS neurological disorders, including AD (Takousis et al., 2019; Nunomura and Perry, 2020). Four miRNAs, miR-31, miR-93, miR-143, and miR-146a, are decreased in the serum of patients with AD and, hence, are biomarkers for AD pathology (Dong et al., 2015).

The transcription factor, p53, is essential for the maintenance of several cellular functions related to the integrity of the genome, which includes cell cycle control, response to DNA damage, and apoptosis (Peña-Bautista et al., 2019; Farmer et al., 2020). Furthermore, the roles of p53 in controlling synaptic function, regulating the inflammatory process, and reducing Aβ are observed as factors of great importance in preventing the manifestation and progression of neurodegenerative diseases (Abate et al., 2020). Thus, in AD, the highest concentration of Aβ peptides mediates the degradation of HIPK-2 protein, affecting the conformation of p53 (Mantzavinos and Alexiou, 2017). Consequently, the unfolded p53 protein forms oligomers and fibrils that are associated with AD pathology (Farmer et al., 2020). In addition, severe stress caused by AD can trigger the induction, by P53, of increased cellular oxidative stress by increasing ROS production, which induces neuronal apoptosis and contributes to the development of AD (Farmer et al., 2020; Beacon and Davie, 2021).

OXIDATIVE STRESS, SYNAPTIC DYSFUNCTION AND ALZHEIMER'S DISEASE

ROS are chemical compounds that contain oxygen with reactive characteristics, which can be produced by enzymatic means (such as in macrophages) to inactivate invading agents or by non-enzymatic means (such as oxidative phosphorylation). The respiratory chain is the largest generator of reactive species, as it has oxygen as its final acceptor. This process is known as ''aerobic cell metabolism,'' which continuously synthesizes reactive species, such as superoxide anions, hydrogen peroxide, and hydroxyl radicals. Physiologically, ROS levels are controlled and preserved in lower concentrations in the body; however, in AD, there is an irregularity in the cytochrome C oxidase enzyme, one of the mitochondrial electron transport enzymes/complexes, which causes greater production of ROS, making the cells more prone to apoptosis (Kamat et al., 2016). Thus, significant accumulation of these substances is known as ''oxidative stress.''

The energy necessary for the maintenance of the human body is acquired through reduction reactions (in the transfer of electrons) via the electron transport chain (ETC) located in mitochondrial crests. Ingested food and its processed products generate electrons, which are donated to the mitochondrial complexes of the ETC to be finally accepted by oxygen, which has a high reduction capacity, and consequently, prominent reaction energy. In these reactions, oxygen normally receives four protons and four electrons to generate two water molecules (Cheignon et al., 2018). However, owing to genetic alterations and aging, the enzymatic complexes of the respiratory chain become less effective and alter the redox activity, leading to a high formation of ROS and RNS, which cause mitochondrial dysfunction that is linked to the progression of neurodegenerative diseases, such as AD, and cognitive impairment (Cheignon et al., 2018).

Neurons, which are the essential operating unit of the brain, have a high metabolic rate compared to that of other cells in the body, thus showing greater susceptibility and damage to oxidative stress. Considered as a common pathological feature in AD, oxidative stress has not yet been established, as it acts in pathophysiology. However, it has been suggested that, in addition to the destruction or insufficiency of the constituents of the antioxidant system – such as superoxide dismutase (SOD), catalase (CAT,) and glutathione peroxidase (GPx) – in the mitochondria and cytosol, mitochondrial dysfunction, tau hyperphosphorylation, Aβ accumulation, inflammation, and metal accumulation are implicit means of its induction (Chen and Zhong, 2014). A contributing factor to the progression of oxidative stress is that 700 mL of blood flow per minute in the brain and, hence, is responsible for the consumption of approximately 20% of the oxygen generated owing to the gas exchange occurring in the respiratory system (Gallucci Neto et al., 2005).

In addition, according to Chen and Zhong (Chen and Zhong, 2014), phospholipids in the brain are essential for the basis and process of neurotransmission and cognition and have a high proportion of polyunsaturated fatty acids. However, in AD, an increase in ROS and free radicals causes a decrease in polyunsaturated fatty acids, an increase in malondialdehyde and 4-hydroxynonenal, syn-

thesis of isoprostanes (F2-IsoPs and F4-IsoPs), and slight cognitive impairment (Shinto et al., 2014). The oxidation of proteins, mainly tyrosine, by ROS and RNS gives rise to di-tyrosine and 3-nitrotyrosine, which are unfavorably related to scores on the Mini Mental State Examination; in addition, protein nitration is considered an early milestone in the pathogenesis of AD. Concomitantly, DNA oxidation results in the generation of 8-hydroxydeoxyguanosine and 8-hydroxyguanosine (8-OHG), which increase in the parietal, temporal, and frontal cortices of individuals with AD(Kawamoto et al., 2005; Weimann et al., 2018).

8-OHG is related to the precedence of characteristic features of the disease, such as the accumulation of Aβ plaques and NFTs, usually years before the onset of clinical signs (Chen and Zhong, 2014). In early-onset AD, missense mutations in presenilin 1 or 2 are indicated in the literature as the major causes, resulting in relative increases in the production of Aβ42/43 peptides. These peptides have hydrophobic characteristics, facilitating their self-aggregation and exacerbated Aβ deposition in middle age. As a result, there are two cleavage lines from Aβ48/49 or Aβ49/50 ε. Overall, presenilin mutations directly affect C- to N-terminal cleavage and, consequently, the relative production of longer Aβ peptides increases, which are more hydrophobic and self-aggregating (Selkoe and Hardy, 2016).

Thus, there is an increase in the Aβ42/Aβ40 ratio in humans, which are highly auto-aggregating, while Aβ40 may be anti-amyloidogenic (Kim et al., 2007). Studies in mice indicate that human Aβ42 oligomers induce tau hyperphosphorylation on AD-relevant epitopes and cause neuritic dystrophy in neurons, and when modulated by co-administration of Aβ antibodies, this scenario was completely avoided. From another perspective, studies demonstrate that the inheritance of a missense mutation in APP that decreases Aβ production and aggregation throughout life protects against AD and age-related cognitive decline (Selkoe and Hardy, 2016).

In AD, most cases are due to the influence of external and environmental factors, and only 1% of cases are related to familial mutations in genes encoding APP or preselins (PS1 and PS2). The deposition of intracellular Aβ residues occurs before the accumulation of extracellular Aβ, which is present in the mitochondria, ER, trans-Golgi network, and lysosomal and endosomal membranes, that damages synaptic activity, leading to synaptic dysfunction and memory deficits (Tönnies and Trushina, 2017). Although the function of APP is still unknown, it is closely related to the regulation of intracellular calcium, cell adhesion and growth, metal ion homeostasis, and axonal transport of vesicles (Smith et al., 2007).

According to a study by de Paula et al. (2009), the tau protein, located in the axons, stabilizes microtubules through the incorporation of tubulin and can present in soluble and insoluble forms; the latter configuration is detected in the basic element of NFTs, defined as paired helical filaments. Hyperphosphorylation can occur because of the increase in the functioning of kinases, such as taukinases, and the sub-impact of phosphatases or both. However, in line with a study by Tönnies and Trushina (2017), the formation of Aβ causes a translocation in the tau protein, causing it to be hyperphosphorylated, causing it to lose its stabilization capacity, displacing the microtubules, and suspending the neuronal circulation mechanism. Tau hyperphosphorylation is not very well understood but is known to affect the functionality of mitochondrial complex I, and its NFTs are found in other neurological diseases, causing morphological and biological dysfunctions in neurons.

