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Chapter

Alzheimer's Disease Neuroprotection: Associated Receptors

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Abstract

Research with humans and animals has been developed over the past few years to identify receptors involved in Alzheimer's disease, aiming at a better understanding of the mechanisms and pathophysiological aspects associated with the disease. Such receptors, whether or not directly associated with current AD therapy, are relevant since their blockage or activation might result in improving or worsening the clinical scenario of the disease. In other words, such receptors might be involved in the AD prognosis. This chapter discusses some relevant points about the receptors involved with AD.

Keywords: neuroprotection, Alzheimer disease, receptors, beta-amyloid peptides, central nervous system, agonists, antagonists

1. Introduction

Alzheimer's disease (AD) is the most recurring chronic and incurable neurodegenerative disorder. The main neuropathological findings on AD are beta-amyloid protein plaque (APP) deposition, an accumulation of hyperphosphorylated neurofibrillary tangles, inflammation, neurotransmitter signaling dysregulation, brain atrophy, and neuronal changes. AD affects the central nervous system (CNS) and results in an impaired emotional state, loss of synapses, neuronal death, and progressive cognitive decline. Some risk factors such as advanced age, genetic factors, and head trauma (among others) are involved in AD progression. Alzheimer's disease is responsible for marked morbidity and mortality due to the difficulty in treatment and irreversible damage. However, there is condition stabilization in some cases, and the individual can postpone their life expectancy for years [1].

2. Alzheimer's disease-associated receptors

2.1 Nicotinic acetylcholine receptor

Nicotinic acetylcholine receptors (nAChR) are involved with neuroprotective effects in AD. Furthermore, nAChR agonists and antagonists have been shown to have positive effects on memory. Cotine and methyl cyclonite are examples of nAChR ligands associated with brain protection when in vitro and in vivo tests

have been performed. In addition, nAChR and the muscarinic acetylcholine receptor family (mAChR) are acetylcholine targets in the brain. The nAChR family is affected in AD because beta-amyloid peptides ($A\beta$) can interact with these receptors [1]. Acetylcholine (Ach) plays a crucial role in CNS. Choline acetyltransferase enzyme is responsible for ACh synthesis from acetyl-CoA and choline in the cytoplasm. The acetylcholine vesicular transporter absorbs the neurotransmitter in synaptic vesicles. After depolarization, ACh undergoes exocytosis in reaching the synaptic cleft, where it can bind with its receptors. The ACh in the synaptic cleft is readily hydrolyzed by the acetylcholinesterase enzyme, forming acetate and choline, which is recycled at the presynaptic nerve terminal by the high-affinity choline transporter. Cholinergic neurons located in the basal forebrain, including the neurons which form Meynert's basal nucleus, are severely affected in AD. The loss of cholinergic neurons contributes to memory and attention deficits. Therefore, drugs acting on the cholinergic system represent a promising option for treating AD patients [2]. The conventional therapeutic prescription for AD consists of three acetylcholinesterase inhibitors and one NMDA receptor antagonist. Researchers around the world are developing new nAChR agonists to develop drugs with lower risks and adverse effects [3].

2.2 Estrogen receptor

Another important target in AD is the estrogen receptor (ER), which may represent a promising therapeutic approach since its activation through agonists prolongs survival, improves spatial recognition memory, and decreases the amyloid pathology progression in animal models of AD. On the other hand, estrogen receptor genetic polymorphisms have been associated with cognitive impairment, accelerated brain aging, and increased risk of AD, predominantly in women. A methylation promoter in estrogen receptor α is also related to impaired cognitive function and quality of life in AD patients by inhibiting ER α mRNA expression and transcription [4]. Estrogen can increase neural plasticity, cognitive functions, and the brain's regenerative potential. The beneficial effects of estrogen on neural plasticity occur at three levels: cellular, morphological, and synaptic function. Studies have shown that estradiol can increase neurogenesis in several brain regions, such as the hippocampal gyrus. These estrogen-induced hippocampal neurons contribute to learning and memory. Estradiol can also rapidly increase the number of dendritic spines in the hippocampus, amygdala, and hypothalamus and thus improve the performance in a hippocampal-dependent memory task. Moreover, estradiol is an effective enhancer of synaptic transmission in the hippocampal system. Estradiol plays an important role in promoting neurogenesis and neuronal plasticity to maintain healthy cognitive function and protect against women's cognitive decline during aging [5]. Therefore, estrogen with selective effects on ER α or G protein-coupled estrogen receptors (GPER1 or GqMER) can be used to influence the inflammation process resolution, with positive effects on AD progression [6].

2.3 Ryanodine receptor

Ryanodine receptors (RyR) are an ion channel family responsible for calcium release from intracellular reserves during muscle contraction. Calcium homeostasis is known to be related to cognition; thus, RyR may be associated with AD, especially RyR 3, which is found in various nervous system areas. In addition, RyR 1 and RyR 2 are also found in the brain, although they are not predominantly present in the nervous system. Ryanodine receptors can be regulated by several proteins and ions, as well as redox modifications. Antioxidants importantly prevent cognitive decline,

long-term depolarization, and memory loss by inhibiting RyR sensitization [7]. Calcium-dependent signaling pathways are related to AD pathogenesis. A pharmacological approach (using a RyR stabilizing drug) or gene therapy of calcium leakage (mediated by RyR2) improved synaptic plasticity, and behavioral and cognitive functions and reduced A β loading. Genetically, altered mice (congenital leaking of RyR2) exhibited premature and severe defects in synaptic plasticity, and behavioral and cognitive function. These data provide an underlying mechanism for RyR2 channels, which can be considered as possible therapeutic targets in AD [8]. Additionally, calcium accumulation may result in the calpain and CaMKK2 activation, contributing to A β production and tau phosphorylation. Ryanodine receptor dysfunction can also lead to abnormal activation and accumulation of PKR kinase in AD brains. PKR kinase is linked to calcium accumulation and PKR autophosphorylation can be triggered by A β peptides in neuronal cultures in a calcium-dependent manner. In turn, PKR activation may lead to A β production by regulating BACE1 levels and abnormal tau protein phosphorylation by GSK3 activation. Dantrolene, a RyR inhibitor, may be an AD treatment [9].