The accumulation of Aβ, generation of NFTs, and presence of hyperphosphorylated tau compromise axonal transport and synapse processing, which can lead to the suppression of cell viability, degradation of the microtubular cytoskeleton, and neuronal death (de Paula et al., 2009). These events may be related to oxidative stress (intensified through signaling stress in neurons), activation of the NMDAR (a neurotransmitter mediated by the cationic channel glutamate and an essential element of excitatory synaptic transmission), excitotoxicity, and neuronal plasticity. Activation of postsynaptic NMDARs induces an abundant influx of calcium ions (Ca^{2+}) into postsynaptic cells, resulting in synaptic dysfunction, tau phosphorylation, mitochondrial operational deficiencies, activation of permeability transition pores in the inner mitochondrial membrane, loss of ATP, cytochrome C release, and continuous synthesis of ROS from intracellular cascades owing to the high concentration of cytoplasmic Ca^{2+} (Kamat et al., 2016).

In addition to Aβ plaques inducing cytoplasmic deposition of Ca^{2+}, they boost the extracellular accumulation of glutamate, which corroborates the increased synthesis of ROS and oxidative stress. Glutamate receptor over-induction can lead to apoptosis, with neuronal cell death triggered by a set of toxic events. Excitotoxicity, defined by a sustained induction of excitatory amino acid receptors (NMDARs), occurs owing to toxic events such as the alteration of Ca^{2+} homeostasis, harmful over-regulation of the signaling means, RNS and ROS, which cause more nitrosative and oxidative stress, resulting in activation of apoptotic processes. The activation of caspases (caspase-3 and caspase-9) via central apoptosis is determined by a mitochondrial disorder that releases cytochrome C, which mediates the breakdown of synaptic proteins, such as the degradation of α-amino-acid receptor subunits. 3-hydroxy-5-methyl-4-isoxazolpropionic combined with the glutamate dose sample causes a decrease in the influx of Ca^{2+}, leading to excitotoxicity (Kamat et al., 2016).

According to a study by Kamat et al. (2016), high levels of caspase-3 in the postsynaptic density portion of the AD brain can be linked to excitatory synaptic transmission variation, reduction in size and spinal density, memory impairment, and long-term depression (Snigdha et al., 2012). Therefore, the suppression of caspase-3 by pharmacological intervention may improve synapse transmission, memory impairment, and spine size and is considered opportune to reduce cognitive decline (Snigdha et al., 2012; Wessels et al., 2020). Another triggering factor for neuronal apoptosis is the relationship

between age and mitochondrial oxidative stress, in which mitochondria influence the course of cell aging owing to damage caused to their structures by oxidative stress in pyramidal neurons and, hence, are subjected to neurodegeneration (Vassar, 2007). The main causes of neurodegeneration are damage to mitochondrial respiration, decreased synthesis and/or depletion of ATP, and deterioration of energy metabolism through the inhibition of important enzymes such as cytochrome C oxidase (Vassar, 2007).

AD neurodegeneration is also linked to several metals such as zinc and copper, which can substantially aggravate neuronal toxicity because the high concentration of Aβ plaques forms insoluble amyloid fibers that adhere to metals. This results in the development of high-affinity complexes with neurotoxicity depending on the type of metal connected to the senile plates, with copper and zinc being able to solubilize them (Sereniki et al., 2008). Tönnies and Trushina (2017) pointed out that soluble Aβ residues can be even more toxic to the body, influencing several molecular mechanisms that induce synapse abnormalities. In addition to the action on amyloid plaques, the altered homeostasis of bioactive metals can interfere with the synthesis of oxidative stress and free radicals and the deposition of tau protein. As a result, altered neuronal metal homeostasis in AD generates accumulation of a certain metal to compensate for the deficiency.

Zinc occasionally affects APP processing by binding to the membrane along with copper, iron, and aluminum binding directly to Aβ, leading to its agglomeration. The binding of iron and copper to Aβ plates can produce even more hydrogen peroxide, which reveals that metals and Aβ plates act synergistically for the elaboration of extra-mitochondrial ROS and oxidative stress (Tönnies and Trushina, 2017). Hydrogen peroxide is harmful in the presence of active redox metals, as it produces hydroxyl radicals from the Haber-Weiss or Fenton reaction. Enzymes such as GPx and CAT, which regulate the concentrations of hydrogen peroxide and act as antioxidant components of the protective mechanism, are found in smaller amounts in the brains of patients with neurodegenerative diseases such as AD. This contributes to an increased imbalance between pro-oxidants and antioxidants (Cheignon et al., 2018).

The human body has an antioxidant defense system that aims to reduce the damage caused by oxidative stress and free radicals and is composed of the following elements: non-enzymatic – can be endogenous (such as glutathione) or exogenous (acquired from the intake of vitamins C and E, minerals, carotenoids, organosulfur, and cofactors) (Awad et al., 2018) – and enzymatic- are endogenously synthesized, neutralize free radicals, restore structures, and associate peroxidized lipids and xenobiotics. Enzymatic antioxidants are composed of SOD, CAT, glutathione S-transferase, γ-glutamylcysteine synthase, GPx, and glutathione reductase and are responsible for oxidative damage and cell death (Mantzavinos and Alexiou, 2017) (Fig. 3).

Under physiological conditions, antioxidant enzymes such as SOD, GPx, CAT, glutaredoxins, and thioredoxins operate as a free radical excluding machinery and regulate the degree of ROS. This protective system is aided by the activation of nuclear factor 2 related to erythroid-2 (Nrf2), a transcription factor that undergoes ubiquitination by the E3 ubiquitin ligase, that is negatively mediated by its binding to the analogous ECH-associated protein to Kelch from stress sensor 1 (KEAP 1) and to the cytoplasmic repressor, passing as a substrate adapter (Kawamoto et al., 2005). When chemical reactives are present, such as metals and toxic reactive species, KEAP 1 releases Nrf2 into the cell nucleus, which is responsible for activating the transcription of cytoprotective genes through promoter segments that have conserved antioxidant response constituents. This increases the concentration of antioxidant enzymes and induces replacement of damaged organelles. However, in AD, the levels of Nrf2 and antioxidant response element (AREs) may be increased or decreased by mechanisms that are not yet known but are influenced by the organization of the disease and aging (Tönnies and Trushina, 2017) (Fig. 3).

Basic neurochemical changes in the cholinergic system are reported in AD indicating that cholinergic dysfunction is linked to changes in learning, memory, attention, and cognitive processing. Cholinergic dysfunction can be caused by the fraction of muscarinic receptors, intracellular signaling stimulated by these receptors, or by the influence of excessive amounts of endogenous low-molecular-weight inhibitor protein. This induces an endogenous divergence of muscarinic cholinergic receptors, causing a decrease in the brain levels of ACh and, thus, revealing the typical clinical manifestations of this disease (Ventura et al., 2010).

CHOLINERGIC SYSTEM AND TREATMENT OF ALZHEIMER'S DISEASE

The triggering of events that lead to late AD (one that is not derived from the autosomal dominant form) presents a complex polygenic form, with interactions between several molecular cascades. These late manifestations are related to several factors, such as age, APOE ε4, possible cardiovascular conditions, and lifestyle (Rasch et al., 2006; Kuo et al., 2007). Furthermore, the implication of the neurotransmitter ACh in important physiological pathways, such as the response to stress, memory, learning, sleep and wakefulness, and sensory information, was highlighted by Ferreira-Vieira et al. (2016). The disease presents itself as a chronic syndrome that affects the CNS and has some factors that may contribute to its manifestation, such as Aβ aggregates and increased phosphorylation of tau protein, which collaborate with the progressive degeneration of the disease, causing harmful effects on the cognitive system, altering language, memory, judgment, orientation, learning, and deficits in decision-making (Sharma, 2019).

Tau protein plays an important role in the proper functionality of this system and is hyperphosphorylated

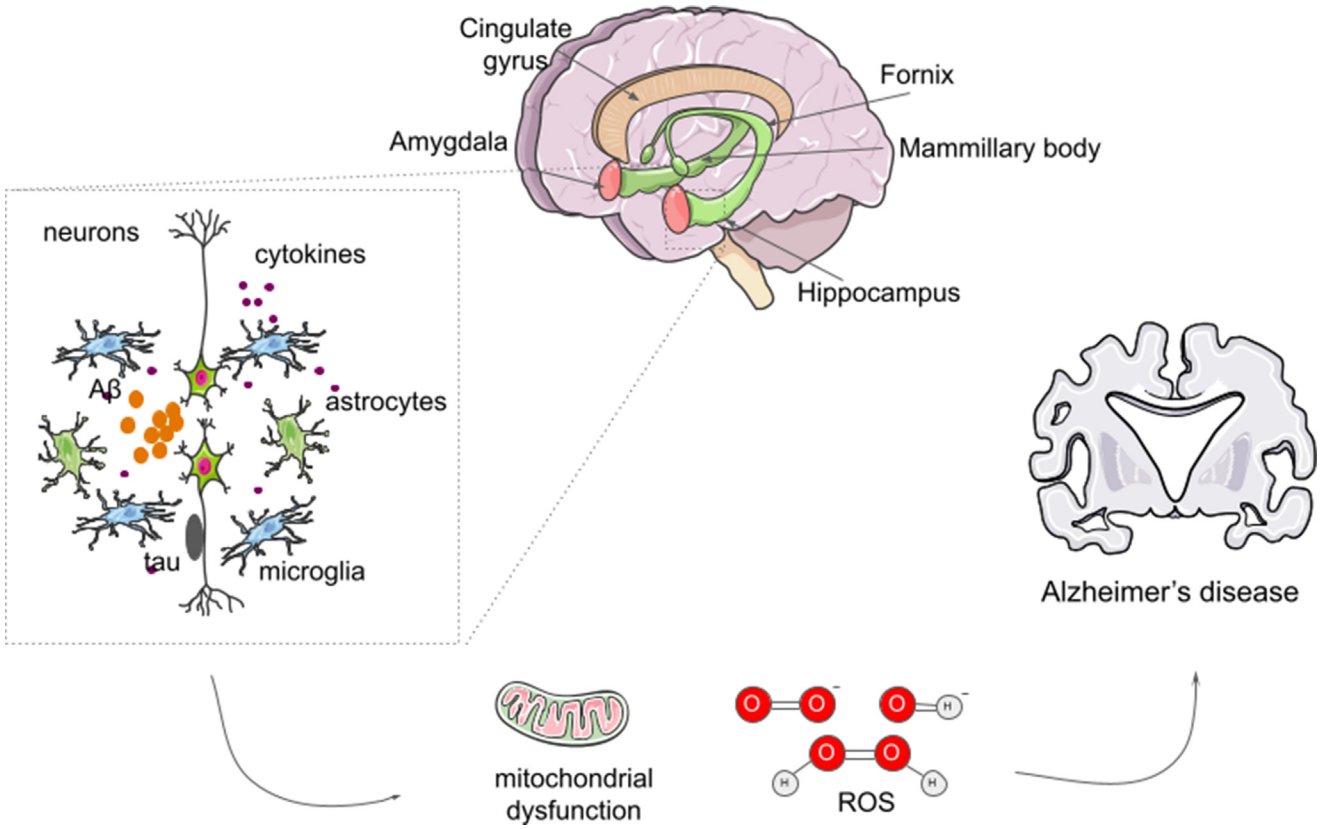

Fig. 3. The formation of amyloid plaques can occur through increased levels of reactive oxygen species (ROS), mitochondrial dysfunction, inflammation, genetic mutations, etc., which interfere with intramembrane proteolysis, mediated by β-secretase and γ-secretase of amyloid precursor protein (APP), leading to the accumulation of β-amyloid peptide (Aβ) in the synaptic cleft and tau protein neurofibrillary tangles. The location of senile plaques occurs mainly in the cerebellar tonsils, hippocampus and entorhinal cortex of the temporal lobe, resulting in neural and synaptic dysfunction, loss of neurons and synapses, atrophy of different brain areas and, consequently, dementia and others characteristic clinical signs of Alzheimer's disease (AD).

in the pathophysiology of AD, culminating in brain damage (Iqbal et al., 2005; Gauthier et al., 2016). Tau, which is associated with microtubules of normal neurons, plays a major role in the clinical manifestations and neurodegenerative signs of the disease as well as links APOE ε4 to the development of pathogenesis, as this allele has the capacity to influence Aβ deposition (Shi et al., 2017). All AD patients show progressive Aβ deposition followed by neuritic and surrounding glial cytopathology in brain regions that serve memory and cognition (Selkoe and Hardy, 2016). Currently, the main approach to cognitive and behavioral symptoms of early and late stages of AD has been the restoration of the cholinergic system. In age-associated neurodegenerative diseases, cholinergic atrophy and cognitive decline are accelerated (Giacobini, Cuello and Fisher, 2022). Furthermore, abnormal central cholinergic changes can also induce abnormal tau protein phosphorylation, nerve cell inflammation, cell apoptosis, and other pathological phenomena (Chen et al., 2022). Thus, reduced synthesis of this neurotransmitter is associated with loss of cholinergic neurons, as highlighted in the cholinergic theory of AD. New investigations indicate that memory loss related to both AD and other pathologies may be triggered by alterations in APP processing or ACh-mediated neuronal function, or both, which in turn trigger amyloid beta overexpression, synaptic malfunction and loss of trophic factor in targeted regions, eventually leading to synaptic and dendritic loss with age (Ferreira-Vieira et al., 2016; Sharma, 2019).

ACh is produced through choline acetyltransferase, with choline and acetate as precursor substrates and is subsequently stored in synaptic vesicles that are transferred to two classes of postsynaptic receptors: nicotinic (ionotropic) and muscarinic (metabotropic) receptors. Each of them has its specificities: nicotinic are oriented by ionic ligands, and muscarinic are associated with the G protein, which has five subclasses, each of which is found in smaller or larger amounts in the organism. M1 receptors, one of the subtypes of G protein receptors, are found abundantly in some brain regions, such as the cerebral cortex, hippocampus and striatum and, as inferred from their location, are involved in learning and memory mechanisms (Renard and Jean, 2017). Furthermore, cholinergic structures are found in both parasympathetic (pre- and post-ganglionic neurons) and sympathetic systems (pre-ganglionic neurons) (Ferreira-Vieira et al., 2016).

The five subtypes of muscarinic receptors can act on both excitability and cell rest, depending on the characteristics of the activated cell and may inhibit either potassium (K^+) or Ca^{2+} channels to promote

excitability or cell rest, respectively. M1 and M3 receptors are mostly found at the postsynaptic level, whereas M2 and M4 receptors are usually located presynaptically. Although these receptors have the capacity for depolarization and repolarization, they often involve excitation, particularly in the cortical region, in addition to modulating other molecular pathways such as GABAergic inhibition and glutamatergic stimulation via secondary messengers, resulting in brain excitation (Ferreira-Vieira et al., 2016).