2.4 Gamma-Aminobutyric Acid receptor

Gamma-Aminobutyric Acid receptor (GABAR) inhibition is also related to a better prognosis in AD. Gamma-Aminobutyric Acid receptor regulates learning, memory, and cognition, inhibits Adenylyl Cyclase and the cAMP cascade, as well as controls GABA and glutamate release. CGP35348 is a GABA receptor antagonist, and the CGP35348 hippocampal concentration is a crucial point for improving memory by reducing APP toxicity. Several neurological and psychiatric disorders occur with neuronal hyperexcitability in specific regions of the brain or spinal cord, partly due to some loss and/or dysfunction of GABAergic inhibitory interneurons [10]. Strategies which improve inhibitory neurotransmission in the affected brain regions may decrease deficits associated with these disorders. This perception has prompted an interest in testing the efficacy of GABAergic interneuron grafting in the brain or spinal cord regions which exhibit hyperexcitability, GABAergic interneurons scarcity, or impaired inhibitory neurotransmission, using preclinical models of neurological and psychiatric disorders [10]. Defective GABAergic neuronal functions can lead to cortical network hyperactivity and aberrant neuronal oscillations and thereby generate a detrimental change in memory processes [11]. In this context, GABAergic cell therapy may decrease neurological deficits in AD preclinical models [10]. Alzheimer patients have low GABA levels in the brain and spinal cerebrospinal fluid (SCF), and these changes are more severe in ApoE4 allele carriers. ApoE4 is associated with increased brain activity at rest and memory tasks, possibly reflecting impaired GABAergic inhibitory control. In addition, GABA levels in human SCF change with aging, constituting the strongest AD risk factor. Therefore, ApoE4 may at least partially contribute to the AD pathogenesis, causing age-dependent impairment in GABAergic interneurons [12].

2.5 Receptor for advanced glycation end products

The relationship between the receptor for advanced glycation end products (RAGE) and AD has also recently been established; RAGE is widely expressed and regulated in the AD brain. Furthermore, RAGE is involved with the transport of beta-amyloid protein through the blood-brain barrier (BBB) to the brain parenchyma. Interactions between RAGE and APP result in inflammatory responses and oxidative stress, as well as reduce cerebral blood flow. The receptor also inhibits the elimination of APP and RAGE ligands such as AGE, HMGB1, and S100 β , which are

involved in the neurodegenerative disease progression. Additionally, RAGE/AGE interactions induce the apoptosis cascade and neuronal inflammation [7]. In addition, RAGE has been considered as a therapeutic approach in AD; in fact, a RAGE antagonist demonstrated a protective effect in an animal model. Chronic oral dosing of PF-04494700 antagonist in transgenic AD mice reduced A β levels, improved performance in spatial memory testing, and normalized the electrophysiological recordings of hippocampal slices. According to the results of the Phase II clinical study [13], the RAGE inhibitor has an excellent safety profile and is well-tolerated for over 10 weeks in patients with oral AD. These inhibitors block the binding of A β peptides to the RAGE V domain as well as inhibit the cell stress induced by A β in cells expressing RAGE in vitro, as well as in the brains of mice [14].

Moreover, a RAGE inhibitor (FPS-ZM1) has no animal toxic activity and easily crosses the BBB. In aged mice with AD, FPS-ZM1 can inhibit the RAGE-mediated influx of A β 40 and A β 42 in the brain. FPS-ZM1 binds exclusively to RAGE in the brain, inhibiting A β production and suppressing microglia activation and neuroinflammatory response. Blocking RAGE actions in the SCF and brain normalizes cognitive performance and cerebral blood flow. FPS-ZM1 is a potent RAGE blocker, thereby controlling the progression of A β -mediated brain disorder [14]. Furthermore, metabolic syndrome is a risk factor for cognitive decline in AD, and RAGE has been associated with metabolic syndrome, as this receptor directly contributes to an inflammatory process and oxidative stress. Thus, the RAGE inhibition is able to reduce cellular toxicity, and therefore, RAGE inhibitors have therapeutic potential in retarding AD progression [15].

2.6 Vitamin D receptor

Vitamin D (VD) acts through the vitamin D receptor (VDR), expressed in various tissues, including the nervous system. Vitamin D receptor is related to memory and cognitive functions. Research has reported a higher prevalence of VD deficiency in AD patients and individuals with VD deficiency had twice the risk of developing AD compared with individuals with sufficient VD concentrations. Several potential mechanisms which link low VD levels to the risk of dementia have been identified. First, VDR is expressed throughout the brain, including areas involved in memory, such as the hippocampus. The enzyme which synthesizes the active form of VD, 1 α -hydroxylase, is also produced in various brain areas. Second, the VD active form (1,25dihydroxyvitamin D3 or 1,25-D3) regulates neurotrophin expression, such as neurotrophin 3, Glial cell-derived neurotrophic factor (GDNF) and neural growth factor (NGF). NGF has been implicated in maintaining and regulating the normal function of the septohippocampal pathway, which is involved in learning and memory. In addition, NGF levels are substantially reduced in AD patients and NGF negatively modulates APP protein gene expression, while increased APP expression is observed after NGF suppression. Furthermore, VD analogs increase APP binding to the NGF promoter, inducing NGF expression. Therefore, 1,25-D3 contributes to the development, survival, and function of neural cells [16].