Nicotinic receptors are selective for cations, such as K^+, Na^+, and Ca^{2+}, and are formed by five subunits: α, β, δ, γ (fetal), and ε (adult). The distinct combinations of these subunits form nine subclasses of nicotinic receptors, which are manifested in different structures that may occasionally have different specificities and purposes. Ganglia and muscles consist of receptors with five subunits, with alpha being doubled, while neurons comprise receptors with only two subunits, α 2–10 and β 2–4. The CNS has an accentuated α7 subunit with a particularly modulatory function, whereas the receptor reflects synaptic transmission in the PNS. Another relevant contrast between these receptors in different systems is that in the CNS, they are usually found in the presynaptic membrane and can modulate several neurotransmitters, such as glutamate, GABA, dopamine, serotonin, norepinephrine, and ACh, which are usually located in the postsynaptic membrane (Ferreira-Vieira et al., 2016).

ACh and cholinergic neurons are also present in the CNS (at the neuromuscular junction) and autonomic nervous system (sympathetic and parasympathetic), presenting specific nicotinic and muscarinic receptors in each of these structures. After its biosynthesis and exocytosis to the synaptic cleft, ACh is degraded by AChE, which functions to decrease its concentration, consequently culminating in the depression of its action on postsynaptic receptors. Anticholinergic denomination is also attributed to processes that act in the reduction of ACh, which may occur in different ways, such as the reduction in the synthesis or release of ACh, increase in the functioning of AChE, or inhibition of receptors. In addition, the brain expresses five subclasses of muscarinic receptors; however, M1 plays a significant role in anticholinergic manifestations, such as cognitive impairment, confusion, sedation, delirium, and dizziness (Volpicelli-Daley et al., 2003).

The cholinergic system widely innervates brain regions; has memory, learning, and aspects of cognition involved in its regulation; has ACh as a neurotransmitter; and has the capacity to promote the plasticity of neurons; hence, it is involved in the central and peripheral modulation of the nervous system. Notably, the Meynert basal nucleus and its cholinergic composition play a fundamental role in the memory mechanism, and the degradation of neurons in this area leads to loss of functionality in the region, which is characteristic of AD (Rasch et al., 2006; Kuo et al., 2007). The cholinergic and serotonergic systems are responsible for cognitive, emotional, and behavioral processes. Damage to these chemical structures and mechanisms reflects the AD process. This is because the brain regions of the basal forebrain, thalamus, and hippocampus are the main areas affected by the disease, and with the neural tissue destroyed, there is a depletion of both cholinergic nuclei in the basal area of the forebrain and cholinergic innervation directed to the cerebral cortex (Klaassens et al., 2019).

The forebrain is characterized by cholinergic aggregates and has a basal Meynert nucleus, which contains ramifications of neurons in the cortex and amygdala, with modulatory physiological functions acting on cortical activities. Under the effects of AD, this nucleus manifests as neuronal degeneration (Ferreira-Vieira et al., 2016). These aspects of Meynert nucleus appear as one of the three hallmarks of the cholinergic hypothesis, the other two being presynaptic cholinergic markers in scarcity in the cerebral cortex, confirming that cholinergic antagonists impair memory. Hence, cholinergic depletion highlighted in AD neuropathology was observed, since there is a significant reduction in the action of the AChE enzyme in the cerebral cortex and limbic system in individuals with AD (Rasch et al., 2006; Kuo et al., 2007).

The cholinergic lesions that arise in AD are presynaptic and appear in the prodromal state of the disease; that is, they are asymptomatic, resulting in the depletion of neurons in the Meynert nucleus and axonal projections of the cerebral cortex, affecting nicotinic and muscarinic receptors. However, this highlights the involvement of cortical postsynaptic nicotinic receptors, given that there is a partial preservation of M1 that eventually becomes dysfunctional. The action of cholinergic agonists can also be observed, which have a positive modulation in neurochemical cascades in the neuronal configuration of AChE in the cerebral cortex. ACh has other brain implications such as neuroplasticity and the hemodynamic system owing to its capacity for cortical remodeling through the synchronization and connectivity of the neuronal network as well as the promotion of vasodilation and perfusion of the brain (Rasch et al., 2006; Kuo et al., 2007).

AChE is an important modulator for ACh supply in the synaptic cleft and has a significantly accentuated expression in the muscles and brain; therefore, AChE inhibitors are a method of therapy, as in the case of anesthetics, when promoting muscle block, and selective AChE inhibitors are used in the treatment of AD (Ferreira-Vieira et al., 2016). Furthermore, AChE inhibitors can help in the treatment of AD, as they improve the cognitive symptoms of AD by preventing degradation of ACh. In addition, the serotonergic theory suggests that reduced functionality in AD contributes to the worsening of cognitive, behavioral, and mood changes, which are already compromised by the depletion of the cholinergic system (Klaassens et al., 2019).

The cholinergic theory, based on the adequate maintenance of acetylcholine levels in synapses, is of fundamental importance for the therapeutic method in AD because the signs and symptoms observed in this disease result, among other factors, from the decay of this neurotransmitter. Therefore, compounds that have

the potential to block AChE can be used in the management of the disease to promote a higher concentration of ACh for metabolism. Drugs approved by the Food and Drug Administration for the treatment of AD include substances capable of inhibiting AChE, such as donepezil, rivastigmine, and galantamine (Sangaleti et al., 2021). These drugs have shown improvement in cognition and some behavioral areas and are administered in symptomatic treatments (Rasch et al., 2006; Rosengarten et al., 2006; Kuo et al., 2007).

Traditional acetylcholinesterase enzyme inhibitor (IAChE) inhibitors include physostigmine, tacrine, donepezil, rivastigmine, galantamine, and metrifonates (Rosengarten et al., 2006). Physostigmine, also known as eserian, has a short half-life and marked side effects; therefore, although it can cross the BBB, it has little therapeutic use. Tacrine has been approved for the treatment of AD but has been discontinued owing to its impact on metabolism (eg., hepatotoxicity). Donepezil, an IAChE, is the most prescribed drug (∼68%) for the treatment of the mild-moderate stage of the disease (Rosengarten et al., 2006; Cornelli, 2010). By modulating neurotransmitter levels, it is able to act at the molecular and cellular levels at various stages of the pathogenesis of the disease, such as, for example, depressing the expression of inflammatory cytokines and reducing the impact of oxidative stress (Hampel et al., 2018; Sharma, 2019). Rivastigmine has slow activation kinetics, inactivates AChE for a limited time, and causes significant side effects. Metrifonate is a long-acting organophosphate inhibitor, and although it shows considerable improvement in people with mild to moderate AD, its development was discontinued owing to its adverse repercussions, one of them being respiratory paralysis. Galantamine binds to nicotinic cholinergic receptors and is effective in the treatment of cognitive symptoms of AD, and the tolerability of this drug is associated with a gradual increase in dosage (Sharma, 2019; Sangaleti et al., 2021). Galantamine can also reduce the mortality of individuals with AD and improve cognitive depression (Ferreira-Vieira et al., 2016; Sangaleti et al., 2021).

There is a discrepancy between the proper uses of cholinesterase inhibitors as these drugs are prescribed for less than half of the consultations for individuals with AD. Certain barriers prevent the proper use of these drugs such as the lack of medical knowledge and experience in the use of cholinesterase inhibitors in primary care and judicious requirements on the part of professionals regarding the clinical effectiveness of these inhibitors; furthermore, neurologists and psychiatrists are more inclined to prescribe these drugs (Rosengarten et al., 2006; Cornelli, 2010; Sangaleti et al., 2021). Thus, although this therapy has the potential to attenuate the signs of cognitive impairment commonly seen in all stages of AD, there are different and complex clinical contexts in the fickle use of these cholinesterase blockers (Rasch et al., 2006; Kuo et al., 2007).

The uncoupled muscarinic M1 receptor is associated with the worsening of AD, and the impaired functionality of this receptor is characteristically present in AD. Another property of this receptor is its ability to transfer the APP processing pathway in a non-amyloidogenic direction and to depress tau hyperphosphorylation. These muscarinic singularities have become instruments of disease therapies through M1 ACh agonists, such as M1 AF267B, which can recover the cognitive impairment representative of neurodegeneration and prevent the manufacture of Aβ peptide by increasing the α enzyme secretase. Furthermore, allosteric M1 modulators may contribute to Aβ depletion, and selective muscarinic agonists for M1 and M4 can, depending on the dose, decrease memory deficits, mood disorders, agitation, and hallucinations (Ferreira-Vieira et al., 2016). Overall, M1 agonists act as negative regulators of both the amyloidogenic processes and neural protection that is provided by the excitation of nicotinic receptor 7 against the toxicity produced by Aβ, in addition to its connection with the anti-inflammatory pathways provided by this receptor (Hampel et al., 2018). Simultaneously, positive allosteric modulators and agonist have the ability to increase cholinergic function in neuronal degeneration processes (Renard and Jean, 2017).

The α 7 nicotinic acetylcholine receptor (α7nAChR) is encoded by a gene with variability and polymorphism and has high Ca^{2+} permeability, with rapid desensitization and, consequently, activation, in addition to being located in several brain regions, particularly the prefrontal cortex and hippocampus. In addition, this receptor plays a significant role in anti-inflammatory signaling owing to its ability to activate one of the modulators responsible for regulating oxidative stress (Nrf2). Thus, selective α7 agonists are analyzed with the aim of developing a drug route for the treatment of AD, such as encenicline, which showed improvement on cognitive impairments, pozanicline, ABT-418, etc. However, they have considerable side effects; hence, several studies on these drugs have been discontinued (Hoskin et al., 2019). The importance of the α 7 receptor is also because of its manifestation in cells as a precursor of oligodendrocytes, endothelial cells, astrocytes, and microglia, which play roles in immunity, inflammation, and neurological protection. Thus, this nicotinic receptor has cholinergic anti-inflammatory potential and acts in several different pathological contexts, including neurodegenerative processes, such as AD (Bouzat et al., 2018) (Fig. 4; Table 1).

PURINERGIC THERAPEUTIC POTENTIAL IN ALZHEIMER'S NEUROINFLAMMATION

The purinergic system comprises an organization of specific receptors, enzymes, and signaling components and is responsible for promoting essential organic functions for body balance (Burnstock, 2020). Among these components, it is extremely important to mention adenosines, UTP, UDP and ATP, which act on different purinergic receptors, such as P1 (subdivided into A1, A2, A3 and A4) and P2 (subdivided into ionotropic P2X, containing seven subunits, and the metabotropic P2Y, containing eight subunits) (Burnstock, 2020; Simões and Bagatini, 2021). Under normal homeostasis conditions,

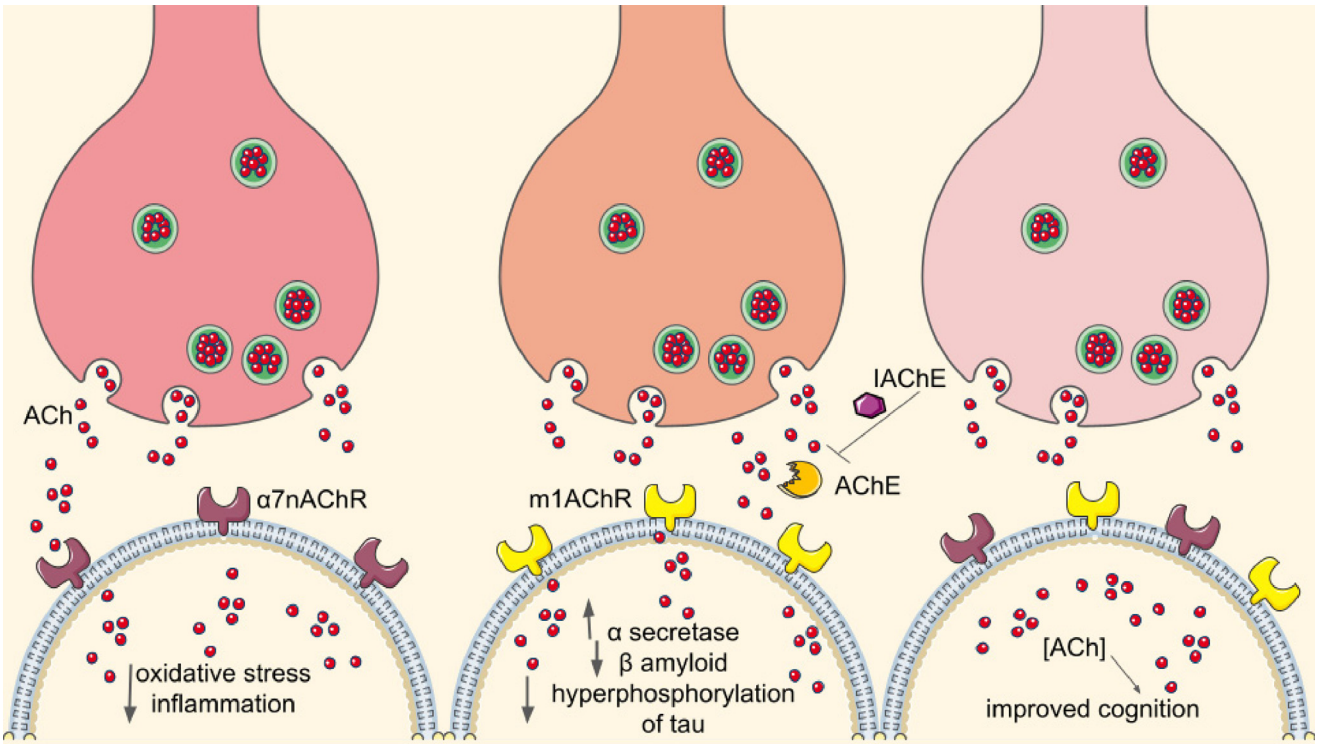

Fig. 4. The α 7 nicotinic receptors (α7nAChR) found in various locations in the body are one of the synaptic cleft acetylcholine scavengers. Additionally, they have the ability to regulate the concentrations of reactive oxygen species via the activation of an oxidative stress modulator nuclear factor 2 related to erythroid-2 (Nrf2) and, concomitantly, act in the signaling of the anti-inflammatory pathway. Thus, the use of α7nAChR agonists is one of the drug alternatives for the adjuvant treatment of Alzheimer's disease (AD) with the aim of promoting neurological protection. Muscarinic M1 receptors also act to capture the neurotransmitter acetylcholine to increase the concentration of the enzyme α secretase, which depresses the manufacture of β-amyloid peptide (Aβ) and decreases the hyperphosphorylation of tau protein. Thus, M1 receptor agonists act as negative modulators of amyloidogenic processes, as they allow the processing of amyloid precursor protein (APP) to a non-amyloidogenic pathway, which, consequently, increases cholinergic functions. Thus, appropriate levels of acetylcholine (ACh) are important in the maintenance of cognitive processes; therefore, the use of acetylcholinesterase (AChE) inhibitors promotes greater availability of this neurotransmitter in the synaptic cleft and provides an improvement in cognitive symptoms of Alzheimer's.

Table 1. Role of cholinergic receptors in Alzheimer's disease.