Third, VD can stimulate macrophages, which increases amyloid plaque clearance. Fourth, the antioxidant effect of VD may be related to the modulation of antioxidant gene expression. Oxidative stress is known to contribute to the pathophysiology of neurodegenerative diseases, which leads to impaired cognitive and behavioral function. Genetic analyses of the human genome have pointed to several genes playing a role in susceptibility to AD, such as genes which are involved in inflammation and oxidative stress [7]. Fifth, VD also plays a role in vascular protection. Sixth, VD regulates neurotransmitter metabolism in the CNS, such as

acetylcholine, dopamine, serotonin, and aminobutyric gamma acid. Finally, VD also reduces A β -induced cytotoxicity and apoptosis in primary cortical neurons. A recent study found that A β induction of nitric oxide synthase, part of the AD inflammatory process, depends on the VDR pathway disruption. VD supplementation improves age-related cognitive decline, learning, and memory in older rats. A cross-sectional study found that VD deficiency was associated with increased white matter volume and reduced gray matter volume. In summary, low VD concentrations may increase the risk of dementia and AD through vascular and neurodegenerative mechanisms [16].

2.7 Retinoid X receptor

Vitamin D receptor interacts with the retinoid receptor X (RXR) to perform VD actions. Retinoid receptor X activation can stimulate the normal physiological processes by which APP is eliminated from the brain. Thus, RXR agonists may be useful in treating AD. Two-week treatment with an RXR agonist (bexarotene) in an AD animal model resulted in clearance of intraneuronal amyloid deposits. Additionally, treatment with bexarotene improved remote memory stabilization in fear-conditioned mice and improved olfactory habituation. In addition, bexarotene pretreatment improved neuronal survival in response to glutamate-induced excitotoxicity. The bexarotene effects were accompanied by reduced amyloid plaque levels, decreased astrogliosis and suppression of inflammatory gene expression. Therefore, treatment with RXR agonists can decrease neuron loss, reverse cognitive deficits, and improve neural circuit function in aggressive AD models [17]. Retinoid receptor X agonists can increase the expression of ApoE, ABCA1, and ABCG1 by activating RXR heterodimers. On the other hand, these beneficial effects are blocked by the RXR antagonist, which can accentuate cellular oxidative stress [18].

Interestingly, RXR decreased expression was identified in the AD mouse model and in cells treated with A β peptides [19]. However, the action mechanism of RXR ligands remains unknown, particularly in the context of human ApoE [20]. Retinoids have effects on various physiological and pathological processes in the brain. For example, retinoic acid (RA) signaling is widely detected in the adult CNS, including the amygdala, cortex, hypothalamus, hippocampus, and other brain areas. Retinoids are mainly involved in neural patterns, axon differentiation, and cell growth. Retinoids also play a key role in preserving the differentiated state of adult neurons. Impaired RA signaling may result in neurodegeneration and AD progression. Recent studies have shown severe deficiencies in mouse learning and memory during RA deprivation, indicating its importance in preserving memory. Defective cholinergic neurotransmission is related to cognitive deficits in AD. Retinoic acid is also known to increase choline acetyltransferase expression and the activity in neuronal cell lines. In addition, retinoids have been shown to inhibit the expression of proinflammatory chemokines and cytokines in microglia and astrocytes, which are activated in AD [21].

2.8 N-methyl-d-aspartate receptors

N-methyl-d-aspartate receptors (NMDAR) participate in CNS development and are involved in synaptic plasticity, which is essential for learning and memory. Cognitive symptoms associated with learning and memory deficits have been associated with glutaminergic neurotransmission disorders. Excitatory glutaminergic neurotransmission via NMDAR is critical for synaptic plasticity and neuron survival. However, excessive neuron stimulation by the glutamate neurotransmitter causes cytotoxicity and results in neuronal damage and death, underlying a

potential mechanism of neurodegeneration in AD. Therefore, blocking NMDAR receptor-mediated glutaminergic neurotransmission can decrease cytotoxicity, thereby preventing further damage to neurons and cellular oxidative damage [22]. Therefore, NMDAR antagonists have emerged as potential compounds for AD patients since the receptor itself has many subunits and its variants have several brain functions. For example, conantokine acts as an NMDA receptor antagonist and plays an important role in understanding the importance of NMDA receptor inhibition in the AD treatment. Moreover, NMDAR activation might be blocked by an AD drug, memantine, an NMDAR antagonist which selectively blocks the function of extra synaptic NMDARs, but does not affect normal neurotransmission. However, memantine (and other current medications used to treat AD) only relieve the symptoms and do not alter the disease progression [23].

2.9 Cholesterol receptors

Regarding cholesterol receptors, some specific genotypes have been related to a higher or lower risk of dementia and AD. Even genotypes associated with AD neuropathology attenuation could be associated with late-onset of dementia. Liver nuclear X receptors (LXRs) are the main regulators of cholesterol homeostasis and CNS inflammation. The brain, which contains about 25% of total body cholesterol, requires a complex and balanced cholesterol metabolism to maintain neuronal function. Deregulation of cholesterol metabolism has been implicated in several neurodegenerative diseases, including AD. Due to their anti-inflammatory activities, LXRs play a crucial role in CNS function. Although LXR agonists have therapeutic potential in neurological diseases, the use of LXR in these pathologies remains problematic. The recent discovery of cholesterol derivatives which function as LXR agonists has shown new roles for LXRs in midbrain neurogenesis. Elucidating the repertoire of endogenous ligands for LXR will improve the understanding of how this receptor regulates CNS lipid metabolism [24].

Nuclear X receptor signaling affects AD development through various pathways. Studies indicate that LXR genetic loss in transgenic mice results in increased amyloid plaques. Studies also suggest that LXRs activation in mice improves the expression of cholesterol efflux-linked genes (ApoE and ABCA-1), induces APP processing, and reduces A β synthesis, with significant improvement in memory. Furthermore, LXR agonists have also been shown to inhibit neuroinflammation by modulating microglial phagocytosis and repressing COX2, MCP1, and INOS expression in glial cells [25]. The T allele of NR1H2 (rs2695121) presents the most significant risk for AD among all LXR- β gene polymorphisms. Taken together, these findings suggest that brain-penetrable LXR agonists or LXR modulators may be useful therapeutic agents for AD treatment and prevention [26].

Additionally, chromosome 12p has been recognized as an AD-associated region. This chromosome includes genes for LDL receptor 1 (LRP1) and oxidized low-density lipoprotein receptor 1 (OLR1). OLR1 is a class E scavenger receptor and is a transmembrane glycoprotein. In vitro factors such as oxidized LDL, oxidative stress, and inflammatory cytokines, as well as in vivo factors such as diabetes mellitus, hyperlipidemia, and hypertension, may induce OLR1 expression. Increased oxidized LDL levels induce endothelial cell activation and dysfunction, apoptosis, and impaired vessel relaxation, thus contributing to atherosclerosis development and progression through OLR1. Epidemiological and clinical literature has reported an association between atherosclerosis, vascular risk factors, and AD. Therefore, OLR1 variations may lead to low efficiency in the oxidized LDL removal and therefore increased A β levels, which may result in neuronal death. Indeed, a single nucleotide polymorphism in OLR1 located in the 3' untranslated region of the gene

may influence regulatory microRNA binding and OLR1 homeostasis. Several studies have reported an association between this variant and AD [27].

2.10 Toll-like receptors

Toll-like receptors (TLRs) are innate immune system receptors which are activated by pathogens (PAMP) or damage-associated molecular patterns (DAMPs). Toll-like receptors are associated with neuronal injury in chronic inflammatory conditions but also with functional recovery after nerve injury. Amyloid aggregates seem to be a type of DAMP and may interact and activate standard recognition receptors. Two TLR actions (ligand binding and immune signaling) may have beneficial effects on AD pathology. Moreover, microglial activation represents an important AD hallmark. Analysis of genetic polymorphisms suggested relationships between TLR polymorphisms and AD risk, further supporting the hypothesis that TLRs are involved in AD [28]. In fact, TLR2 is elevated in the hippocampus and cortex of AD patients and mice. In this context, it was observed that a TLR2-binding peptide (WT TIDM) inhibited A β -induced microglial activation, reduced A β load, attenuated neuronal apoptosis, and improved memory and learning in mice. However, WT TIDM peptide was not effective in TLR2 knockout mice [29].

Importantly, TLR5 binds to APP with high-affinity, forming complexes which block APP toxicity. In turn, APP fibrils modulate the human TLR5 activation via flagellin, but APP cannot activate TLR5 signaling by themselves. Thus, TLR5-related biological data suggest this receptor as a potential agent in AD therapy [30]. A new TLR9 signaling pathway has recently been associated with the immune-inflammatory response, reducing A β levels in AD mice. Therefore, TLR9 may represent a functional candidate gene for AD [31]. Moreover, TLR4 has also been described in the brain and seems to regulate some physiological processes such as neurogenesis. In this sense, TLR4 plays an important role during neurodegenerative disorders. PRDX6 has been shown to inhibit neural stem cell neurogenesis by down-regulating the TLR4 signaling pathway [32]. An early TLR3-mediated signal improves A β neuronal autophagy, although it increases neuronal apoptosis in the late stage of AD. Similarly, TLR7, TLR8, and TLR9 may improve early A β microglial uptake, but over time, they contribute to neuroinflammation. Therefore, TLRs, in particular TLR2 and TLR4, represent suitable targets for therapeutic intervention in AD and carefully targeting them may increase A β autophagy and phagocytosis, as well as reduce inflammatory responses. Several modulators with selective TLR agonist or antagonist activity have been developed, and many of them could produce a therapeutic benefit in AD patients [33].

2.11 Chemokine receptors

Another molecule involved in AD is the chemokine receptor CX3C1 (CX3CR1), which performs IL-1 β -dependent cognitive functions. It is known that CX3CR1 maintains microglial homeostasis and is essential for microglia function in synaptic support since it is highly expressed in microglia. In vivo, CX3CR1-GFP knock-in mice (in which GFP replaced a CX3CR1 allele) were used to study the role of microglia in AD and other brain diseases. Under physiological conditions, decreased CX3CR1 function affects cognitive functions in an IL-1 β -dependent manner, as well as exacerbates LPS-induced inflammation, suggesting that CX3CR1 is essential for nerve synapses. In this context, CX3CL1/CX3CR1 axis dysregulation in AD may have neuroprotective and neurotoxic effects depending on the model used. It is also possible that CX3CR1 is involved in the death of neurons with intracellular TAU deposits and the subsequent TAU release [34]. Still, regarding chemokine

receptors, CCL2 receptor (CCR2) was also associated with AD since CCR2 promotes the recruitment of bone marrow monocytes into the APP deposition sites in the parenchyma, where APP phagocytosis occurs. In mice, CCR2 deficiency accelerated early AD progression, impairing mononuclear phagocyte accumulation. CCR2^{-/-} mice exhibited high APP levels and low CD11b+ cell recruitment in the brain. Importantly, these mice had increased mortality in a dose-dependent manner of the CCR2 gene. Subsequent studies showed that APP reduction is due to the monocyte accumulation in the perivascular spaces and possibly its infiltration into the brain parenchyma. These findings were corroborated by the fact that CCR2 deficiency worsened memory and increased soluble APP levels in mice [34].