Receptor	Modulation	Application	Reference
M1 receptors	Agonists	Learning and memory	Renard and Jean, 2017
M1-M4 receptors	GABAergic inhibition and glutamatergic stimulation	Brain excitement	Ferreira-Vieira et al., 2016
α7nAChR	Modulation of several neurotransmitters, such as: glutamate, GABA, dopamine, serotonin, norepinephrine, and acetylcholine in the CNS	CNS modulation	Hoskin et al., 2019
M1 receptors	Modulation of processes that act to reduce acetylcholine	Cognitive impairment, confusion, sedation, delirium, and dizziness	Migirov and Datta, 2022
Cholinergic agonist receptors	Positive modulation in the neuronal configuration of choline acetyltransferase from the cerebral cortex	Neuroplasticity, vasodilation, and brain perfusion	Hampel et al., 2018
M1 and M4 receptors	Modulation of β-amyloid peptide manufacturing	Decreased memory deficits, mood disorder, agitation, and hallucinations	Ferreira-Vieira et al., 2016
α7nAChR	Modulation of Nrf2 activation (oxidative stress regulation)	Improved anti-inflammatory signaling	Hoskin et al., 2019
α7nAChR	Modulation of cells as the precursors of oligodendrocytes, endothelials, astrocytes and microglia	Enhanced immunity, anti-inflammatory potential and neurological protection	Bouzat et al., 2018

the balance of these nucleotides is unaltered; however, under stress, inflammation, and apoptosis conditions, cells release extracellular ATP that activates some of the purinergic receptors, which may lead to imbalance and negative outcomes in homeostasis (Gratal et al., 2020). P2X and P2Y receptors (P2XR and P2YR) are found in astrocytes, oligodendrocytes, neurons, microglia, and endothelial cells in the CNS (Di Virgilio et al., 2009). Adenosine P1 receptors (P1R) are found in astrocytes, microglia, and neurons (Cieślak and Wojtczak, 2018). Furthermore, ATP is associated with neurotransmission, neurosecretion, and neuromodulation, particularly in the short term. In the long term, it plays an important role in the signaling involved in cell proliferation, differentiation, and death (Burnstock, 2020).

The main pathophysiology of AD is the accumulation of Aβ, followed by the deposition of NFTs, as previously discussed. This process may activate an inflammatory response, with an emphasis on the action of microglia, astrocytes, and neurons that may release ATP into the extracellular environment when exposed to Aβ (Orellana et al., 2011a,b). This characteristic can play an important role in disease progression, particularly in more advanced cases. However, microglial activation is not the underlying cause of the pathological process but a synergistic epiphenomenon that occurs along with the negative outcomes brought about by long-term exposure to Aβ.

In initial and acute neuroinflammatory situations, microglial activity can contribute to the balance of neuronal homeostasis by increasing the clearance of Aβ and dead neurons as they phagocytose these components, reducing their neurotoxicity (Kim et al., 2012; Heppner et al., 2015; Erb et al., 2019). This glial cell has two phenotypes with important roles in neuromodulation, namely M1, which is considered the classic form, characterized by the production of ROS and pro-inflammatory cytokines, such as IL-1β, IL-12, IL-23, STAT3, and TNF-α. M2 is characterized by its remodeling, repair, and angiogenesis owing to the release of anti-inflammatory cytokines, such as TGF-β, IL-10, IL-4, and IL-13. During advanced stages of the disease, microglia undergo a change in their phenotype—from the neuroprotective M2 to the classic M1 form (Wang et al., 2015), which helps to explain the pathophysiological changes according to the stage of the disease.

Purinergic receptors may be associated with this special feature of microglial cells, since under control conditions, with low levels of ATP and consequently low activation of the P2X7 receptor (P2X7R), they act as auxiliary receptors that phagocytize extracellular sediments. However, under temporary stimulation, autophagy is stimulated, material is degraded, and microglia expresses a mixed M1/M2 phenotype. Finally, in the case of prolonged stimulation of P2X7R, there was an increase in lysosomal pH with the extracellular release of autophagosomal content. Microglia expresses genes and proteins associated with M1 activation state (Campagno and Mitchell, 2021). Thus, in the pathogenesis of AD, an acute inflammatory response would be able to promote a protective effect in the CNS, while chronic neuroinflammation could contribute to neurodegenerative outcomes due to the increased release of pro-inflammatory cytokines that contribute to neuronal loss (Heppner et al., 2015; Erb et al., 2019; Thawkar and Kaur, 2019). The notion that different treatments should be targeted according to the temporal phase of the disease and that the purinergic system can play important roles in this cascade can help in its management and in the search for new therapeutic targets.

Continuing on the effects of microglia on the pathogenesis of the disease (Orellana, Froger et al., 2011b; Orellana, Shoji et al., 2011a), microglia releases cytokines, such as TNF-α and IL-1β, under stress conditions after exposure to Aβ, resulting in the increase of ATP and glutamate release via Cx43 hemichannels in astrocytes, which activate Pannexin 1 (PANX-1) in neurons through NMDAR and P2XR. The PANX-1 opening further increases ATP release, creating a vicious cycle by activating more P2XR, which may have a role in intracellular neurotoxic cascades. The blockage of receptors involved in the opening of this hemichannel, such as P2X7R, may contribute to reduced pro-inflammatory activity at the CNS level, reducing Aβ-induced neuronal death (Ryu and McLarnon, 2008; Orellana et al., 2011b). P2X7R is one of the most studied purinergic receptors in neurodegenerative diseases. It plays a role in AD neuroinflammation by activating nuclear factor-kappa B and the NLRP3 inflammasome, which are essential molecules in inflammatory cascade initiation (Thawkar and Kaur, 2019). P2X7R upregulation is also related to an increase in ROS production by microglia, which occurs mainly in chronic conditions and can lead to synaptic loss and death of cortical cells (Parvathenani et al., 2003). Munoz et al. (2017) and Bartlett et al. (2013) showed that the activation of P2X7R by ATP induces the uptake of organic cations, ROS formation, and cell death, and these events may be inhibited by the use of AZ10606120 and A438079 (P2X7R antagonists). Thus, the purinergic system is associated with oxidative stress, which, as described in this article, participates in the pathophysiology of AD.

Other mechanisms involving this receptor have been described by Sanz et al. (2009), who showed that wild-type rats exposed to Aβ had greater ATP release, IL-1β secretion and accumulation, and microglial plasma membrane permeability than that of P2X7R knockout rats. In addition, this last group of the study showed a reduction in the number of amyloid plaques in the hippocampal region due to an increase in α-secretase activity (Diaz-Hernandez et al., 2012). Coincidentally, α-secretase activity decreases under conditions of enhanced P2X7R expression (Cieślak and Wojtczak, 2018). McLarnon et al. (2006) demonstrated that AD patients had increased expression of P2X7R compared to those without the disease, and that cells exposed to Aβ also had higher expression of the P2X7R than those without contact with this agent. The use of P2X7R antagonists is also related to neuroprotection by reducing the inflammatory response and improving cognition and memory in Aβ-induced AD rat models (Ryu and McLarnon, 2008; Chen et al.,

2014). Therefore, a correlation between the blockage of these receptors and neuroprotection in the pathophysiology of AD is plausible.