2.12 Glucocorticoid receptors

The main AD risk factor is aging, but there is growing evidence that chronic stress or stress-related disorders may increase the chance of developing AD. Thus, depressive disorder may be a risk factor for AD [35]. Stress promotes AD progression on neurons and glial cells, supporting an important pro-inflammatory role of glucocorticoid (GC) in the CNS [36]. Glucocorticoids act via two receptors: mineralocorticoid and glucocorticoid receptors (GR) and can participate in APP generation and APP activity in the brain. There is a cross-talk between APP and GRs in hippocampal excitatory synapses, which may contribute to abnormal brain activity during the AD pathogenesis. Both AD patients and AD mice have dysregulated hypothalamic-pituitary-adrenal (HPA) axis, marked by hypercortisolemia early in the AD pathology. Thus, in early AD, while APP levels slowly increase in the brain, GR activity is probably abnormally high [37]. Moreover, GRs hyperactivation induces brain changes similar to AD changes. In the brain, GCs are regulators of dendritic spine renewal and microglia activity, two strongly altered phenomena in AD. Although well established that GCs initiate the brain neuroinflammatory response, it is not known whether GRs modulate dendritic spine plasticity and microglial activity in AD [36].

Several strategies aiming GR has been tested to counteract HPA axis dysregulation and GC overproduction. Given the GR ubiquitous expression, antagonists have many side effects, limiting the GR therapeutic potential. However, a new class of selective molecules has been developed, acting as GR modulators. They selectively reduce GR-dependent pathogenic processes while retaining the beneficial aspects of GR signaling. Indeed, these “selective GR modulators” induce receptor conformations that allow the activation of only a subset of downstream signaling pathways, explaining their ability to combine agonistic and antagonistic properties. Therefore, targeting GR with selective modulators, alone or in association with current strategies, is attractive to develop new strategies aiming disorders associated with HPA axis dysregulation [35]. Dexamethasone, a GR agonist, was able to reduce the dendritic spine density, induced the microglia proliferation, and activated the microglia in the mouse hippocampus. Besides, *in vitro* microglial cells were activated by dexamethasone. In contrast, treatment with mifepristone, a GRs antagonist, strongly increased dendritic column density, decreased microglia density, and improved mice behavioral performance [36].

2.13 G-protein-coupled receptor 40

There are a large number of polyunsaturated fatty acids in the nervous system, such as docosahexaenoic acid (DHA), an omega 3 carboxylic acid. The DHA binds to G-protein-coupled receptor 40 (GPR40) and exerts protective effects on the nervous system. For example, GPR40 can increase synaptic plasticity, neuronal

activity, and inhibits neuronal apoptosis. In this context, GPR40 was considered a possible target in dementia [38]. The receptor is expressed in several brain areas, including the hippocampus, which is involved in learning and spatial memory. However, few studies are investigating the functional role of GPR40 in the brain [39]. One study evaluated the GPR40 functional role in the AD mouse model. Groups treated with GPR40 significantly improved cognitive performance and GPR40 agonist-treated groups improved learning and memory skills in various tests. Besides, GPR40 activation caused CREB phosphorylation and increased neurotrophic factors levels, including brain-derived neurotrophic factor (BDNF), nerve growth factor (NGF), neurotrophin-3 (NT-3), and neurotrophin-4 (NT-4) in hippocampal neurons. These results suggest that GPR40 can be a therapeutic candidate for neurogenesis and neuroprotection in AD treatment and prevention [39] since GPR40 agonists can promote adult neurogenesis, inhibit neuronal apoptosis, and play a vital role in protecting nerves and decreasing brain damage [38].

2.14 Triggered receptor expressed on myeloid cells 2

The triggered receptor expressed in myeloid cells 2 (TREM2) is a soluble protein carried by macrophages through ventricles and choroid plexus, entering the brain parenchyma through radial glial cells. TREM2 is important for innate immunity, but it is also essential for neuroplasticity and myelination. During later stages of life, the TREM2 absence can accelerate aging processes, neuronal cell loss and reduce microglial activity, leading to neuroinflammation. Inflammation plays an important role in neurodegenerative diseases and TREM2 can be important to immunomodulation and neuroprotection [40]. As a member of the immunoglobulin superfamily, TREM2 can suppress inflammatory responses, mediates phagocytic pathways, is involved with neuronal survival and neurogenesis, as well as contributes to CNS neuroimmune homeostasis. Changes in TREM2 are involved in AD-related neuropathology, including A β deposition, tau hyperphosphorylation, neuroinflammation, and neuronal and synaptic losses in AD animal models. However, the precise underlying mechanisms about TREM2 have not yet been fully characterized [41]. Besides, TREM2 might be related to microglial activation, promoting the association of microglial cells with APP plaques. Therefore, microglia can decrease APP plaque growth, limiting APP toxicity. On the other hand, this phagocytotic capacity is impaired by TREM2 deficiency. Moreover, different mutations in TREM2 are associated with AD [42, 43]. Interestingly, recent findings also suggested that the association between TREM2 variants and the AD risk varies according to different ethnicities and populations [41].

2.15 5-Hydroxytryptamine 6 receptor

The serotonergic neurotransmitter system has been implicated in AD pathogenesis. The 5-hydroxytryptamine 6 receptor (5HTR6) is expressed in brain areas involved with cognitive processes and has been investigated as a possible therapeutic target in AD symptomatology. Besides, 5HTR6 may be added to currently approved “Food and Drug Administration” therapies: cholinesterase inhibitors and NMDA receptor antagonists since 5HTR6 controls the pyramidal neurons’ migration during corticogenesis. In addition, 5HTR6 is a TOR signaling activator and seems to regulate GABAergic, glutamatergic, and cholinergic activity. Therefore, 5HTR6 is involved in cognition, anxiety, memory, affective state, among others [44]. Several kinds of research have been conducted with selective 5HTR6 antagonists. These antagonists act by modulating the glutamate and GABA levels, consequently increasing dopamine, ACh, and norepinephrine concentrations in

the brain, all compromised in AD. Besides, 5HT₆ agonists have also been shown to have pro-cognitive effects. Partial or inverse agonists may produce promising cognitive effects [44, 45]. Moreover, 5HT₆ gene variants can be a genetic risk factor for late-onset AD and 5HT₆ polymorphisms are possibly involved with AD susceptibility, such as the C267T polymorphism [44]. However, there are relatively few genetic studies investigating the association between AD and gene variants involved in the serotonergic system.

2.16 Cannabinoid receptors

Evidence regarding the involvement of the endocannabinoid system (ECS) in the AD pathogenesis raised questions about the development of new therapeutic approaches for AD based on endocannabinoid regulation. The endocannabinoid system is composed of receptors, endogenous ligands, and enzymes, which are involved in AD pathogenesis [46]. Endocannabinoid system-directed drugs can exert beneficial effects on mood, as well as modulate neuroinflammation, synaptic plasticity, neurotoxicity, apoptosis, cell proliferation, cell differentiation, and oxidative stress [47, 48]. Moreover, cannabis tetrahydrocannabinol (THC) induces neurogenesis, removes A_β peptides, and decreases neurofibrillary tangles. The hippocampus and microglia, key actors in dementia pathophysiology, express 1 and 2 cannabinoid receptors, respectively [49]. Type 2 cannabinoid receptor (CNR2) is overexpressed in activated microglia in different areas of the nervous system. Activated CNR2 has the potential to disrupt the AD process and treat the symptoms, reducing neurodegeneration, neuroinflammation, and improving spatial memory [50]. The role of the type 1 cannabinoid receptor (CNR1) is unclear. However, CNR1 can up-regulate anti-apoptotic proteins in rats [49].

2.17 Peroxisome proliferator-activated γ receptor

Peroxisome proliferator-activated γ receptor (PPAR γ) regulates the transcription of several genes involved in inflammation, immune response, insulin sensitivity, and lipid metabolism. The pathways governed by PPAR γ overlap the biological pathways implicated in AD pathogenesis according to various pieces of evidence. Besides, PPAR γ regulates the expression of seven AD-associated genes, including ApoE, ABCA1, and ABCG1. Increasing ApoE lipid levels facilitate soluble A_β degradation. Studies using AD animal models have suggested that PPAR γ exerts direct and indirect effects on APP protein metabolism [51]. Peroxisome proliferator-activated γ receptor is up-regulated in AD due to existing neuroinflammation and PPAR γ agonists can be used in AD and shows anti-inflammatory effects, as well as improve learning and memory. Thus, PPAR γ might be a significant new therapeutic target in AD treatment [52]. In addition, emerging evidence suggests that PPAR γ effectively regulates microglia activation under physiological and pathological conditions, facilitating A_β microglial phagocytosis [53]. In addition, PPAR γ polymorphisms have been studied in AD; however, the results are controversial and inconclusive [54].

2.18 NOD-like receptor pyrin domain-containing-3

The NOD-like receptor pyrin domain-containing-3 (NLRP3) is the best known member of the NLR family. Importantly, APP can activate the NLRP3 inflammasome and increase NLRP3, caspase1, and IL1- β genes expression [55]. In microglia, NLRP3 activation is essential for interleukin-1 β (IL1- β) maturation and subsequent inflammatory events. Besides, NLRP3 is possibly involved in AD

pathogenesis through oxidative stress [56]. One study showed that NLRP3 knock-out mice were largely protected from spatial memory loss and other AD-associated sequelae, showing reduced caspase-1 and IL1- β activation, as well as increased A β clearance. Microglial activation by A β can initiate innate immune responses in CNS via NLRP3, even before the A β deposition. These results show an important role of the NLRP3 axis in the AD pathogenesis and suggest that NLRP3 inflammasome inhibition might be a new therapeutic intervention for the disease [57]. Non-steroidal anti-inflammatory drugs can inhibit NLRP3 inflammasome via reversible blockade of volume-regulated anionic channels in the plasma membrane, inhibiting cognitive impairment in AD mice models [58]. The loss of NLRP3 inflammasome function also reduced tau hyperphosphorylation and aggregation (involved in AD pathogenesis) by regulating tau kinases and phosphatases. Tau, in turn, activated the NLRP3 inflammasome. The intracerebral injection containing A β induced tau pathology in an NLRP3-dependent manner. Therefore, these data suggest an important role of NLRP3, microglia, and inflammasome activation in AD tauopathies [59]. Finally, virgin coconut oil improved hippocampal health, memory, and learning in AD mice models by inhibiting NLRP3 and reducing oxidative stress [55].