P2X4R and P2Y6R are other receptors that may also play a role in microglia-mediated neuroinflammation and contribute to AD neurodegeneration (Di Virgilio et al., 2009; Godoy et al., 2019). P2X4R expression increases after nerve tissue damage (Varma et al., 2009) and its upregulation can be induced in AD cases by ATP release by microglia via Aβ induction, leading to neuronal death (Woods et al., 2016). This receptor drives microglial motility via phosphatidylinositol-3-kinase/Akt, in addition to being involved in the production of prostaglandin E2 (PGE2), brain-derived neurotrophic factor, and TNF-α, which may be related to the pathophysiology of the disease. P2X4R has a synergistic relationship with P2X7R (the absence of expression of one can further activate the other, acting as a compensation and complementation mechanism) (Suurväli et al., 2017; Castillo et al., 2022). Finally, it is highly expressed in cases of spinal cord diseases, inflammatory pain, and pre-term hypoxia–ischemia and may also act on LTP and plasticity at CA1 synapses in the rat hippocampus, suggesting that its overexpression may be related to synaptic dysfunction and microglial phagocytic function in patients with AD (Castillo et al., 2022). P2Y6R is selectively activated by UDP, is upregulated after neuronal damage, and is associated with the release of cytokines, such as CCL2 and CCL3, in microglia and astrocytes (Kim et al., 2011; Morioka et al., 2013; Woods et al., 2016). Koizumi and collaborators (Koizumi et al., 2007) showed that kainic acid exposure in the hippocampus of rats increased extracellular uridine nucleotide levels and phagocytic activity of microglia. This phagocytic activation may increase Aβ clearance; however, as a consequence, it can also result in phagocytosis of viable neurons, which is associated with neurodegeneration (Brown and Neher, 2014; Anwar et al., 2020). The use of P2Y6R antagonists reduces neuronal death after LPS exposure in rats (Neher et al., 2014) and reduces neuronal loss and memory deficits in knockout mice induced by Aβ or tau oligomers (Puigdellívol et al., 2021).

Receptors associated with neuroprotection, such as the metabotropics P2Y1 and P2Y2, have also been studied (Peterson et al., 2010; Cieślak and Wojtczak, 2018). Mishra et al. (2006) showed that the activation of these receptors could increase the proliferation of neural stem cells and act on neurogenesis, which may be a new therapy to regenerate damaged hippocampal neurons in patients with AD or even attenuate its progression. In addition, P2Y1R protects neuronal tissue against oxidative stress, with IL-6 being the main signaling molecule for this event (Fujita et al., 2009), which may have dual activity in neural inflammation (Rothaug et al., 2016). However, recent studies have shown that its action can worsen AD dysfunction because it is involved in astrocytic hyperactivity (Reichenbach et al., 2018), which is associated with the worsening of AD dysfunction. Delekate et al. (2014) demonstrated that P2Y1R antagonism returned astroglial network dysfunction to its normal state. Further studies are required to confirm its protective effects. P2Y2R is present in several cells in the CNS and its activation may occur owing to the release of ATP in the presence of Aβ (Cieślak and Wojtczak, 2018).

Deletion of P2Y2R in mice increased Aβ, causing neurological deficits, and decreased the expression of the microglial marker CD11b, which is associated with the severity of microglial activation (Ajit et al., 2014); hence, it acts on the recruitment of microglial cells and Aβ clearance. Aβ clearance may occur by the upregulation of P2Y2R, which plays a role in Aβ degradation by the phagocytic action of microglial cells (Kim et al., 2012). Kong et al. (2009a) reinforced that this role can be mediated by P2X2R via IL-1β through the IκB-α/NF-κB signaling pathway, which stimulates α-secretase activity mediated by ADAM10/17 metalloproteinases (Kong et al., 2009b). An important finding is that the activity of P2X7R is related to the reduction of α-secretase, whereas P2Y2R has the opposite effect, increasing the release of α-secretase (León-Otegui et al., 2011). Based on this finding, it is suggested that P2Y2R activation concomitant with P2X7R antagonism leads to an efficient activation of α secretase; thus, they are promising candidates as new therapeutic targets in AD.

Finally, the adenosine-activated receptor P1 family, such as A1 and A2A, are most studied in relation to neurological diseases and can affect the glutamatergic, dopaminergic, and cholinergic signaling pathways and alter synaptic plasticity in regions responsible for learning and memory development (Ribeiro et al., 1996; Gomes et al., 2011; Cieślak and Wojtczak, 2018). Antagonism of these receptors is related to cognitive improvement and a reduced risk of dementia (Woods et al., 2016). Caffeine is an antagonist of these receptors and reduces the neurotoxicity induced by Aβ, which was verified by blocking A2AR but not A1R (Huang et al., 2011; Wang et al., 2014). In a recent *in vivo* study, Faivre et al. (2018) showed that long-term treatment for 6 months with the A2AR antagonist MSX-3 in a mouse model of AD prevented memory deficits and reduced Aβ1-42 levels in the cortex, and Stazi et al. (2021) showed that treatment for 4 months reduced the loss of neurons in the hippocampus and improved neurogenesis, memory, and learning ability, which may reflect A2AR antagonism. Similar results in cognitive abilities were found in mouse models with tauopathy and those with transgenic lack of A2AR gene encoding (Laurent et al., 2016). Finally, A1R and A2AR modulate cortical release of ACh in the prefrontal cortex, acting on behavioral excitation and sleep (Van Dort et al., 2009). A1R antagonism is also associated with the transmission of ACh in the cortical region and an increase in its extracellular levels in cholinergic terminals (Rahman, 2009), which provides opportunities for further studies to elucidate its behavior and therapy in AD.

SARS-CoV-2 exacerbates the immune system, promoting the worsening of inflammation, which contributes to the advancement of the disease and activation of purinergic receptors negatively involved in the pathophysiology of AD. Thus, therapeutic measures aimed at the analysis of these receptors are essential to prevent the neural progression of the disease in these patients, not only for those who had contact with the

Table 2. Purinergic receptors and main roles in Alzheimer Disease.

Receptor	Agonist	Cell activation	Main role	Reference
P2X7	ATP, ADP	Microglia	– Acute response *scavenger* receptor, promote M2 microglia phenotype – Chronic response promote M1 microglia phenotype – Linked to Panx-1 hemichannel opening – Activation of nuclear factor-kappa B (NF-kB) and NLRP3 inflammasome – ROS production – Decrease α-secretase activity	Bartlett et al., 2013; Diaz-Hernandez et al., 2012; Munoz et al, 2017; Parvathenani et al., 2003; Orellana et al., 2011a; Thawkar and Kaur, 2019; Wang et al., 2015;
P2X4	ATP	Microglia	– - Synergic to P2X7R response	Castillo et al., 2022; Suurväli et al., 2017
P2Y6	UDP	Microglia and astrocytes	– Cytokines release – Phagocytosis of neurons Aβ induced	Anwar et al., 2020; Brown and Neher, 2014; Erb et al., 2019; Kim et al., 2011; Morioka et al., 2013;
P2Y2	UTP	Microglia	– Increase α-secretase release and promotes Aβ clearence	Ajit et al., 2014; Kim et al., 2012
P2Y1	ADP, ATP	Microglia and astrocytes	– Astrocytic hyperactivity – Neuroprotection via microglia activation	Delekate et al. 2014; Fujita et al., 2009; Reichenbach et al., 2018;
A2A	Adenosine	Microglia	– Reduces the neurotoxicity induced by Aβ – Neurogenesis	Dall'Igna et al., 2003; Faivre et al., 2018; Stazi et al., 2021

new coronavirus but also for the uninfected ones that can benefit from treatment with these therapeutic targets (Table 2).