3. Conclusion

Nuclear receptors family and G-protein-coupled receptors are probably the receptors families most involved with AD (**Table 1**). Additionally, the cerebral cortex is the main area where most of the receptors involved in AD express themselves. The cerebral cortex's physical area, its complexity, and its involvement with several relevant functions in AD probably justify this fact. Despite the small size of the hippocampus, this region is significantly affected in AD. While the cerebral cortex is mainly involved in decision making, subjective thinking, consequences of action assessment, perception, and attention, the hippocampus is mainly related to memory. As a key component of cortico-hippocampal networks, the perirenal cortex plays an important role in memory processes, especially familiarity-based recognition memory. Therefore, disrupted functional connectivity of this cortical region as a result of early neurodegeneration may contribute to altered brain rhythms and cognitive failures observed in the early clinical phase of AD patients [11].

Although few receptors involved with AD are expressed in the hypothalamus and amygdala (when compared to the expression in the cortex, hippocampus, pons, medulla, and basal ganglia), it is known that AD is closely associated with changes in mood and motivation. However, these associations depend on the AD stage. Most of the receptors involved with AD are expressed in more than one nervous system area, showing the involvement of several brain regions in AD. Additionally, microglia is one of the main cell types in which AD-associated receptors express themselves, highlighting the relevance of microglia in AD, especially in the removal of toxic peptides. Additionally, AD-associated receptors are involved with several metabolic pathways, which may be directly or indirectly related to the disease. The APP elimination or the blockage of pathways related to the APP synthesis is the main function performed by the receptors involved with AD (**Table 1, Figure 1**). Besides, many receptors are directly involved with cognitive, memory, and/or learning functions and many receptors are associated with more than one AD-related function (**Table 1, Figure 1**). Finally, AD-associated receptors are also related to nervous system plasticity, including neuronal and microglial survival, nervous system development (positive plasticity), and neuronal death (negative plasticity).

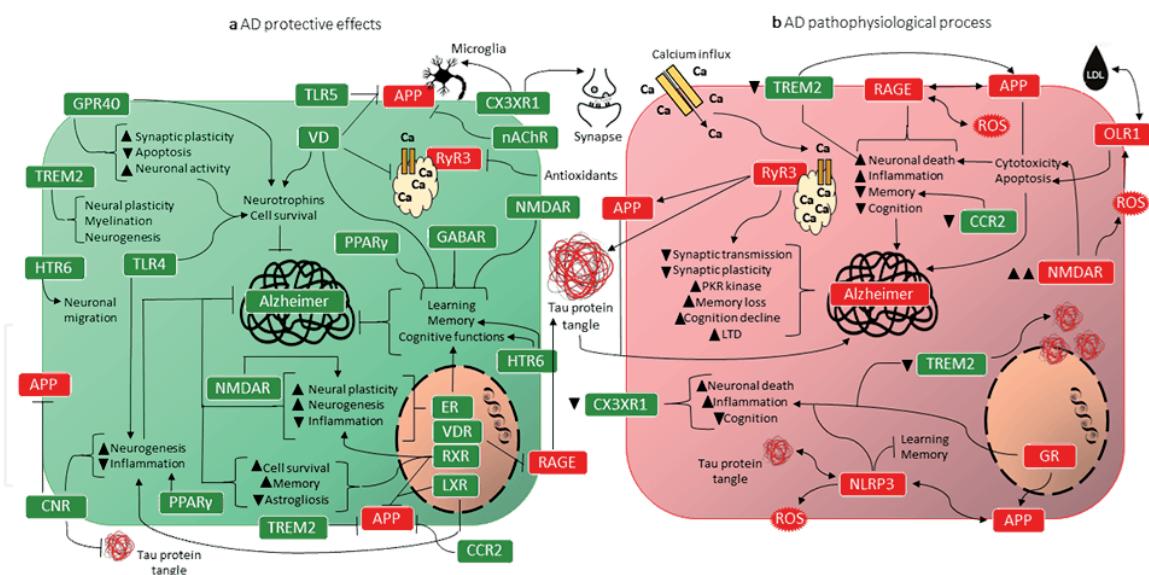
Receptor/family	Main expression area in human CNS	Main roles in AD
Acetylcholine receptors (AChR) Nicotinic Receptors	Cerebral cortex and cerebellum	Interacts with APP protein and exert positive effects on memory and attention [1, 2].
Estrogen receptors (ER) Nuclear receptor family	Basal ganglia and hippocampus	Increases neural plasticity and neurogenesis, affecting cognitive functions and the brain regenerative potential. May play beneficial effects in reducing the brain inflammatory process [4–6].
Ryanodine receptor 3 (RyR3) Calcium channels	Basal ganglia	Plays negative effects related to synaptic transmission and synaptic plasticity. Associated with memory loss and age-related cognition decline [7–9].
Gamma-Aminobutyric Acid receptor (GABAR) Ionotropic receptor	Cerebral cortex	Regulates learning, memory, cognitive function, controls the glutamate release, and reduces APP toxicity [10–12].
Receptor for advanced glycation end products (RAGE) Immunoglobulins superfamily	Cerebellum	Contributes to neuronal death and inflammation and is involved with the APP transport, oxidative stress, and cerebral blood flow [14, 15].
Vitamin D receptor (VDR) Nuclear receptor family	Cerebral cortex and hippocampus	Interacts with SMAD3, regulating APP transcription through TGF β signaling. Suppress APP gene promoter activity [16].
Retinoid X receptor (RXR) Nuclear receptor family	Cerebral cortex	Stimulates physiological mechanisms of APP elimination, decreasing APP-induced deficits [17, 18, 21].
N-methyl-D-aspartate receptors (NMDAR) Ionotropic receptor	Cerebral cortex and hypothalamus	Participates in CNS development and is involved in synaptic plasticity, essential for learning and memory [22, 23].
Liver X receptor β (LXR) Nuclear receptor family	Cerebral cortex	Regulates the cholesterol homeostasis and inflammation in CNS. May play roles in neurogenesis, APP processing, and microglial phagocytosis modulation [24–26].
Low-density lipoprotein receptor (LDLR) Lipoprotein receptor family	Pons and medulla	Mediates the increase in ApoE expression induced by APP protein [27].
Oxidized low-density lipoprotein receptor 1 (OLR1) Lipoprotein receptor family	Midbrain	Mediates the uptake and internalization of low-density oxidized lipoprotein (oxLDL), which may be involved in AD [27].
Toll-like receptor 4 (TLR4) Toll-like receptor family	Hippocampus	Induces CREB signaling, which regulates neuron survival, neuronal gene expression, and neurogenesis in the adult subventricular zone [28, 32, 33].
Toll-like receptor 5 (TLR5) Toll-like receptor family	Thalamus	Binds to APP oligomers and fibrils, forming complexes that block APP toxicity [28, 30, 31].
C-C chemokine receptor type 2 (CCR2) Chemokine receptor family	Pons and medulla	Promotes monocyte recruitment to APP deposition sites, where these cells can phagocytize APP proteins [34].
Chemokine receptor CX3C 1 (CX3CR1) Chemokine receptor family	Midbrain, pons, and medulla	Maintains microglial function in synaptic support and performs IL-1 β dependent cognitive functions [34].