FUTURE PROPOSALS

Neurodegeneration as a result of AD mainly affects cholinergic pathways, such as forebrain neurons, affecting memory deficits. Thus, pharmacology focused on this area is a promising segment for the treatment of the disease (Richter et al., 2018), since abnormal cholinergic pathways result in inefficiency of distribution and function in the body, for eg., cognitive deficits (Rasch et al., 2006; Kuo et al., 2007). In addition, cholinesterase inhibitors are relevant tools in therapies aimed at improving AD, given their ability to increase the availability of ACh in the synaptic cleft and, consequently, to the body (Ferreira-Vieira et al., 2016) as well as anti-amyloid and anti-tau interventions (Rasch et al., 2006; Kuo et al., 2007). Furthermore, studies aimed at understanding the complexity of AD pathophysiology can improve treatment by analyzing triggering and aggravating factors, considering oxidative stress, aggregation of Aβ and tau protein, genetic predisposition, inflammatory mechanisms, and mitochondrial disturbances (Hampel et al., 2018; Sharma, 2019). Considering these involvements, multifactorial diseases can be better interpreted and oriented, contributing to the development of personalized drug therapies and interventions (Rasch et al., 2006; Kuo et al., 2007) (Fig. 4).

Active investigation into anti-inflammatory methods triggered by some receptors, such as nicotinic 7, is significantly relevant, as they can be used and directed to improve cognition in several pathologies, including AD. Understanding their functionality and impact on organisms may point to useful modulation pathways for treatments and as targets for pharmacological tools (Bouzat et al., 2018). Because of the wide location of brain nicotinic receptors, their impact on AD pathophysiology, and their effects and means of regulation, cholinergic receptors have become potential therapeutic targets, enabling the use of agonists that stimulate the cholinergic system to play a role in the organism as this system is compromised in AD. Thus, the study of the cholinergic pathway is essential to contribute to the improvement of brain impairment caused by AD (Hoskin et al., 2019) (Fig. 4).

Other receptors that comprise the purinergic system are also essential tools for AD pharmacotherapy. The P2X7R is one of the most closely related receptors to the pathophysiology of AD. Its activation, depending on the stage of the disease, is related to negative outcomes and affects the inflammatory response, with a role in microglial modulation, release of ROS, and reduction in the levels of α-secretase (Cieślak and Wojtczak, 2018; Campagno and Mitchell, 2021). P2X4R has a synergistic role with P2X7R in inflammation, and its antagonism may be an adjuvant target in treatment as well (Castillo et al., 2022). Other receptors such as P2Y6 and P2Y1 have setbacks in this field: although the former is associated with an increase in α-secretase, it is linked with neuronal damage and the latter has a protective effect against ROS but is associated with possible negative outcomes by worsening astrocyte activity (Fujita et al., 2009; Anwar et al., 2020). Hence, these receptors need further studies to elucidate their pathophysiology of neurodegenerative diseases. The activity of P2Y2 is closely related to neuroprotection, and agonism of P2Y2 promotes an increase in α-secretase and Aβ clearance

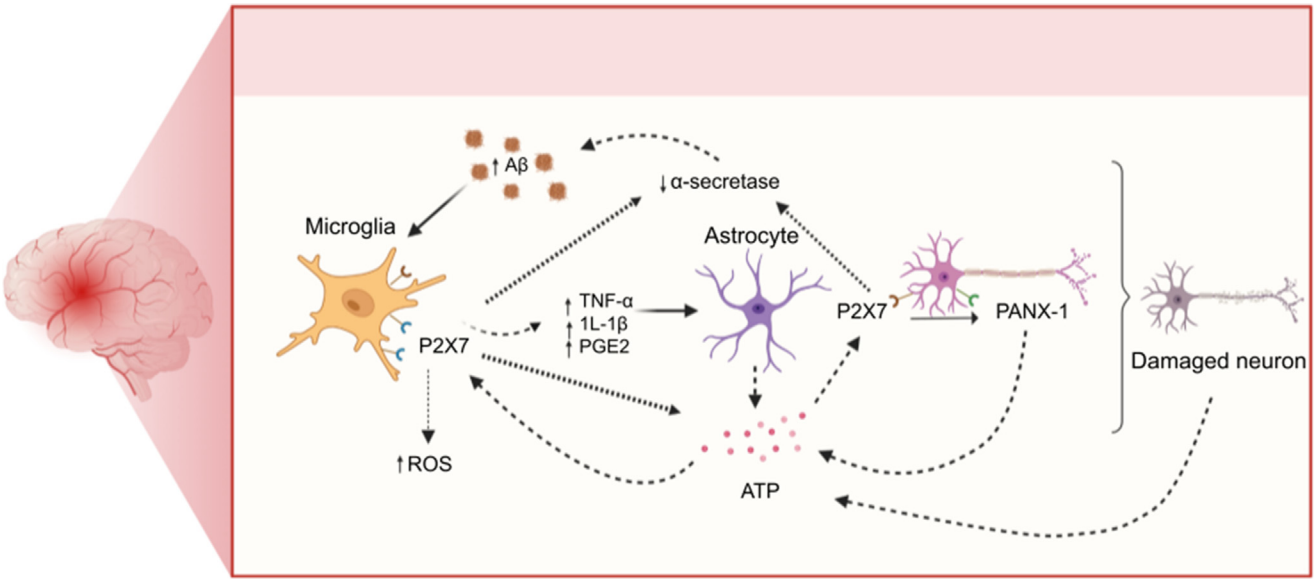

Fig. 5. Adenosine triphosphate (ATP) is released via neuronal damage/tissue inflammation or microglial cell exposure to β-amyloid peptide (Aβ), which liberate tumor necrosis factor alpha (TNF-α) and Interleukin 1 beta (IL-1B), acting on astrocyte and releasing additional ATP. It activates P2X7 receptor (P2X7R) in macroglia and neuron, causing α-secretase reduction and activating PANX-1, which is involved in ATP secretion. P2X7R is also involved in reactive oxygen species (ROS) liberation. P2X4R has effects similar to P2X7 and is involved in TNF-α and prostaglandin E2 (PGE2) secretion.

(Cieślak and Wojtczak, 2018). The antagonism of P1 family receptors, such as A2A, is also associated with positive outcomes in neurodegenerative models, as it improves aspects of cognition, such as memory, and protects neural tissue against Aβ-induced damage (Woods et al., 2016). Therefore, purinergic receptors are promising therapeutic targets against the progression of AD, and further studies on their roles in the course of this neurodegenerative disease are essential to find a feasible elucidation of their use in clinical practice (Fig. 5).

The global pandemic triggered by SARS-CoV-2 has led to several analyses regarding the impact of COVID-19 on the body. Its involvement in the neural network can aggravate other pre-existing dysfunctions, as is the case in individuals with AD who already have a neurodegenerative condition and owing to the hyperinflammation produced by the virus along with the oxidative stress process, result in prominent nerve damage. Thus, because of the involvement and impairment of the nervous system, studies on anti-inflammatory modulation pathways may contribute to attenuating the effects of COVID-19 and neural degeneration processes of AD. The cholinergic system, acting through the neurotransmitter ACh and cholinergic neurons, contributes to the anti-inflammatory potential through muscarinic and nicotinic receptor agonists, which have protective effects against neurodegenerative processes. The cholinergic system could be beneficial in preventing these neurological disorders; additionally, the purinergic system is a promising target. The antagonism of purinergic receptors, such as P2X7, P2X4, P2Y6, and A2A, and agonism of P2Y2 showed improvement in inflammation, oxidative stress, and cognition. Therefore, the use of cholinergic and purinergic therapies is a tool for modulating the nervous system and providing an alternative drug for the treatment of some physiological disorders.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

CONSENT FOR PUBLICATION

Informed consent and consent for publication were obtained from each participant.

AVAILABILITY OF DATA AND MATERIALS

Not applicable.

COMPETING INTERESTS

The authors declare no conflicts of interest.

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AUTHORS' CONTRIBUTIONS

JLBS conceptualized the paper. JLBS, LDS, IFL, MVRS, JVC, and MDB performed the literature search and data analysis as well as drafted and critically revised the work.

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