Receptor/family	Main expression area in human CNS	Main roles in AD
Glucocorticoid receptor (GCRs) Glucocorticoid receptor family	Cerebellum	Participates in the generation and activity of APP protein in the brain [36, 37].
G-protein-coupled receptor 40 (GPR40) G-protein-coupled receptor family	Spinal cord	Promotes neurogenesis, inhibits neuronal apoptosis, and plays a role in protecting nerves and decreasing brain damage [38, 39].
Triggered receptor expressed on myeloid cells 2 (TREM-2) Immunoglobulins superfamily	Midbrain	Participates in microglial survival, inflammatory response, phagocytosis, dendritic cell maturation and others [40–43].
5-hydroxytryptamine 6 receptor (5 HTR6) G-protein-coupled receptor family	Basal ganglia	Controls the pyramidal neurons migration during corticogenesis, activates TOR signaling, and regulates the GABAergic, glutamatergic, and cholinergic activity. Involved in cognition, anxiety, memory, mood, among others [44, 45].
Cannabinoid receptor (CNR) G-protein-coupled receptor family	Cerebral cortex	Disrupt the AD process, reduce symptoms, neurodegeneration, neuroinflammation, and improve spatial memory [47–50].
Peroxisome proliferator-activated γ receptor (PPAR γ) Nuclear receptor family	Amygdala	Participates in pathways involved with lipid metabolism and immune response implicated in AD etiology. PPAR γ acts as a transcriptional regulator of several genes involved in AD pathogenesis [51–53].
NOD-like receptor pyrin domain-containing-3 (NLRP3) NOD-like receptor family	Pons and medulla	The NLRP3 activation leads to IL-1 β and IL-18 production that play a role in the inflammatory response and oxidative stress in AD pathogenesis. [56–59].
Sigma-1 receptor (σ 1R) Chaperone protein	Cerebral cortex	Inhibits enzymes involved in AD, such as acetylcholinesterase, 5-lipoxygenase, and monoamine oxidase. Protects neurons against oxidative stress, contributing to neuronal tissues repair [64].
Calcium sensing receptor (CaSR) G-protein-coupled receptor family	Cerebral cortex and hippocampus	Role in hippocampal neurons degeneration. APP is able to increase intracellular calcium by opening calcium-permeable cationic channels in hippocampal neurons [65].

Table 1.
Alzheimer's disease associated receptors.

This suggests that these receptors participate in several long-term changes in the nervous system (long-term plasticity) [60].

Finally, most of the receptors involved in AD (67%) are associated with beneficial effects on the disease. These receptors include nuclear receptors, such as VDR, membrane receptors, such as TLR5, and cytoplasmic receptors, such as GABAR. Most of the AD-associated receptors are found in the membrane of nerve cells (61%). Among the neuroprotective receptors, we can highlight the vitamin D receptor, responsible for vitamin D actions. Vitamin D is increasingly recognized as a substance involved in neuronal survival, taking part in psychiatric and

**Figure 1.**

Proteins associated with AD. Proteins related to AD are shown according to their protective (a) or pathological (b) effects in AD. The receptors located in the green boxes are associated with neuroprotective effects on AD. Receptors located in red boxes are associated with AD pathophysiology. Proteins are shown according to their location in the cell (nucleus, membrane, intracellular or extracellular). Arrows/triangles represent activation, induction or increase. Inverted bars/triangles represent inhibition, deficit or decrease. Protein associated to AD protection are related to proteins involved in AD pathophysiological process. Two triangles represent overactivation. Elements in the figure are not showed in real scale. ROS, reactive oxygen.

neurodegenerative diseases such as AD. The participation of vitamin D in neuronal survival may be related to its role in inhibiting the cellular oxidative stress and APP synthesis. Therefore, supplementation with vitamin D can help in the current AD treatment [61]. A beneficial role in inflammation, played by some receptors acting on inflammatory pathways, such as TLRs, has also been shown to be beneficial in the AD treatment [62]. More and more new treatments are being researched for AD, but unfortunately, the improvements have not been significant. What has been sought are combinations of treatments, which can result in some side effects in the elderly patient. Besides, current treatments are only symptomatic, that is, they do not modify the AD stage. These are cholinesterase inhibitors, used in all AD stages as they result in some beneficial effects on cognition and behavior. However, therapies affecting the AD stage are still under development. Therefore, efficient research must be conducted in this direction, instead of alleviating only the symptoms. Immunotherapy, for example, can be a viable option soon [63].

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